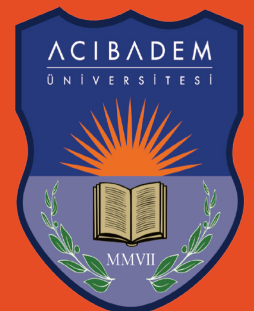
ISSN 1309-470X



ACIBADEM ÜNİVERSİTESİ

SAĞLIK BİLİMLERİ DERGİSİ

Cilt **12** / Sayı **3** / Temmuz **2021**

Cilt: **12**, Sayı: **3,** Temmuz **2021**

ISSN: 1309-470X
e-ISSN: 1309-5994

YAYIN TÜRÜ

Hakemli Süreli Yayın
(Dergi, yılda 4 sayı olarak Ocak, Nisan, Temmuz, Ekim aylarında yayımlanır)

YAYIN SAHİBİ

Acıbadem Mehmet Ali Aydınlar Üniversitesi Adına
Rektör, Prof. Dr. Ahmet Şahin

EDİTÖR

Prof. Dr. Enis Özyar

EDİTÖR YARDIMCISI

Dr. Öğr. Üyesi Akif Enes Arıkan

DERGİ SORUMLUSU

Ezgi Karaduman

ADRES / YÖNETİM YERİ

Acıbadem Üniversitesi Sağlık Bilimleri Dergisi Acıbadem Üniversitesi Tıp Fakültesi Kayışdağı Cad. No:32
34752 Ataşehir / İstanbul
Tel : +90 (216) 500 42 96
Faks : +90 (216) 576 50 76
e-posta : editor@acibadem.edu.tr

Acıbadem Üniversitesi Sağlık Bilimleri Dergisi
ULAKBİM TR Dizin, EBSCO ve Türkiye Atıf Dizini'nde indekslenmektedir.

Kapak resmi: Prof. Dr. Erkmen Böke (1939-2014):

İzmir'de 1939 yılında doğdu. 1962 yılında Ankara Üniversitesi Tıp Fakültesi'ni bitirdi. 1970 yılında Almanya Heidelberg Üniversitesi'nden Genel Cerrahi uzmanlığını aldı. Türkiye'ye döndükten sonra Hacettepe Üniversitesi'nde 1970 yılında Genel Cerrahi Uzmanı, 1973 yılında da Göğüs ve Kalp-Damar Cerrahisi Uzmanlığını aldı. Aynı üniversitede 1976 yılında Doçentliğe, 1982 yılında da Profesörlüğe atandı. 1982-1988 yılları arasında Hacettepe Üniversitesi Hastaneleri Başhekimliği görevinde bulundu. Almanca ve İngilizce bilen Prof. Dr. Böke, evli ve iki çocuk babasıdır.

Resim çalışmalarına 2003 yılından beri yoğun olarak devam etmiş olan Prof. Dr. Böke, ilk iki yağlıboya kişisel resim sergisini Hacettepe Üniversitesi Ahmet Göğüş Sanat Galerisi'nde 2005 ve 2007 yıllarında, üçüncü kişisel sergisini Arsuz İskender Sayek Evi'nde "Füsun'un Çiçekleri" adıyla ve dördüncü sergisini de 2011 yılında Ankara Elele Sanat Galerisi'nde açmıştır. Prof. Dr. Erkmen Böke, yedi karma sergiye katılmıştır.

KURUCU EDİTÖRLER / HONORARY EDITORS

Dr. Nurdan Tözün
Dr. Necmettin Pamir

DANIŞMA KURULU* / ADVISORY BOARD

Dr. Agop Çıtak, *Türkiye*
Dr. Ahmet Alanay, *Türkiye*
Dr. Albert Bart, *Hollanda*
Dr. Anne W. M. Lee, *Çin*
Dr. Bülent Atilla, *Türkiye*
Dr. Cem Alhan, *Türkiye*
Dr. Cem Önal, *Türkiye*
Dr. Cüneyt Üneri, *Türkiye*
Dr. David I. Rosenthal, *A.B.D*
Dr. Deniz Yücel, *Türkiye*
Dr. Ertan Ural, *Türkiye*
Dr. Ferah Yıldız, *Türkiye*
Dr. Ferran Urquisa Pellise, *İspanya*
Dr. Gülten Dinç, *Türkiye*
Dr. Haluk Berk, *Türkiye*
Dr. Henrik Vedel Nielsen, *Danimarka*
Dr. James C. Fang, *A.B.D*
Dr. Menno de Bree, *Hollanda*
Dr. Metin Ertem, *Türkiye*
Dr. Muhittin Serdar, *Türkiye*
Dr. Munsih Gupta, *A.B.D.*
Dr. Önder Us, *Türkiye*
Dr. Özgür Kurt, *Türkiye*
Dr. Remzi Tözün, *Türkiye*
Dr. Roberto Andorna, *İsviçre*
Dr. Ükke Karabacak, *Türkiye*
Dr. Ülgen Zeki Ok, *Türkiye*
Dr. Volkan Kavas, *Türkiye*
Dr. Yeşim Işıl Ülman, *Türkiye*
Dr. Yusuf Özbel, *Türkiye*

*Tüm Acıbadem Üniversitesi Öğretim Üyeleri Acıbadem Üniversitesi Sağlık Bilimleri Dergisi'nin Danışma Kurulu Üyesidir.
**All Faculty Members of Acibadem University are members of the Advisory Board.*

Volume: **12**, Issue: **3**, July **2021**

ISSN: *1309-470X*
e-ISSN: *1309-5994*

JOURNAL TYPE

Refereed Periodicals
(The journal is published four times a year in January, April, July and October)

JOURNAL OWNER

On behalf of Acıbadem Mehmet Ali Aydınlar University
Rector, Prof. Dr. Ahmet Şahin

EDITOR

Prof. Dr. Enis Özyar

DEPUTY EDITOR

Assist. Prof. Dr. Akif Enes Arıkan

SECRETARY

Ezgi Karaduman

ADDRESS / EDITORIAL OFFICE

Acıbadem University Health Sciences Journal Acıbadem University, School of Medicine Kayışdağı Cad. No: 32
34752 Ataşehir / İstanbul
Phone : +90 (216) 500 42 96
Fax : +90 (216) 576 50 76
e-mail : editor@acibadem.edu.tr

Acıbadem University Health Sciences Journal is indexed in ULAKBİM TR Dizin, EBSCO and Türkiye Atıf Dizini.

Cover image: Prof. Dr. Erkmen Böke (1939-2014):

He was born in Izmir in 1939. He graduated from Ankara University Faculty of Medicine in 1962. In 1970, he received his General Surgery specialty from Heidelberg University, Germany. After returning to Turkey, General Surgeon at Hacettepe University in 1970, also in 1973, took/finished the Thoracic and Cardiovascular Surgery Specialty. He was appointed Associate Professor in 1976 and Professor in 1982 at the same university. Between 1982-1988, he worked as the Chief Physician of Hacettepe University Hospitals. Speaking German and English, Prof. Dr. Böke is married and has two children.

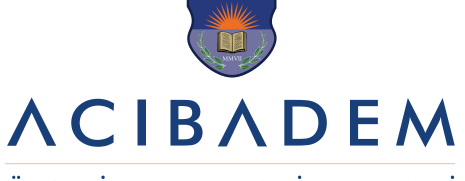
Prof. Dr. Böke opened his first two personal oil painting exhibitions at Hacettepe University Ahmet GÖĞÜŞ Art Gallery in 2005 and 2007, the third one at the Arsuz İskender Sayek House under the name "Flowers of FÜSUN" and the fourth one at the Ankara Elele Art Gallery in 2011. Prof. Dr. Erkmen Böke participated in seven group exhibitions.

ALAN EDİTÖRLERİ / *SPECIALTY EDITORS*

Dr. Selçuk Görmez
Dr. Ceyda Erel Kırışoğlu
Dr. Bahar Temur
Dr. Özlem Naciye Atan Şahin
Dr. Serpil Yaylacı
Dr. Ahmet Erdem Kılavuz
Dr. Ali Rıza Cenk Çelebi
Dr. Akif Enes Arıkan
Dr. Faruk Suat Dede
Dr. Berna Eren
Dr. Taner Korkmaz
Dr. Borçak Çağlar Ruhi
Dr. Özdal Ersoy
Dr. Özlem Çelik
Dr. Cemaliye Akyerli Boylu
Dr. Özgül Gök
Dr. Özden Hatırnaz NG
Dr. Fatma Tokat
Dr. Emel Baloğlu
Ahmet Levent Güler
Dr. Zeynep Tokcaer Keskin
Dr. Mustafa Seçkin
Dr. Esra Uğur
Dr. Yasemin Uslu
Dr. Gizem Köse
Dr. Melis Yavuz
Dr. Meral Bayramoğlu
Dr. Nuray Alaca
Dr. Kahraman Berkhan Yılmaz
Dr. Yeşim Yasin
Dr. Gamze Uğurluer
Dr. Ceren İlikan Rasimoğlu
Dr. Bora Özveren

Dergimizdeki bilimsel yazı İngilizce düzeltmeleri, Ekim 2018 yılından itibaren, Motassem Bowarshi tarafından yapılmaktadır.

English Editing for Scientific Writing services provided by Motassem Bowarshi, since October, 2018.



ACIBADEM ÜNİVERSİTESİ SAĞLIK BİLİMLERİ DERGİSİ

Cilt: 12, Sayı: 3, Temmuz 2021

İçindekiler/*Contents*

ARAŞTIRMA / *ORIGINAL ARTICLE*

Moleküler Biyoloji ve Genetik / Molecular Biology and Genetics

- Sensitive Detection of Molecular Targets in Cancer by Minisequencing....547
  Minidizileme ile kanserdeki moleküler hedeflerin hassas tayini
  Şirin K. Yüksel, Cemaliye B. Akyerli

Biyokimya ve Moleküler Biyoloji / Biochemistry and Molecular Biology

- Transcriptomics Analysis of Nrf2 Regulators in Cancer Resistant and Long-Lived Naked Mole-Rats....553
  Kansere ve yaşlanmaya karşı üstün dirençli farelerde Nrf2 yolağını düzenleyen faktörlerin transkriptomik düzeyde analizi
  Perinur Bozaykut Eker

Radyoloji / Radiology

- Risk Factors Associated with Dysfunction of Permanent Tunneled Cuffed Hemodialysis Catheters; Single Center Experience....558
  Kalıcı Tünelli Hemodiyaliz Kateter Disfonksiyonu ile İlişkili Risk Faktörleri; Tek Merkez Deneyimi
  Işıl Yıldız
- The Usage and Efficiency of DrugEluting Stents in Vertebral Ostial Stenosis....564
  Vertebral Ostial Stenoz Tedavisinde İlaç Salınımlı Stent Uygulaması ve Etkinliği
  Burcu Erkan, Serdar Geyik, Kıvılcım Yavuz, Işıl Saatçi, Saruhan Çekirge

Aile Hekimliği / Family Medicine

- From Whom did you Receive This Information?(A study on Using Complementary and Alternative Medicine (CAM) Methods in Elderly Individuals)......574
  Bu Bilgiyi Kimden Aldın? (Yaşlı Bireylerde Tamamlayıcı ve Alternatif Tedavi (TAT) Yöntemleri Kullanımı Hakkında bir Araştırma)
  Deniz Say Şahin

Halk ve Çevre Sağlığı / Public and Environmental Health

- An Evaluation of e-Health Literacy in University Students: The Example of Yozgat Bozok University....579
  Üniversite Öğrencilerinde e-Sağlık Okuryazarlığının Değerlendirilmesi
  Şemsinnur Göçer, Elçin Balcı, Nursel Üstündağ Öcal

Acil Tıp / E mergency Medicine

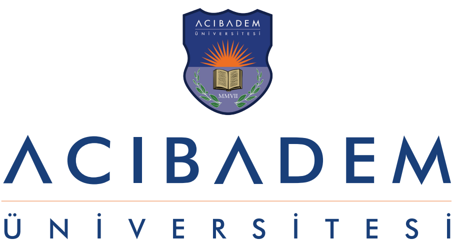
- The Relationship Between Serum Levels of Procalcitonin, Lactate, HgA1c and Functional Outcome in Acute Ischemic Stroke Patients....585
  İskemik Serebrovasküler Olay Geçirmiş Hastalarda Hemoglobin A1c, Laktat, Prokalsitonin Seviyelerinin Fonksiyonel Sonuç ile İlişkisi
  Zuhal Kalyon Karaman, Çiğdem Özpolat, Özge Ecmel Onur, Haldun Akoğlu, Arzu Denizbaşı
- Retrospective Analysis of Management of Ingested Foreign Bodies in Emergency Department....591
  Yabancı Cisim Alımı ile Acil Servise Başvuran Hastaların Retrospektif Değerlendirilmesi
  Rezan Karaali, Ahmet Kayalı, Osman Sezer Çınaroğlu, Zeynep Karakaya, Firdevs Topal

Göğüs Hastalıkları / Chest Diseases

- The Effect of COPD Presence, Quality of Life and Nutritional Status on ShortTerm Survival in Patients with Non-Small Cell Lung Cancer....596
  Küçük Hücre Dışı Akciğer Kanseri Olan Hastalarda KOAH Varlığı, Hayat Kalitesi ve Beslenme Durumunun Kısa Dönem Sağkalım Üzerinde Etkisi
  Murat Yıldız, Sema Avcı, Oral Menteş, Meriç Ünver, Deniz Çelik, Pınar Akın Kabalak, Ülkü Yılmaz

Dermatoloji / Dermatology

- Investigation of Patient Awareness and Attitude in Dermatology....604
  Dermatolojide Hasta Farkındalığının ve Tutumunun İncelenmesi
  Melek Aslan Kayıran, İlknur Özcan, Mehmet Salih Gürel



Volume: 12, Issue: 3, July 2021

İçindekiler/*Contents*

Pediatri / Pediatrics

- Diagnosis And Treatment in Children With Nutcracker Syndrome: A Single-Center Experience ... 610
  Nutcracker Sendromlu Çocuklarda Tanı ve Tedavi: Tek Merkez Deneyimi
  Serçin Güven, Sevinç Kalın, Neslihan Çiçek

Gastroenteroloji ve Hepatoloji / Gastroenterology and Hepatology

- Fecal S100A12 as a Biomarker in Behcet's Disease ... 616
  Behçet Hastalarında Yeni Biyobelirteç: Fekal S100A12
  Cem Şimşek, Berkan Armağan, Alper Sarı, Abdulsamet Erden, Levent Kılıç, Ali Akdoğan
- Artificial Intelligence to Predict Esophageal Varices in Patients with Cirrhosis ... 625
  Sirozlu Hastalarda Yapay Zeka ile Özofagus Varis Tahmini
  Cem Şimşek, İbrahim Emir Tekin, Hasan Şahin, Taha Koray Şahin, Yasemin Hatice Balaban

Göz Hastalıkları / Ophthalmology

- Endonasal Dacryocystorhinostomy; the Learning Curve and Our Experience ... 630
  Endonazal Dakriyosistorinostomi; Öğrenme Eğrisi ve Tecrübelerimiz
  İsmet Emrah Emre, Ali Rıza Cenk Çelebi

Plastik ve Rekonstrüktif Cerrahi / Plastic and Reconstructive Surgery

- Surgical Outcomes and Complications in Patients with Early Stage Dupuytren's Contractures ... 634
  Erken Evre Dupuytren Kontraktürü Olan Hastalarda Cerrahi Sonuç ve Komplikasyonlar
  Yahya Baltu

Cerrahi / Surgery

- Comparison of Laparascopic and Open Adrenalectomy ... 639
  Laparoskopik ve Açık Adrenalektominin Karşılaştırılması
  Onur Dülgeroğlu, Tayfun Bilgiç, Mehmet Hacıyanlı
- Usual and Unusual Pathologies of Appendicitis: A Retrospective Analysis of 385 Patients ... 645
  Apandisitin Olağan ve Olağandışı Patolojileri: 385 Hastanın Retrospektif Analizi
  Veysi Hakan Yardımcı, Cihan Uras

Kadın Hastalıkları ve Doğum / Obstetrics and Gynecology

- The Use of Bevacizumab Alone and in Combination with Classical Chemotheropathics in Ishikawa Endometrial Cancer Cell Culture ... 651
  Ishikawa Endometrial Kanser Hücre Kültüründe Bevacizumabin Tek Başına ve Klasik Kemoteropatiklerle Birlikte Kullanımı
  Ceren Yıldız Eren, Hulusi Göktuğ Gürer, Özlem Özgür Gürsoy, Ayşe Tansu Koparal, Sabit Sinan Özalp

Üroloji / Urology

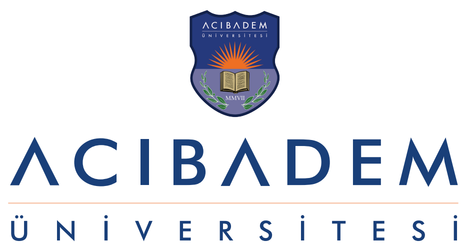
- Bir Üniversite Hastanesine Başvuran Erkek İnfertilite Tanılı ve Asemptomatik Hastalarda Testis Tümörü Sıklığı ... 658
  Frequency of Testicular Tumor in Patients with a Diagnosis of Infertility and Asymptomatic Male Applied to a University Hospital
  Metin Yığman, Semih Tangal

Hemşirelik / Nursing

- Effectiveness of Simulation-Based Cooperative Learning Method in Electrocardiography Education ... 662
  Simülasyona Dayalı İşbirlikçi Öğrenme Modeline Göre Tasarlanan Temel EKG Kursu'nun Etkinliği
  Yasemin Uslu, Vildan Kocatepe, Vesile Ünver, Ükke Karabacak

Sağlık Yönetimi / Healthcare Management

- Analysis of Studies on COVID-19 Pandemic with Science Mapping Technique ... 670
  COVID-19 Pandemisi Üzerine Yapılan Çalışmaların Bilim Haritalama Tekniğiyle Analizi
  İlknur Arslan Çilhoroz, Yasin Çilhoroz, Enver Bozdemir



Cilt: 12, Sayı: 3, Temmuz 2021

İçindekiler/*Contents*

Sağlık Politikaları ve Hizmetleri / Health Policies and Services

- Determinants of Health System Performance in Europe: A Study Based on Clustering Analysis....682

  Avrupa'da Sağlık Sistemi Performansının Belirleyicileri: Kümeleme Analizine Dayalı Bir Çalışma
  Pınar Yalçın Balçık, Şenol Demirci, Murat Konca

- Evaluation of Family Physicians' Opinions on Defensive Medicine Practices: The Case of the Province of Isparta/Turkey....690

  Defansif Tıp Uygulamalarında Aile Hekimlerinin Görüşlerinin Değerlendirilmesi: Isparta İli Örneği
  Oğuzhan Yüksel

OLGU SUNUMU / *CASE REPORT*

Kulak Burun Boğaz / Otolaryngology

- Olfactory and Taste Dysfunction as an Initial Symptom of COVID-19....697

  COVİD-19: İlk Semptom Olarak Koku ve Tat Disfonksiyonu
  Altuğ Özagar, Senem Almaç Deniz

Gastroenteroloji ve Hepatoloji / Gastroenterology and Hepatology

- Inverted Colonic Diverticula Cases....700

  Ters dönmüş kolonik divertikül: İki Olgu Sunumu
  Arzu Tiftikçi, Emrehan Parlak, Bircan Boğa, Serpil Yılmaz, Bahattin Çiçek

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 547-552
https://doi.org/10.31067/acusaglik.851006

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   Molecular Biology and Genetics / Moleküler Biyoloji ve Genetik

Sensitive Detection of Molecular Targets in Cancer by Minisequencing

Şirin K. Yüksel[1], Cemaliye B. Akyerli[2]

[1]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Fen Edebiyat Fakültesi, Moleküler Biyoloji ve Genetik Bölümü, İstanbul, Türkiye

[2]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, İstanbul, Türkiye

Şirin K. Yüksel, Öğr. Gör. Dr.

Cemaliye B. Akyerli, Dr. Öğr. Üyesi

Correspondence: Cemaliye B. Akyerli
Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, İstanbul, Türkiye
Phone: -
E-mail: cemaliye.boylu@acibadem.edu.tr

Received : 07 September 2020
Accepted : 04 November 2020

ABSTRACT

Purpose: Molecular alterations leading to specific mutations are essential for tumor development and survival. Accurate analysis of these molecular targets is important for diagnosis, early detection, forecasting of prognosis and aiding in the treatment of different cancer types. Therefore, for sensitive analysis of molecular markers, we aimed to optimize and use minisequencing protocols besides Sanger sequencing.

Methods and Materials: Sanger sequencing and minisequencing were performed for *IDH1* R132, *IDH2* R140/R172 and *TERT* promoter C228/C250 mutations using genomic DNA isolated from glioma samples. Minisequencing reactions were performed with detection primers using SnaPshot Multiplex Ready Reaction Mix and run on an automated capillary electrophoresis. Multiplex peaks were analyzed with GeneMapper Software.

Results: In the multiplex minisequencing analyses, peaks corresponding to wild type alleles and different mutations were detected. The presence of the peaks next to the wild type peaks points to the presence of variations in that location and the nature of the mutation can be identified according to the color.

Conclusions: Identification of molecular markers in cancer is very important. Minisequencing is a reliable method for the detection of molecular targets.

Keywords: *IDH*, minisequencing, molecular targets, mutations, *TERT* promoter

Minidizileme ile kanserdeki moleküler hedeflerin hassas tayini

ÖZET

Amaç: Belirli mutasyonlara neden olan moleküler değişiklikler tümör gelişimi ve sağkalımı için gereklidir. Bu moleküler hedeflerin doğru analiz edilmesi farklı kanser tiplerinde tanı, erken teşhis, prognoz tahmini ve tedavide yol gösterme açısından önemlidir. Bu nedenle, moleküler belirteçlerin hassas tayini için Sanger dizilemenin yanı sıra minidizileme protokolünü de optimize ederek kullanmayı amaçladık.

Yöntem: Gliom örneklerinden elde edilmiş genomik DNAlar kullanılarak *IDH1* R132, *IDH2* R140/R172 ve *TERT* promotör C228/C250 mutasyonları için Sanger dizileme ve minidizileme yapılmıştır. Minidizileme reaksiyonları mutasyon saptama primerleri ile "SnaPshot Multiplex Ready Reaction Mix" kullanılarak gerçekleştirilmiş ve otomatik kapiler elektroforezinde yürütülmüştür. Çoklu eğriler "GeneMapper Software" kullanılarak analiz edilmiştir.

Bulgular: Minidizileme analizlerinde, yabanıl tip alellere ve farklı mutasyonlara ait eğriler tespit edilmiştir. Yabanıl tip piklerin yanında yer alan eğriler, o noktada varyasyona işaret etmekte ve mutasyon renge göre tanımlanmaktadır.

Sonuç: Moleküler belirteçlerin kanserde tayini oldukça önemlidir. Minidizileme yöntemi moleküler hedeflerin belirlenmesinde güvenilir bir yöntemdir.

Anahtar sözcükler: *IDH*, minidizileme, moleküler hedefler, mutasyonlar, *TERT* promotör

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Cancer is a group of diseases which involves the uncontrolled growth of abnormal cells. It has the potential to invade other tissues and also spread to different parts of the body. When cancer is considered at a cellular level, it is generally caused by the molecular alterations leading to specific mutations (1). Recent advances in molecular biology and genetics have provided us to study cancers with valuable prognostic and predictive significance. Many genetically altered molecular targets are described in cancer cells which are essential for tumor development and survival. There are many known molecular markers which allow early detection of different cancer types. These lead to a decrease in mortality rate. Furthermore, in some cases, targeted therapy of tumors and patient follow-up appear to be possible. Therefore, it is extremely important to study various molecular markers for diagnosis, prognosis and therapy in cancer patients (2).

Recently, isocitrate dehydrogenase (*IDH1* and *IDH2*) and human telomerase reverse transcriptase (*TERT*) promoter mutations were detected in different cancer types. *IDH1/2* mutations lead to the conversion of α-ketoglutarate (αKG) to D-2-hydroxyglutarate (D2HG) oncometabolite (3). Since the structure of D2HG is similar to αKG, the catalytic activity of αKG-dependent dioxygenases is inhibited, resulting in deregulation of histone modification and DNA demethylation (4). *IDH* mutations, predominantly *IDH1* R132 and *IDH2* R140/R172, were identified in a variety of myeloid malignancies and solid tumors (5).

Upregulation of telomerase activity by *TERT* promoter mutations enabling replicative immortality is a hallmark of cancer (6). De novo ETS binding site creating hotspot mutations in the *TERT* promoter, C228T (c.-124C>T, chr5: 1295228 C>T) and C250T (c.-146C>T, chr5:1295250 C>T), were reported to occur in melanomas and a few other tumors (7). These mutations were shown especially to be useful biomarkers for early detection of urinary and liver tumors and classification and prognostication of brain tumors, respectively (8).

Detection of *IDH* and *TERT* mutations in patient samples is useful for the diagnosis and prediction of prognosis in different cancer types. Sanger sequencing by automated capillary electrophoresis is regarded as the gold standard for variant detection. The limit of detection of Sanger analysis is 15-20% in cancer samples depending on the heterogeneity of tumors (9). Since the sensitivity of the analysis method is very important, we aimed to optimize a more sensitive method for the detection of hotspot *IDH1/2* and *TERT* promoter mutations by minisequencing.

Minisequencing, also referred as primer extension, is a method used to determine the base immediately 3′ to a detection primer by enzymatically extending the primer by one base only (10, 11). In this method, the absence of dNTPs and presence of 3′-OH lacking chain-terminating 2′,3′-dideoxynucleotide triphosphates (ddNTPs) ensures the termination of elongation after the incorporation of a single base. With the use of labeled ddNTPs, single nucleotide changes can be identified by automated capillary electrophoresis (11, 12). Up to twelve detection primers can be used simultaneously for multiplex mutation analysis by increasing the primer size with the addition of oligonucleotide tails (13).

In this context, it is very important to use sensitive methods for the analysis of molecular targets in order to avoid false results. Therefore, together with Sanger sequencing, our aim is to use and optimize minisequencing and also consider these methods for molecular marker detection.

Materials and Methods

Genomic DNA isolation

Genomic DNA was extracted from paraffin-embedded (FFPE-sections) or fresh frozen glioma tumor samples stored in liquid nitrogen by QIAamp DNA Mini Kit (Qiagen, USA) according to the manufacturer's instructions. Deparaffinization of FFPE-tissues was performed by xylene/ethanol before DNA isolation. The archival glioma tumor samples were kindly provided by Prof. Dr. Necmettin Pamir, Acibadem Mehmet Ali Aydinlar University Department of Neurosurgery.

Product amplification and purification

PCR amplifications were performed for the regions of *IDH1* (NG_023319.2), *IDH2* (NG_023302.1) and *TERT* (NG_009265.1) genes spanning the *IDH1* R132, *IDH2* R140 and R172, *TERT* promoter C228T and C250T mutations, respectively. Some primers were designed using Primer3web (v.4.1.0) software (http://primer3.ut.ee/) and the others were taken from the literature (Table 1). PCR was carried out in a total of 25 µl reaction volume, consisting of 50-100 ng DNA, 1X Colorless GoTaq Flexi Buffer, 1.5 mM MgCl2, 200 µM dNTP, 1% DMSO, 10 pmoles of each primer and 0.8 U GoTaq Flexi DNA polymerase (Promega, USA). Cycling conditions were an initial denaturing step at 96°C for 2 min, followed by 35 cycles of denaturation at 95°C for 30 sec, annealing at 55-64°C for 35 sec, extension at 72°C for 45 sec, and a final extension at 72°C for 5 min. All the amplicons were checked on 2% agarose gel. Then, 5 µl of PCR product was purified with 2 µl of the enzyme

using ExoSAP-IT kit (Affymetrix, USA) according to the manufacturer's recommendations.

Sanger sequencing

1 µl of the purified amplicons was Sanger sequenced with 20 pmoles of forward and reverse primers (Table 1) using GenomeLab DTCS - Quick Start Kit (Beckman Coulter Life Sciences, USA). Cycle sequencing conditions were 25 cycles of denaturation at 96°C for 10 sec, annealing at 50°C for 5 sec, extension at 60°C for 4 min. Sequence reactions were loaded on Beckman Coulter GeXP Genetic Analysis System (Beckman Coulter Life Sciences, USA) after dye removal by ethanol precipitation. Sequence analysis was performed by Lasergene SeqMan II, v5.08 (Dnastar Inc., Madison, USA). GenBank sequences NM_005896.4, NM_002168.4, NG_009265.1 were used as reference sequences for *IDH1*, *IDH2* and *TERT* genes, respectively.

Minisequencing

Multiplex minisequencing analyses were performed in a total of 4 µl reaction volumes with 1.5 µl of the purified amplicons and 10 pmoles of specific detection primers for *IDH1*-R132G/S/C, *IDH1*-R132L/H/P, *IDH2*-R140Q/L, *IDH2*-R140W, *IDH2*-R172K/M, *IDH2*-R172W, *hTERT*-C228T and *hTERT*-C250T mutations (Table 2) using 0.5 µl SnaPshot Multiplex Ready Reaction Mix (Applied Biosystems, USA). The colors of individual ddNTPs assigned by the manufacturer are: green (A), black (C), blue (G), red (T). Minisequencing conditions were 25 cycles of denaturation at 96°C for 10 sec, annealing at 50°C for 5 sec, extension at 60°C for 30 sec. Minisequencing reactions were run on Applied Biosystems 3130XL Genetic Analyzer (Applied Biosystems, USA) using 1.5 µl sample in 9 µl Hi-Di Formamide (Applied Biosystems, USA) and 1 µl LIZ-120 size marker (Applied Biosystems, USA). Multiplex peaks were analyzed with GeneMapper Software, version 5 (Applied Biosystems, USA).

Table 2. Detection primers used for the minisequencing analysis of *IDH1* R132, *IDH2* R140/R172, *TERT* promoter C228T and C250T mutations

Detection primer	Primer sequence
IDH1-R132G/S/C	TGGGTAAAACCTATCATCATAGGT
IDH1-R132L/H/P	TTTTATGACTTACTTGATCCCCATAAGCATGA
IDH2-R140Q/L	TGGAAAAGTCCCAATGGAACTATCC
IDH2-R140W	TTTTTGTGGAAAAGTCCCAATGGAACTATC
IDH2-R172K/M	TTTTTCCCTGGCTGGACCAAGCCCATCACCATTGGCA
IDH2-R172W	TTTTTTTTTTTTCCCTGGCTGGACCAAGCCCATCACCATTGGC
hTERT-C228T	GAGGGGCTGGGAGGGCCCGGA
hTERT-C250T	TTTTCGCGGACCCCGCCCCGTCCCGACCCCT*

(*): Initially TERTp-C250T: 5'- CGCGGACCCCGCCCCGTCCCGACCCCT- 3' primer was used for the detection of C250T mutation. Because the two peaks (for C228 and C250) were not easily distinguished especially in heterozygous samples, hTERT-C250T primer was designed and used.

Results

Sanger sequencing analysis was performed for *IDH1* R132, *IDH2* R140 and R172, *TERT* promoter C228T and C250T mutations in glioma samples. A representative result of the Sanger sequencing analysis for *IDH1*-R132H mutation is shown in Figure 1.

In the initial experiments, various annealing temperatures (55-64°C) were tried to achieve optimum PCR amplifications. In the minisequencing analysis, in order to confirm that the detection primers are working, first of all, each of them was studied alone and then the reactions were multiplexed.

Multiplex minisequencing analyses were performed with mutation specific primers in three separate reactions. Since almost all *IDH* and *TERT* mutations are heterozygous in glioma (8, 14), peaks corresponding to wild type must be detected in the analysis.

Table 1. Primers used for the amplification of regions spanning the *IDH1* R132, *IDH2* R140/R172, *TERT* promoter C228T and C250T mutations

Primer name	Primer sequence	Product size (bp)	Annealing (°C)	Analysis method
IDH1fc*	ACCAAATGGCACCATACGA	254	60	Sanger sequencing
IDH1rc*	TTCATACCTTGCTTAATGGGTGT			
IDH1-Exon4-1F	ACCAAGGATGCTGCAGAAGCTAT	363	55	Minisequencing
IDH1-Exon4-2R	TACCTTGCTTAATGGGTGTAGATACCA			
IDH2-Exon4-1F	CTGTCCTCACAGAGTTCAAGCTGAAG	207	55	Sanger sequencing & minisequencing
IDH2-Exon4-2R	CAGGTCAGTGGATCCCCTCTCCA			
TERT-F**	GGCCGATTCGACCTCTCT	489	61	Sanger sequencing
TERT-R**	AGCACCTCGCGGTAGTGG			
TERT-PRMT-3F	GCGGAAAGGAAGGGGAGGGGCT	112	64	Minisequencing
TERT-PRMT-4R	CTTCACCTTCCCAGCTCCGCCTCCT			

Taken from (*) Balss et al. (14) and (**) Killela et al. (8).

Any other peak next to these peaks implies the presence of mutations in that location and can be identified depending on the color of the peak, according to the manufacturer's instructions. The colors of the wild type and mutant peaks are given in Table 3. Minisequencing analysis results of *IDH1* R132H, *IDH2* R172K and *TERT* C250T mutations are given in Figure 2, 3 and 4, respectively.

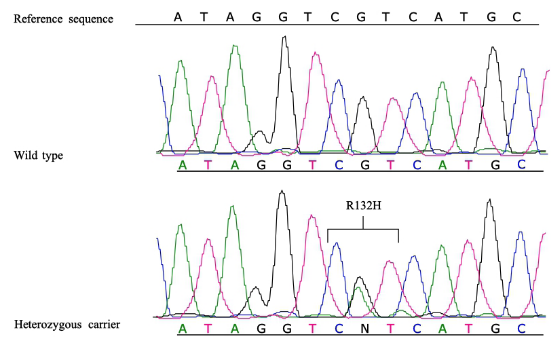


Figure 1: Sanger sequencing analysis of an *IDH1* R132H heterozygous patient sample. The gray line is the reference sequence (GenBank NM_005896.4). The bracket on the electropherogram shows the heterozygous R132H variation (lower line) compared with the homozygous wild type sample (upper line).

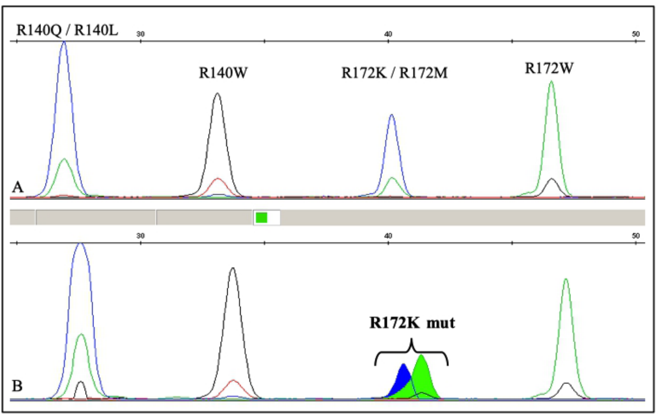


Figure 3: Minisequencing analysis of an *IDH2* R172K heterozygous patient sample. A) Four wild type peaks correspond to *IDH2*-R140Q/L (blue), *IDH2*-R140W (black), *IDH2*-R172K/M (blue), *IDH2*-R172W (green), respectively. B) The green peak next to the third peak (second blue) indicates a heterozygous R172K mutation.

In our study, mutation results of minisequencing analysis perfectly overlapped with Sanger sequencing, whereas approximately 1% of the samples tested negative with Sanger sequencing were found to be positive with minisequencing. Immunohistochemistry (IHC) is also a powerful technique used for the diagnosis of the diseases, such as cancers. We have also performed some preliminary experiments on samples that were found to be IDH negative by IHC and were able to detect *IDH* mutations by minisequencing as well.

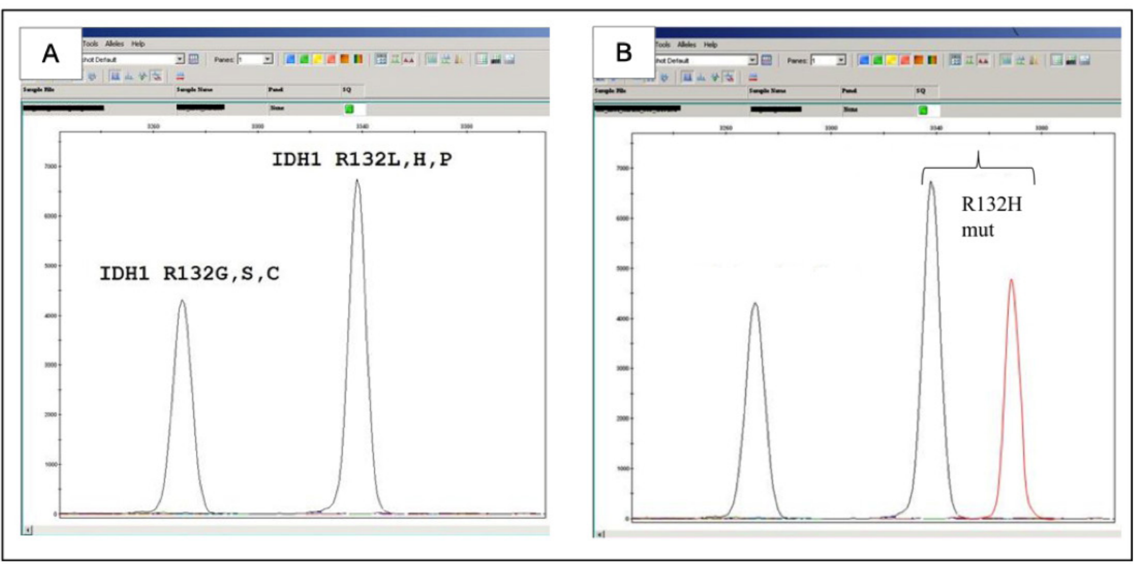


Figure 2: Minisequencing analysis of an *IDH1* R132H heterozygous patient sample. A) The two peaks correspond to wild type *IDH1*-R132G/S/C and *IDH1*-R132L/H/P, respectively. B) The red peak next to the second peak points to the heterozygous R132H mutation.

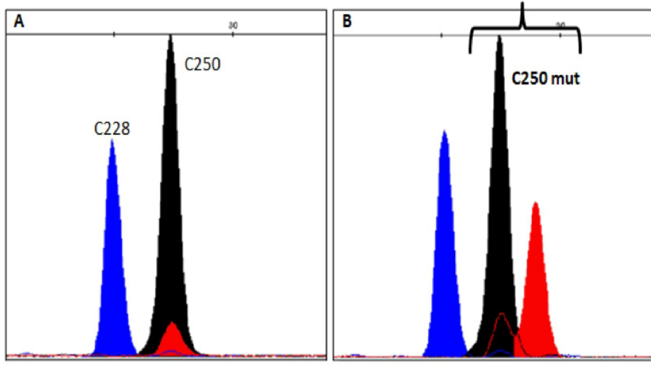


Figure 4: Minisequencing analysis of a *TERT* promoter C250T heterozygous patient sample. A) The blue and black peaks correspond to wild type *TERT* promoter C228 and C250, respectively. B) The red peak next to the black peak points to the heterozygous C250T mutation.

Table 3. Properties of detected mutations and peaks in minisequencing analysis

Detection primer	Nucleotide change	Wild type peak color	Mutant peak color
IDH1-R132G/S/C	R132G (C>G)	Black	Blue
IDH1-R132G/S/C	R132S (C>A)	Black	Green
IDH1-R132G/S/C	R132C (C>T)	Black	Red
IDH1-R132L/H/P	R132L (G>T)	Black	Green
IDH1-R132L/H/P	R132H (G>A)	Black	Red
IDH1-R132L/H/P	R132P (G>C)	Black	Blue
IDH2-R140Q/L	R140Q (G>A)	Blue	Green
IDH2-R140Q/L	R140L (G>T)	Blue	Red
IDH2-R140W	R140W (C>T)	Black	Red
IDH2-R172K/M	R172K (G>A)	Blue	Green
IDH2-R172K/M	R172M (G>T)	Blue	Red
IDH2-R172W	R172W (A>T)	Green	Red
hTERT-C228T	C>T	Green	Green
hTERT-C250T	C>T	Red	Red

Discussion

Molecular markers, which are the genetic signatures of alterations in gene sequences, expression levels and protein structures or functions, are very important in carcinogenesis. Their detection in different types of cancer is reported to be helpful for diagnosis, detection of early development, and aiding in treatment (2). With the advances in molecular biology, many techniques evolved for the detection of molecular markers. The golden standard, Sanger sequencing, was developed by Frederick Sanger and colleagues in 1977, as a chain-termination method based on the selective incorporation of ddNTPs (15, 16). In this method, minute amounts of ddNTPs are added to the dNTP containing reactions, leading to random termination of polymerase-mediated elongation resulting in a cocktail of extension products. However, there are still drawbacks of this method as the limit of detection and heterogeneity testing.

Testing in heterogenous tumors is very challenging. For more sensitive results, it is better to use higher percent tumor samples, tumor sorting or single-cell sequencing; however, it is not possible for every patient and/or cancer type. The development of next generation technologies in the last decade targeted at solving these problems using very high coverages; however, they are very expensive. Taking these factors into consideration, minisequencing is more favorable, being a simple, inexpensive and more sensitive method that can be used for the multiplex detection of cancer biomarkers.

Due to the fact that glioma tumors are very heterogenous and the sensitivity of Sanger sequencing is approximately 15-20% (9), difficulties were encountered in the analysis of molecular markers, especially in low percent tumor samples. Therefore, we have optimized minisequencing protocols and used multiplex primers for *IDH1* R132, *IDH2* R140/R172 and *TERT* promoter C228 and C250 mutations.

Preliminary experiments were performed at different annealing temperatures and PCR conditions to get clear amplifications. As minisequencing is a primer-driven reaction, clear PCR amplifications and post-PCR purification are essential to avoid background noise. Some problems were encountered especially in the multiplexing of reactions, for example, a longer detection primer for *TERT* promoter C250T mutation was designed to better distinguish the two mutations in the heterozygous samples (Table 2). After the optimizations, the studied mutations were successfully identified by minisequencing analysis.

Being a fluorescence-based DNA mutation analysis protocol, minisequencing is a sensitive and reliable method, which is easily applicable especially for the detection of low amount samples (17). Accurate analysis and data interpretation may easily be performed with the aid of automated capillary electrophoresis and computer assisted visualization of mutations. One of the main benefits is that with the use of labelled ddNTPs, there is no need for labelled detection primers, making the procedure inexpensive and easily applied. Multiplex analysis may be achieved by only extending the detection primers with the addition of nucleotide tails, which leads to short turnaround times in routine clinical testing.

In conclusion, for more accuracy, it is better to evaluate the status of molecular markers taking the result of various techniques into consideration, like immunohistochemistry, Sanger sequencing and minisequencing. Primer extension is a promising principle for mutation detection and genotyping. Our study is very important for the evaluation of the reliability of minisequencing.

Acknowledgements: Minisequencing protocol has been optimized and used in the projects (grant number 112-S-149 and 214-S-097) supported by TÜBITAK (Scientific and Technological Research Council of Turkey).

REFERENCES

1. Chakravarthi BV, Nepal S, Varambally S. Genomic and Epigenomic Alterations in Cancer. Am J Pathol 2016;186(7):1724-35.
2. Nair M, Sandhu SS, Sharma AK. Cancer molecular markers: A guide to cancer detection and management. Semin Cancer Biol 2018;52(Pt 1):39-55.
3. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer- associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462(7274):739-44.
4. Xu W, Yang H, Liu Y, Yang Y, Wang P, Kim SH, et al. Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of alpha-ketoglutarate-dependent dioxygenases. Cancer Cell 2011;19(1):17- 30.
5. Waitkus MS, Diplas BH, Yan H. Biological Role and Therapeutic Potential of IDH Mutations in Cancer. Cancer Cell 2018;34(2):186-195.
6. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100(1):57-70.
7. Vinagre J, Almeida A, Pópulo H, Batista R, Lyra J, Pinto V, et al. Frequency of TERT promoter mutations in human cancers. Nat Commun 2013;4:2185.
8. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. Proc Natl Acad Sci USA 2013;110(15):6021-6.
9. Tsiatis AC, Norris-Kirby A, Rich RG, Hafez MJ, Gocke CD, Eshleman JR, et al. Comparison of Sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations. J Mol Diagn 2010;12(4):425–432.
10. Syvänen AC, Aalto-Setälä K, Harju L, Kontula K, Söderlund H. A primer-guided nucleotide incorporation assay in the genotyping of apolipoprotein E. Genomics 1990;8(4):684-92.
11. Syvänen AC. From gels to chips: "minisequencing" primer extension for analysis of point mutations and single nucleotide polymorphisms. Hum Mutat 1999;13(1):1-10.
12. Pastinen T, Kurg A, Metspalu A, Peltonen L, Syvänen AC. Minisequencing: a specific tool for DNA analysis and diagnostics on oligonucleotide arrays. Genome Res 1997;7(6):606-14.
13. Carvalho CMB, Pena SDJ. Optimization of a multiplex minisequencing protocol for population studies and medical genetics. Genet Mol Res 2005;4 (2):115-125.
14. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol 2008;116(6):597-602.
15. Sanger F, Coulson AR. A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. J Mol Biol 1975;94(3):441-8.
16. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci USA 1977;74(12): 5463–5467.
17. Fiorentino F, Magli MC, Podini D, Ferraretti AP, Nuccitelli A, Vitale N, et al. The minisequencing method: an alternative strategy for preimplantation genetic diagnosis of single gene disorders. Mol Hum Reprod 2003;9(7):399-410.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 553-557
https://doi.org/10.31067/acusaglik.864377

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Biochemistry and Molecular Biology / Biyokimya ve Moleküler Biyoloji

Transcriptomics Analysis of Nrf2 Regulators in Cancer Resistant and Long-Lived Naked Mole-Rats

Perinur Bozaykut Eker[1]

[1]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Fen Edebiyat Fakültesi, Moleküler Biyoloji ve Genetik Anabilim Dalı, İstanbul, Türkiye

Perinur BOZAYKUT EKER, Dr. Öğr. Üyesi

Correspondence: Perinur Bozaykut Eker
Acıbadem Mehmet Ali Aydınlar Üniversitesi, Fen Edebiyat Fakültesi, Moleküler Biyoloji ve Genetik Anabilim Dalı, İstanbul, Türkiye
Phone: +905558232919
E-mail: perinur.eker@acibadem.edu.tr

Received : 19 January 2021
Accepted : 25 June 2021

ABSTRACT

Purpose: Naked mole-rats (NMR, Heterocephalus glaber) have extreme resistance to cancer although they are known as the longest-living rodent with their 30-year maximum lifespan. Therefore, NMRs have rapidly emerged as a natural model for biomedical research. Studies have shown that NMRs can better tolerate stress due to mechanisms, such as upregulation of the Nrf2 pathway. Another mechanism proposed to contribute to their protection from stress involves stem cells. Therefore, in this study, we aimed to identify the regulation of Nrf2 signaling in NMR fibroblasts and induced pluripotent stem cells (iPSCs).

Methods: The transcriptomics data of NMR and laboratory mice (Mus musculus) were used in the study. Particularly, the genes that are accepted as Nrf2 activators (Dpp3, Sqstm1, Palb2, Amer1, Mapk14, Trp53) and inhibitors (Keap1, Siah1, Btrc) were comparatively analyzed in fibroblasts and iPSCs of both species.

Results: Our data demonstrated differentially expressed gene expressions between different cell types. Among target Nrf2 activators, Palb2 RNA expression was found to be increased significantly ($p<0.0001$) in NMR fibroblasts when compared to mouse fibroblasts. In addition, the expression of Palb2 was even more increased in NMR iPSCs when compared to NMR fibroblasts ($p<0.0001$).

Conclusion: It was shown, for the first time, Palb2 could be partially responsible for the activation of Nrf2 pathway. These results contribute to literature on the stress resistance of the NMRs and its relationship with their superior features of aging and cancer.

Keywords: Transcriptomics, stress resistance, naked mole-rat, Nrf2 signaling, aging, cancer

Kansere ve yaşlanmaya karşı üstün dirençli farelerde Nrf2 yolağını düzenleyen faktörlerin transkriptomik düzeyde analizi

ÖZET

Amaç: Çıplak Kör Fareler (ÇKF), 30 yılı aşkın sıra dışı uzun yaşam sürelerine sahip olmaları ve bu uzun yaşamları boyunca kanser gelişimi göstermemeleri ile biyomedikal araştırmalarda kullanılmaktadır. Yapılan çalışmalar, ÇKF'lerin üstün bir stres direncine sahip olduğunu ve temel bir oksidatif stres mekanizması olan Nükleer faktör-eritroit 2 ilişkili faktör (Nrf2) sinyal yolağının önemli bir rolü olduğunu göstermektedir. ÇKF'leri stresten koruyan başka bir mekanizmanın ise sağlık alanında sıklıkla kullanılan kök hücreler olduğu düşünülmektedir. Bu sebeplerden dolayı yapılan çalışmanın amacı, kör farelerin fibroblast ve indüklenmiş pluripotent kök hücrelerinde Nrf2 ekspresyonunu düzenleyen faktörlerin tayin edilmesidir.

Yöntem: ÇKF'ler ve laboratuvar farelerinin (Mus musculus) RNA sekanslama metodu ile elde edilen transkriptom verileri kıyaslamalı olarak analiz edildi. Bu 2 türe ait fibroblast ve indüklenmiş pluripotent kök hücrelerine ait veriler spesifik olarak Nrf2 aktivatörleri (Dpp3, Sqstm1, Palb2, Amer1, Mapk14, Trp53) ve inhibitorleri (Keap1, Siah1, Btrc) olarak kabul edilen genler açısından incelendi.

Bulgular: Elde edilen bulgular, ÇFK hücrelerinde Nrf2 aktivatör ve inhibitör adayları arasındaki RNA ekspresyonları değişimlerini gösterdi. Fare fibroblast hücrelerine kıyaslandığında, ÇKF fibroblast hücrelerinde Nrf2 aktivatörü olarak kabul edilen Palb2 RNA ekspresyonunda önemli düzeyde artış ($p<0.0001$) olduğu ve ÇKF iPSC hücrelerinde Palb2 ekspresyonunun daha da fazla arttığı ($p<0.0001$) görüldü.

Sonuç: Elde edilen bulgular, ÇKF'lerde Nrf2 yolağının aktivasyonunda Palb2'nin rolü olabileceğini göstermektedir. Bu veriler, yaşlanma ve kansere karşı sıra dışı özelliği olan bu türlerin stres direnci ile ilgili mekanizmalarının aydınlatılmasına katkı sağlamaktadır.

Anahtar Kelimeler: Transkriptomiks, çıplak kör fare, Nrf2, yaşlanma, kanser

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Naked mole-rats (NMR, *Heterocephalus glaber*), the longest-lived rodent known, have rapidly emerged as a natural model of aging based upon its more than 30-year maximum lifespan and positive healthspan. NMR lives 8 times longer than similar-sized mouse and sustains good health for most of its life, which would be equivalent to 80-year-old humans exhibiting a 30-year-old 'biological age'. NMRs demonstrate negligible senescence, no age-related increase in mortality, and high fecundity until death (1). Most importantly, NMRs do not exhibit age-related cancer pathologies different from mice. This information points the importance of molecular mechanisms related to the superior properties of NMRs (2).

Several studies have already revealed molecular mechanisms of NMRs. As such, NMRs exhibit minimal or no age-related differences in biochemical processes and protein homeostasis, in contrast to laboratory mice (*Mus musculus*) (3). A study, which was conducted on NMR genome and transcriptome sequences, has shown that there are significant differences between gene expressions associated with oxidative stress (4). This study revealed that the activity of peroxiredoxins and glutathione peroxidase 1 (GPX 1) which are closely related to oxidative stress are lower in NMRs. Given the fact that NMRs have superior resistance to aging and cancer, the low expression levels of these antioxidant enzymes are surprising since oxidative stress has significant role in the development of cancer, neurodegenerative and cardiovascular diseases (5).

It is considered that different proteins and cellular defense mechanisms play a role under these properties (6). Of these, it has been suggested that the activation of the nuclear factor-erythrocyte 2 related factor (Nrf2) antioxidant pathway is effective in the cellular defense mechanism of NMRs. When activated, Nrf2 translocates into the nucleus and increases the transcription of antioxidant proteins, subunits of proteasome, and autophagy-related genes. As a result, with the Nrf2 signaling pathway activation, misfolding and aggregation of proteins due to oxidative stress is prevented (6-8). Besides, the Nrf2 signaling pathway has also been associated with various human diseases such as cancer (9), atherosclerosis (10), and neurodegeneration (11). A study demonstrated that gene expressions of Nrf2 and its downstream antioxidant enzymes, were higher in NMR fibroblasts when compared to mouse fibroblasts under normal stress conditions (1). Previous studies have also revealed that the Nrf2 pathway may be responsible for longevity and stress resistance in NMRs; however, how Nrf2 pathway is regulated in NMRs is not well-known.

Induced pluripotent stem cells (İPSCs) are promising biological materials, particularly for regenerative medicine (12), and it is proposed that the stem cell characteristics could contribute to the superior biology of NMRs (2, 13). Regarding this information, the aim of this study is to examine the molecular mechanisms underlying the stress resistance of NMR at the transcriptome level in İPSCs, in addition to fibroblasts. Therefore, it is aimed to determine the regulators of Nrf2 pathway in NMRs, as they show a superior stress resistance throughout their lives in addition to having a longer lifespan and cancer-resistance.

Method

RNA Sequencing and analysis of raw data

The RNA sequencing analysis of fibroblasts and İPSCs of laboratory mice (n=4) and NMRs (n=6) were performed in the previous study (2) and raw data (*SRP116326*) were reanalyzed in terms of Nrf2 signaling pathway activators and inhibitors for this study. Briefly, embryonic fibroblast cells and İPSC were obtained as follows; Mouse embryos were collected from the fetus on day 13 and rinsed with PBS and lysed with 0.25% trypsin-EDTA solution. Trypsin was inactivated by DMEM (Dulbecco's Modified Eagle's medium), containing 20% FBS (Fetal bovine serum). The obtained mouse embryonic fibroblast cells were cultured in DMEM containing 10% FBS, penicillin/streptomycin (10,000 U/ml), 1 × non-essential amino acid, 0.1 mM β-mercaptoethanol at 37°C and 5% CO2. Following the isolation of NMR embryonic cells in the same way, they were cultured in hypoxic (3% O2) and hypothermic (32° C) conditions containing 5% CO2, which meet the optimal oxygen and temperature conditions for NMR cells (13). Cells were, then, reprogrammed into İPSCs as follows; Fibroblast cells were transduced with lentiviruses carrying polycistronic mouse OSKM and FUW-M2rtTA vectors. Viral supernatants were added to cell media two times for 24 hours. After 3 days of incubation, they were seeded on mitomycin C inactivated cells and N2B27 + 2i reprogramming medium containing 2 µg/ml doxycycline was added to the cells. The culture media was renewed with 24-hour intervals. Embryonic stem cell-like colonies were incubated in N2B27 + 3i medium. Cells were cultured for 6 days and doxycycline was withdrawn (13).

The protocol for RNA sequencing analysis of obtained cells is as follows; Total RNA was isolated using RNA Mini kit (Qiagen, Germany). The amount and purity of RNA were quantified using a Qubit fluorometer (Thermo-Fisher Scientific, America). The library quantification was sequenced in 2 directions using TruSeq Sample Prep kit v2

(Illumina, USA) with 101 base-pairs in all directions (2). For the analysis of RNA expression Mus musculus (GRCm38) and Heterocephalus glaber (hetGla2) reference genomes were used from the NCBI database (https://www.ncbi.nlm.nih.gov/genome/). For differential gene expression analysis, the data were first analyzed with the FastQC quality control tool, and the reference genomes of the raw data were mapped to the transcriptome, which were generated using the software of STAR-ultra-fast RNA-Seq aligner. The files, which had been obtained after mapping, were quantified via the software of Salmon, and converted into transcript numbers that were expressed in each sample. Genes, that are accepted as activators and inhibitors of Nrf2, were retrieved from these data. Differential gene expression analysis was performed through the DESeq2 library running on the R analytics platform, and differentially expressed genes that were statistically significant among the compared groups were identified with their upregulated/downregulated status and their p-values.

Statistical analysis

Statistical analysis between groups was conducted using the software of GraphPad Prism 7.0. One-way analysis of variance (ANOVA) and Tukey's test were used to determine statistical difference and p values. In the same species analysis, the groups were compared as mouse fibroblast vs mouse iPSC and NMR fibroblast vs NMR iPSC. In across the species analysis, the groups were compared as mouse fibroblast vs NMR fibroblast and mouse iPSC vs NMR iPSC. The results were considered statistically significant at $p<0.05$.

Results

In this study, RNA expressions of Nrf2 pathway regulators were investigated in fibroblasts and İPSCs in comparison to mice. Studies on other species have identified Dipeptidyl Peptidase 3 (Dpp3), Sequestosome 1 (SQSTM1), Partner and Localizer of BRCA2 (Palb2), APC Membrane Recruitment Protein 1 (Amer1 or WTX), Mitogen-Activated Protein Kinase 14 (Mapk14) and Tumor Protein P53 (Trp53 or p53) as Nrf2 activators (14-17). On the other hand, Kelch-like ECH-Associated Protein 1 (Keap1), E3 Ubiquitin Protein Ligase 1 (Siah1), and Beta-Transducin Repeat Containing E3 Ubiquitin Protein Ligase (BTRC) have been identified as Nrf2 inhibitors (15, 18). However, it is not known which genes are responsible for Nrf2 pathway activation in NMRs and it was investigated at the transcriptome level in the present study.

Our RNA expression findings on Nrf2 activators demonstrated that Dpp3 was significantly increased in mouse İPSCs compared to mouse fibroblasts (Fig. 1a). No significant change was found between groups in Amer1 RNA expressions (Fig. 1b). However, it was observed that Mapk14 RNA expression decreased in NMR fibroblasts compared to mouse fibroblasts (Fig. 1c).

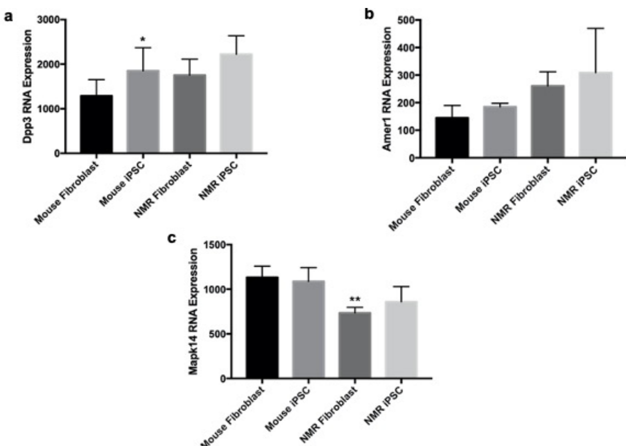


Fig. 1. RNA expression levels of various Nrf2 activators obtained from RNA-Sequencing analysis. a) Dpp3 RNA expression, *$p<0.05$ vs mouse fibroblast. b) Amer1 RNA expression, no significant change. c) Mapk14 RNA expression, **$p<0.005$ vs mouse fibroblast.

Palb2 RNA expression was significantly higher in iPSCs compared to fibroblasts of both species, while the expression was found to be higher in NMR fibroblasts compared to mouse fibroblasts (Fig. 2a). Palb2 RNA expression in NMR iPSCs was also significantly increased when compared to mouse iPSCs (Fig. 2a) as well. On the other hand, it was determined that Sqstm1 RNA expressions were decreased in iPSCs compared to fibroblasts in both species (Fig. 2b). Besides, there was no significant change in Trp53 RNA expressions (Fig. 2c).

The results on Nrf2 inhibitors showed that the expression of Btrc was increased in NMR fibroblasts compared to mouse fibroblasts (Fig. 3a), and Siah1 expression was expressed at high levels in NMR iPSCs (Fig. 3c). However, no significant change was observed in Keap1 RNA expressions (Fig. 3b).

These results indicate that RNA expression of Palb2, which is known as an Nrf2 activator, could be effective on the activation of Nrf2 pathway in NMRs, as it increases significantly in both NMR fibroblast and NMR iPSCs when compared to mice.

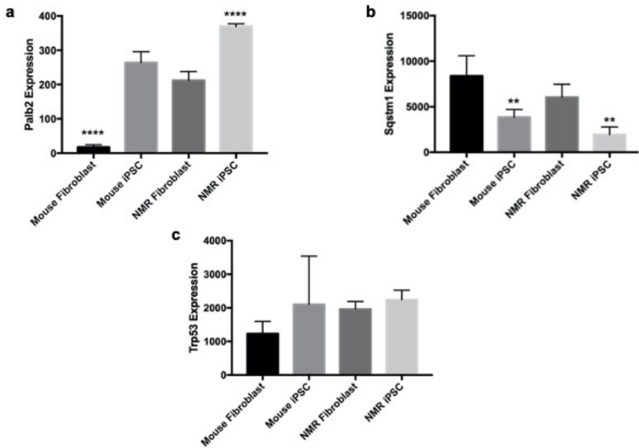


Fig. 2. RNA expression levels of various Nrf2 activators obtained from RNA-Sequencing analysis. a) Palb2 RNA expression, ****$p<0.0001$ mouse fibroblast vs mouse iPSC, mouse fibroblast vs NMR fibroblast, NMR fibroblast vs NMR iPSC and mouse iPSC vs NMR iPSC. b) Sqstm1 RNA expression, **$p<0.005$ mouse fibroblast vs mouse iPSC, NMR fibroblast vs NMR iPSC. c) Trp53 RNA expression, no significant change.

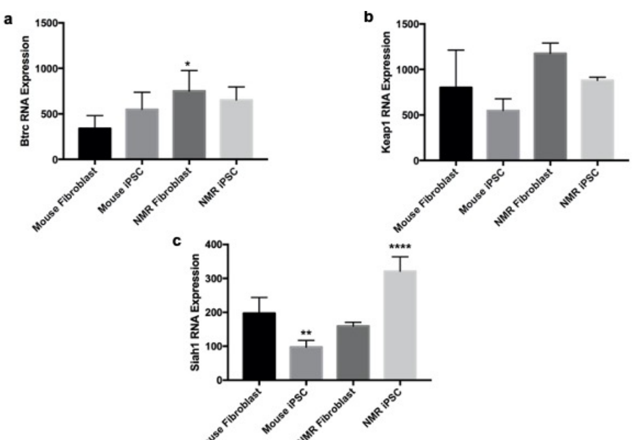


Fig. 3. RNA expression levels of Nrf2 inhibitors obtained from RNA-Sequencing analysis. a) Btrc RNA expression, *$p<0.05$ vs mouse fibroblast. b) Keap1 RNA expression, no significant change. c) Siah1 RNA expression, ****$p<0.0001$ vs NMR fibroblast and mouse iPSC, **$p<0.005$ vs mouse fibroblast.

Discussion

Oxidative stress mainly results from an imbalance between reactive oxygen species and antioxidant defense mechanisms of the cell. Oxidative stress has been closely associated with aging and aging-associated diseases, therefore, resistance to oxidative stress is indicated to lead extension of healthspan and lifespan (1). NMRs are frequently used in biomedical research as their metabolic rates are very slow and their protein structures are not affected by oxidative stress throughout aging process (6). It is considered that these superior characteristics might be associated with various molecular mechanisms and that, in particular, activation of the Nrf2 antioxidant pathway is proposed to be responsible for their stress resistance (6).

Nrf2 is a transcription factor, which is expressed in all tissues and activated under stress conditions (21). Under normal conditions, Nrf2 is in the cytosol and in its inactive form. However, under stress conditions, it translocates to the nucleus, activating the transcription of numerous crucial genes (22). These molecules include redox regulators such as glutathione-S-transferase (GST), NAD (P) H: quinone oxidoreductase (NQO1), molecular chaperones, and proteasome subunits (1, 6). A previous study has shown that Nrf2 expression is three times higher in NMR fibroblasts compared to mouse fibroblasts indicating the essential role of Nrf2 pathway for the extraordinary resistance of NMRs against aging-associated cancer, cardiovascular diseases, and neurodegenerative diseases (21). However, detailed analysis of the factors regulating Nrf2 expression in NMR's fibroblasts and iPSCs has not been performed yet. Hence, activators and inhibitors associated with the Nrf2 antioxidant pathway were investigated at the level of RNA expression in the present study. For this aim, Dpp3, Sqstm1, Palb2, Amer1, Mapk14, Trp53 as Nrf2 activators and Keap1, Siah1, Btrc proteins as Nrf2 inhibitors, were analyzed in NMR cells. To elucidate Nrf2 pathway activation in NMRs, the obtained results were examined in terms of the increase in RNA expression level of activator genes or the decrease in RNA expression level of inhibitor genes.

The studies that have been performed so far show that the NMR has been mainly investigated by comparing with mice (21-23), thus, in our study, NMR RNA expressions were analyzed comparatively with mice. Our results demonstrated that among Nrf2 activators, Palb2 was increased significantly in NMR fibroblasts and iPSCs compared to mice. The increase of Palb2 in both fibroblasts and iPSCs in NMRs indicates that Palb2 could play a role in the activation of Nrf2 pathway in NMRs. Besides, Palb2 is a protein that binds to BRCA genes and regulates the functions of BRCA factors which are closely associated with breast cancer. Studies have shown that the Palb2 mutation is mainly responsible for genetically derived breast cancer (24). Palb2 is known to bind Nrf2 inhibitors so the possible role of Palb2 in the Nrf2 pathway could be indirect activation of Nrf2 that results in the transcription of antioxidant genes (25).

Nrf2 can also be activated by phosphorylation with kinase proteins such as Mapk14 (16). However, our findings show that Mapk14 RNA expression decreases in NMR fibroblasts. On the other hand, as this decrease is not as high as the increase observed in Palb2, it is considered that its impact on Nrf2 pathway activation might be minor. Moreover, it is hypothesized that the Nrf2 pathway is regulated by the combinational effect of various regulator proteins rather than being under the control of a single protein.

Based on the findings gained from the study; it is observed that the RNA expressions of activators and inhibitors associated with the Nrf2 pathway are not expressed at the same levels between different species and cells. Although Palb2 expression were analyzed for the first time in NMR fibroblasts and iPSCs, our findings indicate that Palb2 expression could have a role in the regulation of Nrf2 activation consistent within the previous studies. However, further studies are required to clarify the direct effect of Palb2 in Nrf2-signaling for the extra-ordinary properties of NMRs.

Acknowledgments

This study is supported by Scientific and Technological Council of TURKEY (1059B191501668). I would like to thank Prof. Vadim Gladyshev and Dr. Sang Goo Lee for their support in this study.

References

1. Lewis KT, Mele J, Hornsby PJ, Buffenstein R. Stress Resistance in the Naked Mole-Rat:The Bare Essentials – A Mini-Review. Gerontology 2012; 58: 453-462.
2. Lee SG, Mikhalchenko AE, Yim SH, et al. Naked mole rat induced pluripotent stem cells and their contribution to interspecific chimera. Stem Cell Rep 2017; 9: 1706-1720.
3. Buffenstein R. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. J Comp Physiol B 2008; 178: 439-445.
4. Fang X, Wang J, Gladyshev VN et al. Adaptations to a Subterranean Environment and Longevity Revealed by the Analysis of Mole Rat Genomes. Cell Reports 2014; 8: 1354-1364.
5. Andziak B, O'Connor TP, Qi W, et al. High oxidative damage levels in the longest-living rodent, the naked mole-rat. Aging Cell 2006; 5: 463-471.
6. Rodriguez KA, Wywial E, Perez VI, et al. Walking the Oxidative Stress Tightrope: A Perspective from the Naked Mole-Rat, the Longest-Living Rodent. Curr Pharm Des 2011; 17(22): 2290-2307.
7. Waal EM, Liang H, Pierce A, et al. Elevated protein carbonylation and oxidative stress do not affect protein structure and function in the long- living naked mole-rat: a proteomic approach. Biochemical and Biophysical Research Communications 2013; 4: 815–819.
8. Lewis KN, Mele J, Hayes JD, et al. Nrf2, a guardian of healthspan and gatekeeper of species longevity. Integrative & Comparative Biology 2010; 5: 829–843.
9. Hayes JD, McMahon M. NRF2 and KEAP1 mutations: permanent activation of an adaptive response in cancer. Trends Biochem Sci 2009; 34: 176–188.
10. Bozaykut P, Karademir B, Yazgan B, et al. Effects of vitamin E on peroxisome proliferator-activated receptor γ and nuclear factorerythroid 2-related factor 2 in hypercholesterolemia induced atherosclerosis. Free Radical Biology&Medicine 2014; 70: 174–181.
11. Kraft AD, Johnson DA, Johnson JA. Nuclear factor E2-related factor 2-dependent antioxidant response element activation by tert – butylhydroquinone and sulforaphane occurring preferentially in astrocytes conditions neurons against oxidative insult. J Neurosci 2004; 24: 1101–1112.
12. Lemey C, Milhavet O, Lemaitre JM. iPSCs as a major opportunity to understand and cure age-related diseases. Biogerontology 2015; 16: 399-410.
13. Lee SG, Mikhalchenko AE, Yim SH, et al. A naked mole rat iPSC line expressing drug-inducible mouse pluripotency factors developed from embryonic fibroblasts. Stem Cell Reports, 2018; 197-200.
14. Komatsu M, Kurokawa H, Waguri S, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat. Cell Biol 2010; 12, 213–223.
15. Camp ND, James RG, Dawson DW, et al. Wilms tumor gene on X chromosome (WTX) inhibits degradation of NRF2 protein through competitive binding to KEAP1 protein. J Biol Chem 2012; 24;287(9):6539-50.
16. Mitra A, Ray A, Datta R, et al. "Cardioprotective role of P38 MAPK during myocardial infarction via parallel activation of α-crystallin B and Nrf2". Journal of Cellular Physiology, 2014; 229 (9): 1272–82.
17. Tonelli C, Chio IIC, Tuveson DA. Transcriptional Regulation by Nrf2. Antioxid. Redox Signal 2018;29:1727–1745.
18. Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends in biochemical sciences 2014; 39 (4): 99-218.
19. Harper JM, Salmon AB, Leiser SF, et al. Skin-derived fibroblasts from long- lived species are resistant to some, but not all, lethal stresses and to the mitochondrial inhibitor rotenone. Aging Cell 2007; 6: 1–13.
20. Salmon AB, Akha AAS, Buffenstein R, et al. Fibroblasts from naked mole-rats are resistant to multiple forms of cell injury, but sensitive to peroxide, ultraviolet light, and endoplasmic reticulum stress. J Gerontol A Biol Sci Med Sci 2008; 63: 232-241.
21. Lewis KN, Wason E, Edrey YH, et al. Regulation of Nrf2 signaling and longevity in naturally longed-lived rodents. Proc Natl Acad Sci U S A 2015; (12): 3722–3727.
22. Rodriguez KA, Edrey YH, Osmulski P, et al. Altered composition of liver proteasome assemblies contributes to enhanced proteasome activity in the exceptionally long-lived naked mole-rat. PLoS ONE 2012; 7(5):e3589.
23. Bozaykut P. Cellular stress responses of long-lived and cancer-resistant naked mole-rats. Turkish Journal of Biochemistry 2021; 46:2. DOI: 10.1515/tjb-2020-0480.
24. Rahman N, Seal S, Thompson D, et al. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. Nat. Genet 2007; 39: 165– 167.
25. Ma J, Cai H, Wu T, et al. PALB2 interacts with KEAP1 to promote NRF2 nuclear accumulation and function. Mol. Cell. Biol 2012; 32:1506–1517.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 558-563
https://doi.org/10.31067/acusaglik.885199

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Radiology / Radyoloji

Risk Factors Associated with Dysfunction of Permanent Tunneled Cuffed Hemodialysis Catheters; Single Center Experience

Işıl Yıldız[1]

[1]Acibadem University Atakent Hospital Department of Radiology, Istanbul,Turkey

Işıl YILDIZ, Dr. Öğr. Üyesi

ABSTRACT

Purpose: Permanent tunneled cuffed catheters are frequently preferred for hemodialysis in patients with chronic renal failure (CRF), but the factors associated with the dysfunction of these catheters are not well known. Our goal is to investigate these risk factors.

Materials and Methods: All cases with a diagnosis of CRF and a permanent tunneled cuffed catheter inserted into the central vein for the first time in our radiology clinic between 2014 and 2019 and who developed catheter dysfunction were included in the study. Demographic and clinical data of the cases were obtained from file records. The relationship between the causes of catheter dysfunction and the presence of diabetes and hypertension was investigated.

Results: Of the total 123 cases, 78 (63.4%) were male, 45 (36.6%) were female, the median age was 55 (28-78). Twenty-nine (23.6%) of the cases had thrombosis, 72 (58.5%) had venous stenosis and 22 (17.9%) had catheter dysfunction due to fibrin sheath. Dysfunction groups were compared with each other in terms of age, gender, duration of operation of the catheter, CRF etiology, comorbid diseases, the vein where the catheter was placed and the use of anticoagulants. The most important cause of catheter dysfunction in the early period was thrombosis ($p = 0.003$). When the causes of dysfunction were examined, the most common causes of dysfunction were venous stenosis in patients with hypertension, thrombosis in patients with diabetes as a concomitant disease without diabetes in the etiology of CRF, and thrombosis in patients with diabetes in CRF etiology ($p < 0.001$). In addition, it was found that catheter dysfunction due to thrombosis developed less in patients using anticoagulants ($p < 0.001$). There was no statistically significant difference between the groups in terms of other parameters ($p > 0.05$).

Conclusion: The use of low-dose anticoagulants plays a protective role against thrombosis. The use of low-dose anticoagulants in patients without contraindications, especially in diabetic patients, may reduce especially early catheter dysfunction.

Keywords: Fibrin, hemodialysis, permanent tunneled cuffed hemodialysis catheter, stenosis, thrombosis

Kalıcı Tünelli Hemodiyaliz Kateter Disfonksiyonu ile İlişkili Risk Faktörleri; Tek Merkez Deneyimi

ÖZET

Amaç: Kronik böbrek yetmezliği (KBY) olan hastalarda hemodiyaliz için kalıcı tünelli kaflı kateterler sık tercih edilmektedir, ancak bu kateterlerin disfonksiyonu ile ilişkili risk faktörleri yeterince bilinmemektedir. Amacımız bu risk faktörlerini araştırmak.

Gereç ve Yöntem: Çalışmaya, KBY tanısı ile 2014-2019 yılları arasında hastanemiz Radyoloji kliniğinde, santral vene ilk defa kalıcı tünelli kateter yerleştirilmiş ve izlemde kateter disfonksiyonu gelişmiş tüm hastalar dahil edildi. Hastaların demografik ve klinik verileri dosya kayıtlarından elde edildi. Kateter disfonksiyon nedenleri ile diyabet ve hipertansiyon varlığı arasındaki ilişki karşılaştırıldı.

Bulgular: Toplam 123 hastanın 63'ü (%63,4) erkek ve medyan yaş 55 (28-78) yıl saptandı. Hastaların 29'unda (%23,6) tromboz, 72'sinde (%58,5) venöz stenoz ve 22'sinde (%17,9) fibrin kılıfına bağlı kateter disfonksiyonu gelişti. Disfonksiyon grupları birbiriyle yaş, cinsiyet, kateterin çalışma süresi, KBY etiyolojisi, komorbid hastalıklar, kateterin yerleştirildiği ven ve antikoagülan kullanımı açısından karşılaştırıldı. Tromboz erken döenemde gelişen disfonksiyonun en önemli nedeni idi. Hipertansiyonu olan hastalarda en önemli disfonksiyon nedeninin venöz stenoz, KBY etiyolojisinde diyabeti olanlarda ve KBY'ne eşlik eden diyabeti olanlarda ise en önemli tromboz nedeninin tromboz olduğu görüldü ($p<0,001$). Ayrıca antikoagülan kullanan hastalarda tromboza bağlı kateter disfonksiyonu daha nadir geliştiği saptandı ($p<0,001$). Diğer parametreler açısından gruplar arasında istatistiksel fark saptanmadı ($p>0,05$).

Sonuç: Diyabet ve hipertansiyon kateter disfonksiyonu için risk faktörüyken, düşük doz antikoagülan kullanımı tromboza karşı koruyucu rol oynamaktadır. Tansiyon ve diyabet kontrol altında tutularak, kontrendikasyonu olmayan hastalara düşük doz antikoagülan verilerek kateter disfonksiyonu azaltılabilir.

Anahtar kelimeler: fibrin, kalıcı tünelli hemodiyaliz kateteri, stenoz, tromboz

Correspondence: Işıl Yıldız
Acibadem University Atakent Hospital
Department of Radiology, Istanbul,Turkey
Phone: +905323560244
E-mail: drisilyildiz@gmail.com

Received : 23 February 2021
Accepted : 16 May 2021

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

For patients with chronic renal failure (CRF), arteriovenous fistulas or arteriovenous grafts are preferred for long-term hemodialysis due to the low possibility of infection and high possibilty of long-term use . However, hemodialysis with a permanent tunnel cuffed catheter is recommended for elderly patients who are in the process of arteriovenous fistula and arteriovenous graft maturation, are waiting for renal transplantation, and have high risk associated with diabetes and cardiovascular diseases (1, 2). In addition, permanent tunneled cuffed catheters are preferred if arteriovenous fistula may cause an increase in the symptoms of underlying heart diseases or respiratory failure (3, 4). According to the Kidney Disease Outcomes Quality Initiative, if a temporary catheter is required for more than 3 weeks, if an arteriovenous fistula cannot be opened and life expectancy is short, a permanent tunnel cuffed catheter is recommended (5). Although tunneled cuffed catheters can be placed in many central veins, the internal jugular vein is most frequently preferred (6). Tunneled cuffed hemodialysis catheters have advantages such as easy placement, low damage to the vascular endothelium due to their soft structure, and low cause for intravascular coagulation, but it is known that various problems such as thrombosis, infection, fibrin sheath formation and central venous stenosis develop due to these catheters (2). Numerous studies have reported that the morbidity and mortality of hemodialysis patients that are associated with the central venous route used for hemodialysis, but few studies have reported risk factors associated with permanent tunneled hemodialysis catheter dysfunction. In this study, the relationship between the cause of catheter dysfunction and the presence of CRF, diabetes, and hypertension in CRF patients with a permanent tunneled cuffed hemodialysis catheter was investigated.

Materials and Methods

This study was conducted cross-sectionally and retrospectively. A retrospective analysis of 513 cases with a diagnosis of CRF and in whom a permanent tunneled cuffed hemodialysis catheter was placed in the interventional radiology clinic of our hospital between 2014 and 2019. Cases with catheter dysfunction during follow-up were included in the study. Cases with the same central vein previously catheterized with a permanent or temporary catheter were not included in the study.

Digital records of a total of 123 cases who met the inclusion criteria were examined, some of the patients were contacted by phone and information was obtained. Age, gender, follow-up time, duration of catheter operation, comorbid diseases, CRF etiology, use of anticoagulants unrelated to catheter use and causes of catheter dysfunction were recorded.

The relationship between the causes of catheter dysfunction and possible risk factors for catheter dysfunction was examined.

A hemodialysis catheter was placed in all cases included in the study by the same interventional radiologist. Central veins were evaluated with gray scale and duplex ultrasound before catheterization. After the necessary sterilization was provided, local anesthesia (2% lidocaine) was applied to the procedure area. The jugular vein was catheterized using the modified Seldinger technique. The length of the tunnel that needs to be formed was determined by making necessary measurements for each patient. Following local anesthesia, the catheter tunnel was opened over the pectoral fascia. The tunneled cuffed catheter can be advanced into the central vein through the peel away sheath. The tunneled cuffed catheter was positioned so that its distal tip remained distal to the superior vena cava.

A 14.5 French carbothane permanent tunnel cuffed hemodialysis catheter (Covidien, Mansfield, MA, USA) was used in all cases. A 24 cm long catheter was inserted through the right jugular vein and a 28 cm long catheter was inserted through the left jugular vein.

If the hemodialysis blood pump rate is lower than 300 mL / min, it was considered as catheter dysfunction (7). All of the catheters with dysfunction were evaluated angiographically by injection of contrast media.

SPSS 26.0 and Modeler 18.1 (IBM Corporation, Armonk, New York, United States) programs were used in the analysis of variables. The conformity of univariate data to normal distribution was evaluated by Kolmogorov-Smirnov test and Shapiro-Wilk francia test, while variance homogeneity was evaluated with Levene test. Quantitative variables are mean ± SD in tables. (standard deviation) and Median (Percentile 25% / Percentile 75%), while categorical variables were shown as n (%). Variables were analyzed at a 95% confidence level and a p value of less than 0.05 was considered significant.

Results

Of the total 123 cases, 78 (63.4%) were male, 45 (36.6%) were female, and the median age was 55 (28-78) years. The mean follow-up period was 24.5 ± 5.6 months, and the mean working time of the permanent tunnel cuffed catheter was 16.7 ± 12.0 months. The right jugular vein was used for access in 86 (69.9%) of the cases, and the left jugular vein in 37 (30.1%). During follow-up thrombosis developed in 29 (23.6%) of the cases, central venous stenosis in 72 (58.5%), and catheter dysfunction due to fibrin sheath in 22 (17.9%). Diabetes in 20 (16.3%), hypertension in 12 (9.8%), both diseases in 6 (4.9%), and chronic polycystic kidney disease in 26 (21.1%) patients. Etiology of 59 (48%) patients could not be determined. 35 (28.5%) of the cases had diabetes, 43 (35%) had hypertension, and 38 (30.9%) had both comorbid diseases. The Mann Whitney u Test was tested using Monte Carlo simulation results in the comparison of thrombosis, stenosis, and fibrin sheath groups individually and without group discrimination according to gender and duration of catheter occlusion variables (Table 1).

