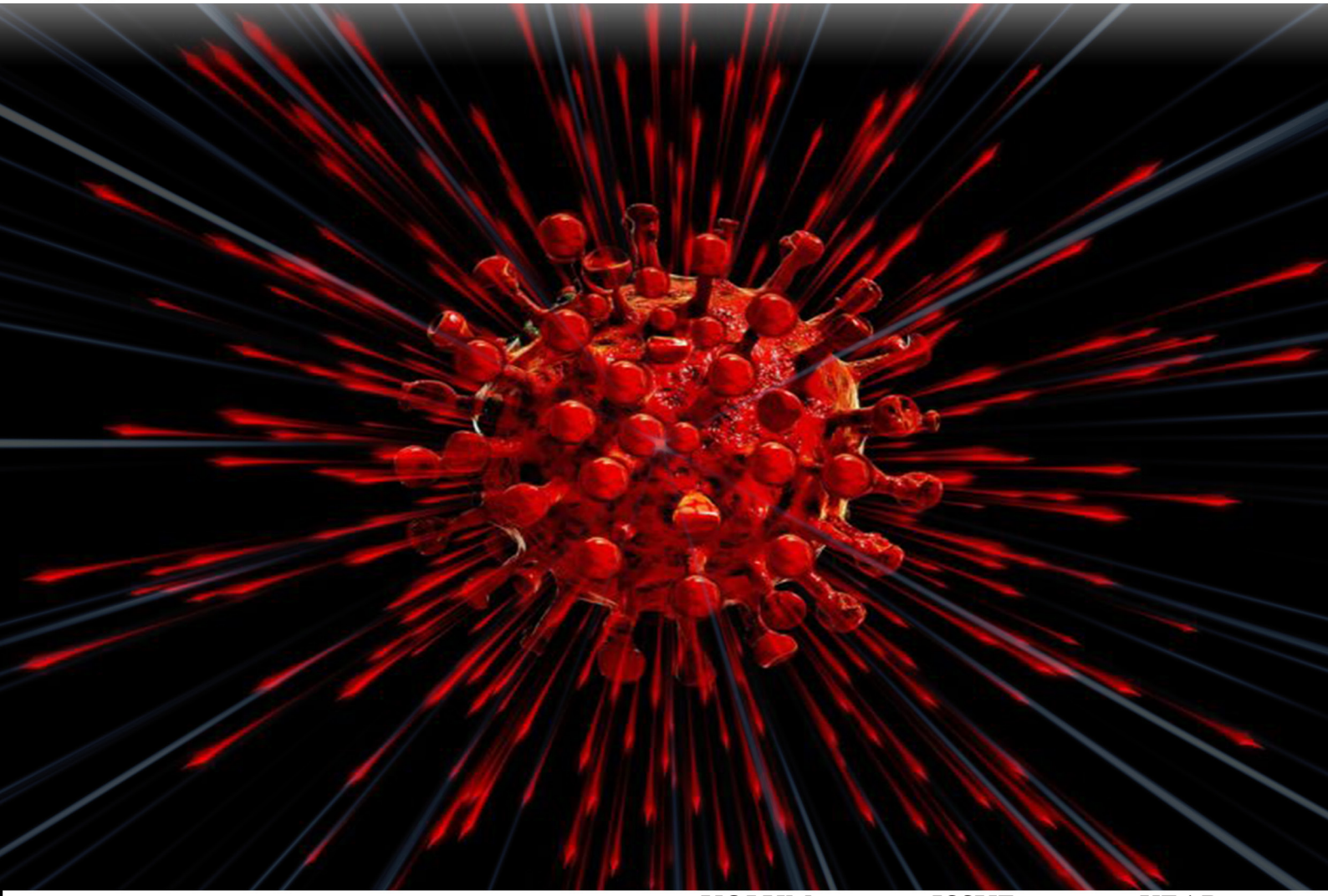
e-ISSN: 2718-0115

ACMJ

Anatolian Current Medical Journal



VOLUM: 3 ISSUE: 3 YEAR: 2021

PUBLICATION BOARD

FRANCHISE OWNER

MediHealth Academy Publishing
(***www.medihealthacademy.com***)