Table 1. Demographic datas.	
Age (years)*	55 (28-78)
Gender, n (%)	
Male	78 (%63,4)
Female	45 (36,6)
Follow-up period (months)**	24,5±5,6
Patency (months)**	16,7±12,0
CRF Etiology, n(%)	
Diabetes	20 (16,3)
Hypertension	12 (9,8)
Hypertension and diabetes	6 (4,9)
Polycystic kidney disease	26 (21,1)
Unknown	59 (48)
Comorbidities, n (%)	
Diabetes	35 (28,5)
Hypertension	43 (35)
Hypertension and diabetes	38 (30,9)
No comorbidity	7 (5,7)
Access vein n(%)	
Right jugular vein	86 (69,9)
Left jugular vein	37 (30,1)
On anticogulants , n(%)	100 (81,3)
Cause of catheter dysfuction, n(%)	
Thrombosis	29 (23,6)
Stenosis	72 (58,5)
Fibrin sheath	22 (17,9)

* Median (min-max), ** Mean ± Standard deviation, CRF: Chronic renal failure

The median value of the patency of the catheters in diabetic patients was 15 months and 16 months in hypertensive patients. The median value of catheter patency in patients with diabetes and hypertension was 9 months. The median values of patency in patients with only diabetes or hypertension were statistically significantly higher than the median value of catheter patency in patients with both diabetes and hypertension (p = 0.020, p = 0.019, respectively). There was no statistically significant difference between the median values of patency of catheters in diabetic patients (15 months) and the median values of patency of catheters in patients with hypertension (16 months) (p = 0.901). The Kruskal-Wallis H Test was used with Monte Carlo simulation technique results for the comparison of thrombosis, stenosis and fibrin sheath groups according to comorbid diseases and occlusion time variables separately and without group discrimination, and Dunn's Test was used for Post Hoc analyzes (Table 2).

No significant difference was found between the patency of the catheters between men and women (P = 0.062). No statistically significant difference was found between the patency of the permanent cuffed tunnel catheters inserted with the right jugular vein access and the permanent cuffed tunnel catheters inserted with the left jugular vein access (p = 0.234). Pearson Chi-Square test was used to compare thrombosis, stenosis, and fibrin sheath groups according to gender and categorical variables of the catheter placed vein.

Each case group that developed thrombosis, stenosis and catheter dysfunction due to fibrin sheath was compared with the other case groups in terms of age, gender, CRF etiology, comorbid diseases, the vein in which the catheter was placed, and the use of anticoagulants. It was found that catheter dysfunction in the early period mostly developed due to thrombosis (p = 0.003). It was determined that the most important cause of catheter dysfunction was thrombosis in patients with comorbid diabetes, and central vein stenosis was the most important cause of dysfunction in patients with hypertension (p <0.001). It was found that catheter thrombosis developed more frequently in patients whose chronic renal failure etiology is diabetes when compared with both central venous stenosis and fibrin sheath groups (p <0.001). In addition, it was found that catheter dysfunction due to thrombosis was less common in patients using anticoagulants (p <0.001). There was no statistical difference between the groups in terms of other parameters (p> 0.05) (Table 3).

Table 2. Comparison of catheter patency

	Thrombosis		Stenosis		Fibrin sheath		Total	
	n	Median (Q1 / Q3)	n	Median (Q1 / Q3)	n	Median (Q1 / Q3)	n	Median (Q1 / Q3)
Gender								
Female	7	10 (5 / 28)	31	18 (8 / 21)	7	20 (9 / 32)	45	18 (8 / 21)
Male	22	8 (4 / 14)	41	14 (10 / 18)	15	21 (12 / 33)	78	13 (8 / 21)
P value		0.243 [u]		0.394 [u]		0.581 [u]		0.236 [u]
Access Vein								
Right jugular vein	18	8.5 (4 / 15)	51	15 (9 / 19)	17	21 (13 / 32)	86	14.5 (9 / 21)
Left jugular vein	11	8 (5 / 15)	21	16 (9 / 22)	5	20 (12 / 21)	37	12 (8 / 21)
P value		0.992 [u]		0.944 [u]		0.406 [u]		0.550 [u]
Comorbidities								
Diabetes (A)	12	9.5 (7 / 14)	15	18 (12 / 23)	8	22.5 (18.5 / 29)	35	15 (9 / 23)
Hypertension (B)	5	15 (11 / 36)	33	16 (10 / 19)	5	16 (13 / 22)	43	16 (10 / 21)
DM+HT (C)	12	4.5 (3 / 13)	22	11.5 (8 / 18)	4	9.5 (7 / 21.5)	38	9 (6 / 18)
P value		0.062 [kw]		0.234 [kw]		0.421 [kw]		0.026 [kw]
Pairwise comparation	A->B	ns.		ns.		ns.		0.901
	A->C	ns.		ns.		ns.		0.020
	B->C	ns.		ns.		ns.		0.019

[u] Mann Whitney u test (Monte Carlo), [kw] Kruskal Wallis Test (Monte Carlo); Post Hoc Test : Dunn's Test, Q1: Percentile 25, Q3: Percentile 75

Table 3. Relationship of catheter dysfunction with clinical and demographic characteristics.

	Thrombosis, n=29	Stenosis, n=72	Fibrin sheath n=22	p
Gender, n(%)				
Male	22 (75,9)	41 (56,9)	15 (68,2)	0,193
Female	7 (24,1)	31 (43,1)	7 (31,8)	
Age**	54,7±11,6	55,1±11,1	52,4±9,7	0,575
Patency*	8 (5-15)	15 (9-19,5) [a]	20,5 (12-32) [a]	0,003
Comorbidities, n(%)				
Diabetes+ hypertension	12 (41,4)	22 (30,6)	4 (18,2)	<0,001
Hypertension	5 (17,2)	33 (45,8)[a]	5 (22,7)	
Diabetes	12 (41,4) [b]	15 (20,8)	8 (36,4)	
No Comorbidities	0 (0,0)	2 (2,8)	5 (22,7)[ab]	
Etiology of CRF, n(%)				
Others	4 (13,8)	41 (56,9) [a]	14 (63,6) [a]	<0,001
Hypertension	4 (13,8)	7 (9,7)	0 (0,0)	
Diabetes	11 (37,9)[bc]	7 (9,7)	0 (0,0)	
Diabetes+ hypertension	7 (24,1) [b]	1 (1,4)	1 (4,5)	
Polycystic kidney	3 (10,3)	16 (22,2)	7 (31,8)	
Access vein, n(%)				
Right jugular vein	68 (62,1)	51 (70,8)	17 (77,3)	0,519
Left jugular vein	11 (37,9)	21 (29,2)	5 (22,7)	
Anticoagulan , n(%)	7 (24,1)	71 (98,6)[a]	22 (100,0)[a]	<0,001

* Median (min-max), ** Mean ± Standard deviation, CRF: Chronic renal failure, a Significant compared to thrombosis group, b Significant compared to the stenosis group, c Significant compared to the fibrin sheath group.

One-Way Anova (Robust Test: Brown-Forsythe) test, one of the parametric methods, was used to compare thrombosis, stenosis and fibrin sheath groups with each other according to their age, while the Kruskal-Wallis H Test, one of the nonparametric tests, was used with the results of the Monte Carlo simulation technique, and the Post Hoc analysis.

In our study, we found that early catheter dysfunction was associated with the presence of diabetes in the etiology of CRF, and the presence of diabetes and hypertension among comorbid diseases in patients with permanent tunneled cuffed catheters for hemodialysis. The most important cause of catheter dysfunction in the early period was thrombosis and it was found that thrombosis-related catheter dysfunction developed less frequently in patients using low-dose anticoagulants. In the comparison of comorbid disease, CRF etiology, and anticoagulant use according to categorical variables, the Fisher-Freeman-Holton test was tested using the Monte Carlo Simulation technique, and the column ratios for significant variables were compared with each other and expressed according to the Benjamini-Hochberg corrected p value results.

In order to predict the causes of catheter dysfunction, variables that are significant in Table 2 (Anticoagulant use, catheter working time, comorbid diseases and CRF etiology.) were included in the independent model in Neural Network (Multilayer Perceptron) analysis. According to this model, the rate of accurately predicting thrombosis was 86.2%, stenosis 90.3%, fibrin sheath 40.9%, and overall correct prediction rate 80.5%. The significance rates of the variables were determined as 100% anticoagulant use, 61.6% catheter working time, 49.2% comorbid diseases and 40.8% renal disease etiology, respectively.

Discussion

Various risk factors associated with tunneled cuffed catheter dysfunction have been reported in the literature (8). One of these risk factors is related to the central vein where the catheter will be placed through. In many studies, it has been reported that jugular vein catheters remain patent longer than other central veins (9). In the study of Engstrom BI, et al. (10), it was reported that catheters which has access from right jugular vein were patent longer than the left jugular vein catheters. In our study, the catheter was used in all cases with right or left jugular vein access. Unlike the literature, there was no significant difference between the type of catheter dysfunction and the patency. We think that the reason for this is that the follow-up periods in our study were shorter compared to these studies. In the study of Shingarev, et al. (11) it was reported that only 34% of tunnel cuffed catheters has central vein access for the first time worked at the end of the first year Shi M, et al. (12) reported that 82% of the catheters which have central venous access were patent for 1 year and the median patency was 45 months. In another similar study, it was reported that 74.5% of the catheters were patent end of the first (13). In our study, similar to the literature, 56% of the catheters were patent at the end of the first year and the average patency was 16.7 months.

In the study of Shi M ,et al (12), 6.9% of the cases with tunneled cuffed catheter dysfunction was caused by infection, 51.7% by thrombus formation, 27.6% by central vein stenosis, and 13.8% by fibrin sheath. In the study of Ponce D, et al. (14), it was reported that dysfunction developed mostly due to thrombosis at a rate of 45%. Unlike the literature, central venous stenosis was the most common cause of catheter dysfunction (58.5%) in our study. We think that dysfunction due to thrombosis developed less because most of our patients used low-dose anticoagulants for various reasons. In the literature, conflicting results have been reported about the relationship between the presence of polycystic kidney disease in advanced age, gender and CRF etiology and the development of catheter dysfunction (15). In the study of Shi M, et al. (12) advanced age was reported to be a risk factor for catheter dysfunction. In the study of Szarnecka-Sojda A, et al. (16) it was reported that there was a relationship between gender and catheter dysfunction. In the study of Fox J, et al. (17), it was reported that there was a relationship between polycystic kidney disease and catheter dysfunction. In our study, no relationship was found between the development of catheter dysfunction and the presence of polycystic kidney disease in advanced age, gender and CRF etiology. This may be due to the relatively short follow-up time of our study. In the study of Valliant AM, et al. (18) diabetes was reported to be a risk factor for catheter dysfunction. In another study uncontrolled diabetes was reported to be a risk factor for catheter thrombosis (19). In our study, it was determined that the presence of diabetes in the etiology of CRF or as a comorbid disease is a risk factor for catheter thrombosis, similar to the literature. In addition, it was determined that catheter dysfunction due to thrombosis developed in the early period compared to other causes of dysfunction. In other words, diabetes was found to be a risk factor for early dysfunction.

Studies have reported that stenosis developed in catheterized central veins due to trauma (20). In addition, it has been reported that central vein stenosis is mostly seen in patients who are catheterized for short-term hemodialysis (21). In our study, hypertension was determined as a risk factor for early catheter dysfunction due to central venous stenosis. The reason for this has been interpreted as hypertension increases vascular trauma possibility. Similar to the literature, in our study, contrast-enhanced angiographic evaluation was performed in all cases with catheter dysfunction, and it was found that 17.9% of the cases developed catheter dysfunction due to the fibrin sheath. Studies have reported that the use of low-dose aspirin and warfarin reduces catheter thrombosis (23). In a study, it was reported that low-dose warfarin use decreased the frequency of thrombosis from 38% to 10% in patients with central venous catheter receiving chemotherapy (24). In our study, it was found that catheter dysfunction due to thrombosis was less common in patients using low-dose anticoagulants in accordance with the literature. The first limitation of our study is that it is a retrospective study, and the second limitation is that we could not give the results of different applications because catheterization was performed by the same interventional radiologist in a single center. We believe that these limitations of our study will not change the results we found.

Conclusion

While diabetes and hypertension are risk factors for tunneled cuffed catheter dysfunction, the use of low-dose anticoagulants plays a protective role in catheter thrombosis. Among patients who are catheterized with tunneled cuffed catheters, the use of low-dose anticoagulants may be effective in preventing thrombosis and early dysfunction in patients with no contraindications.

References

1. Peter R and Bream PR Jr. Update on insertion and complications of central venous catheters for hemodialysis. Semin Intervent Radiol. 2016;33:31-8. DOI:10.1055/s-0036-1572547
2. Quarello F, Forneris G, Borca M, et al. Do central venous catheters have advantages over arteriovenous fistulas or grafts? J Nephrol. 2006;19:265-79.
3. Labriola L and Pochet JM. Any use for alternative lock solutions in the prevention of catheter-related blood stream infections? J Vasc Access. 2017;18:S34-8. DOI: 10.5301/jva.5000681
4. Ibeas-Lopez, J. New technology: Heparin and antimicrobial-coated catheters. J Vasc Access. 2015;S16:48-53. DOI:10.5301/jva.5000376
5. Lok C, Huber T, Lee T, et al. KDOQI Clinical Practice Guidelines for Vascular Access: 2019 Update. Am J Kidney Dis. 2020;75:S1-164. DOI:10.1053/j.ajkd.2019.12.001
6. Timsit JF. What is the best site for central venous catheter insertion in critically ill patients? Crit Care. 2003;7:397-9. DOI:10.1186/cc2179
7. Kelber J, Delmez JA and Windus DW. Factors affecting delivery of high-efficiency dialysis using temporary vascular access. Am J Kidney Dis. 1993;22:24-9. DOI:10.1016/s0272-6386(12)70162-2
8. Rathi M, Pinnamaneni VST and Sakhuja V. Non-imaging assisted insertion of un-cuffed, non-tunneled internal jugular venous catheters for hemodialysis: Safety and utility in modern day world. Biomed J. 2016;39:283-8. DOI:10.1016/j.bj.2015.12.004
9. Maya ID and Allon M. Outcomes of tunneled femoral hemodialysis catheters: Comparison with internal jugular vein catheters. Kidney Int. 2015;68:2886-9. DOI: 10.1111/j.1523-1755.2005.00762.x
10. Engstrom BI, Horvath JJ, Stewart JK, et al. Tunneled internal jugular hemodialysis catheters: Impact of laterality and tip position on catheter dysfunction and infection rates. J Vasc Interv Radiol. 2013;24:1295-1302. DOI:10.1016/j.jvir.2013.05.035
11. Shingarev R, Barker-Finkel J and Allon M. Natural history of tunneled dialysis catheters placed for hemodialysis initiation. J Vasc Interv Radiol. 2013;24:1289-94. DOI:10.1016/j.jvir.2013.05.034
12. Shi M, Cui T, Ma L, et al. Catheter failure and mortality in hemodialysis patients with tunneled cuffed venous catheters in a single center. Blood Purif. 2017;43:321-6. DOI: 10.1159/000455062
13. Coentrao L, Santos-Araujo C, Dias C, et al. Effects of starting hemodialysis with an arteriovenous fistula or central venous catheter compared with peritoneal dialysis: A retrospective cohort study. BMC Nephrol. 2012;13:88. DOI: 10.1186/1471-2369-13-88
14. Ponce D, Mendes M, Silva T, et.al. Occluded tunneled venous catheter in hemodialysis patients: Risk factors and efficacy of alteplase. Artif Organs. 2015;39:741-7. DOI:10.1111/aor.12462
15. Wang K, Wang P, Liang X, et.al. Epidemiology of haemodialysis catheter complications: A survey of 865 dialysis patients from 14 haemodialysis centres in Henan province in China. BMJ Open. 2015;5:e007136. DOI:10.1136/bmjopen-2014-007136
16. Szarnecka-Sojda A, Jacheć W, Polewczyk M, et.al. Risk of complications and survival of patients dialyzed with permanent catheters. Medicina (Kaunas). 2019;56:2. DOI:10.3390/medicina56010002
17. Fox J, Joubert G and Loggenberg E. Tunnelled haemodialysis catheters in central free state: Epidemiology and complications. SA J Radiol. 2019;23:1791. DOI:10.4102/sajr.v23i1.1791
18. Valliant AM, Chaudhry MK, Yevzlin AS, et.al: Tunneled dialysis catheter exchange with fibrin sheath disruption is not associated with increased rate of bacteremia. J Vasc Access. 2015;16:52-6. DOI:10.5301/jva.5000301
19. Vats HS. Complications of catheters: Tunneled and non-tunneled. Adv Chronic Kidney Dis. 2012;19:188-94. DOI: 10.1053/j.ackd.2012.04.004
20. Campean V, Neureiter D, Varga I, et al. Atherosclerosis and vascular calcification in chronic renal failure. Kidney Blood Press Res. 2005;28:280-9. DOI:10.1159/000090182
21. Afzal A, Ulhaq AU, Ahmed A, et al. Hemodialysis patients; Central vein stenosis following temporary double lumen catheterization in internal jugular and subclavian veins. The Prof Med J. 2017;24:8
22. Schon D and Whittman D. Managing the complications of long-term tunneled dialysis catheters. Semin Dial. 2003;16:314–22. DOI: 10.1046/j.1525-139x.2003.16060.x
23. Rackoff WR, Weiman M, Jakobowski D, et al. A randomised, controlled trial of the efficacy of a heparin and vancomycin solution in preventing central venous catheter infections in children. J Pediatr. 1995;127:147-51. DOI:10.1016/s0022-3476(95)70276-8
24. Bern MM, Lokich JJ, Wallach SR, et al. Very low doses of warfarin can prevent thrombosis in central vein catheters. Ann Intern Med. 1990;112:423-8. DOI:10.7326/0003-4819-76-3-112-6-423

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 564-573
https://doi.org/10.31067/acusaglik.850835

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Radiology / Radyoloji

The Usage and Efficiency of Drug-Eluting Stents in Vertebral Ostial Stenosis

Burcu Erkan[1], Serdar Geyik[2], Kıvılcım Yavuz[3], Işıl Saatçi[4], Saruhan Çekirge[4]

[1]Koç Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, İstanbul, Türkiye
[2]İstanbul İstinye Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, İstanbul, Türkiye
[3]Ankara Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Ankara, Türkiye
[4]Yüksek İhtisas Üniversitesi Koru Hastanesi, Radyoloji Anabilim Dalı, Ankara, Türkiye

Burcu ERKAN, Dr. Öğr. Üyesi
Serdar GEYİK, Prof. Dr.
Kıvılcım YAVUZ, Prof. Dr.
Işıl SAATÇİ, Prof. Dr.
Saruhan ÇEKİRGE, Prof. Dr.

Correspondence: Burcu Erkan
Koç Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, İstanbul, Türkiye
Phone: +905326528206
E-mail: bakpinar@kuh.ku.edu.tr

Received : 09 September 2019
Accepted : 20 June 2020

ABSTRACT

Objectives: Extracranial vertebral artery atherosclerosis is an insidious and hazardous disease. With technological development and accumulating experience, antiproliferative drug-eluting stents became a viable option for reducing the in-stent restenosis of the origin of the vertebral artery. Here, we evaluated the technical success rates, efficiency, clinical and angiographic results of the usage of drug-eluting stents in vertebral ostial stenosis.

Patients and Methods: 28 stents were implanted in 24 patients with vertebral artery origin stenosis. Digital subtraction angiographic or CT angiographic follow-up was made at 6, 12 and 24 months.

Results: Paclitaxel-eluting stents were placed with high technical success for the treatment of vertebral artery origin stenosis. There was no procedure-related mortality. However, one patient succumbed to death due to aspiration pneumonia for a basilar artery stroke with successful stenting and thrombolysis procedure. There was only one limited subclavian artery dissection in a patient (%4.1) during the procedure which was managed conservatively. One stent (%3.7) had in-stent restenosis in the early period (6th month) and one patient (%4.1) had recurrent neurological symptoms on follow-up (9th month). In a median follow-up of 13 months (6-25 months), none of the patients had late stent thrombosis.

Conclusion: Vertebral artery ostial stenosis can be treated effectively and safely with high technical success and low in-stent restenosis rates with paclitaxel drug-eluting stents. With low restenosis rates, antiproliferative drug-eluting stents are an option for reducing the vertebral artery in-stent restenosis.

Keywords: Vertebral artery origin, stenosis, paclitaxel, drug-eluting stent

Vertebral Ostial Stenoz Tedavisinde İlaç Salınımlı Stent Uygulaması ve Etkinliği

ÖZET

Amaç: Ekstrakraniyal vertebral arter aterosklerotik hastalığı sinsi ve tehlikeli bir hastalıktır. Gelişen teknoloji ve artan tecrübelerle birlikte antiproliferatif ilaç salınımlı stentler vertebral arter orjininde stent içi stenozu azaltmaya alternatif oluşturmaktadır. Biz de çalışmamızda vertebral ostial stenozlarda ilaç salınımlı stent uygulamasının teknik başarısını, etkinliğini, klinik ve anjiyografik sonuçlarını değerlendirdik.

Hastalar ve Yöntemler: Vertebral arter orijin darlığı olan 24 hastaya toplam 28 adet stent yerleştirildi. 6, 12, 24. aylarda anjiyografi veya BT anjiyografi ile takip edildi.

Bulgular: Vertebral arter orijin darlıklarının tedavisinde paclitaxel salınımlı stent yüksek teknik başarı ile uygulandı. İşleme bağlı mortalite izlenmedi. Baziler arter inmesi nedeniyle başarılı stentleme ve tromboliz uygulanmış bir olgu aspirasyon pnömonisi nedeniyle kaybedildi. İşleme bağlı bir hastada (%4.1) subklavyen arterde sınırlı diseksiyon gelişti ve medikal tedavi ile takip edildi. Takipte bir adet stentte (%3.7) erken dönem (6.ay kontrol) stent içi restenoz gelişti, bir hastada (%4.1) rekürren nörolojik semptom izlendi (9.ay). Hastaların hiçbirinde geç dönem tromboz izlenmedi.

Sonuç: Vertebral arter ostial stenozlarında ilaç salınımlı stentler yüksek teknik başarı ve düşük stent içi restenoz oranları ile etkin ve güvenle kullanılabilir. Düşük restenoz oranları ile de antiproliferatif ilaç salınımlı stentler VA orjininde stent içi stenozu azaltmaya alternatif oluşturmaktadır.

Anahtar Sözcükler: Vertebral arter orijin, stenoz, paclitaxel, ilaç salınımlı stent

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Vertebrobasilar infarcts are 25% of all cerebral infarcts (1). 5-year recurrent stroke rate is reported to be about 22-35% after a vertebrobasilar transient ischemic attack (TIA) or stroke (2). Ostium is the most common place for vertebral artery (VA) stenosis (3).

Medical treatment is classically the initial treatment in VA stenosis (4). In cases where medical treatment is inadequate, angioplasty and stenting are preferred options for symptomatic vertebrobasilar atherosclerotic disease to avoid surgical-related morbidity (4-6). Primary stenting with balloon-expandable coronary stents is reported to be applied safely with high technical success in VA origin stenosis (OS). Nevertheless, relative in-stent restenosis (ISR) is still a problem to be solved. Antiproliferative drug-eluting stents (DES) offer an alternative for decreasing the ISR in VA origin. In our study, we assessed the technical success, efficiency, clinical and angiographic results of DESs in vertebral ostial stenosis.

Methods

The institutional review board approved this retrospective study and waived informed consent.

Patient Information

Patients who had VAOS with percutaneous endovascular Paclitaxel eluting stenting procedure in our institution between 2006 to 2008 were included in this retrospective study.

Age, gender, medical histories, clinical findings of the subjects and administered stent diameter were collected from medical records.

Stenting procedure

Endovascular treatment was indicated for the patients that had vertebrobasilar insufficiency or a history of TIA or stroke with 50% and higher VAOS which was determined by vertebral angiography. VAOS rates were measured with modified NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria (7), which was used for carotid stenosis, using diagnostic digital subtraction angiograms (DSA). All patients had pre and post-neurological examinations. Before the procedure, all patients were informed of the procedure and complications, and all patients signed the informed consent form. All procedures were performed by experienced interventional neuroradiologists in a DSA system (Artis, Siemens Medical Solutions, Erlangen, Germany).

In our procedure, all elective patients were medicated with clopidogrel bisulfate 75 mg/day, acetylsalicylic acid (ASA) 300 mg/day, starting 5 days before the procedure. In emergency situations, 300 mg clopidogrel bisulfate and 300 mg ASA were administered before the procedure as a loading dose.

During the procedure after 70-100 U/kg bolus heparin infusion, 7- 10 U/kg/hour heparin infusion was given to keep the activated clotting time level between 250-300 seconds.

Stent diameter was chosen according to the distally normal VA diameter, stent length was chosen to cover the entire atherosclerotic plaque.

After the procedure, we recommended ASA, 100 mg/day, lifelong, and clopidogrel, 75 mg/day, for two years.

In our clinic, we keep the patients under a control schedule at 6,12, 24 months. Stents were evaluated with DSA at 6th and 24th months, with computed tomography angiography (CTA) at 12th months.

Evaluation

The location of the lesion and stenosis rates were reviewed from the pre-procedure DSA. Stenting procedure of the vertebral ostial stenosis and other necessary locations, additional findings and complications were reviewed and noted. The pre and post-procedural Magnetic Resonance imaging (MRI) were reviewed if available.

Follow-up DSA and CTA findings were evaluated from Picture Archiving and Communication System (PACS®) and noted retrospectively. For CTA datasets, the axial 0.5 mm thin slices, coronal and sagittal reformatted images with maximum intensity projections obtained by dual source CT scanner (SOMATOM Definition, Siemens Medical Solutions, Erlangen, Germany) were reviewed. Hemodynamically significant ISR is considered in >50% stenosis. Morbidity and mortality rates as well as restenosis rates in 6,12 and 24 months were noted.

Results

Four patients were lost to follow-up after discharge, so they were excluded from the final analysis. Twenty-four patients (M: F= 20:4, mean age 60, range 47-81) who had VAOS with a total of 28 Paclitaxel eluting stents (PES) (Taxus- Boston Scientific) implanted by percutaneous endovascular procedure, were included in the study.

The majority of the patients were referred to our clinic from neurology clinics for a previous cerebrovascular event or persistent ischemic symptoms of posterior circulation despite optimal medical treatment. Three patients were diagnosed during cardiovascular evaluations (case 8, 10, 23).

All patients' medical histories were investigated and summarized in table 1. 22 patients had a history of TIA, stroke or vertebrobasilar insufficiency. Nine patients had a previous stroke history (3 of them from posterior circulation) and 2 patients had cerebrovascular events meanwhile. Basically, vertebrobasilar insufficiency was evaluated by clinical information. Four patients had pre-procedural CTA.

There were 2 asymptomatic patients, diagnosed during the cardiovascular work-up (case 10) and angiography investigation for the leg angina (case 8). These patients were treated for the diagnosis of high stenosis (>90%) rates of the VA with accompanying cerebrovascular occlusions and/or stenosis.

Nineteen patients had pre-procedural MRI and 3 of them (case 6, 11, 17) had acute ischemic lesions (15.7%).

The VAOS rates were subclassified as >90% (n=13), 90-70% (n=8) and 69-50% (n=6) when measured with modified NASCET. There was one unclassified intervention which was a broken stent (case 12), previously installed in another institution.

Nineteen patients had predisposing factors for atherosclerotic disease (79.1%). Nine patients had one or more findings of hemiparesis, loss of sensation, cerebellar ataxia, dysphasia, during the neurological examination (37.5 %).

In our study, all vessels were stented successfully with the percutaneous endovascular method. During the stenting procedure, none of the lesions needed predilatation balloon angioplasty. A DSA example of a case with pre and post-stenting images is shown in Fig. 1.

After the procedure, none of the control angiograms showed either an intracranial missing branch or an intraluminal filling defect suggestive of distal embolization. One patient (case 19) among 24 patients (4.1%) was diagnosed with a limited proximal subclavian artery dissection on post-procedure control angiogram. The patient was only anticoagulated without additional intervention. One week later the control CTA revealed the findings as stable.

None of the patients developed permanent neurological symptoms or any deficit on post-procedure neurological examinations. Two patients with temporary neurological symptoms had post-procedural MRI performed. One patient with a complaint of numbness on the left hand developed two millimetric lesions in the right postcentral gyrus with restricted diffusion (case 3) and another patient with the clinical finding of emotional indifference-agitation had a millimeter sized hemorrhagic lesion in the corpus of the left caudate nucleus (case 6). The clinical findings of both were disappeared during early follow-up (within one week).

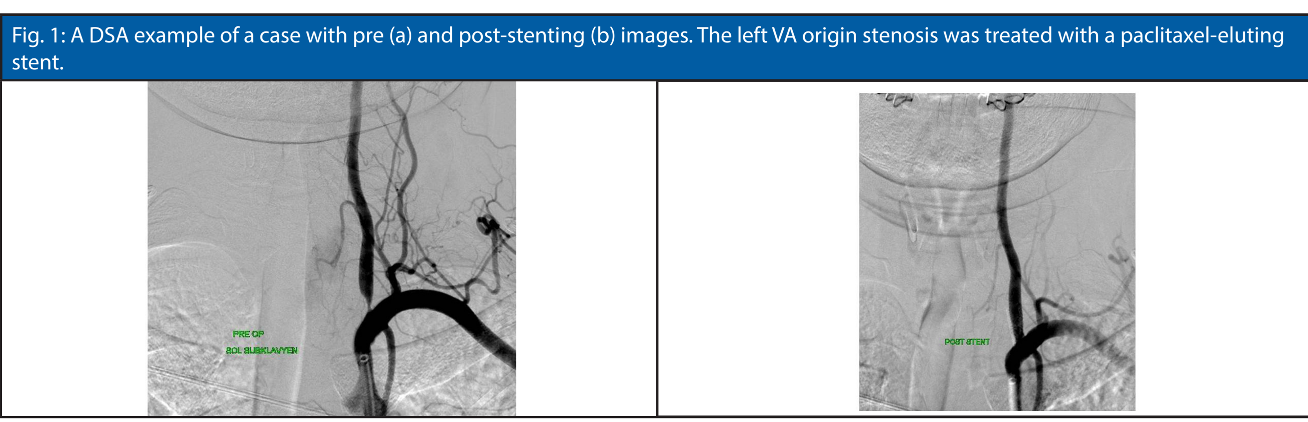


Fig. 1: A DSA example of a case with pre (a) and post-stenting (b) images. The left VA origin stenosis was treated with a paclitaxel-eluting stent.

Table 1. Patients demographics, findings and treatments														
Case No	Sex	Age	Symptoms	Clinical Findings	Imaging finding-pre	Imaging findings-post	Comor bidity	Lesion location	Stenosis %	Stent Taxus (mm)	6th Month Control Angio	1st Year Control CTA	2nd Year control Angio	Other stented area/ stenosis Additional findings	Complication
1	W	53	V, NV, At	-	MRI: No acute ischemic lesion. A couple millimetric nonspesific lesion	-	Ht	RVA LVA	70-90 70-90	2.5x12 4.5x12	P MIH	P P	P MIH	-	-
2	M	66	V, Hd, Wk temporary D, Di	-	-	-	Ht, DM,HL, C	LVA	50-70	5x12	P	-	MIH	L ICA %50-70 L Renal A	-
3	W	48	Vd	-	MRI: A couple milimetric chronic ischemic lesion	MRI: Peripheral and median milimetric acute ischemic lesion on R postcentral gyrus	DM, Ht, RA,Hs	RVA LVA	>90 >90	4x12 4.5x16	MIH MIH	P P	P P	R ICA>%90 (L ICA stenosis-follow-up)	-
4	M	61	Vd, L Hp	(Previous CVE) LUE 3/5, LLE 4/5	MRI: Chronic ischemic lesion on R putamen, centrum semiovale Wallerian degeneration, large R lateral ventricule	-	-	LVA	50-70	5x12	P	MIH	-	L ICA %70-90 (R subclav, brakiocef occlusion, steal) (L subclav stenosis-follow-up)	-
5	M	60	R H	(Previous CVE- L PCA) Loss of sensation Incompetant cerebellar examination	MRI: Chronic ischemic lesion on left occipital, posterior talamus, bilateral cerebellar	-	HT	LVA	50-70	4.5x12	MIH	P	-	(Hypoplastic RVA) (L ICA stenosis-follow-up	-
6	M	48	L Hp	(Previous CVE) LUE 4/5	MRI: RMCA area large chronic infarct, volume loss. Front nearby- 5 mm acute ischemic lesion	MRI: Milimetric new hemorrhagic lesion on the corpus of left caudat nucleus	-	RVA	70-90	3.5x12	p	p	p	R ICA>%90 L ICA %70-90	-
7	M	54	L Hp, Fp	(Previous CVE) Indistinct L nasolabial sulcus, LUE 3/5, LLE 4/5 L hyperactive DTR	MRI: Chronic ischemic gliotik lesion on R temporal lobe CTA: Saccular aneurism on arcus aorta	-	C	LVA	>90	4.5x12	MIH	p	p	R ICA >%90 (RVA stenosis-follow-up)	-
8	M	70	EA	-	MRI: Chronic ischemic gliotic lesions on bilateral centrum semiovale, posterior periventricular area	-	CAD	RVA LVA	>90 >90	4x12 4.5x12	P MIH	P P	MIH P	R ICA >%90	-

Table 1. Patients demographics, findings and treatments (continued)														
Case No	Sex	Age	Symptoms	Clinical Findings	Imaging finding-pre	Imaging findings-post	Comor bidity	Lesion location	Stenosis %	Stent Taxus (mm)	6th Month Control Angio	1st Year Control CTA	2nd Year control Angio	Other stented area/ stenosis Additional findings	Complication
9	M	54	R Hp, D	(Previous CVE) RUE, RLE 2/5, LUE, LLE 3/5, dysphasia	MRI: Left MCA area- chronic large hemorrhagic infarct, Wallerian degeneration	-	DM, C	RVA	50-70	3x12	MIH	P	BTA: P	(L ICA occlusion RVA stenosis-follow-up	-
10	M	63	Hd	-	-	-	CAD	LVA	>90	4.5x12	ISR	-	-	L ICA >%90 (R ICA, RVA occlusion)	-
11	M	81	N, Hd, R Hp	CVE; Opens his eyes to verbal stimulus, head movements to the questions, localizes the pain with L hand, L arm, leg spontaneous movement, R extremity extantion???	MRI: Bilateral cerebellar, tectal, R hipocampal, bilateral occipital acute ischemic lesions	-	-	LVA	50-70	4.5x12	-	-	-	(BA thrombolysis)	-
12	M	66	V, D, At	(Previous CVE) Ataxic walk, bilateral intantional tremor, Romberg+	MRI: A couple milimetric noncpesific lesion in L frontal subcortical white matter CTA: Intimal hyperplasia and mechanical complication (broken stent) likely to cause hemodynamically significant stenosis in L vertebral ostial stent	-	DM	LVA Broken stent	-	4.5x16	P	-	-	RVA occlusion	-
13	W	54	NV, V, At	(Previous CVE) Ataxic walk, RUE movement and cerebellar examination awkward	CT, CTA: R cerebellar enfarct, L ICA >50% stenosis	-	DM	RVA LVA	>90 >90	5x12 5x16	P MIH	P MIH	-	(L ICA stenosis-follow-up)	-
14	M	64	Temporary D	(Previous CVE) -	-	-	DM, Ht, C, CAD	LVA	50-70	5x12	MIH	MIH	-	(L ICA occlusion R ICA stenosis-follow-up)	-
15	M	67	S, temporary visual, hearing loss	(Previous CVE) -	-	-	Ht	LVA	>90	4.5x12	MIH	P	-	(R ICA, L ICA stenosis-follow-up)	-
16	M	66	N-L arm	-	MRI: bulbus posterior R sided hyperintense milimetric lesions possibly due to chronic ischemia CTA: Soft plaques that do not cause stenosis in bilateral carotid bifurcation, L distal CCA	-	Ht, DM	LVA	>90	4x16	MIH	P	-	RVA>90	-

Table 1. Patients demographics, findings and treatments (continued)

Case No	Sex	Age	Symptoms	Clinical Findings	Imaging finding-pre	Imaging findings-post	Comor bidity	Lesion location	Stenosis %	Stent Taxus (mm)	6th Month Control Angio	1st Year Control CTA	2nd Year control Angio	Other stented area/ stenosis Additional findings	Complication
17	M	47	V, NV, Vd, Di, At	CVE: double vision at left glance, nistagmus, quadranopsia, obliterated L nasolabial fold, At to the L, minimally awkward knee heel test	MRI: LPCA area, bilateral talamic, upper pons, bilateral serebellar acute infact areas CTA: LVa occlusion 4 cm distal to the origin, no prebasilar segment, thin, irregular basilar artery, LPCA occlusion	-	C	LVA	70-90	4.5x16	MIH	P	-	(Hypoplastic RVA)	-
18	M	70	EA, V	-	MRI: No acute ischemic lesion	-	Ht	RVA	>90	4x16	P	-	-	R ICA>90 (LVA, L subclav, L ICA stenosis-follow-up)	-
19	M	53	V, NV, S	-	MRI: A couple milimetric nonspesific gliotic lesion in bilateral subcortical area	-	C	LVA	70-90	4x16	MIH	P	-	(RVA stenosis-follow-up)	L subclav dissection
20	W	72	Hd, V, D, N-L arm	-	MRI: L cerebellar chronic ischemic lesion. Milimetric ischemic gliotic lesions in cerebral subcortikal white matter	-	Ht	RVA	>90	4x12	MIH	-	-	R ICA %70-90 RVA cervical %50-70 (LVA occlusion)	-
21	M	62	V	-	MRI: No acute ischemic lesion. Bilateral milimetric chronic ischemic lesions	-	DM	RVA	70-90	4x12	P	P	-	(RVA intradural stenosis Milim ACoA aneurism-follow-up)	-
22	M	55	V, Vd, N-L face	-	MRI: No acute ischemic lesion	-	Ht, HL, COPD	LVA	>90	4.5x16	MIH	-	-	L ICA occlusion-reconstruction with cervical collateral	-
23	M	65	Previous TIA, V	-	MRI: No acute ischemic lesion. L frontal chronic enfarct. Lacunar enfarct in L caudat nucleus	-	C, CAD	RVA	70-90	4x16	P	-	-	RVA intracran stenosis stent, R PICA origin aneurism coil emb	-
24	M	44	V, N-L arm- lip	-	MRI: No acute ischemic lesion. A couple millimetric nonspesific lesion	-	Ht, renal artery stent	RVA	70-90	4x16	MIH	-	-	-	-

ACoA, anterior communicating artery; At, ataxia; BA, basilar artery; C, smoker; CAD, coronary artery disease; CCA, common carotid artery; COPD, chronic obstructive pulmonary disease CVE, cerebrovascular event; Di, diplopia; D, dysarthria; DM, diabetes mellitus; DTR, deep tendon reflex; EA, lower extremity angina; Fp, facial paresis; H, hypoesthesia; Hd, headache; HL, hiperlipidemi; Hp, hemiparesis; Hs, Hashimoto Tiroiditi; Ht, hypertension; ICA, internal carotid artery; ISR, instent restenosis; L, left; LLE, left lower extremity; LUE, left upper extremity; M, man; MIH, minimal intimal hyperplasia; N, numbness; NV, nausea-vomiting; P, patent; PICA, posterior inferior cerebellar artery; R, right; PCA, posterior cerebral artery; RA, Romatoid Arthritis; RLE, right lower extremity; RUE, right upper extremity; S, syncope; V, vertigo; VA, vertebral artery; Vd, visual disturbance; TIA, transient ischemic attack; U, unconscious; W, woman; Wk, weakness

During the early postoperative period within the seven days, one patient (case 1) had vomiting twice with a fifteen seconds long asystole. ECG and cardiac enzymes were normal with no additional problems.

One patient (case 11) succumbed to death due to aspiration pneumonia 11 days after the procedure. The patient was brought to the hospital unconscious with a basilar artery stroke. Additional left VA stenosis was diagnosed and treated with PES during the same session of angiography for intraarterial thrombolysis. The patient benefited from intraarterial thrombolysis, neurological symptoms regressed and was extubated. Nevertheless, he couldn't survive.

Follow-up

The mean follow-up was 447 days, the median follow-up was 399 days.

The follow-up findings are summarized in table 2. Twenty-three of the 24 patients with a total of 27 PES were evaluated at the 6th month (median 187 days) with DSA. Only one stent (case 10) out of 27 stents was diagnosed with hemodynamically significant ISR (3.7%). The patient was a 63-year-old male, diagnosed with a right VA and ICA occlusion with 90% stenosis of left VA and ICA during cardiology controls. Left VA and left ICA stenoses were treated with endovascular stenting. At the 6th month follow-up, there was MIH in the left ICA stent but hemodynamically significant (>50%) ISR in the left VA stent (Fig. 2). Meanwhile, the patient stopped using the ASA but continued to use clopidogrel due to stomach bleeding. We planned a treatment session of balloon angioplasty, unfortunately, the patient refused the treatment due to an additional recent diagnosis of lung carcinoma. Furthermore, he didn't continue follow-ups and died of complications of lung carcinoma.

At the first and second-year evaluations, no other hemodynamically significant ISR were investigated.

Table 2. Follow-up findings

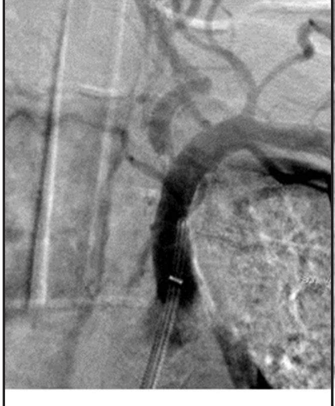
Month	Median day	Patient (n)	Stent (n)	DSA/ CTA	Patent (n)	Patent (%)	MIH (n)	MIH (%)	ISR (n)	ISR (%)
6	187	23	27	27/-	10	37%	16	59%	1	3.7%
12	370	17	22	2/20	18	81.80%	4	18.20%	-	-
24	736	7	11	8/3	8	72.72%	3	27.30%	-	-

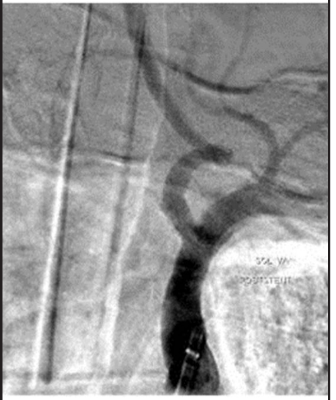
n: number

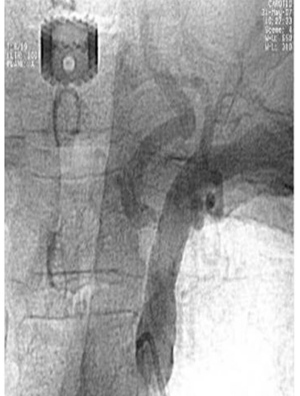
Only one patient (4.1%) had recurrent neurological symptoms during the follow-ups (case 12). The patient had recurrent complaints of balance and speech problems. Two months before being referred to our clinic, he was treated with left vertebral ostial stenting in another clinic. The patient had a broken stent and was treated with PES through both segments of the fragmented stent (Fig. 3). The 6th month follow-up after this procedure yielded a normal DSA. 9 months after the second procedure there was worsening of the cerebellar symptoms. Nevertheless, the left VA ostial stent was patent at angiographic controls. No lesion that had restricted diffusion on MRI. No other findings on spinal MRI explained the symptoms. The cerebellar findings were recovered and the patient was discharged after 10 days of hospitalization.

In a median follow-up of 13 months (6-25 months), none of the patients had late stent thrombosis. The procedural and post-procedural events are collected in table 3.

Fig. 2: Case 10: Stenosis (a) and paclitaxel-eluting stent implantation (b) of the left vertebral artery are seen. In-stent restenosis is observed at the sixth-month control angiogram (c, d).







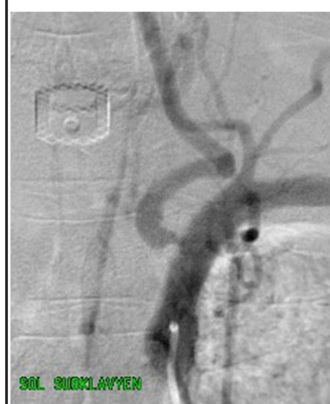


Table 3. Procedural, post-procedural events

	Major event	n	%	Minor event	n	%
Procedure related complications	-	-	-	Limited proximal subclavian artery dissection	1	4.1
30 days adverse events	Exitus due to aspiration pnomonia	1	4.1	Temporary numbness on left hand/ Two milimetric acute ischemic lesion- R postcentral gyrus Emotional indifference- agitation/ Milimetric hemorrhagic lesion- L caudate nucleus Vomiting- vagal stimulation, 15 seconds asystole	3	12.5
Long period events	-	-	-	Worsening of cerebellar symptoms	1	4.1

Fig. 3: Case 12 : It was observed that the stent, previously placed on the VA origin, was broken (a, b). Angiography images (c, d) obtained after insertion of the paclitaxel-eluting stent through the broken components are observed.

Discussion

Proximal extracranial VA is the second most common stenotic area after carotid artery bifurcation. The origin of the VA is a difficult region to display (8).

Currently, catheter angiography is the gold standard in the evaluation of the VA origin and plaque, the detection of ulceration and thrombus, and the evaluation of extra and intracranial blood flow (9). However, it includes the risks of invasiveness, hospitalization, ionizing radiation, contrast agent allergy and nephropathy. Therefore, DSA is not the first method of choice in the diagnosis of extracranial VA atherosclerotic disease. Color Doppler Ultrasonography (US) and MRI have some technical and anatomical limitations in VA origin imaging. Spiral and multislice CTA can display extracranial VA without the risks of DSA (10).

We included DSA for the diagnosis of VA stenosis in the study. CTA was alternated with DSA to decrease the risks of DSA for the follow-up of the cases.

Classically the VA ostial atherosclerotic disease is treated with antiplatelet medication and anticoagulation. The benefit of an intervention over medical treatment alone is unclear. Various small trials were conducted to determine the efficiency of endovascular treatment modality relative to medical therapy alone. Nevertheless, these trials failed to demonstrate the superiority of stenting over the best medical therapy (11-13). Large randomized controlled trials are required to elucidate this question.

The generally accepted interventional indications are symptomatic VA stenosis, persistent posterior system ischemic symptoms despite optimal medical therapy, or intolerance to medical therapy. However, published studies may justify attempts without a medical treatment with symptomatic disease (14). The severity of stenosis, angiographic appearance (vulnerability, presence of ulceration), adequacy of collateral flow and patient age are the effective factors for decisions (14).

In embolic posterior circulation ischemia when cardiac causes are eliminated, the embolic event should be considered primarily due to VA origin disease. In these cases, treatment is recommended even the degree of stenosis is less than 50%, as it is a source of embolism (15).

Asymptomatic patients with significant stenosis in the origin of VA are controversial. Although most of the asymptomatic patients don't require, some researchers suggest endovascular treatment to high grade (more than 70%) stenosis in dominant VA or single VA origin for the increased risk of embolism (16). In a young asymptomatic patient, endovascular treatment is also recommended for severe ulcerated stenosis without good collateral flow. Another group of researchers argues that asymptomatic patients should be treated in cases where collateral circulation is necessary and is of great importance, such as carotid occlusion (8).

In our hospital, endovascular treatment is recommended for patients with posterior circulation ischemic symptoms despite optimal medical treatment, and those with more than 50% stenosis in the origin of VA in DSA. In addition, endovascular treatment is recommended to patients with an ulcerated plaque in the origin of VA, regardless of whether they are symptomatic or asymptomatic.

The ostial VA stenoses are highly elastic lesions due to the well-developed muscular layer of VA origin like coronary arteries. Thus, for successful treatment, it is necessary to use stents with high radial force (17). In the SSYLVIA trial, the increased restenosis rates in VA origin lesions compared to the lesions in intracranial vessels and VA segments prior to posterior inferior cerebellar artery have been associated with the lesions' high elastic nature and the stent's design (18).

Primary stenting with balloon-expandable coronary stents were reported to be applied safely with high technical success in VAOS (17). Although percutaneous stenting decreases the rate of procedural complications such as failed balloon dilatation or risk of dissection, the high ISR-rates remain as a problem to be solved (17, 19).

In parallel with the data of the decreased ISR-rates of antiproliferative DES in coronary arteries (20), DES were started to be used in VAOS as an alternative. The first-generation DES is sirolimus and PES. It is known that paclitaxel and sirolimus-eluting stents decrease the neointimal hyperplasia by inhibiting the induced smooth muscle proliferation by mitogens (21).

Although some studies revealed no differences in the ISR-rate between DES and bare-metal stents (BMS) (22) the results of two metanalyses showed a reduction of the ISR-rate and a lower rate of recurrent symptoms- symptomatic restenosis for DES compared with the BMS group (23, 24). It is indicated that the relative ISR problem remains relevant (24, 25). The prospective randomized STOVAST trial revealed no evidence for ISR reduction with DES versus BMS group (26). In this trial, cobalt-chromium stents in the BMS group were observed to have the lowest ISR-rates (8.3%, 1/12 patients) whereas the PES in the DES group was observed to have the highest ISR-rate (50%, 2/4 patients). Our data differ from the STOVAST trial significantly. We have found only 3.7% (only one asymptomatic case among 27 stent applications) hemodynamically significant (which is >50%) ISR-rate occurred in about 6 months after stenting with PES in our retrospective study within a mean of 447 days of follow-up. The patient had a combined contralateral ICA and VA occlusion. In a recent study, the contralateral VA occlusion at the time of stenting is postulated as an increased risk factor for ISR (27). The differences between the reported restenosis rates may be connected with the number of patients, the median interval follow-up time and the differences of the evaluation methods as well as application-related differences.

Although DESs are being used in the supra-aortic and intracranial vessels, the long period results are not clear. The late and very late thrombosis remains as a problem. In the light of these data and considering the costs, as of today, DESs are preferred to be used in the ostial VA stenosis for stent-in-stent placement for ISR of BMS and/or broken stents.

Treatment protocols of VAOS still maintain their dynamism. Recently, the use of distal protection devices and the self-expandable stents for the treatment of ostial VA stenosis have been investigated (28, 29). To define the best therapy option, prospective studies with long-term results are required.

We assessed the technical success, efficiency, clinical and angiographic results of PES in vertebral ostial stenosis. Despite the shortcomings of a retrospective study, we showed that VAOS can be treated effectively and safely with high technical success and low ISR-rates with paclitaxel DESs. With low restenosis rates, the antiproliferative DESs are still an alternative for reducing the VA ISR.

REFERENCES

1. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337(8756):1521-1526.
2. Phatouros CC, Higashida RT, Malek AM, Meyers PM, Lefler JE, Dowd CF, Halbach VV. Endovascular treatment of noncarotid extracranial cerebrovascular disease. Neurosurgery clinics of North America 2000;11(2):331-350.
3. Hass WK, Fields WS, North RR, Kircheff, II, Chase NE, Bauer RB. Joint study of extracranial arterial occlusion. II. Arteriography, techniques, sites, and complications. Jama 1968;203(11):961-968.
4. Cloud GC, Markus HS. Diagnosis and management of vertebral artery stenosis. QJM : monthly journal of the Association of Physicians 2003;96(1):27-54.
5. Jenkins JS, White CJ, Ramee SR, Collins TJ, Chilakamarri VK, McKinley KL, Jain SP. Vertebral artery stenting. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2001;54(1):1-5.
6. Jenkins JS, White CJ, Ramee SR, Collins TJ, McKinley KL. Vertebral Insufficiency: When to Intervene and How? Current interventional cardiology reports 2000;2(2):91-94.
7. 7. North American Symptomatic Carotid Endarterectomy Trial. Methods, patient characteristics, and progress. Stroke 1991;22(6):711-720.
8. Henry M, Henry I, Klonaris C, al. e. Angioplasty and stenting of the carotid and supra-aortic trunks: Percutaneous transluminal angioplasty and stenting of extracranial VA stenosis. 1st ed. London, UK: Taylor and Francis Medicine, 2003.
9. Berteloot D, Leclerc X, Leys D, Krivosic R, Pruvo JP. [Cerebral angiography: a study of complications in 450 consecutive procedures]. Journal de radiologie 1999;80(8):843-848.
10. Omori Y, Komatsu S, Murakawa T, Hirayama A, Sato Y, Fujisawa Y, Higashide T, Takahashi M, Kodama K. MDCT detection of left subclavian artery obstruction accompanied by anomalous origin of the left vertebral artery. International journal of cardiology 2007;115(2):244-245. doi: 10.1016/j.ijcard.2006.01.055
11. Coward LJ, McCabe DJ, Ederle J, Featherstone RL, Clifton A, Brown MM. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Stroke 2007;38(5):1526-1530. doi: 10.1161/STROKEAHA.106.471862
12. Compter A, van der Worp HB, Schonewille WJ, Vos JA, Boiten J, Nederkoorn PJ, Uyttenboogaart M, Lo RT, Algra A, Kappelle LJ. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. The Lancet Neurology 2015;14(6):606-614. doi: 10.1016/S1474-4422(15)00017-4
13. Markus HS, Larsson SC, Kuker W, Schulz UG, Ford I, Rothwell PM, Clifton A. Stenting for symptomatic vertebral artery stenosis: The Vertebral Artery Ischaemia Stenting Trial. Neurology 2017;89(12):1229-1236. doi: 10.1212/WNL.0000000000004385
14. Mukherjee D, Rosenfeld K. Manual of peripheral vascular intervention: Vertebral artery disease. Philadelphia, 2005.
15. Piotin M, Spelle L, Martin JB, Weill A, Rancurel G, Ross IB, Rufenacht DA, Chiras J. Percutaneous transluminal angioplasty and stenting of the proximal vertebral artery for symptomatic stenosis. AJNR American journal of neuroradiology 2000;21(4):727-731.
16. Wehman JC, Hanel RA, Guidot CA, Guterman LR, Hopkins LN. Atherosclerotic occlusive extracranial vertebral artery disease: indications for intervention, endovascular techniques, short-term and long-term results. Journal of interventional cardiology 2004;17(4):219-232. doi: 10.1111/j.1540-8183.2004.04055.x
17. Lin YH, Juang JM, Jeng JS, Yip PK, Kao HL. Symptomatic ostial vertebral artery stenosis treated with tubular coronary stents: clinical results and restenosis analysis. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2004;11(6):719-726. doi: 10.1583/04-1336.1
18. Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA): study results. Stroke 2004;35(6):1388-1392. doi: 10.1161/01.STR.0000128708.86762.d6
19. Lin YH, Liu YC, Tseng WY, Juang JM, Hung CS, Lin JW, Jeng JS, Yip PK, Kao HL. The impact of lesion length on angiographic restenosis after vertebral artery origin stenting. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2006;32(4):379-385. doi: 10.1016/j.ejvs.2006.02.016
20. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. The New England journal of medicine 2002;346(23):1773-1780. doi: 10.1056/NEJMoa012843
21. Axel DI, Kunert W, Goggelmann C, Oberhoff M, Herdeg C, Kuttner A, Wild DH, Brehm BR, Riessen R, Koveker G, Karsch KR. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation 1997;96(2):636-645.
22. Raghuram K, Seynnaeve C, Rai AT. Endovascular treatment of extracranial atherosclerotic disease involving the vertebral artery origins: a comparison of drug-eluting and bare-metal stents. Journal of neurointerventional surgery 2012;4(3):206-210. doi: 10.1136/neurintsurg-2011-010051
23. Tank VH, Ghosh R, Gupta V, Sheth N, Gordon S, He W, Modica SF, Prestigiacomo CJ, Gandhi CD. Drug eluting stents versus bare metal stents for the treatment of extracranial vertebral artery disease: a meta-analysis. Journal of neurointerventional surgery 2016;8(8):770-774. doi: 10.1136/neurintsurg-2015-011697
24. Langwieser N, Buyer D, Schuster T, Haller B, Laugwitz KL, Ibrahim T. Bare metal vs. drug-eluting stents for extracranial vertebral artery disease: a meta-analysis of nonrandomized comparative studies. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2014;21(5):683-692. doi: 10.1583/14-4713MR.1
25. Musialek P, Langwieser N. Commentary: vertebral artery ostial stenosis stenting technique: the concept reversed? Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2015;22(3):445-448. doi: 10.1177/1526602815583490
26. http://spo.escardio.org/eslides/view.aspx?eevtid=54&fp=3170.
27. Li J, Hua Y, Needleman L, Forsberg F, Eisenbray JR, Li Z, Liu R, Tian X, Jiao L, Liu JB. Arterial occlusions increase the risk of in-stent restenosis after vertebral artery ostium stenting. Journal of neurointerventional surgery 2018. doi: 10.1136/neurintsurg-2018-014243
28. Geng X, Hussain M, Du H, Zhao L, Chen J, Su W, Ma L, Gao Z, Ding Y, Ji X. Comparison of self-expanding stents with distal embolic protection to balloon-expandable stents without a protection device in the treatment of symptomatic vertebral artery origin stenosis: a prospective randomized trial. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists 2015;22(3):436-444. doi: 10.1177/1526602815579406
29. Chung SY, Lee DH, Choi JW, Choi BS, In HS, Kim SM, Choi CG, Kim SJ, Suh DC. Use of self-expanding stents for the treatment of vertebral artery ostial stenosis: a single center experience. Korean journal of radiology 2010;11(2):156-163. doi: 10.3348/kjr.2010.11.2.156

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 574-578
https://doi.org/10.31067/acusaglik.849439

From Whom did you Receive This Information?(A study on using complementary and alternative medicine (CAM) methods in elderly individuals)

Deniz Say Şahin[1]

[1]Mehmet Akif Ersoy Üniversitesi, Sosyal Hizmet, Burdur, Türkiye

Deniz SAY ŞAHİN, Doç. Dr.

ABSTRACT

Objective: This study was planned to determine elderly patients' statuses of using complementary and alternative medicine (CAM), why they prefer these methods and their attitudes towards CAM.

Material and Method: After receiving the necessary permissions, the study was carried out with 400 participants at or over the age of 65 who visited the polyclinics of a state hospital. Questionnaires were applied by the researchers with the face-to-face interview method, and the data were collected between 1 January 2018 and 1 January 2019. For data collection, a 22-question questionnaire form that was developed by the researchers based on the literature was utilized. The data were analyzed by using "SPSS 20.0 for Windows"; arithmetic means and standard deviations for the measurement values and percentages for the counted values were calculated. Chi-squared test was used to determine the significance of the difference between the two groups; while $p<0.05$ was accepted to be statistically significant.

Results: All sociodemographic variables were found to be significant regarding the elderly participants' usage of CAM practices ($p\leq0.05$). Herbal therapies were the most frequently preferred CAM method (87.9%); the participants used CAM for the purpose of improving general health status by 91.3%, and 82.6% of them learned about these methods from other users (relatives, friends, neighbors, etc.).

Conclusion: While CAM practices, which are among the current treatment concepts today, are increasingly abundant; the responsible performance of these practices requires a knowledge base. For this reason, healthcare personnel should have sufficient knowledge about CAM methods, follow scientific developments/updates about CAM and inform and guide their patients regarding CAM practices/updates.

Keywords: Aged, complementary therapies, attitude, knowledge bases, health personnel

Bu Bilgiyi Kimden Aldın? (Yaşlı bireylerde tamamlayıcı ve alternatif tedavi (TAT) yöntemleri kullanımı hakkında bir araştırma)

ÖZET

Amaç: Bu çalışma yaşlı hastaların tamamlayıcı ve alternatif tedaviyi (TAT) kullanma durumlarını, neden bu yöntemleri tercih ettiklerini, tamamlayıcı ve alternatif tedaviye ilişkin tutumlarını belirlemek amacıyla planlanmıştır.

Materyal ve Metot: Çalışma gereken izinler alındıktan sonra bir devlet hastanesi polikliniklerine başvuran 65 yaş ve üzeri 400 katılımcı ile yürütülmüştür. Anketler araştırmacılar tarafından yüz yüze görüşme tekniği ile uygulanarak veriler 1 Ocak 2018-1 Ocak 2019 tarihleri arasında toplanmıştır. Verilerin toplanması için araştırmacılar tarafından literatüre dayalı hazırlanan 22 soruluk anket formu kullanılmıştır. Araştırmadan elde edilen veriler "SPSS 20.0 for Windows" programı kullanılarak analiz edilmiş, ölçümsel değerler aritmetik ortalama, standart sapma ve sayımla belirlenen değerler sayı yüzde olarak hesaplanmıştır. İkili gruplardaki anlamlılığın hesaplanması için ki-kare testi, karşılaştırmalarda $p<0.05$ değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Yaşlıların TAT uygulamalarını kullanımına ilişkin sosyodemografik değişkenlerin tamamı istatistiksel olarak anlamlı bulundu ($p\leq0.05$). Yaşlı bireylerin kullanmayı en çok tercih ettikleri TAT yönteminin bitkisel terapiler (%87.9), kullanma amaçlarının %91.3 oranında genel sağlık durumunu iyileştirmek ve yöntemi %82.6 oranında diğer kullanıcılardan (eş, dost, akraba, komşu vb.) öğrendikleri saptandı.

Sonuç: Günümüzde güncel tedavi kavramı içerisinde yer alan TAT uygulamaları giderek artış göstermekle birlikte bu uygulamaların bilinçli yapılabilmesi bazı temel bilgi birikimini gerektirmektedir. Bu sebeple sağlık personelleri TAT yöntemleri hakkında yeterli bilgiye sahip olmalı, TAT konusunda bilimsel gelişmeleri takip etmeli ve hastalarını TAT uygulamaları hakkında bilgilendirmeli ve rehberlik etmelidir.

Anahtar Kelimeler: Yaşlı, tamamlayıcı terapiler, tutum, bilgi düzeyi, sağlık personeli

Correspondence: Deniz Say Şahin
Mehmet Akif Ersoy Üniversitesi, Sosyal Hizmet, Burdur, Türkiye
Phone: +905052362620
E-mail: saysahind@mehmetakif.edu.tr

Received : 04 December 2019
Accepted : 07 April 2020

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Humanity has used complementary therapies, which are defined as methods that are applied in parallel with modern medicine since the day it existed for gaining health. According to archeological findings remaining from the first ages, people have firstly utilized plants to overcome various health problems (1). As it is affected by several different cultures that exist in the world, the meaning of complementary and alternative medicine (CAM) may vary from country to country, physician to physician and even patient to patient (2). Although the concepts of complementary treatment and alternative treatment have different meanings, they are frequently used together in the literature. While complementary treatment refers to methods used by patients to support modern medicine, alternative treatment includes treatments or options that are used instead of modern medical practices, and their effects are not scientifically proven (2-4). In the general sense, CAM is defined as treatments that are applied in addition to medical treatment such as traditional natural products and exercise techniques that are used by the individual to better understand themselves, their family and environment and protect their physical and mental health (5, 6). In parallel with the fast developments in the diagnoses; care and treatments of diseases starting with the mid-20th century; there has been an increase also in the usage of CAM. Indifference to the medical treatments recommended by modern medicine, usage of CAM methods is increasingly becoming prominent and prevalent worldwide (3).

While complementary treatment refers to methods used by patients to support modern medicine, alternative treatment includes treatments or options that are used instead of modern medical practices, and their effects are not scientifically proven (3, 6). Today, the most important reasons for patients to turn towards CAM include the increased lifespan and chronic diseases, difficulties in accessing high-cost treatments and new technologies, deficiencies or side effects of drugs and suspicions about treatment options. Additionally, the limited time allocated for patients by healthcare professionals is also shown as a reason that increases the frequency of using CAM (4, 5). While the frequency of using CAM methods is increasing nowadays, it is seen that patients do not inform healthcare professionals about the methods that are using. As irresponsible usage of CAM methods may decrease the effectiveness of medication treatment, it may also lead to unwanted drug interactions and side effects, increase treatment times or organ dysfunctions (5, 7, 8). For this reason, in order to prevent and control complications that may develop in elderly patients, who are the most frequently encountered patient group by healthcare professionals, it is important to question the patients' CAM usage statuses, from where they have learned it and their reasons for using it. This study was planned for determining elderly patients' statuses of using complementary and alternative medicine (CAM), why they prefer these methods and their attitudes towards CAM.

Material and Method

The population of the study consisted of individuals aged 65 or older who visited the polyclinics of a state hospital between 1 January 2018 and 1 January 2019. The sample size in the study was determined based on the number of people ????unknown???? to the population with the method of single-stage random probability sampling. In the study, the required sample size was calculated with Epi-info software as 378 based on 5% acceptable error rate, in a 95% confidence interval and with a probability of 50% that the event took place in the population. After obtaining the necessary permissions, the study was carried out with 400 participants at or over the age of 65 who visited the polyclinics of a state hospital. The participants were included in the study after they were informed, and their consent was obtained. The questionnaires were applied by the researchers with the face-to-face interview method, and the data were collected between 1 January 2018 and 1 January 2019.

The data were collected by using a 22-question questionnaire form that was prepared by the researchers based on the literature. The form consisted of two parts. The first part consisted of 7 questions on the sociodemographic characteristics of the elderly, while the second part consisted of 15 questions on the methods they used as CAM, why they preferred these methods and their knowledge, attitudes and behaviors related to these methods. Before starting the study, written permission was obtained from the Ethics Committee of Burdur Mehmet Akif Ersoy University (No: 2017/118).

Statistical Analysis

The data obtained from the study were analyzed by using "SPSS 20.0 for Windows", while arithmetic means and standard deviations for the measured values and percentages for the counted values were calculated. Chi-squared test was used to determine the significance of the difference between the two groups, while $p<0.05$ was accepted as statistically significant.

Results

40.5% of the participants were male, 39.8% had primary school or lower degrees, 87% were married, and 51.7% had incomes equal to their expenditures. 82.2% of the elderly (n=329) used at least one CAM method, and there was a significant (gender, education status, income level, chronic status) difference between those that used these

methods and those that did not (Table 1). The mean age of the participants was 73.3±3.1.

Table 1. Sociodemographic variables regarding the participants' usage of CAM practices

Socio-demographic Characteristics	CAM users n=329		CAM non-users n=71		Chi-squared (p)
	Frequency	Percentage (%)	Frequency	Percentage (%)	
Age					
65-74	183	45.8	47	11.9	0.05
75-84	134	33.5	20	5.0	
85 or older	12	3.0	4	1.0	
Gender					
Female	217	54.3	21	5.2	0.001
Male	112	28.0	50	12.5	
Education Status					
Literate	23	5.8	0	0.0	0.005
Primary School	121	30.2	15	3.8	
Secondary School	96	24.0	17	4.2	
High School	51	12.7	23	5.8	
University	38	9.5	16	4.0	
Income Level					
Income less than exp.	132	33	22	5.5	0.001
Income equal to exp.	181	45.2	26	6.5	
Income more than exp.	16	4.0	23	5.8	
Marital Status					
Married	236	59.0	28	7.0	0.05
Single	2	0.5	1	0.3	
Divorced	12	3.0	6	1.5	
Widowed	79	19.7	36	9.0	
Chronic Disease					
Has	268	67.0	52	13.0	0.001
Does not have	61	15.3	19	4.7	
Family Type					
Nuclear Family	161	40.3	42	10.5	0.05
Extended Family	81	20.2	22	5.5	
Alone	87	21.7	7	1.8	

All CAM methods that were tried by the elderly participants were considered, and it was determined that they preferred herbal therapies the most (87.9%) and they practiced the bioenergy method the least (2.6%) (Tables 2). Participants applied these practices to improve their general health status by 91.3% (Table 3).

Table 2. CAM methods used by the participants and distributions (n=329)

Method	Usage Rate (%)*
Herbal therapy	87.9
Massaging	61.2
Cupping	40.2
Chiropractic	24.3
Leeching	23.6
Bloodletting	22.1
Ozone therapy	16.4
Pouring lead	16.2
Acupuncture	10.7
Naturopathy	9.6
Chinese medicine	8.8
Homeopathy	8.8
Ayurveda	7.6
Chelation treatment	3.9
Neural therapy	3.4
Bioenergy	2.6

*: The participants were allowed to select multiple options.

Table 3. The participants' CAM usage reasons (n=329)

Reasons	Rate (%)*
Improving general health status	91.3
Pain management	80.4
Chronic medical problems	76.3
Thinking it is harmless	60.1
Recommendation of other users	50.9
Being afraid of the side effects of drugs	50.7
Dissatisfaction with medical treatment	38.6
Because it is cheap and easily accessible	37.5
Stress relief and relaxation	37.4
Personal interest	21.2

*: The participants were allowed to select multiple options.

The participants received information on CAM methods the most from others who used the product such as friends, relatives and neighbors (82.6%) and the least from advertisement messages delivered to their mobile phones (8.4%) (Table 4).

Table 4. The participants' sources of information about CAM methods (n=329)

Source of information on CAM methods	Rate (%)*
Other users of the product (friends, family, neighbor, etc.)	82.6%
Television and radio	71.7%
Sales representatives that publicize the product	65.4%
Internet	42.1%
Healthcare personnel	34.9%
Newspapers and magazines	34.2%
Posters and billboards	17.5%
Messages coming to mobile phones	8.4%

*: The participants were allowed to select multiple options.

Discussion

Studies have determined that CAM usage frequency varies in the world between 9% and 80%; there are significant differences in usage rates based on sociodemographic characteristics, and these are increasingly gaining popularity (10-13). Studies in Turkey on the topic have revealed that CAM usage frequency varies between 7% and 76%, and there are significant differences between those who use CAM and those who do not, based on their demographic characteristics (11, 14). According to our results, 82.2% of our participants tried one of these methods at least once (n=329), and there was a statistically significant difference between those who used CAM methods and those who did not (n=71), based on their gender, education status, income level, chronic diseases (Table 1). In this respect, our study contributes to the CAM methods that are increasing in frequency in Turkey and the world, as well as the determination of the situation among the elderly.

According to our results, the top reason for the elderly to use CAM methods was to improve their general health status. This was followed by pain management and chronic problems (Table 3). By this aspect, our study was in agreement with the literature, and most studies have found the primary reasons of preferring CAM methods as improving general health status and pain management (15-18). In both our study and the literature, the most frequently used CAM practices were herbal therapies to achieve the aforementioned goals (Table 2) (16-21).

Today, many patients with life-threatening diseases prefer to use complementary and alternative treatment methods. The report of WHO (World Health Organization) on CAM stated that most people use CAM methods with the thought that "what is natural is safe" (22). In our study, we determined that 60.1% of the elderly participants who used CAM methods found them harmless as they are natural (Table 3).

Most studies have shown that patients do not ask for the information they want to gain on the usage of CAM methods from healthcare team members who are responsible for their treatment and care, and they rather obtain information about the issue from their relatives, friends, family and the media (10, 11, 14, 15). This showed that people do not primarily consult with healthcare personnel regarding the usage of CAM methods (23). Akıncı et al. (24) concluded that most patients were aware of CAM methods and used them, and their sources of information were mostly people around them. In the literature review of Tait et al. (25) on studies on the usage of CAM by hypertension patients, it was reported that the sources of news and information of the vast majority of patients regarding CAM methods were friends, relatives and neighbors. Other studies on CAM usage carried out with patients who had different diseases also determined that patients stated people who are not healthcare professionals as their source of information (5, 14, 20, 21, 24). If patients do not reach information about CAM practices from accurate sources, this may lead them to obtain unreliable information and gain negative health behaviors, therefore making it harder to take their disease under control. In our study, in agreement with the literature, we found that the participants obtained information related to CAM methods primarily from other individuals who used the products (friends, neighbors, relatives, etc.) (Table 4).

Conclusion

While CAM practices, which are among the current treatment concepts today, are increasingly abundant, the responsible performance of these practices requires a knowledge base. CAM methods that are used among elderly patients irresponsibly and without consulting healthcare personnel are worrying for two reasons. First of all, when the communication between the patient and the physician is weak, elderly patients hesitate to share the CAM methods they are using or planning to use with healthcare personnel, and they do not state this issue. Second of all, as there is no open communication, one might not be aware of the potentially harmful interactions between the CAM method that is used and regularly used medications, and this may affect the health of the elderly person negatively. For this reason, healthcare personnel should have sufficient knowledge about CAM methods, follow

scientific developments about CAM and inform and guide their patients regarding CAM practices.

References

1. Faydaoglu E, Sürücüoglu MS. History of the Use of Medical and Aromatic Plants and their Economic Importance. Kastamonu University Journal of Forestry Faculty 2011;11(1):52-67.
2. Khorshid L, Yapucu Ü. The Nurse's Role in Complementary Therapies. Journal of Anatolia Nursing and Health Sciences 2005;2:124-30.
3. Tashan TT, Koyuncu SB. Traditional methods that women us efor labor and factors affecting them. ACU Health Science Journal 2018;9(2),150-5.
4. Kocabas D, Eke E, Demir M. Evaluation of the attitudes of the individuals on traditional and alternative methods in the use of health care. Bolu Abant Izzet Baysal University Journal of Graduate School of Social Sciences 2019;19(1):63-80.
5. National Center for Complementary and Integrative Health (NCCAM). Complementary, Alternative or Integrative Health:What's In a Name? [Internet]. [2018.12.12]. https://nccih.nih.gov/health/integrative-health.
6. Sirois FM. Provider-based complementary and alternative medicine use among three chronic illness groups: associations with psychosocial factors and concurrent use of conventional health-care services. Complement Ther Medicine 2008;16:73-80.
7. Önal Ö, Durukan E. Frequency of polypharmacy and risk factors in the elderly in Burdur. Turkish J Geriatr. 2018;21(4):550–6.
8. Tachijan A, Maria V, Jahangir A. Use of herbal products and potential interaction in patients with cardiovascular disease. Journal of the American College of Cardiology 2010;55(6):516-25.
9. Altun F, Yazici H. The relationships between life satisfaction, gender, social security, and depressive symptoms among elderly in Turkey. Educ Gerontol 2015;41: 305–14.
10. Oliveria SA, Chen RS, McCarthy BD, Davis CC, Hill MN. Hypertension knowledge, awareness, and attitudes in a hypertensive population. J Gen İntern Med 2005;20(3):219-25.
11. Ernst E. Prevalence of use of complementary/alternative medicine: a systematic review. Bulletin of the World Health Organization 2000;78(2):258-66.
12. Chen YF, Chang JS. Complementary and alternative medicine use among patients attending a hospital dermatology clinic in Taiwan. Int J Dermatol 2003;42(8):616-21.
13. Nottingham EN. Complementary and alternative medicine: nurse practitioner education and practice. Holistic Nursing Practice 2006;20(5):242-6.
14. Kav S, Hanoğlu Z, Algier L. Use of Complementary and Alternative Medicine by Cancer Patients in Turkey: A Literature Review. International Journal of Hematology & Oncology 2008;18(1):52-7.
15. Astin JA. Why patients use alternative medicine: results of a national study. JAMA 1998;279:1548-53.
16. Cohen RC, Ek K, Pan XC. Complementary and Alternative Medicine (CAM) Use by Older Adults A Comparison of Self-Report and Physician Chart Documentation. J Gerontol: Medical Sciences 2002;57(4):223-7.
17. Foster DF, Phillips RS, Hamel MB, Eisenberg DM. Alternative Medicine Use in Older Americans. J Am Geriatr Soc 2000;48(12):1560-5.
18. Onyiapat JL, Okoronkwo IL, Ogbonnaya NP. Complementary and Alternative Medicine Use Among Adults in Enugu, Nigeria. BMC Complement Altern Med 2011;4(11):19-24.
19. Hanssen B, Grimsgaard S, Launso L, Fonnebo V, Falkenberg T, Rasmussen N. Use of Complemantary and Alternative Medicine in Scandinavian Countries. Scand J Prim Health Care 2005;23:57-62.
20. Khalaf AJ, Whitford DL. The Use of Complementary and Alternative Medicine by Patients with Diabetes Mellitus in Bahrain: a Cross-sectional Study. BMC Complement Altern Med 2010;14(10):35-42.
21. Lim MK, Sadarangani P, Chan HL, Heng JY. Complementary and Alternative Medicine Use in Multiracial Singapore. Complement Ther Med 2005;13(1):16-24.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 579-584
https://doi.org/10.31067/acusaglik.871560

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   Public and Environmental Health / Halk ve Çevre Sağlığı

An Evaluation of e-Health Literacy in University Students: The Example of Yozgat Bozok University

Şemsinnur Göçer[1], Elçin Balcı[2], Nursel Üstündağ Öcal[3]

[1]Sarikaya Physiotherapy and Rehabilitation, Yozgat / Turkey

[2]Erciyes University, Faculty of Medicine, Department of Public Health, Kayseri / Turkey

[3]Yozgat Bozok University Health Services Vocational School, Yozgat / Turkey

Şemsinnur GÖÇER, Dr. Öğr. Üyesi

Elçin BALCI, Prof. Dr.

Nursel ÜSTÜNDAĞ ÖCAL, Dr. Öğr. Üyesi

This study was presented as a poster at the 3rd International 21st National Public Health Congress held in Antalya between 26-30 November 2019.

Correspondence: Nursel Üstündağ Öcal
Yozgat Bozok University Health Services Vocational School, Istanbul / Turkey
Phone: +903542421034
E-mail: nursel.ustundagocal@yobu.edu.tr

Received : 31 January 2021
Accepted : 14 April 2021

ABSTRACT

Aim: It is stated that social media sites, which has been started to be used widely also in the field of health, are used as a potential resource for health information. In our work; It is aimed to determine the level of e-health literacy level among university students.

Methods: This research is a descriptive study. The study was carried out on the students of Yozgat Bozok University, Faculty of Education. This research was conducted in May and June 2019. Ethical approval for the research was obtained from Erciyes University Clinical Research Ethics Committee. The research was carried out with the necessary permission from Yozgat Bozok University. The research was completed with 310 people who are willing to participate in the study and have no communication problems. Questions containing socio-demographic information and e-health literacy scale were given to collect data from students.

Results: The average age of the group participating in the study was 21.0 ± 0.1 years, 69.0% of the participants were women. 69.7% of the participants stated that they had problems in complying with the medical advice or suggestions and that they received the necessary support from the physicians. 57.7% of the participants stated that they could understand that they did not have any problems with the informed consent forms. The total score average of the students on the e-health literacy scale was 28.4 ± 0.3

Conclusion: In our study, it was determined that the e health literacy score averages of the students were above the middle level.

Keywords: Health literacy, internet, social media, students

Üniversite Öğrencilerinde e-Sağlık Okuryazarlığının Değerlendirilmesi

ÖZET

Amaç: Sağlık alanında da yaygın olarak kullanılmaya başlayan sosyal medya sitelerinin online sağlık bilgileri için de potansiyel bir kaynak olarak kullanıldığı belirtilmektedir. Yaptığımız çalışmada; e-sağlık okuryazarlık düzeyinin üniversite öğrencilerindeki düzeyinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu araştırma Tanımlayıcı tipte bir araştırmadır. Çalışma Yozgat Bozok Üniversitesinde Eğitim Fakültesinde öğrenim gören öğrenciler üzerinde gerçekleştirilmiştir. 2019 Mayıs ve Haziran aylarında bu araştırma gerçekleştirilmiştir. Araştırma için etik onay Erciyes Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan alınmıştır. Yozgat Bozok Üniversitesi'nden gerekli izin alınarak araştırma gerçekleştirilmiştir. Araştırma çalışmaya katılmakta istekli olan ve iletişim sorunu bulunmayan 310 kişi ile tamamlanmıştır. Öğrencilerden veri toplamak için sosyo-demografik bilgileri içeren anket soruları ve e-sağlık okuryazarlığı ölçeği kullanılmıştır.

Bulgular: Araştırmaya katılan grubun yaş ortalaması 21,0±0,1 yıl idi, katılımcıların %69,1'i kadındı. Katılımcıların %69,7'si verilen tıbbi tavsiye veya önerilere uyma konusunda problem yaşadıklarını gerekli desteği hekimlerden aldıklarını bildirmişlerdir. Katılımcıların %57,7'si aydınlatılmış onam formlarında sorun yaşamadıklarını anlayabildiğini bildirmişlerdir. Öğrencilerin %57,4'ü internetin sağlıkla ilgili kararlar almada ve sağlık konuları ile ilgili kaynaklara ulaşmada katkı sağladığını bildirmişlerdir. Öğrencilerin, e-sağlık okuryazarlığı ölçeği toplam puan ortalaması ise 28,4±0,3 idi.

Sonuç: Araştırmamızda, öğrencilerin e-sağlık okuryazarlığı puan ortalamalarının orta düzeyin üzerinde olduğu belirlenmiştir.

Anahtar Kelimeler: Sağlık okuryazarlığı, internet, sosyal medya, öğrenciler

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Today, it is one of the most frequently used sources to access internet information sources. Health is one of these issues, and about half of the people trying to access information about health issues on the Internet are; They stated that it has an important effect on understanding health problems and communicating with physicians (1,2).

Interactive web environments, which are considered as indispensable means of information in recent years and called new media, are important in terms of health literacy, apart from tools such as television, newspapers and radio classified as traditional media.

In addition, social networks enable the spread of health information to be shared online, building masses, spreading the message to large audiences, and changing interactions with other people and human relations through rapid announcement and impact (3) It is stated that they are widely used in the health field and recently, social media sites are becoming a potential source for online health information (4).

Considering e-health literacy as a concept, it is a multifaceted concept that is in the middle between health literacy and information technology literacy dimensions. (5).

Although eHealth literacy is associated with health or health literacy, it requires the ability to learn about and use electronic resources. (6).

Pourravazi et al. (7) Defining e-health literacy as contributing to the improvement of healthcare by using information and communication Technologies, Norman and Skinner (8) define this as the process of searching, collecting, interpreting, and evaluating health-related issues from electronic sources such as information communication technologies. (8).

“E-health literacy”, which is developed for the literacy level of users, especially young people, who scan information in the field of health, is an important resource in this sense.

When health-related searches are made over the Internet, many uncontrolled misinformation can affect health, but may also cause individuals to be misled.

For this reason, it is important for individuals to have knowledge and awareness at the point of e-health literacy.

In this study; nowadays, access to the internet is getting easier with the effect of advanced technology, and it is aimed to determine the information search, find and use cases with the e-health literacy scale to get information about any health problem from internet resources or to solve this problem in university students with a high rate of internet usage.

Materials and Methods

Descriptive type research, in Yozgat Bozok University Faculty of Education

It was held in May-June 2019. In the study, it was planned to do not go to the sample account, but with 400 students who are studying in the last year of the faculty.

Since 30 students did not agree to participate in the study and 60 students could not be reached, the study was completed with 310 students. The rate of participation in the research is 77.5%.

A socio-demographic questionnaire consisting of demographic questions such as age, gender and social security and e-health literacy scale were used as data collection tools.

The e-health literacy scale, which was developed by Norman and Skinner (8) in 2006 and whose Turkish validity and reliability study was conducted by Tamer Gencer (9) in 2017, includes items related to internet usage and measuring internet attitude. There are a total of 8 questions in the scale. Scale items; It was arranged as “1 = strongly disagree, 2 = disagree, 3 = undecided, 4 = agree, 5 = absolutely agree” with 5-point likert type scaling method. It is known that the lowest score that can be obtained from the scale is 8 and the highest score is 40. High scores from the scale indicate a high level of e-health literacy. (9).

Ethical approval

For the study, ethical approval from Erciyes University Clinical Research Ethics Committee with the number 2019/252 and dated 03.04.2019 and institutional permission from Yozgat Bozok University were obtained.

Data Analysis

Normality analysis was performed using the Shapiro Wilk test. Since the data showed normal distribution, the T test was used to compare pairs of groups, and One way Anova was used to compare three or more groups.

In statistical analysis, the data obtained from the e-health Literacy Scale were scored according to the instructions of the scale. Number and percentage were used in descriptive data, and One Way Anova t test was used in data related to the scale. P <0.05 values were considered significant.

Results

Results regarding the descriptive characteristics of the students are given in Table 1. The average age of the study group is 21.0 ± 0.1 years, 69.0% were women. 52.3% were studying in the department of basic education sciences. 87.4% had social security, 70.6% of them were living in a dormitory.

Table 1. Descriptive characteristics of students

SPECIFICATIONS		n	%
Age groups	18-24	298	96.1
	25 and above	12	3.9
Gender	Female	214	69.0
	Male	96	31.0
Department	Basic educational sciences	162	52.3
	Liberal arts	129	41.6
	Science	6	1.9
	Educational Sciences	13	4.2
Social security	Yes	271	87.4
	No	39	12.6
Living place	With the family	53	17.1
	With friend	38	12.3
	Student dormitory	219	70.6
Family type	Elementary Family	256	82.8
	extended family	42	13.6
	parents separated	11	3.6
Mother education level	illiterate	28	9.0
	literate	18	5.8
	Primary education	195	62.9
	High school and above	69	22.3
Father education level	illiterate	6	1.9
	literate	3	1.0
	Primary education	201	64.8
	High school and above	100	32.3
Illness	Yes	44	14.2
	No	266	85.8
Total		310	100.0

82.8% of the students had a nuclear family. According to the results about the mother (62.9%) and father (64.8%) education level of the students, the rate of the students at primary education level was higher. 14.2% of the students stated that they have a disease.

Table 2. Distribution of students' informed consent and knowledge of the concept of e-health literacy, and their thoughts on the use of the Internet in relation to health and the usefulness of the Internet in e-health literacy

		n	%
Where do you get the most health-related information?	Physician	174	56.2
	Internet, media tools	121	39.0
	TV	15	4.8
Where do you get the most information on adherence to medical adviceor recommendations?	Physician	216	69.7
	TV	93	30.0
	Internet, media tools	1	0.3
Do you think the internet is useful in making health-related decisions?	Not useful at all	19	6.1
	Not helpful	46	14.8
	No idea	49	15,8
	Helpful	178	57,4
	Very helpful	18	5,8
How important is it to access health resources on the internet?	Does not matter	7	2.3
	It does not matter	42	13.5
	No idea	38	12,3
	Important	178	57,4
	Very important	45	14.5
Do you know about e-health literacy?	Yes	65	21.0
	No	148	47.7
	Partially	97	31.3
Can you understand the informed consent forms?	Yes	179	57.7
	No	131	42.3
Total		310	100.0

56.2% of the students stated that they received the support from the physician when they had problems with their health-related information, 69.7% of the medical advice or recommendations. 57.4% of the students stated that the internet plays an important role in searching and finding health information and is useful in making decisions about health.

It has been determined that the rate of students who have information about e-health literacy is 21% and 57.7% of the students can understand the informed consent forms.

Table 3. Comparison of students' e-health literacy total score average and total scores in terms of some characteristics			
	Mean±SS	t	p
Age group			
18-24	28,4 ±5,8	0,735	0,463
≥ 25	27,6±6,8		
Gender			
Female	28,1±5,9	-0,366	0,714
Male	29,0±5.7		
Social security			
Yes	28,6±5,8	1,110	0,268
No	26,8±6,4		
Disease state			
Yes	28,0±5,7	-0,244	0,807
No	28,5±5,9		
Department			
Basic educational sciences	29,4±5,5		
Liberal arts	27,0±5,5	12,140	0,001
Science*	34,3±8,4		
Educational sciences	27,4±8,5		
Family type			
Elementary family	28,5±5,8	6,092	0,014
Extended family	27,3±6,0		
Parents separated*	29,5±7,8		
Mother education level			
Illiterate	28,3±6,0		
Literate	27,2±6,8	0,119	0,731
Primary education	28,1±5,7		
High school and above	29,5±6,0		
Father education level			
Illiterate	25,5±6,5		
Literate	26,0±6,5	3,490	0,063
Primary education	27,9±5,9		
High school and above	29,7±5,6		
E-health literacy scale total score	28.4±0.3		
* The group that the difference originates from / Mean: Average SS: Standard deviation			

When the total scores of the e-health literacy scale are compared between the departments in which students study The total score average of the students studying in the science department was found to be significantly higher than the students studying in other departments. (p <0.005).

Again, when the scale total scores are compared with the family type status of the students, the total score averages of the students whose parents were separated were found to be significantly higher than the other groups. (p <0.005).

Although the e-health literacy scale total score averages were higher in the 18-24 age group, males, those with social security, those who stated that they had no illness, and those whose mother and father had high school and above education level, there was no significant difference (p> 0.005) .

The total mean score of the students from the e-health literacy scale was 28.4 ± 0.3.

Table 4. Comparison of the benefit of the internet in e-health literacy with the total scores of the e-health literacy scale with informed consent information	
	Mean±SS
Do you think the internet is useful in making health-related decisions?	
Not useful at all	21,2±5,8
Not helpful	25,6±6,5
No idea	25,8±5,2
Helpful	29,9±4,4
Very helpful	35,8±4,1
F=5,611	
p<0,001	
How important is it to access health resources on the internet?	
Does not matter	18,7±3,0
It does not matter	23,2±6,2
No idea	24,9±4,6
Important	29,7±4,6
Very Important	32,4±5,1
F=6,592	
p<0,001	
Can you understand the informed consent forms?	
Yes	29,1±6,1
No	27,2±5,3
t=2,367	
p<0,001	
Mean: Average SS: Standard deviation	

The total score average of the e-health literacy scale was significantly higher than the other groups in the students who stated that the internet was very useful in health-related decisions (p <0.005).

The total score average of the scale of the students who stated that the Internet plays a very important role in reaching health-related issues was found to be significantly higher than the other groups. (p <0.005). The scale total score mean of the students who stated that they could understand the informed consent forms was found to be significantly higher than the other groups (p <0.005).

Discussion

The average age of the study group was 21.0 ± 0.1 years, 69.0% of them were women. 52.3% were studying in the department of basic educational sciences. 87.4% of them had social security, 70.6% of them were living in a student dormitory (Table 1).

In our study, the rate of those who stated that they received support from a physician when they had problems regarding their health-related information and compliance with medical advice or recommendations was high (Table 2). In addition, students stated that the internet was effective in reaching health-related issues and making decisions as a result of this information. (Table 2). This result obtained; Although students express that they receive support from physicians in health-related issues, they think that they see the web environment as an important tool in accessing useful and health-related resources and can refer to internet resources when they feel incomplete.

Approximately one-fifth (21.0%) of the students in our study had knowledge about e-health literacy, the vast majority (57.7%) stated that they could understand the informed consent forms. (Table 2). This result obtained from the study; Although they do not have a problem with informed consents, it suggests that there may be a lack of conceptual knowledge about e-health literacy among students.

In our study, the total score that university students got from the scale was found to be 28.4 ± 0.3. (Table3). In our study, it was determined that the e-health literacy scale mean scores of the students were above the middle level.

In the study conducted by Tsukahara et al. (2020) with university students, the students' score on the scale was found to be 23.6. When looking at other studies in the literature, Dashti et al. (2017), in a study they conducted with university students in Iran, the average e-health literacy score of the students was found to be 28.2. Britt et al. (2017) in the study they conducted with 422 undergraduate students in America, the average e-health literacy score of the students was determined as 31.9. Although our study is compatible with the literature, there are studies in which the total score of e-health literacy is higher than our study. It can be thought that this difference may be due to the differences in students' access to information and self-expression.

Şengül et al. (10); It was stated that the use of the Internet, primarily in communication and information exchange, affects e-health literacy levels, students generally have e-health literacy perception and use the Internet at a high rate. Yang et al. (2017) found that university students with higher e-Health literacy participated more in health-promoting activities than those with functional and interactive literacy.

In our study, the total score average of the students studying in the science department was significantly higher than the students studying in other departments (Table 3).

Students in this group on health issues They use the internet more to get information and the reason for this may be that they are effective in accessing and interpreting information about health problems.

In our study, the total score average of the students whose parents were separated was significantly higher than the other groups (Table 3). This result may be due to the fact that he is a member of the broken family, unable to reach and consult the parents about their own health decisions, and therefore they see the Internet as more accessible to information..

In our study, the total score average of the students who reported that access to health-related issues using the internet was effective in making decisions based on this was found to be higher. (Table 4).

This result obtained from the answers given to the questions measuring the usefulness of the internet in e-health literacy in our study reveals that the internet access to health-related topics they are curious about is common among students.

In the study of Şengül et al. (10), it was stated by students that the internet is an important resource in making decisions about their health and accessing health resources.

According to a study conducted with young people aged 15-24 (11); Internet usage rate is 90.0%, more than two-thirds of them get online health information, half of the youth learn about a specific disease such as cancer, and four out of ten of the youth stated that they use the internet to research sexually transmitted diseases and similar issues. In addition, approximately four out of ten people participating in the study reported that the health information they obtained from the internet was "very useful", while one in seven reported that they contacted a healthcare provider after the health information they received.

The students who stated that they could understand the informed consent forms obtained from the scale significantly higher than the other groups. (Table 4).

This result obtained; It is suggested that these skills of young people can be developed in terms of seeking, accessing, understanding and interpreting information from internet resources on health-related issues.

Conclusion

In this study, which was conducted to determine the e-health literacy levels of students studying at the faculty of education and their attitudes towards internet use and the factors affecting this attitude, it was found that students' use of the Internet in the field of health was above the medium level; It was concluded that when students had problems in compliance with health-related information and medical advice or recommendations, they mostly received support from physicians, as well as they found web tools useful and important in making health-related decisions and accessing resources on health issues. Due to the increase in the use of social media and the accessibility of information and applications in the field of health through the internet, it is possible to conduct studies in wider and different groups, students who use internet tools intensively to access and use correct and reliable resources related to health on the Internet. recommended to be informed.

Limitations of the study: Since the study was conducted in a university, it is not possible to generalize the results obtained to all students.

References

1. Ergün, S., Sürücüler, H. K., & Işık, R. (2019). Ergenlerde e-Sağlık Okuryazarlığı ve Sağlıklı Yaşam Biçimi Davranışları: Balıkesir Örneği. JAREN, 5(3), 194-203. DOI: 10.5222/jaren.2019.65002
2. Bertot JC, Jaeger PT, Hansen D. The Impact Of Polices On Government Social Media Usage: Issues, Challenges, And Recommendations. Government Information Quarterly 2012; 29(1):30-40. https://doi.org/10.1016/j.giq.2011.04.004
3. Chretien KC, Kind T. Social media and clinical care ethical, professional, and social implications. Circulation 2013; 127(13):1413-1421. https://doi.org/10.1161/CIRCULATIONAHA.112.128017
4. Babacan M, Haşlak İ, Hira İ. Sosyal Medya ve Arap Baharı. Akademik İncelemeler Dergisi 2011; 6(2):63-92.
5. Aslantekin, F, Yumrutaş M. Sağlık Okuryazarlığı Ve Ölçümü. TAF Preventive Medicine Bulletin 2014;13(4):327- 334. DOI:10.5455/pmb1-1364566995
6. Çimen, Z., Bayık Temel A. Kronik Hastalığı Olan Yaşlı Bireylerde Sağlık Okuryazarlığı ve Sağlık Algısı İlişkisi. Ege Üniversitesi, Sağlık Bilimleri Enstitüsü, Halk Sağlığı Hemşireliği, Yayınlanmamış Yüksek Lisans Tezi, İzmir 2015.
7. Pourrazavi, S., Kouzekanani, K., Bazargan-Hejazi, S., Shaghaghi, A., Hashemiparast, M., Fathifar, Z., & Allahverdipour, H. (2020). Theory-based E-health literacy interventions in older adults: a systematic review. Archives of public health = Archives belges de sante publique, 78, 72. https://doi.org/10.1186/s13690-020-00455-6.
8. Norman CD, Skinner HA. eHealth literacy: essential skills for consumer health in a networked world. Journal of Medical Internet Research 2006; 8(4): e27. doi: 10.2196/jmir.8.2.e9
9. Tamer Gencer Z. Norman ve Skınner'ın E-Sağlık Okuryazarlığı Ölçeğinin Kültürel Uyarlaması İçin Geçerlilik ve Güvenilirlik Çalışması. İstanbul Üniversitesi İletişim Fakültesi Dergisi; 2017(52):131-145. https://doi.org/10.17064/iuifd.333165
10. Şengül H, Çınar F, Çapar H, Bulut A, Çakmak C. Sağlık Bilimleri Fakültesi Öğrencilerin E-Sağlık Okuryazarlığı Düzeyleri Ve İnternet Kullanımına Yönelik Tutumları: Bir Vakıf Üniversitesi Örneği. Journal of Social And Humanities Sciences Research 2017; 4(12): 1277-1287. Jshsr.com Journal of Social and Humanities Sciences Research (ISSN:2459-1149)
11. Rideout, Victoria (2001). Generation Rx.Com: How Young People Use the Internet for Health Information. A Kaiser Family Foundation Survey. California,USA.
12. Dashti S, Peyman N, Tajfard M, Esmaeeli H. E-Health literacy of medical and health sciences university students in Mashhad, Iran in 2016: a pilot study. Electronic Physician. 2017 Mar;9(3):3966-3973. DOI: 10.19082/3966.
13. Britt R, Collins W, Wilson K, Linnemeier G, Englebert A eHealth Literacy and Health Behaviors Affecting Modern College Students: A Pilot Study of Issues Identified by the American College Health Association J Med Internet Res 2017;19(12):e392 URL: https://www.jmir.org/2017/12/e392 DOI: 10.2196/jmir.3100
14. Tsukahara, S., Yamaguchi, S., Igarashi, F., Uruma, R., Ikuina, N., Iwakura, K., Koizumi, K., & Sato, Y. (2020). Association of eHealth Literacy With Lifestyle Behaviors in University Students: Questionnaire-Based Cross-Sectional Study. Journal of medical Internet research, 22(6), e18155. https://doi.org/10.2196/18155
15. Yang, S. C., Luo, Y. F., & Chiang, C. H. (2017). The Associations Among Individual Factors, eHealth Literacy, and Health-Promoting Lifestyles Among College Students. Journal of medical Internet research, 19(1), e15. https://doi.org/10.2196/jmir.5964
16. Hsu, W., Chiang, C., & Yang, S. (2014). The effect of individual factors on health behaviors among college students: the mediating effects of eHealth literacy. Journal of medical Internet research, 16(12), e287. https://doi.org/10.2196/jmir.3542.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 585-590
https://doi.org/10.31067/acusaglik.849083

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Emergency Medicine / Acil Tıp

The Relationship Between Serum Levels of Procalcitonin, Lactate, HgA1c and Functional Outcome in Acute Ischemic Stroke Patients

Zuhal Kalyon Karaman[1], **Çiğdem Özpolat**[2], **Özge Ecmel Onur**[2]
Haldun Akoğlu[2], **Arzu Denizbaşı**[2]

[1]Şanlıurfa Mehmet Akif İnan Eğitim ve Araştırma Hastanesi, Acil Tıp, Şanlıurfa, Türkiye
[2]Marmara Üniversitesi, Acil Tıp, İstanbul, Türkiye

Zuhal KALYON KARAMAN, MD
Çiğdem ÖZPOLAT, Asst. Prof.
Özge ECMEL ONUR, Prof. Dr.
Haldun AKOĞLU, Prof. Dr.
Arzu DENİZBAŞI, Prof. Dr.

Correspondence: Özge Onur
Marmara Üniversitesi, Acil Tıp, İstanbul, Türkiye
Phone: -
E-mail: ozberkozge@gmail.com

Received : 25 October 2019
Accepted : 29 February 2020

ABSTRACT

Objectives: Prognostic parameters in stroke management are important for emergency department physicians to reduce mortality and morbidity. No parameters could be determined for prognosis in acute stroke. In this study, we aimed to determine whether serum procalcitonin (PCT), lactate and HgA1c levels at admission and changes of PCT and lactate levels in 2 hours were associated with short-term functional outcome (3rd day) after acute ischemic stroke.

Materials and Methods: This was a prospective observational prognostic test study. All consecutive patients admitted to the emergency department and diagnosed as the first episode of acute ischemic stroke were included in the study. On admission and 2nd hour, PCT and lactate levels and admission HgA1c levels were collected from all subjects. Our primary aim was to correlate these values with the Modified Rankin Scale (mRS) which shows the functional outcome. Our secondary aim was determining correlation with mortality on the 3rd day and to determine their predictive value.

Results: There was no statistically significant difference between the favorable (mRS <2) and non-favorable groups in terms of PCT and lactate values and PCT and lactate clearances. There was a statistically significant difference between the two groups in terms of HgA1c value. When the threshold value analysis was performed to determine the non-favorable outcome, the threshold value was determined as 5.7.

Conclusion: Our results demonstrate that ischemic stroke patients with higher levels of HgA1c at the time of initial presentation have an increased risk for poor functional neurological outcome (high mRS) on the 3rd day. We couldn't analyze mortality due to the low patient number.

Keywords: procalcitonin, lactate, HgA1c, stroke

İskemik Serebrovasküler Olay Geçirmiş Hastalarda Hemoglobin A1c, Laktat, Prokalsitonin Seviyelerinin Fonksiyonel Sonuç ile İlişkisi

ÖZET

Amaç: İnme yönetiminde prognostik parametrelerin ortaya konması, acil servis hekimleri için mortalite ve morbiditeyi azaltmada önemlidir. Akut inmede prognoz için belirlenebilmiş herhangi bir parametre bulunamamıştır. Bu çalışmada, serum prokalsitonin(PCT), laktat ve HgA1c düzeylerinin başvuru sırasındaki ve PCT ve laktat düzeylerinin 2 saat içindeki değişikliklerinin akut iskemik inmeden sonra kısa dönem fonksiyonel sonuçla (3. gün) ilişkili olup olmadığını belirlemeyi amaçladık.

Hastalar ve Yöntem: Bu prospektif gözlemsel prognostik test çalışmasıydı. Ardışık tüm hastalar çalışmaya dahil edildi. Giriş ve 2. saatte tüm deneklerden PCT ve laktat seviyeleri ve giriş HgA1c düzeyleri toplandı. Bu değerleri 3. günde Modifiye Rankin Skalası (mRs) ve mortalite ile ilişkilendirmeyi ve prediktif değerlerini belirlemeyi amaçladık.

Bulgular: İyi (mRS <2) ve kötü sonlanımlı gruplar arasında PCT ve laktat değerlerinin kendileri ile PCT ve laktat değer değişimleri açısından istatistiksel olarak anlamlı bir fark bulunamadı. İki grup arasında geliş HgA1c değeri açısından istatistiksel olarak anlamlı bir fark vardı. Olumsuz sonucu belirlemek için eşik değer analizi yapıldığında, eşik değer 5.7 olarak belirlendi.

Sonuç: Çalışma sonuçları, ilk başvuru sırasında daha yüksek HgA1c düzeyi olan iskemik inme hastalarının 3. günde kötü fonksiyonel nörolojik sonuç risk artışı olduğunu göstermiştir.

Anahtar Kelimeler: Prokalsitonin, Laktat, HgA1c, inme

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Ischemic stroke is the third leading cause of mortality and morbidity in most countries in the world[1]. An assessment of early risk with an estimation of the severity and prognosis is necessary for ideal care and effective use of health care sources to improve outcomes (2).

Inflammatory processes have the main roles in stroke in both the etiology and the pathophysiology of cerebral ischemia (3). Procalcitonin (PCT) is known as a useful marker to discriminate infection from inflammation and has recently become popular as an early marker for sepsis. Recent research have targeted the relationship between serum levels of PCT and atherosclerotic diseases (3,4).

Lactate is traditionally seen as a marker of ischemia and a waste product of anaerobic glycolysis. In acute stroke, accumulation of lactate in ischemic regions of the brain has been documented, both in animal models and patients (5,6).

Hyperglycemia or diabetes mellitus is a known risk factor for stroke and pre-ischemic hyperglycemia and was found to aggravate the post-ischemic outcome. Most clinical studies have concluded that hyperglycemia predicts increased stroke mortality independently of age, stroke type, and severity (7,8).

In this study, we aimed to determine whether serum PCT, lactate and HgA1c levels at admission were associated with short-term functional outcome (3rd day) after acute ischemic stroke (AIS). Up to date, none of the current studies searched for this acute period. The secondary aim was to investigate the changes of PCT and lactate levels in the emergency department period (2 hours) and to evaluate the relationship between these changes and the short-term functional outcome.

Material and Method

This was a single-center, prospective observational study performed in the emergency department (ED) of a training and research hospital between June 2016 – October 2017. The study has been approved by the university ethics committee.

Patients were eligible for inclusion if they were admitted to the ED with the onset of symptoms within 24 h and diagnosed and treated as AIS defined according to the American Heart Association (AHA) (9).

Patients were excluded if they were aged < 18, pregnant, had cerebrovascular disease (CVD) history, arrested?! (had a cardiac arrest) in the ED, intracranial hemorrhage on cranial CT, systemic infections or malignancy. They were also excluded if they had thrombolysis or thrombectomy treatment. Written informed consent was obtained from the patients or their next of kin.

Patients were initially evaluated by the ED physician and then the neurology attending physician. AIS was confirmed by neurologic examination, and cranial imaging showed ischemic lesions compatible with the clinical findings.

Patient forms were recorded including their demographic information, physical examination findings and medical histories. On admission, routine blood samples including PCT, lactate and HgA1c were collected from all subjects. Blood samples were re-collected 2 hours later to check the changes of lactate and PCT levels.

In our study, the Bio-Rad kit was used as the HgA1c kit. The procalcitonin kit is the Roche brand Elecsys Brahms. Radiometer ABL 735 Blood Gas Analyzer was used for lactate levels.

Functional outcome was obtained on the 3rd day after admission according to the modified Rankin Scale (mRS). Outcome assessment was performed by using medical records or by telephone interviews on the 3rd day of admission. Functional outcome was defined as favorable if the mRS score was 0 to 2 and non-favorable if higher than 2.

The study cohort was prospectively followed up for mortality. On the 3rd day of admission, patients were checked for mortality using medical records or telephone interviews.

Statistical Analysis

Continuous variables were reported with means and standard deviations (95% confidence intervals (CI)) or medians and interquartile ranges (IQR) according to their distribution patterns. Mann–Whitney U and student t-test were used to compare independent groups. Categorical variables were reported with frequencies and percentages. Categorical variables were compared with the chi-squared test. Index test Hgb A1c levels were analyzed by a receiver operating characteristic curve (ROC) to assess their prognostic utility in estimating short-term mortality. The area under the curve (AUC, accuracy), sensitivity,

specificity, and likelihood ratios were reported with their 95% CIs. MedCalc Statistical Software version 18 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org) was used for all analyses.

STARD 2015 guidelines for reporting of diagnostic accuracy studies were used as a reference while preparing for this report (10).

Results

During the study period, 258 patients with AIS were screened. A total of 90 patients enrolled in the study (Figure 1). The median age was 72 (62-79) years. The male ratio was slightly higher (%55.6), vital signs and comorbid diseases are as seen in Table 1.

Of the patients included in the study, 18 (20%) had an mRS score of 0-2 (as a favorable outcome group) (Table 2).

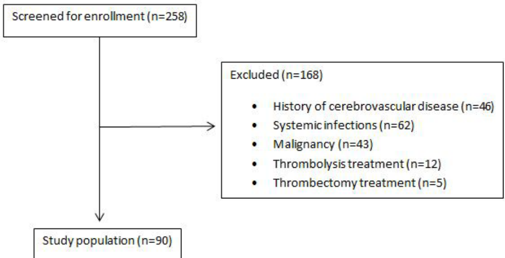


Figure 1. Study Flowchart

The median lactate level of the 90 patients included in the study was found to be 1.9 mmol / L (IQR: 1.6-2.4). The median lactate value of 18 patients in the favorable outcome group was 2.0 mmol / L, while the median lactate value of 72 patients in the non-favorable outcome group was determined as 1.9 mmol / L. There was no statistically significant difference between these groups (p: 0.8955). Median lactate level was found to be 1.76 (IQR: 1.4 / 2.4) at the second hour of the same patients. The lactate clearance of these patients was calculated as -0.2 (IQR: -0.4 / 0.2). The median lactate clearance of the patients in the group with a favorable outcome was calculated as -0.30 mmol / L. The median lactate clearance value was calculated as -0.20 in the non-favorable outcome group. There was no statistically significant difference between the two groups in terms of lactate clearance (p: 0.2221) (Table 1, Table 3).

Table 1. Demographics, vital parameters on admission, lab parameters and medical history of patients

Demographics	Total
Age (years), median (IQR)	72 (62 - 79)
Male, n (%)	50 (55.6)
Vital Signs, median (IQR)	
SBP (mmHg)	152 (130 - 175)
DBP (mmHg)	89.5 (80.0, 99.0)
HR (bpm)	88 (76 – 101)
Temperature (C)	36.5 (36.1 - 36.6)
RR (/min)	16 (14 - 18)
SaO2 (%) Oxygen saturation	96.5 (96.0 – 97.0)
Medical history, n (%)	
DM	36 (40)
HT	56 (62.2)
CAD	19 (21.1)
Lab	
Lactate admission (mmol/L), median(IQR)	1.90 (1.60- 2.40)
Lactate 2nd hour (mmol/L), median(IQR)	1.75 (1.40- 2.40)
Lactate clearance(mmol/L), median(IQR)	-0.20 (-0.40-0.20)
PCT admission (ng/ml), median(IQR)	0.05 (0.03- 0.08)
PCT 2nd hour(ng/ml), median(IQR)	0.05 (0.03-0.08)
PCT clearance(ng/ml), median(IQR)	0.00 (-0.01-0.01)
HgA1c (n:77), median(IQR)	5.80 (5.30-6.73)

IQR: interquartile range, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, RR: respiratory rate, SaO2: Oxygen saturation, DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, PCT: Procalcitonin

Table 2. mRS of groups

mRS	n (%)		n (%)
0	2 (2.2)	favorable	18 (20)
1	5 (5.6)		
2	11 (12.2)		
3	23 (25.6)	non-favorable	72 (80)
4	20 (22.2)		
5	28 (31.1)		
6	1 (1.1)		

mRS: Modified Rankin Scale

In our study, the median value of PCT was 0.05 ng / mL (IQR: 0.03 / 0.08). The median PCT value of 18 patients in the favorable outcome group was 0.04, while the median PCT value of 72 patients in the non-favorable outcome group was 0.055. There was no statistically significant difference in PCT values between the two groups (p: 0.2905). The median value of procalcitonin was found to be 0.05 ng / mL (IQR: 0.03 / 0.08) at the 2nd hour of the same patients.

The PCT clearance of these patients was 0.00 (IQR: -0.01 / 0.01). The median PCT clearance was calculated as 0.00 in patients with favorable or non-favorable outcome groups. There was no statistically significant difference between the two groups in terms of PCT clearance (p: 0.6002) (Table 1, Table 3).

Table 3. Median lactate, PCT and HgA1c values of groups

Laboratory Values	Favorable			Non-Favorable			
	n	median	Average Rank	n	median	Average Rank	P*
Lactate (mmol/L)	18	2.0	44.78	72	1.9	45.68	0.8955
PCT	18	0.04	39.72	72	0.055	46.94	0.2905
Δ Lactate (mmol/L)	18	-0.30	38.78	72	-0.20	47.18	0.2221
Δ PCT	18	0.00	42.64	72	0.00	46.22	0.6002
HgA1c (n:77)	15	5.40	27.97	62	5.90	41.67	0.0332

PCT: Procalcitonin

In our study, the HgA1c values of 77 patients were reached. The HgA1c median value of 77 patients was determined to be 5.8 (IQR: 5.3-6.7). The HgA1c value of 3 patients in the favorable outcome group could not be reached, and the median HgA1c value of 15 patients was found to be 5.4. The median HgA1c value of 62 patients in the non-favorable outcome group was determined as 5.9 and the HgA1c value of 13 patients could not be reached. There was a statistically significant difference between the two groups in terms of HgA1c value (p: 0.033) (Table 1, Table 3). Of the diabetic patients, 30 patients had HgA1c values. Four of the patients were in the non-favorable group (mean HgbA1c was 6.20) and 26 were in the favorable group (mean HgbA1c was 7.25). There was no difference in HgA1c between the groups of diabetic patients. Of the non-diabetic patients, 47 had HgbA1c values.

Eleven of them were in the non-favorable group, and the mean HgbA1c levels were 5.30; 36 were in the favorable group and the HgbA1c levels were 5.65. There was a significant difference between the groups (0.046).

The discriminative values of HgA1c levels for the prediction of non-favorable outcome were investigated with the use of ROC curve analysis. Serum HbA1c levels significantly discriminate non-favorable outcome with an AUC of 0.678 (p: 0.0206) (Figure 2).

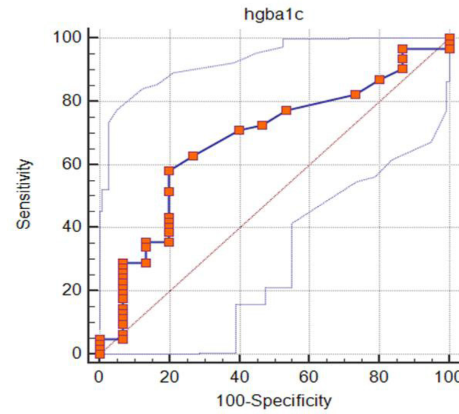


Figure 2. ROC curve of neurological outcome according to HgA1c values and mRS score

Then, when the threshold value analysis was performed to determine the non-favorable outcome, the threshold value was determined as 5.7 according to the Youden index. The sensitivity was 58.065% (44.847% -70.485%) and the specificity was 80.000% (51,911% -95.699%). The area under the threshold is 0.690 (0.575 - 0.791). The prevalence of the disease was 80.519% (69.913% - 88.667%). The positive predictive value was 92.308% (81.014% - 97.122%) and negative predictive value was 31.579% (23.862% - 40.465%) (Figure 3).

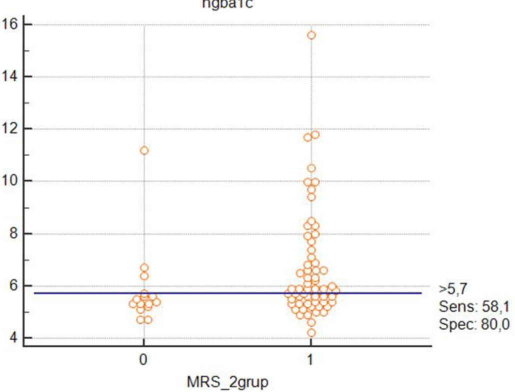


Figure 3. Threshold analysis of HgA1c level in poor outcome

Only one of our patients died in a 3 day follow-up period.

Discussion

Our results demonstrate that ischemic stroke patients with higher levels of HgA1c at the time of initial presentation to the ED have an increased risk for poor functional neurological outcome on the 3rd day. Whereas initial

serum PCT and lactate levels and also changes in the acute period do not predict short term functional outcome in patients with acute stroke.

Some studies found that PCT levels were associated with the presence and functional outcome of atherosclerotic disease (1,4). Tian et al showed that serum PCT levels were significantly elevated in case of acute ischemic stroke as compared with control cases (11). They concluded that elevated levels of PCT could be considered as a diagnostic marker for ischemic stroke. Also in 2015, a study reported that the PCT level of AIS patients at admission was an independent predictor of long-term (1 year) mortality (12). In our study, serum PCT levels at admission did not correlate with short-term neurologic outcomes. But probably 3rd day functional score was too early for consideration for PCT. Miyakis et al studied PCT and searched the prognostic value of PCT. They found that serial PCT levels did not correlate with stroke mortality or neurologic outcome at discharge (13). They found the highest median PCT level was recorded on days 2 and 3. No statistically significant differences were observed for the comparison of PCT values between individual days. Serial serum PCT levels did not correlate with stroke mortality or neurologic outcome at discharge in their study, too. A statistically significant association was observed between cases exhibiting peak PCT levels on day 7 and the presence of fever. In our study, we excluded patients who had a systemic infection. Maybe this was the reason that we could not found any correlation for serum PCT levels at admission or acute term PCT change, with short-term neurologic outcome in this study.

In hypoperfusion states, lactate may be produced and efflux by anaerobic glycolysis in affected neuronal cells (14,15). But the blood-brain barrier permeability of lactate is low and blood and CSF lactate balance slowly with the aid of monocarboxylate transporters (16). Brouns et al showed that lactate levels in CSF—but not in the blood—can be used as a reliable marker for the metabolic crisis in acute ischemic stroke and correlate with poor outcome (17). Whereas Jo et al found that initial hyperlactatemia represents an independent risk factor for the poor outcome at 3months (6). In this study, serum lactate levels at admission did not correlate with short-term neurologic outcomes. In the acute period, CSF lactate may be a better indicator of local metabolism than blood lactate.

HgA1c is an indicator of chronically elevated blood glucose levels associated with DM or insulin resistance. Sunaga et al showed that the relationship of the risk of stroke, especially ischemic stroke, to HbA1c in the general population appears to be graded without any apparent threshold (7). They concluded that the ischemic stroke risk would increase from a relatively mild HbA 1c level of ≥ 6.0%. Cloonan et al stated that this plasma metabolite marks the state of endothelial dysfunction and predicts the severity of white matter hyperintensity in patients with ischemic stroke (8). In another study, it was shown that increased HgA1c increased poor outcome and mortality in ischemic stroke (18). Mansur et al showed that hyperglycemia, acute or chronic, was associated with increased mortality and worse clinical outcomes in AIS patients treated with tPA (19). The relationship was found nonlinear, with a plateau observed at glucose levels above 200 mg/dL and HbA1C levels above 8.0% in their study. Kocaman et al showed that an HgbA1C level above 6% is correlated with recurrent ischemic stroke, too (20). Our study also indicates a relationship between HbA1c level and short-term outcome (3 rd day) in ischemic stroke patients and a level above 5.7% was found to be a risk factor for poor outcome. These findings provide evidence that chronic hyperglycemia may influence the prognosis of acute ischemic stroke patients.

There are some limitations in this study. We studied only the baseline 0 and 2nd hour measurement for PCT and lactate levels and therefore cannot clarify the variability of the PCT levels during all courses of ischemic stroke. We have a small sample size in one centre. Therefore, our results might not be generalizable.

Conclusion

Short term (3rd day) outcome is poorer in ischemic stroke patients with higher HbA1c levels on admission. We couldn't find such an association with admission and 2 nd hour PCT and lactate levels.

References

1. Wang C, Gao L, Zhang ZG, Li YQ, Yang YL et al. Procalcitonin Is a Stronger Predictor of Long-Term Functional Outcome and Mortality than High-Sensitivity C-Reactive Protein in Patients with Ischemic Stroke. Mol Neurobiol. 2016;53(3):1509-1517. doi: 10.1007/s12035-015-9112-7.
2. Tu WJ, DongX, Zhao SJ, YangDG, Chen H. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. J Neuroendocrinol 2013; 25:771–778. doi: 10.1111/jne.12052.
3. Katan M, Moon YP, Paik MC, Mueller B, Huber A et al. Procalcitonin and Midregional Proatrial Natriuretic Peptide as Markers of Ischemic Stroke: The Northern Manhattan Study. Stroke. 2016;47(7):1714-9. doi: 10.1161/STROKEAHA.115.011392

4. Zhang Y, Chen Z, Tang Y, Shan W, Wang L et al. Association between procalcitonin levels and carotid atherosclerosis in acute ischemic stroke patients. Int J Neurosci. 2018 Mar;128(3):237-242. doi: 10.1080/00207454.2017.1387114.
5. Yang DY, Tsai TH, Cheng CH, Lee CW, Chen SH et al. Simultaneous monitoring of extracellular glucose, pyruvate, lactate and glutamate in gerbil cortex during focal cerebral ischemia by dual probe microdialysis. J Chromatogr A 2001;913:349–54.
6. Jo S, Jeong T, Lee JB, Jin YH, Yoon J et al. Initial hyperlactatemia in the ED is associated with poor outcome in patients with ischemic stroke. Am J Emerg Med. 2012 Mar;30(3):449-55. doi: 10.1016/j.ajem.2011.12.019.
7. Sunaga K, Miura K, Naruse Y, Sakurai M, Morikawa Y et al. Glycated hemoglobin and risk of stroke, ischemic and hemorrhagic, in Japanese men and women. Cerebrovasc Dis. 2008;26(3):310-6. doi: 10.1159/000149579.
8. Cloonan L, Fitzpatrick KM, Kanakis AS, Furie KL, Rosand J et al. Metabolic determinants of white matter hyperintensity burden in patients with ischemic stroke. Atherosclerosis. 2015 May;240(1):149-53. doi: 10.1016/j.atherosclerosis.2015.02.052.
9. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947. doi: 10.1161/STR.0b013e318284056a.
10. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP et al. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies. BMJ. 2015;351:h5527. doi: 10.1136/bmj.h5527.
11. Tian D, Zhang S, He X, Liu H. Serum procalcitonin as a diagnostic marker in acute ischemic stroke. Neuroreport. 2015 Jan 7;26(1):33-7. doi: 10.1097/WNR.0000000000000298.
12. Li YM, Liu XY. Serum levels of procalcitonin and high sensitivity C-reactive protein are associated with long-term mortality in acute ischemic stroke. J Neurol Sci. 2015;352(1-2):68-73. doi: 10.1016/j.jns.2015.03.032.
13. Miyakis S, Georgakopoulos P, Kiagia M, Papadopoulou O, Pefanis A et al. Serial serum procalcitonin changes in the prognosis of acute stroke. Clin Chim Acta. 2004;350(1-2):237-9. doi: 10.1016/j.cccn.2004.08.002
14. Walz W, Mukerji S. Lactate production and release in cultured astrocytes. Neurosci Lett 1988;86:296-300.
15. Schurr A, Rigor BM. Brain anaerobic lactate production: a suicide note or a survival kit? Dev Neurosci 1998;20:348-57.
16. LaManna JC, Harrington JF, Vendel LM, bi-Saleh K, Lust WD et al. Regional blood-brain lactate influx. Brain Res 1993;614:164–70.
17. Brouns R, Sheorajpanday R, Wauters A, De Surgeloose D, Mariën P et al. Evaluation of lactate as a marker of metabolic stress and cause of secondary damage in acute ischemic stroke or TIA. Clin Chim Acta. 2008 Nov;397(1-2):27-31. doi: 10.1016/j.cca.2008.07.016.
18. Lei C, Wu B, Liu M, Chen Y. Association between hemoglobin A_1C levels and clinical outcome in ischemic stroke patients with or without diabetes. J Clin Neurosci. 2015 Mar;22(3):498-503. doi: 10.1016/j.jocn.2014.08.030.
19. Masrur S, Cox M, Bhatt DL, Smith EE, Ellrodt G et al. Association of Acute and Chronic Hyperglycemia With Acute Ischemic Stroke Outcomes Post-Thrombolysis: Findings From Get With The Guidelines-Stroke. J Am Heart Assoc. 2015 Sep 25;4(10):e002193. doi: 10.1161/JAHA.115.002193.
20. Kocaman G, Dürüyen H, Koçer A, Asil T. Recurrent Ischemic Stroke Characteristics and Assessment of Sufficiency of Secondary Stroke Prevention. Noro Psikiyatr Ars. 2015 Jun;52(2):139-144. doi: 10.5152/npa.2015.7499.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 591-595
https://doi.org/10.31067/acusaglik.849957

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Emergency Medicine / Acil Tıp

Retrospective Analysis of Management of Ingested Foreign Bodies in Emergency Department

Rezan Karaali[1], Ahmet Kayalı[1], Osman Sezer Çınaroğlu[1]
Zeynep Karakaya[1], Firdevs Topal[2]

[1]İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi, Acil Tıp, Karabağlar, Türkiye

[2]İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi, Gastroenteroloji, Karabağlar, Türkiye

Rezan KARAALİ, M.D.
Ahmet KAYALI, Asst. Prof. Dr.
Osman Sezer ÇINAROĞLU, M.D.
Zeynep KARAKAYA, Assoc. Prof. Dr.
Firdevs TOPAL, Prof. Dr.

Correspondence: Rezan Karaali
İzmir Katip Çelebi Üniversitesi Atatürk Eğitim ve Araştırma Hastanesi, Acil Tıp, Karabağlar, Türkiye
Phone: +905052681673
E-mail: rezantahtaci@hotmail.com

Received : 19 March 2020
Accepted : 28 April 2020

ABSTRACT

Purpose: A foreign body in the airway or gastrointestinal system is a common cause of emergency presentations in adults.

Patients and Methods: This single center, retrospective study involved patients presenting to a tertiary emergency department with foreign bodies in the airway or gastrointestinal system. Non-traumatic, non-pregnant patients aged 18 or over were scanned through the ICD-10 diagnostic code. Age and sex, reasons for ingestion/insert on (unintentional, for suicide, or for sexual gratification), the type of object, test data, treatment, complications and mortality were recorded.

Results: The mean age of the 189 patients included was 36, and 59.2% were women. Ingest on was unintentional in 86.2%, for suicide in 10.6%, and for sexual gratification in 3.2%. Unintentional ingestion was more common in women, while ingestion for self-harm was unique to men. Fish bones, pins, garlic, and teeth were most frequently encountered in unintentional ingestions. The most commonly ingested objects for self-harm were sharp items such as razor blades and nails. Flexible laryngoscopy was employed in 40.7% of cases and endoscopic interventions in 57.6%. Foreign bodies were removed with flexible laryngoscopy or endoscopy in 61.3% of cases, and surgery was performed on 6.9%. Foreign bodies were most encountered in the larynx-pharynx, esophagus, and stomach.None of the patients died. No complications were detected.

Conclusion: Foreign body ingestion is a widespread, global clinical problem. Our hospital receives many presentations involving foreign body ingestion, and the emergency and gastroenterology departments have considerable experience in this area. The endoscopic approach was the safest and most effective method due to its high success and low complication rates.

Keywords: Emergency department, foreign body, diagnose, emergency management

Yabancı Cisim Alımı ile Acil Servise Başvuran Hastaların Retrospektif Değerlendirilmesi

ÖZET

Amaç: Beslenme ya da solunum yolunda yabancı cisim olması erişkinlerde acil başvurularının sık bir nedenidir.

Hastalar ve Yöntem: Bu çalışma 3. Basamak acil servise başvuran hastalarla, tek merkezli, retrospektif olarak yapıldı.18 yaş üzeri, gebe olmayan, travması olmayan ve dosyalarında yeterli veriye ulaşılabilen hastalar çalışmaya alındı. Hastaların yaşı, cinsiyeti, alımın nedeni (yanlışlıkla, suicid amaçlı, cinsel amaçlı), cismin türü, yapılan tetkikler, uygulanan tedavi yöntemi, komplikasyon ve mortalite durumu kaydedildi.

Bulgular: Çalışmaya alınan 189 hastanın yaş ortalaması 36, hastaların % 59,2'si kadın olarak bulundu. Hastaların % 86,2'si yanlışlıkla, %10,6'sı suicidal amaçlı ve %3,2'si cinsel amaçlı almıştı. Yanlışlıkla alımlar kadınlarda fazla saptanırken, self harm amaçlı alımlara sadece erkeklerde rastlandı. Yanlışlıkla alımlarda en fazla kılçık, iğne, gıda, sarımsak ve dişe rastlandı. Self harm amaçlı alımlarda en fazla kullanılan maddeler jilet, çivi gibi keskin cisimlerdi. Olguların %40,7'sine fleksible laringoskopi, %57,6'sına endoskopik girişim yapıldı. %61,3'ünden yabancı cisim fleksible laringoskopi ve endoskopik girişim ile çıkarılırken; %6,9'una cerrahi işlem yapıldı. Yabancı cisimlerin en sık rastlandığı yerler ise larenks- farenks, özefagus ve mide olarak bulundu. Komplikasyona rastlanmadı. Hastalardan hiçbiri ölmedi.

Sonuç: Yabancı cisimlerin yutulması dünya çapında yaygın bir klinik problemdir. Hastanemize yabancı cisim yutulma şikayetiyle başvuruların çok olması nedeniyle acil servis ve gastroentereoloji klinikleri bu konuda tecrübeli ve deneyimlidir. Çalışmamızın sonucunda, yüksek başarı ve düşük komplikasyon oranı nedeniyle endoskopik yaklaşım en güvenilir ve efektif yöntem olarak değerlendirilmiştir.

Anahtar Sözcükler : Acil servis, yabancı cisim, tanı, acil yaklaşım.

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Foreign body ingestion or aspiration is frequently encountered in the pediatric age group. Unintentional ingestion may be seen in mentally disabled or substance-addicted adult patients, while numerous foreign bodies may be ingested for purposes of suicide among individuals with psychiatric disorders (1,2). Unintentionally ingested bodies frequently include pins, toothpicks, fish and chicken bones. Obstructions may also occur during consumption of normal foods or large morsels among adults with physiological narrowing or stricture resulting after surgery (3, 4). The annual reported mortality rate among adults in the USA is approximately 1500. Eighty to ninety percent of foreign bodies are expelled spontaneously from the body, while 10-20% can be removed with endoscopy, and 1% require surgery (3-6). The factors determining the emergency approach adopted are the type of body, whether it is sharp or pointed, its location, and the patient's symptoms. The complication rate is less than 1%. These may include gastrointestinal bleeding, perforation, fistula development, and intra-abdominal abscess (1, 4). It is important for the patient to be well examined and for treatment to be well managed.

The purpose of this study was to describe our emergency approach in patients presenting to the emergency department of a tertiary hospital due to foreign body ingestion, aspiration, or insertion, together with the outcomes.

MATERIAL AND METHOD

The study commenced following receipt of ethical committee approval (No. 2019GOKAE-1360 dated 21.01.2010).

Patient selection

Patients presenting to the emergency department of a tertiary hospital in Turkey between 01.10.2014 and 01.10.2019 due to foreign body ingestion or aspiration were scanned retrospectively from the hospital automation system using the ICD-10 diagnostic code. Non-pregnant and non-traumatic patients aged over 18 and with sufficient data available in their records were included.

Data collection

Patients' age and sex were recorded, together with reasons for ingestion (unintentional, for purposes of suicide, or sexual gratification), the type of object, test data, the treatment applied, complications and mortality.

Statistical analysis

Data were analyzed on IBM Statistics Version 24.00 software. For the descriptive quantitative variables, the mean, standard deviation, median, IQR, the largest and the smallest value are given. Number and percentage values are given for qualitative variables. Descriptive data were given in numbers of cases, % and median (IQR). The distribution of continuous variables was examined using the Kolmogorov Smirnov test. Mann-Whitney U statistical analysis was applied to compare continuous data between two groups. p values <0.05 were considered statistically significant.

RESULTS

One hundred eighty-nine patients with a mean age of 36 (26) years were included. Women constituted 59.2% of patients, with a mean age of 39 (27), while the mean age of the male patients was 31 (25). No statistically significant difference was determined between the sexes (Table 1).

Table 1. Cases' mean age and distributions by gender

Sex	Mean (IQR)	Minimum-Maximum	p*
Male	31 (25)	17-74	.017
Female	39 (27)	18-81	
Total	36 (26)	17-81	

*: using the t test

The nature of foreign body ingestion/insertion was also examined. Ingestion was unintentional in 86.2% (n=163) of the 189 patients and for purposes of suicide in 10.6% (n=20), while insertion for sexual gratification was observed in 3.2% (n=6). Analysis by gender revealed that ingestion for suicidal purposes was solely among men, that insertion for sexual gratification was more common among men, and that unintentional ingestion was more common among women. Ingestion for suicidal purposes was significantly higher in men, while unintentional ingestion was significantly higher among women ($p_{suicide}<0.001$ and $p_{unintentional}<0.001$). No difference was observed between the sexes in terms of insertion for sexual gratification (p>0.05).

Foreign bodies were most commonly detected in the larynx in both men and women. No significant relationship was observed between gender and foreign body location.

Intervention involved flexible laryngoscopy in 40.7% of cases (n=77) and endoscopy in 57.6% (n=109). No significant association was observed between gender and endoscopic intervention and flexible laryngoscopy. Following these procedures, the foreign body was removed with flexible laryngoscopy and endoscopic intervention in 61.3% (n=116) of cases, while surgery was required for removal in 6.9% (n=13). The incidence of foreign body removal with endoscopic intervention or flexible laryngoscopy was statistically significantly higher in males (p=0.023).

Recurrence of foreign body ingestion was observed in 12.7% of male cases and 2.5% of female cases. This was statistically significant (p=0.013).

Foreign bodies were detected using x-rays in 30.7% of cases (n=58), while cross-sectional imaging was employed in 16.9% (n=32). Foreign bodies were determined using x-ray in 36.4% (n=40) of men and in 22.8% (n=18) of women. This difference was statistically significant (p=0.046). No gender difference was observed in terms of cross-sectional imaging requirements (Table 2).

When cases were differentiated based on the radio-opacity of the foreign bodies involved, and visibility on x-ray was evaluated, 98.3% of visualized foreign bodies were radio-opaque. In addition, 37.4% (n=49) of substances that were not visible on x-ray were radio-opaque, 33.6% (n=44) were not radio-opaque, and the foreign body could not be detected in 29% (n=38) of cases.

Flexible laryngoscopy was employed for foreign body extraction in 40.7% (n=77) of cases, and the foreign body was removed in 36.4% (n=29) of cases undergoing the procedure. Endoscopic procedures were performed on 55.7% (n=109) of the 189 cases, the bodies being extracted in 81.7% of cases undergoing the procedure.

None of the patients died. No complications were detected.

Table 2. Distribution of foreign body removal methods and locations by gender

Parameter	Sub-Parameter	Sex			p
		Female n (%)	Male n (%)	Total n (%)	
Suicide status	Not for suicidal purposes	79 (100.0)	90 (81.8)	169 (59.4)	<0.001*
	For suicidal purposes	0 (0.0)	20 (18.29	20 (10.6)	
Unintentional ingestion/ aspiration	Intentional	1 (1.3)	25 (22.7)	26 (13.8)	<0.001*
	Unintentional	78 (98.7)	85 (77.3)	163 (86.2)	
Sexual gratification	Not for sexual gratification	78 (98.7)	105 (95.5)	183 (96.8)	.202**
	For sexual gratification	1 (1.3)	5 (4.5)	6 (3.2)	
Location of foreign body	Esophagus	23 (29.1)	31 (19.1)	44 (23.3)	.517**
	Larynx	31 (39.2)	40 (36.4)	71 (37.6)	
	Stomach	14 (17.7)	29 (26.4)	43 (22.8)	
	Small Bowel	6 (7.6)	9 (8.2)	15 (7.9)	
	Large Bowel	1 (1.3)	3 (2.7)	4 (2.1)	
	Rectum-Anus	2 (2.5)	6 (5.5)	8 (4.2)	
	Cecum	2 (2.5)	2 (1.8)	4 (2.1)	
Flexible laryngoscopy	Not performed	45 (57.0)	67 (60.9)	112 (59.3)	.586*
	Performed	34 (43.0)	43 (39.1)	77 (40.7)	
Endoscopic intervention	Not performed	35 (44.39	45 (40.9)	80 (42.39	.641*
	Performed	44 (55.7)	65 (59.1)	109 (57.7)	
Foreign body removal	Not extracted	38 (48.1)	35 (31.8)	73 (38.6)	.023
	Extracted	41 (51.9)	75 (68.2)	116 (61.4)	
Surgery	Not performed	73 (92.4)	103 (93.6)	176 (93.1)	.741*
	Performed	6 (7.6)	7 (6.4)	13 (6.9)	
Recurrence	No recurrence	77 (97.5)	96 (87.3)	173 (91.5)	.013*
	Recurrence occurred	2 (2.5)	14 (12.7)	16 (8.5)	
Detection with x-ray imaging	Not detected	61 (77.2)	70 (63.6)	131 (69.3)	.046*
	Detected	18 (22.8)	40 (36.4)	58 (30.7)	
Tomography and visualization status	Not visualized	66 (83.5)	91 (82.7)	157 (83.1)	.883*
	Visualized	13 (16.5)	19 (17.3)	32 (16.9)	

DISCUSSION

Foreign body ingestion or aspiration in adults frequently assumes the form of attempting to swallow large pieces of food or of normal-sized pieces becoming trapped due to physiological or pathological narrowing. Deliberate ingestion for purposes of self-harm among patients with psychiatric disorders or with secondary objectives, such as imprisoned individuals, is also seen among adult patients. Adult studies have reported a mean age of 50-53 years (7). The mean age in the present study was 31-33 years.

Although unintentional ingestion or aspiration is more common in the pediatric age group, previous studies have also reported it in the adult age group. Li et al. and Okan et al. both reported adult patients presenting due to unintentional foreign body ingestion. Food bolus impaction was most frequently determined in these studies (8, 9). Unintentional pin ingestion was also observed in Kızıltan et al.'s report concerning seven patients with indications for surgery (4). The most commonly ingested objects in Hong et al.'s study were fish bones, medications, shells, and meat (1). In the present study, unintentional ingestion most commonly involved fish bones, pins, foodstuffs garlic, and teeth. Fish bones being the most frequently ingested items are expected findings since the city where the study was performed is a coastal one and fish consumption rates are high. One reason for the greater incidence of unintentional ingestion in women than in men may be related to the use of headscarves among women in Turkey, and to pins intended for attaching headscarves being held in the mouth before use.

Although unintentional ingestion was more common among women, ingestion for purposes of self-harm was observed only among men. The objects most frequently ingested for purposes of self-harm were sharp objects such as razor blades and nails. Ingestion for self-harm generally involves the swallowing of numerous, large sharp/pointed objects. Ninety-two percent of the patients in Palta et al.'s study had swallowed objects such as toothbrushes, pens, and forks for purposes of self-harm (6). Sharp objects were found in all patients with ingestions intended for self-harm in Robertson et al.'s study (10). Due to the prevalence of ingestions for purposes of self-harm, the European Society of Gastrointestinal Endoscopy (ESGE) produced a separate heading for these patients. Since a secondary aim is usually present in recurring presentations involving ingestions of numerous sharp objects ingested for purposes of self-harm, the ESGE recommends that hospitalization of these patients be kept as short as possible by doing endoscopy quickly. Psychiatric consultations are essential, and patients without indications for hospitalization must be discharged as quickly as possible (5). Since sharp and pointed objects were detected in patients ingesting for self-harm in the present study, these all underwent esophagogastroduodenoscopy (EGD), and psychiatric consultations were requested. Our approach to these patients was consistent with the guideline recommendations.

Foreign bodies are also inserted via the anal route for sexual gratification. According to Coşkun et al., Yıldız et al., Principe et al., and the ESGE, this is more frequent in the male gender (5, 11-13). No difference was observed between male and female gender in terms of insertion for sexual gratification in the present study. This may be attributed to the low number of such patients (six patients).

In terms of the locations of foreign bodies, in the present study, these were most commonly detected in the larynx-pharynx, the esophagus, and the stomach. No significant difference was observed between men and women in terms of foreign body locations. This is because the location of the foreign body largely depends on its shape and size. Geraci et al, reported food bolus impaction involving fish and other small bones frequently in the pharynx (7). Hong et al. most frequently observed objects in the esophagus, and Li et al. in the esophagus and stomach (1, 8). Since large and sharp objects are generally employed ingestions intended for self-harm, these are frequently detected in the stomach and duodenum (6). Consistent with previous studies, objects inserted for sexual gratification were detected in the rectum (11-13).

Recommendations also exist concerning the imaging methods to be employed in cases presenting due to foreign body ingestion. According to the ESGE, the decision should depend on whether or not the object is radio-opaque. Patients can thus be protected against unnecessary radiation exposure, and other definite diagnostic methods can be applied sooner. X-ray is not recommended in case of fish or other small bones, or small metal objects (5). In the present study, X-rays were taken for every patient presenting to the emergency department. However, 46% of radio-opaque objects could not be visualized on X-ray. Advanced tests may be recommended when objects cannot be determined on X-ray due to low sensitivity. Imaging is important in terms of determining the optimal form of treatment and, as emphasized by the ESGE, the most appropriate imaging technique must be selected based

on the type of object involved and the patient's condition. Asymptomatic patients must be taken for follow-up in the presence of blunt objects not causing an obstruction. Therapeutic EGD must be performed within two hours in case of sharp objects and/or objects causing obstruction in the esophagus. In case of objects that have passed the stomach, EGD is recommended within 24-h in the presence of sharp objects, magnets, batteries, and large objects, and within 72-h in case of medium-sized blunt objects (5).

The type of treatment administered in our patient group was also selected based on the type and location of the object in the question, although the rate of EGD was higher than recommended and higher than that in other studies. Since our hospital provides a 24-h endoscopy service and receives referrals from external centers, patients undergoing EGD and being discharged from the emergency department, rather than being admitted to the emergency department or the ward, provided a significant advantage in terms of patient comfort and shortening the length of hospital stay. No patients in the present study were hospitalized apart from those with indications for surgery, and no complications developed after EGD. Our complication rate was low compared to other studies involving EGD in the approach to foreign bodies (1, 6, 7). One advantage of EGD being performed on all patients in Li et al.'s study was that new diseases involving the gastrointestinal system were detected, and the therapeutic process was also initiated for these (8). EGD is therefore a useful therapeutic technique in terms of removal of foreign bodies and also due to its ability to detect incidental diseases.

LIMITATIONS

The principal limitations of this study were its retrospective and single-center nature.

CONCLUSION

In conclusion, foreign body ingestion is a widespread and global clinical problem. Due to the large number of presentations involving foreign body ingestions received by our hospital, our emergency department and gastroenterology clinic have significant experience on this subject. Our study indicates that due to its high success and low complication rates, the endoscopic approach is the most effective and reliable method in such cases.

REFERENCES

1- Hong KH, Kim YJ, Kim JH, Chun SW, Kim HM, Cho JH Risk Factors For Complications Associated With Upper Gastrointestinal Foreign Bodies. World J Gastroenterol 2015;21(26):8125-31.

2- Choi PW, Surgical Removal of Multiple Gastric Foreign Bodies. Case Report. American Journal of Medical Case Reports 2019;7(1):1-4.

3- Nicolodi GC, Trippia CR,. Caboclo MFFS, de Castro FG, Miller WP, de Lima RR et al. Intestinal Perforation By An İngested Foreign Body. Radiol Bras 2016;49(5):295–9.

4- Kızıltan R, Yılmaz Ö, Aras A, Toktaş O, Batur A, Ağar F et al. Ingested Intraabdominal Foreign Bodies That Require Surgical Intervention. Ulus Travma Acil Cerrahi Derg 2016;22(3):269–272.

5- Birk M, Bauerfeind P, Deprez PH, Häfner M, Hartmann D, Hassan C et al. Removal Of Foreign Bodies in The Upper Gastrointestinal Tract in Adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016; 48: 489–96

6- Palta R, Sahota A, Bemarki A, Salama P, Simpson N, Laine L. Foreign-Body Ingestion: Characteristics And Outcomes in A Lower Socioeconomic Population With Predominantly Intentional Ingestion. Gastrointestinal Endoscopy 2009;69(3):1-2.

7- Geraci G , Sciume C, Di Carlo G, Picciurro A, Modica G. Retrospective Analysis Of Management Of Ingested Foreign Bodies And Food Impactions in Emergency Endoscopic Setting in Adults. BMC Emergency Medicine 2016;16:42.

8- Li ZS, Sun ZX, Zou DW, Xu GM, Wu RP, Liao Z. Endoscopic Management Of Foreign Bodies in The Upper-GI Tract: Experience With 1088 Cases in China. Gastrointestinal Endoscopy. 2006;64(4): 485-92.

9- Okan İ, Akbaş A, Küpeli M, Yeniova AÖ, Esen M, Özsoy Z. Management Of Foreign Body Ingestion And Food Impaction in Adults: A Cross-Sectional Study. Ulus Travma Acil Cerrahi Derg 2019;25(2):159-66.

10- Robertson AR. Self-harm by Sharp Foreign Body Ingestion. Suicide Life Threat Behav 2019;49(3):735-8.

11- Coskun A, Erkan N, Yakan S, Yıldirim M, Cengiz F. Management of rectal foreign bodies. World Journal of Emergency Surgery 2013; 8(11):2-5.

12- Yildiz SY, Kendirci M, Akbulut S, Ciftci A, Turgut HT, Hengirmen S. Colorectal Emergencies Associated With Penetrating Or Retained Foreign Bodies. World Journal of Emergency Surgery 2013; 8(25):2-5.

13- Principe DR, Rubin J, Narbutis M, Cabrera J ,Mitsiev I. Repeat Presentation Of Large Rectal Foreign Body Requiring Surgical Intervention. Journal of Surgical Case Reports 2019;4:1–3.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 596-603
https://doi.org/10.31067/acusaglik.850937

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Chest Diseases / Göğüs Hastalıkları

The Effect of COPD Presence, Quality of Life and Nutritional Status on Short-Term Survival in Patients with Non-Small Cell Lung Cancer

Murat Yıldız[1], Sema Avcı[2], Oral Menteş[1], Meriç Ünver[1], Deniz Çelik[1], Pınar Akın Kabalak[1], Ülkü Yılmaz[1]

[1]Ankara Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları, Ankara, Türkiye

[2]Amasya Üniversitesi, Acil Tıp, Amasya, Türkiye

Murat YILDIZ, Uzm. Dr.
Sema AVCI, Uzm. Dr.
Oral MENTEŞ, Uzm. Dr.
Meriç ÜNVER, Uzm. Dr.
Deniz ÇELİK, Uzm. Dr.
Pınar AKIN KABALAK, Uzm. Dr.
Ülkü YILMAZ, Uzm. Dr.

Correspondence: Sema Avcı
Amasya Üniversitesi, Acil Tıp, Amasya, Türkiye
Phone: +905308431363
E-mail: dr.semaavci@outlook.com

Received : 26 March 2020
Accepted : 05 September 2020

ABSTRACT

Objectives: The aim of this study is to evaluate the association of survival with nutritional status, comorbidity and life quality of patients with locally advanced and advanced non-small cell lung cancer (NSCLC) coexisting with chronic obstructive pulmonary disease (COPD).

Patients and methods: This study was performed with 64 patients (6 female, 58 male) diagnosed with locally advanced and advanced NSCLC from March to August 2015. Demographic features of the patients were evaluated with Mini Nutritional Test (MNT), Charlson Comorbidity Index (CCI), Fat Free Mass Index (FFMI), Nutritional risk screening (NRS 2002), European Organization for Research and Treatment of Cancer (EORTC), Quality of Life (QOL) Group (EORTC-QLQ-C30). The association of those scales' results with survival was analyzed.

Results: Of the patients, 34.4% (n=22) had the diagnosis of COPD. A significant relationship between the presence of COPD and survival was not detected. According to NRS 2002, 33% of the patients were under the risk of nutritional deficiency. According to MNT, 18.8% of the patients showed the presence of malnutrition. According to CCI, the patients were in low, moderate and high-risk groups respectively 57.8%, 37.5% and 4.7%. FFMI averages of the survivors and ex ones were 19.74 kg/m^2 and 18.10 kg/m^2, respectively. After 6 month-follow up, 25% of the patients died. In the univariate analyses, MNT (p=0.000), NRS 2002 (p=0.000) and FFMI (p=0.012) were associated with survival. According to the EORTC-QLQ-C30 scale, performance status, functional scale, physical, occupational, social function values and symptom scores were associated with survival.

Conclusion: In the study, when nutritional status was evaluated with FFMI and life quality scales, the result was detected to be associated with survival. On the other hand, whether or not the patient was diagnosed with COPD, histological type of cancer, stage of the disease, metastasis sites and CCI were not detected to be associated with survival.

Keywords: Non-small cell lung cancer, chronic obstructive pulmonary disease, survival

Küçük Hücre Dışı Akciğer Kanseri Olan Hastalarda KOAH Varlığı, Hayat Kalitesi ve Beslenme Durumunun Kısa Dönem Sağkalım Üzerinde Etkisi

ÖZET

Amaç: Bu çalışmanın amacı, lokal ileri ve ileri evre küçük hücre dışı akciğer kanseri (KHDAK) ve kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda beslenme durumu, komorbidite ve yaşam kalitesinin sağkalım ile ilişkisini değerlendirmektir.

Hastalar ve yöntem: Bu çalışma Mart-Ağustos 2015 tarihleri arasında KHDAK tanısı alan lokal ileri ve ileri evre olan 64 hasta (6 kadın, 58 erkek) ile yapıldı. Hastalara ait demografik özellikler, Mini Nutrisyonel Test (MNT), Charlson komorbidite indeksi (CCI), Fat Free mass indeks (FFMI), Nutritional risk screening (NRS 2002), European Organization for Research and Treatment of Cancer (EORTC), Quality of Life (QOL) Group (EORTC QLQ-C30) yaşam kalitesi ölçeği değerlendirildi. Bu ölçeklere ait sonuçların sağkalım ile ilişkisi analiz edildi.

Bulgular: Hastaların %34,4'ünde (n=22) KOAH tanısı mevcuttu. KOAH varlığı ile sağkalım arasında anlamlı ilişki saptanmadı (p>0,05). NRS 2002'ye göre hastaların %67'si nutrisyonel açıdan normal, %33'ü beslenme yetersizliği riski altındaydı. MNT'ye göre hastaların %29,7'sinde malnutrisyon riski ve %18,8'inde ise malnutrisyon mevcuttu. CCI'ye göre hastaların %57,8'i düşük, %37,5'i orta ve %4,7'si yüksek risk grubundaydı. Hastaların FFMI ortalaması 19,33 kg/m^2 idi (sağ kalanlar;19,74 kg/m^2, ex;18,10 kg/m^2). Altı aylık takip sonrasında hastaların %25'i kaybedildi. Tek değişkenli analizlerde MNT (p=0,000*), NRS 2002 (p=0,000*) ve FFMI (p=0,012) sağkalım ile ilişkiliydi. EORTC-QLQ-C30 ölçeğine göre genel sağlık durum, fonksiyonel ölçek, fiziksel fonksiyon, uğraş fonksiyonu, sosyal fonksiyon değerleri ve semptom skorları sağkalım ile ilişkili idi.

Sonuç: Çalışmamızda nutrisyonel durum FFMI ve yaşam kalitesi ölçekleri ile değerlendirildiğinde sağkalım ile ilişkili saptandı. Buna karşın hastada, KOAH tanısı olup olmaması, kanserin histolojik tipi, hastalığın evresi, metastaz bölgeleri ve komorbidite indeksi sağkalım ile ilişkili saptanmadı.

Anahtar sözcükler: Küçük hücre dışı akciğer kanseri, kronik obstrüktif akciğer hastalığı, sağkalım

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Lung cancer accounts for 18% of cancer-related deaths in women and men in the world (1). Lung cancer is the most common type of cancer in our country, the first in men and the 5th in women (2). Smoking is the most important known risk factor for this disease. Other risk factors are passive smoking, air pollution, radon gases, radiation, occupational contact, asbestos fibers, pulmonary diseases such as comorbid chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, nutrition and genetic-environment interaction (3).

79.2 % of the cases with lung cancer are non-small cell lung cases (NSCLC) (2). Despite all the modern therapy models, the control of the disease in advanced NSCLC patients is very difficult (4). Factors associated with the tumor and the individual affect the length of life more than the therapy. Classic prognostic factors in lung cancer are identified as the stage, performance status, weight loss and gender (5). Advanced stage, Eastern Cooperative Oncology Group performance-status score 3 or 4, weight loss of more than 5% and male gender were found to be associated with poor prognosis. Age is not among the classic prognostic factors (6). Whereas age is not an independent factor affecting survival, Charlson Comorbidity Index (CCI) ≥1 was found to be associated with increased mortality (7). In patients with advanced stage NSCLC, skin and liver metastasis and the presence of more than 4 metastasis are negative prognostic factors. However, brain, bone and liver metastasis were seen not to be efficient in the length of life (8, 9). Knowing the prognostic factors in this group of patients with low survival rates helps in determining the treatment option and separating the patients into subgroups (10). Lung cancer is 3-4 times more common in COPD patients than that in smokers and is an important cause of mortality in these patients (8). Increasing lung cancer risk in COPD patients has been reported to be associated with increased systemic inflammation and oxidative stress (9). Proinflammatory cytokines are thought to stimulate tumor angiogenesis and facilitate cell growth and metastasis (11). The aim of this study is to evaluate the effects of COPD, other comorbidities and sarcopenia on survival and life quality in locally advanced and advanced stage NSNLC cases.

METHODS

By taking June 2015 dated and 889 numbered approval of Kecioren Research and Training Hospital ethical committee, this study was performed with 64 patients diagnosed with NSCLC from March to August 2015 and whose treatment and follow up was done in Ankara Pulmonary Diseases and Thoracic Surgery Research and Training Hospital. Newly diagnosed locally advanced stage NSCLC were included in the study. In the study, age, gender, histopathological type and stage of lung cancer, metastasis sites, diagnosis and stage of COPD, mini-nutritional test (MNT), CCI, fat free mass index (FFMI), nutritional risk screening (NRS 2002), European Organization for Research and Treatment of Cancer (EORTC), Quality of Life (QOL) Group (EORTC-QLQ-C30) quality of life scale were evaluated. Diagnosis and staging of COPD were performed based on the GOLD 2014 guide. Survival duration was determined from the date of diagnosis to the end of the study or the time until death. Six-month survival data were obtained by detecting patients who died in the first 6 months after diagnosis. Forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were measured at baseline using a spirometer (Spirolab III-MIR, Italy).

CCI

CCI is a high reliable scale in the elderly and patients with 1-year mortality (12). Scoring is done after the evaluation of comorbid factors. The scores of patients were between 0 (with no comorbidity) and 31 (with most comorbidity). In addition, analysis patients were evaluated in four groups according to their scores, which shows 0 low risk (Charlson-0), 1-2 moderate risk (Charlson-1), 3-4 high risk (Charlson-2) and 5 and above very high risk (Charlson-3).

NRS 2002

Patients are evaluated in terms of nutritional deficiency and disease severity. NRS 2002 consists of two stages: beginning and end scan (13). In patients who give a yes answer to any question in the initial screening, the last scan is started. None (0), mild (1), moderate (2) and severe (3). Patients with a total score of ≥ 3 are considered to be at risk of nutrition. NRS 2002 Initial and Final Screening are presented in Table 1 and 2.

Table 1. NRS 2002 Initial Screening

1. Is BMI <20.5?	YES	NO
2. Has the patient lost weight the last 3 months?	YES	NO
3. Has the patient had a reduced dietary intake in the last week?	YES	NO
4. Is the patient severely ill? (e.g. in intensive therapy)	YES	NO

Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed.
No: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

Table 2. NRS 2002 Final Screening			
Impaired nutritional status		Severity of disease (≈ increase in requirements)	
0	Normal nutritional status	0	Normal nutritional requirements
1	Wt loss >5% in 3 mths or food intake below 50–75% of normal requirement in preceding wee	1	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. Chronic hemodialysis, diabetes, oncology
2	Wt loss >5% in 2 mths or BMI 18.5 – 20.5 + impaired general condition or food intake 25–60% of normal requirement in preceding week	2	Major abdominal surgery* Stroke* Severe pneumonia, hematologic malignancy
3	Wt loss >5% in 1 mth (<15% in 3 mths) or BMI <18.5 + impaired general condition or food intake 0-25% of normal requirement in preceding week in preceding week.	3	Head injury* Bone marrow transplantation* Intensive care patients (APACHE-10).
Score ≥3: the patient is nutritionally at-risk and a nutritional care plan is initiated score <3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

EORTC-QLQ-C30

EORTC-QLQ-C30 3.0 version is a 30-item survey which measures the disease-specific quality of life in cancer patients. The questionnaire administered by the patients themselves includes 30 items associated with 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain, nausea), general health scale and symptoms in cancer patients (dyspnea, loss of appetite, sleep disorders, constipation and diarrhea, etc.) (14). Each parameter has a score between 0 and 100. Whereas high scores on the functional scale indicate good health status, high scores on the symptom scale indicate the excess of symptoms. On the general health scale, a high score indicates a high quality of life.

MNT

MNT includes anthropometric evaluation (body mass index (BMI), mid-arm circumference, thigh circumference, weight loss in the last three months), general evaluation, personal assessment (a psychological or medical problem in the last three months), diet and appetite evaluation (15). Patients are evaluated out of 30. Those with a score of 12 or above for the first six questions are considered to be normal in terms of nutrition. Total score> 23.5 is considered to be normal, 17-23 malnutrition risk, <17 malnutrition.

FFMI

FFMI measurement gives information about muscle breakdown. FFMI threshold values are accepted as; <16 kg/m^2 for men and <15kg/m^2 for women (16).

Statistical Analysis

The data obtained in this study were analysed with SPSS 22.0 package program. Descriptive statistics were used for frequency and percentage distributions of variables. Mann-Whitney U test was used for two-group comparisons. Kaplan-Meier method was used in life analyses for patients. P-value <0.05 was considered to be significant.

RESULTS

Demographic characteristics of the patients included in the study are given in Table 3. 71.9% of the patients were ex-smokers, 15.6% were still smoking and 12.5% had never smoked. 51.6% of the patients evaluated with MNT were healthy in terms of nutrition, 29.7% had malnutrition risk and 18.8% had malnutrition. According to the CCI used in the evaluation of comorbidity, 57.8% of the patients were in the low risk group, 37.5% in the medium risk group, and 4.7% in the high-risk group. There were no patients in the very high-risk group. According to NRS 2002 used for malnutrition, 67% of the patients were normal and 33% were at risk. According to the 6-month survival data of the patients, 25% of the lost cases died during this period. Of the dead patients, 43.8% had COPD diagnosis. The follow-up period was short, though. There was no significant relationship between the presence of COPD and mean survival periods (p>0.05). Despite not being statistically significant, the mean survival time was lower in the patients with COPD diagnosis. When the association of age, smoking status, pathology, TNM classification and metastasis sites with 6-month survival were examined; 6.3% (n = 1) of the dead were female and 93.8% (n = 15) were male. There was no significant difference between genders in terms of mean survival time (p>0.05). Although it was not statistically significant, the mean survival time was lower in women. Histopathological distribution in the dead patients was 56.3% (n = 9) adenocarcinoma and 31.3% squamous cell carcinoma (n = 5). There was no significant difference between histopathological types in terms of mean survival time (p>0.05). 81.3% (n = 13) of the patients who died were advanced stage, 18.8% (n = 3) were local advanced stage and there was no significant difference between the groups in terms of mean survival (p>0.05). There was no significant difference between the metastasis sites in terms of mean survival (p>0.05). Although it was not statistically significant, patients with metastasis in bones and multiple regions had a lower survival time (Table 3).

Table 3. The relationship between 6 months survival and smoking status, sex, pathological diagnosis, TNM classification, area of metastasis

		Survived		Exitus		Total		p
		n	%	n	%	n	%	
Sex	Male	43	89.6	15	93.8	58	90.6	0.700
	Female	5	10.4	1	6.3	6	9.4	
	Total	48	100.0	16	100.0	64	100.0	
Smoking status	Never smoked	7	14.6	1	6.7	8	12.7	0.848
	Quit	33	68.8	12	80.0	45	71.4	
	Active smoking	8	16.7	2	13.3	10	15.9	
	Total	48	100.0	15	100.0	63	100.0	
Pathological diagnosis	Adenocarsinoma	25	52.1	9	56.3	34	53.1	0.985
	Squamous	19	39.6	5	31.3	24	37.5	
	NOS	4	8.3	1	6.3	5	7.8	
	Sarcomatoid	0	0.0	1	6.3	1	1.6	
	Total	48	100.0	16	100.0	64	100.0	
TNM classification (7th edition)	Stage 3B	11	22.9	3	18.8	14	21.9	0.729
	Stage 4	37	77.1	13	81.3	50	78.1	
	Total	48	100.0	16	100.0	64	100.0	
Areas of metastasis	Lung	8	16.7	1	6.3	9	14.1	0.818
	Bone	6	12.5	4	25.0	10	15.6	
	Multi organ	12	25.0	6	37.5	18	28.1	
	LAP	3	6.3	1	6.3	4	6.3	
	Adrenal	3	6.3	1	6.3	4	6.3	
	Liver	2	4.2	0	0.0	2	3.1	
	Pleural fluid	2	4.2	0	0.0	2	3.1	
	Other	1	2.1	0	0.0	1	1.6	
	Total	48	100.0	16	100.0	64	100.0	

The nutritional status of the patients was evaluated with NRS 2002 and MNT and its relationship with 6-month survival was evaluated. In 18.8% of the patients, MNT was <17 (malnutrition), and the mean survival time was significantly lower than those with a test score of 17-23.5 and> 23.5 (p<0.05). In the 34.4 % of the patients, NRS was 2002>=3 (nutritional deficiency), the mean survival time of these patients was significantly lower compared to those <3 (p<0.05).

Relationship of 6-month survival was evaluated with CCI by which comorbidity was evaluated. There was no significant difference between CCI and survival time (p>0.05) (Table 4).

Table 4. The relationship between 6 months survival and CCI, MNT ve NRS 2002 test results.

		Survived		Exitus		Total		p
		n	%	n	%	n	%	
MNT	<17 malnutrition	2	4.2	10	62.5	12	18.8	<0.0001
	>23.5 normal	31	64.6	2	12.5	33	51.6	
	17-23 risk of malnutrition	15	31.3	4	25.0	19	29.7	
	Total	48	100.0	16	100.0	64	100.0	
CCI	Mild	29	60.4	7	43.8	36	56.3	0.103
	Moderate	16	33.3	9	56.3	25	39.1	
	Severe	3	6.3	0	0.0	3	4.7	
	Total	48	100.0	16	100.0	64	100.0	
NRS 2002	<3	37	77.1	5	31.3	42	65.6	<0.0001
	>=3	11	22.9	11	68.8	22	34.4	
	Total	48	100.0	16	100.0	64	100.0	

The mean FFMI of the study population was 19.33 kg/m2 (survivors; 19.74 kg/m2, ex ones; 18.10 kg/m2). FFMI values were significantly lower in dead patients (p<0.05).

According to EORTC-QLQ-C30, general health status values, functional scale scores, physical function values, occupational function values, social function values were significantly lower in ex-patients (p<0.05). Symptom scores, fatigue values, pain, shortness of breath and insomnia scores, loss of appetite scores were significantly higher in ex-patients (p<0.05) (Table 5, Table 6 and Table 7, respectively).

DISCUSSION

The association between lung cancer and COPD has been suggested in several epidemiological, pharmacological and observational studies. For the first time, Skillrud et al. have suggested an independent relationship between COPD and lung cancer (17). The relationship between COPD and lung cancer can provide significant improvement in the prevention and clinical treatment of both diseases. Based on this idea, we aimed in our study to determine the relationship between the combined assessment results of the patient's groups newly diagnosed with NSCLC local advanced and advanced stage with or without COPD diagnosis and survival. 25% of our patients died within 6 months of the diagnosis. According to the literature, while the 5-year survival rate is 15% in all lung cancer patients, the 5-year survival rate in stage 3B in NSCLC is 5-20%, the median duration varies between 9-20 months.