DESIGN

Fatih Şamil ULUDAĞ
(fsuludag@gmail.com)

CORRESPONDENCE ADDRESS

MediHealth Academy Publishing
Emniyet Mah., Yukarı Sk., 6/1, Yenimahalle, Ankara, Türkiye
E-mail / E-posta: info@medihealthacademy.com
Phone / Tel: +90 312 349 77 77

ARTICLE SUBMISSION ADDRESS

https://dergipark.org.tr/en/journal/2384/submission/step/manuscript/new

Our dear readers,

We are proud to publish the third issue of our journal for 2021 with 15 articles. In this issue, there are 11 original articles, 2 case reports, one letter to the editor, and one upto-date and comprehensive review that we think will attract your attention. We increase the scientific quality of our journal day by day.Our goal is to improve our publication quality day by day with the support of all our writers and readers and to appeal to a wider readership. Principally, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering indexes such as PubMed, SCI and SCI-Expanded. I would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal. I would also like to thank our referees and editors who gave us their precious time. We hope that this issue will be useful to our readers.

Sincerely yours.

Assoc. Prof. Dr. Kenan ÇADIRCI
Assoc. Editor

CONTENTS

Original Article

CONTENTS

Review

Case Report

Letter to the Editor

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.867179

Anatolian Curr Med J 2021; 3(3); 188-191

Thromboprophylaxis decreases the risk of pulmonary embolism in COVID-19

Murat Uğur[1], Taha Yusuf Kuzan[2], Nurettin Yiyit[3]

[1]Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Education and Research Hospital, Department of Cardiovascular Surgery, İstanbul, Turkey

[2]Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Education and Research Hospital, Department of Radiology, İstanbul, Turkey

[3]Health Sciences University, Sancaktepe Şehit Prof. Dr. İlhan Varank Education and Research Hospital, Department of Thoracic Surgery, İstanbul, Turkey

Cite this article as: Uğur M, Kuzan TY, Yiyit N. Thromboprophylaxis decreases the risk of pulmonary embolism in COVID-19. Anatolian Curr Med J 2021; 3(3); 188-191.

ABSTRACT

Aim: Pulmonary embolism caused by micromboli and microthrombuses might be associated with increased mortality and morbidity in COVID-19. Routine thromboprophylaxis application might contribute to clinical recovery by reducing the risk of pulmonary embolism. In this study, the effects of thromboprophylaxis on clinical outcomes were investigated by examining the rates of computed tomographic angiography requests for the differential diagnosis of pulmonary embolism in the patients with COVID-19.

Material and Method: Patients who underwent computed tomography (CT) between 10 March and 25 May 2020 in our hospital were retrospectively analysed. Patients who received simultaneous PCR tests during CT examination were included in the study. In the follow-up of these patients, rates of pulmonary CT angiography request with the suspicion of pulmonary embolism and it's were investigated.

Results: During the study period, thorax CT was performed in 11142 patients and pulmonary CT angiography was performed in 161 (1.4%) of them. Ninety-nine patients who were performed CT angiography and PCR test during the hospitalization period were included in the study. PCR test was positive in 22% (n=21) of the patients (22%) and pulmonary embolism was detected in 6 of them (6.3%). PCR test was negative in 74 patients (78%) and 17 (17.9%) had pulmonary embolism.

Conclusion: Routine thromboprophylaxis contributes to the treatment of COVID-19 by preventing the development of microthrombosis and thrombotic complications in the respiratory system.

Keywords: COVID-19, Coronavirus, pulmonary embolism, thrombosis

INTRODUCTION

COVID-19, originating from China, has been declared a pandemic in the short term and has become a disease that threatens the whole world and changes life habits. Tendency to thrombosis increases in the etiopathogenesis of the disease. Abnormal blood clotting and thrombosis have been reported as a predictive factor for the poor prognosis (1). In COVID-19, similar to SARS CoV, thrombosis might develop in small and medium-sized pulmonary arteries (2). The disease is characterized by pulmonary involvement and pulmonary embolism might worsen the clinical course (2,3). Pulmonary embolism was detected in 23-37% of critically ill patients with COVID-19 (4,5).