Table 5. The relationship between 6 months survival and FFMI, EORTC-QLQ-C30 (General health status and functional score)										
		Result						Mann-Whitney U testi		
		n	Mean	Median	Min	Max	SS	Mean rank	U	p
FFMI	Survived	48	19.74	19.87	15.80	26.20	2.49	35.86	222.5	0.012
	Exitus	16	18.10	17.69	14.87	24.12	2.14	22.41		
	Total	64	19.33	19.29	14.87	26.20	2.50			
Global health status / Quality of life	Survived	48	66	67	0	100	24	37.75	132	<0.0001
	Exitus	16	35	37	0	67	22	16.75		
	Total	64	58	50	0	100	27			
Functional scales	Survived	48	82	87	36	100	16	36.93	171.5	0.001*
	Exitus	16	58	52	23	98	25	19.22		
	Total	64	76	84	23	100	21			
Physical functioning (PF)	Survived	48	72	80	0	100	28	36.92	172	0.001
	Exitus	16	38	37	0	100	34	19.25		
	Total	64	64	74	0	100	33			
Role functioning	Survived	48	82	100	0	100	28	36.56	189	0.001*
Emotional functioning	Survived	48	82	84	17	100	20	33.41	340.5	0.488
	Exitus	16	76	84	34	100	25	29.78		
	Total	64	81	84	17	100	21			
Cognitive functioning	Survived	48	89	100	34	100	17	33.71	326	0.314
	Exitus	16	87	84	50	100	15	28.88		
	Total	64	89	100	34	100	16			
Social functioning	Survived	48	88	100	0	100	23	35.75	228	0.006*

Tablo 6. The relationship between 6 months survival and EORTC-QLQ-C30 (Symptom scales /items)										
		Result						Mann-Whitney U testi		
		n	Mean	Median	Min	Max	SS	Mean rank	U	p
Symptom scales / items	Survived	48	21.10	15.38	0.00	71.79	17.26	28.05	170.5	0.001*
	Exitus	16	39.42	41.02	0.00	64.10	17.39	45.84		
	Total	64	25.68	21.79	0.00	71.79	18.93			
Fatigue	Survived	48	33.45	33.33	0.00	77.77	24.71	28.15	175	0.001*
	Exitus	16	60.41	66.66	0.00	100.00	27.21	45.56		
	Total	64	40.19	33.33	0.00	100.00	27.75			
Nausea and vomiting	Survived	48	10	0	0	67	18	31.14	318.5	0.241
	Exitus	16	22	0	0	100	30	36.59		
	Total	64	13	0	0	100	22			
Pain	Survived	48	21	17	0	100	24	29.16	223.5	0.011*
	Exitus	16	43	33	0	100	30	42.53		
	Total	64	27	17	0	100	27			
Dyspnea	Survived	48	33	33	0	100	34	29.75	252	0.033*
	Exitus	16	54	67	0	100	32	40.75		
	Total	64	39	33	0	100	34			
Insomnia	Survived	48	22	0	0	100	31	29.22	226.5	0.008*
	Exitus	16	42	33	0	67	26	42.34		
	Total	64	27	17	0	100	31			

Tablo 7. The relationship between 6 months survival and EORTC-QLQ-C30 (Symptom scales/items)

		Result						Mann-Whitney U testi		
		n	Mean	Median	Min	Max	SS	Mean rank	U	p
Loss of appetite	Survived	48	20	0	0	100	29	28.33	184	0.001*
	Exitus	16	56	50	0	100	40	45.00		
	Total	64	29	17	0	100	35			
Constipation	Survived	48	15	0	0	100	24	31.71	346	0.492
	Exitus	16	23	0	0	100	34	34.88		
	Total	64	17	0	0	100	27			
Diarrhea	Survived	48	6	0	0	67	15	31.88	354	0.492
	Exitus	16	8	0	0	33	15	34.38		
	Total	64	7	0	0	67	15			
Financial difficulties	Survived	48	15.97	0.00	0.00	100.00	26.62	33.33	344	0.441
	Exitus	16	14.58	0.00	0.00	100.00	32.13	30.00		
	Total	64	15.62	0.00	0.00	100.00	27.84			

While the 1-year survival rate in stage IV NSCLC is 30-35%, the median survival time is 8-10 months. Most cases with lung cancer are detected in advanced (stage IV) or locally advanced stage (stage IIIA and IIIB) (18). In the study of the Thoracic Society Pulmonary and Pleural Malignancies Working Group, 83.6% of the patients were seen to be diagnosed with local advanced and advanced stages (19). When the patients were diagnosed in our study, 78.1% of them were stage 4, 21.6% were stage 3B. 56.3% of the patients were adenocarcinoma and 31.3% were squamous cell carcinoma. There was no significant difference in terms of mean survival time. 81.3% of the patients who died were stage 4 and 18.8% were stage 3B. There was no significant difference between the stages in terms of survival time. The low number of patients included in the study and the short follow-up period of the patients may have caused not being able to identify any difference in terms of survival between the stages and histopathological types. In the study, 36% of stage 4 NSCLC patients had multiple metastases and bone metastasis was detected to be the most common one. There was no significant relationship between metastasis sites and mean survival time. Although it was not significant, the mean survival time was lower in patients with bone and multiple metastases. In a study by Luketich et al., skin and liver metastasis and the presence of more than four metastasis were negative prognostic factors in advanced NSCLC patients [20]. Schuchert et al. showed that brain, bone and liver metastasis had no effect on survival time [21]. Çalıkuşu et al. identified that there was not a significant difference between survival time and the number and the sites of metastasis in NSCLC diagnosed patients (22). This discrepancy in the literature may be due to insufficiency in the distribution of patient groups. In the study, 34.4% of the patients had a diagnosis of COPD. In a similar study by Çilli et al., this rate was 23.5% (23). Janssen-Heijnen et al. reported the prevalence of COPD as 22% in their large series of 3864 lung cancer studies (24). In another study by Kurishima et al., they identified the prevalence value as 76% without gender discrimination (25). Differences in the study results may be caused from the differences in smoking rates, differences in exposure to environmental toxins, genetic susceptibility and methodology for the definition of COPD. In our study, 43.8% of the ex-patients had a diagnosis of COPD. There was no significant difference between being diagnosed with COPD or not in terms of survival time. Although it is not significant, mean survival was lower in patients with COPD. Malnutrition is a common problem in advanced patients and it accounts for a risk factor for morbidity and mortality. In a study by Priegnitz et al., it was reported that in 705 patients who were admitted to the respiratory care clinic, 14.3% had nutritional risk and 2.5% had malnutrition according to NRS 2002 (26). In a study of 401 oncologic patients by Planas et al., 33.9% of patients had a risk of malnutrition (NRS 2002 score>3) (27). In our study, 67% of the patients whose nutritional status was evaluated with NRS 2002 were found to be normal and 33% were at risk for malnutrition in accordance with this literature. Mean survival time was significantly lower in patients with NRS 2002> = 3 (34.4%) than those with <3. When patients were evaluated according to FFMI, these values were significantly lower in ex-patients. In recent years, FFMI provides more accurate results in the assessment of muscle destruction

for that reason it is more preferred than BMI. In the literature, NRS 2002 is mostly used to evaluate preoperative nutritional deficiencies in hospitalized patients. In our study, we used the nutritional status of the patients with NRS 2002 without any distinction between outpatients and inpatients. NRS 2002 may be a valuable indicator of prognosis in patients at risk of malnutrition. In the study, of the patients whose nutritional status were evaluated with MNT, 29.7% were detected to be under risk of malnutrition, 18.8% were detected to have malnutrition. In the study of Gioulbasanis et al. on 115 lung cancer patients, it was reported that according to MNT, 51.3% of the patients were under the risk of malnutrition and 25.2% had the diagnosis of malnutrition. Survival, age, number of metastasis were associated with MNT score and leptin among the patients (28). In the study of Gioulbasanis et al. on 171 patients with metastatic lung cancer, the MNT score was important in determining prognosis (29). Being compatible with the literature in our study, mean survival time was significantly lower in those with <17 MNT score (malnutrition) than 17-23.5 (malnutrition risk) and>23.5 (normal). However, the number of patients was not sufficient in order to make a multivariable analysis. In cancer patients, the risks and the benefits of the patients should be measured and how much comorbid diseases may affect survival time and tolerability of treatment should be evaluated (30). It was supported by a study that the presence of comorbid conditions may also affect the patient's tolerance to cancer treatment. In patients over 70 years with advanced stage NSCLC, the ones with CCI ≥2 were detected to quit chemotherapy at an early period at higher rates (31). In the study performed by Canadian International Cancer Institution on 1255 NSCLC patients, the rate of patients with CCI≥1 was 42% in patients over 65 years old and it was 26% in the young group. Also, it was detected that age only itself was not an effective independent factor in survival and comorbidity and CCI score 1 and above had an association with increased mortality (7). Birim et al. displayed that survival time decreased as CCI increased in 205 NSCLC patient group (32). When the 6-month short-term survival of the patients was examined in our study, there was no relationship between CCI and mean survival time.

There are many quality of life scales evaluating the health-related quality of life in NSCLC patients. Some of them are EORTC-QLQ-C30 and EORTC-QLQ-LC13 peculiar to lung cancer module, lung cancer symptom scale and Functional Assessment of Cancer Therapy-Lung Cancer Quality of Life Instrument. For being more reliable and comprehensive, EORTC-QLQ-C30 is the most commonly used questionnaire in the routine (33). Braun et al. detected that categories of general health and physical function in the EORTC-QLQ-C30 quality of life questionnaire were important prognostic factors for NSCLC patients. They emphasized that physical function, nausea, vomiting, insomnia, and diarrhea categories were important for survival in newly diagnosed patients whereas only physical function was important in previously treated patients (34).

In a study performed on 225 lung cancer patients whose data were obtained from multicentered hospitals, it was detected that change of general well-being in EORTC-QLQ-C30 scale through the time determined survival at a significant level and death risk was decreased as general well-being increased. The risk of death was seen to be decreased as physical, occupational, emotional and cognitive functions improved. It was detected that fatigue, nausea and vomiting, pain, shortness of breath, insomnia, loss of appetite, constipation, changes in financial difficulties over time affected survival significantly. The effect of change of symptoms in the scale was seen to have a similar effect on survival (35). In our study, general health status, functional scale, physical function, occupational function, social function scores were significantly lower in ex-patients. Symptoms, fatigue, pain, shortness of breath and insomnia, loss of appetite scores were significantly higher in ex-patients. There was no significant difference between the groups in terms of other values. As a result, in our study in univariate analysis, it was detected that there was a relationship between nutritional status, FFMI, quality of life and survival.

However, a significant relationship was not detected between the presence or absence of COPD, histological type of cancer, stage of the disease (stage 3B-4), metastasis sites, comorbidity score and short-term survival. Multivariate analysis of survival effects could not be performed due to the insufficient number of patients.

Our study supports that only age, stage and performance status are not determinants of survival in NSCLC patients. Especially comorbid diseases such as COPD and nutritional status have an effect on survival. Prospective studies with longer follow-up periods are needed to evaluate the effects of comorbidities and nutritional status on short and long-term survival and quality of life in patients with lung cancer.

Conflict of interest

The authors state that they have no conflicts of interest in this study.

Funding

There was no funding received for this study.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69-90.
2. Republic of Turkey. Ministry of Health. Turkey Public Health Institution Turkey Cancer Statistics Report. 2017.
3. Metintaş S. Akciğer Kanseri Epidemiyolojisi. In: Özlü T, Metintaş M, Karadağ M, Kaya A, eds. Solunum Sistemi ve Hastalıkları 1. Baskı. İstanbul Medikal Yayıncılık; 2010:1347-429.
4. Fu XL, Zhu XZ, Shi DR, Xiu ZL, Wang LJ, Zhao S, et al. Study of prognostic predictors for non small cell lung cancer. Lung Cancer 1999; 23:143-52.
5. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. J Clin Oncol 2007; 25:1824–31.
6. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. J Natl Cancer Inst 1980; 65:25–32.
7. Asmis TR, Ding K, Seymour L, Shepherd FA, Leighl NB, Winton TL, et al. Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol 2008; 26: 54-9.
8. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidites. Eur Respir J 2006; 28: 1245-57.
9. Zhang H. Moleculer signaling and genetic pathways of senescence: its role tumorigenesis and aging. J Cell Physiol 2007; 210: 567-74.
10. Wagner H. Rational integration of radiation and chemotheraphy in patients with unresectable stage IIIA or IIIB NSCLC. Result from Lung Cancer Study Group, Eastern Cooperative Oncology Group, and Radiation Theraphy Oncology Group. Chest 1993; 103:35-42.
11. Malhotra D, Thimmulappa R, Navas-Acien A, Sandford A, Elliott M, Singh A, et al. Decline in NRF2-regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1. Am J Respir Crit Care Med 2008; 178: 592-604.
12. Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998; 16:1582-7.
13. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003; 22: 415-21.
14. Cankurtaran ES, Ozalp E, Soygur H, Ozer S, Akbıyık DI, Bottomley A. Understanding the reliability and validity of the EORTC QLQ-C30 in Turkish cancer patients. Eur J Cancer Care 2008;17: 98-104.
15. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The mini nutritional assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999; 15:116-22.
16. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr 2005; 82: 53-9.
17. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med 1986; 105:503-7.
18. Spiro SG, Porter JC. Lung cancer-Where are we today? Current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med 2002; 166:1166-96.
19. Goksel T, Akkoclu A; Turkish Thoracic Society, Lung and Pleural Malignancies Study Group. Pattern of lung cancer in Turkey 1994-1998. Respiration 2002; 69:207-10.
20. Luketich JD, Burt ME. Does resection of adrenal metastases from non-small cell lung cancer improve survival? Ann Thorac Surg 1996; 62:1614-6.
21. Schuchert MJ, Luketich JD. Solitary sites of metastatic disease in n on-small cell lung cancer. Curr Treat Options Oncol 2003; 4:65-79.
22. Çalıkuşu Z, Sakallı H, Yılmaz B, Mertsoylu H, Akçalı Z, Özyılkan Ö. Evre I V küçük hücreli dışı akciğer kanserli olgularda prognostik faktörlerin incelenmesi. Acıbadem Üniversitesi Sağlık Bilimleri Derg 2011;2(2):88-91.
23. Çilli A, Özdemir T, Özbulak Ö, Yakışan A, Öğüş C. Akciğer kanserli hastalarda KOAH birlikteliği. Solunum 2003; 5: 20-4.
24. Janssen-Heijnen ML, Schipper RM, Razenberg PP, Crommelin MA, Coebergh JW. Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer 1998; 21:105-13.
25. Kurishima K, Satoh H, Ishikawa H, Yamashita YT, Homma T, Ohtsuka M, et al. Lung cancer patients with chronic obstructive pulmonary disease. Oncol Rep 2001; 8:63-5.
26. Priegnitz C, Galetke W, Treml M, Randerath WJ. Nutritional risk screening 2002 in clinical pneumology. Pneumologie 2014;68(7):478-82.
27. Planas M, Álvarez-Hernández J, León-Sanz M, Celaya-Pérez S, Araujo K, García de Lorenzo A; PREDyCES® researchers. Prevalence of hospital malnutrition in cancer patients: a sub-analysis of the PREDyCES® study. Support Care Cancer 2015;27: 1049-59.
28. Gioulbasanis I, Georgoulias P, Vlachostergios PJ, Baracos V. Mini Nutritional Assessment (MNA) and biochemical markers of cachexia in metastatic lung cancer patients: Interrelations and associations with prognosis. Lung Cancer 2011; 74:516-20.
29. Gioulbasanis I, Baracos VE, Giannousi Z, Xyrafas A, Martin L, Georgoulias V, et al. Baseline nutritional evaluation in metastatic lung cancer patients: Mini Nutritional Assessment versus weight loss history. Ann Oncol 2011;22(4):835-41.
30. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of comppeting risks. Ann Intern Med 1996; 124(6):577-84.
31. Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small cell lung cancer. J Clin Oncol 2000; 18:2529-36.
32. Birim O, Maat AP, Kappetein AP, van Meerbeek JP, Damhuis RA, Bogers AJ. Validation of the Charlson comorbidity index in patients with operated primary non-small cell lung cancer. Eur J Cardio Thorac Surg 2003; 23:30-4.
33. Bozcuk H, Dalmis B, Samur M, Ozdogan M, Artac M, Savas B. Quality of life in patients with advanced non-small cell lung cancer. Cancer Nurs 2006; 29:104-10.
34. Braun DP, Gupta D, Staren ED. Quality of life assessment as a predictor of survival in non-small cell lung cancer. BMC Cancer 2011; 11:353.
35. Öz A. Akciğer kanserli hastalarda izlem sürecindeki değişikliklerin yaşam kalitesine etkisinin EORTC-C 30 yaşam kalitesi ölçeği ve izlem sonuçlarıyla değerlendirilmesi. Thesis. 2012.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 604-609
https://doi.org/10.31067/acusaglik.884013

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Dermatology / Dermatoloji

Investigation of Patient Awareness and Attitude in Dermatology

Melek Aslan Kayıran[1] **, İlknur Özcan[1]** **, Mehmet Salih Gürel[1]**

[1]Istanbul Medeniyet University, School of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Departments of Dermatology and Venereology, Istanbul, Turkey

Melek ASLAN KAYIRAN, MD

İlknur ÖZCAN, MD

Mehmet Salih GÜREL, MD, Prof.

Correspondence: Melek Aslan Kayıran
İstanbul Medeniyet University , School of Medicine, Prof Dr Süleyman Yalçın City Hospital, Departments of Dermatology and Venereology, Istanbul, Turkey
Phone: +902165664000
E-mail: melekaslan@gmail.com

Received : 20 February 2021
Accepted : 01 May 2021

ABSTRACT

Purpose: It is known that patients seek to obtain medical information about diseases from the internet before coming to a doctor. Patients' knowledge of dermatological diseases or thoughts on complementary and alternative treatment (CAT) have not been investigated. It was aimed to investigate the concept of health literacy, such as the level and source of knowledge and prejudices in our country.

Methods: Nine multiple choice questions related to conditions that can cause skin diseases, reasons for applying to dermatology, which dermatological diseases they know, the department they apply for sexually transmitted diseases, diseases that can be transmitted by contact, whether they have done CAT, whether they do research the skin diseases on internet, and true-false questions regarding 14 different dermatology myths were asked.

Results: The vast majority of patients thought that the cause of skin diseases was stress. Fungal and parasitic diseases were mostly marked in response to contagious diseases. They often referred to urology and gynecology departments for sexually transmitted diseases. While 29% of the patients had CAT, 63.7% had researched their diseases on internet before consulting a doctor. The vast majority thought that they could sunbathe after applying sunscreen.

Conclusion: The patients had a lack of knowledge about contagious diseases and sunscreen use. It was not the first choice to apply to the dermatology in sexually transmitted diseases. While searching information about their disease on internet is very common, the vast majority of patients relied on the doctor's advice.

Keywords: attitude, dermatology, internet, knowledge, patients

Dermatolojide Hasta Farkındalığının ve Tutumunun İncelenmesi

ÖZET

Amaç: Hastalar hekime gelmeden önce hastalıkları konusunda internetten araştırıp tıbbi bilgiler edinmeye çalıştıkları bilinmektedir. Ancak hastaların dermatolojik hastalıklarla ilgili bilgileri veya alternatif ve tamamlayıcı tıp (ATT) hakkındaki düşünceleri araştırılmamıştır. Ülkemizde bu konudaki bilgi düzeyi, bilginin kaynağı ve önyargılar gibi sağlık okuryazarlığı kavramının araştırılması amaçlandı.

Metod: Hastaların cilt hastalıklarına neden olabilecek durumlar, hastaneye başvurma nedenleri, hangi dermatolojik hastalıkları bildikleri, cinsel ilişki ile bulaşan hastalıklarda başvurdukları bölüm, temasla bulaşabilen hastalıklar, ATT yaptırıp yaptırmadıkları, cilt hastalıkları ile ilgili internetten araştırma yapıp yapmadıkları ile ilgili dokuz adet çoktan seçmeli ve 14 farklı dermatoloji miti ile ilgili doğru yanlış sorusu anket olarak soruldu.

Bulgular: Hastaların en büyük çoğunluğu deri hastalıklarının nedeninin stres kaynaklı olduğunu düşünmekteydi. Temasla bulaşan hastalıklara cevap olarak daha çok mantar ve paraziter hastalıklar işaretlenmişti. Cinsel yolla bulaşan hastalıklar için sıklıkla üroloji ve kadın doğum bölümlerine başvuruyorlardı. Hastaların %29'u ATT yaptırmışken, %63,7'si doktora başvurmadan önce hastalığını internetten araştırmıştı. Büyük çoğunluğu güneş koruyucu sürerek güneşlenebileceğini düşünüyordu.

Sonuç: Hastaların temasla bulaşabilecek hastalıklar ve güneş koruyucu ile bronzlaşma konusunda bilgi eksikliği vardı. Cinsel yolla bulaşan hastalıklarda dermatoloji polikliniğine başvurmak ilk tercih değildi. İnternetten hastalıkları hakkında bilgi araştırmak çok yaygınken hastaların büyük çoğunluğu doktorunun önerilerine ve bilgisine internetten çok daha fazla güveniyordu.

Anahtar Kelimeler: Bilgi, dermatoloji, hastalar, internet, tutum

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Patients who apply to dermatology outpatient clinics with different causes and symptoms every day request information from their physicians about their diseases or try to have information on their own. However, we do not have much knowledge on how patients behave at a cognitive level about skin health and diseases and from which sources they seek information. Today, social media or media organs are widely used for all kinds of information, including health (1). Patients use not only conventional therapy but also complementary and alternative treatment (CAT) methods (2). Patients may often hurt themselves with incomplete or incorrect information about diseases, causes, treatments, or preventive methods, or lose time for proper treatment.

We conducted a survey study about how much information patients have about skin conditions, how they know their diseases and own diagnosis, what they are aware of, what they have done for these complaints before, whether they have used CAT method, whether they have researched their diseases on internet and social media and what they think about dermatological myths.

Materials and Methods

Before starting the study, the necessary study approval was obtained from the ethics committee of the University (2019/64). Patient consent was obtained from the patients who participated in the study.

Survey questions were created by the researchers who participated in the study by reviewing and discussing the literature related to the subject. The questions were summarized in Table 1. The questionnaire was answered by individuals who attended to the dermatology outpatient clinic in between March-August 2019.

Statistical Analysis

SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) was used for the statistical analysis. Statistical significance of the difference between common questions was determined with chi-square test, and the effect of different groups on answering the question was analyzed with Cramér's V test. p values below 0.05 were recognized as statistically significant.

Results

A total of 179 literate people were included in the study. The demographic characteristics of the patients are summarized in Table 2.

Table 1. The main topics of the survey questions
Do you think dermatology and the skin diseases clinic are the same departments?
For your point of view, what are the causes of the dermatological diseases?
Which dermatological diseases do you know?
Why did you apply to dermatology outpatient clinic?
Do you know the name of your own disease, if so please write.
Did you apply to a family physician or a dermatologist for the same reason that you came our clinic? If so, which one?
Which departments do you apply for sexually transmitted diseases?
Which contagious skin diseases do you know?
Did you had CAT for your dermatologic diseases, if so which ones.
Did you research on dermatological diseases on internet? If so, did you share it with your doctor?
Questions: True or False
Most of the skin diseases are caused by liver disfunction.
Allergy tests should be done for all pruritus/egzema cases.
I may have a sunbathe after I apply sunscreen.
Having tan is good for skin and body health.
Having sunbathe under a tree or umbrella gives no harm.
Herbal products/creams are harmless than the drugs.
Herbal products don't give any harm to our body.
I use the creams which were prescribed to family members before I go to doctor.
I don't like using topical therapy like creams and lotions.
Topical therapies are not effective for diseases.
I don't want to use systemic therapy for skin diseases, they may be harmful for my health.
Some systemic treatments for acne may cause infertility.
Onychomycosis cannot be improved unless the nail excised.
CAT, Complementary and alternative treatment

For the question "Are dermatology and skin diseases clinic the same department?", 13.4% of the patients said that they were different departments and 7.8% did not know, while 5% did not answer the question. Primary education graduates (PEG) thought the two departments were different when compared with higher education graduates (HEG) (16%, 8.3%, respectively, p=0.018,).

The answered conditions that may cause dermatological diseases were summarized in Table 3. Stress (79%), sunlight (74%), chemicals (62%) and microbes (58%) were the most marked answers. Only 7% of the patients thought that pregnancy and breastfeeding could cause dermatological diseases.

Table 2. Distribution of patients' age, gender, educational status, and the number of applications to the outpatient clinic						
	Female	Male	PEG	HEG	≤40	>40
Number-Percent	107-%59.8	72-%40.2	119-%66.5	60-%33.5	109	70
Average Age	35.66 ±14.54	42.50 ±18.98	41.01 ±17.17	33.27 ±13.16	-	-
Minimum (Min) and Maximum (Max) age	16-85	16-79	16-85	19-75	-	-
Number of applications to the outpatient clinic (Min-Max)	1-60	1-100	1-100	1-14	1-60	1-100
Average number of applications	5.14± 13.292	6.63± 9.174	6.94± 13.158	3.35± 3.236	3.75± 6.521	8.83 ±15.166

Primary Education Graduate (PEG) represents high school and below. Higher Education Graduate (HEG) university college and above, ≤40 represents under or equal 40 years of age group, >40 represents over 40 years of age group.

Mycosis (84%), verruca (82%), and eczema (82%) were most commonly known cutaneous diseases. HEG knew hives (70%, 56.3% respectively, p=0.076) and verruca (86.7%, 63.9% respectively, p=0.051) more than PEG. Over 40 years of age group (>40), compared to under or equal 40 years of age group (≤40) knew statistically significantly more about hives (72.9%, 53.2%, respectively, p=0.009), leprosy (54.3%, 30.3%, respectively, p=0.001) and syphilis (50%, 29.4%, respectively, p=0.005), and women knew acne more than men (73.8%, 51.4%, respectively, p=0.000).

Women thought that infestation of lice (women 66%, men 34%, p=0.040) , and herpes, (78%, 22%, p=0.014, respectively) and men thought that callus (men 86%, women 14%, p=0.012) would transmit significantly. Fungal disease (58.1%), and infestation with lice (59.2%) were thought to be contagious in general population. Scabies (43%), warts (20.7%), herpes (20.1%), and bacterial skin infections (23.5%) were answered as not contagious. 29.1% of the patients thought that HIV infection would transmit by touch.

32% of the patients knew their skin disease correctly and the majority were women (64%). 73% of the patients applied to another physician for the same complaint. 88% of them went to the dermatologist, the rest to the family doctor and other specialists.

Obstetrics (39.1%), urology (28.5%), infectious diseases department (25.7%) and dermatology (15.6%) were the departments that patients prefer to apply when having sexually transmitted diseases.

29% of the patients had CAT for their dermatologic diseases. Cupping (9.5%), leech (3.4%), acupuncture (2.8%), ozone therapy (1.1%) were performed, nobody had hypnotherapy. Women preferred cupping (10.3%), leech (3.7%) and acupuncture (3.7%) while males preferred cupping (8.4%) and leech (2.8%).

Table 3. Patients' thoughts about conditions that can cause dermatological diseases									
Reasons	Male %	Female %	P value	PEG %	HEG %	P value	≤40 %	>40 %	P value
stress	37	63	0.213	64	36	0.018	64	36	0.222
liver disease	34	66	0.005	58	42	0.213	60	40	0.907
food	30	70	0.006	60	40	0.005	68	32	0.007
sunlight	35	65	0.212	64	36	0.006	59	41	0.239
air pollution	40	60	0.009	56	44	0.212	66	34	0.405
microbes	37	63	0.001	56	44	0.009	69	31	0.027
drugs	30	70	0.053	59	41	0.001	67	33	0.145
chemicals	39	61	0.161	62	38	0.053	61	39	0.864
genetics	38	62	0.000	50	50	0.161	70	30	0.027
visceral diseases	44	56	0.022	56	44	0.000	62	38	0.908
hormones	31	69	0.003	56	44	0.022	67	33	0.112
old age	42	58	0.213	58	42	0.003	60	40	0.805
smoking	40	60	0.112	62	38	0.213	66	34	0.144
alcohol	40	60	0.095	60	40	0.112	68	33	0.105
insomnia	27	73	0.056	56	44	0.095	73	27	0.047
dirty ware	35	65	0.055	60	40	0.056	69	31	0.078
contact with people	32	68	0.537	63	37	0.055	61	39	0.960
pregnancy lactation	15	84	0.001	23	77	0.537	77	23	0.242
contact with animals	45	55	0.126	74	26	0.001	55	45	0.384
I don't know	67	33	0.372	83	17	0.126	100	0	0.053
other	0	100	0.636	50	50	0.372	50	50	0.729

When considering in terms of gender, liver diseases, food, air pollution, microbes, genetic factors, visceral diseases, hormones and pregnancy-lactation were statistically significant in favor of women. When considering in terms of educational status, stress, food, sun, germs, drugs, visceral diseases, hormones, old age and animal contact options were statistically significant in favor of PEG. Considering by the age groups, food, microbes, genetics, insomnia were statistically significantly higher at ≤40.

64% of the patients had searched their diseases on the internet. All of the patients who researched did it through Google. 13% stated that they also used Facebook and Instagram. Internet use rate was significantly higher in ≤40 group (70%) than >40 group (53%) ($p = 0.016$). 34% of the patients did not ask the physicians about the information they found on the internet.

78% said they would trust their physicians, but 9% would consult another physician if they read in the internet research conflict with what the physician said.

We also asked about the common public beliefs about dermatology. The majority of the patients (35%) thought that liver disfunction may cause skin diseases. The patients believed that allergy tests should be done to the patients with pruritus (64%) and eczema (31%). The patients thought that they could sunbathe after applying sunscreen (61%) and under an umbrella (35%), and 15% thought that tanning was beneficial for skin. The percentage of patients who thought that the herbal products are less harmful than the drugs given by the doctor was 10% and 11% thought that the herbal products would not give any harm to the body. 7% of the patients used creams at home or took from someone else for their diseases before going to the hospital. 26% of the patients stated that they do not like to use topical treatment. 20% of the patients thought that topical treatments did not work, using systemic treatment for skin diseases harmed the body, and some systemic acne medications may cause infertility. 10% believed that the nails should be excised for successful treatment of onychomycosis. Considering inter-group differences, men ($p = 0.026$) thought that that topical treatments do not work, PEG ($p = 0.001$, $p = 0.035$, respectively) thought that the sunlight will not harm under the umbrella or tree, the fungus will not heal without nail excising in onychomycosis, and those who thought that an allergy test should be performed at each itching diseases and those who did not want to use systemic treatment for dermatological diseases were more frequently in ≤40 groups ($p=0.024$, $p=0.002$, respectively). There was no statistically significant difference between the groups in other answers.

Discussion

In our country, a complete consensus has not occurred in the name of skin diseases branch. The question of "Are you a dermatologist or a skin doctor?" is asked by patients every day. Also, the fact that the official specialty name of the department is "Skin and Venereal Diseases" complicates this situation. As a result, the perception of patients and their application to physicians are affected in our society. However, as the education level increased, it became clear that the patients are sure about all names belong to the same department..

There are many factors that can cause dermatological diseases. Among these, many causes such as drugs, physical activities, internal organ diseases, old age, microorganisms, chemicals, sun, climatic conditions, allergies, pregnancy, psychological factors can be counted (3-5). Although the etiology in each disease differs, it is not correct to say that psychological factors are the highest cause in etiology as our patients think. However, almost every dermatologist encounters many psychosomatic complaints both due to the disease and due to the psychological distress caused by the dermatological event (6,7). For this reason, it is important for dermatologists to understand patient psychology well and establish the necessary communication with the patient. It is known to us, dermatologists, that there are sections about pregnancy dermatoses in dermatology books and there are some skin diseases that are seen only during pregnancy (8). If we consider these, it is interesting that patients do not count pregnancy and breastfeeding as factors that can cause skin diseases. The reason for this may be that these diseases are not as common in the society as other skin diseases.

When we look at the frequency of the diagnoses of patients who applied to the dermatology outpatient clinic, depending on the age of the patient, geographic area and health institution, the most common ones are eczema, skin infections and acne vulgaris (9,10). Our patients often knew fungal diseases of the skin and eczema. Women (%73.8) knew and remembered acne vulgaris disease more than men (%51.4). As the reasons for applying to the outpatient clinic, the patients mostly applied due to itching, rash and acne.

Contagious diseases are serious health problems in both developing and developed countries. If we look at skin diseases, fungal, bacterial, viral and parasitic infections can be transmitted by contact (11). In addition, antibiotic resistance strains has also been shown to be transmitted by contact (12). For this reason, measures such as educating the society in terms of contact diseases, frequent washing of the hands, keeping the infectious area covered, and reducing the use of common goods prevent the spread of these infections and antibiotic resistance strains (13). However, in order to be protected, it is necessary to know

that these diseases are contagious. According to the results of our study, it is seen that our society needs to be educated on this subject.

The patients may apply to many different branches for sexually transmitted diseases (14). One of these branches is dermatology. However, only 16% of the patients thought they would apply to the dermatologist with this complaint. Therefore, it is seen that it is not fully known that dermatology is a branch that deals with sexually transmitted diseases in our country.

As in the whole world, there are many patients who have applied CAT in our country. Dermatological diseases were not excluded from this trend. While patients who have applied CAT for dermatological diseases worldwide are 35-69%, this rate varies between 12.6-52.1% in our country (15-17). In the present study, this rate was determined to be 29% and similar to the other studies done in our country. There could be some geographical changes for CAT use even in different regions of the countries. This situation seems to explain the differences in percentages in different countries. While the most commonly used methods in our country are topical herbal treatments, prayer and balneotherapy methods, those used all over the world are herbal treatments, food supplements, homeopathy and acupuncture (15,18,19). In our study, patients mostly had cupping and leech therapy. The most common group of patients who use CAT in dermatological diseases were found to be psoriasis vulgaris, acne vulgaris and warts in a study conducted in Turkey(17). Generally, the rate of using CAT was found to be high in elderly patients, women and highly educated (18). In our study, 32% of men, 24% of women, 30% of PEG, 23% of HEG, 28% of ≤40, and 24% of> 40 used CAT. Although there was no statistically significant difference, it was seen in our study that men, PEG and young people applied to CAT method more frequently.

It is a fact that with the introduction of the Internet into our lives, we, physicians receive more questions from patients. Often, people search for what they don't know and wonder on the internet, where they can easily access it. 64% of our patients had searched their disease on the internet before coming to the hospital. However, the majority of patients (78%) relied on their physicians if the information they found on the internet conflict with the doctor. The rate of HEG and younger patients were higher on internet research. The young and highly educated people may access the internet more easily. Especially young patients have more free time, they may easily access the internet even from the phone and they have more control over the technology.

One of the interesting questions about the dermatological myths was that 61% of the patients thought that they could sunbathe after applying sunscreen. We think that the society should be seriously educated about this situation which is against the philosophy of using sunscreen. We, dermatologists know that most of the patients who come with itching complaint request allergy tests. In our study, it was observed that 64% of patients thought this way. Patients should also be trained that it is not meaningful to have an allergy test in every itchy disease. While topical treatments such as cream and lotion are very important in dermatological diseases, ¼ of the patients stated that they did not like to use these treatments and 1/5 of them thought that they did not work. We think that this issue should be emphasized and it should be explained that topical drugs are also a treatment method.

The limitation of the study is that it is conducted in only one center. A larger population with different geographical regions may be reached with a multicenter study.

Conclusion

Although the patients who applied to the dermatology outpatient clinic heard the name of the diseases that are relatively common in the society, they did not have much information about the rarely seen diseases. They needed more training, especially about contagious diseases, and that they cannot sunbathe after using sunscreen. Most people did not think of applying to the dermatology outpatient clinic in sexually transmitted diseases. They still had an interest in CAT methods and started to investigate their diseases in this way with the increasing use of the internet in recent years. The vast majority, however, relied more on doctor information than on the Internet.

Acknowledgment

We would like to thank Onurcan Şahin, PhD who made the statistics of our study, for his contributions.

References

1. Ben-Aharon I, Goshen-Lago T, Turgeman I, et al. Young patients with cancer and a digital social network: the voice beyond the clinic. ESMO Open. 2020;5:e000651. Doi: 10.1136/esmoopen-2019-000651
2. Koo K, Nagayah R, Begum S, et al. The use of complementary and alternative medicine in children with atopic eczema at a tertiary care centre in Malaysia. Complement Ther Med. 2020;49:102355. Doi: 10.1016/j.ctim.2020.102355
3. Chee A, Branca L, Jeker F, et al. When life is an itch: What harms, helps and heals from the patients' perspective? Differences and similarities among skin diseases. Dermatol Ther. 2020;33:e13606. Doi: 10.1111/dth.13606
4. Papadopoulos I. Comparative Study of Dermatological Diseases of the Elderly in Relation to the Rest Population. Clin Cosmet Investig Dermatol. 2020;13:173-8. Doi: 10.2147/CCID.S242294
5. Kayiran MA and Akdeniz N. Diagnosis and treatment of urticaria in primary care. North Clin Istanb. 2019;6:93-9. Doi: 10.14744/nci.2018.75010
6. Nguyen TV, Hong J and Prose NS. Compassionate care: enhancing physician-patient communication and education in dermatology: Part I: Patient-centered communication. J Am Acad Dermatol. 2013;68:353.e1-8. Doi: 10.1016/j.jaad.2012.10.059
7. Roberts JE, Smith AM, Wilkerson AH, et al. "Psychodermatology" knowledge, attitudes, and practice among health care professionals. Arch Dermatol Res. 2020;312:545-58. Doi: 10.1007/s00403-020-02050-9.
8. İnan Yüksel E, Erdemir AV, Turan E, et al. Pregnancy Dermatoses and Treatments. Istanbul Med J 2011;12:30-5. Doi: 10.5505/1304.8503.2011.49469
9. Akpınar Kara Y. Demographic and Clinical Characteristics of Patients in Private Hospital Dermatology Clinic. Turkiye Klinikleri J Med Sci 2018;38:329-33. Doi:10.5336/medsci.2018-61316
10. Özçelik S, Kulaç İ, Yazıcı M, et al. Distribution of childhood skin diseases according to age and gender, a single institution experience. Turk Pediatri Ars 2018; 53:105-12. Doi:10.5152/TurkPediatriArs.2018.6431
11. Svensson A, Ofenloch RF, Bruze M, et al. Prevalence of skin disease in a population-based sample of adults from five European countries. Br J Dermatol. 2018;178:1111-8. Doi: 10.1111/bjd.16248
12. Ross JI, Snelling AM, Carnegie E, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol. 2003;148:467-78. Doi: 10.1046/j.1365-2133.2003.05067.x
13. Koku Aksu A . Bulaşıcı Dermatolojik Hastalıkların Kontrolü Ve Halk Sağlığı Açısından Önemi. Estüdam Halk Sağlığı Dergisi. 2019;4:82-9. Doi: 10.35232/estudamhsd.528241
14. Grønhøj C, Jakobsen KK, Wingstrand VL, et al. Association between head and neck cancer and sexually transmitted diseases: a Danish nationwide, case-control study. Acta Otolaryngol. 2020;140:615-9. Doi:10.1080/00016489.2020.1748709
15. Ernst E. The usage of complementary therapies by dermatological patients: a systematic review. Br J Dermatol. 2000;142:857-61. Doi: 10.1046/j.1365-2133.2000.03463.x
16. Smith N, Weymann A, Tausk FA, et al. Complementary and alternative medicine for psoriasis: a qualitative review of the clinical trial literature. J Am Acad Dermatol 2009;61:841–56. Doi: 10.1016/j.jaad.2009.04.029
17. Kutlu S, Ekmekçi TR, Köşlü A, et al. Complementary and alternative medicine among patients attending to dermatology outpatient clinic. Turkiye Klinikleri J Med Sci 2009;29:1496-502.
18. Boing AC, Ribeiro Santiago PH, Tesser CD, et al. Prevalence and associated factors with integrative and complementary practices use in Brazil. Complement Ther Clin Pract. 2019;37:1-5. Doi: 10.1016/j.ctcp.2019.07.009
19. Demirci GT, Altunay İ, Küçükünal A, et al. Complementary and alternative medicine usage in skin diseases and the positive and negative impacts on patients. Turk J Dermatol 2012;6:150-4. Doi: 10.5152/tdd.2012.32

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 610-615
https://doi.org/10.31067/acusaglik.898335

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Pediatrics / Pediatri

Diagnosis And Treatment in Children With Nutcracker Syndrome: A Single-Center Experience

Serçin Güven[1] **, Sevinç Kalın[2]** **, Neslihan Çiçek[1]**

[1]Marmara University Medical Faculty, Department of Pediatrics, Division of Pediatric Nephrology, Istanbul, Turkey

[2]Umraniye Training and Research Hospital, Division of Pediatric Radiology, Istanbul, Turkey

Serçin GÜVEN, Uzm. Dr.

Sevinç KALIN, Uzm Dr.

Neslihan ÇİÇEK, Uzm. Dr.

Correspondence: Serçin Güven
Marmara University Medical Faculty, Department of Pediatrics, Division of Pediatric Nephrology, Istanbul, Turkey
Phone: +905323433021
E-mail: sercindr@yahoo.com

Received : 03 March 2021
Accepted : 01 May 2021

ABSTRACT

Objective: It has been aimed to report the experience of our center regarding diagnosis and treatment experience in children with Nutcracker syndrome (NCS).

Materials and Methods: The medical records of seven patients who have admitted to the Department of Pediatric Nephrology of our hospital between February 2017 and March 2020 were evaluated retrospectively. The diagnosis of NCS was confirmed with renal Doppler ultrasound (RDUS) and magnetic resonance angiography (MRA) in these patients who have admitted with the complaints of hematuria and proteinuria. The patients' data such as clinical characteristics, radiological findings, radiological signs and information about medical treatment at baseline and last control were recorded.

Results: The mean levels of 24-h urine protein excretion in all patients at baseline and last control were 15,25±9,19 mg/m2/h and 9,8±3,94 mg/m2/h, respectively. The mean levels of 24-h urine protein excretion in patients treated with ACE (angiotensin converting enzyme) inhibitors at baseline and last control were 20±11,53 mg/m2/h and 9,6±6,44 mg/m2/h, respectively. (p=0,073). The mean levels of 24-h urine protein excretion were 11.7±6.39 mg/m2/h and 9.95±1.84 mg/m2/h in patients not receiving ACE inhibitor treatment, at baseline and the last control respectively (p= 0,61). The mean angle value of the left renal vein in the aortomesenteric distance measured by RDUS examination performed in the upright position was 14,71±4,46 degrees. The anteroposterior diameter of the left renal vein (hilar/aortomesenteric) measured in the upright position was 6,4.

Conclusion: The benign nature of NCS in young patients requires maintaining conservative approach.

Keywords: Nutcracker syndrome, orthostatic proteinuria, renal vein

Nutcracker Sendromlu Çocuklarda Tanı ve Tedavi: Tek Merkez Deneyimi

ÖZET

Amaç: Merkezimizin Nutcracker sendromlu (NCS) çocuklardaki tanı ve tedavi deneyiminin paylaşılması istenmiştir.

Gereç ve Yöntemler: Hastanemizin çocuk nefroloji bölümüne Şubat 2017 ile Mart 2020 tarihleri arasında başvuran yedi hastanın medikal kayıtları geriye dönük olarak değerlendirildi. Hematüri ve proteinüri yakınmalarıyla başvuran bu hastalarda NCS tanısı renal doppler ultarasonografi (RDUS) ve MR anjiografi (MRA) ile doğrulandı. Hastaların başvuru ve son kontroldeki klinik özellikleri, radyolojik bulguları, laboratuvar tetkikleri ve medikal tedavileri değerlendirildi.

Bulgular: Hastaların başlangıç ve son kontrolde 24 saatlik idrarda protein atılımı sırasıyla ortalama 15,25±9,19 mg/m2/saat ve 9,8±3,94 mg/m2/saat idi. Anjiotensin dönüştürücü enzim inhibitörü (ACE inhibitörü) kullanılan hastalarda başlangıç ve son kontrolde, 24 saatlik idrarda protein atılımı sırasıyla ortalama 20±11,53 mg/m2/saat ve 9,6±6,44 mg/m2/saat bulundu (p=0,073). Anjiotensin dönüştürücü enzim inhibitörü kullanmayan hastalarda başlangıç ve son kontrolde 24 saatlik idrarda protein atılımı sırasıyla ortalama 11,7±6,39 mg/m2/saat ve 9,95±1,84 mg/m2/saat saptandı (p= 0,61). Ayakta yapılan RDUS incelemede sol renal venin aortomesenterik mesafede açı ortalaması 14,71 ± 4,46 derece idi. Ayakta ölçülen sol renal ven antero-posterior çap oranı (hiler/Aortomesenteric) ortalama 6,4 bulundu.

Görüş: Genç hastalarda NCS'nun selim seyirli olması tedavide konservatif kalınmayı gerektirir.

Anahtar kelimeler: Nutcracker Sendromu, ortostatik proteinüri, renal ven

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Nutcracker Syndrome (NCS) is a clinical picture that emerges due to compression of the left renal vein accompanied with clinical, laboratory and radiological findings. Its most frequent type is termed as "anterior NCS" resulting from the compression of the left renal vein between the aorta and the superior mesenteric artery and its frequency has been reported as 0.8-7.1% (1,2). Less frequently, "posterior type NCS" is observed as a result of the compression between the aorta and the vertebral corpus in the retroaortic field. Pressure on the left renal vein leads to the obstruction of blood flow and increased intrarenal venous pressure (1,2). On the other side, Nutcracker phenomenon, differently from the syndrome, refers to the presence of radiological findings due to the compression of the left renal vein without accompanying clinical and laboratory symptoms and findings (3-5).

The clinical and laboratory findings of Nutcracker Syndrome may present a wide variety. Its common symptoms are microscopic or macroscopic hematuria, orthostatic proteinuria and flank pain. It may be also presented as varicocele, dysmenorrhea, fatigue and orthostatic intolerance in some patients. However, it courses asymptomatically in most patients, particularly in children (6).

Orthostatic proteinuria is defined as the non-detection of protein in the collected urine in the supine position whereas the presence of proteinuria in the collected urine in the upright position.

The diagnosis is established by the clinical findings supported by the specific changes for NCS encountered by the imaging techniques. Nutcracker Syndrome can be diagnosed with various imaging techniques such as renal Doppler ultrasonography (RDUS), MR angiography (MRA) and catheter angiography (7). Although, catheter angiography provides more definite results in the diagnosis of NCS, it is preferred only in the cases in whom diagnostic problems are experienced due to its invasive character. Renal Doppler ultrasonography is preferred for non-invasive nature, non-exposure to radiation and easy applicability. However, operator-dependency and the difficulty of viewing the retroperitoneal area are the disadvantages of this technique (8). The non-invasive and three-dimensional morphological imaging has become possible with the progressively improving cross-sectional imaging techniques (CTA and MRA).

The treatment of Nutcracker Syndrome is controversial except in cases with severe symptoms. Angiotensin converting enzyme inhibitors (ACE inhibitor) may be a treatment option to reduce proteinuria in the patients with orthostatic proteinuria (9,10). In addition, surgical correction may be rarely needed in severe cases (4).

In the present study, we aimed to retrospectively evaluate the clinical, laboratory and imaging findings of the pediatric patients who admitted to the Department of Pediatric Nephrology of our hospital and diagnosed with NCS between 2017 and 2020.

Material and Methods

Totally seven patients who admitted to the Department of Pediatric Nephrology due to proteinuria and/or hematuria and diagnosed with NCS between February 2017 and March 2020 were included in the study. The diagnosis was confirmed with imaging techniques (RDUS and MRA) as well as clinical and laboratory findings. The baseline clinical characteristics, physical examination and radiological findings of the patients at admission, the presence of hematuria at the time of diagnosis and the last control, protein excretion and the use of ACE (angiotensin converting enzyme) inhibitors were recorded. The presence of greater than 5 red cells per mm^3 in centrifuged urine was defined as hematuria while detection of protein higher than 4 mg/m^2/hour in 24-hour urine collection sample was accepted as proteinuria. The diagnosis of orthostatic proteinuria was established based on absence of protein in the first urine in the morning despite detection of proteinuria in 24-hour urine collection. The study included the patients with blood pressure below 90th percentile. Serum BUN, creatinine, complement levels and urinalysis were tested in all the patients.

Renal doppler ultrasonography examinations were performed by the same pediatric radiologist with convex probe (3.5 MHz frequency) using Acuson S3000 USG device (Siemens, Erlangen, Germany) in the supine position. Antero-posterior (AP) diameter of the left renal vein was measured in the hilar and aortomesenteric segments by RDUS examinations performed in the supine and upright positions.

The hilar and aortomesenteric AP diameter ratios were calculated in the upright position. In addition, the aortomesenteric angles were measured in the supin and upright positions.

MRA was performed in all patients to evaluate the morphology more accurately and to reduce operator-dependent

diagnostic failure. MRA imagings were performed using Optima MR450w 1.5 Tesla device (General Electric, Milwaukee, USA) in the supine position. The antero-posterior diameter of the left renal vein in the hilar and aortomesenteric segments was measured and the ratio between these measurements was calculated in the axial MR images obtained after intravenous administration of contrast agent. The aortomesenteric angles were measured in the postcontrast sagittal images (Figure 1).

i)The aortomesenteric angle less than 39 degrees in the RDUS and MRA in the supine position and/ or ii)detection of a lower value of this angle in RDUS examination in the upright position compared with that measured in the supine position and/or iii) the antero-posterior diameter ratio of the left renal vein (hilar/aortomesenteric) greater than 4.9 in RDUS examination in the upright position were accepted as the diagnostic criteria.

The Ethics Committee Approval by the protocol code 09.2020.466 and informed consent forms from the parents of the patients were obtained for this study.

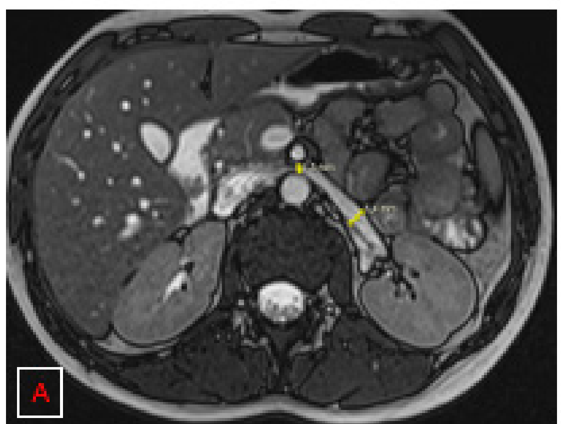
Statistical Analysis

All data was analyzed using Statistical Software Package for The Social Sciences (SPSS Inc., Chicago, Illinois, USA) Version 21.0. The distribution homogeneity of the data was evaluated by Kolmogorov-Smirnov test. The normally distributed data was expressed as mean±standard deviation. Paired test was used for comparison between the initial and final values. A p value less than 0.05 was accepted as statistically significant.

Results

Of the seven pediatric patients diagnosed with NCS; 2 (28%) were female and 5 (72%) were male. Mean age of the patients was 11,7±2,95 years while mean follow-up duration was 34±6,7 months (Table 1). RDUS and MRA were performed as diagnostic tests in all the patients with suspected Nutcracker Syndrome. The demographic, clinical and laboratory characteristics of the patients were shown in Table 1. The admission complaint was abdominal pain in one patient while all other patients admitted due to coincidentally detected proteinuria and/or microscopic hematuria (Table 1). The mean levels of 24-h urine protein excretion in all patients at baseline and last control were 15,25±9,19 mg/m²/h and 9,8±3,94 mg/m²/h, respectively. ACE inhibitor was used in three patients during follow-up period. The mean levels of 24-h urine protein excretion in the patients treated with ACE inhibitors at baseline and last control were 20±11,53 mg/m²/h and 9,6±6,44 mg/m²/h, respectively. (p=0,073). The mean levels of 24-h urine protein excretion were 11,7±6,39 mg/m²/h and 9,95±1,84 mg/m²/h in the patients not receiving ACE inhibitor treatment, respectively (p= 0,61). Kidney function test results were within normal limits in all patients.

The left RDUS and MRA findings of the patients were presented in Table 2. The mean left renal vein diameters at the level of renal hilus and in the aortomesenteric segment were 8.78±2.62 mm and 1.37±0.40 mm, respectively. These values were 6,85±1,59 mm and 1,81±0,52 mm in the supine position, respectively. The mean left renal vein diameters at the level of renal hilus and in the aortomesenteric segment were found 7,94±1,53 mm and 1,91±0,50 mm in the MR angiography, respectively.



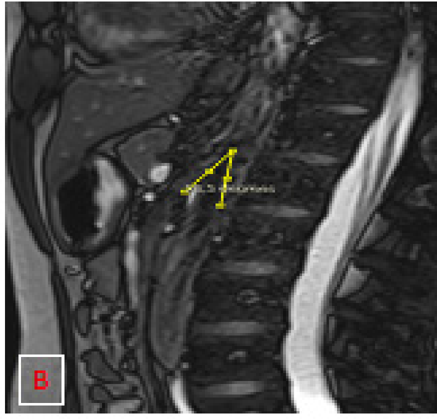


Figure 1: A) Anteroposterior diameter measurements of the left renal vein in the aortomesenteric and hilar regions in the MR angiography, B) Anteroposterior diameter measurement in the MR angiography

Table 1. The demographic, clinical and laboratory characteristics of the patients	
Age (years) mean ±SD	11,7±2,95
Follow-up duration (months) mean ±SD	34±6,7
Gender n(%)	
Female	2 (28)
Male	5 (72)
Clinical (n)	
Microscopic hematuria+proteinuria	(2)
Microscopic hematuria	(1)
Macroscopic hematuria	(1)
Abdominal pain+proteinuria	(1)
Proteinuria	(2)
Protein in the baseline 24-hour urine sample (mg/m2/h) mean ±SD	15,25 ±9,19
Protein in the 24-hour urine sample in the last visit (mg/m2/h) mean ±SD	9,8 ±3,94
Use of ACE inhibitor n (%)	3 (42)
Protein in the baseline 24-hour urine sample in the patients treated with ACE inhibitor (mg/m2/h) mean ±SD	20±11,53
Protein in the 24-hour urine sample in the patients treated with ACE inhibitor in the last visit (mg/m2/h) mean ±SD	9,6 ±6,44
Complement factor 3 Normal n (%)	7 (100)
Complement factor 4 Normal n (%)	7 (100)

Table 2. Renal Doppler ultrasound and MR Angiography findings of the patients

	Renal Doppler Ultrasonography mean ±SD	MR angiography mean ±SD
Upright		
Aortomesenteric angle (degrees)	14,71 ± 4,46	
Left renal vein diameter in the aortomesenteric segment (mm)	1,37 ± 0,40	
Left renal vein diameter at the level of renal hilus (mm)	8,78 ± 2,62	
Supine		
Aortomesenteric angle (degrees)	22,14 ± 7,98	22,08 ± 3,27
Left renal vein diameter in the aortomesenteric segment (mm)	1,81 ±0,52	1,91 ± 0,50
Left renal vein diameter at the level of renal hilus (mm)	6,85 ± 1,59	7,94 ± 1,53

Mean aortomesenteric angle values measured by RDUS and MR angiography in the supine position were detected to be 22,14±7,98 and 22,08±3,27 degrees, respectively. RDUS examination performed in the upright position revealed a mean aortomesenteric angle value of 14,71±4,46 degrees. The mean value of left renal vein anteroposterior diameter ratio (hilar/aortomesenteric) measured in the upright position was 6.4.

Discussion

Anterior NCS and more rarely posterior NCS have been an interesting subject with wide variety of their symptoms and their confusability with many other renal diseases (11,12). The other etiological factors of Nutcracker Syndrome include renal ptosis, high osteal location of the left renal vein or narrow-angle exit of the superior mesenteric artery from the aorta, pancreatic masses and lymphadenomegalies. Nutcracker Syndrome may emerge in any age and shows no difference between genders (13). In our study, mean age at diagnosis was found 11,7 years and males were majority. The most commonly reported symptoms for Nutcracker Syndrome are pelvic pain, hematuria and varicocele (3). Orthostatic proteinuria may occur as a result of increased pressure in the left renal vein and the changes in the release of angiotensin II and norepinephrine caused by impaired renal hemodynamics (14-17). It has been also reported that the obstruction of the renal venous circulation causes formation of varicose veins around the renal pelvis and ureter and that the small ruptures and bleedings in these veins are the reasons of particularly hematuria and proteinuria triggered by exercise (18,19). The most common reason for hospital admission among our patients was coincidentally detected proteinuria. This complaint was followed by microscopic hematuria. Macroscopic hematuria was the cause for admission in only one patient.

According to Kim et al.(9); an angle of <39 degrees between SMA and abdominal aorta in the sagittal plane by CT is 92% sensitive and 89% specific for diagnosis of NCS . This angle normally ranges between 45-90 degrees. However, Ananthan et al. (3) have defined a left renal vein diameter ratio (hilar/aortomesenteric) greater than 4.9 in the CT or MR images and classical "bird's beak" view as the most specific findings for NCS. In our study, the aortomesenteric angle less than 39 degrees in the RDUS and MRA in the supine position and/ or detection of a lower value of this angle in RDUS examination in the upright position compared with that measured in the supine position and/or the antero-posterior diameter ratio of the left renal vein (hilar/aortomesenteric) greater than 4.9 in RDUS examination in the upright position were accepted as the diagnostic criteria. We found the aortomesenteric angle values less than 39 degrees in the RDUS and MRA in the supine

position in all of our patients and mean aortomesenteric angle values measured by RDUS and MR angiography in the supine position were 22,14±7,98 and 22,08±3,27 degrees, respectively. In all of our patients, we found a lower value of the aortomesenteric angle in RDUS examination performed in the upright position compared with that measured in the supine position. In addition, the anteroposterior diameter ratios of the left renal vein (hilar/aortomesenteric) were greater than 4.9 in RDUS examination in the upright position in all of our patients . The mean value of left renal vein anteroposterior diameter ratio (hilar/aortomesenteric) measured in the upright position was 6.4.

There are only a limited number of studies that investigated the clinical course of NCS in children. Tanaka et al. demonstrated that spontaneous remission developed after a 7-year follow-up period in an adolescent patient diagnosed with NCS who had persistent microscopic hematuria (20). None of our patients developed remission in the existing microscopic hematuria. Proteinuria was orthostatic in all of our patients and none of those were at the level of nephrotic range. Orthostatic proteinuria is one of the common causes of asymptomatic proteinuria in the adolescent age group and accepted as a benign condition. The development of spontaneous remission parallelly with continuing growth and weight gain has been reported in many studies (2,14). The possible results of orthostatic proteinuria accompanied with Nutcracker syndrome are not different from the known nephrotoxic effects of proteinuria. However, KDIGO has accepted albuminuria as an indicator of the progression of chronic renal failure in 2012 (21). The use of ACE inhibitor is a treatment option to reduce persistent proteinuria in patients and we initiated the treatment of ACE inhibitor in our patients with protein excretion over 20 mg/m2/h in 24-hour urine sample. As expected the level of baseline proteinuria was higher in our patients initiated with ACE inhibitor treatment. The reduction in the level of proteinuria was remarkable, although statistically not significant, in our patients who used ACE inhibitor (p=0,073). Increased proteinuria was encountered in none of the patients at the end of approximately 3-year follow-up period. The small number of the patients was the limitation of our study. The microscopic examination of urine sediment was performed in all of the patients who admitted due to the complaint of macroscopic or microscopic hematuria and morphic erythrocyte morphology was detected in our patients except one patient. Kidney biopsy was performed in our patient with dysmorphic type of erythrocyte morphology and C3 glomerulopathy was detected in kidney pathology besides the RDUS and MRA findings consistent with NCS. With this example, we aimed to emphasize the importance of microscopic examination of urine sediment in the differential diagnosis of other causes of hematuria.

Conclusion

Nutcracker syndrome should be investigated in the presence of orthostatic proteinuria and/or persistent microscopic/macroscopic hematuria. The benign nature of NCS in young patients requires maintaining conservative approach. The differential diagnosis of other diseases that cause proteinuria and/or hematuria should be made carefully.

Funding: None

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose

Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose

This article does not contain any studies with animals performed by any of the authors.

Ethical approval: All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted (IRB approval number 09.2020.466)

Informed consent: “Informed consent was obtained from all individual participants included in the study.”

References

1. Avgerinos ED, McEnaney R, Chaer RA. Surgical and endovascular interventions for nutcracker syndrome. Semin Vasc Surg 2013;26:170-7.
2. Alaygut D, Bayram M, Soylu A.et al. Clinical course of children with nutcracker syndrome. Urology 2013;82:686-90.
3. Ananthan K, Onida S, Davies AH. Nutcracker Syndrome: An Update on Current Diagnostic Criteria and Management Guidelines. Eur J Vasc Endovasc Surg 2017;53:886-94
4. Venkatachalam S, Bumpus K, Kapadia SR.et al. The nutcracker syndrome. Ann Vasc Surg 2011;25:1154-64.
5. Shin JI, Lee JS. Nutcracker phenomenon or nutcracker syndrome? Nephrol Dial Transplant 2005;20:2015. doi: 10.1093/ndt/gfi078.
6. Kargın Çakıcı E, Yazılıtaş F, Çınar HG. et al. Nutcracker syndrome in children: the role of Doppler ultrasonography in symptomatic patients. Turkish J Pediatr Dis / 2019; 5: 348-52
7. Kim SH. Doppler US and CT diagnosis of Nutcracker Syndrome. Korean J Radiol 2019; 20(12):1627-37
8. Gulleroglu K, Gulleroglu B, Baskin E. Nutcracker syndrome. World J Nephrol 2014;3: 277-81.

9. Kim KW, Cho JY, Kim SH. et al. Diagnostic value of computed tomographic findings of nutcracker syndrome: correlation with renal venography and renocaval pressure gradients. Eur J Radiol 2011;80:648-54
10. Ha TS, Lee EJ. ACE inhibition can improve orthostatic proteinuria associated with nutcracker syndrome. Pediatr Nephrol 2006;21(11):1765-68
11. Zhang H, Li M, Jin W.et al. The left renal entrapment syndrome: diagnosis and treatment. Ann Vasc Surg 2007;21:198-203.
12. Kurç E, Barutca H, Kanyılmaz M. et al. S Nutcracker Syndrome. Turk Gogus Kalp Dama. 2013;21:146-50.
13. Shin JI, Lee JS. ACE inhibition in nutcracker syndrome with orthostatic proteinuria: how about a hemodynamic effect? Pediatr Nephrol 2007;22:758. author reply 759-60
14. Takahashi Y, Sano A,MatsuoM. An effective “transluminal balloon angioplasty” therapy for pediatric chronic fatigue syndrome with nutcracker phenomenon. Clin Nephrol 2000;53:77-8.
15. Park SJ, Lim JW, Ko YT.et al. Diagnosis of pelvic congestion syndrome using transabdominal and transvaginal sonography. AJR Am J Roentgenol 2004;182: 683-8.
16. Pascarella L, Penn A, Schmid-Schonbein GW. Venous hypertension and the inflammatory cascade: major manifestations and trigger mechanisms. Angiology 2005;56(Suppl. 1):S3-10.
17. De Schepper A. “Nutcracker” phenomenon of the renal vein and venous pathology of the left kidney. Radiology 1972; 55: 507-11.
18. Li H, Sun X, Liu G. et al. Endovascular stent placement for nutcracker phenomenon. J Xray Sci Technol 2013; 21: 95-102
19. Tanaka H, Waga S. Spontaneous remission of persistent severe hematuria in an adolescent with nutcracker syndrome seven years observation. Clin Exp Nephrol. 2004;8:68-70.
20. Fuhrman DY, Schneider MF, Dell KM, et al. Albuminuria, Proteinuria, and Renal Disease Progression in Children with CKD. Clin J Am Soc Nephrol 2017;12:912-20
21. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease Kidney Int Suppl. 2013; 3: 1-150

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 616-624
https://doi.org/10.31067/acusaglik.928333

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Gastroenterology and Hepatology / Gastroenteroloji ve Hepatoloji

Fecal S100A12 as a Biomarker in Behcet's Disease

Cem Şimşek[1], Berkan Armağan[2], Alper Sarı[2], Abdulsamet Erden[2], Levent Kılıç[2], Ali Akdoğan[2]

[1]Hacettepe University Faculty of Medicine, Division of Gastroenterology, Ankara, Turkey
[2]Hacettepe University Faculty of Medicine, Division of Rheumatology, Ankara, Turkey

Cem ŞİMŞEK, M.D.
Berkan ARMAĞAN, M.D.
Alper SARI, M.D.
Abdulsamet ERDEN, M.D.
Levent KILIÇ, M.D.
Ali AKDOĞAN, M.D.

Correspondence: Cem ŞİMŞEK
Hacettepe University Faculty of Medicine,
Division of Gastroenterology,
Ankara, Turkey
Phone: +905342964684
E-mail: cemgsimsek@gmail.com

Received : 26 April 2021
Accepted : 14 June 2021

ABSTRACT

Background: Gastrointestinal involvement in Behcet's disease impacts morbidity and mortality. The diagnosis of gastrointestinal disease requires comprehensive evaluation with endoscopic and radiologic examinations which is costly and impractical. A biomarker is essential for non-invasive detection. Fecal S100A12 is an established biomarker in gastrointestinal inflammatory diseases and its serum levels are known to increase in Behcet's Disease. In this study, we aimed to tests fecal S100A12 levels in Behcet's patients, its relation with gastrointestinal symptoms to its potential as a biomarker in gastrointestinal involvement.

Methods: We prospectively enrolled 48 cases of Behcet's disease patients fulfilling International Study Group criteria from a university hospital. We excluded patients with other autoimmune conditions, active or recent infection, using NSAIDs and antibiotics. Control group was selected from volunteers who had applied to the rheumatology outpatient clinic. Patients with BD were categorized into 5 groups according to organ involvement. Also we evaluated and recorded disease activity with the BDCAF 2006. Fecal S100A12, fecal calprotectin and acute phase reactants were also collected.

Results: Fecal calprotectin levels were six-fold higher in BD than controls (p<0.0001). Fecal S100A12 was also two-fold higher albeit without statistical significance (p=0.132). Fecal calprotectin and fecal S100A12 levels were positively correlated (r:0.530, p<0.0001). Both fecal calprotectin (138.1 µg/g vs 50.1 µg/g, p=0.006).) and fecal S100A12 (48.3 ng/mL vs 19.4 ng/mL, p=0.023) were higher in Behçet's patients with gastrointestinal symptoms compared to those without. Fecal calprotectin and fecal S100A12 levels were not correlated with total BDCAF score, CRP and ESR levels.

Conclusion: Fecal S100A12 is correlated with fecal calprotectin and higher in Behcet's patients with gastrointestinal involvement. This is the first study of fecal S100A12 in Behcet's disease and its potential use in Behcet's disease patients with gastrointestinal symptoms.

Keywords: Behcet's disease, gastrointestinal involvement, S100A12, fecal biomarker

Behçet Hastalarında Yeni Biyobelirteç: Fekal S100A12

ÖZET

Giriş ve amaç : Behçet hastalığında (BH) gastrointestinal tutulum, morbidite ve mortaliteyi etkiler ancak tanısı endoskopik ve radyolojik incelemelerle kapsamlı bir değerlendirme gerektirir. Fekal S100A12, gastrointestinal inflamatuar hastalıklarda kullanılan bir biyobelirteçtir, aynı zamanda serum düzeylerinin Behçet Hastalığında arttığı bilinmektedir, dolayısıyla non-invaziv bir tanı yöntemi olabilir. İşte bu çalışmada, Behçet hastalarında fekal S100A12 düzeylerinin, gastrointestinal semptomlarla ilişkisinin ve dolayısıyla gastrointestinal tutulumda bir biyobelirteç olma potansiyelini araştırmayı amaçladık.

Gereç ve yöntem: Bir üniversite hastanesinden International Study Group kriterlerine uyan 48 Behçet hastasını prospektif olarak değerlendirdik. NSAII'ler ve antibiyotikler kullanan diğer otoimmün durumları, ve enfeksiyonu olan hastaları dışladık. Kontrol grubu Romatoloji polikliniğine başvuran gönüllülerden seçildi. BH olan hastalar organ tutulumlarına göre 5 gruba ayrıldı. Ayrıca BDCAF 2006 ile hastalık aktivitesini değerlendirdik ve kaydettik. Fekal S100A12, fekal kalprotektin ve akut faz reaktanları da çalışıldı.

Bulgular: Fekal kalprotektin düzeyleri BH'da kontrollere göre altı kat daha yüksekti(p<0.0001). Fekal S100A12 de istatistiksel olarak BH'da kontrollere göre anlamlı olmasa da iki kat daha yüksekti(p=0.132). Fekal kalprotektin ve fekal S100A12 seviyeleri pozitif korelasyon gösterdi(r:0.530, p<0.0001). BH ve gastrointestinal semptomları olan hastalarda hem fekal kalprotektin(138.1 µg/g'a karşılık 50.1 µg/g, p=0.006) hem de fekal S100A12(48.3 ng/mL'ye karşı 19.4 ng/mL, p=0.023) olmayanlara göre daha yüksekti. Fekal kalprotektin ve fekal S100A12 seviyeleri toplam BDCAF skoru, CRP ve ESR seviyeleri ile korele değildi.

Sonuç: Gastrointestinal semptomları olan Behçet hastalarında fekal S100A12 fekal kalprotektin ile koreledir ve daha yüksektir. Bu, Behçet hastalığında dışkı S100A12'nin ilk çalışmasıdır ve gastrointestinal semptomları olan Behçet hastalığı hastalarında potansiyel kullanımını göstermektedir.

Anahtar Kelimeler: Behçet hastalığı, gastrointestinal tutulum, S100A12, fekal biyobelirteç

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Behçet's disease (BD) is a chronic, relapsing multisystem vasculitis that skin, mucosa, joints, eyes, vascular, central nervous system, and the gastrointestinal system (GIS) involvement can be seen in the disease course with time and severity varying patterns of attacks and organ involvements (1). Assessing the activity of BD is challenging since its subclinical organ involvement and subjective nature of symptomatology. Although, acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are used in clinical practice to estimate disease activity for various rheumatic inflammatory diseases, those markers perform limited reliability and a reduced utility in BD patients (2, 3). An alternative way is to utilize multimodality scores to monitor disease course. One such tool is Behçet's Disease Current Activity Form (BDCAF) which is a widely established to asses BD overall disease activity (4, 5). BDCAF was found to have a good interobserver reliability in British population to assessing general disease activity (5). However, in Turkish populations there was a poor agreement for BDCAF between and within observers for their overall impression of disease activity albeit the score demonstrated limited utility to assess the orogenital ulcers and ocular involvement (6). Therefore, it is an imperative need to identify organ involvements, attacks and overall disease activity in BD.

Gastrointestinal involvement in BD (GBD) is known to be caused by vasculitic involvement of mesenteric and intramural arterial and venous systems. GBD has different frequencies in Eastern and Western Hemispheres ranging from 1% to 50% albeit this data comes from studies with different methodologies. Regardless of its frequency, GBD poses important challenges in the management of BD as its presence in severe cases, longer time to diagnosis, a challenging differential diagnosis list, and high proportion of complicated cases. Among those, diagnosis of GBD remains a principal issue as current treatments for BD are well known to remission in GBD when diagnosed. Current practice to diagnose GBD relies on upper and lower endoscopic examinations and small bowel imaging when in doubt. This practice relies on the assumption that ileocolonic area is most commonly involved, however it has become clear that isolated small bowel involvement is not infrequent. This poses the question that should every BD patient should be for GBD, and if yes, how?

Use of fecal biomarkers have been a widely utilized way to monitor disease activity and gastrointestinal tract pathologies. The widely established Calprotectin (i.e. S100 8/9) is a dimer of S100A9 and S100A8 and is a calcium binding, pro-inflammatory protein mainly released by activated granulocytes, macrophages and endothelial cells (7, 8). S100A12 is another protein from the same family with similar functions and structure, however predominantly expressed by neutrophilic leucocytes (9) which we may pose the question of an additional diagnostic value in BD. These proteins are known to be expressed at sites of inflammation and a higher concentrations are found in various inflammatory sites including serum, feces, synovial fluid, urine and saliva. They are used in the diagnosis, activity and demonstration of gastrointestinal involvement in many rheumatologic or non-rheumatologic diseases, especially inflammatory bowel disease (IBD) (10) (11-13).

In the literature, serum levels of calprotectin and S100A12 have been studied. Our current knowledge is mostly about disease activation and organ involvement in rheumatologic diseases, while studies about fecal levels of these markers are scarce (7, 13, 14). In BD patients, serum levels of calprotectin was higher than healthy controls but there was no correlations with the BDCAF (15). Higher fecal calprotectin (FC) level was an independent predictor for intestinal involvement of BD and correlate with the disease activity index of intestinal BD (16). The correlation of the elevated serum levels of S100A12 and BDCAF scores was also shown in BD patients (13). The S100A12 is a reasonable biomarker for BD as its differential expression by Neutrophils, its demonstrated reliability and feasibility as a fecal marker, and challenges in diagnosing and monitoring gastrointestinal involvement in this population, however has not yet been studied to the best of our knowledge.

The aim of our study was to evaluate both the fecal levels of calprotectin and S100A12 in active and inactive BD patients. We also examined their relationships with gastrointestinal and other symptoms and organ involvements.

METHODS

Study Population

Between February 2017 and May 2018, a total of 48 BD patients who were admitted to the Rheumatology Outpatient Clinic of Hacettepe University Hospital were prospectively enrolled in this study. Our study was approved by Hacettepe University Institutional Review Board. All patients with BD fulfilled the International Study Group

criteria for diagnosis of BD at their time of diagnosis(17). Patients younger than 18 years of age, having other autoimmune conditions, history of malignancy, active or recent infection in past 3 weeks, using non-steroidal anti-inflammatory drugs in past 3 weeks and pregnancy were excluded at the time of study enrollment. Control group was selected from 14 healthy volunteers who had applied to the rheumatology outpatient clinic with non-specific pain, without gastrointestinal symptoms and diseases, and without inflammatory diseases sharing the same exclusion criteria. All patients and healthy participants were informed about the study before and consents were obtained before enrollment visit. The study protocol was approved by our institutional review board.

Study design

Every subject was evaluated by a detailed medical history and a physical examination at the enrollment visit when all participants were thoroughly questioned about signs, symptoms and history of any articular, gastrointestinal, vascular, ocular and neurological involvement. Data regarding demographics, comorbidities, smoking status, disease duration, type of systemic involvement, previous and current medications were obtained from medical records and by face to face interview at that time.

Patients with BD were categorized into 5 groups according to organ involvement: group 1: mucocutaneous and articular involvement, group 2: ocular involvement, group 3: vascular involvement, group 4: gastrointestinal involvement and group 5: neurologic involvement. BD patients with two or more organ involvement except mucocutaneous and articular involvement were excluded. Remaining 31 patients: 14 patients with mucocutaneous and articular involvement, 12 patients with ocular involvement, and 5 patients with vascular involvement were also separately evaluated as BD with isolated organ involvement.

We evaluated and recorded disease activity with the BDCAF 2006 (5) which was . tested and validated for Turkish patients by Hamuryudan et al (6). Patients were considered to have an active disease if a minimum of two items in 'BDCAF' were observed (15). We also evaluated the BD patients separately for the presence of symptoms indicative of gastrointestinal involvement as follows: oral ulcer, nausea/vomiting/abdominal pain, and diarrhea or frank blood per rectum as gastrointestinal complaint. We also evaluated the BD patients separately according to BDCAF's domains of nausea/vomiting/abdominal pain, and diarrhea or frank blood per rectum as gastrointestinal complaint.

Conventional inflammatory biomarkers as CRP, ESR, white blood cells, platelet count and haemoglobin were also recorded. CRP and ESR upper normal levels were 0.8 mg/dL and 20 mm/hr, respectively.

Measurements of fecal S100A12 and fecal calprotectin concentrations

Using a disposable stool sampler, approximately 50 mg of fecal specimen from BD patients and controls was collected and immediately frozen at –80°C in a standard refrigerator until further analysis. FC levels were measured by EUROIMMUN Calprotectin ELISA test (Lübeck, Germany) and fecal S100A12 by BioVendor ELISA test (Brno, Czech Republic) according to the manufacturer's instructions. The detection limits of the assays 6.5 µg/g and 0.01 ng/ml, respectively. Cut-off of 50 mg/kg was used for fecal calprotectin as previously used in similar studies (18).

Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, USA). Continuous data were described as mean (standard deviation, SD) or median (IQR) and categorical variables as percentages. Chi-square and Fisher's exact test was used to compare categorical variables. The variables were investigated using visual (histograms, probability plots) and analytical methods to determine whether or not they are normally distributed. Kruskal-Wallis and Mann Whitney U tests were conducted to compare non-normally distributed variables and Bonferroni correction use to adjust for multiple comparisons. One-way ANOVA and Student T test were conducted to compare normally distributed variables and pairwise post-hoc tests were performed using Tukey's test when an overall significance was observed. Correlation of variables was assessed by Spearman correlation coefficient. p value of <0.05 was considered as significant.

RESULTS

In this study, 48 BD patients and 14 controls were included. There were no statistically significant difference in gender 29 (60%) vs 9 (%64) male as well as the median age of 41.7±11.1 vs 39.6±10.3 between BD and control groups (p=0.794 and p=0.532, respectively). For BD group, median disease duration was 144 (IQR, 12-492) months. Clinical features and disease manifestations of BD patients are summarized in Table 1. Median BDCAF score was 3.0 (IQR, 0-6.0). Regarding the clinical characteristics of BD oral ulcer was the most common involvement with 48 (100%) patients, other involvements with decreasing frequency were as follows: papulo-pustular lesion by 36 (75%), genital ulcer by 30 (63%), uveitis by 25 (52%), erythema nodosum by 23 (48%), vascular involvement by 15 (31%), articular involvement by 14 (29%), neurologic involvement by 8 (17%), and gastrointestinal involvement by 4 (8%).

Table 1. Demographic and clinical characteristics of Behçet disease patients

	Behçet disease patients
Male, n (%)	29 (60)
Age, mean ± SD	41.7 ± 11.1
Disease duration (months), median (IQR)	144 (12-492)
Oral ulcer, n (%)	48 (100)
Genital ulcer, n (%)	30 (63)
Erythema nodosum, n (%)	23 (48)
Papulo-pustular lesion, n (%)	36 (75)
Articular involvement, n (%)	14 (29)
Uveitis, n (%)	25 (52)
Pathergy, n (%)	7/15 (47)
Vascular involvement, n (%)	15 (31)
Neurologic involvement, n (%)	8 (17)
Gastrointestinal involvement, n (%)	4 (8)
BDCAF, median (IQR)	3 (0-6)

BDCAF; Behçet's Disease Current Activity Form

An overview of biomarkers for both BD and control groups were presented in Table 2. Hematologic parameters of hemoglobin concentration, leucocyte and platelet counts were similar in between the groups. ESR were higher in BD compared to controls though both medians were within normal range (8 mm/h vs 2 mm/h, p=0.028), whereas CRP were similar between the groups (0.49 vs 0.35 mg/dL). Regarding fecal biomarkers, FC levels were approximately six-fold higher in BD (66.5 vs 11.6 µg/g, p<0.0001) than the control group (p<0.0001). Concomitantly, fecal S100A12 was approximately two-fold higher in BD albeit without statistical significance (27.7 vs 10.2 ng/mL, p=0.132)

Table 2. Comparison of demographic data and laboratory features of patients with BD and controls

	Behçet disease patients, n=48	Healthy controls, n=14	p
Hemoglobin (g/dL), mean ± SD	13.8 ± 1.5	14.6 ± 1.3	0.123
White blood cell (mm3), mean ± SD	7239 ± 2002	7592 ± 2019	0.564
Platelets (103 mm3), mean ± SD	237 ± 61	223 ± 36	0.435
ESR (mm/h), median (IQR)	8 (3-22)	2 (2-10.5)	0.028
CRP (mg/dl), median (IQR)	0.49 (0.3-1.5)	0.35 (0.3-0.4)	0.077
Fecal Calprotectin (µg/g), median (IQR)	66.5 (28.8-153.5)	11.6 (6.1-38.3)	<0.0001
Fecal S100A12 (ng/mL), median (IQR)	27.7 (13.7-95.8)	10.2 (8.1-30.3)	0.132

ESR; Erythrocyte sedimentation rate, CRP; C-reactive protein

Fecal calprotectin and fecal S100A12 levels were correlated with each other as expected (r:0.530, p<0.0001). A FC of 50 mcg/g were considered positive for gastrointestinal inflammation. AUC for fecal S100A12 to detect FC greater than 50 mcg/g yielded 0.77 (CI: 0.65 – 0.89) AUC. Youden J Index was 53 for FS to detect FC positivity with specifity 97% and sensitivity 56%. Neither FC nor fecal S100A12 was correlated with total BDCAF score BD patients with or without gastrointestinal symptoms. They were also not correlated with CRP and ESR levels.

BD patients were also evaluated in terms of overall disease activity as total BDCAF score, as well as presence or absence of gastrointestinal symptoms and oral ulcers as included in BDCAF. When we compare our patients disease activity according to BDCAF≥2, there were 37 (77%) active and 11 (23%) inactive patients and fecal markers and serum AFR were shown in the Table 3. There was no statistical significance in fecal and serum activity markers between active or inactive BD groups. When we compared our patients according to gastrointestinal complaint + OA, there were 35 (73%) positive and 13 (27%) negative patients and fecal, and serum disease activity markers were shown in the Table 4. Although BD patients with

gastrointestinal complaint + OA had higher levels of fecal and serum activity markers, there was no statistically significant between BD patients with and without gastrointestinal symptoms + OA. When we compared our patients according to only gastrointestinal symptoms, there were 30 (63%) positive and 18 (37%) negative patients. Fecal, and serum disease activity markers were shown in the Table 5. BD patients with gastrointestinal symptoms had a higher FC levels (138.1 µg/g (IQR:52-296) vs 50.1 µg/g (IQR:22-100); p=0.006). Similarly, fecal S100A12 levels in BD patients with gastrointestinal symptoms were also higher than without those (48.3 ng/mL (IQR: 21-164) vs 19.4 ng/mL (IQR:12-54); p=0.023) with statistical significance in pairwise comparison. There was no significant differences in serum disease activity marker levels.

Table 3. Fecal calprotectin, fecal S100A12 and CRP levels in active (according to BDCAF≥2) and inactive Behçet disease patients and healthy control

	Active BD, n=37	Inactive BD, n=11	Healthy control	p	p*
Hemoglobin (g/dL), mean ± SD	13.9 ± 1.4	13.5 ± 2.0	14.6 ± 1.3	0.198	
White blood cell (mm3), mean ± SD	7256 ± 2209	7181 ± 1125	7592 ± 2019	0.843	
Platelets (103 mm3), mean ± SD	239 ± 58	231 ± 73	223 ± 36	0.682	
Fecal Calprotectin (µg/g), median (IQR)	65.2 (31-156)	93 (26-151)	11.6 (6.1-38.3)	0.001	0.532
Fecal S100A12 (ng/mL), median (IQR)	25.2 (13-126)	32 (11-57)	10.2 (8-32)	0.254	
CRP (mg/dl), median (IQR)	0.5 (0.3-1.5)	0.69 (0.2-1.9)	0.35 (0.3-0.4)	0.208	
ESR (mm/h), median (IQR)	7 (3.5-13.5)	22.5 (3-47)	2 (2-10.5)	0.065	

*p values: Comparison of the active and inactive Behçet disease patients with eachother (*p values for multiple comparisons with Bonferroni correction <0.017).
BD; Behçet disease, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate

Table 4. Fecal calprotectin, fecal S100A12 and CRP levels in Behçet disease patients with and without gastrointestinal symptoms + oral ulcer and healthy control

	BD with GIS+OA, n=35	BD without GIS+OA, n=13	Healthy control	p	p*
Hemoglobin (g/dL), mean ± SD	13.6 ± 1.5	14.4 ± 1.5	14.6 ± 1.3	0.097	
White blood cell (mm3), mean ± SD	7131 ± 2014	7530 ± 2021	7592 ± 2019	0.705	
Platelets (103 mm3), mean ± SD	233 ± 56	247 ± 75	223 ± 36	0.563	
Fecal Calprotectin (µg/g), median (IQR)	68.8 (43-159)	40.1 (12-114)	11.6 (6-38)	<0.0001	0.051
Fecal S100A12 (ng/mL), median (IQR)	30.6 (17-140)	16.0 (5-51)	10.2 (8-30)	0.049	0.059
CRP (mg/dl), median (IQR)	0.61 (0.3-1.5)	0.45 (0.3-0.8)	0.35 (0.3-0.4)	0.143	
ESR (mm/h), median (IQR)	11 (4-23)	5 (2-13)	2 (2-10)	0.017	0.068

p* values : Comparison of the Behçet disease patients with and without gastrointestinal symptoms + oral ulcer. (*p values for multiple comparisons with Bonferroni correction <0.017)
BD; Behçet disease, GIS; Gastrointestinal symptoms, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate

One patient had 3 and 16 patients had 2 different organ involvement in our study. So, we had 48 BD patients with 66 organ involvement (including mucocutaneous and articular involvement). When we excluded the BD patients with multiple organ involvement, 14 patients with mucocutaneous and articular involvement, 12 patients with ocular involvement, and 5 patients with vascular involvement were separately evaluated as BD with isolated organ involvement. Differences in fecal and serum markers of disease activity parameters and total score of BDCAF according to BD organ involvement were presented in Table 6. There was no statistical significant differences among these 3 BD groups with isolated organ involvement. Comparison of BD patients with isolated organ involvements according to gastrointestinal symptoms + OA, and only gastrointestinal symptoms of BDCAF domains were shown in the table 8 and 9, respectively. There were no statistical significant differences in these 3 BD groups with isolated organ involvement in terms of GIS+OA symptoms, and only GIS symptoms or not.

Table 5. Fecal calprotectin, fecal S100A12 and CRP levels in Behçet disease patients with and without gastrointestinal symptoms (without oral ulcer) and healthy control					
	BD with GIS, n=30	BD without GIS, n=18	Healthy control	p	p*
Hemoglobin (g/dL), mean ± SD	13.6 ± 1.7	14.0 ± 1.4	14.6 ± 1.3	0.235	
White blood cell (mm3), mean ± SD	6883 ± 2260	7453 ± 1837	7592 ± 2019	0.541	
Platelets (103 mm3), mean ± SD	232 ± 62	240 ± 61	223 ± 36	0.665	
Fecal Calprotectin (µg/g), median (IQR)	138.1 (52-296)	50.1 (22-100)	10.9 (5-42)	<0.0001	0.006
Fecal S100A12 (ng/mL), median (IQR)	48.3 (21-164)	19.4 (12-54)	10.0 (7-29)	0.024	0.023
CRP (mg/dl), median (IQR)	0.41 (0.3-0.8)	0.55 (0.3-1.6)	0.32 (0.3-0.4)	0.116	0.288
ESR (mm/h), median (IQR)	9 (4-21)	8 (3-22)	5 (2-11)	0.149	0.693

p* values: Comparison of the Behçet disease patients with and without gastrointestinal symptoms. (*p values for multiple comparisons with Bonferroni correction <0.017)
BD; Behçet disease, GIS; Gastrointestinal symptoms, CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate

Table 6. Fecal calprotectin, fecal S100A12, CRP and Behçet disease current activity form of patients according to Behçet disease groups				
	Mucocutaneous and articular (n=14)	Ocular (n=12)	Vascular (n=5)	p
Fecal Calprotectin (µg/g), median (IQR)	79.4 (27-122)	60.0 (23-150)	70.9 (37-190)	0.322
Fecal S100A12 (ng/mL), median (IQR)	16.7 (9-56)	28.9 (15-151)	49.3 (18-122)	0.320
CRP, median (IQR)	0.56 (0.3-1.9)	0.38 (0.3-1.5)	0.83 (0.4-1.5)	0.462
ESR, median (IQR)	5 (2-15)	11.5 (3-22)	13 (6-28)	0.729
BDCAF, median (IQR)	2.5 (1.8-3.5)	3 (2-4)	3 (2-5)	0.448

CRP; C-reactive protein, ESR; Erythrocyte sedimentation rate, BDCAF; Behçet's Disease Current Activity Form

Thirty-seven (77%) patients used colchicine and 21 (44%) patients used one of the immunosuppressive therapies. Although there was no statistically significant in both, patients undergoing colchicine therapy had a lower level of FC and fecal S100A12 than without colchicine therapy, in contrast, patients undergoing immunosuppressive therapies were higher levels of FC and fecal S100A12 than without immunosuppressive therapies.

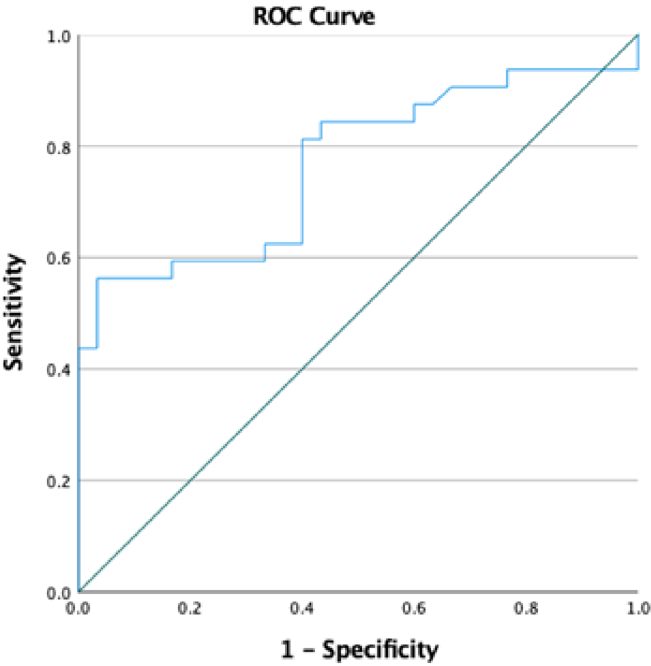


Figure 1. Area under rule operator curve for fecal S100A12 levels in Behçet disease to detect FC greater than 50 mcg/g

Table 7. Fecal calprotectin, fecal S100A12 levels in active and inactive Behçet disease groups (GIS+OA)						
	Fecal S100A12 (ng/mL)			Fecal Calprotectin (μg/g)		
	BD with GIS symptom+OA	BD without GIS symptom+OA	p	BD with GIS symptom+OA	BD without GIS symptom+OA	p
Mucocutaneous and articular (n=14)	18.3 (9-97)	15.5 (6-23)	0.524	79.4 (47-122)	56.0 (8-283)	0.620
Ocular (n=12)	27.7 (19-37)	11.5 (6.6-12.7)	0.116	49.2 (34-62))	8.8 (5-36)	0.229
Vascular (n=5)*	95.8 (75-420)	24.7 (5-44)		182.5 (143-319)	16.2 (4-28)	-
*Statistical comparison was not applied due to the small number of patients.						

Table 8. Fecal calprotectin, fecal S100A12 levels in active and inactive Behçet disease groups (GIS)						
	Fecal S100A12 (ng/mL)			Fecal Calprotectin (μg/g)		
	BD with GIS symptom	BD without GIS symptom	p	BD with GIS symptom	BD without GIS symptom	p
Mucocutaneous and articular (n=14)	34.2(9-158)	15.5 (8-36)	0.571	92.5 (57-286)	79.2 (20-114)	0.396
Ocular (n=12)	27.7 (15-1319)	19.4 (11-31)	0.518	49.2 (34-273)	43.8 (19-62)	0.644
Vascular (n=5)*	420 (96-746)	44.3 (25-49)		319 (182-456)	28.3 (16-66)	-
*Statistical comparison was not applied due to the small number of patients.						

Table 9. Fecal calprotectin, fecal S100A12 levels in Behçet disease using or not colchicine and immunosuppresive drugs						
	BD with colchicine, n=37	BD without colchicine, n=11	p	BD with immunosuppressive, n=21	BD withuot immunosuppressive, n=27	p
Fecal Calprotectin (μg/g), median (IQR)	65.2 (26-131)	97.9 (28-283)	0.411	68.4 (41-213)	58.0 (21-98)	0.149
Fecal S100A12 (ng/mL), median (IQR)	25.7 (15-62)	30.6 (7-141)	0.922	43.7 (13-155)	19.4 (14-45)	0.299

DISCUSSION

In this study, FC levels were six-fold higher in BD than the control group (p<0.0001) and fecal S100A12 was two-fold higher albeit without statistical significance (p=0.132). In terms of classical AFR, ESR were higher in BD compared to controls though both medians were within normal range 0.028), whereas CRP were similar between the groups. Although there was no difference when active BD patients were determined according to total score, as expected, both fecal calprotectin and fecal S100A12 were higher in Behçet's patients with gastrointestinal symptoms compared to those without. Fecal calprotectin and fecal S100A12 levels were correlated with each other but not with total BDCAF score, CRP and ESR levels. On the other hand, FC and fecal S100A12 levels were similar between BD patients using or not colchicine and immunosuppressive drugs.

BD is a multisystem vasculitis with involvement or virtually any vascular field thus organ system as well as hemostatic abnormalities(19). BD has varying prevalence over different geographical regions, and in areas with a high prevalence such as Turkey, disease constitutes an important cause of morbidity. Current research efforts in BD are concentrated to: Firstly to elucidate pathogenesis of the disease, secondly to develop clinical tools and imaging protocols for diagnosing different organ involvements in their earlier courses, and lastly to implement newer agents to BD management. Despite the vast improvement in all these areas, there is a long way ahead for BD and their providers.

Gastrointestinal involvement in BD has varying frequency in different geographical regions spanning from 1% in Western to 50% in Eastern Hemisphere, albeit this difference can be owed to different methodologies and disease characteristics in these populations. Gastrointestinal involvement in BD can be in any region in the oropharyngeal area and gastrointestinal tract, oral ulcers and ileocecal areas are well-known to be characteristic as well as nearly pathognomonic for GBD.

Nevertheless, recent improvements in gastrointestinal, especially small bowel imaging and fecal biomarkers studies pointed out that there might be considerable ongoing inflammation in these parts of the tractus. This new perspective deserves attention as a false negative test for gastrointestinal involvement can cause a failure to induce remission and increase the risk of a serious complication such as perforation or bleeding.

Several studies evaluated the diagnosis of GBD with newer imaging methods and fecal biomarkers. Two studies revealed that up 90% of symptomatic BD patients with negative upper plus lower endoscopies can have ulcers in their small bowels (20, 21). This underlines the importance of multimodality approach for the detection of gastrointestinal involvements presumably with serologic and fecal biomarkers. Anti-Saccharomyces cerevisiae antibodies (ASCA), IgM alpha-enolase antibody, and Interleukin-12 B was suggested as potential serologic biomarkers for GBD, however none has gained wide-spread acceptance (22-24).

S100A12 shows promise as a candidate biomarker in GBD for several reasons. Firstly, neutrophilic inflammation is a hallmark of vasculitic lesions in gastrointestinal BD and also the main source of detectable fecal S100A12 (25). Secondly, like calprotectin, S100A12 is detectable with ELISA after 7 days in fecal material thus stands out as a feasible diagnostic method. Thirdly, S100A12 demonstrated successful diagnostic performances in other gastrointestinal pathologies and becoming closer to be implemented into clinical practice (26).

Our BD cohort are well established and GBD subgroup is comparable to the previous knowledge with 8% frequency. In this study, we did not use GBD as a separate cohort, but utilized a cross-sectional study design with prospective involvement study design to understand the overall diagnostic performance of S100A12 in disease activity and GI involvement. About 8% of our patients had GI symptoms. As a limitation, we did not perform endoscopic and imaging gastrointestinal evaluation in our patients. This is because this study is designed as a pilot for further studies and it is well known that none of the current methods have enough sensitivity to exclude GBD alone especially in asymptomatic patients. S100A12 deserves further effort to be compared to current diagnostic utilities. In this prospective enrollment, 15 of 48 (29%) BD patients demonstrated FC levels greater than 53 ng/mL. In 48 patients, 18 had abdominal symptoms. FC levels were three-fold higher in symptomatic BD group when compared to asymptomatic BDs. FC levels did not any correlation with BDCAF, or serum acute phase biomarkers, as expectable from a fecal biomarker.

In conclusion, although we could not found any correlation between total BDCAF and fecal markers in our study, they have seemed better than classical AFR in showing BD activity and this difference was more pronounced in those with gastrointestinal symptoms. To the best of our knowledge, this is the first study to evaluate fecal S100A12 in BD. Fecal S100A12 demonstrated promising distribution among BD patients and presumably will be of dramatic use to diagnose and follow-up gastrointestinal involvement in BD. Also this is the first study showing S100A12 in addition to fecal calprotectin in Behcet's disease patients with gastrointestinal symptoms.

ACKNOWLEDGEMENTS

This study was supported by Hacettepe University Scientific Research Fund (THD-2017-13174).

References

1. Hatemi G, Yazici Y, Yazici H. Behcet's syndrome. Rheum Dis Clin North Am. 2013;39(2):245-61.
2. Sota J, Vitale A, Rigante D, Orlando I, Lucherini OM, Simpatico A, et al. Correlation of Serum Amyloid-A Levels, Clinical Manifestations, Treatment, and Disease Activity in Patients with Behcet's Disease. Isr Med Assoc J. 2018;20(8):517-21.
3. Melikoglu M, Topkarci Z. Is there a relation between clinical disease activity and acute phase response in Behcet's disease? Int J Dermatol. 2014;53(2):250-4.
4. Lawton G, Bhakta BB, Chamberlain MA, Tennant A. The Behcet's disease activity index. Rheumatology (Oxford). 2004;43(1):73-8.
5. Bhakta BB, Brennan P, James TE, Chamberlain MA, Noble BA, Silman AJ. Behcet's disease: evaluation of a new instrument to measure clinical activity. Rheumatology (Oxford). 1999;38(8):728-33.
6. Hamuryudan V, Fresko I, Direskeneli H, Tenant MJ, Yurdakul S, Akoglu T, et al. Evaluation of the Turkish translation of a disease activity form for Behcet's syndrome. Rheumatology (Oxford). 1999;38(8):734-6.
7. Kopec-Medrek M, Widuchowska M, Kucharz EJ. Calprotectin in rheumatic diseases: a review. Reumatologia. 2016;54(6):306-9.
8. Manolakis AC, Kapsoritakis AN, Tiaka EK, Potamianos SP. Calprotectin, calgranulin C, and other members of the s100 protein family in inflammatory bowel disease. Dig Dis Sci. 2011;56(6):1601-11.
9. Heida A, Van de Vijver E, van Ravenzwaaij D, Van Biervliet S, Hummel TZ, Yuksel Z, et al. Predicting inflammatory bowel disease in children with abdominal pain and diarrhoea: calgranulin-C versus calprotectin stool tests. Arch Dis Child. 2018;103(6):565-71.
10. Johne B, Fagerhol MK, Lyberg T, Prydz H, Brandtzaeg P, Naess-Andresen CF, et al. Functional and clinical aspects of the myelomonocyte protein calprotectin. Mol Pathol. 1997;50(3):113-23.
11. Foell D, Roth J. Proinflammatory S100 proteins in arthritis and autoimmune disease. Arthritis Rheum. 2004;50(12):3762-71.

12. Pietzsch J, Hoppmann S. Human S100A12: a novel key player in inflammation? Amino Acids. 2009;36(3):381-9.
13. Han EC, Cho SB, Ahn KJ, Oh SH, Kim J, Kim DS, et al. Expression of Pro-inflammatory Protein S100A12 (EN-RAGE) in Behcet's Disease and Its Association with Disease Activity: A Pilot Study. Ann Dermatol. 2011;23(3):313-20.
14. Skef W, Hamilton MJ, Arayssi T. Gastrointestinal Behcet's disease: a review. World J Gastroenterol. 2015;21(13):3801-12.
15. Oktayoglu P, Mete N, Caglayan M, Bozkurt M, Bozan T, Em S, et al. Elevated serum levels of calprotectin (MRP8/MRP14) in patients with Behcet's disease and its association with disease activity and quality of life. Scand J Clin Lab Invest. 2015;75(2):106-12.
16. Kim DH, Park Y, Kim B, Kim SW, Park SJ, Hong SP, et al. Fecal calprotectin as a non-invasive biomarker for intestinal involvement of Behcet's disease. J Gastroenterol Hepatol. 2017;32(3):595-601.
17. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990;335(8697):1078-80.
18. Fauny M, D'amico F, Bonovas S, Netter P, Danese S, Loeuille D, et al. Faecal calprotectin for the diagnosis of bowel inflammation in patients with rheumatological diseases: a systematic review. Journal of Crohn's and Colitis. 2020;14(5):688-93.
19. Koşar A, Öztürk M, Haznedaroğlu I, Karaaslan Y. Hemostatic parameters in Behçet's disease: a reappraisal. Rheumatology international. 2002;22(1):9-15.
20. Hamdulay S, Cheent K, Ghosh C, Stocks J, Ghosh S, Haskard D. Wireless capsule endoscopy in the investigation of intestinal Behçet's syndrome. Rheumatology. 2008;47(8):1231-4.
21. Neves FS, Fylyk SN, Lage LV, Ishioka S, Goldenstein-Schainberg C, Sakai P, et al. Behçet's disease: clinical value of the video capsule endoscopy for small intestine examination. Rheumatology international. 2009;29(5):601-3.
22. Choi CH, Kim TI, Kim BC, Shin SJ, Lee SK, Kim WH, et al. Anti-Saccharomyces cerevisiae antibody in intestinal Behçet's disease patients: relation to clinical course. Diseases of the colon & rectum. 2006;49(12):1849-59.
23. Shin SJ, Kim BC, Kim TI, Lee SK, Lee KH, Kim WH. Anti-alpha-enolase antibody as a serologic marker and its correlation with disease severity in intestinal Behçet's disease. Digestive diseases and sciences. 2011;56(3):812-8.
24. Lee HW, Chung SH, Moon CM, Che X, Kim SW, Park SJ, et al. The correlation of serum IL-12B expression with disease activity in patients with inflammatory bowel disease. Medicine. 2016;95(23).
25. Hayasaki N, Ito M, Suzuki T, Ina K, Ando T, Kusugami K, et al. Neutrophilic phlebitis is characteristic of intestinal Behçet's disease and simple ulcer syndrome. Histopathology. 2004;45(4):377-83.
26. Carvalho A, Lu J, Francis JD, Moore RE, Haley KP, Doster RS, et al. S100A12 in Digestive Diseases and Health: A Scoping Review. Gastroenterology Research and Practice. 2020;2020.

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI   Gastroenterology and Hepatology / Gastroenteroloji ve Hepatoloji

Artificial Intelligence to Predict Esophageal Varices in Patients with Cirrhosis

Cem Şimşek[1], İbrahim Emir Tekin[2], Hasan Şahin[2], Taha Koray Şahin[2], Yasemin Hatice Balaban[1]

[1]Hacettepe University Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey

[2]Hacettepe University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey

Cem ŞİMŞEK, M.D.
Emir TEKİN, M.D.
Hasan ŞAHİN, M.D.
Taha Koray ŞAHİN, M.D.
Yasemin Hatice BALABAN, M.D.

Correspondence: Cem Şimşek
Hacettepe University Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey
Phone: +905342964684
E-mail: cemgsimsek@gmail.com

Received : 27 April 2021
Accepted : 06 June 2021

ABSTRACT

Background: Screening for varices remains as the best strategy to decrease associated mortality that reaches 25%. Diagnostic endoscopy is gold standard but invasive for routine screening. Non-invasive stiffness measurements with elastography is costly and impractical. Non-elastogarphic tests that use available laboratory and clinical variables are feasible but their performance remains inferior to elastography. Non-invasive, accessible and accurate test is needed. Machine learning methods can be used in this sense to provide better diagnostic performances. We aimed to test the ability of a machine learning model to predict esophageal varices in patients with cirrhosis.

Materials and methods: We retrospectively evaluated patients with cirrhosis at the time of their screening upper endoscopies from our institutional database. Demographic, clinical, radiologic, endoscopic and laboratory data was collected. Child-Pugh, APRI, FIB-4, AAR, PCSD tests were calculated for each patient. Gradient boosted machine learning algorithm was constructed for the problem. A logistic regression as well as tests' and model's performances with areas under ROCs were compared to detect presence of esophageal varices.

Results: Study population consisted of 201 patients whom 105 had esopheageal varices which 33 were higher risk. Patients with varices were older, advanced Child stages, larger splenic diameters and higher MELD-Na scores. Composite scores' were as follows: FIB-4 0.57 (0.49-0.65), APRI 0.47 (0.38-0.55), PCSD 0.511 (0.42-0.59), AAR 0.481 (0.39-0.56). Machine learning model's mean AUC to predict varices was 0.68(0.060), F1- score was 0.7 and accuracy was 63%.

Conclusions: Machine learning model outperformed non-invasive tests to predict esophageal varices in cirrhotic patients.

Keywords: esophageal varices, artificial intelligence, machine learning, screening, prediction

Sirozlu Hastalarda Yapay Zeka ile Özofagus Varis Tahmini

ÖZET

Giriş ve amaç: Sirozlu hastalarda özofagus varis taraması, ilişkili mortaliteyi %25'e varan oranlarda azaltmak için en iyi strateji olmaya devam etmektedir. Tanısal üst endoskopi altın standarttır ancak invaziv olması rutin taramayı güçleştirmektedir. Elastografi ile non-invaziv fibrosis ölçümleri maliyetli ve pratik değildir. Mevcut laboratuvar ve klinik değişkenleri kullanan testlerin ise performansları elastografiden daha düşük kalmaktadır. Non-invaziv, erişilebilir ve doğru testler gereklidir. Bu bağlamda varis riskini belirlemek için makine öğrenmesi yöntemleri kullanılabilir. Bu çalışmada, bir makine öğrenme modelinin sirozlu hastalarda özofagus varislerini tahmin etme performansını ve kullanılabilirliğini test etmeyi amaçladık.

Gereç ve yöntem: Kliniğimizin veri tabanından üst endoskopi ile varis taraması yapılan sirozlu hastaları geriye dönük olarak değerlendirdik. Demografik, klinik, radyolojik, endoskopik ve laboratuvar verileri toplandı. Her hasta için Child-Pugh, APRI, FIB-4, AAR, PCSD testleri hesaplandı. Problem için gradyan destekli makine öğrenme algoritması oluşturulmuştur. Özofagus varislerinin varlığını tespit etmek için lojistik regresyon ile testlerin ve modelin ROC'lerin altındaki alanlarla olan performansları karşılaştırıldı.

Bulgular: Çalışma popülasyonu, 105'i özofagus varisi olan ve 33'ü daha yüksek riskli olan 201 hastadan oluşturuldu. Varisli hastalar daha yaşlı, ileri Child evreleri, daha büyük dalak boyutları ve daha yüksek MELD-Na skorlarına sahipti. Testlerin varis olan hastaları tahmin performanslarının AUC değerleri: FIB-4 0,57 (0,49-0,65), APRI 0,47 (0,38-0,55), PCSD 0,511 (0,42-0,59), AAR 0,481 (0,39-0,56) şeklindeydi. Makine öğrenimi modelinin varisleri tahmin etmek için ortalama AUC değeri 0.68(0.060), F1- skoru 0.7 ve doğruluk %63 idi.

Sonuçlar: Makine öğrenimi modellerinin, sirotik hastalarda özofagus varislerini tahmin etmekteki performansı, invazif olmayan testlerle karşılaştırılabilir düzeydeydi.

Anahtar Kelimeler: Karaciğer hastalığı, siroz, özofagus varisleri, yapay zeka, makine öğrenmesi

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Variceal bleeding is a major cause of morbidity and mortality in cirrhotic patient. Early identification of varices and primary prophylaxis remains as the most feasible strategy. The gold standard for detecting varices is upper endoscopy but its use is not convenient for repeated screening procedures. Liver stiffness measurements with transient elastography reached performances enough to be implemented in clinical practice as expanded Baveno VI criteria but requires expensive devices along with an experienced operator, thus not also an optimal screening strategy (1). Tests without an elastographic measurements have been proposed but their performance is inferior to elastography. Therefore, a non-invasive but practical test is required to stratify patients for endoscopic screening.

Artificial intelligence is a general term includes several domains of advanced computer programs that can achieve human like cognitive abilities. Machine-learning is a subdomain of artificial intelligence that learns from the data and the problem without needing to be programmed so. These approaches are increasingly being used in virtually every field of medicine as well as hepatology to tackle long-standing problems with their inherent abilities to and integrate a bigger dimensions and extent of data into their solution.

With the need of a screening tool for varices and the promise of machine learning approach, we aimed to test a machine learning model's performance to predict the presence of esophageal varices in patients with cirrhosis. We hypothesize that machine learning's performance will not be inferior to already existing non-invasice clinical/laboratory depedentent scores.

Materials and Methods

Study Design and Patient population

We retrospectively evaluated our endoscopy database for patients who have undergone upper endoscopy for treatment or screening of esophagogastric varices between January 2015 and January 2021. We included patients with an administrative code for cirrhosis or chronic liver diseases (ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems) who undergone upper endoscopy for the purpose of screening or prophylactic therapy of varices. We confirmed diagnosis of cirrhosis through evaluation of patient charts and radiologic studies. We excluded cases with inaccessible endoscopic, clinical, or laboratory data. Patients with incomplete vital signs were not excluded.

Data Collection and Variables

After confirmation of final patient list, we retrospectively collected data from endoscopy reports, physician notes during inpatient and outpatient encounters, laboratory results and abdominal radiology reports. Patient demographics, vital signs during encounter (Temperature, blood pressure, heart rate, respiratory rate) etiology of liver disease, presence of ascites or hepatic encephalopathy, splenic length in abdominal imaging studies and laboratory values (complete blood count, routine biochemistry, coagulation tests) were collected at the nearest time to upper endoscopy. Child-Pugh scores, Child Classes and MELD-Na scores were calculated. Endoscopy reports were evaluated for the presence of esophageal or gastric varices. If present, esophageal varices were classified as higher- and lower-risk (2)

Machine Learning Models, Feature Selection and Model Training

Adopted machine learning method -Light Gradient Boosting Machine- is an ensemble of multiple decision trees algorithms that learns from each tree to generate a final accurate model of its own (Ke et al. 2017; Chen and Guestrin 2016). We used our database both to train and test the algorithms prediction performance. To increasing the generalizability of our results, we used multiple different splits for training and testing the algorithm. We shuffled the data before every iteration and split it into different training and test sets with four to one ratio that was repeated 50 times. As our population size is limited, we were not able to integrate all variables into the final model that would cause overfitting. We used two feature importance techniques - permutation feature importance and leave-one-out feature importance - to determine which variables to include. Those parameters are selected intuitively rather than using a black box optimizer which can induce overfitting. As the output, mean of 50 models' area under the rule operator curves (AUC) is presented

and standard deviation of the scores is the confidence interval

Outcomes and Statistical Analyses

The characteristics of patient populations was presented with descriptive statistics using median with range for non-parametric continuous variables, mean with standard deviation for parametric continuous variables and ratios with percentages for categorical variables. Patients with and without varices were compared using Mann Whitney U and Chi-square tests when appropriate. A binary logistic regression model was used to find variables that predicts presence of varices. Areas under the ROCs of MELD-Na (3), CTP (4), AST to Platelet Ratio Index (APRI)(5), and Platelet Count to Spleen Diameter (PC/SD)(6), FIB-4(7) scores and AST to ALT ratio were compared to machine learning models for prediction of cirrhosis.

Results

Patient Population

We included 201 patients of clinically or radiologically confirmed cirrhosis. Mean age of the population was 58.0 (16.3). Etiologies of cirrhosis were chronic Hepatitis B, chronic Hepatitis C, non-alcoholic steatohepatitis, alcoholic liver disease, autoimmune liver diseases, Wilson's disease, primary and secondary hemochromatosis, congenital liver diseases, Budd-Chiari syndrome, congenital or acquired hypercoagulatory disorders. Median Child-Pugh score of population was 7 (5-13), 86 cases were Class A, 81 cases were Class B and 34 cases were Class C. Median MELD-Na score of the population was 10 (6-40); 93 patients scores were between 6 and 9, 53 patients scores were between 10 and 19, 23 patients scores were between 20 and 29, and 21 patients scores were equal to or greater than 30 (Table 1).

Varices and Predicting Variables

One-hundred and five patients had esophageal varices as opposed to 96 patients. Of 105 varices, 63 were low-risk and 33 were higher risk. Patients with varices were older (63 vs 54), higher Child-Pugh scores, larger splenic diameters (15.1 vs 13.9) advanced Child stages (64 Child B-C vs. 52 Child B-C)as well as higher MELD-Na scores (19 vs 13).

A binomial logistic regression was performed to ascertain the effects of age, splenic vein diameter, platelet counts and MELD-Na scores on the likelihood that patients have varices. The logistic regression model was statistically significant, $\chi 2(4) = 19.20$, $p < .001$. The model explained 14.0% of the variance in presence of esophageal varices and correctly classified 52.% of cases. Composite scores were calculated and their AUCs to classify presence of varices were as follows: FIB-4 0.57 (0.49-0.65), APRI 0.47 (0.38-0.55), PCSD 0.511 (0.42-0.59), AAR 0.481 (0.39-0.56) (Figure 1).

Table 1. Characteristics of our study population

		Mean (SD) / Number (%)
Age		58 (1)
Gender	Male	97 (48.3%)
	Female	104 (51.7%)
Etiology of Liver Disease	Chronic Hepatitis B	28 (14.4%)
	Chronic Hepatitis C	6 (3.1%)
	Non-alcoholic steatohepatitis	27 (13.9%)
	Alcoholic liver disease	12 (6.2%)
	Cryptogenic	58 (29.9%)
	Autoimmune liver diseases	6 (3.1%)
	Vascular and hypercoagulability	39 (20.1%)
	Malignancy	12 (6.2%)
	Congenital liver diseases	6 (3.1%)
Child Class	Class A	86 (42.8%)
	Class B	81 (40.3%)
	Class C	34 (16.9%)
MELD-Na Group	<10	93 (48.9%)
	19-Oct	53 (27.9%)
	20-29	23 (12.1%)
	>30	21 (11.1%)
Hemoglobin (g/dL)		12.4 (3)
Platelet Count (^3 / mL)		137 (6)
Sodium (mg/dL)		136 (0)
Creatinine (mg/dL)		0.88 (0.04)
ALT (IU/mL)		35 (2)
AST (IU/mL)		56 (5)
ALP (IU/mL)		149 (9)
GGT (IU/mL)		123 (11)
Bilirubin (mg/dL)		686 (392)
INR		2817 (951)

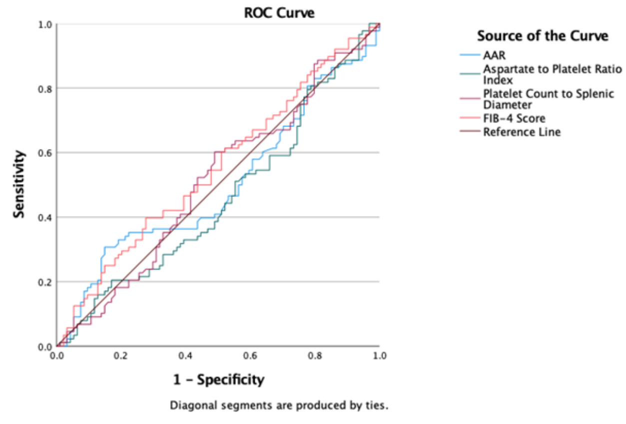
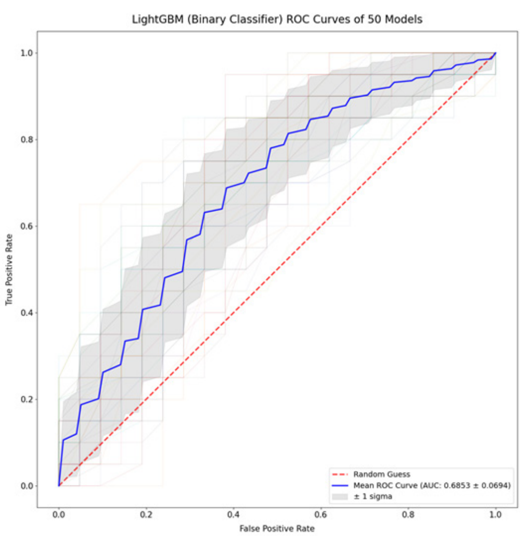


Figure 1. Area under the rule operator curves for APRI, AAR, FIB-4 scores and PCSD ratio to classify patients with cirrhosis.

Model Outputs

Machine learning model's classification performance was tested with prediction of esophageal varices in patients with cirrhosis. Feature selection as described choose following variables: Gender, presence of ascites, presence of encephalopathy, Child-Pugh Score, Platelet counts. Machine learning models mean AUC to predict varices was 0.68(0.060), F1- score was 0.7 and accuracy was 63%. (Figures 2).

Table 2. Features of patients with and without cirrhosis				
		Varices at Upper Endoscopy		p
		No	Yes	
		Mean (SD)	Mean (SD)	
Age		54 (17)	63 (14)	0.000
Platelet Count		144 (94)	129 (87)	0.235
Splenic largest diameter (cm)		15.1 (3.9)	13.8 (3.5)	0.06
Child Class	Class A	53	33	0.06
	Class B	38	43	
	Class C	14	20	
MELD-Na		13.9252	19.3 (11)	0.006
Aspartate to Platelet Ratio Index		1.94 (4.72)	1.58 (1.84)	0.875
Platelet Count to Splenic Diameter		10.54 (8.86)	10.16 (8.04)	0.893
FIB-4 Score		5.04 (4.08)	5.95 (4.53)	0.65



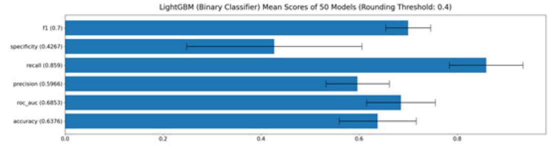


Figure 2. Mean of 50 machine learning models area under rule operator curves to classify patients with cirrhosis.

Discussion

We tested the feasibility of a machine learning model to predict presence of esophageal varices in cirrhotic patients. Our model achieved a higher performance for this task when compared to other composite scores with an AUC of 0.68 which was higher than FIB-4's (0.57), APRI's (0.47), AAR (0.481) and PCSD's (0.511).

Screening for varices is an essential component of clinical management of patients with cirrhosis. Upper endoscopy remaining as the gold standard, current recommendation is the use of non-invasive tests to stratify patients for screening endoscopy. Transient elastography reached sensitivities and specifities over 90% and with the expanded Boveno IV criteria it is now incorporated into clinical practice (1). However, transient elastography is operator dependent and requires costly imaging. In contrast, non-elastographic tests such as APRI score, PCSD ratio, FIB-4 and AAR use readily available laboratory data. However, the tests without elastography have not reached the performance of transient elastography and low to moderate accuracy (8). Previous studies with APRI score

demonstrated specifities between 51%-89% and sensitivities varying between 56% to 71% (9-11). FIB-4 score's and AAR index's performances were similar with sensitivities between 37%-85% and specifities of 64%-81% of (10, 12); sensitivities of 68%-69% and specifities of 34%-89% (8).

Above mentioned non-elastographic scores and indexes use one to three variables to predict a and a complex physiology and a multifactorial condition. Artificial intelligence provides a new perspective to this problem with its ability to integrate greater number and extent of variables to the final decision. As such, there have been several studies using this approach to predict varices. Dong et al created a score using a similar decision tree based machine learning algorithm to create a formula using INR, platelets, BUN, Hemoglobin and ascites. This composite score classified patients with varices with AUC of 0.81 in validation cohort (13).

We acknowledge our studies limitations inherent to retrospective design, small population size, and the use of machine learning methods. Artificial intelligence own specific limitations such as over-fitting regardless of multiple training and test splits as mentioned. Further validation of our model in different and larger datasets is required. We also acknowledge neither AUC of 0.68 of our algorithm nor the sample size of our study is enough to implement artificial intelligence alone by a mean of varix screening but only as a proof of concept for this clinical problem. Moreover, we need to test different algorithms for prediction of varices in different contexts as their pathophysiology, therefore predictive factors, will be presumably different(14).

Knowledge gaps in the management of liver diseases can be targeted with artificial intelligence methods as we already own the required big multimodal data that include radiology, genomics, clinical and laboratory variables. Despite this promise, the future of artificial intelligence in hepatology depends on further efforts and prospective studies.

References

1. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology. 2017;66(6):1980-8.
2. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases (vol 65, pg 310, 2017). Hepatology. 2017;66(1):304-5.
3. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-70.
4. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.
5. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53(3):726-36.
6. Giannini EG, Botta F, Borro P, Dulbecco P, Testa E, Mansi C, et al. Application of the platelet count/spleen diameter ratio to rule out the presence of oesophageal varices in patients with cirrhosis: a validation study based on follow-up. Dig Liver Dis. 2005;37(10):779-85.
7. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317-25.
8. Deng H, Qi XS, Guo XZ. Diagnostic Accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis A Systematic Review and Meta-Analysis. Medicine. 2015;94(42).
9. Tafarel JR, Tolentino LHL, Correa LM, Bonilha DR, Piauilino P, Martins FP, et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J Gastroen Hepat. 2011;23(9):754-8.
10. Stefanescu H, Grigorescu M, Lupsor M, Maniu A, Crisan D, Procopet B, et al. A New and Simple Algorithm for the Noninvasive Assessment of Esophageal Varices in Cirrhotic Patients Using Serum Fibrosis Markers and Transient Elastography. J Gastrointest Liver. 2011;20(1):57-64.
11. Wang JH, Chuah SK, Lu SN, Hung CH, Chen CH, Kee KM, et al. Transient elastography and simple blood markers in the diagnosis of esophageal varices for compensated patients with hepatitis B virus-related cirrhosis. J Gastroen Hepatol. 2012;27(7):1213-8.
12. B CL-GN, De Vinatea-Serrano L, Piscoya A, Segura ER. [Performance of the FIB-4 index in esophageal varices screening in patients with the diagnosis of liver cirrhosis]. Rev Gastroenterol Peru. 2020;40(1):29-35.
13. Dong TS, Kalani A, Aby ES, Le L, Luu K, Hauer M, et al. Machine Learning-based Development and Validation of a Scoring System for Screening High-Risk Esophageal Varices. Clinical Gastroenterology and Hepatology. 2019;17(9):1894-901.e1.
14. Beyazit Y, Ibis M, Purnak T, Turhan T, Kekilli M, Kurt M, et al. Elevated levels of circulating angiotensin converting enzyme in patients with hepatoportal sclerosis. Digestive diseases and sciences. 2011;56(7):2160-5.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 630-633
https://doi.org/10.31067/acusaglik.849518

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Ophthalmology / Göz Hastalıkları

Endonasal Dacryocystorhinostomy; the learning curve and our experience

İsmet Emrah Emre[1], Ali Rıza Cenk Çelebi[2]

[1]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, KBB-BBC ABD, İstanbul, Türkiye

[2]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, Göz Hastalıkları, İstanbul, Türkiye

İsmet Emrah EMRE, Dr. Öğr. Üyesi

Ali Rıza Cenk ÇELEBİ, Doç. Dr.

Correspondence: Ali Rıza Cenk Çelebi
Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, Göz Hastalıkları, İstanbul, Türkiye
Phone: +902124044080
E-mail: arcenkcelebi@gmail.com

Received : 24 December 2019
Accepted : 23 April 2020

ABSTRACT

Aim: It was aimed to give an insight on the learning curve adopted by an ophthalmic surgeon while performing endonasal dacryocystorhinostomy under the supervision of an otolaryngologist with the results experienced during this survey.

Materials and Methods: In this retrospective study, consecutive cases with endonasal dacryocystorhinostomy (DCR) surgery were performed by a single ophthalmic surgeon while a second otolaryngologist was overlooking the procedures. A total of 29 surgeries were performed on 23 patients. Patients that were diagnosed with complete nasolacrimal duct obstruction were then evaluated and proceeded to the surgery. The intraoperative video was recorded in all surgical cases and recording time was noted for each case. All of the complications that occurred during or at the postoperative stages were noted.

Results: The mean age of the 23 patients was 55.25±18.6 years (15 y-80 y), of which 20 cases (87%) were female. The left side was involved in 69% (20/29) of cases. At the final follow-up of the mean of 12,4 months, the anatomical and functional success was achieved in 89% (26/29) cases. The mean time spent in the operating theatre was 84±17.2 minutes (range, 40–110 min). It was found that the only 3 failed surgeries were in the first 5 surgeries performed with no surgical failure in the remaining 24 eyes.

Conclusions: Endonasal dacryocystorhinostomy is a safe, effective and cosmetically pleasing surgery for the treatment of nasolacrimal duct obstruction. Although it has a somewhat longer learning curve than some surgeries, once handling of the endoscope has been mastered and familiarity with the surgical field is improved, the duration of the surgery will decrease significantly. We believe multidisciplinary coordination plays an important role in decreasing potential complication rates and also in perfecting the technique.

Keywords: Endonasal Dacryocystorhinostomy, Ophthalmologist, Surgery Time, Learning Curve

Endonazal Dakriyosistorinostomi; Öğrenme Eğrisi ve Tecrübelerimiz

ÖZET

Amaç: Bu araştırma sırasında elde edilen sonuçlar ile bir kulak burun boğaz uzmanının gözetimi altında bir oftalmik cerrah tarafından gerçekleştirilen endonazal dakriyosistorinostomi operasyonunun öğrenme eğrisi hakkında bilgi verilmesi amaçlandı.

Hastalar ve Yöntem: Bu retrospektif çalışmada, endonazal dakriyosistorinostomi ameliyatı olan ardışık olgular, tek bir oftalmik cerrah tarafından ikinci bir kulak burun boğaz uzmanı gözetiminde gerçekleştirildi. 23 hastaya toplam 29 ameliyat yapıldı. Tam nazolakrimal kanal tıkanıklığı tanısı konulan hastalar değerlendirildi ve ameliyat edildi. Tüm cerrahi vakalar intraoperatif olarak kaydedildi ve her vaka için kayıt süresi belirlendi. Postoperatif dönemde veya sonrasında meydana gelen komplikasyonların tümü kaydedildi.

Bulgular: 23 hastanın yaş ortalaması 55.25 ± 18.6 yıl (15 yaş-80 yaş) idi; bunlardan 20'si (% 87) kadındı. Sol taraf tıkanıklığı vakaların % 69'unda (20/29) yer aldı. Ortalama 12,4 aylık takip sonunda, % 89 (26/29) olguda anatomik ve fonksiyonel başarı elde edildi. Ameliyathanede harcanan ortalama süre 84 ± 17,2 dakika idi (aralık, 40-110 dakika). Sadece 3 başarısız ameliyatın ilk 5 ameliyat arasında olduğu tespit edildi, geri kalan 24 vakada başarısızlık saptanmadı.

Sonuç: Endonazal dakriyosistorinostomi, nazolakrimal kanal tıkanıklığının tedavisi için güvenli, etkili ve kozmetik açıdan kabul edilen bir ameliyattır. Bazı ameliyatlardan biraz daha uzun bir öğrenme eğrisine sahip olmasına rağmen, endoskopun kullanımı ustalaştıktan ve cerrahi alanın aşinalığı geliştirildikten sonra, ameliyat süresi önemli ölçüde azalacaktır. Multidisipliner koordinasyonun potansiyel komplikasyon oranlarının azaltılmasında ve tekniğin mükemmelleştirilmesinde önemli bir rol oynadığına inanıyoruz.

Anahtar Sözcükler: Endonazal Dakriyosistorinostomi, Oftalmolog, Cerrahi Süre, Öğrenme Eğrisi

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Dacryocystorhinostomy (DCR) was first described over 100 years ago (1) and is the treatment of choice for patients with nasolacrimal duct obstruction. In this surgery, the nasolacrimal duct is bypassed via an alternative tract formed between the lacrimal sac and the nasal cavity. It can be performed via an external or endonasal approach. Although the endonasal approach (2) was described earlier than the external technique, (1) it was not until the advent of the nasal endoscope (3) that the endonasal technique gained popularity. This was mainly due to the limited visibility of the surgical site and nasal anatomy during the endonasal approach. McDonogh first described the technique used today in 1989 (4). The major advantages of the endonasal approach are the absence of an external scar, the preservation of the orbicularis oculi pump action on the lacrimal sac and the avoidance of dividing the medial canthal ligament (5). However, this technique also has disadvantages including a higher equipment cost, a steeper learning curve, a smaller opening between the lacrimal sac and the nasal cavity and a higher recurrence rate (6). Both otolaryngologists and ophthalmologists have been adopting the endonasal approach more frequently with the advance in equipment made available for this surgery. In this study, we aim to show our results and also give an insight on the learning curve adopted by the novice ophthalmic surgeon (ARCC) while performing this surgery under the supervision of the experienced otolaryngologist (IEE).

Materials and Methods

Study Design

This was a retrospective study involving consecutive cases with surgery performed by a single surgeon (ARCC) with a second surgeon (IEE) overlooking procedures.

During the period between 2017-2019, a total of 29 surgeries were performed on 23 patients. All patients were evaluated for symptoms including excessive epiphora and recurrent eye infections. All patients were first evaluated by an ophthalmologist and a dacryoscintigraphy was performed for each patient. Patients who were diagnosed with nasolacrimal duct obstruction were then evaluated by an otorhinolaryngologist prior to surgery. Patients were examined for the presence of any anatomical obstruction that could have hindered the endonasal DCR including septal deviation, turbinate hypertrophy or concha bullosa. An informed consent was obtained from each patient regarding every aspect of the surgery.

Surgical Procedure

All surgeries were carried out in a supine position under general anesthesia. Before the beginning of surgery, cotton pledges soaked in 0.05% oxymetazoline were placed in the nasal cavity and between the middle turbinate and lateral nasal wall. These pledges were removed after 5-10 minutes and the lateral nasal wall mucosa was then infiltrated with local anesthetic (Jetokain HCL/adrenaline) under direct visualization with a rigid fiber-optic endoscope. A reverse and upside -down L incision was made on the mucosa with a horizontal 1.5 cm incision made from the anterior part of the attachment of the middle turbinate and a vertical incision made downwards towards the inferior turbinate. The mucosa was then elevated using a freer elevator and the bone medial to the lacrimal sac was fully exposed. We then removed the lacrimal bone with a high-speed drill and a combination of rongeurs. After the exposure of the lacrimal sac, we then infiltrated the sac with gel to facilitate easier removal of the medial wall of the sac. A vertical incision was placed in the sac and a large portion of the medial wall was removed. Bi-canalicular silicon tube insertion through both the upper and lower puncta was then performed and adequate opening of the sac was confirmed if both ends of the silicone tube passed freely through the opening. The silicone was then knotted in the nasal cavity.

Results

Twenty-nine endonasal DCR procedures were performed on 23 patients with a mean age of 55.25±18.6 years (15 y-80 y), of which 20 cases (87%) were female. All cases had complete nasolacrimal duct obstruction (NLDO) confirmed with dacryoscintigraphy. The left side was involved in 69% (20/29) of cases. Three cases (13%) required septoplasty (with sub-mucosal resection performed by IEE) at the time of DCR. Endonasal DCR in these cases were all successfully completed (ARCC).

The mean time spent in the operating theatre was 84±17.2 minutes (range, 40–110 min). This included packing of the nasal cavity, local infiltration, surgery and early recovery. The intraoperative video was recorded in all surgical cases and recording time was noted. There were no intra-operative complications; however, postoperatively 3 patients (10%) had significant adhesions between the lateral wall of the nose and nasal septum. Of the 3 failed cases, all underwent revision surgery with removal of adhesions.

Video analysis of the primary surgery highlighted inadequate exposure of the maxillary crest in the 2 failed cases

which were both earlier cases in respect to this study. In the remaining one case, the posterior nasal mucosal flap was not fully retroplaced during removal of the maxillary crest. No significant bleeding occurred in that case. Revision surgery required removal of adhesions in 2 of the 3 cases and one case required granuloma excision. All revision surgeries were anatomically successful with complete recovery from symptoms.

Postoperative complications that were noted included mild epistaxis seen in 7% (2/29) and stent prolapse, which was found in 3% (1/29). Stent prolapse occurred 1 week following surgery and repositioning was done under endoscopic guidance in an outpatient facility. Stent extrusion was not noted. Ostium granulomas occurred in two cases and were managed conservatively in one with the use of topical steroids; the second case underwent revision surgery.

At the final follow-up of the mean of 12,4 months, anatomical and functional success was achieved in 89% (26/29) cases. Of the three cases that failed, the presenting diagnosis was recurrent chronic dacryocystitis.

Discussion

The endonasal DCR is a widely adopted, effective and safe treatment for nasolacrimal duct obstruction. However, there is no consensus on how to perform the surgery. There are multiple components that are still being debated today including the use of mitotic agents, the use of a silicone tube during surgery and the use of the laser to create an opening in the nasal cavity. Some surgeons prefer to apply antimitotic agents to decrease the incidence of granuloma formation, which is expected to be the major cause of surgical failure (7). A study by Qin et al (8) showed a significantly higher success rate in patients undergoing endonasal DCR who also had mitomycin C (MMC) applied during the surgery. However, Roozitalab et al found that the application of MMC was not beneficial in their study of external DCR (9). In our experience, we did not use any type of anti-mitotic agent and had 2 cases of failure due to granuloma formation. This rate of failure due to granuloma formation was similar to previous studies regarding failed endonasal DCR (7)

Another debatable subject is the use of silicone tubing during the surgery. The placement of a silicone tube through both puncta which is then knotted in the nasal cavi-ty has been proposed to decrease rates of failure. However, multiple studies have found this not to be true (10-12). In our study, we used silicone tubing in 28 of our cases and did not use tubes in only 1 patient. Our reason for this was because all patients had some degree of canalicular obstruction prior to surgery.

Although every surgery has a learning curve, the curve for this surgery is hindered by the inexperienced surgeons' lack of endoscope use. The otorhinolaryngologist is adapted to use the endoscope from the first day of residency; however, the ophthalmologist who does not perform endonasal DCR may never have used the endoscope in their career. In our study, we noted a slow decrease in the overall time for surgery until the 12th case. From this point onwards, there was a major decrease in surgical time which was attributed to improved handling of the endoscope and increasing familiarity with the surgical field (figure 1). Although a study by Onerci et al (13) stated a higher percentage of complications between experienced and novice surgeons, we found there to be no major difference in complication rates to previous studies performed by experienced surgeons. This we feel is the result of a multidisciplinary approach of two specialties dedicated to learning and teaching. Another study that looked into the training curve for endoscopic DCR showed a sharp decrease in operative time after the 27th case (14). We also found there to be a sharp decrease after the 12th surgery that continued to decrease until the 29th surgery. Lee et al (15) showed an increase in positive surgical outcomes after 30 cases in their study. In our study, we also found that the only 3 failed surgeries were in the first 5 surgeries performed with no surgical failure in the remaining 24 eyes.

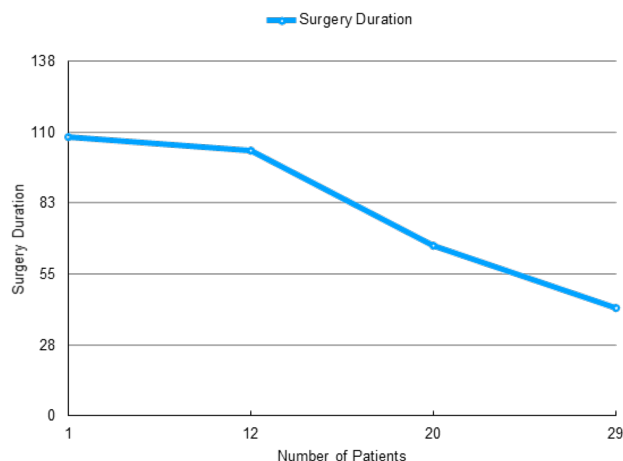


Figure 1: A chart depicting the decrease in the duration of the surgical session. Note the significant decrease in surgical time after surgery number 12.

Conclusion

Endoscopic DCR is a safe, effective and cosmetically pleasing surgery for the treatment of nasolacrimal duct obstruction. Although it has a somewhat longer learning curve than some surgeries, once handling of the endoscope has been mastered and familiarity with the surgical field is improved the duration of the surgery will decrease significantly. We believe that a multidisciplinary coordination plays an important role in decreasing potential complication rates and also in perfecting the technique.

References

1. Toti A. Nuovometodoconservatore di cura radicle delle suppurazonicroniche del saccolacrimale (Dacriocistorinostomia). Clin Mod Fir 1904; 10: 385-7.
2. Caldwell GW: Two new operations for obstruction of the nasolacrimal duct, NYJ Med 1893; 57: 581-2.
3. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recur-ring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. Oto-laryngol Head Neck Surg. 1986; 94: 143-7.
4. J McDonogh M, Meiring JH. Endoscopic transnasal dacryocystorhinostomy. Lar-yngol Otol. 1989; 103: 585-7.
5. Hartikainen J, Antila J, Varpula M, Puukka P, Seppa H & Grenman R. Prospective randomized comparison of endonasal endoscopic dacryocystorhinostomy and ex-ternal dacryorhinostomy. Laryngoscope 1998; 108: 1106– 13.
6. Jawaheer L, MacEwen CJ, Anijeet D. Endonasal versus external dacryocystorhi-nostomy for nasolacrimal duct obstruction. Cochrane Database Syst Rev. 2017;24(2):CD007097.
7. Baek JS, Jeong SH, Lee JH, Choi HS, Kim SJ, Jang JW. Cause and management of patients with failed Endonasal Dacryocystorhinostomy. Clin Exp Otorhinolaryn-gol. 2017; 10: 85-90.
8. Qin ZY, Lu ZM, Liang ZJ. Application of mitomycin C in nasal endoscopic dacryo-cystorhinostomy. Int J Ophthalmol 2010; 10: 1569-71.
9. Roozitalab MH, Amirahmadi M, Namazi MR. Results of the application of in-traoperative mitomycin C in dacryocystorhinostomy. Eur J Ophthal 2004; 14: 461-3.
10. Smirnov G, Tuomilehto H, Terasvirta M, Nuutinen J, Seppa J. Silicone tubing after endoscopic dacryocystorhinostomy: is it necessary?. Amer J Rhino 2006; 20: 600-2.
11. Unlu HH, Gunhan K, Baser EF, Songu M. Long term results in endoscopic dacryo-cystorhinostomy: is intubation really required?. Otolaryngology - Head & Neck Sur-gery 2009; 14: 589-95.
12. Feng YF, Cai JQ, Zhang JY, Han XH. A meta-analysis of primary dacryocystorhi-nostomy with and without silicone intubation. Can J Ophthalmol. 2011; 46: 521-7.
13. Onerci M, Orhan M, Ogretmenoğlu O, Irkeç M. Long-term results and reasons for failure of intranasal endoscopic dacryocystorhinostomy. Acta Otolaryngol. 2000; 120: 319-22.
14. Kamal S, Ali MJ, Nair AG Outcomes of endoscopic dacryocystorhinostomy: Experi-ence of a fellowship trainee at a tertiary care center.Indian J Ophthalmol. 2016 Sep;64(9):648-653.
15. Lee JJ, Lee HM, Lim HB, Seo SW, Ahn HB, Lee SB. Learning Curve for Endoscop-ic Endonasal Dacryocystorhinostomy. Korean J Ophthalmol. 2017 Aug;31(4):299-305.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 634-638
https://doi.org/10.31067/acusaglik.847284

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Plastic and Reconstructive Surgery / Plastik ve Rekonstrüktif Cerrahi

Surgical Outcomes and Complications in Patients with Early-Stage Dupuytren's Contractures

Yahya Baltu[1]

[1]Özel Muayenehane, Plastik ve Rekonstrüktif Cerrahi, Ankara, Türkiye

Yahya BALTU, M.D.

ABSTRACT

Aim: This study aimed to assess the functional outcomes and complications of patients operated on for early-stage Dupuytren's contracture.

Patients and Methods: We retrospectively included 40 patients who presented to our clinic with early-stage Dupuytren's contracture. Age, sex, involved hand and finger(s), and contracture grade were assessed. All patients were examined for concurrent trigger finger, penile curvature, or plantar flexion contracture of the foot. The study involved patients with painful nodules and contractures of 0-45 degrees at the metacarpophalangeal joint.

Results: A total of 52 hands of 40 patients (24 men, 16 women; mean age: 57.6 years) underwent partial fasciectomy. The contractures were located in the right hand in 12 cases; left hand in 16; and both hands in 12; they were located in the fourth finger in 10 hands; fifth finger in 6 hands; fourth and fifth fingers in 12 hands; and along with third, fourth and fifth fingers in 24 hands. The mean follow-up period was 25.9 (range 2-100) months. No patient developed infection, hematoma, skin necrosis, nerve or vessel cuts postoperatively. Three patients had an opening of the sutures which were left to secondary healing. No patient was re-operated for Dupuytren's contracture. Trigger finger was observed in 7 (17.5%) patients and accompanying plantar fibromatosis in 4 (10%) patients.

Conclusion: Early surgery for Dupuytren's contracture can achieve high surgical success and low complication rates. Surgery performed when adhesions to the skin and adjacent tissues and skin contracture are mild has been shown to reduce re-operation rate.

Keywords: Dupuytren; contracture; palmar; fascia; fibromatosis

Erken Evre Dupuytren Kontraktürü Olan Hastalarda Cerrahi Sonuç ve Komplikasyonlar

ÖZET

Amaç: Bu çalışmada erken evre Dupuytren kontraktürü nedeniyle ameliyat edilen hastalar incelenip fonksiyonel sonuç ve komplikasyonların değerlendirilmesi amaçlanmıştır.

Hastalar ve Yöntem: Kliniğimize erken evre Dupuytren kontraktürü nedeniyle başvuran 40 hasta retrospektif olarak incelendi. Hastaların yaş, cinsiyet, hangi el ve elde hangi parmakların etkilendiği, kontraktür derecesi irdelendi. Beraberinde tetik parmak, penil kontraktür veya ayakta plantar kontraktür varlığı açısından incelendi. Çalışmaya ağrılı nodülleri olan ve metakarpofalangeal eklemde 0-45 derece kontraktürü olan hastalar dahil edildi. Daha ciddi kontraktürü olan hastalar çalışmaya dahil edilmedi.

Bulgular: 40 hastada (24 erkek, 16 kadın; ortalama yaş: 57.6) toplam 52 elde parsiyel fasciektomi yapıldı. Vakaların 12'si sağ elde; 16'sı sol elde; 12'si bilateral olarak raporlandı. 10 elde dördüncü parmakta, 6 elde beşinci parmakta, 12 elde dört ve beşinci parmakta 24 elde ise üç, dört ve beşinci parmak trasesinde kontraktür mevcut idi. MP eklemde Ortalama cilt kontraktürü 14,2 derece idi. Hastalar ortalama 25,9 (2-100) ay takip edildi. Hastaların postoperatif dönemde hiçbirinde enfeksiyon, hematom, cilt nekrozu ve sinir ya da damar kesilmesi görülmedi. 3 hastada sütür açılması görüldü, ikincil iyileşmeye bırakıldı. Hiçbir hasta elde Dupuytren kontraktürü nedeniyle tekrar ameliyat edilmedi. Tetik parmak 7 hastada(%17.5) eş zamanlı olarak görüldü. 4(%10) hastada aynı zamanda plantar fibromatozis mevcut idi.

Sonuç: Erken dönemde yapılan Dupuytren kontraktürü cerrahisinde yüksek cerrahi başarı ve düşük komplikasyon oranı elde edilebilir. Ayrıca, cilde ve etraftaki dokulara yapışıklığın az olduğu dönemde yapılan cerrahinin re-operasyon oranını azalttığı görülmüştür.

Anahtar kelimeler: dupuytren; kontraktür; palmar; fasya; fibromatozis

Correspondence: Yahya Baltu
Özel Muayenehane, Plastik ve Rekonstrüktif Cerrahi, Ankara, Türkiye
Phone: +905323978887
E-mail: baltuyahya@gmail.com

Received : 16 December 2019
Accepted : 23 February 2020

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Dupuytren's contracture is a disease state characterized by benign proliferation of the digito-palmar fascia on the palmar surface of the hand and the flexor aspect of the fingers. It manifests with flexion contractures in the hand as a result of the thickened palmar aponeurosis. Although its etiology is not entirely clear, a positive family history and different incidences across populations suggest a genetic transmission. Studies have shown an increased prevalence with certain conditions such as alcoholism and smoking, renal and hepatic disorders, and diabetes. Whereas it is frequent in Northern European and Scandinavian populations, it is less common in Asian and African countries. In Japanese, the disease starts later and progresses more slowly. This suggests a genetic influence on the condition (1,2). Dupuytren disease typically begins 10 years earlier and has a more severe natural course in men than in women, in whom contractures often develop more slowly and later in life. Contractures are usually found bilaterally; when they are unilateral, the condition has a milder course. The clinical course is more severe among alcoholics and patients with epilepsy than patients with a trauma history (2-4).

Dupuytren's contracture is diagnosed on clinical grounds. Various classification schemes have been defined to grade Dupuytren's contracture. Tubiana's classification is a commonly used clinical classification system for Dupuytren's contracture (1).

Patients and Materials

The medical information of 40 patients who presented to our clinic with early-stage Dupuytren's contracture was retrospectively reviewed. Age, sex, family history, involved hand and finger(s), and contracture grade were assessed. Patients were examined for the presence of trigger finger, penile curvature, or plantarflexion contracture of the foot. The study used the Tubiana grading to select patients with painful nodules and grade 1 (contractures of 0-45 degrees) contractures of the metacarpophalangeal (MCP) joint. Patients with more severe contractures involving digits and proximal interphalangeal (PIP) joints were excluded.

Surgical technique

All surgeries were performed under tumescent local anesthesia infiltrated to a wide area or under general anesthesia. Ten minutes after achieving local anesthesia using epinephrine, superficial palmar fascia leading toward the third, fourth, and fifth fingers was excised. Then, partial fasciectomy was performed using Bruner zig-zag incisions in cases with mild skin contractures and multiple Z-plasties in those with moderately severe skin contractures. The bands traversing toward tendons were freed using blunt and sharp dissections while preserving neurovascular structures. After achieving hemostasis, a Penrose drain was placed and the skin was closed with 4/0 non-absorbable sutures (Fig. 1).

Results

Partial fasciectomy was carried out in a total of 52 hands of 40 patients (24 men, 16 women). The mean age was 57.6 (36-82) years. Contractures were located in the right hand in 12 cases; left hand in 16; and both hands in 12. They were located to the fourth finger in 10 hands; fifth finger in 6 hands; fourth and fifth fingers in 12 hands; and along third, fourth and fifth fingers in 24 hands. The patients were followed for a mean of 25.9 (2-100) months. None of the patients suffered infection, hematoma, skin necrosis, or nervous or vascular injury postoperatively. Three patients had an opening of sutures which were left to secondary healing. The most common accompanying condition was trigger finger (7 patients (%17.5)), which was corrected at the operation. Penile curvature was not observed in any patient. Four (10%) patients had concurrent plantar fibromatosis. All specimens sent to histopathological examination were reported to contain palmar fibromatosis (Fig. 2).

Discussion

Although the exact underlying cause of Dupuytren's contracture cannot be explained, mechanisms related to connective tissue and cellular changes occurring in its histopathology have been well explained. It is generally argued that Dupuytren disease is characterized by an uncontrolled increase of collagen III and extracellular matrix. Luck et al (5) divided the disease into three phases, namely proliferative, involutional, and residual phases. In the proliferative phase, myofibroblasts begin to show a dramatic increase. These nodules expand toward the surface, replace subcutaneous fat tissue, and adhere to deep layers of the skin. In the involutional phase, nodules become smaller and firmer along the longitudinal axis, mostly on the ulnar side. The condition's progress is characterized by the formation of cords by the organization of the abnormal connective tissue and Type 3 collagen accumulation.

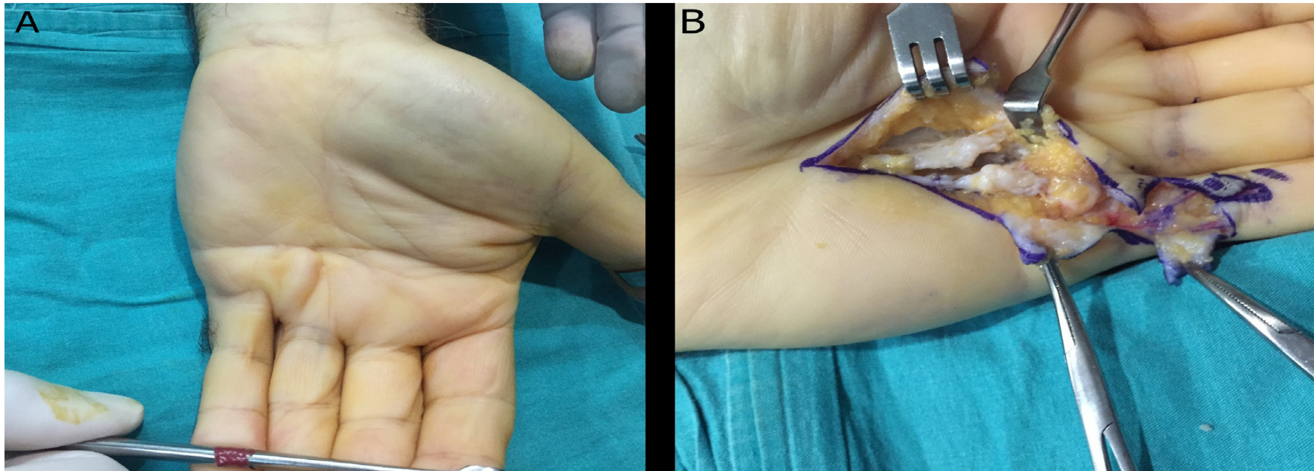


Figure 1: A: A 65-year-old patient with a Dupuytren's contracture extending from the palm to the PIP joints of the 4th and 5th fingers. B: The contractures were opened with Z-plasties. A partial fasciectomy was performed.

Figure 2: A 56-year-old patient with palmar fibromatosis causing a flexion contracture of approximately 30 degrees that extended from the palm to the PIP joint of the fourth finger. A: The front view of the Dupuytren contracture. B: Palmar fibromatosis cords (intraoperative view). C: The area was cleared off the contractures with multiple Z-plasties. D: The view at 3rd month after surgery.

Abnormal collagen cross-links, coupled with contraction force produced by myofibroblasts, leads to contracture development. In the residual phase, nodular appearance vanishes and tendon-like thick fibrous bands develop. The cords may shorten and become more prominent, and they may cause more flexion and contracture in the MCP and PIP joints (5-7).

Although former clinical studies have shown that triamcinolone and collagenase injections are effective for management when the disease is in the early, nodular form, the recurrence rates have been reported to be high. Therefore, the current gold standard treatment for Dupuytren disease is still surgical excision of fibrotic bands causing contractures and correction of contractures (2,3).

There are several surgical options including percutaneous fasciectomy, partial fasciectomy, total fasciectomy, segmentary fasciectomy. Percutaneous needle fasciectomy, as a procedure commonly performed under local anesthesia on an outpatient basis, may become a cost- and resource-effective option particularly for elderly patients or for those who are unwilling to undergo a more serious invasive treatment or who have medical comorbidities. However, Dupuytren's contracture has a very high recurrence rate with needle fasciotomy; among patients undergoing percutaneous fasciotomy who experienced the return of Dupuytren's contracture suffered a recurrence rate of 65% to 90% between 3 to 5 years. The complication rates are lower, but complications such as transient neuropraxia or injury to the 5th digit's digital nerve may occur (4,8,9).

Partial fasciectomy is the most commonly preferred technique owing to a lower recurrence rate (about 20-25%) compared to percutaneous fasciotomy. However, complications such as infection, hematoma formation, and injury to a digital nerve or vascular structures are more common (10). In this study, patients with early-stage Dupuytren's contracture were enrolled. All patients were operated on with partial fasciectomy. None of them needed re-operation. Högemaan et al. reported a recurrence rate of 10.8% and a complication rate of 13.8% following total fasciectomy (11). We considered that as our patients also had early-stage Dupuytren's contracture, not only the site of contracture, but also palmar fascia leading to the 3rd, 4th, and 5th fingers were included by the incision, which reduced the recurrence rate.

In cases with Dupuytren's contracture, palmar fascia may be injured owing to its anatomic proximity to nerves and vessels. As the volume of contracture increases, palmar fascia invades surrounding nerves, skin, and tissues to a greater degree and anatomically deeper structures. Yenidünya et al. (12), in a study of 18 patients with most having a contracture of less than 30 degrees; reported a low complication rate with only one patient having had partial necrosis on skin flap. In our study, no major or minor complication was seen except for suture opening in 3 patients. These findings indicate that the complication rate of early Dupuytren surgery is lower than that performed in patients with more severe contractures. Particularly in cases with bilateral hand involvement, operating the other hand early in the course may achieve a more functional outcome.

Conclusion

Dupuytren's contracture surgery performed at an early period can achieve high surgical success and low complication rates. Surgery performed when the adhesions to the skin and adjacent tissues and skin contracture are mild has been shown to reduce the re-operation rate.

References

1. Tubiana R. Evaluation of deformities in Dupuytren's disease. Annales de chirurgie de la main: organe officiel des societes de chirurgie de la main. 1986;5(1):5-11.
2. Şakı MC, Ersen B, Tunalı O, Aksu İ, Kahveci R. Dupuytren Kontraktürü: 87 Olgunun Retrospektif İncelenmesi. Uludağ Üniversitesi Tıp Fakültesi Dergisi. 2014; 40(1):19-21.
3. Ketchum LD, Donahue TK. The injection of nodules of Dupuytren's disease with triamcinolone acetonide. The Journal of hand surgery. 2000 Nov 1;25(6):1157-62.
4. Çiloğlu NS, Duran A. Parsiyel Fasiektomi Uygulanan 56 Dupuytren Kontraktürü Hastasının Geriye Dönük Değerlendirilmesi. Türk Plastik, Rekonstrüktif ve Estetik Cerrahi Dergisi (Turk J Plast Surg). 2013;21(3):27-30..
5. Luck JV. Dupuytren's contracture: a new concept of the pathogenesis. J Bone Joint Surg Am. 1959;41:635-64.
6. Mandel DR, DeMarco PJ. Overview of the pathogenesis, diagnosis and treatment of Dupuytren's disease. International Journal of Clinical Rheumatology. 2014 Apr 1;9(2):217.
7. Battaloglu ED, Deshmukh RG. Dupuytren's contracture: Current understanding of the condition and its management. Hard Tissue. 2014 Feb 10;10:3.
8. van Rijssen AL, ter Linden H, Werker PM. Five-year results of a randomized clinical trial on treatment in Dupuytren's disease: percutaneous needle fasciotomy versus limited fasciectomy. Plast Reconstr Surg. 2012;129(2):469-77.
9. Pess GM, Pess RM, Pess RA. Results of needle aponeurotomy for Dupuytren contracture in over 1,000 fingers. The Journal of hand surgery. 2012;37(4):651-6.
10. Gök Ü, Gültekin A, Gök ND. (2017). Dupuytren Kontraktürü Nedeniyle Parsiyel Fasyektomi Uygulanan Hastaların Retrospektif Değerlendirilmesi. Kocaeli Tıp Dergisi. 2017;6(3):50-3.

11. Högemann A, Wolfhard U, Kendoff D, Board TN, Olivier LC. Results of total aponeurectomy for Dupuytren's contracture in 61 patients: a retrospective clinical study. Archives of orthopaedic and trauma surgery. 2009;129(2):195-201.
12. Yenidünya MO, Bavli S, Karakaş AÖ. Guillauma Dupuytren' den 178 Yıl Sonra Dupuytren Hastalığı: 18 olgu eşliğinde literatürün gözden geçirilmesi. Yeni Tıp Dergisi. 27, 221-226.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 639-644
https://doi.org/10.31067/acusaglik.862954

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Surgery / Cerrahi

Comparison of Laparascopic and Open Adrenalectomy

Onur Dülgeroğlu[1,2], Tayfun Bilgiç[3], Mehmet Hacıyanlı[1]

[1]Department of General Surgery, İzmir Katip Çelebi University, School of Medicine, Izmir, Turkey

[2]Acibadem Mehmet Ali Aydinlar University, Vocational School of Health Sciences, Istanbul, Turkey

[3]Nişantaşı University, Vocational School of Health Sciences, Istanbul, Turkey

Onur DÜLGEROĞLU, M.D.

Tayfun BİLGİÇ, Asist. Prof.

Mehmet HACIYANLI, Prof.

Correspondence: Onur Dülgeroğlu
Acibadem Mehmet Ali Aydinlar University, Vocational School of Health Sciences, Istanbul, Turkey
Phone: +905332595230
E-mail: onur.dulgeroglu@acibadem.edu.tr

Received : 23 January 2021
Accepted : 14 April 2021

ABSTRACT

Purpose: Laparoscopic adrenalectomy, which was performed successfully for the first time in 1992, has become the preferred method in adrenal surgery especially in adrenal diseases. In this study, our aim is to compare the demographic and operative data of laparoscopic and open adrenalectomies performed in the general surgery clinic of our hospital.

Methods: The records of the patients who were operated in hospital due to a surrenal mass between August 2006 and December 2012 have been retrospectively assessed. Demographic characteristics of the patients, such as age, sex, the size and location of tumors were included. Surgical indications were classified in terms of their radiologic and biochemical investigations. Type of the surgery (lateral transperitoneal laparoscopic or open approach), the incision used in these surgeries (midline, subcoastal and paramedian), the length of operation, the length of hospital stay, postoperative complications and the final pathology results were all examined.

Results: During the afformentioned period, adrenalectomy was performed in 106 patients. Eighty of these patients (%75,4) were operated by open and 26 of them (%24,6) by lateral transperitoneal laparoscopic surgery. Subcostal incision was used 61 of 80 patients (% 82,4), whereas 17 patients (% 22,9) were operated by midline incision and 2(% 2,7) were by paramedian incision. No mortality was encountered. Operation time was statistically significantly shorter in the open group ($p<0,0166$). Duration of hospital stay was statistically significantly longer in open group ($p<0,0083$). Hospital stay time was statistically significantly longer in midline incision group ($p<0,0083$). Except for the weight of masses, statistically significant difference was not found between two groups (laparascopic and open surgery) in demographic and operative features (age,gender,side,pathological diagnose,size of mass) releated to postoperative complications.

Conclusion: In carefully selected group of patients laparoscopic adrenalectomy offered lesser postoperative hospital stay than the open adrenalectomy. The longer operative time can be decreased when more experience is gained in laparascopic adrenalectomy. Laparoscopic adrenalectomy should be preferred in adrenal disease as the gold standard in centers with completed learning curve.

Keywords: Adrenalectomy; Surgery ; Laparoscopy

Laparoskopik ve Açık Adrenalektominin Karşılaştırılması

ÖZET

Amaç: İlk olarak 1992 yılında başarılı bir şekilde gerçekleştirilen laparoskopik adrenalektomi adrenal hastalıklarda ilk tercih edilen yöntem olmaktadır. Bizim bu çalışmada amacımız; hastanemiz genel cerrahi kliniğinde yapılan laparaskopik ve açık sürrenalektomilerin demografik ve operatif sonuçlarını karşılaştırmaktır.

Method: Hastanemizde 2006 Ağustos-2012 Aralık tarihleri arasında genel cerrahi kliniğinde sürrenal kitle nedeni adrenalektomi uygulanmış hastaların kayıtları retrospektif olarak incelendi. Hastaların yaş, cinsiyet, tümör boyutu ve lokalizasyon gibi demografik özellikleri incelendi. Preoperatif klinik, radyolojik ve biyokimyasal özelliklerine göre operasyon endikasyonları gruplandırıldı. Operasyon tipi (lateral transperitoneal laparaskopik veya açık) , operasyonda kullanılan insizyon (median , subkostal , paramedian) , operasyon süreleri , ameliyat sonrası hastanede kalış süresi , postoperatif komplikasyon ve patoloji sonuçları incelendi.

Bulgular: Retrospektif olarak incelenen tarih aralığında 106 hastaya adrenalektomi uygulandı. Opere edilen hastaların 80'ine (%75,4) açık cerrahi , 26'sına (%24,6) ise laparaskopik lateral transperitoneal adrenalektomi uygulanmıştır. Açık cerrahi uygulanan 80 hastanın 61'inde (82,4%) subkostal , 17'sinde (22,9%) median ve 2'sinde (2,7%) paramedian kesi kullanıldığı görüldü. Herhangi bir mortaliteye rastlanmadı. Açık cerrahi uygulanan grupta operasyon sürelerinin istatistiksel olarak anlamlı kısa olduğu görüldü ($p<0,0166$). Açık adrenalektomi uygulanan hastalarda yatış süresinin istatistiksel olarak anlamlı yüksek olduğu görüldü ($p<0,0083$) . Median insizyonla opere edilen olguların yatış sürelerinin istatistiksel olarak anlamlı yüksek olduğu görüldü ($p<0,0083$). Demografik ve operatif özellikler (yaş, cinsiyet, taraf, patolojik tanı, kitle boyutu) açısından kitle ağırlığı dışında postoperatif komplikasyonlarla ilgili iki grup arasında (laparoskopik ve açık cerrahi) istatistiksel anlamlı bir fark bulunamadı.

Sonuç: Dikkatlice seçilmiş hasta gruplarında, laparaskopik adrenalektomi açık adrenalektomiye göre daha kısa postoperatif yatış süresine sahiptir. Laparaskopik adrenalektomilerde deneyim artıkça daha uzun olan ameliyat süresi kısalacaktır. Öğrenme eğrisi tamamlandığı zaman adrenal hastalıklarda laparaskopik adrenalektomi altın standart olarak tercih edilmelidir.

Anahtar Kelimeler: Adrenalektomi; Cerrahi ; Laparoskopi

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Adrenal masses are pathologies that are at high risk of malignancy and can be presented with very different clinical, laboratory and radiological features. Today, there has been a significant increase in the introduction of high-tech radiological diagnostic methods and the development of diagnostic tests and the detection of adrenal gland masses (1).

Adrenal masses show a fairly deep and well-restricted settlement in the abdominal area. These masses can be benign or malignant, and hormone active or non-active. The separation of benign and malignant adrenocortical masses can be difficult (2). During radiological examinations for various reasons not related to adrenal glands, or during the laparotomies coincidentally found; in anamnesis, physical examination, asymptomatic adrenal masses that do not show adrenal mass or adrenal dysfunction are called incidentalome. Most of these masses, which are detected by chance, are benign lesions (cysts, adenomas) and are usually cortical adenomas that are not of disruptive properties and are randomly detected as a result of radiological examinations. Incidence ranges from 1.4% to 8.7% (4.5%).

The masses of the adrenal gland are classified as histopathological adenoma, adrenal gland cancer, pheochromocytoma, myelolipoma, ganglioneuroma, oncocytoma, adrenal gland cyst, hemangioma, metastases of the adrenal gland and other pathologies (3). In these masses, surgical treatment is applied to lesions, which are thought to be hyper secretive or malignant. Today, adrenalectomy is recommended on lesions of 5 cm or above, which are detected by abdominal tomography or magnetic resonance imaging techniques (4). Laparascopic and robotic surgery has been preferred in adrenal gland diseases in the last 30 years with an increasing rate (5). In this study, the diagnostic methods and surgical treatments of 106 patients who had adrenal mass were detected in the General Surgery Clinic and underwent adrenalectomies analyzed.

Material & Methods

In our study, 106 patients who were operated due to adrenal mass in our hospital general surgery clinic retrospectively examined by obtaining approval from the ethics committee of our hospital. (11.11.2013/208) Demographic information of all patients (age, gender, tumor size, tumor weight, localization, adrenal disease) were investigated from file records. Also, routine blood and urine hormone examinations were recorded and included in the study to determine whether the masses were functional for patients who were found to have adrenal mass with radiological examinations. Laboratory examinations of blood cortisol and aldosterone values were measured. Cortisol levels, valine mandelic acid (VMA), metanephrine and nonmetanephrine levels of urine samples of the patients were also assessed. All of the masses removed from the surgery were histopathologically examined.

The localization and size of the masses were determined using radiological examinations such as computed tomography (CT) and magnetic resonance imaging (MRI). Surgical intervention was performed on masses that were hormonally active, larger than 5 cm in diameter, suspected malignancy or symptomatic. Subcostal, paramedian or median incisions were prefered in open adrenalectomy. Laparoscopic interventions were performed with a transabdominal lateral approach. Morbidity, operative time and length of hospital stay of the patients underwent surgery were evaluated. Lapararoscopic and open surgery subgroups were compared in terms of postoperative early and late complications, mortality, and hospital stay time.

Statistical Analyses

The data were evaluated using a statistical package for the Social Sciences (SPSS) 25 for Windows (SPSS® Inc. Chicago, IL, USA program. Comparing categorical data between groups, Pearson Chi-Square, and Fisher's Exact test, comparing continuous data between two groups, Mann Whitney U, Kruskal Wallis H (post hoc Bonferroni corrective Mann Whitney U) statistical analyses were considered statistically significant.($p<0.005$)

Results

One hundred and six patients who had an adrenal mass and underwent adrenalectomy were retrospectively evaluated. The demographic characteristics, side and duration of the surgery, size and weight of the tumour, hospital stay time, number of early and late complications and preoperative functional status of the 106 patients are shown in Table 1.

When the indications of the patients were examined, 67 (63.2%) were operated due to non-functional adrenal mass. In the functional patient group, 10 (9.4%) patients were diagnosed with cushing syndrome and the other 29 (27.3%) patients were operated due to symptoms of pheochromocytoma. One of the patients diagnosed with cushing syndrome was radiologically bilateral mass and the remaining nine patients were operated due to unilateral

Table 1. Age, gender, side, size and weight of mass, operative time, length of hospital stay, imaging techniques, complications and preoperative functional status of patients					
		Surgery Type		Total	p
		Laparoscopic	Open		
Gender	Male n(%)	8 (7.5%)	34 (32%)	42 (39.6%)	0.288
	Female n(%)	18 (16.9%)	46 (4.3%)	64 (60.4%)	
Age (years)		47.2±12.55	51.7±12.72	50,61±12,77	0.009
Side	Left n(%)	12 (11.3%)	26 (24.5%)	38 (35.8%)	0.047
	Right n(%)	11 (10.3%)	52 (49%)	63 (59.4%)	
	Bilateral n(%)	3 (2.8%)	2 (1.8%)	5 (4.7%)	
Size (cm)		4.67±1.72	6.35±3.07		0.072
Weight (gr)		35.38±26.12	96.67±120.16		0.001*
Operative time (min)		151.19±16.2	133.55±12.2		0.219
Length of hospital stay (day)		4±1.54	5.15±2.33		0.110
Early complication n(%)		0	16 (15%)	16	0.013
Late complication n(%)		0	9 (8%)	9	0.074
Preoperative functional status	Pheochromocytoma (n)	8 (7.5%)	21 (19.8%)	29 (27.3%)	0.789
	Cushing Syndrome (n)	3 (2.8%)	7 (6.6%)	10 (9.4%)	
	Non-functional (n)	15 (14.1%)	52 (49%)	67 (63.2%)	
Imaging technique	CT	5 (4.7%)	38 (35.8%)	43(40.5%)	
	MRI	21 (19.8%)	42 (39.6%)	63(59.4%)	
	CT+MRI	9 (8.4%)	15 (14.1%)	26(24.5%)	

cm: centimeter , gr: gram , min :minute, CT: Computerized Tomography, MRI: Magnetic Resonance Imaging

mass. The patient with a bilateral mass was also functional and unilateral subtotal adrenalectomy was performed. Five patients who were operated due to the clinic of pheochromocytoma underwent cortex preserving adrenalectomy. Sixtythree (59.4%) of radiologically detected masses were on the right and thirtyeight (35.8%) on the left as seen on Table 1. No statistically significant difference was found between the laparoscopic and open surgery groups in terms of demographic characteristics, except for the weight of the masses (p <0.005).

Radiological examination methods used for localization of masses are shown in Table 1. Histopathological examination of sixtyseven patients who were operated due to non-functional adenoma revealed that 37 (34.9%) of these patients actually have adrenocortical adenoma. The pathology results of ten (9.4%) patients who were operated due to clinical or subclinical Cushing syndrome was adenoma. Other pathological diagnoses (adrenocortical hyperplasia, malignant epithelial tumor metastasis, myelolipoma, schwannoma, cyst (haemorrhagic, adrenocortical, endothelial), ganglioneuroma) are shown in Table 2.

80 (75.4%) of the 106 patients detected were open adrenalectomy, and laparoscopic lateral transabdominal intervention was preferred for 26 (24.6%). Fifteen (57%) of patients started laparoscopically were suspended for various reasons such as bleeding, insuffcent exposure, difficulty of manuplation and hemodynamic insatbility. These fifteen patients were included in open group for analyses. In 61 (82.4%) of the 80 patients undergoing open adrenalectomy were subcostal incision, 17 (22.9%) median incision, and paramedian incision was preferred in 2 (2.7%).

The mean duration of laparoscopic adrenalectomy was 151.19±16.27 minutes (min), while the mean time of the subcostal incision was 132.93±11.27 min, while the mean time of the median incision was 136.12±16.02 min. The mean operation time of the two patients who were operated by paramedian incision was 130.5±3.54 min. A statistically significant difference between the operation times of cases according to incision selection (p<0.05). Duration of surgery who were operated laparoscopically was statistically high in the duration of patients with median and subcostal incision (p=0.0083)(Table 3). The mean weight and size of the masses after histopathological examination were given in detail in Table 2.

Table 2. Functional status, average size and weight values of masses and distribution of pathologic diagnoses						
		Pathological Diagnose				Total
		Pheochromocytoma	Adrenocortical Adenoma	Adrenocortical Carcinoma	Other*	
Hormone Active	Pheochromocytoma n (%)	29 (27.3%)				29 (27.3%)
	Cushing Syndrome n (%)		10 (9.4%)			10 (9.4%)
Nonhormone active	Nonfunctional n(%)		37 (34.9%)	5 (4.7%)	25(23.5%)	67 (63.2%)
Weight (gr)		124,52±142,02	44,22±43,72	245±165,48	59,1±73,5	
Median(Min.-Max.)		65 (23-691)	25 (8-220)	190 (75-450)	40(5-310)	
Size (cm)		6,9±2,54	4,83±2,19	9±2,55	6,25±4,7	
Median(Min.-Max.)		6,75 (2-14)	4,75 (1,5-14)	9 (5-12)	5,5 (2,5-20)	

gr: gram , cm:centimeter, min:minimum, max:maximum
*Other diagnoses; adrenocortical hyperplasia, malignant epithelial tumor metastasis, myelolipoma, schwannoma cyst (hemorrhagic, adrenocortical, endothelial),ganglioneuroma

When file records are examined; in 16 patients (15%) wound infections, evisseration and postoperative bowel obstruction developed within first thirty days which were evaluated as early complications. Eight patients (7.5%) developed postoperative wound infection, while postoperative bowel obstruction was observed in three patients (2.8%). One of these three patients also developed evisseration (0.9%). Incisional hernias which developed in long-term from scars after discharge, were also evaluated as late complications. In 9 patients (8.4%) incisional hernia was observed during postoperative period. All of the patients who developed incisional hernia were found to have been operated by median incision. Postoperative complications in early and late periods were observed in surgeries that were performed with a preference of median and subcostal incision. Statistically significant difference between groups was found in terms of postoperative complication rates according to incision type (p=0.001) (Table 4). As a result of the operations, no patients had mortality.

Table 3. Type of incision subgroup and operative time				
	Operative time (min)			
Incision type	Time	Median	Min.	Max.
Laparoscopic (n=26)	151,19	148,5	130	195
Median incision (n=17)	136,12	133,0	115	170
Paramedian incision (n=2)	130,5	130,5	128	133
Subcostal incision (n=61)	132,93	132,0	112	160

According to type of operation, a statistically significant difference between the length of hospital stay of the patients (p<0.05). Open surgery group patients hospital stay times were found to be statistically significantly higher than laparoscopic patients staying in hospital (p=0.012) (Table 1).

A statistically significant difference between the length of hospitalization of cases according to incision subgroup (p<0.05). Duration of hospital stay for the patients operated by median incision was found to be longer than that of patients operated with laparoscopic adrenalectomy and subcostal incision(p=0.001)(Table4).

Table 4. Average distribution of length of hospital stay and postoperative complications by incision							
Incision type	Stay Time (day)				Postoperative complications		P
	Mean	Median	Min.	Max.	Early n (%)	Late n (%)	
Laparoscopic	4	3,5	2	9	-	-	0,001
Median incision	7,12	6,0	2	13	8 (7.5%)	9 (8.4%)	
Paramedian incision	3	3,0	2	4	-	-	
Subcostal incision	4,67	5,0	2	11	8 (7.5%)	-	

*Pearson Chi-Square p<0.05

Discussion

Adrenal masses can be presented with very different clinical, laboratory and radiological data. Furthermore, adrenal masses are lesions that carry an approxiamtely 4-12% risk of malignancy (6). In many publications, it is observed that patients are in the 6th decade (3, 7).

The incidence of incidental masses found in children is more likely to be malignant. It is also known that the risk of cancer increases as the size of the mass increases.

4 cm and greater adenomas in the 12,000 autopsy series 4 cm and greater adenomas 4; 6 cm and greater adenomas were rarely reported (8). In our series, the mean size of the masses detected in pheochromocytoma is 6.9±2.54 cm (2-14cm), the mean size of the masses detected in adenomas is 4.83±2.19 cm (1,5-14cm), the mean size of the masses detected in adrenal cortical carcinoma 9±2.55cm (5-12cm), benign reported (Myelolipoma, ganglioneuroma, adrenal cyst, schwannoma) was found to have an mean size of 6.25±4.07cm (2.5-20cm). In our series, 46 patients had a mass of more than 6 cm, and adrenocortical carcinoma was detected in 4 (8.6%) of these cysts.

Adrenal malignancies are generally large and very few are small. Some pathologists also report that size is the most important criterion for the differential diagnosis of benign or malignant adrenal masses (9). Based on these results and the lack of biochemical and imaging methods to make benign/malignant separation definitively in adrenal tumor, they recommend surgical excision in all nonfunctioning adrenal incidentalomas, taking into account that they encounter a high level of malignity (10). In our series, adrenocortical carcinoma was found in 5 patients (4.7%) and the mean size of these masses was found 9±2.55cm (5-12cm).

Among the exact diagnostic criteria are those who think that using the dimension can cause serious misconceptions. Waiting for a small audience to increase in size may mean giving time to turn into carcinoma and invasive. And once the disease progresses, it will be easier to diagnose malignancy. This will not allow early diagnosis and radical surgical intervention. Treatment of nonfunctional adrenal masses with diameters between 3 and 6 cm is controversial. Many surgeons are concerned about the follow-up of these masses and recommend surgery (11).

Adrenal malignancies may be cystic. Because some of the masses identified as adrenal cysts are pseudocysts caused by cystic degeneration in a pathological gland. Some recommend the exploration of all adrenal cysts to uncover an underlying malignancy (12). The adrenal cyst was detected in 5 patients in our series and no cancer was detected in the pathological examination of these cases.

Although adrenalectomy can be performed with classical open technique in very large tumors that show an invasive environmental tissue with no obvious boundaries, and give the image of heterogeneity, recent studies have shown the effectiveness of laparoscopic technique in adrenal tumors larger than 6 cm and no signs of malignancy.

Besides, laparoscopic surgery can now be performed with evolving techniques even in tumors with larger masses and surrounding tissue invasion (13). In our study, laparoscopic surgery was performed on unilateral and under 5 cm masses. However, as laparoscopic experience increases, it is also thought to be applied in larger tumors.

In the literature, the mean operation time in laparoscopic adrenalectomy performed with the transperitoneal approach was 80 to 360 minutes (14). In our series, the duration of operation of patients undergoing laparoscopic intervention was 151.19±16.27 minutes. According to the open approach, this difference, which is statistically significantly more than that, is thought to depend on our laparoscopic learning curve.

In literature, the transition to open approach in laparoscopic adrenalectomy is approximately 2% (0-13%)(15). The most common causes of exposure are small venous bleeding. Also, inferior vein or renal vein injuries may be included in this group. Local or vascular invasion due to malignancy during laparoscopy is another problem of exposure. Other situations include abdominal adhesions, organ injuries, diaphragma injury, obesity, massive hepatomegaly and giant benign tumors (16). In our series, 15 (36%) of the 41 patients we started laparoscopic were suspended and the majority of these cases were intended not to increase the complication rate due to lack of experience in laparoscopy.

The rate of operative complications is 5-10% in laparoscopic adrenalectomy performed in experienced centers, and this rate is often higher in open adrenalectomy (17). In our series, 21 patients (19.8%) developed complications early and/or late. Statistically significant difference between groups was found in terms of postoperative complication rates according to incision type (p=0.001).

In European and American publications, the mean length of hospital stay in the laparoscopic method is 3 days, and the open method is 6.5 days on average.(18) In our series, patients who underwent open surgery and preferred subcostal incision have an mean hospital stay of 4.67±1.76 days, median incision preferred patients 7.12±3.1 days, paramedian incision preferred patients 3±1.41 days, and laparoscopic surgery patients have an mean hospital stay period of 4±1.55 days. As a result, it can be argued that complications can be prevented, and that minimally invasive surgery can achieve its goal in terms of its advantages (19, 20).

Conclusion

In selected patient groups, laparoscopic adrenalectomy causes shorter postoperative hospitalization time and less postoperative complications than open adrenalectomy. Therefore, laparoscopic adrenalectomy preferences are increasing day by day, and even in large tumors and surrounding tissue invasions, laparoscopy is the first preferred method.

References

1. Prager G, Heinz-Peer G, Passler C, et al. Surgical strategy in adrenal masses. Eur. J. Radiol. 2002;41:70-7. DOI:10.1016/s0720-048x(01)00441-7
2. Amberson JB, Vaughan ED, Jr., Gray GF, et al. Flow cytometric analysis of nuclear DNA from adrenocortical neoplasms. A retrospective study using paraffin-embedded tissue. Cancer. 1987;59:2091-5. DOI:10.1002/1097-0142(19870615)59:12<2091::aid-cncr2820591221>3.0.co;2-u
3. Mantero F, Terzolo M, Arnaldi G, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J. Clin. Endocrinol. Metab. 2000;85:637-44. DOI:10.1210/jcem.85.2.6372
4. Di Buono G, Buscemi S, Lo Monte AI, et al. Laparoscopic adrenalectomy: preoperative data, surgical technique and clinical outcomes. BMC Surg. 2019;18:128. DOI:10.1186/s12893-018-0456-6
5. Fu B, Li H, Ma X, et al. Robotic Adrenalectomy. In: Zhang X, ed. Laparoscopic and Robotic Surgery in Urology: Springer; 2020. p. 25-33.
6. Dinnes J, Bancos I, Ferrante Di Ruffano L, et al. MANAGEMENT OF ENDOCRINE DISEASE: Imaging for the diagnosis of malignancy in incidentally discovered adrenal masses: a systematic review and meta-analysis. Eur. J. Endocrinol. 2016;175:R51-64. DOI:10.1530/EJE-16-0461
7. Luton JP, Martinez M, Coste J, et al. Outcome in patients with adrenal incidentaloma selected for surgery: an analysis of 88 cases investigated in a single clinical center. Eur. J. Endocrinol. 2000;143:111-7. DOI:10.1530/eje.0.1430111
8. Copeland PM. The incidentally discovered adrenal mass. Ann. Surg. 1984;199:116-22. DOI:10.1097/00000658-198401000-00021
9. Lau SK and Weiss LM. The Weiss system for evaluating adrenocortical neoplasms: 25 years later. Hum. Pathol. 2009;40:757-68. DOI:10.1016/j.humpath.2009.03.010
10. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur. J. Endocrinol. 2016;175:G1-G34. DOI:10.1530/EJE-16-0467
11. Gaujoux S, Mihai R, Joint Working Group Of E, et al. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. Br. J. Surg. 2017;104:358-76. DOI:10.1002/bjs.10414
12. Fassnacht M, Dekkers OM, Else T, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. Eur. J. Endocrinol. 2018;179:G1-G46. DOI:10.1530/EJE-18-0608
13. Fiori C, Checcucci E, Amparore D, et al. Adrenal tumours: open surgery versus minimally invasive surgery. Curr. Opin. Oncol. 2020;32:27-34. DOI:10.1097/CCO.0000000000000594
14. Chalkoo M, Awan N, Makhdoomi H, et al. Laparoscopic Adrenalectomy; A Short Summary with Review of Literature. 2017.
15. Raffaelli M, De Crea C and Bellantone R. Laparoscopic adrenalectomy. Gland Surg. 2019;8:S41-S52. DOI:10.21037/gs.2019.06.07
16. Koçak S and Özbaş S. Endoskopik Adrenalektomi. Turkiye Klinikleri Journal of Surgical Medical Sciences. 2007;3:29-36.
17. Aporowicz M, Domosławski P, Czopnik P, et al. Perioperative complications of adrenalectomy–12 years of experience from a single center/teaching hospital and literature review. Archives of medical science: AMS. 2018;14:1010.
18. Lodin M, Privitera A and Giannone G. Laparoscopic adrenalectomy (LA): keys to success: correct surgical indications, adequate preoperative preparation, surgical team experience. Surg. Laparosc. Endosc. Percutan. Tech. 2007;17:392-5. DOI:10.1097/SLE.0b013e3180f6174b
19. Chan JE, Meneghetti AT, Meloche RM, et al. Prospective comparison of early and late experience with laparoscopic adrenalectomy. Am. J. Surg. 2006;191:682-6. DOI:10.1016/j.amjsurg.2006.01.042
20. Haveran LA, Novitsky YW, Czerniach DR, et al. Benefits of laparoscopic adrenalectomy: a 10-year single institution experience. Surg. Laparosc. Endosc. Percutan. Tech. 2006;16:217-21. DOI:10.1097/00129689-200608000-00004

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 645-650
https://doi.org/10.31067/acusaglik.888217

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Surgery / Cerrahi

Usual and Unusual Pathologies of Appendicitis: A Retrospective Analysis of 385 Patients

Veysi Hakan Yardımcı[1], **Cihan Uras**[2]

[1]İstanbul Gelişim Üniversitesi, Sağlık Bilimleri Yüksekokulu, İstanbul, Türkiye
[2]Acıbadem Mehmet Ali Aydınlar Üniversitesi, Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, İstanbul, Türkiye

Veysi Hakan YARDIMCI, Dr. Öğr. Üyesi
Cihan URAS, Prof. Dr.

Correspondence: Veysi Hakan Yardımcı
İstanbul Gelişim Üniversitesi, Sağlık Bilimleri Yüksekokulu, İstanbul, Türkiye
Phone: +905324139193
E-mail: hakanyardimci@yahoo.com

Received : 04 March 2021
Accepted : 24 April 2021

ABSTRACT

Purpose: Appendectomy is the most common abdominal surgery performed worldwide. In this report, we evaluated the results of pathological examinations of acute appendicitis specimens.

Methods: We performed a retrospective analysis of patients operated on for acute appendicitis at our surgical department from 2009 to 2017. Data on age, gender, and pathological diagnostic parameters were analyzed.

Results: A total of 385 patients (168 women [43.6%] and 217 men [56.4%]), were classified into acute appendicitis (Group 1), normal appendix (Group 2), and unusual pathological findings (Group 3) groups. The patients undergoing appendectomy were mostly in the 21–30 (n = 136, 35.3%) and 31–40 years (n = 118, 30.6%) age groups. The negative appendectomy rate was 4.4% in Group 2, and the proportion of women (70.6%) was significantly higher in that group than the other groups ($p < 0.05$). In total, 24 (6.2%) patients had unexpected findings. Among the appendix tumors (n = 12 [3.1%]) in our series, low-grade mucinous neoplasm (n = 6, 1.6%) was the most common, followed by a well-differentiated neuroendocrine tumor (n = 3, 0.8%).

Conclusion: Although unusual pathological findings are rare during appendectomy, all appendectomy specimens should be sent for routine histopathological examination. The abnormal incidental findings of 24 cases in this series had a significant impact on management. Patients with rare abnormalities should be treated according to the results of their pathological reports.

Keywords: Appendicitis, appendectomy, appendix, histopathology

Apandisitin Olağan ve Olağandışı Patolojileri: 385 Hastanın Retrospektif Analizi

ÖZET

Amaç: Apendektomi, dünya çapında en yaygın olarak uygulanan abdominal ameliyattır. Bu çalışmada, akut apandisit piyeslerinin, patolojik inceleme sonuçlarını değerlendirdik.

Yöntemler: Cerrahi bölümümüzde 2009-2017 yılları arasında akut apandisit nedeniyle ameliyat edilen hastaların retrospektif bir analizini gerçekleştirdik. Yaş, cinsiyet ve patolojik tanı parametrelerine ilişkin veriler analiz edildi.

Bulgular: Toplam 385 hasta (168 kadın [% 43.6] ve 217 erkek [% 56.4]), akut apandisit (Grup 1), normal apendiks (Grup 2) ve olağandışı patolojik bulgular (Grup 3) grupları olarak sınıflandırıldı. Apendektomi yapılan hastalar en çok 21-30 (n = 136,% 35,3) ve 31-40 yaş (n = 118,% 30,6) yaş grubundaydı. Negatif apendektomi oranı Grup 2'de % 4,4 idi ve bu grupta kadınların oranı (% 70,6) diğer gruplara göre anlamlı olarak yüksekti ($p < 0{,}05$). Toplamda 24 (% 6,2) hastada beklenmedik patolojik bulgulara rastlandı. Serimizdeki apendiks tümörleri (n = 12 [% 3,1]) arasında, düşük dereceli müsinöz neoplazm (n = 6,% 1,6) en yaygın olanıydı, bunu iyi diferansiye nöroendokrin tümör (n = 3,% 0,8) takip etti.

Sonuç: Apendektomi sırasında olağan dışı patolojik bulgular nadir olmakla birlikte, tüm apendektomi örnekleri rutin histopatolojik incelemeye gönderilmelidir. Bu serideki 24 vakanın anormal tesadüfi bulguları, hastaların tedavi yönetimi üzerinde önemli bir etkiye sahipti. Olağan dışı patolojik tanı alan hastalar, patoloji raporlarının sonuçlarına göre doğru tedavi şansını yakalarlar.

Anahtar Kelimeler: Apandisit, apendektomi, apendiks, histopatoloji

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Acute appendicitis is the most common abdominal emergency encountered in general surgery services worldwide (1,2). The overall lifetime risk of this disease is approximately 7% (8.6% in men and 6.7% in women) (3,4). Luminal obstruction is the most common etiology of acute appendicitis (5). Obstruction of the lumen causes mucosal secretions to accumulate and increases intraluminal pressure, which disrupts venous and lymphatic drainage; in turn, this leads to necrosis and perforation.

Epidemiological studies have shown that the incidence of acute appendicitis peaks between the ages of 10 and 30 years, in parallel with the development of the lymphoid system in humans (6). Although fecaliths and lymphoid hyperplasia are the most common causes of this clinicopathological condition, some rare conditions can result in appendix obstruction. Endometriosis (7,8), diverticulitis (9), foreign body obliteration (10), neurofibroma (4), enterobiasis (11), tuberculosis (12), amebiasis (12), actinomycosis (1,13), and schistosomiasis (12), as well as appendix malignancies such as neuroendocrine tumor (carcinoid) (1,14), hyperplastic polyp (15), mucocele (1,6), mucinous cystadenoma (2), adenocarcinoma (6), mucinous cystadenocarcinoma (1), gastrointestinal stromal tumor (2), and lymphoma (2), are known to cause acute appendicitis.

In this report, we evaluated the histopathological results of patients who underwent appendectomy for acute appendicitis, to determine the frequency of unexpected appendicitis pathologies. We also discuss the value of routine pathological examinations.

Material and Methods

The demographic data and pathology reports of patients with a diagnosis of acute appendicitis who underwent an appendectomy in the surgical department of Acıbadem Bakırköy Hospital, between January 2009 and January, 2017, were obtained from the electronic registry system of the hospital and analyzed retrospectively. Patient age, gender, and histopathological diagnoses were recorded. Cases of appendectomy in conjunction with pelvic surgery, and pediatric (aged < 14 years) appendicitis cases, were excluded. All cases in our study were completed laparoscopically. The histopathological examination results of all cases were evaluated in the pathology department of our hospital. Patients were informed of the details of the laparoscopic appendectomy, and written informed consent was obtained prior to the operation. The study was approved by the local ethics committee of İstanbul Gelişim University and met all necessary governmental criteria.

The patients were assigned to acute appendicitis (Group 1), normal appendix (Group 2), and unusual pathological findings (Group 3) groups according to the results of the pathology report. Histopathological findings were examined according to age and gender. Cases without microscopic evidence of inflammation or fibrosis in the appendix were considered normal (negative appendectomy).

Statistical Analysis

Statistical analyses were performed using SPSS software (ver. 20.0 for Windows; IBM Corp., Armonk, NY). The data were analyzed using the Chi-square test and one-sample t-test. Results with a p-value <0.05 were considered statistically significant.

Results

In total, 385 patients (168 women [43.6%] and 217 men [56.4%]; gender ratio, 1:1.29) who met the inclusion criteria were included in this study. The mean age of the study group was 33.2 ± 11.6 years (range: 14–85 years). Most of the patients (~65.9%) undergoing appendectomy were aged 21–30 (n = 136, 35.3%) or 31–40 years (n = 118, 30.6%) (Table 1).

The majority of Group 1 patients exhibited acute appendicitis, based on the pathological examination (n = 344, 89.4%), Group 2 had a low rate of inflammation of the appendix (n = 17, [4.4%]), and some patients in Group 3 showed unusual pathological findings (n = 24, [6.2%]).

The unusual findings were as follows: fibrous obliteration, n = 2; appendicular diverticulitis, n = 3; endometriosis, n = 3; foreign body reaction, n = 1; actinomycosis, n = 1; granulomatous inflammation, n = 2; well-differentiated neuroendocrine tumor(carcinoid), n = 3; hyperplastic polyp, n = 2; mucinous cystadenoma (mucocele, n = 1; and low-grade mucinous neoplasm, n = 6 (Table 2). The average age of Groups 1–3 was 32.88, 32.29, and 37.91 years, respectively, compared to 33.17 years for all of the appendectomy patients in our study (p> 0.05).

Acute appendicitis and unusual findings were more common in males. Group 1 contained 57% males and 43% females, and Group 3 contained 66.7% males and 33.3% females; there were no significant difference in gender ratio between these groups (p=0.239), Group 2 contained a higher proportion of females (70.6%) than the other two groups (p <0.05) (Table 3).

Table 1. Distribution of the Incidence of the Groups According to Patient Age.

		Age groups							Total
		14-20	21-30	31-40	41-50	51-60	61-70	71-84	
Group 1 (Acute appendicitis)	n	41	123	104	47	20	7	2	344
	%	11,90%	35,80%	30,20%	13,70%	5,80%	2,00%	0,60%	100,00%
Group 2 (Negative appendicitis)	n	2	7	6	1	1	0	0	17
	%	11,80%	41,20%	35,30%	5,90%	5,90%	0,00%	0,00%	100,00%
Group 3 (Unusual findings)	n	1	6	8	4	4	1	0	24
	%	4,20%	25,00%	33,30%	16,70%	16,70%	4,20%	0,00%	100,00%
Total	n	44	136	118	52	25	8	2	385
	%	11,40%	35,30%	30,60%	13,50%	6,50%	2,10%	0,50%	100,00%

Table 2. Histopathological Diagnoses Encountered in the Appendectomy Specimens.

Histopathological Diagnosis		n	percentage
Acute appendicitis	(Group 1)	344	89.4%
Normal appendix	(Group 2)	17	4.4%
Unusual pathological findings	(Group 3)	24	6.2%
Fibrous obliteration		2	0.5%
Appendicular diverticulitis		3	0.8%
Endometriosis		3	0.8%
Foreign body reaction		1	0.25%
Actinomycosis		1	0.25%
Granulomatous inflammation		2	0.5%
Neuroendocrine tumor, well differentiated (carcinoid)		3	0.8%
Hyperplastic polyp		2	0.5%
Mucinous cystadenoma (mucocele)		1	0.25%
Low-grade mucinous neoplasm		6	1.55%
Total		385	100%

Table 3. Gender Distribution of Patients in Groups.

		Gender		Total	p-value
		Male	Female		
Group 1	n	196	148	344	
	%	57,00%	43,00%		
Group 2	n	5	12	17	0,047
	%	29,40%	70,60%		
Group 3	n	16	8	24	
	%	66,70%	33,30%		
Total	n	217	168	385	
	%	56,40%	43,60%		
p=0.047					

Perforated appendicitis was found in 22 (6.4%) of the 344 patients in Group 1 diagnosed with acute appendicitis. Although the frequency of perforation in male patients (n = 14, 6.5%) was higher than in female patients (n = 8, 4.8%), there was no significant difference gender difference in the perforation rate in any group (p> 0.05) (Table 4).

Table 4. Gender Distribution in Subgroups of Acute Appendicitis.

Acute Appendicitis		Gender		Total	p-value
		Male	Female		
Catarrhal	n	72	61	133	
	%	54,10%	45,90%		
Phlegmonous	n	97	70	167	
	%	58,10%	41,90%		
Gangrenous	n	13	9	22	
	%	59,10%	40,90%		
Perforated	n	14	8	22	0.811
	%	63,60%	36,40%		
Total	n	196	148	344	
	%	57,00%	43,00%		
p=0,811					

Acute appendicitis and negative appendicitis were most common in the 21–30 years age group, while unusual appendiceal pathologies were most common in the 31–40 years age group (Table 1). The average age of patients with perforation (37.73 years) was higher than the average age of Group 1 (32.88 years), but the difference was not significant (p = 0.120).

Of the 385 patients who underwent appendectomy, 24 (6.2%) (8 women and 16 men) had unusual findings. Of the appendix tumors (n = 12, 3.1%) in our series, low-grade mucinous neoplasm (n = 6, 1.6%) was the most common type, followed by a well-differentiated neuroendocrine tumor (carcinoid) (n=3, 0.8%).

Discussion

Although acute appendicitis can occur at any age, it is most common in the second and third decades of life (16). In our series, patients who underwent appendectomy with a diagnosis of acute appendicitis were mostly in the second (35.3%) and third (30.6%) decades of life.

While the rate of acute appendicitis is higher in men, women are more likely to undergo a negative appendectomy (3). The difficulty of differential diagnosis of acute appendicitis in women may be associated with the high rate of negative appendectomy (3,6). In our study, the rate of negative appendectomy was significantly higher in women (70,6%) ($p <0.05$). Diseases encountered in women during the premenopausal period, such as dysmenorrhea, ovarian torsion, ectopic pregnancy, and pelvic inflammatory disease, complicate the differential diagnosis (16). Negative appendectomy rates of 15–25% have been reported (17). It has been suggested that negative appendectomy may reflect subclinical appendicitis, and that symptoms normally resolve after surgery (15).

In recent years, a general decrease in the rate of negative appendectomy has been reported in association with more frequent use of preoperative imaging modalities, such as computed tomography (CT), especially in pediatric patients (18). While some have argued that routine preoperative imaging can reduce the rate of negative appendectomy, others disagree (19,20). In our series, in addition to physical examination and laboratory tests for the diagnosis of acute appendicitis, ultrasonography (US) examinations were performed for each patient. If the diagnosis was unclear, CT was performed, and approximately 45% of our cases were evaluated with CT. The rate of negative appendectomy in our series was 4.4%, and was highest in women in the second and third decades of life. Our low negative appendectomy rate may be due to the use of adequate radiological methods during diagnosis.

Perforation of an inflamed appendix is another undesirable outcome of inadequate management of acute abdomen. The rate of perforated appendicitis (6.4%) in our study was consistent with previous studies (3,18).

After appendectomy for acute appendicitis, unexpected and rare diseases are sometimes diagnosed. Previous studies have shown that the frequency of unexpected diagnoses, such as parasitic and granulomatous diseases, is lower in western compared to eastern countries (4, 21). Fungal infection, parasites, yersinia pseudotuberculosis, mycobacterium tuberculosis, actinomyces infection, Crohn's disease, foreign body reactions, and sarcoidosis can all cause granulomatous appendicitis. In our series, in agreement with previous reports, the rates of unexpected diagnoses such as actinomycosis (0.25%), foreign body reactions (0.25%), and granulomatous inflammation (0.5%) were relatively low. Patients diagnosed with granulomatous inflammation were referred to the gastroenterology department for further examination. Our patient, who was diagnosed with actinomycosis, was treated with appropriate antibiotherapy for 6 months after surgery.

Fibrous obliteration is also known as neurogenic appendicopathy and appendiceal neuroma. Hyperplasia due to neurogenic proliferation in the appendix lumen results in acute appendicitis (22). In previous studies, the incidence of appendiceal neuroma was reported as 0.2–4.5% (4). In our appendectomy series, the prevalence of fibrous obliteration was 0.5%.

Appendicular diverticulitis is a very rare cause of acute appendicitis during pathological examinations (0.004–2.1%) (9). Given the difficulty of preoperative diagnosis, appendicular diverticulitis is only revealed by postoperative histopathological examinations. In our study, three patients (0.8%) were diagnosed with appendicular diverticulitis histopathologically.

Although intestinal endometriosis is common in the rectum and sigmoid colon, it is uncommon in the appendix and rarely causes acute appendicitis. Hormonotherapy is required for postoperative follow-up (4).

Among our patients unexpectedly diagnosed with appendicitis, hyperplastic polyps were detected in two cases. The clinical significance of hyperplastic polyps

remains unclear, but there is very minimal malignant potential (15).

Mucinous cystadenoma (mucocele) is a rare (0.2–0.7%) appendix pathology (6). Appendix mucoceles can have a malignant or benign cause, and it is important that the mucocele be resected without rupture during surgery. Otherwise, the spread of mucinous tumor cells from the appendix to the abdomen may cause pseudomyxoma peritonei. In our case with mucocele, which was the cause of acute phlegmonous appendicitis, perforation did not occur during surgery. In the postoperative period, she was referred to the gastroenterology department to be evaluated for colon-ovarian malignancy.

After appendectomy, appendix tumors are found in less than 3% of cases (2). The most common appendix tumors are carcinoid tumors and mucinous neoplasms. In our series, in agreement with previous reports (0.3–0.9%) (17), three neuroendocrine tumors (carcinoid) related to appendicitis were detected. None of the three patients initially diagnosed with acute appendicitis showed symptoms of carcinoid syndrome, or were diagnosed with an appendicular tumor on preoperative abdominal tomography. If carcinoid tumors are smaller than 1 cm, appendectomy is sufficient regardless of whether there is mesoappendix invasion. Right hemicolectomy is recommended in cases with tumor greater than 2 cm in size (1,2). Right hemicolectomy was performed in one of our cases for this reason, as well as due to deep invasion in the mesoappendix. Appendectomy was sufficient in the other two patients. The prevalence of appendix mucinous neoplasms after appendectomy was approximately 0.2–0.4% (1). In our series, low-grade mucinous neoplasm was detected in six patients (1.6%); in five of the patients, the tumor was located distally in the appendix; in the remaining cases, it was located in the middle part. Appendectomy was considered an adequate treatment, as dysplastic epithelium was not observed at the surgical margins.

Whether routine histopathological examination of all removed appendectomy specimens is necessary remains controversial. While some centers send all resected appendixes for histopathological examination, others only examine specimens that appear macroscopically abnormal (15).

Khan et al. reported that routine histopathological examination results did not have a positive effect on the treatment outcome in their pediatric patient series. Cases should be evaluated on an individual basis in terms of cost-effectiveness (23). In their study, Matthyssens et al. suggested that routine pathological examination is unnecessary because of the rarity of abnormal pathologies in cases of acute appendicitis, and that examining selected cases based on the macroscopic findings of the surgery would be appropriate (24).

Rare pathologies found during pathological examinations may affect the treatment strategy. Long-term additional antibiotic treatment may be considered in rare infectious diseases. In addition, gastroenterology, gynecology, and oncology consultations may be required, as well as advanced surgical interventions such as right colectomy and ileocolic resection.

Conclusion

While the incidence of abnormal pathological findings is low, routine histopathological examination is expensive and constitutes a major part of the workload of pathologists. The main purpose of routine histopathological examination after appendectomy is to achieve a definitive diagnosis while considering incidental findings during the operation. The pathology report is a medico-legal document that can improve the quality of outcomes by informing surgical decision-making.

Appropriate radiological imaging methods shorten the time to diagnosis of inflammatory appendicitis, and reduce the frequency of both perforated appendicitis and negative appendectomy. However, they are not always sufficient for the diagnosis of abnormal appendix pathology, and even intraoperative macroscopic diagnosis may not be possible despite the advantages for laparoscopic surgery.

The unexpected diagnoses detected by chance in 24 cases in our series had a significant impact on treatment management; serious pathological diagnoses could be overlooked, which would affect the treatment for some patients if samples are not sent for routine histopathological analysis. Therefore, all appendectomy specimens should be subjected to histopathological examination.

References

1. Limaiem F, Arfa N, Marsaoui L, Bouraoui S, Lahmar A, Mzabi S. Unexpected Histopathological Findings in Appendectomy Specimens: a Retrospective Study of 1627 Cases. Indian J Surg. 2015;77: 1285-90. DOI:10.1007/s12262-015-1278-8.
2. Akbulut S, Tas M, Sogutcu N, et al. Unusual histopathological findings in appendectomy specimens: a retrospective analysis and literature review. World J Gastroenterol. 2011;17: 1961-70. DOI: 10.3748/wjg.v17.i15.1961.
3. Elfaedy O, Benkhadoura M, Elshaikhy A, Elgazwi K. Impact of routine histopathological examination of appendectomy specimens on patient management: a study of 4012 appendectomy specimens. Turk J Surg. 2019;35: 196-201. DOI: 10.5578/turkjsurg.4253.
4. Dincel O, Göksu M, Türk BA, Pehlivanoğlu B, İsler S. Incidental Findings in Routine Histopathological Examination of Appendectomy Specimens; Retrospective Analysis of 1970 Patients. Indian J Surg. 2018;80 :48-53. DOI: 10.1007/s12262-016-1557-z.
5. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol. 1990;132: 910-25.DOI: 10.1093/oxfordjournals.aje.a115734.
6. Unver N, Coban G, Arıcı DS, et al. Unusual Histopathological Findings in Appendectomy Specimens: A Retrospective Analysis of 2047 Cases. Int J Surg Pathol. 2019;27: 142-6. DOI: 10.1177/1066896918784650.
7. Tumay V, Ozturk E, Ozturk H, Yilmazlar T. Appendiceal endometriosis mimicking acute appendicitis. Acta Chir Belg. 2006;106: 712-3. DOI: 10.1080/00015458.2006.11679989.
8. Faucheron JL, Pasquier D, Voirin D. Endometriosis of the vermiform appendix as an exceptional cause of acute perforated appendicitis during pregnancy. Colorectal Dis. 2008;10: 518-9. DOI: 10.1111/j.1463-1318.2007.01428.x.
9. Yardimci AH, Bektas CT, Pasaoglu E, et al. Retrospective study of 24 cases of acute appendiceal diverticulitis: CT findings and pathological correlations. Jpn J Radiol. 2017;35: 225-32. DOI: 10.1007/s11604-017-0625-z.
10. Klingler PJ, Seelig MH, DeVault KR, et al. foreign bodies within the appendix: A 100-year review of the literature. Dig Dis. 1998;16: 308-14. DOI: doi: 10.1159/000016880.
11. Yildirim S, Nursal TZ, Tarim A, Kayaselcuk F, Noyan T. A rare cause of acute appendicitis: parasitic infection. Scand J Infect Dis. 2005;37: 757-9. DOI: 10.1080/00365540510012161.
12. Chamisa I. A clinicopathological review of 324 appendices removed for acute appendicitis in Durban, South Africa: a retrospective analysis. Ann R Coll Surg Engl. 2009;91: 688-92. DOI:10.1308/003588409X12486167521677.
13. Nissotakis C, Sakorafas GH, Koureta T, Revelos K, Kassaras G, Peros G. Actinomycosis of the appendix: diagnostic and therapeutic considerations. Int J Infect Dis. 2008;12: 562-4. DOI: 10.1016/j.ijid.2007.12.015.
14. Shapiro R, Eldar S, Sadot E, Venturero M, Papa MZ, Zippel DB. The significance of occult carcinoids in the era of laparoscopic appendectomies. Surg Endosc. 2010;24: 2197-9. DOI: 10.1007/s00464-010-0926-0.
15. Jones AE, Phillips AW, Jarvis JR, Sargen K. The value of routine histopathological examination of appendicectomy specimens. BMC Surg. 2007;7: 17. DOI: 10.1186/1471-2482-7-17.
16. Rabah R. Pathology of the appendix in children: an institutional experience and review of the literature. Pediatr Radiol. 2007;37: 15-20. DOI: 10.1007/s00247-006-0288-x.
17. Ma KW, Chia NH, Yeung HW, Cheung MT. If not appendicitis, then what else can it be? A retrospective review of 1492 appendectomies. Hong Kong Med J. 2010;16: 12-7.
18. Charfi S, Sellami A, Affes A, Yaïch K, Mzali R, Boudawara TS. Histopathological findings in appendectomy specimens: a study of 24,697 cases. Int J Colorectal Dis. 2014;29: 1009-12. DOİ: 10.1007/s00384-014-1934-7.
19. Khairy G. Acute appendicitis: is removal of a normal appendix still existing and can we reduce its rate? Saudi J Gastroenterol. 2009;15: 167-70. DOI: 10.4103/1319-3767.51367.
20. Chiang DT, Tan EI, Birks D. 'To have...or not to have'. Should computed tomography and ultrasonography be implemented as a routine work-up for patients with suspected acute appendicitis in a regional hospital? Ann R Coll Surg Engl. 2008;90: 17-21. DOI: 10.1308/003588408X242259.
21. Bastiaenen VP, Allema WM, Klaver CEL, et al. Routine histopathologic examination of the appendix after appendectomy for presumed appendicitis: Is it really necessary? A systematic review and meta-analysis. Surgery. 2020;168: 305-12. DOI: 10.1016/j.surg.2020.03.032.
22. Patel AV, Friedman M, MacDermott RP. Crohn's disease patient with right lower quadrant abdominal pain for 20 years due to an appendiceal neuroma (Fibrous obliteration of the appendix). Inflamm Bowel Dis. 2010;16: 1093-4. DOI: 10.1002/ibd.21143.
23. Khan RA, Ghani I, Chana RS. Routine histopathological examination of appendectomy specimens in children: is there any rationale? Pediatr Surg Int. 2011;27: 1313-5. DOI: 10.1007/s00383-011-2926-0.
24. Matthyssens LE, Ziol M, Barrat C, Champault GG. Routine surgical pathology in general surgery. Br J Surg. 2006;93: 362-8. DOI: 10.1002/bjs.5268.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 651-657
https://doi.org/10.31067/acusaglik.915637

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Obstetrics and Gynecology / Kadın Hastalıkları ve Doğum

The Use of Bevacizumab Alone and in Combination with Classical Chemotheropathics in Ishikawa Endometrial Cancer Cell Culture

Ceren Yıldız Eren[1], Hulusi Göktuğ Gürer[1], Özlem Özgür Gürsoy[1], Ayşe Tansu Koparal[2], Sabit Sinan Özalp[3]

[1]Eskisehir Acibadem Hospital, Obstetrics and Gynecology Clinic, Eskisehir, Turkey

[2]Anadolu University Açıköğretim Faculty. Department of Medical Services and Techniques Eskisehir, Turkey

[3]Eskişehir Osmangazi University Department of Obstetrics and Gynecology (retired), Eskisehir, Turkey

Ceren Yıldız EREN, M.D.
Hulusi Göktuğ GÜRER, M.D.
Özlem Özgür GÜRSOY, M.D.
Ayşe Tansu KOPARAL, Prof. Dr.
Sabit Sinan ÖZALP, M.D.

Correspondence: Ceren Yıldız Eren Eskisehir Acibadem Hospital, Obstetrics and Gynecology Clinic, Eskisehir, Turkey
Phone: +9 05547555050
E-mail: cyeren@yaani.com

Received : 14 April 2021
Accepted : 21 June 2021

ABSTRACT

Purpose: The aim of our study is to determine the effects of an antiangiogenic agent (bevacizumab) in combination with or without classic chemotherapeutics on the endometrium carcinoma and use these information in our clinic practice.

Materials and Methods: In vitro tests were done to determine the cytotoxic and apoptotic effects of Cisplatin, Adriablastine and Bevacizumab. Cytotoxic effect was determined by the standard MTT assay (Tetrozolium Test) and apopthosis by DAPI staining, caspase-3 on human endometrium cancer cell culture (Ishikawa).

Results: The MTT assay determined that 9.6 mg/ml dose of bevacizumab caused a higher rate of decrease in cell number on Ishikawa cells compared to the highest doses of Cisplatin and Adriablastine. Therewithal, when Bevacizumab, Cisplatin, and Adriablastine were applied together for 24 hours, the number of cells decreased with an increasing dose. With the use of the triple combination with DAPI staining, it is seen that the cell silhouettes are effaced and the findings indicating apoptosis become more apparent. When bevacizumab was applied alone, the caspase 3 activity it produced was ascertained to be higher than the other two drugs individually and in combination. Caspase-3 activity was ascertained to have increased significantly as a result of the collective usage of 40 µM Cisplatin + 20 µM Adriablastine + 9.6 µgram / ml Bevacizumab, and this was found to be the highest cytotoxic activity compared to other applications.

Conclusion: Bevacizumab has significant anticancer activity alone or in combination with other chemotherapeutics.

Keywords: Endometrial carcinoma, angiogenesis, VEGF, Ishikawa, apoptosis.

Ishikawa Endometrial Kanser Hücre Kültüründe Bevacizumabin Tek Başına ve Klasik Kemoteropatiklerle Birlikte Kullanımı

ÖZET

Amaç: Çalışmamızın amacı anti anjiogenik ajanların (bevacizumab) endometriyum kanserinde klasik kemoterapilerle kombine ve tek başına kullanımlarının etkilerini araştırmak ve klinik pratiğe yansıtmaktır.

Gereç ve Yöntem: Cisplatin, Adriablastin, Bevacizumab kombinasyonlarının sitotoksik ve apoptotik etkilerini saptamak için in vitro testler yapılmıştır. Bunun için Ishikawa (insan endometriyum kanser hücresi) hücre kültürü üzerinde sitotoksik etkiyi belirlemek için MTT testi (Tetrozolium Testi), apoptosizi saptamak için ise DAPI boyama, caspase–3 testi kullanılmıştır.

Bulgular: Bevacizumabın 9,6 mg/ml'lık dozunun Ishikawa hücreleri üzerinde Cisplatin ve Adriablastinin en yüksek dozlarına göre hücre sayısında daha yüksek bir oranda düşüşe neden olduğu MTT testi ile belirlenmiştir. Aynı zamanda Bevacizumab, Cisplatin ve Adriablastininin 24 saat birlikte uygulandığında doz artışı ile hücre sayısında azalma meydana gelmiştir. DAPI boyama ile üçlü kombinasyonun kullanımı ile hücre silüetlerinin silindiği ve apoptozisi gösteren bulguların daha bariz hale geldiği görülmektedir. Bevacizumab tek başına uygulandığında oluşturduğu kaspaz 3 aktivitesi diğer iki ilacın tek tek ve ikili kombinasyonundan daha yüksek bulunmuştur. 40 µM Cisplatin + 20 µM Adriablastin + 9,6 µgram/ml Bevacizumabın birlikte uygulanması sonucunda kaspaz-3 aktivitesinin önemli ölçüde artış gösterdiği saptanmış ve bu diğer uygulamalarla kıyaslandığında en yüksek sitotoksik aktivite olarak bulunmuştur.

Sonuç: Bevacizumab yalnız başına veya diğer kemoterapötüklerle birlikte önemli antikanser etkiye sahiptir.

Anahtar Kelimeler: Endometrium kanseri, angiogenezis, VEGF, Ishikawa, apoptosiz.

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Endometrium carcinoma is the most common malignant tumor of the female genital tract and ranks seventh in most cancer-related deaths (1). It has been ascertained that the lifetime possibility of developing endometrial cancer for women is 2-3% in the whole population (2). The average age at diagnosis is 60. (3).

Curative and primary treatment in endometrial cancer is surgery (4,5). The most actively used chemotherapeutic agents are doxorubicin, paclitaxel, cisplatin, and carboplatin (6). Most of the responses obtained with these agents are partial and usually average three-six months, with median survival ranging from 4 to 8 months in recurrent cases (7).

Cancer is modern day's deadly disease, the answer to which is hidden deep within cell biology. Today, studies have shown that the results obtained from cell culture tests are more realistic and specific to investigate the possibility of any drug. (8).

Gynecological oncology is one of the new application areas of these new agents and treatment strategies. Various target treatments are also being tried in endometrial cancer. One of them is antiangiogenic agents (9).

If the tumors cannot produce new vessels, they are fed by diffusion from the surrounding vessels and can grow up to a maximum volume of 0.5 - 1 cm3. Angiogenesis is required for proliferation and metastasis after this volume (10).

Vascular Endothelial Growth Factor (VEGF) is the most important and most emphasized one in tumor-related angiogenesis studies. Among the primary targets, VEGF receptors are the most preferred.

One of the monoclonal antibodies against VEGF, rhuMab VEGF (Bevacizumab, [Avastin™] Genentech, South San Francisco, California USA) is a recombinant human monoclonal VEGF antibody with anti-angiogenic and antitumor activity (11). Also, in randomized phase III studies, when combined with standard chemotherapeutics in patients with metastatic colorectal cancer, compared to conventional therapy, it was found that patients had a significant increase in survival, a significant decrease in tumor progression, and no increase in thromboembolic complications (12).

The aim of our study is to determine the effects of bevacizumab alone and in combination with classic chemotherapeutics on the endometrium carcinoma and use these information in our clinic practice.

MATERIALS AND METHODS

Ishikawa cells were provided by Istanbul University Çapa Faculty of Medicine academic staff member Prof. Dr. Ayhan Bilir. Ishikawa cells, DMEM / F12 (1: 1) (Sigma Aldrich Chemical Co, USA) containing ten% Fetal Bovine Serum, penicillin-streptomycin (Sigma Aldrich Chemical Co, USA), were grown by culturing in a medium containing sodium bicarbonate at 37oC in an environment containing five % CO2. As a result of DAPI staining applied after obtaining the cells, it was examined under a fluorescent microscope.

The doses were prepared by mixing Bevacizumab (Altuzan) (Roche) directly into the medium. Cisplatin (Sigma Aldrich Chemical Co, USA), Adriablastine (Sigma Aldrich Chemical Co, USA), Dimethyl Sulfoxide (DMSO-Riedel de Haen). The doses were prepared by dissolving the medium (1:40). Doses were used as soon as they were prepared.

In Vitro Cytotoxicity Test (MTT Assay)

To determine the cytotoxic effects of Cisplatin, Adriblastine, and Bevacizumab, effective doses were determined by performing an MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] (Sigma Aldrich Chemical Co, USA) assay on Ishikawa cells.

For this purpose, the viability of the grown cells was determined by Trypan Blue staining, then the cells were counted with Thoma slide, and they were cultivated in 96-well plates at $2x10^4$ per well and cultured for 24 hours. At the end of 24 hours, the medium in the wells was emptied and the media containing different concentrations of test substances were placed in the plates. The media were removed from the cells treated with test substances for a certain period at the end of the incubation period. The cells were incubated for two hours with five mg / ml-1 MTT solution to convert the MTT dye into water-insoluble formazan salt as a result of mitochondrial metabolic activities of living cells. At the end of this period, MTT dye was

removed from the cells. 0.1 ml DMSO was added to each well to dissolve the formazan salts formed by living cells. Optical densities of the cells in the plates were measured in an ELISA at a wavelength of 570 nm. Viability rates of test cells are expressed as a percentage, assuming the control cell viability rate not treated with test substance as 100%. The experiments in which the cells were planted in parallel eight for each test substance dose in the experiment sets were repeated three times independently from each other. SPSS program was used in the statistical evaluation of the results of MTT experiments and the significance of the obtained data was determined by applying one-way ANOVA and Tukey test as a post-hoc. P <0.05 was accepted as the significance value.

For the detection of apoptosis, morphological examination (DAPI Staining) with fluorescent staining was performed and the Caspase-3 test was used.

Morphological Examination with Fluorescent Staining (DAPI Staining)

DAPI (Sigma Aldrich Chemical Co, USA) staining was performed to determine whether the doses of Cisplatin, Adriablastine, and Bevacizumab determined as a result of the MTT assay had an apoptotic effect on Ishikawa cells. Cells inoculated into six-well plates with sterile round coverslips were cultured for 24 hours in a CO_2 incubator. At the end of this period, the medium in the wells was removed and the effective doses determined as a result of the cytotoxicity tests of the substances were applied to the cells adhering on the coverslip for 12 hours. After 12 hours, the medium was removed from the wells, and the coverslips were washed with sterile phosphate buffer solution (PBS: 137 µM NaCl, 2.7 µM KCl, 15 µM KH2PO4, 8 µM NaHPO4; PH 7.3), with 3.7% paraformaldehyde solution dissolved in PBS. They were determined for 15 minutes at 37 oC. After the fixation process, coverslips were washed three times with PBS and incubated for 30 minutes at 37 oC with one mg/ml DAPI (4'6-diamidino-2 phenylindole) in the dark environment. The coverslips were then covered by washing with PBS and examined under a fluorescent microscope and photographs were taken.

Caspase-3 assay

Cells were lysed to collect their cell contents (Chemicon APT165). As a result of the experiment, the plates were scanned with an Eliza microplate reader at a wavelength of 405 nm (R&D systems, Inc. 1-800-343-7475). SPSS program was used in the statistical evaluation of the results, and the significance of the obtained data was determined by applying one-way ANOVA and post-hoc Tukey test. P <0.05 was accepted as the significance value.

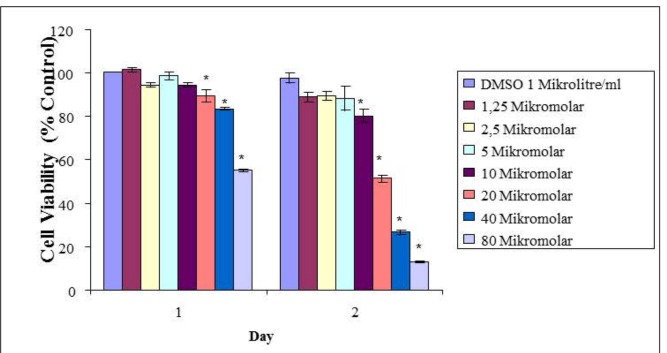
RESULTS

MTT Assay Results

Researchers have reported that 20 µM dose of cisplatin is effective in MTT studies (13). For this reason, 20, 40 and 80 µM doses of cisplatin were selected in MTT experiments.

The 20 µM dose of Cisplatin caused cell proliferation by an 11% decrease on the first day, and 49% on the second day. The 80 µM dose of cisplatin caused a 45% decrease in cell count on the first day and 87% on the second day (Figure 1).

Adriablastine 0.625 µM dose reduced cell proliferation by 19% on the first day and 44% on the second day. The highest dose of Adriablastine, 160 µM, caused cell proliferation todecrease by 76% on the first day and 88% on the second day (Figure 1).



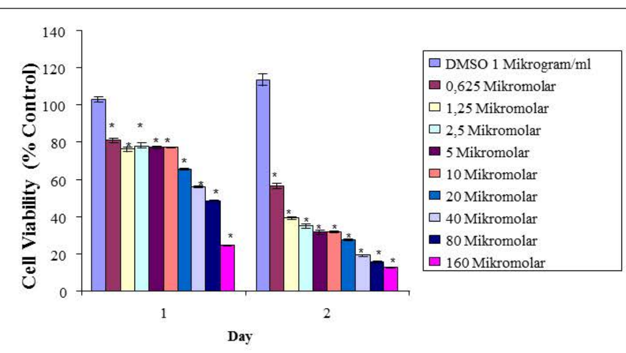
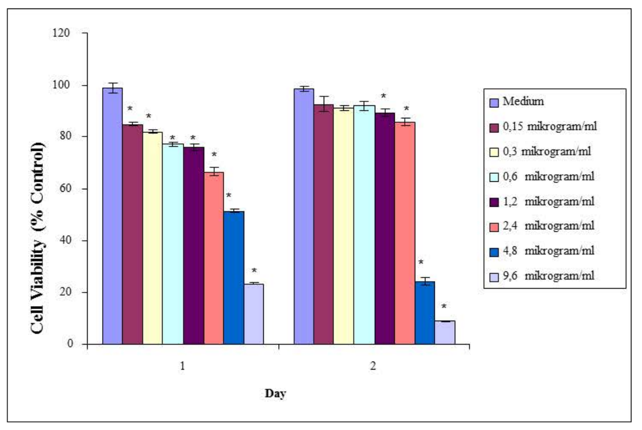


Figure 1. Effects of Cisplatin Adriablastine and on Ishikawa cells by MTT test (*) sign shows significant differences compared to the control group (p <0.05).



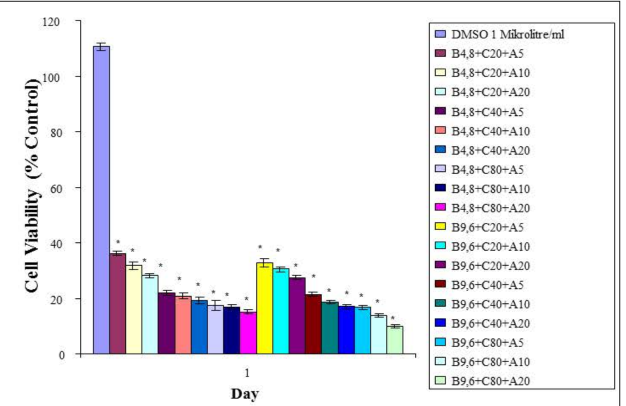


Figure 2. Effects of Bevacizumab and co-administration of different doses of Bevacizumab, Cisplatin and Adriablastin on Ishikawa cells by MTT test (*) sign shows significant differences compared to the control group (p <0.05).

Bevacizumab doses of 0.15, 0.3, 0.6, 1.2 and 2.4 mg / ml caused a decrease in cell number on Ishikawa cells on the first day, while the second day caused a lesser decrease in cell number compared to the first day. It was determined by the MTT assay that a 9.6 mg / ml dose of bevacizumab caused a higher rate of decrease in cell number on Ishikawa cells compared to the highest doses of Cisplatin and Adriablastine (Figure 2).

A dose-dependent effect was observed on the number of Ishikawa cells when cisplatin and Adriablastine were co-administered for 24 hours. At the same time, a dose-dependent effect was observed in the number of cells in Ishikawa cells where Bevacizumab, Cisplatin and Adriablastine were administered together for 24 hours. The number of cells decreased with the increase in dose. It has been determined that triple combination application prevents cell proliferation more effectively than Cisplatin and Adriablastine application (Figure 2).

DAPI Staining Results

In order to morphologically determine the apoptotic effects of Cisplatin, Adriablastine and Bevacizumab alone and together on Ishikawa cells, doses found to be effective as a result of the MTT assays were applied to the cells, followed by DAPI staining. Arrows in photographs of Ishikawa cells where Cisplatin, Adriablastine and Bevacizumab were administered alone and together indicate apoptotic cells. In apoptotic cells, it has been observed that the cell nuclei are divided into small pieces, strangulation occurred in the nuclei and the nuclei are condensed. There was no change in cell morphology with DMSO, that is, the solvent applied to Ishikawa cells. In Ishikawa cells where 20, 40 and 80µM doses of cisplatin were applied for 12 hours, it was observed that fragmentation in the cell nuclei increased depending on the dose.

It was found that the number of apoptotic cells was not high in the DAPI staining results, which serve to show the preapoptotic effect when compared to the control group at doses of five, 10, 20 µM of Adriablastine. At both doses of bevacizumab that were found to be effective with MTT, it was observed that fragmentation in the cell nucleus increased depending on the dose. In combination of Adriablastine and cisplatin, and especially in the combination of Adriablastine, Cisplatin and Bevacizumab, it is seen that the cell silhouettes are erased and the findings indicating apoptosis become more pronounced (Figure 3).

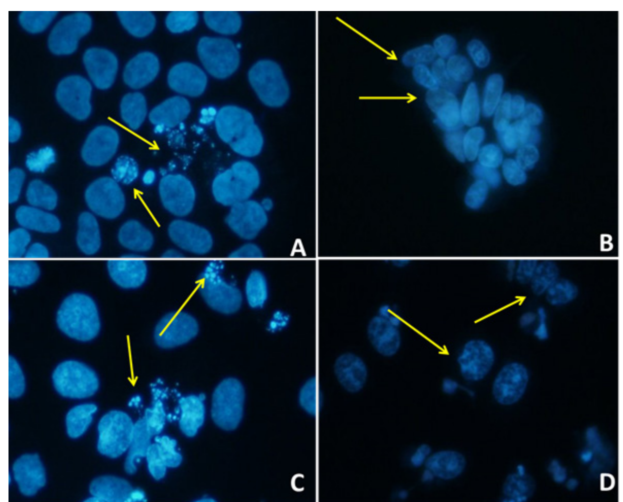


Figure. 3. DAPI staining of Ishikawa cells. A. Cisplatin 80µM; B. Adriablastin 20 µM; C. Bevacizumab 9.6 µg / ml; D. Bevacizumab 9,6 µg / ml + Cisplatin 40 40µM + Adriablastin 20µM

Caspase-3 Results

High caspase 3 activity is an indicator of irreversible apoptosis (14). After treatment of Ishikawa cells with drugs for

12 hours, caspase 3 activity was measured by fluorimetric method. The effects of Cisplatin, Adriablastine and Bevacizumab alone and together on the caspase 3 activities of Ishikawa cells are observed in Figure 4. The caspase 3 activity created by bevacizumab alone was found to be higher than the single and double combination of the other two drugs. As a result of the co-administration of 40 µM Cisplatin + 20 µM Adriablastine + 9.6 µgram / ml Bevacizumab, a significant increase in caspase-3 activity was found, and this was found to be the highest compared to the others. The caspase-3 results of drugs administered alone are lower than when the three are administered together.

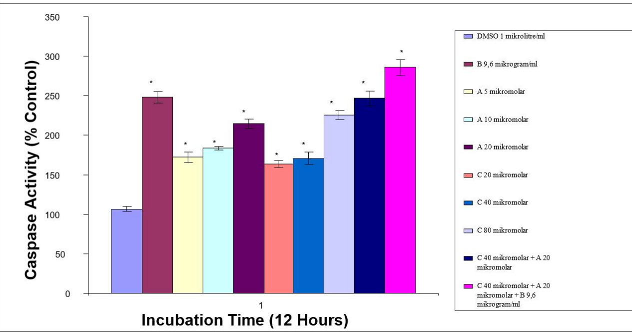


Figure 4. Caspase-3 results. Ishikawa cells 12-hours treatment with Cisplatin (C), Adriablastin (A) and Bevacizumab (B) alone and combination. Control cells were treated with DMSO. The (*) sign indicates significant differences compared to the control group ($p < 0.05$).

DISCUSSION / CONCLUSION

Endometrial cancer is usually diagnosed at an early stage and is considered a benign cancer. Chemotherapy in endometrium cancer comes to the fore especially in the treatment of advanced stage and recurrent disease. The most commonly used agents for this purpose are Doxorubicin, Cisplatin and Paclitaxel (15,16).

However, in advanced stage or recurrent endometrial cancer, the average response rate of Doxorubicin Cisplatin combination is 45-63%, and the response rate to doxorubicin alone is 19-27% (17). Single agent paclitaxel can also be used in patients with advanced stage endometrial cancer, but the average response rate is 36% (18). In the study conducted by Fleming et al., the average response rate was found to be 46% in patients with advanced stage endometrial cancer who received doxorubicin, Cisplatin and paclitaxel combination therapy (19).

If endometrial cancer is recurrent or metastatic, the prognosis is poor. In the studies of the Gynecological Oncology Group, the average survival with hormonotherapy or chemotherapy was generally found to be one year or less (20). Various cytotoxic agents are effective in the treatment of recurrent endometrial cancer. However, the general age of this patient group, previous pelvic radiotherapy exposure and the presence of comorbidities such as obesity, hypertension, and diabetes mellitus increase the morbidity and mortality of chemotherapy (21). In the GOG study published in 2004, the average age of the patients participating in the study was found to be 65, and this group had a history of pelvic radiotherapy at a rate of 68% (22).

The methods applied using the cell culture technique is fast and reproducible in drug research and development studies. For this reason, these methods are used extensively to determine the effectiveness of new drug candidates developed by the pharmaceutical industry against cancer. In this study, a cell culture study was designed to examine the use of bevacizumab, which is known to have antiangiogenetic effects in endometrial cancer, alone or in combination with other chemotherapeutics, and the in vitro drug effects were examined.

Inhibition of apoptosis is one of the steps in cancer development. Cancer cells die with apoptosis in response to chemotherapy and radiotherapy. However, in the late stages of the disease, there is a resistance to apoptosis, which leads to treatment failure. Therefore, initiation of effective apoptosis activation in cancer cells has gained importance in treatment strategies. In studies, demonstration of apoptosis and cytotoxicity is necessary to demonstrate the efficacy of treatment. In the detection of apoptosis, DAPI staining is used as an indicator for determining nucleus size and morphology. While DAPI experiments showed that the use of bevacizumab alone and in combination has pre-apoptotic effects, it was found as a result of the Kaspaz-3 tests that the use of Bevacizumab alone or together was more effective on Ishikawa cells.

There are studies revealing the in vivo efficacy of bevacizumab. In the retrospective study of Rose et al., it was found that there was a high response to the combined use of bevacizumab, paclitaxel, and carboplatin in the treatment of advanced stage and recurrent endometrial carcinoma, resulting in a significant difference in survival rates (23).

However, in the MITO END-2 study of Lorusso et al., the use of bevacizumab in combination with chemotherapy in the treatment of advanced stage or recurrent endometrial carcinoma did not show a significant effect on survival (24).

As a result of the meta-analysis of Chen et al., it was revealed that chemotherapy combined with bevacizumab had a high effect on disease-free survival and recovery rates on patients with advanced stage or recurrent endometrial cancer (25).

A prospective multicenter observational study was conducted in Japan on the subject. The efficacy and safety of bevacizumab-paclitaxel combination therapy as first- or second-line chemotherapy for metastatic breast cancer has been studied. Multivariate analyses were conducted to identify prognostic factors. According to the results of the study, combined bevacizumab–paclitaxel is very effective. This effectiveness is as remarkable as in former studies (26).

Glioblastoma is one of the most aggressive tumors in adults. Median survival is 20.9 months. In one study, bevacizumab was used in a cohort of 1082 glioma patients to determine whether bevacizumab could increase the anti-angiogenic effect. Found that anti-angiogenic effect (VEGFA expression levels) the response to treatment in cell culture. This data indicate that bevacizumab can improve clinical results in Glioblastoma therapy (27).

The cytotoxic effect of bevacizumab and other VEGF antibodies on cancer cells has been proven in many in vivo and in vitro studies as in our study. Considering that it has fewer side effects compared to conventional chemotherapeutics, its use in primary care in the treatment of endometrial cancer should be kept in mind. Combination with classical chemotherapeutics used especially in advanced stage disease is a promising treatment approach.

The most important challenge in cancer therapy nowadays is the lack of anticancer medication with great efficaciousness, broad-spectrum and minimum side effects. It is accepted that this question can be solved with combination treatment. It is considered that the results obtained in this study strengthen this focus.

Acknowledgment

This article is produced from our thesis. We would like to thank the Hulusi Göktuğ GÜRER and Özlem Özgür GÜRSOY. They took part in the preparation of the article for publication.

REFERENCES

1. Marcus D, Savage A, Balog J, Kudo H, Abda J, Dina R, et al. P74 Endometrial cancer: Can the iKnife diagnose endometrial cancer? Int J Gynecol Cancer. 2019;29:A100-A101
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics. 2017; 67(1): 7–30.
3. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. The Lancet. 2016;387:1094-108.
4. Lu KH. Management of early stage endometrial cancer. Semin Oncol. 2009;36:137-44.
5. Hogberg T.Adjuvant chemotherapy in endometrial carcinoma:overview of randomized trials.Clin Oncol (R Coll Radiol).2008;20:463.
6. Aghajanian C, Filiaci V, Dizon DS, Carlson JW, Powell MA, Alvarez Secord A, et al. A Phase II Study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol. 2018;150:274-81.
7. Howlader, N; Noone, AM; Krapcho, M, et al. SEER cancer statistics review, 1975-2012. National Cancer Institute. 2014.
8. Shay, Jerry & Wright, Woodring. Shay JW, Wright WEHayflick, his limit, and cellular ageing. Nat Rev Mol Cell Biol. 2000;1:72-76.
9. Delmonte A,Sessa C. Moleculer targeted agents in endometrial carcinoma:overview of randomised trials.Clin Oncol (R Coll Radiol.) 2008; 20: 554.
10. Bates DO, Hillman NJ, Williams B et al. Regulation of microvascular permeability by vascular endothelial growth factors. J Anat. 2002; 200: 587-597.
11. Minami H, Ebi H, Tahara M et al. A phase I study an oral VEGF receptor tirozin kinaz inhibitor ZD6474 in Japanese patients with solid tumors. Proc Am Soc Clin Oncol 2003; 22: 194
12. Trarbach T, Shleucher N, Riedel U et al. Phase I/II study of the oral vascula ebdothelial growth factor (VEGF) receptor inhibitor PTK787/ZK222854 in combination with irinotecan/5-fluorouracil/leucoverin in patients with metastatic colorectal cancer. Proc Am Soc Clin Oncol. 2003; 22:285
13. Zhuo, W., Wang, Y., Zhuo, X., Zhang, Y., Ao, X., Chen, Z., (2008), Knockdown of Snail, a novel zinc finger transcription factor, via RNA interference increases A549 cell sensitivity to cisplatin via JNK/mitochondrial pathway. Lung Cancer. 2008; 62: 8-14.
14. Caruso, F., Villa, R., Rossi, M., Pettinari, C., Paduano, F., Pennati, et al. Mitochondria are primary targets in apoptosis induces by the mixed phosphine gold species chlorotriphenylphosphine-1,3 bis(diphenylphosphino) propanegold(I) in melanoma cell lines, Biochemical Pharmacology. 2007; 73: 773-781.
15. Bruzzone M, Miglietta L, Franzone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV endometrial cancer patients. Gynecol Oncol. 2004;93:345-352.
16. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol Oncol. 2009;112:543-552.
17. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2004;22:3902-3908.
18. Sreedevi MS, Pavan KK, Neelakantan A. Carboplatin and paclitaxel: Role in the treatment of endometrial cancer Editor(s): Rama RM, Ganji PN. A Theranostic and Precision Medicine Approach for Female-Specific Cancers, Academic Press, 2021. p. 165-177.

19. Fleming GF,Fowler JM,Waggoner SE,et al.Phase 1 trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubisin in advanced endometrial carcinoma and other gynecologic malignencies: a Gynecologic Oncology Group Study. J Clin Oncol. 2001;19:1021-1029.
20. Randall ME, Filiaci VL, Muss H, et al. Randomized Phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2006;24:36–44.
21. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008; 109(1): 11–18
22. J. Tate Thigpen, Mark F. Brady, Howard D. Homesley, John Malfetano, Brent DuBeshter, Robert A. Burger, Shu Liao Phase III Trial of Doxorubicin With or Without Cisplatin in Advanced Endometrial Carcinoma: A Gynecologic Oncology Group Study. Journal of Clinical Oncology. 2004;22(October 1): 3902-3908.
23. Rose PG, Ali S, Moslemi-Kebria M, Simpkins F. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. Int J Gynecol Cancer. 2017;27:452-58.
24. Lorusso D, Ferrandina G, Colombo N, Pignata S, Pietragalla A, Sonetto C, et al. Carboplatin-paclitaxel compared to carboplatin-paclitaxel-bevacizumab in advanced or recurrent endometrial Cancer: MITO END-2-A randomized phase II trial. Gynecol Oncol 2019;155:406-12
25. Chen, Hui, Minglin Liang, and Jie Min. Efficacy and Safety of Bevacizumab-Combined Chemotherapy for Advanced and Recurrent Endometrial Cancer: A Systematic Review and Meta-analysis. Balkan medical journal. 2021;38:7-12.
26. Yamamoto Y, Yamashiro H, Toh U. et al. Prospective observational study of bevacizumab combined with paclitaxel as first- or second-line chemotherapy for locally advanced or metastatic breast cancer: the JBCRG-C05 (B-SHARE) study. Breast Cancer. 2021; 28: 145–160.
27. García-Romero N, Palacín-Aliana I, Madurga R. et al. Bevacizumab dose adjustment to improve clinical outcomes of glioblastoma. BMC Med. 2020; 18: 142.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 658-661
https://doi.org/10.31067/acusaglik.842744

Bir Üniversite Hastanesine Başvuran Erkek İnfertilite Tanılı ve Asemptomatik Hastalarda Testis Tümörü Sıklığı

Metin Yığman[1] , Semih Tangal[2]

[1]Ufuk Üniversitesi Tıp Fakültesi, Dr.Rıdvan Ege Hastanesi, Üroloji Anabilim Dalı, Ankara, Türkiye
[2]Ufuk Üniversitesi Tıp Fakültesi, Üroloji Anabilim Dalı, Ankara, Türkiye

Metin YIĞMAN, Dr. Öğr. Üyesi
Semih TANGAL, Dr. Öğr. Üyesi

Correspondence: Metin Yığman
Ufuk Üniversitesi Tıp Fakültesi, Dr.Rıdvan Ege Hastanesi, Üroloji Anabilim Dalı, Ankara, Türkiye
Phone: +903122044326
E-mail: m.yigman@hotmail.com

Received : 18 December 2020
Accepted : 7 February 2021

ÖZET

Amaç: Testis tümörü genç erişkin erkeklerde en sık görülen kanserdir. İnmemiş testis, testis tümörü riskini artıran en önemli sebep olmakla birlikte birinci derece akrabalarda testis kanseri öyküsü, karşı testiste insitu germ hücre neoplazisi ve testiküler disgenezis sendromu etyolojide yer almaktadır. Bu çalışmadaki amaç erkek infertilitesi tanısı ile incelenen hastalarda testis tümörü sıklığını araştırmaktır.

Hastalar ve Yöntem: Ağustos 2015 - Ağustos 2018 tarihleri arasında üroloji polikliniğine infertilite şikayeti ile başvuran veya kadın hastalıkları ve doğum kliniklerinden konsülte edilen erkek faktörü tanılı 954 erkek hastanın retrospektif değerlendirilmesi yapıldı. Hastaların anamnez, fizik muayene ve spermiogram bulguları kayıt edildi. Yapılan rutin fizik muayenelerinde testiküler kitle saptanan ve bu nedenle radikal orşiektomi yapılan hastaların verileri analiz edildi.

Bulgular: İncelenen 954 erkek hastanın dördünde sağ, birinde ise sol testiküler kitle saptandı. Hastaların yaş ortalaması 31,6 (30-35) idi. Bu hastaların hiçbirinde inmemiş testis öyküsü mevcut değildi. Tüm hastaların tümör belirteçleri normal, yapılan bilgisayarlı tomografilerinde lenf nodu veya organ metastazı izlenmedi. Beş hastanın üçünde oligospermi , ikisinde azospermi mevcuttu. Yapılan inguinal orşiektomi operasyon patolojileri ise tüm hastalarda saf seminom olarak raporlandı.

Sonuç: Özelllikle infertil erkek hastalarda testis muayenesi yapılırken artmış risk nedeniyle dikkatli olunmasının ve bu popülasyondaki bireylere kendi kendine yapılacakları testis muayenesinin erken tanıda önemli olduğu düşünülmektedir.

Anahtar sözcükler: Testis tümörü, infertilite, seminom

Frequency of Testicular Tumor in Patients with a Diagnosis of Infertility and Asymptomatic Male Applied to a University Hospital

ABSTRACT

Objective: Testicular tumor is the most common cancer among the young adult men. Although the undescended testicle is the most common cause which increases the risk of testicular tumor, the testicular cancer diagnosis of any of the first degree relatives, in situ germ cell neoplasia of the other testicle and the testicular dysgenesis syndrome are also included in the etiology. The aim of this study is to investigate the frequency of testicular tumor in patients with infertility.

Patient and Methods: 954 male patients, who presented to the urology polyclinic with a complaint of infertility or who were consulted from gynecology and obstetrics clinics with male infertility factor, between August 2015 and August 2018, were evaluated retrospectively. Medical records, physical examination and spermiogram findings were considered. The data of the patients who were diagnosed with testicular mass through physical examinations and underwent radical orchiectomy, were analyzed.

Results: Of 954 evaluated male patients with a mean age of 31,6 (30-35) years, four had right testicular mass and one had left testicular mass. None of these patients had a medical record of undescended testicle. Tumor markers of all patients were normal and neither lymph node nor organ metastasis were observed through computerized tomography analysis. 3 of 5 patients had oligospermia and 2 had azoospermia. Pathologic diagnosis of inguinal orchiectomy materials were reported as pure seminoma in all patients.

Conclusions: Especially in infertile male patients, when performing testicular examination it should be taken into consideration that there is an increased risk of testicular tumor. It is considered that informing individuals of this population about doing an examination of testicle is important in early diagnosis.

Keywords: Testicular tumor, infertility, seminoma

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Testis kanseri erkek cinsiyette tümörlerin %1'ini ve tüm ürolojik kanerlerin %5'ini oluşturmaktadır (1). Batı toplumlarında yıllık insidansı yüz binde 3 ila 10'dur (2). Tanı anında olguların sadece % 1-2'si bilateral olup olguların %90-95'inde histolojik tipi germ hücreli tümörler oluşturmaktadır (1). Saf seminomların pik insidansı dördüncü dekat iken seminom dışı germ hücreli kanserler için üçüncü dekattır (1).

Testis kanseri gelişiminin risk faktörleri arasında ailede testis kanseri öyküsü, karşı testiste tümör veya insitu germ hücre neoplazisi, kriptorşidizm, hipospadias ve azalmış spermatogenezin gösterildiği subfertilite veya infertilite bileşenlerini içeren testiküler disgenezis sendromu sorumlu tutulmaktadır (3).

İnfertil erkek popülasyonda yapılan çalışmalarda artmış testis kanseri literatürde birçok çalışmada saptanmıştır (4,5). Y kromozom delesyonu, epigenetik hipermetilasyon, DNA eşleşme tamir gen mutasyonu veya delesyonu ve anöploidi gibi mekanizmaların hücre kültürlerinde ve insan dokularında infertilite ve kanser ile ilişkisi gösterilmiştir (6-10).

Testis kanseri genellikle tek taraflı ağrısız ele gelen kitle şikayetiyle ile tanısı konulmaktadır (11). Skrotal ağrı hastaların yaklaşık %20'sinde ilk semptom olabilirken jinekomasti genellikle seminom dışı tümörlü hastaların %7'sinde, metastazlara bağlı sırt ve yan ağrıları ise olguların yaklaşık %11'inde mevcuttur (11,12).

Biz bu çalışmamızda infertilite şikayeti ile kliniğimize başvuran veya diğer kliniklerden yönlendirilen asemptomatik erkek infertil popülasyonda testis tümörü sıklığının araştırılmasını amaçladık.

GEREÇ VE YÖNTEM

Retrospektif kesitsel bu çalışma üniversite etik kurul onayı sonrasında Ağustos 2015 - Ağustos 2018 tarihleri arasında üroloji polikliniğine infertilite şikayeti ile başvuran veya kadın hastalıkları ve doğum kliniklerinden konsülte edilen erkek faktörü tanılı erkek hastanın verilerinin değerlendirilmesi ile yapıldı. Kayıtlarına tam olarak ulaşılabilen toplam 954 hasta çalışmaya alındı. Hastaların anamnez, fizik muayene, spermiogram bulgularına ek olarak sperm konsantrasyonu <5milyon/ml olan hastalardan istenilen karyotip ve Y kromozom mikrodelesyon analiz sonuçları kayıt edildi.

Hastaların daha önce farketmediği ancak yapılan fizik muayenelerinde saptanan testiküler kitlesi olan hastaların da preoperatif tahlil ve tetkik sonuçları ile tüm hastalara uygulanan radikal orşiektomi patoloji raporları da değerlendirildi. Mevcut veriler ile erkek infertil ve asemptomatik hastaların 3 yıllık testis kanseri insidansı hesaplandı.

BULGULAR

Değerlendirilen 954 hastanın ortalama yaşı 34,61 (24-55) idi. Hastaların 59'unda (%6,1) özgeçmişinde unilateral veya bilateral inmemiş testis öyküsü mevcuttu. Özgeçmiş ve soygeçmişlerinde ise hiçbir hastada testis kanser öyküsü mevcut değildi. Genetik incelemesi yapılan toplam 133 (%13,9) hastanın ise sadece 17'sinde (%1.7) genetik bozukluk saptandı (Tablo 1).

Tablo 1. Hastaların demografik özellikleri	
Yaş (ort) (min-maks)	34,61 (24-55)
İnmemiş Testis Öyküsü (n, %)	
Var	59 (%6,1)
Yok	895 (%93,8)
Testiküler Kanser Öyküsü (n, %)	-
Ailesel Testis Kanser Öyküsü (n,%)	-
Genetik İnceleme (n, %)*	
Normal	116 (%87,2)
Kleinfelter Sendromu	12 (%9)
Y mikrodelesyonları	3 (%2,2)
Diğer (XXY vs.)	2 (%1,5)
Toplam	133/954 (%13,9)
*Sperm sayısı <5milyon/ml olan hastaların genetik incelemesi yapıldı	

İncelenen 954 erkek hastanın dördünde sağ, birinde sol olmak üzere toplam 5'inde (%0,52) testiküler kitle saptandı. Hastaların yaş ortalaması 31,6 (30-35) idi. Bu hastaların hiçbirinde inmemiş testis öyküsü mevcut değildi. Tüm hastaların tümör belirteçleri normal, yapılan bilgisayarlı tomografilerinde ise lenf nodu veya organ metastazı izlenmedi. Beş hastanın üçünde oligospermi , ikisinde azospermi mevcuttu. Yapılan inguinal orşiektomi operasyon patolojileri ise tüm hastalarda saf seminom olarak raporlandı (Tablo 2). Çalışmamızda infertil ve asemptomatik yani hastaların kendilerinin fark etmediği testiküler tümörün 3 yıllık insidansı %0.524 olarak bulunmuştur.

Tablo 2. Testis tümörlü hastaların bulguları									
Hasta	Yaş	Tümör Tarafı	Spermiogram	β-HCG	AFP	LDH	Tümör Çapı	Rete Testis İnvazyonu	Patoloji
1	30	Sağ	Oligospermi	N	N	N	3cm	-	Seminom
2	35	Sağ	Oligospermi	N	N	N	2cm	-	Seminom
3	31	Sağ	Oligospermi	N	N	N	2cm	-	Seminom
4	32	Sağ	Azospermi	N	N	N	3cm+2cm	-	Seminom
5	30	Sol	Azospermi	N	N	N	1,5cm	+	Seminom

β-HCG: Beta İnsan koryonik gonadotropin; AFP: Alf- fetoprotein; LDH: Laktat dehidrogenaz; N:Normal değer

TARTIŞMA

İnfertilite ve testis tümörü arasındaki ilişki net olarak ortaya konulmamıştır. Testis kanserli erkeklerde fertilitesinin bozulmasında birçok neden sorumlu tutulmaktadır. Bunlardan en önemlisi bu hastaların operasyon öncesinde sperm parametrelerinde yüksek oranda bozulmasıdır. Zapzalka ve ark. yaptıkları çalışmada germ hücreli testis tümörüne sahip hastaların %22-63'ünde normal spermiogram parametrelerinin sahip olduğunu vurgulamışlardır (13). Ayrıca Hartman ve ark. testis kanseri saptanan olguların sağlam testislerinde % 8,7 karsinoma in situ ve % 25,2 testiküler disgenezi saptamış ve anormal spermiyogram parametrelerinde rolü olduğunu belirtmişlerdir (14). Literatürde radikal orşiektomi materyallerinde germ hücreli kansere komşu alanlarda spermatogenezin diğer alanlara göre daha düşük olduğu da gösteren çalışmalarda mevcuttur (15). Fertilizasyon açısından klinik anlamı tartışmalı olsa da testis kanserinde kan testis bariyerini bozması sonucu oluşan anti-sperm antikorlar da sorumlu tutulan etkenlerden biridir (16). Yapılan çalışmalarda sağlıklı bireylerde anti-sperm antikor pozitifliği %8 iken kanserli olgularda %73 pozitiflik raporlanmıştır (17). Hormon bağımlı bir süreç olan spermatogenezin testis tümörlerinden salgılanan beta insan koryonik gonadotropin (β-HCG) ve alfa fetoprotein (AFP) ile de negatif yönde etkilendiği gösterilmiştir (18,19).

İnfertilitede erkek faktörü değerlendirilmesinin ilk aşamasını semen değerlendirilmesi oluşturmaktadır. Yapılan çalışmalar fertiliteyi semen parametrelerine göre değerlendirip artmış kanser riski ile ilişkili olduğunu göstermiştir. Walsh ve ark.'nın yapmış olduğu retrospektif epidemiyolojik çalışmada erkek infertilitesi tanısı sonrasında testis kanseri tanısı alan hastaların fertil erkek gruba göre 2,8 kat riskli olduğunu tespit etmişlerdir (4). Jacobsen ve ark. ise semen parametreleri ile testis kanseri ilişkisini incelemiş ve düşük konsantrasyon, zayıf motilite ve artmış anormal sperm morfolojisi ile artmış risk raporlamışlardır (20). Benzer şekilde Hanson ve ark.'nın yakın dönemde yayımladıkları çalışmada da hem kötü sperm parametleri ile hem de normoozospermik infertil hastalarda fertil gruba göre artmış testis kanseri riski tespit etmişlerdir (21). Ancak azospermi ile testis kanseri arasında bir ilişki gösterememişlerdir. Buna karşın Eisenberg ve ark. ise yaptıkları çalışmada sadece azospermik infertil hasta grubunda artmış testis kanseri riski bulurken azospermik olmayan infertil hasta grubunda ise lokal popülasyonla benzer olduğunu belirtmişlerdir (5).

Raman ve ark. yaklaşık 10 yıllık retrospektif taramalarında 3847 infertil erkekte 10 testis kanser olgusu saptamış ve normal popülasyona göre artmış risk sonucuna ulaşmış ayrıca tüm olgularda seminom patolojisi ve sadece 2 olguda risk faktörlerinden inmemiş testis öyküsü olduğunu bildirmişlerdir (22). Benzer çalışmalarda infertil popülasyonda testis tümörü patolojik tipi sıklıkla seminom olarak saptanmıştır (4,20).

Testis kanser insidansı coğrafik, ırksal ve etnik farklılık göstermektedir. Afrika ve Asya'nın büyük çoğunluğunda 100.000'de 1'den az ve Amerika Birleşik Devletleri'nde siyahi toplumda 100.000'de 1,2 gibi düşük oranlar görülürken; Avrupa ülkelerinde 100.000'de 9,4 - 9,9 gibi yüksek oranlar mevcuttur. Testis kanseri insidansı beyaz ırkta olmak üzere 100.000'de 6-11 arasında olup yıllık artış %3-6 arasındadır (3,23,24).

Biz de çalışmamızda 3 yıllık bir süreçte 954 infertil erkekte 5 olguda testis kanseri tespit ettik. Ancak bizim çalışmamıza hastanın şikayeti veya kendisinin farkettiği ele gelen kitle olmaksızın başvuru esnasında doktor muayesinde tespit edilen hastalar dahil edildi. Bununla birlikte ele gelen kitle veya semptomatik olup da önceden bilinen infertilite öyküsü olanlar çalışmaya alınmadı.

Buna rağmen 3 yıllık bir süreçte yaklaşık 1000'de 5 gibi bir artmış bir oranda tespit ettik. Aynı zamanda da literatürle benzer şekilde tüm olgularda da histopatolojik tanı seminom olarak görüldü.

Özellikle infertil erkek popülasyonda hastanın kendi kendine yapılacağı testis muayenesi erken tanıya katkıda bulunabilir. Avrupa Üroloji Derneği (EAU) prognozun direk olarak erken tanı ile ilişkili olmasından dolayı risk faktörleri olan erkeklerde kendi kendine muayeneyi önerilebilir bulmaktadır (25). Ancak testis kanseri taramasında kendi kendine yapılan testis muayenesinin hastalarda yersiz endişe ve gereksiz doktor ziyaretine neden olabileceğinden önerilmediği çalışmalarda literatürde mevcuttur (26).

Sonuç olarak özelllikle infertil erkek hastalarda testis muayenesi yapılırken artmış risk nedeniyle dikkatli olunmasının ve bu popülasyondaki bireylere kendi kendine yapılacakları testis muayenesinin erken tanıda önemli olduğu düşünülmektedir.

KAYNAKLAR

1. La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol 2010;21:1323-60.
2. Rosen A, Jayram G, Drazer M, Eggener SE. Global trends in testicular cancer incidence and mortality. Eur Urol 2011;60:374-9.
3. Manecksha RP, Fitzpatrick JM. Epidemiology of testicular cancer. BJU Int 2009;104:1329-33.
4. Walsh TJ, Croughan MS, Schembri M, Chan JM, Turek PJ. Increased risk of testicular germ cell cancer among infertile men. Arch Intern Med 2009;169:351-6.
5. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI. Increased risk of cancer among azoospermic men. Fertil Steril 2013;100:681-5.
6. Dada R, Kumar M, Jesudasan R, Fernández JL, Gosálvez J, Agarwal A. Epigenetics and its role in male infertility. J Assist Reprod Genet 2012;29:213-23.
7. Hotaling JM, Walsh TJ. Male infertility: a risk factor for testicular cancer. Nat Rev Urol 2009;6:550-6.
8. Gonsalves J, Sun F, Schlegel PN, Turek PJ, Hopps CV, Greene C et al. Defective recombination in infertile men. Hum Mol Genet 2004;13:2875-83.
9. Maduro MR, Lamb DJ. Understanding new genetics of male infertility. J Urol 2002;168:2197-205.
10. Ji G, Long Y, Zhou Y, Huang C, Gu A, Wang X. Common variants in mismatch repair genes associated with increased risk of sperm DNA damage and male infertility. BMC Med 2012;10:49.
11. Germà-Lluch JR, Garcia del Muro X, Maroto P, Paz-Ares L, Arranz JA, Gumà J et al. Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). Eur Urol 2002;42:553-62.
12. Moul JW. Timely diagnosis of testicular cancer. Urol Clin North Am 2007;34:109-17.
13. Zapzalka DM, Redmon JB, Pryor JL. A survey of oncologists regarding sperm cryopreservation and assisted reproductive techniques for male cancer patients. Cancer 1999;86:1812-7.
14. Hartmann JT, Albrecht C, Schmoll HJ, Kuczyk MA, Kollmannsberger C, Bokemeyer C. Long-term effects on sexual function and fertility after treatment of testicular cancer. Br J Cancer 1999;80:801-7.
15. Ho GT, Gardner H, DeWolf WC, Loughlin KR, Morgentaler A. Influence of testicular carcinoma on ipsilateral spermatogenesis. J Urol 1992;148:821-5.
16. Agarwal A, Allamaneni SS. Disruption of spermatogenesis by the cancer disease process. J Natl Cancer Inst Monogr 2005;(34):9-12.
17. Höbarth K, Klingler HC, Maier U, Kollaritsch H. Incidence of antisperm antibodies in patients with carcinoma of the testis and in subfertile men with normogonadotropic oligoasthenoteratozoospermia. Urol Int 1994;52:162-5.
18. Petersen PM, Skakkebaek NE, Rørth M, Giwercman A. Semen quality and reproductive hormones before and after orchiectomy in men with testicular cancer. J Urol 1999;161:822-6.
19. Petersen PM, Hansen SW, Giwercman A, Rørth M, Skakkebaek NE. Dose-dependent impairment of testicular function in patients treated with cisplatin-based chemotherapy for germ cell cancer. Ann Oncol 1994;5:355-8.
20. Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE et al. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ 2000;321:789–92.
21. Hanson HA, Anderson RE, Aston KI, Carrell DT, Smith KR, Hotaling JM. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. Fertil Steril 2016;105:322-8.e1.
22. Raman JD, Nobert CF, Goldstein M. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol 2005;174:1819-22.
23. Znaor A, Lortet-Tieulent J, Jemal A, Bray F. International variations and trends in testicular cancer incidence and mortality. Eur Urol 2014;65:1095-106.
24. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127:2893-917.
25. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K et al. European Association of Urology. Guidelines on Testicular Cancer: 2015 Update. Eur Urol 2015;68:1054-68.
26. Westlake SJ, Frank JW. Testicular self-examination: an argument against routine teaching. Fam Pract 1987;4:143-8.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 662-669
https://doi.org/10.31067/acusaglik.849615

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Nursing / Hemşirelik

Effectiveness of Simulation-Based Cooperative Learning Method in Electrocardiography Education

Yasemin Uslu[1] **, Vildan Kocatepe[1]** **, Vesile Ünver[1]** **, Ükke Karabacak[1]**

[1]Acibadem Mehmet Ali Aydinlar University, Nursing Department, Istanbul, Turkey

Yasemin USLU, Dr. Öğr. Üyesi
Vildan KOCATEPE, Dr. Öğr. Üyesi
Vesile ÜNVER, Prof. Dr.
Ükke KARABACAK, Prof. Dr.

Correspondence: Vesile Ünver
Acibadem Mehmet Ali Aydinlar University, Nursing Department, Istanbul, Turkey
Phone: 05379646859
E-mail: vunver1@gmail.com

Received : 10 March 2020
Accepted : 23 April 2020

ABSTRACT

Objective: The study was conducted to evaluate the effectiveness of basic electrocardiography education designed in accordance with the simulation-based cooperative learning method.

Methods: This is a single group, quasi-experimental study. A two-day electrocardiography (ECG) education program was designed for the nursing internship (4th year) program (n=125). Data were gathered with pre-posttest, Students' Satisfaction and Self-Confidence Scale, Simulation Design Scale and Educational Practices Questionnaire.

Results: The knowledge pretest score and the knowledge posttest score averages of the students were 40.36±20.24 and 75.39±11.46 respectively, with a significant difference (p=.001; t=-14.78). The mean score for satisfaction with current learning was 4.77±.42 and the mean score for self-confidence was 4.51±.54. The mean total score for Simulation Design Scale was 4.44±.67 and the mean total score for Educational Practices Questionnaire was 4.66±.56.

Conclusion: After simulation-based cooperative learning method, knowledge and skills of the students improved also had high self-confidence and satisfaction with learning.

Keywords: Electrocardiography, simulation-based experience, cooperative learning, nursing education

Simülasyona Dayalı İşbirlikçi Öğrenme Modeline Göre Tasarlanan Temel EKG Kursu'nun Etkinliği

ÖZET

Amaç: Bu çalışma, Simülasyona Dayalı İşbirlikçi Öğrenme Modeli'ne göre tasarlanan Temel Elektrokardiyografi (EKG) Kursu'nun etkinliğini değerlendirmek amacıyla yapılmıştır.

Yöntem: Tek gruplu, yarı deneysel bir çalışmadır. Hemşirelik intörn öğrencilerine (4. sınıf) 2 günlük EKG eğitim programı tasarlandı (n=125). Veriler ön-son test bilgi formu, Öğrencilerin Memnuniyet ve Öz-Güven Ölçeği, Simülasyon Tasarımı Ölçeği ve Eğitim Uygulamaları Anketi ile toplanmıştır.

Bulgular: Öğrencilerin kurs öncesi bilgi puan ortalamaları 40.36±20.24, kurs sonrası puan ortalamaları 75.39±11.46 olup istatistiksel olarak anlamlı bulundu (p=.001; t=-14.78). Öğrenmede öğrenci memnuniyet puan ortalamaları 4.77±.42, özgüven puan ortalamaları ise 4.51±.54'dür. Simulasyon tasarımı toplam puan ortalamaları 4.44±.67, Eğitim Uygulamaları toplam puan ortalamaları 4.66±.56'dır.

Sonuç: Simülasyona Dayalı İşbirlikçi öğrenme modelinde kurs sonrası öğrencilerin bilgi ve beceri düzeylerini geliştirmiş ayrıca öğrenmede öğrenci memnuniyetleri ve özgüvenleri yükselmiştir.

Anahtar Kelimeler: Elektrokardiyografi, simülasyona dayalı öğrenme, işbirlikçi öğrenme, hemşirelik eğitimi

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Cardiovascular diseases are the leading cause of death in Turkey and other countries; thus, treatment, care, and follow-up of patients with these conditions are important (1). Patients frequently arrive at emergency and intensive care units with cardiovascular diseases and receive critical care. In order for nurses to be able to maintain high-quality and effective care in these units, they are expected to be equipped with sufficient knowledge and skills about patients for whom they provide care (2, 3).

Emergency and intensive care nurses should be able to recognize sudden changes in patients earlier as well as implement appropriate interventions as quickly as possible. They should have adequate knowledge and skills to read monitors, perform ECG, interpret rhythms, and initiate interventions independently. As technology develops, it is also important that they use medical devices correctly (4).

Nurses having sufficient knowledge about the aforementioned skills; can carry out early and effective interventions, and save patients' lives. However, it has been reported in the literature that emergency and intensive care nurses do not have a sufficient level of knowledge about emergency ECG signs and interventions (5, 6). Several studies have shown that most nurses working in critical fields do not receive education about ECG, and that those that do receive education are not competent enough to evaluate ECG recordings and to design/start appropriate interventions (6). It is crucial to enhance nurses' knowledge so that they can offer more effective care and make fewer mistakes. It is recommended that nurses who actively perform and interpret ECG should be given experiential education about ECG at regular intervals (7-9). It has been noted in the literature that education based on a model and supported by different teaching methods like simulation helps nurses to improve their skills in recognizing the rhythms (8, 10).

Cooperative learning is one learning method in which students play active roles and work in groups of two or more to achieve the same goal (11, 12). It improves students' thinking and communication skills, encourages them to think critically, allows them to express their opinions throughout the learning process, and helps them to take responsibility for their learning. It creates an effective learning environment where students do not consider teachers as the only source of knowledge (12). Cooperative learning facilitates students' cooperation with each other in the learning process, and is thought to be achieved through simulation-based education when enhancing clinical skills in nursing.

Simulation is increasingly used in education, being rapidly integrated into curricula (13, 14). High-fidelity simulation is a simulation method that utilizes real mannequins, which are able to react to physiological results of diseases and injuries, treatments, and interventions (15). In simulation-based education, high-fidelity mannequins are most frequently used. In a systematic review of types of education using these mannequins, simulation-based education has been reported to be effective in recognizing changes in patients and in acquiring knowledge and skills (16).

This study was conducted to evaluate the effectiveness of basic ECG education designed in accordance with the simulation-based cooperative learning method.

METHODS

This single-group, quasi-experimental study with pre- and post-tests was performed with nursing internship (4th year) program at a university in Turkey. The study population comprised of final year nursing students at a nursing school in 2017 (n=125). Sixty-six students volunteered to participate in the study and took the Emergency Care and Intensive Care Nursing courses in Specific Fields. However, data from eleven students who did not take the pre and post-knowledge tests were not included in the analysis. Of all the participants, 18.1% (n=10) were male and 81.9% (n=45) were female. All the students were informed about the study before taking basic ECG education.

Data Collection Tools: Data were gathered via pre and post-knowledge of ECG tests, Students' Satisfaction and Self-Confidence Scale (SCLS), Simulation Design Scale (SDS), and Educational Practices Questionnaire (EPQ). The pre- and post-tests were prepared by the researchers and were composed of ten questions measuring knowledge of ECG. One question of the test is presented in that SCLS, SDS, and EPQ are used to evaluate the effectiveness of simulation-based education (17, 18). They were developed by Jeffries in 2012, and their psychometric measurements were established by Franklin in 2014 (18, 19). Their validity and reliability for the Turkish population were tested by Unver et al. in 2017 (20).

Procedure: Within the framework of the Emergency Care and Intensive Care Nursing courses in Specific Fields, a two-day ECG education program was designed. It

involved an eight-hour theoretical class and an eight-hour simulation class, which together lasted two days. On the first day, the students were offered theoretical knowledge through the conventional teaching method based on the goals of the education program, and they were provided with the content material. On the second day, the simulation was conducted in three steps.

First, the students applied skill training. Second, they were divided into groups and they interpreted ECGs in the cases given to them. Last, they took a knowledge quiz (Table 1). To evaluate the effectiveness of the education, the students were administered the pre-test involving questions about knowledge of ECG rhythms before the theoretical class, as well as the post-test involving the same questions after the simulation class.

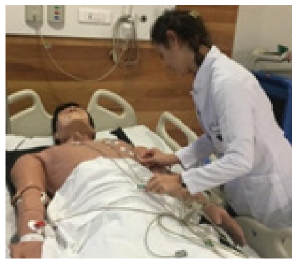
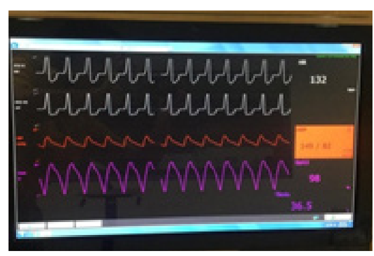
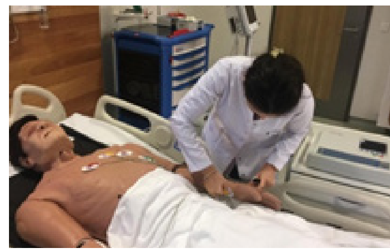
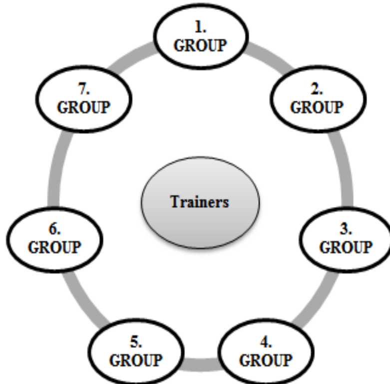
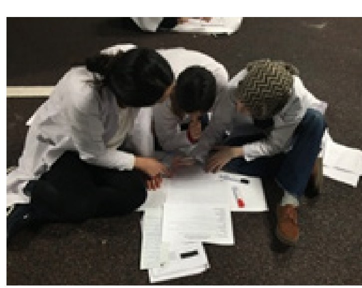
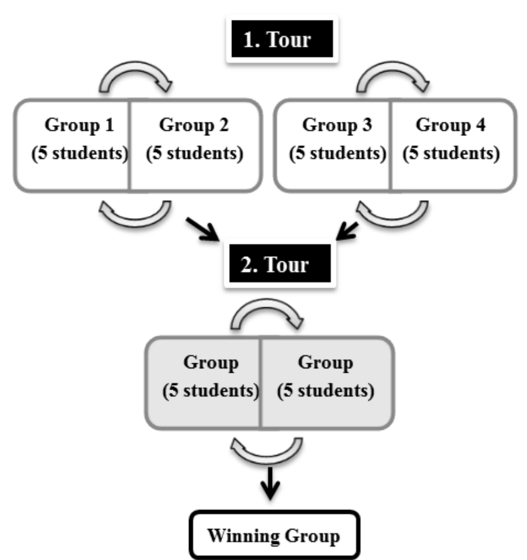
Table 1: Content of Education – Simulation Center
Step 1: I perform ECG correctly
Applied Skill Training The students monitored the mannequins, read and interpreted ECG values and placed ECG leads under the supervision of a trainer.
  
Step 2: Workshop
Case Study The students were divided into seven groups, each having three students. Target nine ECG rhythms were printed out. Images of each rhythm were given to the students in order and the students were asked to record the information about the rhythms asked in the ECG interpretation form. They were encouraged to discuss their interpretations in their groups and they were given 10 minutes to interpret each rhythm.



Table 1: Content of Education – Simulation Center

Step 3: ECG Quiz



The students were randomly assigned into groups and each group included five students. In the first round, the groups were matched in pairs and they competed against each other. The winners got the right to join the quiz in the second round. The group winning the competition in the second round was rewarded.

Rules of the Quiz:

- The group members are seated and one member gets ready to ring the bell every time a question is asked.
- The member wanting to answer a question rings the bell and gives his/her answer.
- If he/she gives the correct answer, he/she gets points. After that, another member gets ready to answer the next question.
- If he/she gives a wrong answer, the rival team gets the right to answer the question. If a member of the rival group gives the correct answer, that groups gets points.
- If both groups give a wrong answer, they discuss the question. Whichever group rings the bell first gets the right to answer the question.
- In each round, the group providing the highest number of correct answers passes that round. If there is a draw, one more question is asked and the group answering that question first wins.

Statistical Analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA) for Windows version 21.0. The normality of data was tested with the Kolmogorov–Smirnov test. The descriptive statistics; mean and standard deviation, minimum-maximum values, frequency, and percentage were used. The results obtained were compared by using Wilcoxon Signed-Ranks Test. A p-value of <0.05 was considered statistically significant.

RESULTS

The pre- and post-tests results, satisfaction with learning, self-confidence, simulation design, and educational practices were evaluated. Table 2 presents the mean scores for the pre- and post-tests. The mean pre-test knowledge score was 40.36±20.24, and the mean post-test knowledge score was 75.39±11.46; there was a significant difference (*p*=.001, *t*=-14.78). Table 3 outlines the mean scores for satisfaction with learning and self-confidence, simulation design, and educational practices. The mean score for satisfaction with current learning was 4.77±42, and the mean score for self-confidence was 4.51±54. The mean score for simulation design was 4.44±67, and the mean score for educational practices was 4.66±56.

Table 2. Pre- and Post-Tests Knowledge Scores (N=55)

Score	Min-Max	$\bar{X}$ ±SD	Statistical test*
Pre-test	0-75	40.36±20.24	t=-14.78
Post-test	43-95	75.39±11.46	P=0.01

*Wilcoxon Signed Ranks Test

Table 3. Students' Satisfaction and Self-Confidence Scale, Simulation Design Scale and Educational Practices Scores (N=55)

	Min-Max	$\bar{X}$ ±SD
Satisfaction with Current Learning	3-5	4.77±.42
Self-confidence in Learning	2.71-5	4.51±.54
Simulation Design Scale		
Objectives and Information	3-5	4.56±.57
Support	2-5	4.32±.82
Problem-Solving	1.6-5	4.39±.81
Feedback/Guided reflection	1.25-5	4.59±.69
Fidelity(Realism)	1-5	4.33±.95
Total	1.77-5	4.44±.67
Educational Practices Questionnaire		
Active learning	2.3-5	4.54±.59
Collaboration	2.5-5	4.69±.57
Diverse Ways of Learning	1-5	4.71±.68
High Expectations	1.5-5	4.7±.61
Total	1.83-5	4.66±.56

DISCUSSION

At present, cardiovascular diseases are the leading cause of death (21). Course content about the prevention and treatment of these diseases along with care for patients with these diseases were described in the National Nursing Core Curriculum in 2014 (22).

Many studies have shown that nurses do not have sufficient basic knowledge and skills of ECG. This evidence led nursing educators to utilize different models and methods to teach ECG (2-4, 23). Prior studies have used online web-based programs (e-learning) (24) algorithms (25), dance and movement (26), and the six-stage method (27) to help nurses recognize ECG rhythms and plan appropriate interventions. Unlike the reported studies, in the present study, the teaching method that was employed was designed in accordance with the simulation-based cooperative learning.

Knowledge of ECG

The students scored very high on the post-test. The mean test score increased from 40.36±20.24 to 75.39±11.46 (Table 2). It is known that cooperative learning, an active learning strategy, helps in acquiring desirable educational skills and attitudes like academic success, social skills, ability to express opinions, and critical thinking skills (12). Therefore, the learning outcomes of skill training in the cooperative learning method can be equal to and even better than those achieved through individual learning (28). It has also been reported that pedagogically-shared efforts in cooperative learning positively affect learning (29). In fact, student contributions to their peers' learning through the intragroup exchange of knowledge and discussions might have increased the post-test scores in the present study.

The simulation-based education utilized to teach ECG skills in the present study increases the fidelity of nursing education programs and is effective in improving critical thinking skills, ability to recognize changes in ECG monitors, and psychomotor skills in nursing students (16). The simulation-based method in nursing education—in which two-thirds of the curriculum involves practice—is important to improve psychomotor skills (30-32); furthermore, there is evidence that this method contributes to patient care. Performing practices in a high-fidelity environment provide students with an opportunity to enhance their decision-making and problem-solving skills and experience cases they may rarely encounter in their real life (30, 33).

In the present study, thanks to the simulation-based method, the students had a chance to recognize basic ECG rhythms and in particular manage lethal arrhythmia. The literature reports that offering theoretical knowledge combined with using simulation to teach ECG increases nurses' success. It has been emphasized that both paper-based and electronically-monitored ECG rhythms should be utilized since their interpretations can be different (34). In the present study, the students worked in groups to analyze ECG cases. They experienced rhythm interpretation techniques by using electronically-recorded rhythms from the mannequins.

The students placed ECG leads on the mannequins and interpreted the rhythms they obtained, which strengthened their psychomotor skills (Table 3). It has been noted in the literature that offering theoretical knowledge along with using simulation for skill training increases students' success (35). In a study by Alinier et al. (2004), a significant increase was detected in psychomotor and cognitive skills following simulation-based education (36). In a systematic review, simulation-based education was recommended as preferable, since it enhances the psychomotor skills of nurses (31).

In the current study, the students were given various ECG cases to improve their critical thinking skills. The students worked in groups to analyze and discuss these cases. Many studies have shown that discussions in groups revolving around case analyses can ameliorate critical thinking skills (37, 38). Consistent with the literature, in the present study, knowledge quizzes conducted for a general revision of what was learned showed an improvement in the students' ability to make quick decisions about ECG.

Students' Satisfaction and Self-Confidence

As a result of the simulation-based education, the mean scores for current student satisfaction with learning (4.77±.42) and current student self-confidence (4.51±.54) increased (Table 3). The students noted that the teaching methods used in education were effective, motivating, and helpful for learning. In a study of the effects of simulation-based ECG education on critical thinking and self-confidence, the students in the simulation group had higher self-confidence (42). Comparable with the literature (37, 39, 40), the students in the present study were found to be satisfied with the simulation-based education and were self-confident in terms of their skills.

Educational Practices

The mean total score for educational practices was 4.66±.56, which was very high. Sumner et al. found that simulation in which nurses actively participated was effective in learning ECG (8). In a study by Brannan et al., the effectiveness of a classroom lecture was compared to the use of simulation in terms of knowledge gain. They showed that education given through simulation-based learning about patients with acute myocardial infarction led to a significant increase in the post-test scores of the students, compared to the education given through the conventional method (41). The results of the present study also suggest that the active learning underlying simulation-based education has positive effects on students.

Simulation Design

The mean total score for simulation design was 4.44±.67, which indicated that the simulation-based ECG education was very effective (Table 3). National Council of State Boards of Nursing reported that it is difficult to create evidence-based practices due to lack of standardization, although it supports using simulation in education. Therefore, it is recommended that educational content should be created using the best-practice standards provided by the International Nursing Association for Clinical Simulation and Learning, and that the education should be evaluated with valid and reliable tools (42). The mean high score for simulation design in the present study can be attributed to the simulation education planned in accordance with the best-practice standards.

CONCLUSION

Basic ECG education that is developed in accordance with the simulation-based cooperative learning model created positive learning outcomes. The use of different teaching techniques and the active involvement of the students were found to positively influence learning. It was also observed that the students contributed to their peers' learning. In addition, the students' self-confidence and satisfaction with learning increased. However, further studies are needed to evaluate the effectiveness of the model in terms of learning outcomes, satisfaction, and self-confidence in different subjects.

Limitations

The fact that this study was performed in only one nursing school restricts the generalizability of its results.

Compliance of Ethical Statement

Ethical approval was obtained before starting the study from the ethical committee of the university where the study was conducted (approval number: 2017-13/7). We are allowed to use pictures of the students.

Conflict of Interest

All authors declare no conflict of interest.

Acknowledgments

None declared.

Financial Disclosure/Statement

None declared.

Author Contribution

All authors contributed equally to the preparation of this article.

REFERENCES

1. Pagidipati NJ, Gaziano TA. Estimating Deaths from Cardiovascular Disease: A Review of Global Methodologies of Mortality Measurement. Circulation. 2013;127(6):749-56.
2. Çelik Y, Karadaş C, Akdağ C, Özkeçeci G. Evaluation of ECG Knowledge of the Employees in the Emergency and Intensive Care Nurses. Turkish Journal of Cardiovascular Nursing. 2015;6(9):75-85.
3. Doğu Ö, Gündüz H, Dede E. An Evaluation of the State of Cardiology, Intensive Care and Emergency Nurses' Recognizing the Findings of ECG and Their Initiatives of Appropriate Nursing. Sakarya Medical Journal. 2014;4(4):178-81.
4. Göz F, Baran G. Determining of the Nurses Assessments about ECG and Need of Education. Journal of Cumhuriyet University School of Nursing. 2000;4(2):33-9.
5. Keller K, Raines D. Arrhythmia Knowledge: A Qualitative Study. Heart & Lung: The Journal of Acute and Critical Care. 2005;34(5):309-16.
6. Nickasch B, Marnocha S, Grebe L, Scheelk H, Kuehl C. 'What Do I Do next?'Nurses' Confusion and Uncertainty with ECG Monitoring. MedSurg Nursing. 2016;25(6):418-23.
7. Özoğul A, Yolaçan A, Erkuş B. Evaluating the Education Results of the Nurses Who Had Basic Electrocardiography Education in Acıbadem Health Group: Recognizing Deadly Rythms. Turkish Journal of Cardiovascular Nursing. 2015;6(10):112-20.
8. Sumner L, Burke S, Chang L, McAdams M, Jones D. Evaluation of Basic Arrhythmia Knowledge Retention and Clinical Application by Registered Nurses. Journal for Nurses in Professional Development. 2012;28(2):E5-E9.
9. Üzel G, Ulupınar S. Knowledge and Opinions of Nurses about Electrocardiography. Journal of the Turkish Society of Critical Care Nurse 2011;15(1):1-8.
10. Granero-Molina J, Fernández-Sola C, López-Domene E, Hernández-Padilla J, Preto L, Castro-Sánchez A. Effects of Web-Based Electrocardiography Simulation on Strategies and Learning styles. Revista da Escola de Enfermagem da USP. 2015;49(4):0650-6.
11. Dillenbourg P. What Do You Mean by Collaborative Learning? P. Dillenbourg ed: Oxford: Elsevier; 1999. p. 1-19.
12. Şimşek U, Şimşek Ü, Doymuş K. A Review on Cooperative Learning Method III: the Useful in Education Environment of Cooperative Learning Method Atatürk University Kazım Karabekir Education Faculty Journal 2006(13):415-28.
13. Solnick A, Weiss S. High fidelity Simulation in Nursing Education: a Review of the Literature. Clinical Simulation in Nursing. 2007;3(1):41-5.
14. Aebersold M, Tschannen D. Simulation in Nursing Practice: the Impact on Patient Care. Online Journal of Issues in Nursing. 2012;18(2):6-.
15. Decker S, Sportsman S, Puetz L, Billings L. The Evolution of Simulation and Its Contribution to Competency. The Journal of Continuing Education in Nursing. 2008;39(2):74-80.
16. Lapkin S, Levett-Jones T, Bellchambers H, Fernandez R. Effectiveness of Patient Simulation Manikins in Tteaching Clinical Rreasoning Skills to Undergraduate Nursing Students: A Systematic Review. Clinical Simulation in Nursing. 2010;6(6):e207-e22.
17. Basak T, Unver V, Moss J, Watts P, Gaioso V. Beginning and Advanced Students' Perceptions of the Use of Low-and High-fidelity Mannequins in Nursing Simulation. Nurse Education Today. 2016;36:37-43.
18. Jeffries P. Simulation in Nursing Education: from Conceptualization to Evaluation. 2nd ed. ed. National League for Nursing, New York 2012.
19. Franklin A, Burns P, Lee C. Psychometric Testing on the NLN Student Satisfaction and Self-Confidence in Learning, Simulation Design Scale, and Educational Practices Questionnaire Using a Sample of Pre-Licensure Novice Nurses. Nurse Education Today. 2014;34(10):1298-304.
20. Unver V, Basak T, Watts P, Gaioso V, Moss J, Tastan S, et al. The Reliability and Validity of Three Questionnaires: The Student Satisfaction and Self-Confidence in Learning Scale, Simulation Design Scale, and Educational Practices Questionnaire. Contemporary Nurse. 2017;53(1):60-74.
21. The Top 10 Causes of Death http://www.who.int/mediacentre/factsheets/fs310/en/: World Health Organization; [Access Date 30.01.2018].
22. Kaya H. National Core Training Program for Nursing http://www.hemed.org.tr/images/stories/hucep-2014-pdf.pdf. 2016 [
23. Rajakumari G, Kumar S, Soli T. Effectiveness of Structured Education on Electrocardiograph Findings Among Nursing Students. Journal of Science. 2015;5(9):787-90.
24. Kim Y. Effects of a Web-Based Teaching Method on Undergraduate Nursing Students' Learning of Electrocardiography. Journal of Nursing Education. 2005;44(1):35.
25. Atwood D. Using an Algorithm to Easily Interpret Basic Cardiac Rhythms. AORN journal. 2005;82(5):757-66.
26. Schultz K, Brackbill M. Teaching Electrocardiogram Basics Using Dance and Movement. American Journal of Pharmaceutical Education. 2009;73(4):70.
27. Varvaroussis D, Kalafati M, Pliatsika P, Castrén M, Lott C, Xanthos T. Comparison of Two Teaching Methods for Cardiac Arrhythmia Interpretation among Nursing Students. Resuscitation. 2014;85(2):260-5.
28. Tolsgaard M, Kulasegaram K, Ringsted C. Collaborative Learning of Clinical skills in Health Professions Education: The Why, How, When and for Whom. Medical Education. 2016;50(1):69-78.
29. Wulf G, Shea C, Lewthwaite R. Motor Skill Learning and Performance: a Review of Influential Factors. Medical Education. 2010;44(1):75-84.
30. Durmaz Edeer A, Sarıkaya A. The Use of Simulation in Nursing Education and Simulation Types. Journal of Education and Research in Nursing. 2015;12(2):121-5.

31. Kim J, Park J, Shin S. Effectiveness of Simulation-Based Nursing Education Depending on Fidelity: a Meta-Analysis. BMC Medical Education. 2016;16(1):152.

32. Eyikara E, Baykara Z. The Importance of Simulation in Nursing Education. World Journal on Educational Technology: Current Issues. 2017;9(1):2-7.

33. Kunst E, Mitchell M, Johnston A. Using Simulation to Improve the Capability of Undergraduate Nursing Students in Mental Health Care. Nurse Education Today. 2017;50:29-35.

34. Smith N, Prybylo S, Conner-Kerr T. Using Simulation and Patient Role Play to Teach Electrocardiographic Rhythms to Physical Therapy Students. Cardiopulmonary Physical Therapy Journal. 2012;23(1):36.

35. Kardong-Edgren S, Anderson M, Michaels J. Does Simulation Fidelity Improve Student Test Scores? Clinical Simulation in Nursing. 2007;3(1):e21-e4.

36. Alinier G, Hunt W, Gordon R. Focus: Determining the Value of Simulation in Nurse Education: Study Design and Initial Results. Nurse Education in Practice. 2004;4:200-7.

37. Howard V. A comparison of Educational Strategies for the Acquisition of Medical-Surgical Nursing Knowledge and Critical Thinking Skills: Human Patient Simulator vs. the Interactive Case Study Approach. PA: University of Pittsburgh: University of Pittsburgh; 2007.

38. Ravert P. Patient Simulator Sessions and Critical Thinking. Journal of Nursing Education. 2008;47(12):557-62.

39. Smith S, Roehrs C. High-Fidelity Simulation: Factors Correlated with Nursing Student Satisfaction and Self-Confidence. Nursing Education Perspectives. 2009;30(2):74-8.

40. Jeffries P, Rizzolo M. Designing and Implementing Modelsfor the Innovative Use of Simulationto Teach Nursing Care of Ill Adults and Children: A National, Multi-Site, Multi-Method Study National League for Nursing. 2006.

41. Brannan J, White A, Bezanson J. Simulator Effects on Cognitive Skills and Confidence Levels. Journal of Nursing Education. 2008;47(11):495-500.

42. Doolen J, Mariani B, Atz T, Horsley T, O'Rourke J, McAfee K, et al. High-fidelity Simulation in Undergraduate Nursing Education: A Review of Simulation Reviews. Clinical Simulation in Nursing. 2016;12(7):290-302.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 670-681
https://doi.org/10.31067/acusaglik.850986

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI Healthcare Management / Sağlık Yönetimi

Analysis of Studies on COVID-19 Pandemic with Science Mapping Technique

İlknur Arslan Çilhoroz[1] , Yasin Çilhoroz[2] , Enver Bozdemir[3]

[1]Ankara Hacı Bayram Veli Üniversitesi, Sağlık Yönetimi, Ankara, Türkiye
[2]Hacettepe Üniversitesi, Sağlık Yönetimi, Ankara, Türkiye
[3]Düzce Üniversitesi, Sağlık Yönetimi, Düzce, Türkiye

İlknur ARSLAN ÇİLHOROZ, Uzm.
Yasin ÇİLHOROZ, Arş. Gör.
Enver BOZDEMİR, Prof. Dr.

Correspondence: Yasin ÇİLHOROZ
Hacettepe Üniversitesi, Sağlık Yönetimi, Ankara, Türkiye
Phone: +903122976356
E-mail: yasin.cilhoroz@hacettepe.edu.tr

Received : 03 June 2020
Accepted : 05 September 2020

ABSTRACT

Aim: COVID-19 pandemic has been one of the biggest threats to human health globally. Since the studies investigating the effects and treatment methods of this pandemic have also increased over time, systematical analysis of these studies has become a requirement. In this sense, the aim of this study was to analyze the studies on COVID-19 using the science mapping technique systematically.

Study Design: For this purpose, Scopus, Web of Science and PubMed databases were searched. As a result of this database search, a total of 10746 publications were collected. VOSviewer, Cite Space, and Carrot Search softwares were used to analyze the collected publications. These softwares have been used in bibliometric studies to ensure that the results are visualized according to authors, keywords, countries, and journals.

Results: Results of the analysis showed that the country contributing the most to the field was China, and the journal was "The Lancet". Besides, the author who has the highest number of publications in the field was Chen NS according to the CiteSpace software, and Liu Y according to the Vosviewer software program.

Conclusion: Accordingly, the results of this study were considered to be a guide for the upcoming studies.

Keywords: Pandemic, COVID-19, bibliometric analysis, science mapping technique

COVID-19 Pandemisi Üzerine Yapılan Çalışmaların Bilim Haritalama Tekniğiyle Analizi

ÖZET

Amaç: Küresel anlamda insan sağlığına yönelik en büyük tehditlerden biri COVID-19 pandemisi olmuştur. Zamanla bu hastalığın etkileri ve tedavi yöntemleri konusunda yapılan çalışmalar da artış göstermiştir. Bu durum bu çalışmaların sistematik olarak analiz edilmesini gerekli kılmaktadır. Bu anlamda bu çalışmanın amacı, COVID-19 konusunda yapılan çalışmaların bilim haritalama tekniğine göre sistematik olarak analiz edilmesidir.

Çalışma Planı: Bu amaçla, son yıllarda bu alanlardaki yayınlarla ilgili bilgiler Scopus, Web of Science ve Pubmed veri tabanlarından elde edilmiştir. Veri tabanlarının taranması sonucunda toplamda 10746 yayına ulaşılmıştır. Ulaşılan yayınlar, VoSViewer, CiteSpace ve Carrot Search yazılım programları yoluyla analiz edilmiştir. Bu yazılım programları bibliyometrik çalışmalarda ve sonuçların yazarlara, anahtar kelimelere, ülkelere ve dergilere göre görselleştirilmesini sağlamak için kullanılmıştır.

Bulgular: Gerçekleştirilen analiz sonucunda alana en fazla katkı sağlayan ülkenin Çin, derginin ise "The Lancet" olduğu görülmüştür. Bunun yanısıra en fazla yayın yapan yazar CiteSpace yazılım programına göre Chen NS, Vosviewer veri tabanına göre Liu Y olmuştur.

Sonuç: Buna göre, daha sonra yapılacak çalışmalar için bu çalışmanın bulgularının rehberlik edebileceği düşünülmektedir.

Anahtar Kelimeler: Pandemi, COVID-19, bibliyometrik analiz, bilim haritalama tekniği

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

From past to present, viral diseases emerge as a serious issue for public health continuously. In the past two decades, various viral outbreaks have occurred such as severe acute respiratory syndrome coronavirus (SARS-CoV) between 2002-2003 and H1N1 influenza in 2009. Recently, Middle East respiratory syndrome coronavirus (MERS-CoV) appeared firstly in Saudi Arabia in 2012. Lastly, in December 2019, an outbreak of a new coronavirus (Covid-19) occurred in Wuhan, China (1). As of May 15, 2020, COVID-19 caused approximately 4.5 million cases and 300 thousand deaths worldwide (2). WHO announced it as a pandemic after a large number of COVID-19 cases were identified in many countries outside of China in a very short time (3).

Although COVID-19 seems likely to be transmitted from animals to humans in relation to a large seafood market where live wild animals are also sold, the disease was found to be transmitted from person to person over time (4). (Li et al., 2020). COVID-19 has a number of symptoms that damage the human respiratory system. However, COVID-19 occurs after a stated incubation period of approximately 5.2 days (4,5) (Rothan & Byrareddy, 2020; Li et al., 2020). The period from the onset of COVID-19 symptoms to death varies between 6-41 days, with an average of 14 days. This period depends on the age of the patient and the situation of the immune system. This period is shorter especially in patients over the age of 70 compared to those under 70 (6). The most common symptoms at the onset of COVID-19 disease are fever, cough, and fatigue. Apart from these, there are sputum, headache, hemoptysis, diarrhea, difficulty breathing, and lymphopenia (6,7,8). The most preferred diagnostic methods for COVID-19 based on these symptoms are PCR (polymerase chain reaction) test and chest radiography or CT (computer tomography) test. These methods ensure the detection of even a small number of viruses (9,10).

After the diagnosis of COVID-19 disease, the next step is the treatment of the disease. At this stage, the isolation of the patient is a priority. Thereafter, treatment procedures start. There is currently no specific drug or vaccine for COVID-19. However, some existing drugs such as oseltamivir, lopinavir, ritonavir, ganciclovir and their compositions are used to treat the disease (11,12,52).

To ensure hand hygiene, to keep at least a 3-meter social distance from other people, to stay away from crowded areas, not to touch the eyes, nose, and mouth with hands, to stay isolated at home, to inform the health institution immediately if there are symptoms of COVID-19, and to obey the recommendations of national and international organizations are the measures to be protected from COVID 19 (13).

The literature search showed that many studies related to COVID-19 have been carried out since December 2019 (14 ,15,16,17,18,19,20,21,22,23,24,25,26,27).

Despite the fact that the main focus of these studies is the COVID-19 pandemic, the associated factors, countries in which they were conducted, the number of authors, etc. A systematical analysis of these studies has become a requirement, in order to get information about these studies in a simple manner. In this sense, the purpose of this study was to analyze the studies on COVID-19 using the science mapping technique systematically.

Study Design

This section explains the purpose, significance and problem of the research, the data collection techniques, and the analysis methods.

This study aimed to analyze the studies on COVID-19 using the science mapping technique systematically.

Advantages of doing bibliometric analysis for the purposes of this study are to provide a better understanding of the structure of scientific data; to give a theoretical opportunity to define, to analyze and evaluate the literature on this subject; to provide valuable information about the chronological development of this research area (past, present, and future); to enable scientists to identify scientifically influential authors, articles, journals, topics, and citations, and to provide the opportunity to determine the degree of interaction among authors, scientific articles and journals, summarize big data sets, and to identify popular issues and research trends.

The model of the study is shown in Figure 1.

"Scopus, Web of Science and PubMed" academic publication databases were used as a data collection method. The data were obtained on May 17, 2020. Each publication in the databases contains many details including the year of publication, authors, authors' fields, titles, summary, source, topic categories, and references.

The keyword used in the publication search was "COVID-19". Quotation marks are included in the search term. Using quotation marks helps to get correct results (28). As a result of the search, it was reached 7,287 studies in Scopus, 3,093 studies in Web Of Science, and 366 studies in PubMed. A total of 10,746 studies were analyzed.

Reading all these studies seems not possible for those who are interested in the field. Rational readers have rational choices in the face of this important knowledge. One of these choices is to use bibliometric analysis techniques (29).

The searching screen of the research is shown in Table 1.

If the same search strategy is performed on a different date, the results may differ slightly. This difference is due to the fact that databases are constantly updated. The criteria and details about this study are presented in Table 2.

The Bibliometric analysis allows an exchange of information between two or more research areas and an in-depth study of the research areas (29). In this study, VoSViewer, CiteSpace and Carrot Search softwares, which are modern visual mapping techniques, were used together. Bibliometric analysis was used to explore the four research aspects from the aspects provided in Figure 2.

VoSViewer was developed by Eck and Waltman (2014) at Leiden University in the Netherlands. With a user-friendly interface, VoSViewer offers both the basic functionality required to visualize bibliometric networks and advanced features to create these networks (30). CiteSpace software was developed by Chaomei Chen at Drexel University in the USA. CiteSpace is a more specialized tool capable of categorizing data into different time subclasses and visualizing networks using various arrangements. As Chen describes, the CiteSpace software program is a true "X-ray machine for literature" and allows users to discover the intellectual field of an information field, see how it evolved over time, and identify research points and boundary directions in a particular area (31). Both software are available online for free and are effective in data visualization (32). These programs have also been used to create co-citation networks, co-authoring networks, co-generation networks, and explosion detections.

Carrot Search is characterized by several features, which are useful for creating custom web search clustering systems. The clear data-driven process of information manipulation defined within decreases the time and effort required for building software and allows performing rapid experiments with search results clustering through component reuse and facilitation of their development (33).

Results

Content Analysis

Table 3 shows the top 10 most cited studies on COVID-19. The top 10 most cited studies belong to the Scopus database. In the study titled "Clinical features of patients infected with the novel coronavirus 2019 in Wuhan, China" conducted by Huang et al (2020), the researchers concluded that COVID-19 infection caused severe respiratory disease and the intensive care acceptance was high. The second study which is conducted by Zhu et al. (2020) concluded that COVID-19 was the seventh member of the coronavirus family that infects humans as both MERS-CoV and SARS-CoV did. Chen et al. (2020) have revealed that COVID-19 infection was more likely to affect older men with comorbidity, and could cause serious and fatal respiratory diseases such as acute respiratory distress syndrome. Guan et al. (2020) stated that in the first 2 months of the current outbreak, COVID-19 spread rapidly to China and caused diseases that have different degrees. Chan et al. (2020) emphasized that this new coronavirus was consistent with person-to-person transmission in hospitals, houses and infected travelers in other geographic areas.

Table 1. Search Screen

Scopus Search Screen	Web Of Science Search Screen	Carrot Search Screen

Table 2. Searching Criteria			
Criteria		Details	
Database	WOS	Article Topic	Citespace
	Scopus	Article title, Summary, Keywords	Vosview
	PubMed	Available Options	Carrot Search
Title		"Covid-19"	
Timeframe		2019-2020	
Document Type		Articles, Books, Book Chapters, Papers, Reviews	
Research History		17 May 2020	

Table 3. Most Cited Publications on Covid-19			
Authors	Title of the Study	Citations	Magazine
Huang et al., 2020	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	1250	The Lancet
Zhu et al., 2020	A novel coronavirus from patients with pneumonia in China, 2019	749	New England journal of medicine
Chen et al., 2020	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	679	The Lancet
Guan et al., 2020	Clinical characteristics of coronavirus disease 2019 in China	615	New England journal of medicine
Chan et al., 2020	A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster	473	The Lancet
Zhou et al., 2020	A pneumonia outbreak associated with a new coronavirus of probable bat origin	455	Nature
Wu et al. 2020	Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention	406	JAMA - Journal of the American Medical Association
Lu et al., 2020	Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding	399	The Lancet
Holshue et al., 2020	First case of 2019 novel coronavirus in the United States	321	New England journal of medicine
Zhou et al., 2020	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	312	The Lancet

In a study by Zhou et al. (2020), the researchers confirmed that COVID-19 was 96% identical to a bat coronavirus at the whole genome level and used the same cell entry receptor (angiotensin-converting enzyme II (ACE2)) as the SARS-CoV. Wu et al. (2020) emphasized the significance of responding effectively such as proactive investment in public health infrastructure during the fight against COVID-19. Lu et al. (2020) found that COVID-19 was different from SARS-CoV, which will be considered as a new human-infected betacoronavirus. The study of Holshue et al. (2020) describes the clinical features of the first reported patient with COVID-19 infection in the United States and focuses on the importance of clinicians who reveal a travel history of COVID-19 infected patient or exposure to patients with COVID-19. Zhou et al. (2020) also indicated that aging, high SOFA score and D-dimer higher than 1 µg / mL are potential risk factors that can help clinicians to prognose the COVID-19 infected patients early (8,9,12,34,35,36,37,38,50,51).

Analysis Based on Topic Categories

According to Figure 3, there are categories in the image created using the CiteSpace software with data from the Web of Science database. Accordingly, the highest number of publications was conducted in the Internal Medicine field with 143 publications. This is followed by Virus Science (34), Nuclear Radiology, and Medical Imaging (30), Surgery (27), and Infectious Diseases (26).

The topic categories of the publications related to COVID-19 are given in Table 4. According to the Web of Science database, 728 publications were conducted in the field of Medicine. This was followed by Public Environmental Health (190), Surgery (183), Radiology and Nuclear Medicine, and Communicable Diseases. According to the Scopus database, 62% of the publications were conducted in the field of Medicine, 9.4% from other fields, 6.7% in Biochemistry, Genetics, and Microbiology, 6.3% in Immunization and Microbiology.

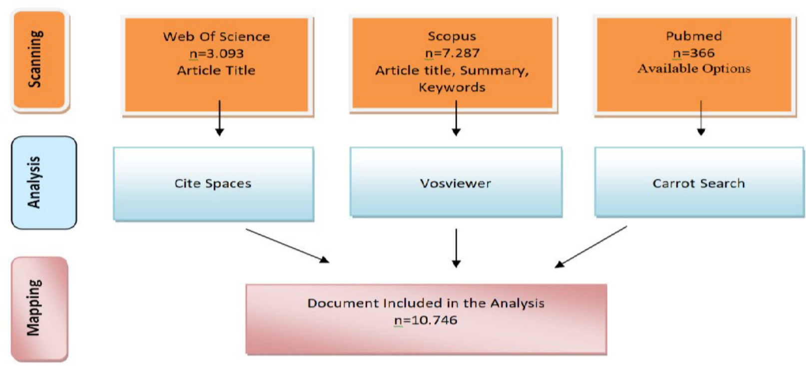


Figure 1. Model of the Study

In this study, "Scopus, Web of Science and PubMed" academic publication databases were used as a data collection method. The data were obtained on May 17, 2020. Each publication in the databases contains many details including the year of publication, authors, authors' fields, titles, summary, source, topic categories, and references.
"COVID-19" was the keyword used in the publication search. Quotation marks are included in the search term. Using quotation marks helps to get correct results (28). As a result of the search, 7,287 studies were accessed in Scopus, 3,093 studies in Web Of Science, and 366 studies in PubMed. A total of 10,746 studies were analyzed.

Figure 2. The Analysis Process of the Research

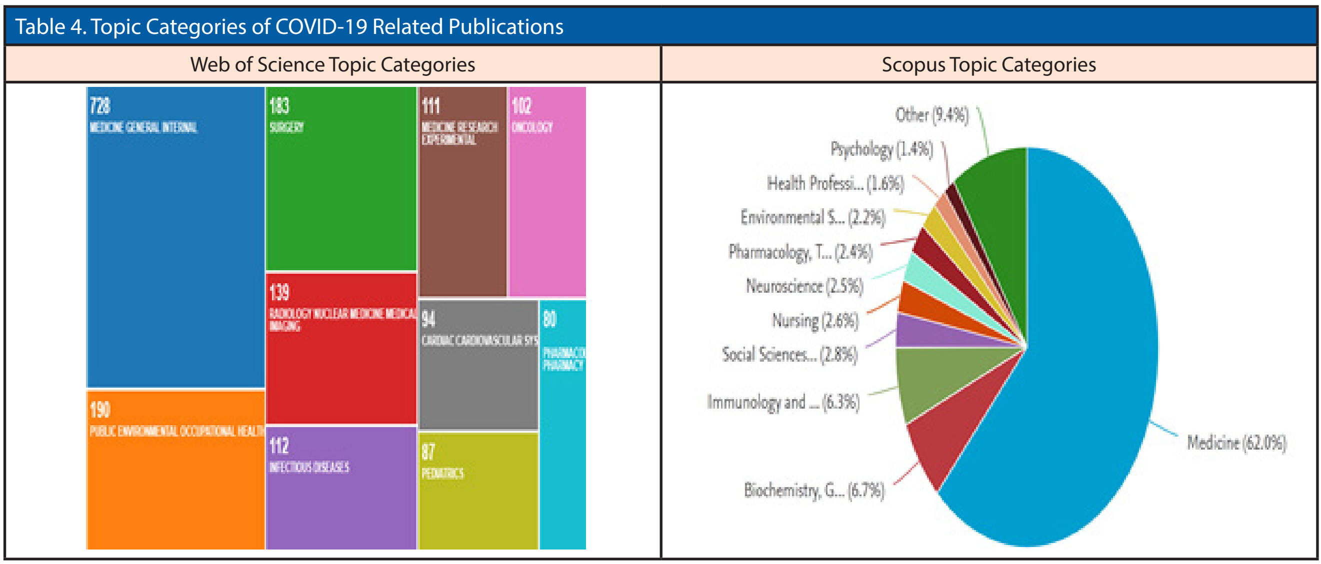
In this study, VoSViewer, CiteSpace ve Carrot Search softwares, which are modern visual mapping techniques, were used together. Bibliometric analysis was used to explore the four research aspects from the following aspects that are provided in Figure 2.

Figure 3. Analysis of Subject Categories According to Cite Space Analysis

According to Figure 3, there are categories in the image created using the CiteSpace software with data from the Web of Science database. Accordingly, the highest number of publications was conducted in the Internal Medicine field with 143 publications. This is followed by Virus Science (34), Nuclear Radiology, and Medical Imaging (30), Surgery (27), and Infectious Diseases (26).

Table 4. Topic Categories of COVID-19 Related Publications

Web of Science Topic Categories	Scopus Topic Categories



Keyword Based Mapping

Figure 4 shows the most used keywords in COVID-19 studies, which were determined with the VoSwiever program keyword analysis of the data from the Scopus database. The threshold value in the program is selected as 10. The most commonly used terms were Covidien (682 times), new coronavirus (186 times), pneumonia (180 times), and Wuhan (137 times).

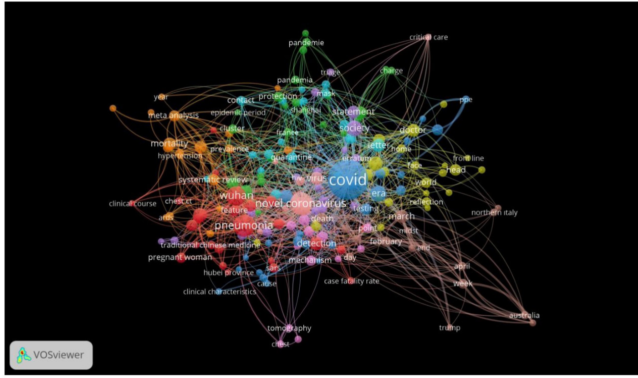


Figure 4. Keyword Analysis with Vosviewer (When 12.087 term minimum 10 is selected, 310 term thresholds meet.)

In Figure 4, for the detection of the most used keywords in COVID-19 studies, the data from the Scopus database were subjected to keyword analysis in the VoSViewer software. The threshold value in the program is selected as 10. The most commonly used terms were Covidien (682 times), new coronavirus (186 times), pneumonia (180 times), and Wuhan (137 times).

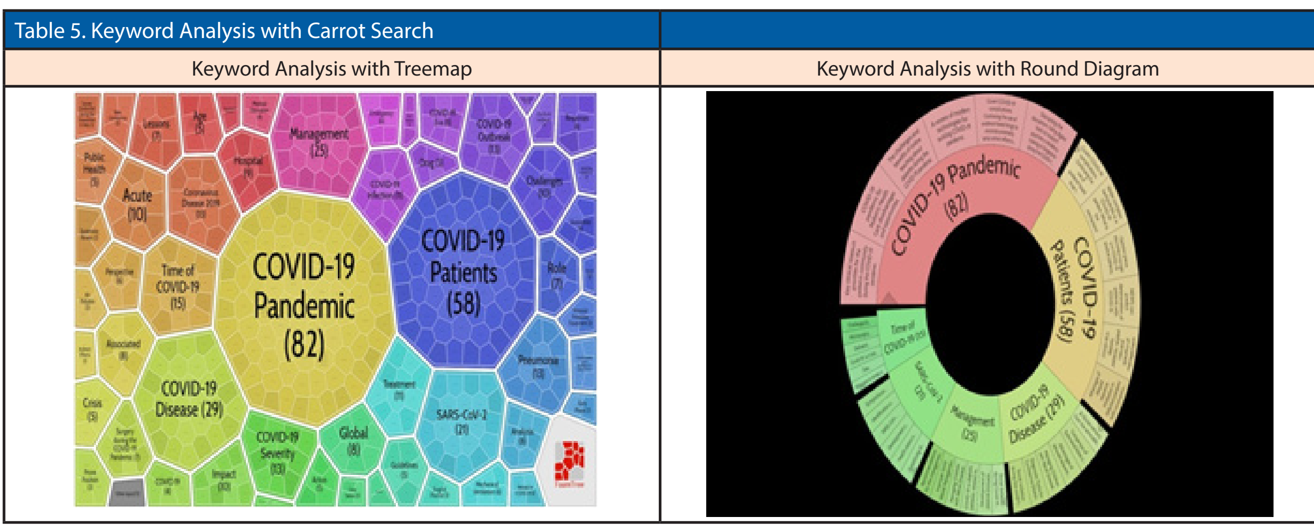
Table 5 shows 366 studies that are accessed through Carrot Search analysis using the PubMed database. The most commonly used keywords were Object (157 times), Covid-19 Pandemic (59 times), Covid-19 Patients (49 times), Disease (27 times), and Coronavirus Covid-19 (22 times).

Figure 5 shows the most commonly used keywords in the analysis of keywords performed via CiteSpace software using the Web of Science database, which are COVID 19 (180 times), Coronavirus (110 times), Sars-Cov-2 (79 times) and Pneumonia (60 times). When the word groups are examined, clusters were 0: Respiratory failure, 1: Sleep quality, 2: Organ protective effect, 3: Covid-19 Infection, 4: operatory consideration, 5: Global transplant perspective.

Attribution and Common Attribution Based Mapping

As Eck and Waltman (2014) mentioned, citation analysis is an effective way to analyze the communication within the academic community, the structure of science from an interdisciplinary perspective, and to explore new knowledge-generating mechanisms.

Table 5. Keyword Analysis with Carrot Search



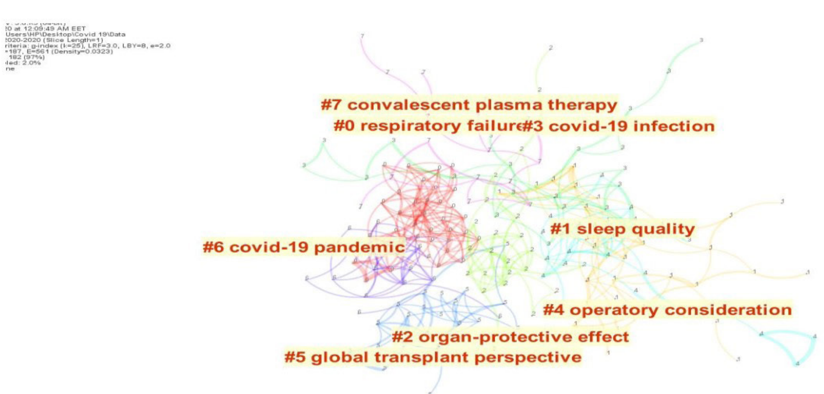


Figure 5. Keyword Analysis with CiteSpace

In Figure 5, COVID-19 (180 times), Coronavirus (110 times), Sars-Cov-2 (79 times), Pneumonia (60 times) were the most commonly used keywords in the analysis of keyword performed via CiteSpace software using Web of Science database. When the word groups are examined, clusters were 0: Respiratory failure, 1: Sleep quality, 2: Organ protective effect, 3: Covid-19 Infection, 4: operatory consideration, 5: Global transplant perspective.

Citations are also extremely important to determine the significance of a scientific article. There is a strong relationship between the frequency of citations and the unique scientific value of the article. The number of citations is the main factor reflecting the quality of an article (40). The citation should be considered as the criterion of the publication value (39). Obviously, older publications are more likely to get more citations than newer publications, but this should not be taken into consideration in the sense that the recently published studies will not have a significant impact in this area (41).

In Figure 6, the analysis of data from the Scopus database was performed in the VosViewer software. Accordingly, the most cited author was Liu, Y with 1634 citations. This was followed by Wang, W (1407), Zhang I (1334), Song J (1172), and Wang J (1157).

In Figure 7, the data from the Scopus database were analyzed by the VosViewer software. Accordingly, the authors who are in contact with each other were clustered into 5 groups. The most commonly cited author was found as Li, X with 737 common citations.

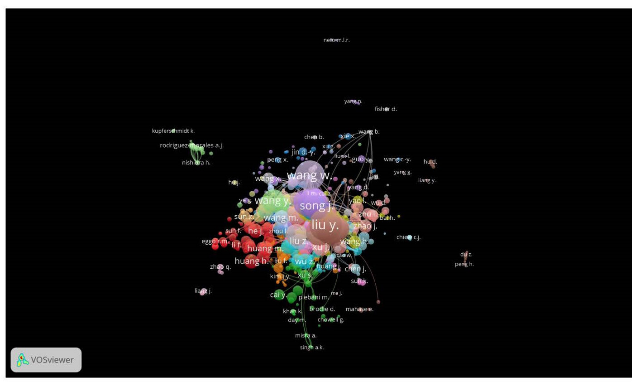


Figure 6. Citation Analysis of Authors with Vosviewer (cluster view: 763 authors meet the 593 threshold when the minimum value of 3 is selected.)

In Figure 6, the analysis of data from the Scopus database was performed in the VoSViewer software. Accordingly, the most cited author was Liu, Y with 1634 citations. This was followed by Wang, W (1407), Zhang I (1334), Song J (1172), and Wang J (1157).

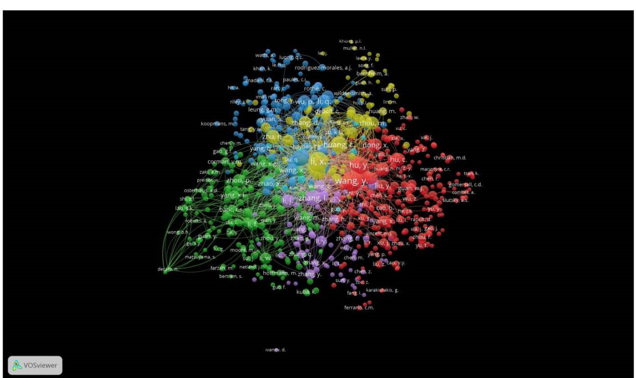


Figure 7. Co-Citation Analysis of Authors with Vosviewer (cluster view: when 32,957 minimum value is selected 20 meets 719 threshold.)

In Figure 7, the analysis of the data from the Scopus database was performed in the VoSViewer software. Accordingly, the authors who are in contact with each other were clustered into 5 groups. The most commonly cited author is Li, X with 737 common citations.

The topic categories of the publications related to COVID-19 were provided in Table 4. According to the Web of Science database, 728 publications were conducted in the field of Medicine.

According to Figure 8, the most cited author was Chen NS with 101 citations using the CiteSpace software when the data from Web of Science database were analyzed using the CiteSpace software. This was followed by Wang DW (89), Li Q (86), Chan JFW (85), Anonymous (84).

Figure 8. Citation Analysis of Authors with CiteSpace

According to Figure 8, the most cited author using the CiteSpace software with data from the Web of Science database was Chen NS with 101 citations. This was followed by Wang DW (89), Li Q (86), Chan JFW (85), Anonymous (84).

In Figure 9, the data from the Scopus database was analyzed in the VosViewer software. Accordingly, the journal that received the highest number of citations from publications in the field of COVID-19 was "The Lancet" with 3986 citations. This was followed by New England Journal of Medicine (2530), Journal of American Medical Association (1113), Radiology (872) and Journal of Medical Virology (756).

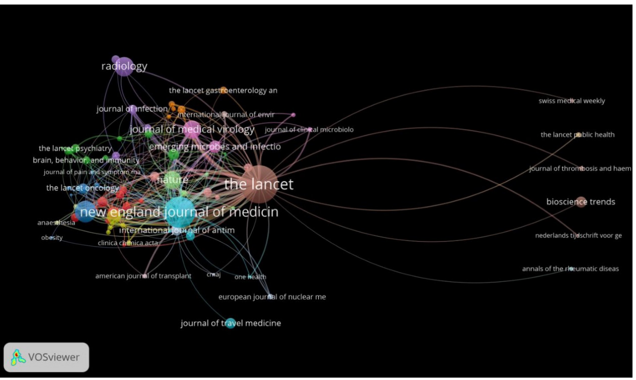


Figure 9. Citation Analysis of Journals with Vosviewer (cluster view: 676 journals meet 93 thresholds when the minimum value is selected 5)

In Figure 9, data from Scopus database performed in the VoSViewer software. Accordingly, the journal that received the highest number of citations from publications in the field of COVID-19 was "The Lancet" with 3986 citations. This was followed by New England Journal of Medicine (2530), Journal of American Medical Association (1113), Radiology (872) and Journal of Medical Virology (756).

The analysis performed in the CiteSpace software program with the data from Web of Science database was as in Figure 10. According to this, the journal which received the most citation was "The Lancet" with 296 citations. This is followed by New England Journal of Medicine (238), Journal of American Medical Association (156), Nature (112) and Journal of Medical Virology (81).

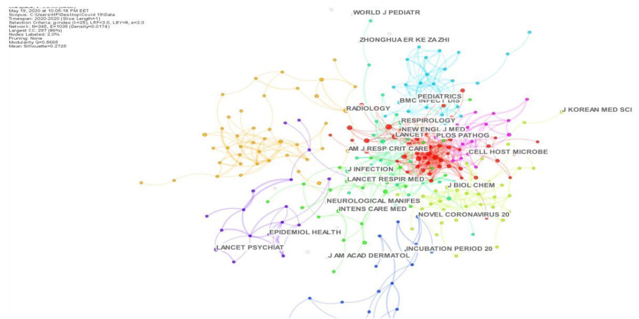


Figure 10. Citation Analysis of Journals with Cite Space

The analysis performed in the CiteSpace software program with the data from Web of Science database was as in Figure 10. According to this, the journal which received the highest number of citations was "The Lancet" with 296 citations. This is followed by New England Journal of Medicine (238), Journal of American Medical Association (156), Nature (112) and Journal of Medical Virology (81).

Country analysis was performed with the data from Web of Science database using CiteSpace software program. Large circles show the most influential countries in the field, the degree of communication between countries and the links between the circles. Accordingly, China was the country with the highest number of citations in studies on COVID-19. This was followed by the USA with 129 citations, England with 74 citations, Italy with 60 citations, Canada with 29 citations and Germany with 26 citations.

Figure 11. Citation Analysis of Countries with Cite Space

Country analysis was performed with data from Web of Science database using CiteSpace software. Large circles show the most influential countries in the field, the degree of communication between countries and the links between the circles. Accordingly, China was the country with the highest number of citations in studies on COVID-19. This was followed by the USA with 129 citations, England with 74 citations, Italy with 60 citations, Canada with 29 citations and Germany with 26 citations.

Analysis of the data from Scopus database was performed in VosViewer software provided in Figure 12. Citing countries tend to be close to each other. Countries with collaborative connectivity were clustered in 8 groups. The most cited country was China with 13,466. This was followed by the USA (3782), England (1760), Hong Kong (1458) and Italy (1277).

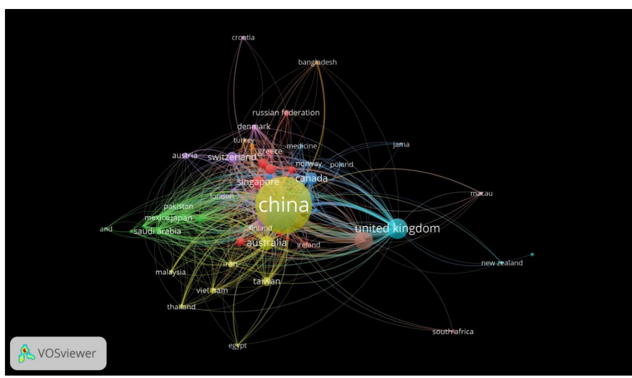


Figure 12. Citation Analysis of Countries with Vosviewer (53 meets threshold when minimum value 5 is selected from 271 countries.)

Analysis of data from Scopus database performed in VoSViewer software program provided in Figure 12. Citing countries tend to be close to each other. Countries with collaborative connectivity were clustered in 8 groups. The most cited country was China with 13,466. This was followed by the USA (3782), England (1760), Hong Kong (1458) and Italy (1277).

Discussion and Conclusion

This study was carried out to analyze the studies on COVID-19 according to the science mapping technique systematically. In this context, the data were obtained through Scopus, Web of Science, and PubMed databases. Then, the data were visualized using VosViewer, CiteSpace and Carrot Search softwares. When the categories of the publications related to COVID-19 were examined in the analysis performed with the CiteSpaces software, it was seen that the highest number of publications was conducted in the field of Medicine, then Virus Science, Nuclear Radiology, and Medical Imaging, Surgery and Communicable Diseases. According to the CiteSpace software program, the author who conducted the highest number of publications was Chen NS and according to the VosViewer software was Liu Y. According to the VoSViewer software, the most co-cited author was Li, X. Wang W was one of the most preferred authors in both citation and co-citation analysis. According to the VosViewer software, The Lancet was the journal having the highest number of publications in the field, and New England Journal of Medicine, Journal of American Medical Association, Radiology and Journal of Medical Virology follow next. According to CiteSpace analysis, The Lancet was again the journal having the highest citation, and New England Journal of Medicine, Journal of the American Medical Association, Nature and Journal of Medical Virology follow next. The first three journals were the same in both analysis programs. The most cited publications related to COVID-19 were collected in "The Lancet".

COVID-19, Coronavirus (Sars-Cov-2), Pneumonia, and Infection were the most used keyword words in the analysis of the data obtained from the Web of Science database using the CiteSpace software. The most frequently used keywords in data obtained from the PubMed database using Carrot Search analysis were Object, Covid-19 Pandemic, Covid-19 Diseases, and Coronavirus. Finally, COVID, New Corona Virus, Pneumonia, and Wuhan were the most used keywords data from the Scopus using VoSViewer software. In line with these results, it was seen that the common keyword is "Covid-19". The most cited countries were China, the USA, the UK, Hong Kong, and Italy according to the VoSViewer program and according to the CiteSpace analysis; those were China, the USA, England, Italy, Canada, and Germany. Since the first 3 rankings were the same in both analyzes, China, the USA, and England can be considered to dominate the literature in the publications related to COVID-19. The reason why China has the highest number of publications is the fact that the disease started there first.

There are also previous studies including bibliometric and content analysis studies conducted on COVID-19 in the literature. A study conducted by Tran et al. (2020), showed that the highest number of publications was conducted in the USA, China, and European countries. In addition, the most discussed topics were emergency care and surgical guides, viral pathogens, and global responses (42). A study conducted by Golinelli et al. (2020) mainly focuses on the calculated Effect Scores of studies on COVID-19 (43). The highest Effect Score belongs to Huang et al. (2020). In another study conducted by Chahrour et al. (2020), studies published in PubMed and WHO databases were examined. As a result of the analysis, 564 publications were accessed. The country where the highest number of studies were conducted was found to be China (8,44). The study by Hossain (2020) examined 422 studies. The study titled "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China" by Huang et al, (2020) in The Lancet (45) was the most cited publication. In a study conducted by Lou et al. (2020), 183 studies were examined through the PubMed database. The researchers found that the highest number of publications were conducted in China and published in the Journal of Medical Virology (46). In another study conducted by Hamidah et al. (2020), where the VoSViewer software program was used to visualize the data, 3513 publications were analyzed through the Scopus database (47). China was again the country where the most highest number of publications were conducted. The most used keywords were detected as coronavirus, pandemic and impact. In another study conducted by Nasab (2020), 92 publications were analyzed through the Web of Science database. Again, the highest number of studies were conducted in China and VoSViewer software program was used to visualize the data (48). In Dehghanbana (2020), 923 publications were reached through Scopus database (49). China and the USA were the countries which contribute the highest number of publications. The Lancet and BMJ Clinical Research Ed became the journals having the highest number of publications in the field. In the study mentioned, VoSViewer was the software used to visualize the data as well. It was seen that these studies were mostly literature reviews and WoSViewer was the commonly used software to visualize the data. Since CiteSpace, Carrot Search and VoSViewer were used together, this study differs from other studies.

The COVID-19 pandemic continues to threaten public health globally (53). To solve such problems, the problem is required to be comprehended deeply and its solutions should be investigated. For this reason, the role of scientific studies is crucial. In this way, the correct information will be obtained by studies relating to all aspects of COVID-19 pandemic. This study provides a global bibliometric evaluation of studies on COVID-19 that can facilitate ongoing and future research. Visualization of the data in this study provides an important convenience for the readers. At the same time, this study serves as a guideline for other researchers for future studies. Academic and professional efforts to understand and to deal with COVID-19 will continue to increase with the knowledge that is available today, that will continue to evolve over time and that enrich science and societies globally.

References

1. Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, SC, & Di Napoli, R. Features, evaluation and treatment coronavirus (COVID-19). In Statpearls, StatPearls Publishing, 2020.
2. WHO. WHO coronavirus disease (COVID-19) Dashboard 2020a. https://covid19.who.int/ . (Accessed 15 May 2020).
3. WHO. WHO announces COVID-19 outbreak a pandemic, 2020b. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic . (Accessed 15 May 2020).
4. Li Q, Guan X, Wu P, Wang X, Zhou L et al. Early transmission dynamics in Wuhan, China, of novel coronavirus – infected pneumonia. New England Journal of Medicine 2020; 382(13): 1199-1207.
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 2020; 102433.
6. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. Journal of Medical Virology 2020; 92 (4): 441-447. doi: 10.1002/jmv.25689
7. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chinese medical journal.

8. Huang C, Wang Y, Li X, Ren L, Zhao J et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223): 497-506. doi: 10.1016/S0140- 6736(20)30183-5
9. Zhou F, Yu T, Du R, Fan G, Liu Y et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395 (10229): 1054-1062. doi: 10.1016/S0140-6736(20)30566-3
10. Fang Y, Zhang H, Xie J, Lin M, Ying L et al. Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology 2020; 200432.
11. 11. H Lu, Drug treatment options for the 2019-new coronavirus (2019-nCoV), Biosci. Trends (2020), https://doi.org/10.5582/bst.2020.01020.
12. 12. Chen N, Zhou M, Dong X, Qu J, Gong F et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020; 395 (10223): 507-513.
13. WHO. Protecting yourself and others from the spread COVID-19, 2020c. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public . (Accessed 15 May 2020).
14. Leite H, Gruber T, Hodgkinson IR. Flattening the infection curve – understanding the role of telehealth in managing COVID-19. Leadership in Health Services, 2019.
15. Wong HYF, Lam HYS, Fong AHT, Leung ST, Chin TWY et al. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology 2020; 201160.
16. Her M. Repurposing and reshaping of hospitals during the COVID-19 outbreak in South Korea. One Health 2020; 100137.
17. Şahin M. Impact of weather on COVID-19 pandemic in Turkey. Science of The Total Environment 2020; 138810.
18. Bettinelli G, Delmastro E, Salvato D, Salini V, Placella G. Orthopaedic patient workflow in CoViD-19 pandemic in Italy. Journal of Orthopaedics 2020; 22: 158.
19. Dexter F, Elhakim M, Loftus RW, Seering MS, Epstein RH. Strategies for daily operating room management of ambulatory surgery centers following resolution of the acute phase of the COVID-19 pandemic. Journal of Clinical Anesthesia 2020; 109854.
20. Ostaszewski M, Mazein A, Gillespie ME, Kuperstein I, Niarakis A et al. COVID-19 Disease Map, building a computational repository of SARS-CoV-2 virus-host interaction mechanisms. Scientific data 2020; 7 (1): 1-4.
21. Tang Y, Wang S. Mathematic modeling of COVID-19 in the United States. Emerging Microbes & Infections 2020; (just accepted) 1-10.
22. 22.Kilicaslan A, Kekec AF, Eren AS, Uzun ST. Peripheral nerve blocks in a patient with suspected COVID-19 infection. Journal of Clinical Anesthesia 2020.
23. Deng W, Xu Y, Kong Q, Xue J, Yu P wt al. Therapeutic efficacy of Pudilan Xiaoyan Oral Liquid (PDL) for COVID-19 in vitro and in vivo. Signal Transduction and Targeted Therapy 2020; 5(1): 1-3.
24. Jeyabaladevan P. COVID-19: an FY1 on the frontline. Medical Education Online 2020; 25(1): 1759869.
25. Gross A, Thiemig D, Koch FW, Schwarz M, Gläser S et al. CT appearance of severe, laboratory-proven coronavirus disease 2019 (COVID-19) in a Caucasian patient in Berlin, Germany. In RöFo-Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren 2020; 192(5): 476-477.
26. Mansoor S, Kelly S, Murphy K, Waters A, Siddiqui NS. COVID-19 pandemic and the risk of infection in multiple sclerosis patients on disease modifying therapies: "what the bleep do we know?". The Egyptian Journal of Neurology, Psychiatry and Neurosurgery 2020; 56: 1-3.
27. Ceylan Z. Estimation of COVID-19 prevalence in Italy, Spain, and France. Science of The Total Environment 2020; 138817.
28. van Nunen K, Li J, Reniers G, Ponnet K. Bibliometric analysis of safety culture research. Safety science 2018; 108: 248-258.
29. Kurutkan MN, Orhan F. Analysis of health policy subject with science mapping techniques. İKSAD Publishing House, Ankara, 2018.
30. Van Eck NJ, Waltman L. Visualizing bibliometric networks. In Measuring scholarly impact, Springer, 2014; 285-320.
31. Chen C. CiteSpace: a practical guide for mapping scientific literature. Nova Science Publishers, Incorporated 2016.
32. Gong R, Xue J, Zhao L, Zolotova O, Ji X et al. A Bibliometric analysis of green supply chain management based on the web of science (WOS) platform. Sustainability 2019; 11(12): 3459.
33. Stefanowski J, Weiss D. Carrot 2 and language properties in web search results clustering. In International Atlantic Web Intelligence Conference (pp. 240-249). Springer, Berlin, Heidelberg, 2003.
34. Zhu N, Zhang D, Wang W, Li X, Yang B et al. A novel coronavirus from patients with pneumonia in China, 2019. New England Journal of Medicine 2020.
35. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ et al. Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine (published online February 28, 2020). doi: 10.1056/NEJMoa2002032
36. Chan JFW, Yuan S, Kok KH, To KKW, Chu H et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet 2020; 395(10223): 514-523.
37. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. Jama 2020; 323(13): 1239-1242.
38. Zhou P, Yang XL, Wang XG, Hu B, Zhang L et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020; 579(7798): 270-273.
39. Whipple ECE, Dixon B, McGowan J. Linking health information technology to patient safety and quality outcomes: A bibliometric analysis and review. Informatics for Health and Social Care 2013; 38(1): 1-14.
40. Tahamtan I, Bornmann L. What do citation counts measure? An updated review of studies on citations in scientific documents published between 2006 and 2018. Scientometrics 2019; 121(3): 1635-1684.
41. Milfont TL, Page E. A bibliometric review of the first thirty years of the journal of environmental psychology. Psyecology 2013; 4(2): 195-216.
42. Tran BX, Ha GH, Nguyen LH, Vu GT, Phan HT et al. Studies of Novel Coronavirus Disease 19 (COVID-19) Pandemic: A Global Analysis of Literature. medRxiv 2020.
43. Golinelli, D. , Nuzzolese, AG, Boetto, E., Rallo, F., Greco, M., Toscano, F., & Fantini, MP (2020). The impact of early scientific literature in response to COVID-19: a scientometric perspective. medRxiv .
44. Chahrour M, Assi S, Bejjani M, Nasrallah AA, Salhab H et al. A bibliometric analysis of Covid-19 research activity: A call for increased output. Cureus 2020; 12 (3).
45. Hossain MM. Current status of global research on novel coronavirus disease (Covid-19): A bibliometric analysis and knowledge mapping. Available at SSRN 2020; 3547824 .
46. Lou J, Tian SJ, Niu SM, Kang XQ, Lian HX et al. Coronavirus disease 2019: a bibliometric analysis and review. Eur Rev Med Pharmacol Sci 2020; 24(6): 3411-21.
47. Hamidah I, Sriyono S, Hudha MN. A Bibliometric Analysis of Covid-19 Research Using VOSviewer. Indonesian Journal of Science and Technology 2020; 5(2): 209-216.

48. Nasab FR. Bibliometric analysis of global scientific research on SARSCoV-2 (COVID-19). medRxiv 2020.

49. Dehghanbanadaki H, Seif F, Vahidi Y, Razi F, Hashemi E et al. Bibliometric analysis of global scientific research on Coronavirus (COVID-19). Medical Journal of The Islamic Republic of Iran (MJIRI) 2020; 34(1): 354-362.

50. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J et al. First case of 2019 novel coronavirus in the United States. New England Journal of Medicine 2020.

51. Lu R, Zhao X, Li J, Niu P, Yang B et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. The Lancet 2020; 395(10224): 565-574.

52. Wang M, Cao R, Zhang L, Yang X, Liu J et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research 2020; 30 (3): 269-271. doi: 10.1038/s41422-020-0282-0.

53. Tufan A, Güler AA, Matuccı-cerınıc M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turkish Journal of Medical Sciences, 2020, 50.SI-1: 620-632.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 682-689
https://doi.org/10.31067/acusaglik.851235

ORIGINAL ARTICLE / ARAŞTIRMA YAZISI

Health Policies and Services / Sağlık Politikaları ve Hizmetleri

Determinants of Health System Performance in Europe: A Study Based on Clustering Analysis

Pınar Yalçın Balçık[1], Şenol Demirci[1], Murat Konca[1]

[1]Hacettepe Üniversitesi, İktisadi ve İdari Bilimler Fakültesi, Sağlık Yönetimi Bölümü, Ankara, Türkiye

Pınar YALÇIN BALÇIK, Doç. Dr.
Şenol DEMİRCİ, Arş. Gör.
Murat KONCA, Dr.

Correspondence: Pınar Yalçın Balçık
Hacettepe Üniversitesi, İktisadi ve İdari Bilimler Fakültesi, Sağlık Yönetimi Bölümü, Ankara, Türkiye
Phone: -
E-mail: pinar.yalcin.balcik@gmail.com

Received : 5 November 2020
Accepted : 03 June 2021

ABSTRACT

Health system performance is influenced by many factors such as behavioral and educational factors other than health system indicators. The aim of this study was to evaluate the effects of behavioral risk factors and educational factors on the health system performance in European Union member and candidate countries. Clustering analysis method was employed in the study. Firstly, clustering analysis was performed using health indicators and then, indicators related to behavioral risk factors and education were included in the analysis and it was investigated whether indicators related to behavioral risk factors and education affected the clusters formed by using health indicators. 4 clusters were formed in the clustering analysis using the health indicators, 5 clusters were formed in the clustering analysis with the addition of indicators related to behavioral risk factors to the health indicators and finally 5 clusters were formed in the clustering analysis with the addition of indicators related to education to the health indicators. It was seen that behavioral risk factors and educational indicators caused changes in clusters formed of countries. Countries that want to improve their health status should take into account behavioral risk factors and the impact of education on health status.

Keywords: Clustering analysis, health systems, performance management

Avrupa'da Sağlık Sistemi Performansının Belirleyicileri: Kümeleme Analizine Dayalı Bir Çalışma

ÖZET

Sağlık sistemi performansı, sağlık sistemi göstergeleri dışında davranışsal ve eğitimsel faktörler gibi birçok faktörden etkilenir. Bu çalışmanın amacı, davranışsal risk faktörleri ve eğitim faktörlerinin Avrupa Birliği üyesi ve aday ülkelerde sağlık sistemi performansı üzerindeki etkilerini değerlendirmektir. Araştırmada kümeleme analizi yöntemi kullanılmıştır. Öncelikle sağlık göstergeleri kullanılarak kümeleme analizi yapılmış, ardından analize davranışsal risk faktörleri ve eğitime ilişkin göstergeler dahil edilmiş ve davranışsal risk faktörleri ve eğitime ilişkin göstergelerin sağlık göstergeleri kullanılarak oluşturulan kümeleri etkileyip etkilemediği araştırılmıştır. Sağlık göstergeleri ile yapılan ilk kümeleme analizinde 4 küme oluşmuş, davranışsal risk faktörlerine ilişkin göstergelerin sağlık göstergelerine eklenmesi ile 5 küme oluşmuş ve son olarak eğitimsel göstergelerin sağlık göstergelerine eklenmesi ile yine 5 küme oluşmuştur. Davranışsal risk faktörlerinin ve eğitim göstergelerinin oluşan kümelerde değişikliklere neden olduğu görülmüştür. Sağlık statüsünü iyileştirmek isteyen ülkeler, davranışsal risk faktörlerinin ve eğitimin sağlık statüsü üzerindeki etkisini dikkate almalıdır.

Anahtar Kelimeler: Kümeleme analizi, sağlık sistemleri, performans yönetimi

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Health systems are the structures that involve all the activities necessary to protect or improve community health. The main purpose of health systems is to increase the health status of societies, but also to meet their expectations and to provide justice in financing in doing so (1). Health systems include resources, organizations, financing mechanisms, and governance models that responsible for the delivery of health care services to the population (2). Demonstrating the extent to which a health system achieves its goals requires performance measurements in health systems and it can be said that there are various methods in this regard. Among these methods, benchmarking can be seen as a powerful tool for decision-makers (3). The use of benchmarking by political decision-makers in the process of determining health policies is a method that has been used for many years (4).

Performance measurement is the assessment of the difference between the production of a person, institution, region or country with a duty to produce goods or services and the predetermined production targets through analytical processes (7). Performance measurement in health systems can be defined as monitoring and evaluating the effectiveness and efficiency of the services provided by the national health systems in meeting the needs and expectations of patients (3). Performance measurement studies in health systems offer benefits to people in decision-making mechanisms in health system on various issues. For example, whether health systems show progress or regress in terms of performance over time can be demonstrated by performance measurements. Similarly, performance improvement can be achieved by taking countries with high health system performance as an example with performance measurements based on the comparison of homogeneous health systems. Another benefit of performance measurement in health systems is that it can enable to determine to what extent the goals by performance measurement have been achieved. Other than these, performance measurements in health systems reveals the deficiencies and strengths, helps to design reform movements, increases accountability, provides evidence-based policies and makes it possible to direct resources to correct expenditures (3,15,33).

It is difficult to determine whether health systems can achieve the predetermined objectives, since some factors other than health care services also affect the outcomes of health systems. So, performance measurements in health systems are difficult (8). Comparing countries with similar socioeconomic structures in performance measurement in health systems can help to overcome this difficulty.

While the history of performance measurement in health systems has been quite old (9,10); it is possible to conclude that an increasing interest in this issue has been observed among the people involved in the decision-making mechanisms (6), because those who take part in decision-makers in the mechanism gave importance and care the impact of the performance of health systems (11). The reasons for increasing interest in performance measurement in health systems can be grouped into two groups as demand-side reasons and supply-side reasons. Demand-side reasons includes increased cost constraint pressure, increased awareness of patients, increased control and surveillance activities for health service providers and increased level of accountability expected from service providers (12,13). The main supply-side reason, which prepares the ground for increasing the interest in performance measurement in health systems, is that data access becomes cheaper and easier due to the development of information technologies (3).

The fact that the accessing data has become easier has enabled the increment of numbers of the studies comparing the performance of the health systems of countries. When the basic methods used in these studies are examined; it is possible to say that some parametric and nonparametric methods such as Data Envelopment Analysis (DEA), Malmquist Total Factor Productivity Analysis (MTFP), Stochastic Frontier Analysis (SFA), Least Squares Regression (LSR) have come to the fore (6,7,14,15). Apart from the aforementioned methods, there are several studies that show similarities and differences of regions or countries in terms of health system by benefiting from clustering analysis and thus provide information about the health system performance of regions or countries (16-23).

As stated in Lalonde Report (1974), health systems are affected not only by health care services but also by many other factors, especially educational and socioeconomic factors (5). From this, it can be concluded that the performance of a health system is affected not only by health care services but also by many other factors (3). It is possible to see some studies supporting this view in the literature. For example, according to the findings of Samut and Cafri (2016), Afonso and Aubyn (2011), Moran and Jacobs (2013), Asghar, Rehman and Ali (2019), Ahmed et al. (2019), Castaldo and Antonelli (2020), education, economic structure and behavioral risk factors affect the performance of health systems (6,34-38). As can be seen, some indicators other than health care services have to take place in the performance measurements specific to health systems.

In this study, the performance of health systems of the European Union (EU) member and EU candidate countries was revealed via clustering analysis. In this context, a clustering analysis was performed based on health indicators in the first step and then a second and a third clustering analysis were performed by adding indicators that are not directly related to health care services. Thus, whether the indicators that are not directly related to health care services influencing the clustering of countries was revealed.

Methodology

The research universe consists of 35 countries that are members or candidates of EU. The data of all countries except Kosovo were obtained and 34 EU member and candidate countries were included in the study sample. Variables used in the study were taken from databases of Organization of Economic Cooperation and Development Countries (OECD) (https://data.oecd.org/), United Nations (http://data.uis.unesco.org/), World Health Organization (WHO) (https://www.who.int/gho/en/) and World Bank (WB) (https://data.worldbank.org/). In the absence of data on the year taken, the data of the nearest year were evaluated. Information about the variables used in the study are given in Table 1.

Table 1. Variables employed in the study

Variables	Explanation	Database (Year)
Number of Physicians	The number of physicians per 1000 individual (in 1 year)	OECD (2016), World Bank (2016)
Number of Nurses	The number of nurses per 1000 individual (in 1 year)	World Bank (2016)
Hospital Bed Number	The number of hospital bed per 1000 individual (in 1 year)	OECD (2016), World Bank (2016)
Life Expectancy at Birth (LEB)	Average life expectancy for a new born	World Bank (2016)
Mother Mortality Rate (MMR)	Mother mortality rate in every 100,000 live birth	World Bank (2015)
Health Expenditure per Capita (HEPC)	Health expenditure per person per year (purchasing power parity - $)	World Bank (2015)
Tobacco Consumption	Tobacco Consumption among the Population over 15 years of age every day (%)	World Bank (2016)
Alcohol Consumption	Alcohol consumption per person over 15 years (Liters) (within 1 year)	WHO (2016)
Obesity Rate	Adult population with body mass index of 30 or more (%)	WHO (2016)
Public Education Expenditure	Share of public education expenditure in Gross Domestic Product (GDP) (%)	World Bank (2015)
Primary School Registration Rate	Proportion of enrolled primary school enrollment (%)	World Bank (2016)
Primary School Teacher/student Ratio	The ratio of the number of primary school students to the number of teachers (%)	UNESCO (2016)

As a result of the literature review conducted, the most used health indicator variables in health system performance measurement and clustering analysis studies were the number of physician, nurse and bed per specific population, life expectancy at birth, maternal mortality rate, infant mortality rate and per capita health expenditure (16-18,22,23). In this study, these variables which are frequently used in the literature, were used.

The second clustering analysis was conducted with behavioral risk factors that had a direct effect on national health systems in many studies. In the third clustering analysis, educational variables, which are thought to have effects on health system performance in many studies (3,6,24-27), were investigated. Obesity ratio, smoking and alcohol consumption are the variables used within the scope of behavioral risk factors. The ratio of public education expenditure to GDP, the rate of enrollment to primary education and the ratio of the number of primary school students to the number of teachers are the variables of education used together with the health indicators in the clustering analyzes.

Statistical Package for the Social Sciences (SPSS) version 22.0 was used to analyze the data obtained. The clustering analysis method was used to group the outcomes of health and educational variables of EU member and candidate countries. Clustering analysis is used to evaluate clusters rather than data. In clustering analysis, ungrouped data is grouped according to similarities. These grouped data constitute clusters and are expected to show homogeneous cluster inside and heterogeneous appearance among themselves (28).

Variables should be standardized so that each variable's contribution to distance can be at the same level (29). The data used in this study are standardized by Z standardization method. In this study, Ward Method, which is one of the hierarchical clustering analysis methods, was used. Sequential Euclidean Distance Measure was chosen as the distance measure of the Ward Method. In the hierarchical clustering method, all data are collected in a single group by forming a tree-like structure. Then, groups are divided into groups and the other groups are formed until they become indivisible (30). Sets are created using the connection methods used to calculate the mathematical distance measure between the data points and possible sets. Ward Method is one of these connection methods (31). In the Ward technique, the mean distance to the observations in the same cluster is based on the observation of the middle of the cluster. Also, in the Ward Method, clusters are formed to minimize the variance within the cluster (32). One-way Analysis of Varriance (ANOVA) test was used to determine whether the clusters exhibited a heterogeneous distribution.

Results

As a result of clustering analysis using health indicators (the number of physician, nurse and bed per 1,000 people, life expectancy at birth, maternal mortality rate, infant mortality rate and per capita health expenditure), 4 clusters were formed. Clusters of countries are given in Table 2. Cluster A includes all EU candidate countries and three countries joined EU in fifth expansion (Turkey, Albania, Macedonia, Hungary, Bosnia and Herzegovina, Montenegro, Latvia, Serbia and Romania). In the Cluster B, most of the former Eastern Bloc and the countries which joined EU in the fifth enlargement process (Poland, Slovakia, Estonia, Lithuania, Bulgaria, Czech Republic and Croatia) are included. The Cluster C includes the Benelux countries (Belgium, the Netherlands, and Luxembourg) and the Central and Western European countries (Ireland, the United Kingdom, Denmark, Sweden, Finland, France, Germany, Austria, Slovenia and Malta). Mediterranean countries constitute the Cluster D (Cyprus, Greece, Spain, Italy and Portugal).

Table 2. Clustering Analysis results according to Health Indicators

Cluster A	Cluster B	Cluster C	Cluster D
Turkey	Poland	Netherlands	Cyprus
Albania	Slovakia	Ireland	Greece
Macedonia	Estonia	United Kingdom	Spain
Hungary	Lithuania	Belgium	Italy
Bosnia Herzegovina	Bulgaria	Luxembourg	Portugal
Montenegro	Czech Republic	Denmark	
Latvia	Croatia	Sweden	
Serbia		Finland	
Romania		France	
		Germany	
		Austria	
		Slovenia	
		Malta	

Table 3 shows the ANOVA test for the health indicators of the clusters. As a result of the clustering analysis, the clusters are expected to be homogeneous in their respective clusters and heterogeneous between clusters. According to the ANOVA test results, it can be said that health indicator results are statistically significant and that the clusters provide homogeneity inside clusters and heterogeneity among them. When the overall rankings of the clusters

are examined by health indicators, it is determined that the countries in the C and D clusters have the best health indicators. It was determined that the countries in the Cluster B were in the second place and the countries in the Cluster A were in the last place.

Table 3. ANOVA results regarding Health Indicators

Variables	Type	Cluster A	Cluster B	Cluster C	Cluster D	F	p*
Number of Physicians	Value	2.50	3.55	3.50	4.60	8.354	<0.001
	Rank	4	2	3	1		
Number of Nurses	Value	4.95	6.61	11.45	5.00	26.179	<0.001
	Rank	4	2	1	3		
Hospital Bed Number	Value	4.70	6.22	4.56	3.44	3.571	0.025
	Rank	2	1	3	4		
LEB	Value	76.34	77.01	81.69	81.98	50.779	<0.001
	Rank	4	3	2	1		
MMR	Value	17.11	7.28	6.92	5.80	10.091	<0.001
	Rank	4	3	2	1		
HEPC	Value	1160.11	1878.00	4736.69	2707.20	57.175	<0.001
	Rank	4	3	1	2		
Overall rank		3	2	1	1		

*Significance level is selected as 0.05.

Table 4 shows the results of clustering analysis by adding behavioral risk factors variables (alcohol consumption, smoking, obesity rate) to health indicators. As a result of clustering analysis, five clusters were formed. Cluster A includes two EU candidate countries (Turkey and Albania). Cluster B includes Macedonia, Slovakia, Estonia, Poland, Bosnia and Herzegovina, Montenegro, Cyprus, Croatia and Greece and Cluster C includes Lithuania, Bulgaria, Latvia, Hungary, Serbia, Romania and the Czech Republic, both of B and C include mainly the countries which are involved in the last enlargement process and located in Eastern Europe. Most of the countries in the Western and Mediterranean (Netherlands, the United Kingdom, Slovenia, Malta, Denmark, Sweden, Finland, Spain, Italy and Portugal) are located in the Cluster D. The Cluster E consists of EU founding members (Belgium, Luxembourg, France and Germany) and Ireland and Austria.

Table 4. Clustering Analysis according to Health Indicators and Behavioral Risk Factors

Cluster A	Cluster B	Cluster C	Cluster D	Cluster E
Turkey	Macedonia	Lithuania	Netherlands	Ireland
Albania	Slovakia	Bulgaria	United Kingdom	Belgium
	Estonia	Latvia	Slovenia	Luxembourg
	Poland	Hungary	Malta	France
	Bosnia Herzegovina	Serbia	Denmark	Germany
	Montenegro	Romania	Sweden	Austria
	Cyprus	Czech Republic	Finland	
	Croatia		Spain	
	Greece		Italy	
			Portugal	

Table 5 shows the results of clustering analysis by adding educational indicators (public education expenditure, primary school enrollment rate, primary school student / teacher ratio) to health indicators. As a result of clustering analysis, five clusters were formed. Five EU candidate countries (Turkey, Albania, Macedonia, Bosnia and Herzegovina and Montenegro) and Romania, which became members in 2007, is located in the Cluster A. The majority of countries in the fifth enlargement process (Poland, Slovakia, Estonia, Lithuania, Bulgaria, Latvia, Hungary, Serbia and Croatia) came together in the Cluster B. Apart from Italy, the EU constituent countries (Netherlands, Belgium, Luxembourg, France and Germany) and most of Central and Western European countries (Ireland, United, Slovenia, Malta, Czech Republic and Austria) in the Cluster C. The Nordic countries (Denmark, Sweden and Finland) are placed in Cluster D. Finally, the Cluster E includes Mediterranean countries (Cyprus, Greece, Spain, Italy and Portugal).

Table 6 shows the general ranking of clusters based on behavioral risk factors and education related indicators added to health indicators in clustering analysis. As a result of clustering analysis carried out by adding behavioral risk factors to health indicators, it was determined that D and E clusters had the best health and behavioral risk factor indicators. It was found that Cluster B was the second, C, and the A clusters become the third respectively.

Table 5. Clustering Analysis Results according to Health and Educational Indicators

Cluster A	Cluster B	Cluster C	Cluster D	Cluster E
Turkey	Slovakia	Netherlands	Denmark	Cyprus
Albania	Estonia	Ireland	Sweden	Greece
Macedonia	Poland	United Kingdom	Finland	Spain
Bosnia Herzegovina	Bulgaria	Slovenia		Italy
Montenegro	Latvia	Belgium		Portugal
Romania	Lithuania	Luxembourg		
	Hungary	Malta		
	Serbia	Czech Republic		
	Croatia	France		
		Germany		
		Austria		

As a result of clustering analysis carried out by adding educational variables to health indicators, it was found that the Cluster D formed by Nordic countries had the best indicator scores. The Cluster E formed by the Mediterranean countries took the second place. The cluster formed of EU founding members, Central and Western European countries in the third place. In the last enlargement process, the Cluster A, in which the EU cluster is located, is the fourth and the Cluster A, which is the EU candidate country, is the last.

Table 6. General Ranking of Clusters According to Utilized Indicators

Variables	Type	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E
Health Indicators	Rank	3	2	1	1	-
Health Indicators + Behavioral Risk Factors	Rank	4	2	3	1	1
Health Indicators + Education Indicators	Rank	5	4	3	1	2

Discussion and Conclusions

Clustering analysis can be seen as one of the ways to gain insight into the performance of countries' health systems. When the literature is examined, various studies on this subject can be found. For example; in the study of Wendt (2009), health systems performance of European countries is compared with clustering analysis by using indicators related to performance, financing, service delivery and access to service (16). In the study of Klomp and Haan (2010), the health system performance of 171 countries was compared with clustering analysis using indicators related to performance, survival, infectious and non-infectious diseases, health workers, hospital bed numbers and immunization rates (17). In the study of Miszczyńska (2013) health system performance of 21 EU member states were compared with indicators such as, financing (health expenditures), health care services (number of physicians and hospital beds) and health status (perceived health status and life expectancy at birth) using clustering analysis (19). In the study of Teleş et al., (2018), the health system performance of 36 European countries were compared in terms of financing (health expenditures), health care resources (number of physicians, number of nurses and number of hospital beds) and health status indicators (expected life expectancy at birth, mean length of stay, infant mortality rate and mother) mortality rate with clustering analysis (22).

The study of Proksch et al. (2019), which compares the health system of 30 OECD countries with cluster analysis for innovative output generating performance, is similar to this study in terms of methodology and in terms of incorporating more than one clustering analysis (23). In the study of Proksch et al. (2019), health expenditure, number of physicians and hospital beds, labor force ratio employed in health sector, number of computed tomography (CT) and magnetic resonance (MR), number of applications to physician, length of hospital stay and rate of over 65 age group were used. In the study, some variables (patents, number of scientific publications, high technology product exports) were added to output variables and how addition of these affected the clusters is reported (23).

In this study, health system performance of member and candidate countries of EU is examined by using indicators related to behavioral risk factors and education. In this context, with clustering analysis, health performance of

EU member and candidate countries were compared. First, a clustering analysis with only health indicators was conducted, and then whether behavioral risk factors and indicators related to education affected the clusters formed as a result of the first clustering analysis was determined.

In the clustering analysis using only health indicators, 4 clusters emerged. When these clusters are analyzed, it is seen that mostly EU member and EU candidate countries form a cluster. The former eastern bloc countries, central European countries and Mediterranean countries formed separate clusters. At this point, in addition to the health care services provided, the style of management and geography can be interpreted as affecting health indicators.

As a result of the clustering analysis with the addition of behavioral risk factors, 5 clusters have emerged. When these clusters are analyzed, both predominantly Muslim countries (Turkey and Albania) seems to form a cluster. It is thought that the prohibition of behavioral risk factors such as alcohol and cigarettes by Islamic religion has laid the ground for the existence of these two countries in the same cluster. There are some studies supporting this view in the literature (39,40). When the other clusters are examined, it is seen that the old eastern bloc countries with high alcohol and cigarette consumption are concentrated in two different clusters. The developed central and western European countries are also concentrated in two clusters. These countries have similar health indicators and behavioral risk factors. Behavioral risk factors, although they are individual preferences, may require the imposition of some restrictions since these risk factors cause some level of negative externality, as well as poses risks towards the society.

It is observed that 5 clusters are formed in clustering analysis with addition of indicators related to education to health indicators. When these clusters are examined, it is seen that a cluster of mostly EU candidate countries, a cluster of former Eastern bloc countries, a cluster of developed central European countries, a cluster of some Scandinavian countries and a cluster of Mediterranean countries were formed. Considering that education is one of the main factors affecting health status, it is recommended that countries that want to improve their health indicators should give importance to educational services together with health care services.

In this study, the effects of behavioral risk factors and educational indicators on health systems of countries are presented with clustering analysis. It was observed that behavioral risk factors and educational indicators caused changes in clustering of countries. In this context, countries that wish to improve their health status should consider the impact of behavioral risk factors and educational factors on health indicators.

References

1. WHO (World Health Organization). The World Health Report 2000. Health Systems: Improving Performance. Geneva: World Health Organization; 2000.
2. Noto G, Corazza I, Kļaviņa K, et al. Health system performance assessment in small countries: The case study of Latvia. Int J Health Plann Mgmt. 2019;1–15.
3. Smith PC, Mossialos E, Papanicolas I, et al. Performance Measurement for Health System Improvement. New York: Cambridge University Press; 2009.
4. Anderson G, Hussey PS. Comparing health system performance in OECD countries. Health Affairs. 2001; 20(3): 219-232.
5. Lalonde M. A New Perspective on the Health of Canadians. Ottawa: Government of Canada; 1974.
6. Samut PK, Cafri R. Analysis of the efficiency determinants of health systems in OECD countries by DEA and Panel Tobit. Social Indicators Research. 2016; 129:113–132.
7. Çetin VR, Bahçe S. Measuring the efficiency of health systems of OECD countries by data envelopment analysis. Applied Economics. 2016; 48(37): 3497-3507.
8. Liu Y, Rao K, Wu J, et al. China's health system performance. The Lancet. 2008; 372(9653): 1914-1923.
9. McIntyre D, Rogers L, Heier EJ. Overview, history, and objectives of performance measurement. Health Care Financing Review. 2001; 22(3): 7–43.
10. Loeb JM. The current state of performance measurement in healthcare. International Journal for Quality in Health Care. 2004; 16(Suppl. 1): 5–9.
11. Tandon A, Murray CJ, Lauer JA, et al. Measuring Overall Health System Performance for 191 Countries. Geneva: World Health Organization; 2000.
12. Power M. The Audit Society: Rituals of Verification. Oxford: Oxford University Press; 1999.
13. Smith PC. Performance measurement in health care: history, challenges and prospects. Public Money & Management. 2005; 25(4): 213–220.
14. Boerma T, Chopra M, Evans D. Health systems performance assessment in the bulletin. Bulletin of the World Health Organization. 2009; 87(1): 2–2A.
15. Ozcan YA. Healthcare Benchmarking and Performance Evaluation. 2nd edn New York: Springer; 2014.
16. Wendt C. Mapping European healthcare systems: a comparative analysis of financing, service provision and access to healthcare. Journal of European Social Policy. 2009; 19(5): 432-445.
17. Klomp J, Jakob de H. Measuring health: a multivariate approach. Social Indicators Research. 2010; 96(3): 433-457.
18. Muntaner C, Haejoo C, Joan B, et al. Hierarchical cluster analysis of labour market regulations and population health: a taxonomy of low-and middle-income countries. BMC Public Health. 2012; 12(1): 1-15.

19. Miszczyńska K. Multivariate analysıs of healthcare systems in selected European Unıon countrıes: Cluster analysis. Quantitative Methods in Economics. 2013;14(2): 99-107.
20. Tanaka OY, Drumond JM, Cristo EB, et al. Cluster analysis as a tool for management improvement in the SUS. Saúde e Sociedade. 2015; 24(1): 34-45.
21. Sonğur C, Top M. Regional clustering of medical imaging technologies. Computers in Human Behavior. 2016; 61: 333-343.
22. Teleş M, Konca M, Çakmak C. Comparison of Health Systems Performance of Countries in the European Union Cycle. Manisa Celal Bayar University Journal of Management and Economıcs. 2018; 25(3): 811-835.
23. Proksch D, Busch-Casler J, Haberstroh MM, et al. National health innovation systems: Clustering the OECD countries by innovative output in healthcare using a multi indicator approach. Research Policy. 2019; 48(1): 169-179.
24. Lopez AD, Mathers CD, Ezzati M, et al. Global Burden of Disease and Risk Factors. USA: The World Bank; 2006.
25. Pronk NP, Anderson LH, Crain AL, et al. Meeting recommendations for multiple healthy lifestyle factors: prevalence, clustering, and predictors among adolescent, adult, and senior health plan members. American Journal of Preventive Medicine. 2004; 27(2): 25-33.
26. Todaro MP, Smith SC. Economic Development. Boston: Pearson; 2015.
27. Murray C, Evans D. Health Systems Performance Assessment: Debates, Methods and Empiricism. Geneva: World Health Organization; 2013.
28. Kaufman L, Peter JR. Finding Groups in Data: An Introduction to Cluster Analysis. USA: John Wiley & Sons; 2009.
29. Alpar R. Multivariate Statistical Methods. Ankara: Detay Publishing; 2013.
30. Hair JF, Babin BJ, Anderson RE, et al. Multivariate Data Analysis. Essex: Pearson, 2014.
31. Clatworthy J, Deanna B, Matthew H, et al. The use and reporting of cluster analysis in health psychology: A review. British Journal of Health Psychology. 2005; 10(3): 329-358.
32. Punj G, Stewart DW. Cluster analysis in marketing research: Review and suggestions for application. Journal of Marketing Research. 1983; 20(2): 134-148.
33. Cylus J, Papanicolas I, Smith PC. Using data envelopment analysis to address the challenges of comparing health system efficiency. Global Policy. 2017; 8(Supplement 2): 60-68.
34. Afonso A, St. Aubyn M. Assessing health efficiency across countries with a two-step and bootstrap analysis. Applied Economics Letters. 2011; 18(15): 1427-1430.
35. 35. Moran V, Jacobs R. An ınternational comparison of efficiency of ınpatient mental health care systems. Health Policy. 2013; 112(1-2): 88-99.
36. Asghar N, Rehman HU, Ali M. Cost productivity of healthcare systems in OIC's member countries: An application of cost Malmquist Total Productivity Index. Review of Economics and Development Studies. 2019; 5(3): 461-468.
37. Ahmed S, Hasan MZ, MacLennan M et al. Measuring the efficiency of health systems in asia: A data envelopment analysis. BMJ Open. 2019; 9: e022155.
38. Castaldo A, Antonelli MA. Determinants of health sector efficiency: Evidence from a two-step analysis on 30 OECD countries. Economics Bulletin. 2020; 40(2): 1651-1666.
39. WHO. Global Status Report on Alcohol and Health 2018. WHO; 2019.
40. Varol M. Alkol raporu. İstanbul: Türkiye Yeşilay Cemiyeti; 2011.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 690-696
https://doi.org/10.31067/acusaglik.903380

Evaluation of Family Physicians' Opinions on Defensive Medicine Practices: The Case of the Province of Isparta/Turkey

Oğuzhan Yüksel[1]

[1]Sağlık Bakanlığı, Isparta Ağız ve Diş Sağlığı Merkezi, Isparta, Türkiye

Oğuzhan YÜKSEL, Dr.

ABSTRACT

Objective: In this descriptive study, the problems physicians are facing and their opinions on medical malpractice, which is frequently heard of today, were questioned. The purpose of this study was to determine family physicians' attitudes and knowledge towards defensive medicine practices.

Methods: The study was conducted by survey method in Isparta province in Turkey. In Isparta, 160 family doctors are employed within the Ministry of Health. The survey study was carried out during November-December 2020 with 77 family physicians who agreed to participate. Likert-type scale (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) was used to classify the answers. In addition, yes-no options were used for questions that measure knowledge level.

Results: Results showed that, of the 77 participants, 18 (23%) did not hear of the concept of defensive medicine before, 48 (62%) did not know enough about the content of the concept of defensive medicine, 5 (6%) were sued for malpractice, 37 (48%) thought that any lawsuit could be filed within the next 10 years. The attitude of "as malpractice cases are often reported in the media, I feel anxiety in medical practice" was highly prevalent among participants (n=46, 59.7%) with this option recording the highest frequency of preference.

Conclusions: The results of the study showed that family physicians working in family health centers affiliated with the Ministry of Health are highly inclined on positive and negative defensive medicine practices.

Keywords: Defensive Medicine, Medical Malpractice, Family Physician

Defansif Tıp Uygulamalarında Aile Hekimlerinin Görüşlerinin Değerlendirilmesi: Isparta İli Örneği

ÖZET

Amaç: Günümüzde sıkça duyulmaya başlanan tıbbi kötü uygulamalar (malpraktis) hakkında hekimlerin karşılaştıkları problemler ve bakış açılarını sorgulayan tanımlayıcı nitelikteki bu araştırmada, aile hekimlerinin defansif tıp uygulamalarında sergiledikleri tutum ve bilgilerinim belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışma Türkiye'deki Isparta ilinde, anket yöntemiyle yapılmıştır. Isparta'da, Sağlık Bakanlığı bünyesinde 160 aile hekimi görev yapmaktadır. Çalışmaya katılmayı onaylayan ve eksiksiz yanıtlayan 77 aile hekimi ile anketler gerçekleştirilmiştir. Sorulara verilen yanıtlar için, Likert tipi durum ölçme ifadeleri (tamamen katılıyorum, çok katılıyorum, orta derecede katılıyorum, az katılıyorum, hiç katılmıyorum) kullanılmıştır. Ayrıca bilgi düzeyini ölçen sorular için ise evet-hayır şıklarından yararlanılmıştır.

Bulgular: Çalışma sonucunda aile hekimlerinden 18'i (%23) daha önce defansif tıp kavramını duymadığını, 48'i (%62) defansif tıp uygulamaları kavramının içeriğini yeterince bilmediğini, 5'i (%6) malpraktis nedeni ile kendisine dava açıldığını, 37'si (%48) önümüzdeki 10 yıl içerisinde herhangi bir dava açılabileceğini düşündüklerini ifade etmişlerdir. Malpraktis davaları medyada fazlaca yer buldukça mesleğimi icra ederken tedirginlik hissediyorum diyen aile hekimlerinin oranı (n=46, %59,7); tutum ölçen sorular arasında en büyük yüzdeye sahip olan seçenek olarak ilk sırada çıkmıştır.

Sonuç: Bu araştırmada elden edilen sonuçlar, Sağlık Bakanlığı'na bağlı aile sağlığı merkezlerinde çalışan aile hekimlerinin önemli oranda pozitif ve negatif defansif tıp uygulamalarına yöneldiğini göstermektedir.

Anahtar Kelimeler: Defansif Tıp, Tıbbi Malpraktis, Aile Hekimi

Correspondence: Oğuzhan Yüksel
Sağlık Bakanlığı, Isparta Ağız ve Diş Sağlığı Merkezi, Isparta, Türkiye
Phone: +902462330504
E-mail: oguzhan@doctor.com

Received : 25 March 2021
Accepted : 03 June 2021

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

The concept of human rights gaining broader meaning worldwide, rapid progress in medical technologies, an increase in the desire of patients to seek their rights, and legal changes, all resulted in development of the concept of patient rights. Medical malpractice and defensive medicine have been shaped in parallel with these developments. Physicians have narrowed their treatment options in risky cases with the instinct to protect themselves and have consciously or unconsciously started using defensive medicine practices.

The concept of defensive medicine, also referred as cautious medicine in the literature, emerged in America in the 1970s. Defensive medicine can be defined as the various behaviors (requesting unnecessary medical tests for diagnosis and treatment, avoiding high-risk medical interventions, etc.) physicians do to protect themselves against criminal cases (1). Since the beginning of the 21st century, the concept of medical law in Turkey has developed very rapidly. Amendments to Turkish criminal law passed in 2005, lead to different practices in the legal responsibilities of forensic medicine and physicians. Such laws, which are not peculiar to Turkey, are also practiced in other countries (2).

Medicine and its minor branches can easily lead to human rights violations. In retrospect, it can be said that some human rights violations were effective in the emergence of the concept of patient rights (3). Recently, the concept of patient rights has been discussed in a broader context, both in the health sector and in the media, turning patient-physician relations and patient experiences during the process of healthcare into an area of interest for lawyers. In the Turkish healthcare system, first-contact primary care is delivered in community-based family health centers. The primary care team members working in these family health centers know the patient-family-environment and regional factors the best. Therefore; family physicians have a great responsibility in the management of first contacts, including diagnostic and treatment procedures.

The Ministry of Health (MoH) of The Republic of Turkey (2020) defines family physicians as follows: "Physicians (specialists of family medicine or practitioners who as part of the primary health care reform, received in-service training organized by the MoH) who provide preventive health services for the person and primary care diagnostic, therapeutic and rehabilitative health services (without distinction of age, gender and disease) and provide mobile health services when necessary" (4). Initiative aimed at creating healthy societies rely on empowered family medicine and primary care. Which one is more meaningful? to give a Hepatitis B vaccine to healthy individuals at the appropriate time, or to give a liver transplantion to a patient with cirrhosis due to hepatitis B infection? It can easily be seen that contrary approaches are also financially unsustainable (5).

The following examples can be given for physicians' defensive medical behaviors (6):

- Prescription of unnecessary drugs,
- Increase in diagnostic tests,
- Requesting more consultation for diagnosis and treatment,
- Keeping a more detailed record (in a way that does not comply with the anamnesis of the patient concerned).

In the code of professional ethics of the Turkish Medical Association, malpractice is defined as follows: "Harming a patient due to lack of knowledge, inexperience or apathy, and poor practice of medicine" (7). When the literature is reviewed, it is seen that defensive medicine is divided into two as positive and negative. Positive defensive medicine (PDM) involve supplying additional services of marginal or no medical value with the aim of reducing adverse outcomes, deterring patients from filing malpractice claims, or persuading the legal system that the standard of care was met. Negative defensive medicine (NDM), on the other hand, reflect physicians' efforts to distance themselves from sources of legal risk. Defensive medicine, particularly avoidance behavior, encompasses both day-to-day clinical decisions affecting individual patients and more systematic alterations of scope and style of practice (8). Examples for PDM applications can be given as; requiring extra analysis-x-ray, unnecessary observation, whereas examples for NDM applications can be given as; failure to perform risky surgical practices, avoiding surgery and redirecting patients to other healthcare facilities.

According to MoH, in 2018, there were 26,252 family medicine units in Turkey, and the average population per unit was 3,124 people. In Isparta, the average population per family doctor was 2,848 people, which was lower than the national average. The number of visits to family medicine

units in Turkey in 2018 was 258,436,607. In the same period, the number of patients admitted to hospitals offering second and tertiary care services was 517,018,981 (9).

Fear of being prosecuted, positive or negative effects of media organizations, miscommunication, motivation for extra earning, healthcare policy and organisation of health care, the desire to be a famous physician are the reasons for defensive medicine behavior (10). Although defensive medicine has been looked into in the past in the USA and Europe and is still an up-to-date research topic, it has not yet been studied much in developing countries (11). The purpose of this study was to portray the views of family physicians who are per definition responsible for preventive care, on defensive medicine.

MATERIAL AND METHODS

Ethical approval was obtained from the Ethics Board of Suleyman Demirel University with a decision dated 30.09.2020 and numbered 45/2. In addition, a letter of permission to carry out this study was obtained from the Isparta Provincial Health Directorate (dated 20.10.2020 reference number 16657963-799). A descriptive survey study was conducted in Isparta/Turkey. There are a total of 160 family physicians working in family health centers in the universe. For enrolment, all of those family physicians were attempted to be contacted face-to-face or by phone, and a total of 77 family physicians participated (response rate 48.1%). The surveys were conducted between November 1st and December 31st, 2020. Due to time and cost constraints (i.e. the difficulty of reaching all family physicians throughout Turkey) the survey was applied only to physicians working in Isparta. The data includes subjective responses of family physicians who answered the questionnaire through their professional experience.

The survey used in the research consists of 3 parts. Sociodemographic characteristics (gender, marital status, whether to have children, expertise in medicine, age, professional experience period, average number of patients per day) are included in the first section. In the second part, the Defensive Medicine Attitude Scale was used to measure the physicians' behaviors. A section prepared to measure the attitudes of physicians to defensive medicine consists of PDM and NDM questions. 5 Likert-type status meter options were used to organize survey questions. The validity and reliability study of the Turkish version of the Defensive Medicine Attitude Scale was made by Başer et al. (12). In the third section, there are questions about the level of knowledge and case status of physicians in defensive medicine and malpractice.

Data were analyzed with SPSS 20.0 program. Descriptive statistics were calculated as mean, standard deviation, frequency, minimum, maximum. In addition, Factor Analysis, Pearson ChiSquare, Fisher Exact, Independence Samples T and One-Way Anowa tests were used. Significance was evaluated at the $p<0.05$ level.

RESULTS

A total of 77 family physicians affiliated with the Isparta Provincial Health Directorate filled out a survey within the scope of the study. Fiftysix physicians (73%) were male and 21 (27%) were female. The average age was 43.02±8.61 years (min:27, max:62). It was found that the average year of professional experience in the patient-physician relationship was 17.75±8.29 years (min:2, max:33). Sixtysix participants were (85.7%) practitioners and 11 participants (15.6%) were specialized in family medicine. Twentynine (37.7%) family physicians declared that they had 50 and more patient visits daily. Most of the participants (84.4%, n=65) had children. Cronbach's Alpha reliability value of the applied survey was 0.758. In Table 1, demographic data are shown in detail.

Table 1. Demographic data of family physicians (n=77)

Gender	n	%	Marriage Status	n	%	Specialty Status	n	%
Male	56	72.7	Married	68	88.3	Medical Practitioner	66	85.7
Female	21	27.3	Single	9	11.7	Specialist Physician	11	15.6
Professional Experience (Year)	n	%	Age	n	%	Number of Patients Per Day	n	%
≤9	14	18.2	≤29	8	10.4	10-30	17	22.1
10-19	31	40.3	30-39	20	26.0	30-50	31	40.3
≥20-	32	41.6	40-49	27	35.1	≥50-	29	37.7
			≥50-	22	28.6			

The first 6 questions in the survey are covering issues of PDM. Of the physicians participating in the study, 37.66% (n=29) of the "In order to protect myself from legal problems, I ask my patients for medical tests other than what I consider necessary." question and 42.86% (n=33) of the "In order to protect myself from legal problems, I prescribe most of the appropriate medications within their indications to my patients." question gave the answers neither agree nor disagree. Nearly one in ten participants (7.79%, n=6) strongly agreed with the statement "I want more consultation to protect myself from legal problems.".

Family physicians who participated in the study strongly disagreed to the statements "I explain medical treatment procedures to my patients in more detail in order to protect them from legal problems.", "I keep the patient records in more detail in order to protect myself from legal problems." and "As malpractice cases are often reported in the media, I feel anxiety in medical practice.". Nearly 40% (37.66%, n=29) of family physicians neither agreed or disagreed with the statement "I devote more time to my patients to protect myself from legal problems." The last 5 items in the survey are NDM questions. One out of ten participants (10.39%, n=8) stated that they strongly disagreed with the "In order to protect myself from legal problems, I avoid patients who are likely to sue and patients with complex medical problems." statement. Nearly half of the participants (46.75%, n=36) agreed to the statement "I avoid treatment with a high complication rate to protect myself from legal problems.". Thirteen percent (12.98%, n=10) of family physicians disagreed or strongly disagreed to the "In order to protect myself from legal problems, I tend to prefer non-invasive rather than surgical treatments." statement. The distribution of the answers given to the survey is shown in Table 2.

The answers given to the questions measuring the knowledge level of family physicians about defensive medicine are shown in Table 3. As can be seen from the table, the vast majority of family physicians (93.51%, n=72) answered no to the "Have you been prosecuted for medical malpractice?" question. In addition, almost half (48.05%, n=37) of family physicians answered the "Do you think that in the next 10 years, any lawsuits can be filed against you for medical malpractice?" question with yes. Nearly eight out of ten (76.62%, n=59) of family physicians stated that they had heard the concept of defensive medicine practices before. The majority (62.34%, n=48) stated that they do not have sufficient knowledge of the content of defensive medicine practices.

The Likert scale preferences to defensive medicine survey options; "strongly agree" were scored with 5 points and "strongly disagree" was scored with 1 point, individual scores for both sub-dimensions (PDM and NDM) were calculated for all participants. In the PDM subdimension, it was understood that family physicians exhibited an above-average (mean score: 3.39±0.60) PDM attitude. Based on this, it can be said that physicians have a defensive attitude (they want more tests and consultations, they approve most of the drugs to be prescribed within the indication, and they keep patients' records in more detail, etc.).

Table 2. Distribution of the answers given to the survey questions

Questions	Strongly agree		Agree		Neither agree nor disagree		Disagree		Strongly disagree	
	n	%	n	%	n	%	n	%	n	%
In order to protect myself from legal problems, I ask my patients for medical tests other than what I consider necessary.	8	10.39	15	19.48	29	37.66	17	22.08	8	10.39
In order to protect myself from legal problems, I prescribe most of the appropriate medications within their indications to my patients.	8	10.39	22	28.57	33	42.86	10	12.99	4	5.19
I want more consultation to protect myself from legal problems.	6	7.79	18	23.38	33	42.86	15	19.48	5	6.49
I explain medical treatment procedures to my patients in more detail in order to protect them from legal problems.	24	31.17	27	35.06	22	28.57	4	5.19	-	-
I devote more time to my patients to protect myself from legal problems.	8	10.39	27	35.06	29	37.66	9	11.69	4	5.19
I keep the patient records in more detail in order to protect myself from legal problems.	18	23.38	32	41.56	22	28.57	5	6.49	-	-
In order to protect myself from legal problems, I avoid treating patients who are likely to sue.	15	19.48	16	20.78	27	35.06	11	14.29	8	10.39
In order to protect myself from legal problems, I avoid patients with complex medical problems.	8	10.39	22	28.57	25	32.47	14	18.18	8	10.39
I avoid treatment with a high complication rate to protect myself from legal problems.	12	15.58	36	46.75	23	29.87	5	6.49	1	1.30
In order to protect myself from legal problems, I tend to prefer non-invasive rather than surgical treatments.	10	12.99	33	42.86	24	31.17	6	7.79	4	5.19
As malpractice cases are often reported in the media, I feel anxiety in medical practice.	46	59.74	19	24.68	8	10.39	4	5.19	-	-

Table 3. Distribution of family physicians' knowledge of defensive medicine				
	Yes		No	
	n	%	n	%
Have you been prosecuted for medical malpractice?	5	6.49	72	93.51
Do you think any lawsuits can be filed against you in the next 10 years?	37	48.05	40	51.95
Have you ever heard of the concept of defensive medicine practices in the past?	59	76.62	18	23.38
Do you have enough information about the content of defensive medicine practices?	29	37.66	48	62.34

When the NDM sub-dimension is examined, again values above average (mean score: 3.58±0.74) are noticeable. In short, family physicians avoid patients who may sue. It is understood they did not choose invasive treatments and were influenced by news of medical malpractice litigation in the press.

In the factor analysis of the defense medicine survey, factors with a preliminary value greater than 1 were evaluated and 4 factors were determined. Kaiser-Meyer-Olkin sampling adequacy (KMO=0.664) and Bartlett's test results (p=0.000<0.05) were found at acceptable levels. Four factors accounted for 68% of the total change. The first factor had the highest weightening (24.3%). Here; 7., 8., 9. and 10. survey questions have a load of over 0.7. There was no question with a load value less than 0.5. Efficiencies on the total change are shown in Table 4.

Tablo 4. Factor analysis results					
	Rotated Component Matrix[a]				
	1	2	3	4	Extraction
Question 1		.715			.636
Question 2				.800	.733
Question 3		.780			.690
Question 4			.779		.617
Question 5		.624			.571
Question 6			.708		.602
Question 7	.737				.692
Question 8	.861				.847
Question 9	.832				.759
Question 10	.755				.668
Question 11				.698	.668

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization. [a]. Rotation converged in 6 iterations.

In the independent sample T-test and One-way Anowa results, it was found that there was no significant difference between the scale scores in both gender and medical specialty variables. It was found that there was a statistically significant difference between marital status and scale scores. In addition, there was no statistically significant difference between professional experience and the average number of patients per day and scale scores. A positive correlation (r=0.324) was found between PDM and NDM.

DISCUSSION

When the findings of the study are examined, it is understood that family physicians exhibit above-average PDM and NDM behavior. In addition, 1 out of every 2 family doctors believes that in the next 10 years, a malpractice lawsuit can be filed against them.

Lawsuits filed as a result of faulty treatments increase the work of documenting and recording, rather than reducing procedures. If a group of physicians is inclined to defensive medicine, they have been sued in the past and have become sensitive to the value of careful documentation (13). Another study in the UK (Summerton-1995) found that 86% of physicians provide detailed explanations of treatment procedures. It was also highlighted that 29% made unnecessary prescribing of drugs, and 59% requested medical diagnostic tests more often than required (6). In their study, Passmore and Leung (2002) reported that about three-quarters of psychiatrists exhibited defensive medical behavior in the last month (14).

Hiyama et al., (2006), conducted a study in Japan with 131 gastroenterologists. Nearly all (96%) were found to avoid high-risk patients and their surgeries. Experienced gastroenterologists (those who have practiced their profession for more than 20 years) were, significantly less likely to display defensive medical behaviors than those in practice for less than 10 years. In addition, nearly all gastroenterologists (98%) reported practicing defensive medicine (15).

Aynaci (2008) investigated the concept of defensive medicine with 762 physicians in Konya/Turkey. It has been found that physicians with medical malpractice insurance perform more defensive medical practices than those who do not. The rate of physicians using defensive medicine was found to be 78.38% (16).

Baser et al. (2014); conducted a study where a defensive medicine survey was applied to family physicians in Izmir/Turkey. It was understood that 21% (n:17) practiced high degree, 49.3% (n:40) practiced moderate degree, and 6.2% (n:5) practiced weak degree of defensive medicine (12).

Ozata et al., (2018) they surveyed 173 physicians working in hospitals in Konya/Turkey. It was shown that 93.6% of physicians practice defensive medicine and are afraid of malpractice cases. In addition, physicians stated that they found medical malpractice insurance insufficient (11). In the results of this study, there is no family physician who says that I am not afraid of malpractice cases. All physicians are more or less concerned about malpractice cases.

A survey was conducted in Brazil with 104 physicians from 28 different specialties. It has been concluded that the results of defensive medicine and the knowledge of patients make the relationship between physician and patient even more difficult. Prolonging the process for diagnosing and treating the disease significantly increases the cost of health care. Seventy-five percent of respondents said they used defensive medicine daily (17).

In Konya/Turkey, the average defensive medicine attitudes of 207 physicians at the Faculty of Medicine were determined at a score of 3.27. Above average results were obtained in PDM and NDM. It has been found that male physicians use NDM practices more often than women. It was observed that those who practiced medicine for 5-10 years increased the use of defensive medicine compared to those over 11 years. Although physicians had previously heard of the concept of defensive medicine, they did not think they had sufficient knowledge (18). In this study, the average defensive medical attitudes score of physicians (3.48) was above average.

Another study was conducted in England (2013) with 204 physicians from 3 different hospitals. It has been found that 78% of physicians practice defensive medicine. Over half of the participants (59%) said they often asked for unnecessary tests; 55% said they preferred to refer their patients to another specialist for a consultation. Nearly one out of ten participants in the U.K. study (9%) said they refused treatment from high-risk patients (19). In this study, the ratio of family physicians who say they do not want unnecessary tests from their patients is only 10% (n=8). On the other hand, 31.1% (n=24) of family physicians stated that they strongly agree that they explain medical procedures in detail in order to protect themselves from legal problems.

In addition to all these, it is clear that unnecessary hospitalizations and observations damage health systems (14). The benefits of defensive medicine are controversial. Physicians can't know exactly what kind of behavior will be protective for them. There is almost no empirical evidence that medically unhelpful actions will reduce the risk of malpractice claims being made (20). The literature on defensive medicine has been examined and it has been observed that the results of the research show similarities with previous studies.

CONCLUSIONS AND SUGGESTIONS

Some physicians use the concept of defensive medicine consciously while others use it unconsciously. Considering the information asymmetry in the health field, defensive medicine emerges as an important current issue being studied.

The clear distinction between complications and malpractice will lead physicians to be more courageous in their treatment processes. Drugs or operational procedures can have side effects and complications in medicine, which is a risky profession. Physicians should not think whether patients would sue them or not, and it should be ensured that they examine and treat the patients without anxiety. This way, physicians will not request unnecessary analysis-x-rays and be afraid of risky practices.

While all precautions are taken, the existence of insurance and legal bases that support physicians and healthcare professionals in possible complications may play a role in preventing defensive medicine practices. Arranging the necessary planning for physicians to devote sufficient time for their patients will prevent errors that may arise from high work load. In the reporting of medical errors, physicians should be able to make objective feedbacks. In future studies, it may be recommended to examine the defensive medicine attitudes of physicians at higher level hospitals and private hospitals.

REFERENCES

1. Dedeoğlu AK. Özel hastanelerde çalışan hekimlerin tıbbi müdahale ve tedavide malpraktisten doğan hukuki ve cezai sorumluluklarına ilişkin farkındalık düzeylerinin ölçümü: Ankara ili özel hastaneler uygulaması [Yüksek Lisans Tezi]. Atılım Üniversitesi Sosyal Bilimler Enstitüsü. Ankara; 2012.

2. Altun G, Yorulmaz AC. Yasal değişiklikler sonrası hekim sorumluluğu ve malpraktis. Trakya Üniversitesi Tıp Fakültesi Dergisi. 2010; 27(1), 7–12.
3. Tacir H. Hastanın kendi geleceğini belirleme hakkı. [Doktora Tezi]. Marmara Üniversitesi Sosyal Bilimler Enstitüsü. İstanbul; 2010.
4. Türkiye Cumhuriyeti Sağlık Bakanlığı (Ministry of Health of The Republic of Turkey). Halk Sağlığı Genel Müdürlüğü, Aile Hekimliği Dairesi Başkanlığı [Internet]. [cited 2020 Sep 25]. Available from: https://hsgm.saglik.gov.tr/tr/ailehekimligi-anasayfa.html
5. Üstü Y, Uğurlu M. Bir analiz: Aile hekimliği ülkemizde etkin kullanılıyor mu? Ankara Medical Journal. 2015; 15(4), 244–248.
6. Summerton N. Positive and negative factors in defensive medicine: A Questionnaire study of general practitioners. Bmj. 1995; 310(6971), 27.
7. Türk Tabipler Birliği (1999). Hekimlik Meslek Etiği Kuralları, [Internet]. [cited 2020 Oct 10]. Available from: https://www.ttb.org.tr/mevzuat/index.php?option=com_content& task=view&id=65&Itemid=31
8. Studdert DM, Mello MM, Sage WM, DesRoches CM, Peugh J, Zapert K, Brennan TA. Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. Journal of the American Medical Association. 2005; 293(21), 2609–2617.
9. Türkiye Cumhuriyeti Sağlık Bakanlığı. Sağlık istatistikleri yıllığı 2018. Sağlık Bilgi Sistemleri Genel Müdürlüğü, Ankara; 2019.
10. Selçuk M. Çekinik (defansif) tıp, [Yüksek Lisans Tezi]. İzmir Üniversitesi. Sosyal Bilimler Enstitüsü, İzmir; 2015.
11. Özata M, Özer K, Akkoca Y. Konya il merkezinde çalışan hekimlerde defansif (çekinik) tıp uygulamalarının araştırılması. Gümüşhane Üniversitesi Sağlık Bilimleri Dergisi. 2018; 7(1), 132–139.
12. Başer A, Kolcu G, Çığırgil Y, Kadınkız B, Öngel K. İzmir Karşıyaka ilçesinde görev yapan aile hekimlerinin defansif tıp uygulamaları ile ilgili görüşlerinin değerlendirilmesi. Smyrna Tıp Dergisi. 2014; 77, 16–24.
13. Tancredi LR, Barondess JA. The problem of defensive medicine. American Association for the Advancement of Science. 1978; 200(4344), 879–882.
14. Passmore K, Leung WC. Defensive practice among psychiatrists: A questionnaire survey. Postgraduate Medical Journal. 2002; 78(925), 671–673.
15. Hiyama T, Yoshihara M, Tanaka S, Urabe Y, Ikegami Y, Fukuhara T, Chayama K. Defensive medicine practices among gastroenterologists in Japan. World Journal of Gastroenterology. 2006; 12(47), 7671–7675.
16. Aynacı Y. Hekimlerde defansif (çekinik) tıp uygulamalarının araştırılması. [Tıpta Uzmanlık Tezi]. Selçuk Üniversitesi, Meram Tıp Fakültesi. Konya; 2008.
17. Vale HM, Miyazaki MC de OS. Defensive medicine: a practice in whose defense? Revista Bioética. 2019; 27(4), 747–755.
18. Banaz M. Hekimlerin defansif tıp ve tıbbi hata tutumlarının incelenmesi. [Yüksek Lisans Tezi]. Hacettepe Üniversitesi Sosyal Bilimler Enstitüsü. Ankara; 2020.
19. Ortashi O, Virdee J, Hassan R, Mutrynowski T, Abu-Zidan F. The practice of defensive medicine among hospital doctors in the United Kingdom. BMC Medical Ethics. 2013; 14(42).
20. Saks M, Landsman S. The paradoxes of defensive medicine. Health Matrix: The Journal of Law-Medicine. 2020; 30(1), 25–83.

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 697-699
https://doi.org/10.31067/acusaglik.850849

CASE REPORT / OLGU SUNUMU

Otolaryngology / Kulak Burun Boğaz

Olfactory and Taste Dysfunction as an Initial Symptom of COVID-19

Altuğ Özagar[1] , **Senem Almaç Deniz**[1]

[1]Acıbadem Dr. Şinasi Can (Kadıköy) Hospital, Department of ENT, Istanbul, Turkey

Altuğ ÖZAGAR, Asst. Prof. Dr.
Senem ALMAÇ DENİZ, M.D.

Correspondence: Altuğ Özagar
Acibadem Dr. Şinasi Can (Kadıköy) Hospital, Department of ENT, Istanbul, Turkey
Phone: +902165444444
E-mail: altugozagar@gmail.com

Received : 13 May 2020
Accepted : 22 August 2020

ABSTRACT

The coronavirus assumed to have originated in Wuhan China, has infected millions of people since December 2019, resulting in a pandemic. Recent changes in symptoms are observed in Covid-19 positive patients, whose symptoms were reported as fever, myalgia and cough in the earlier cases. In this paper we presented two cases where the initial symptom was loss of taste and smell sensation. Both of these patients were diagnosed pneumonia though neither of them had cough nor fever. Considering the positive outcomes with medical treatment, we claim these patients with the only symptom, loss of smell and taste, should be tested for Covid-19.

Keywords: Covid-19, pandemic, olfactory dysfunction, taste dysfunction

COVİD-19: İlk Semptom Olarak Koku ve Tat Disfonksiyonu

ÖZET

Aralık 2019'da Çin'in Wuhan kentinden kaynaklandığı düşünülen ve milyonlarca kişinin enfekte olmasına neden olan koronavirus bir pandemiye yol açmıştır. Enfeksiyonun ilk dönemlerinde sıklıkla görülen semptomlar ateş, miyalji ve öksürük olarak bildirilmiştir. Biz bu yazıda başlangıç bulguları olarak sadece koku ve tat alma fonksiyonunda kaybolma şikayeti ile gelen iki hastayı inceledik. Testleri pozitif çıkan ve pnömoni tanısı konan hastalarda öksürük ve ateş görülmedi. Sadece tat ve koku duyularının kaybolduğu hastaların mutlaka test ile taranması gerektiğini düşünmekteyiz.

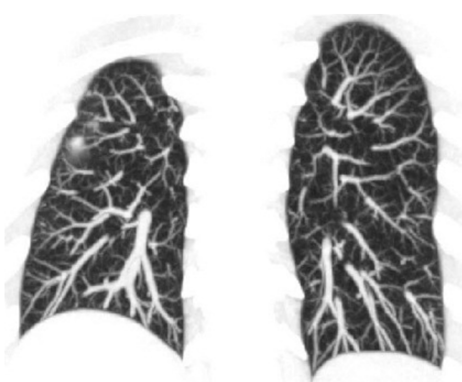
Anahtar Sözcükler: Kovid-19, pandemi, koku disfonksiyonu, tat disfonksiyonu

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Viral and bacterial upper respiratory infections are amongst the most researched diseases. For acute respiratory distress syndrome (ARDS), the major pathogens are influenza, respiratory syncytial virus (RSV), rhinovirus, coronavirus and adenovirus (1). The so-called novel coronavirus, SARS-CoV-2, assumed to be originated in Wuhan, China, has already infected millions of people in a 3 month period. The early papers reported fever (98%), cough (76%), myalgia and fatigue (44%) as the most common symptoms of COVID-19 disease caused by SARS-CoV-19. Sputum production (28%), headache (8%), hemoptysis (5%) and diarrhea (3%) are the less reported other symptoms (2). In this article, we will discuss 2 cases diagnosed within a week in March 2020.

Report of cases

Case 1. A 23-year-old female patient came with a loss of taste and smell sensation for a week. She reported she came from abroad 13 days ago. PCR tested positive for SARS-Cov-2, she had a CT scan done which revealed a crazy-paving pattern infiltration (Fig 1). Treatment was started by hospitalization due to her pneumonia. She was discharged on the 7th day, immediately after her CT findings got better. She informed us later that her loss of taste recovered 1 week, smell 2 weeks after the treatment began.



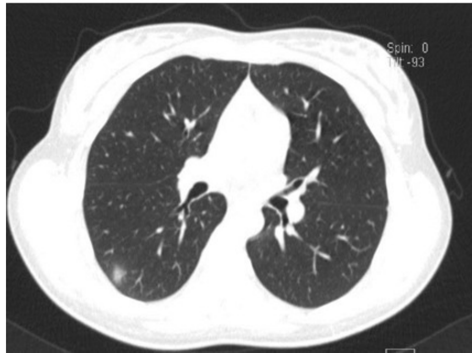


Figure 1. ŞEKİL 1 Figure 1 Thorax Computed Tomographic Image of Coronal and Axial Section Nodular opacity on the periphery of the right sided lung

Case 2. A 55-year-old female patient came with complaints of feeling tired and loss of taste and smell sensation for a week. Her thorax CT revealed a crazy-paving pattern and immediate treatment was started (Fig 2). She was tested positive for SARS-CoV-2. She was transferred to ICU because of a decrease in oxygen saturation and expansion of infiltrated areas in thorax CT. She is extubated after 2 weeks of intubation and discharged from ICU.

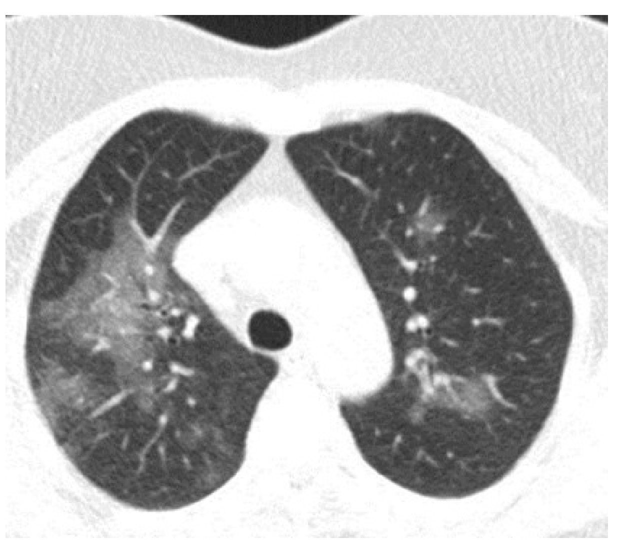


Figure 2. Lung Computed Tomographic Image of Axial Section Ground glass opacification on both sides.

Discussion

The most common symptoms since the beginning of the pandemic are fever, cough and myalgia in COVID-19 patients. These patients are mostly examined in emergency and internal medicine clinics of the hospitals. However, these 2 patients were referred to our otolaryngology clinic; loss of taste and smell sensation was the only complaint and no sign or symptom of infection was detected in one of them, and was the predominant complaint in the other who also had a slight fatigue. Both of their PCR tests came back positive for COVID-19 and had the typical crazy-paving pattern in thorax CT. These two patients were hospitalized and treated accordingly.

In literature, the most common pathogen causing post-viral olfactory disorders is rhinovirus; though Ebstein Barr Virus, coronavirus and parainfluenza are also detected as other pathogens (3,4). It is assumed that the virus invades the central neural system through olfactory neuroepithelium and pathway, though the exact pathophysiology is not clearly known (5). Yamagishi et al, in a 13 patient

study, showed a decrease in the number of olfactory receptors and nerve bundles after upper respiratory infections (6). In some animal studies, it is shown that inoculation of various viruses intranasally causes a destruction in central olfactory pathways (7-8). Recently, Steven et al identified bitter taste receptors on human airway smooth muscle cells (9). We assume it is possible the olfactory cells contain angiotensin-converting enzyme 2 receptors since it is known that SARS-CoV-2 (enters host cells of the human airway via these receptors) performs its action on the human airway through these receptors.

The patients being tested positive with the symptom, loss of smell and taste sensation may suggest the virus might have developed a different behaviour since this symptom wasn't reported previously.

As it is seen, all the patients came with the same symptom, but each progressed differently, which suggests disease progress might be independent from symptoms due to various factors. In patients with loss of taste and smell sensation only, COVID-19 must be kept in mind.

Conclusion

Data regarding Covid-19 have changed substantially since the beginning of the pandemic. In the early days, the defining symptoms were considered to be fever, dry cough and shortness of breath. In this paper, we presented only two of the many patients whose initial complaint was a loss of smell and taste. We suggest that these patients could easily be overlooked if Covid-19 is not kept in mind.

References

1. Mahony JB, Petrich A, Smieja M. Molecular diagnosis of respiratory virus infections. Crit Rev Clin Lab Sci. 2011;48:217-49.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.Lancet. 2020 Feb 15;395(10223):497-506.
3. Detection of parainfluenza virus 3 in turbinate epithelial cells of postviral olfactory dysfunction patients.Wang JH1, Kwon HJ, Jang YJ. Laryngoscope. 2007 Aug;117(8):1445-9.
4. Identification of Viruses in Patients With Postviral Olfactory Dysfunction Motohiko Suzuki, Koichi Saito, Wei-Ping Min, Costin Vladau, Kazunori Toida, Hirotaka Itoh, Shingo Murakami. Laryngoscope, 117:272–277, 2007
5. Stroop MG. Viruses and the olfactory system. In: Doty RL, editor. Handbook of olfaction and gustation. New York: Marcel Dekker; 1995. p. 367–94
6. Yamagishi M, Fujiwara M, Nakamura H. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. Rhinology 1994;32:113–8
7. Perlman S, Evans G, Afifi A. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. J Exp Med 1990;172:1127–32
8. Behavioural deficits and serotonin depletion in adult rats after transient infant nasal viral infection. Mohammed AK1, Magnusson O, Maehlen J, Fonnum F, Norrby E, Schultzberg M, Kristensson K. Neuroscience. 1990;35(2):355-63.
9. An SS, Liggett SB. Taste and smell GPCRs in the lung: evidence for apreviously unrecognized widespread chemosensory system. Cell Signal. 2018;41:82-88. doi:10.1016/j.cellsig.2017.02.002

Acıbadem Univ. Sağlık Bilim. Derg. 2021; 12 (3): 700-703
https://doi.org/10.31067/acusaglik.870389

CASE REPORT / OLGU SUNUMU

Gastroenterology and Hepatology / Gastroenteroloji ve Hepatoloji

Inverted Colonic Diverticula Cases

Arzu Tiftikçi[1], Emrehan Parlak[2], Bircan Boğa[2], Serpil Yılmaz[3], Bahattin Çiçek[1]

[1]Acıbadem Mehmet Ali Aydınlar University Medical Faculty, Gastroenterology Department, Istanbul/Turkey

[2]Acıbadem Mehmet Ali Aydınlar University Medical Faculty, Istanbul/Turkey

[3]Nişantaşı Pathology Group, Istanbul/Turkey

Arzu TİFTİKÇİ, Prof. Dr.
Emrehan PARLAK
Bircan BOĞA
Serpil YILMAZ, Uzm. Dr.
Bahattin ÇİÇEK, Prof. Dr.

Correspondence: Arzu Tiftikçi
Acıbadem Mehmet Ali Aydınlar University Medical Faculty, Gastroenterology Department, Istanbul/Turkey
Phone: +905323562217
E-mail: arzutiftikci@gmail.com

Received : 29 January 2021
Accepted : 28 February 2021

ABSTRACT

Colonic diverticula are outpouchings of mucosa and submucosa through the large intestine wall. Inverted colonic diverticula can be confused with colonic adenoma. It is important to differentiate them. Here we report two cases of inverted diverticula that seem to like adenomas.

Keywords: Diverticula, polyp, inversion

Ters dönmüş kolonik divertikül: İki Olgu Sunumu

ÖZET

Kolonik divertikula kolon duvarında mukoza ve submukozanın içe çökmesi şeklinde görülür. Ters dönmüş divertikül, kolonik adenomla karışabilir. Biz burada adenoma benzeyen iki ters dönmüş kolonik divertikül olgusu sunuyoruz.

Anahtar Sözcükler: Ters dönmüş kolonik divertikül, adenom, polipektomi

Colonic diverticula are outpouchings of mucosa and submucosa through the large intestine wall (1,2) accompanied by structural changes like muscular thickening, mucosal folding and taenia coli elastosis (2). They are classified as pseudodiverticula (1) unlike the appendix which is a true diverticulum that also includes the muscular layer. Focal weaknesses in the colonic wall such as areas where arterial vasa recta and nerves meet the circular muscular layer or areas adjacent to taenia coli have tendency to form diverticula (3). Although diverticula are mostly asymptomatic and are found incidentally on colonoscopy, some of them give symptoms and have potentially dangerous complications such as infection, perforation, obstruction, and bleeding (1). Even intussusception have been reported as a complication of diverticula (4).

Copyright © 2021 the Author(s). Published by Acibadem University. This is an open access article licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND 4.0) International License, which is downloadable, re-usable and distributable in any medium or format in unadapted form and for noncommercial purposes only where credit is given to the creator and publishing journal is cited properly. The work cannot be used commercially without permission from the journal.

Inverted colonic diverticula (ICD) are observed in nearly %0.7 of the population (5) and are mostly seen in sigmoid colon. In colonoscopy it is hard to differentiate ICD from neoplastic polypoid structures. Resection of an ICD assumed to be a neoplastic polyp can lead to serious complications. These include perforation of the colonic wall and peritonitis due to the discharge of the colonic content (6). Therefore, it is crucial to distinguish ICD from neoplastic polyps. Some approaches exist to help diagnose ICD during colonoscopy. However, there are few studies in literature showing both macroscopic and microscopic characteristic features of ICD. For this reason, our study aims to report the colonoscopic and histopathologic findings of two of our patients diagnosed with ICD.

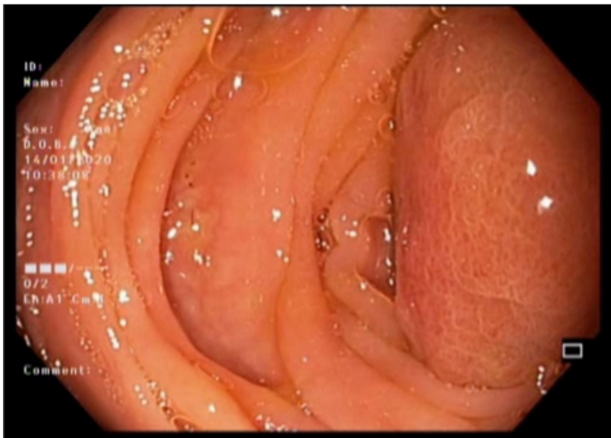


Figure 1: Endoscopic apparance of inverted diverticulum that looks like sesille adenomatous polyp

Data

Case 1

A 49-year-old man without any gastrointestinal complaints presented for his first screening colonoscopy. His past medical history included nephrolithiasis, a previous cholecystectomy and routine usage of a beta blocker for hypertension. The patient was a heavy smoker and drinker. Endoscopic inspection revealed an irregular zone (3 cm x 5 cm in diameter) in the sigmoid colon which, by inspection, showed properties of an eroded polyp or an ICD (figure 1). After being elevated by saline injection, an endoloop was applied and the lesion was partially removed with snare cautery (figure 2). The remaining zone was marked with Indian Ink. Colonoscopy was continued until the terminal ileum and revealed multiple diverticula throughout the colon. The patient did not have a history of complications (such as bleeding, inflammation and perforation) related to widely distributed diverticula. Small polyps were detected in the cecum and were removed with biopsy forceps. As visualized 15 cm of terminal ileum and rectum seemed normal. The patient tolerated the procedure well without any complaints. Histopathological evaluation of sample revealed reactive changes in colonic mucosa characterized by crypt hyperplasia and increased goblet cell density. The lesion didn't have characteristics of typical colonic polyps and morphological findings supporting mucosal changes seen in colonic diverticular disease (figure 3).

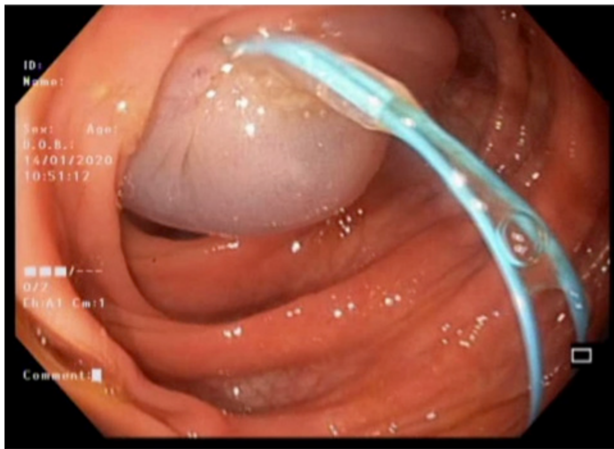


Figure 2: Endoscopic apperance of snare polypectomy after insertion of endoloop

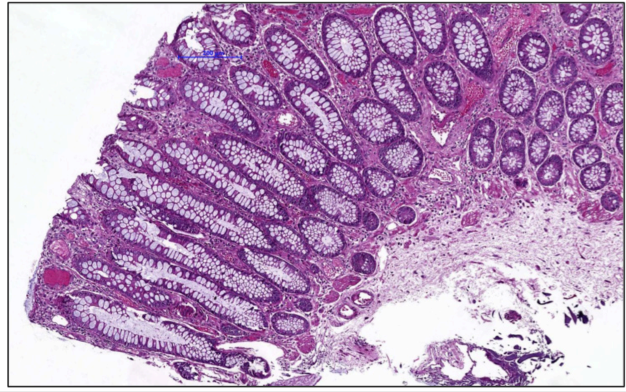


Figure 3: Crypt hyperplasia and increased goblet cell density (hematoxylin and eosin,x7,48)

Case 2

A 51-year-old man presented for his routine screening colonoscopy. His past medical history included right hemicolectomy due to frequent diverticulitis and also previous tubular adenoma removal. The patient was a heavy smoker and drinker. Endoscopic examination revealed a hyperemic lesion (2 cm x 3 cm in diameter) possibly related to infection or incarceration of colonic mucosa (Figure 4). The undetermined lesion seemed to be compatible with an ICD on gross view thus multiple biopsies were taken from it. The remaining sigmoid colon included an adenomatous sessile polyp and also a diverticular opening. Rectum included a sessile polyp. The rest of the colon seemed to be normal until the anastomosis. The patient tolerated the procedure well without any complaints.There were 5 biopsy samples between 1mm. and 5 mm. in diameter. At histopathological examination colonic mucosa with mildly active chronic inflammatory infiltration, crypt hyperplasia, architectural distortion and dilatation, serration of superficial and crypt epithelium and myofibroblastic proliferation surrounding the crypts was seen. The lesion had properties of a mucosal prolapse. Morphological findings supported mucosal changes seen in colonic diverticular disease (figure 5).

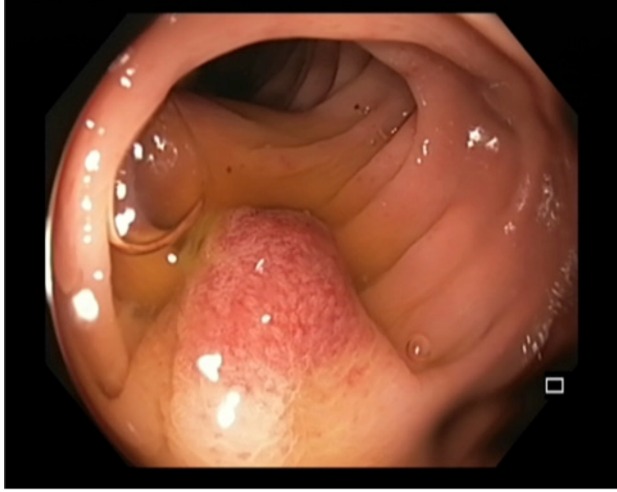


Figure 4: Endoscopic apparance of inverted diverticulum that looks like mucosal jamming or adenomatous polyp

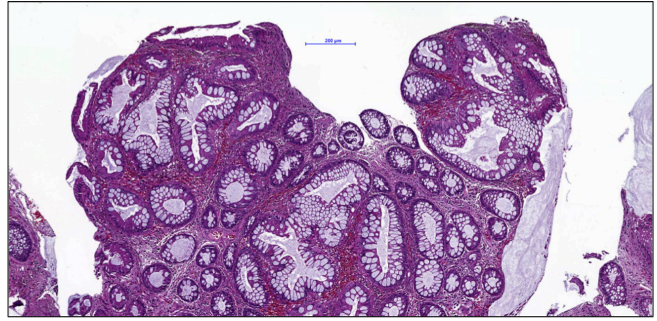


Figure 5: Crypt hyperplasia, architectural distortion and dilatation, serration of superficial and crypt epithelium and myofibroblastic proliferation surrounding the crypts. (hematoxylin and eosin,x7,57)

Discussion

Colonic diverticula are commonly encountered lesions on colonoscopy. Although most of the diverticula have typical apperance, rarely they can be inverted and resemble colonic hyperplastic or adenomatous polyps. Resection of these ICD may lead to colonic perforation and even ICD, itself may lead to serious complications such as intussusception (4) Endoloop assisted biopsies of such lesions could be helpful in terms of exact diagnosis. Various studies described some criteria to differentiate ICD from typical colonic polyps. One study suggested polypoid lesions seen in diverticular segments of the colon have a high possibility of being an ICD if they are voluminous, soft, congestive and broad-stalked (7). ICD's larger than 2 cm are subject to be misdiagnosed as a pedunculated polyp compared to smaller lesions (8). It is crucial to distinguish ICD from neoplastic polyps. Some approaches exist to help diagnose ICD during colonoscopy, such as attempting to revert the lesion with forceps (9), air insufflation, checking water jet deformation sign (10), radiating pillow sign or looking for concentric pale rings surrounding the lesion referred as Aurora rings (11). Both cases in our study had their ICD located in sigmoid colon with other typical diverticular and polypoid structures nearby. They were encountered incidentally on routine colonoscopy. Our patients had different past medical histories however both of them did not report any complaints or complications specifically related to their ICD. If these lesions were accepted as typical colonic polyps and the possibility of an ICD was not considered during colonoscopy, resection of them would lead to life threatening serious complications such as perforation which can be seen in one out of 1400 of all colonoscopy procedures (12). This complication occurs possibly more often in misdiagnosed ICD resections.

Taking biopsies or large resection after endoloop insertion can be an option to differentiate ICD from adenomatous polyp histopathologically. However this approach may need a second colonoscopy in true polipoid cases.

Newer technological approaches that help to identify such undetermined lesions are being devised in order to minimize the complication risk and increase the diagnostic accuracy during colonoscopy. However, most of these magnifying based technologies are limited to differentiate malignant polyps from nonneoplastic ones. Future studies should focus on discovering technologies and techniques to maximize the diagnostic accuracy during colonoscopy for patients' safety and speed recovery.

References

1. Travis AC. Diverticular disease of the colon. In: Greenberger NJ, Blumberg RS, Burakoff R. eds. Current diagnosis and treatment Gastroenterology, Hepatology and Endoscopy. Cham: MC Graw-Hill Education.. A lange medical book: publishing 2016. p 274-88
2. Gearhart S. Diverticular disease and common anorectal disorders. In: Longo DL, Fauci AS eds. Harrison's Gastroenterology and Hepatology. Cham: MC Graw-Hill Education. publishing 2013. P 212-26
3. Matrana MR and Margolin DA. Epidemiology and pathophysiology of diverticular disease. Clin Colon Rectal Surg. 2009; 22 (3):141-8
4. Zhang B, Wang J, Li X , et al. Intussusception Caused by an Inverted Colonic Diverticulum: A Case Report. J Med Case Rep. 2018; 27;12(1):114. DOI:10.1186/s13256-018-1652-9
5. Merino RC, Kinney T, Santander R, et al. Inverted Colonic Diverticulum:An infrequent and dangerous endoscopic finding. Gastrointesti Endosc. 2005 ; 61(5) AB257: W1120
6. Yusuf SI and Grant C. Inverted colonic diverticulum: a rare finding in a common condition? Gastrointest Endosc. 2000; 52(1): 111–5.
7. Dumas O, Jouffre C, Desportes R et al. Inverted sigmoid diverticulum: a misleading polyp. Gastrointest Endosc. 1991;37(5): 587–8.
8. Paoluzi OA, Tosti C, Andrei F. et al. Look out before polypectomy in patients with diverticular disease--A case of a large inverted diverticulum of the colon resembling a pedunculated polyp. Can J Gastroenterol. 2010;24(1) :61-3
9. Adioui T and Seddik H. Inverted colonic diverticulum. Ann Gastroenterol. 2014; 27(4):411
10. Cappel MS. The water jet deformation sign: a novel provocative colonoscopic maneuver to help diagnose an inverted colonic diverticulum. South Med J. 2009 ; 102(3):295-8
11. Share MD, Avila A, Dry SM, et al. Aurora rings:a novel endoscopic finding to distinguish inverted colonic diverticula from colon polyps. Gastrointest Endosc. 2013; 77(2): 308-12
12. Iqbal CW, Cullinane DC, Schiller HJ, et al. Surgical management and outcomes of 165 colonoscopic perforations from a single institution. Arch Surg. 2008;143(7): 701-6