In Turkey, according to the treatment algorithm, determined by the Ministry of Health, it was aimed to avoid the complications related to thrombosis by prophylaxis with low molecular weight heparin to every hospitalized patient, besides hydroxychloroquine (6). Pulmonary computed tomography (CT) angiography is a diagnostic imaging method for the diagnosis of pulmonary embolism. It is the first applied diagnostic method to confirm the diagnosis in case of doubt. In this study, number of pulmonary CT angiography and rates of pulmonary embolism were evaluated in our hospital, which is a pandemic hospital in the fight against COVID-19.

Corresponding Author: Murat Uğur, drmugur@gmail.com

Received: 27.03.2021 **Accepted:** 24.04.2021

MATERIAL AND METHOD

Patients who underwent computed tomography (CT) between 10 March-25 May 2020 in our hospital were evaluated retrospectively. Patients older than 18 years old and who underwent PCR testing for COVID-19 concomitant to chest CT were included in the study. Patients under the age of eighteen and not performed PCR testing were excluded from the study. Patients, who were performed thorax CT, were determined from the patients' files. Pulmonary CT angiography examination rates with the suspicion of pulmonary embolism were evaluated. The study was carried out with the permission of Scientific Researches Ethics Committee of Sancaktepe Sehit Prof. Dr. İlhan Varank Education and Research Hospital (Date: 19.09.2020, Decision No: 2020/1). All procedures were performed adhered to the ethical rules, and principles of the Helsinki Declaration.

Samples were taken for PCR test from all patients, who were admitted to our hospital with the suspicion of COVID-19, during the pandemic period. According to the our hospital criteria, thorax CT was performed in the patients with signs of pulmonary involvement or all hospitalized patients due to its high sensitivity and low specificity in the diagnosis of COVID-19 (7). Since thorax CT was not planned without PCR testing from any COVID-19 suspected patient, patients who underwent thorax CT without PCR testing were excluded from the study.

Patients with the diagnosis of COVID-19 were treated according to the treatment algorithms of the Ministry of Health (6). While hydroxychloroquine treatment was started routinely in all patients, low molecular weight heparin was added to the routine treatment since April 12. Before this date, prophylactic thromboprophylaxis was applied to immobile patients, patients with moderate-to-severe respiratory failure and patients necessitating intensive care unit. In patients with severe respiratory distress, low molecular heparin was administered with treatment dose. The data were analyzed in Microsoft Office Excel.

RESULTS

In our hospital, 11,142 thorax CT was performed between March 10 and May 25, 2020. Pulmonary CT angiography was performed in 161 (1.4%) of these patients. PCR test was not requested in 62 of the patients underwent pulmonary CT angiography were not suspected of Covit-19. Pulmonary CT angiography was done in 99 patients with PCR tests due to suspicion of pulmonary embolism. Four of the pulmonary CT angiographies were non-diagnostic. PCR test was positive in 21 (22%) of the remaining 95 patients, and pulmonary embolism was detected in 6 (6.3%) of them (**Figure 1-2**). PCR was negative in 74 (78%) of which 17 (17.9%) had pulmonary embolism.

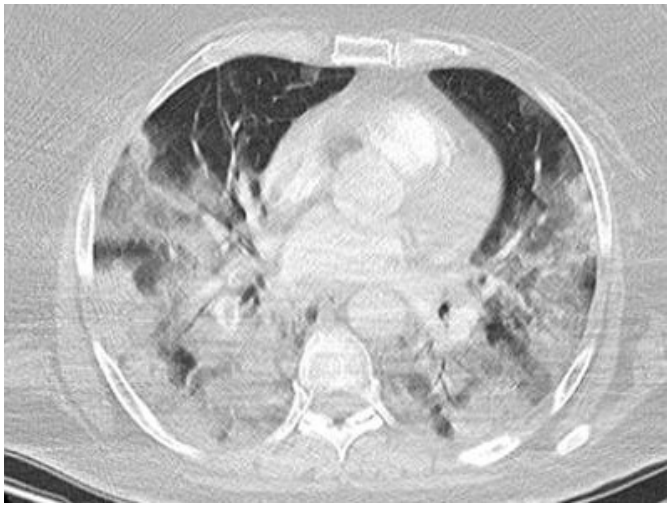


Figure 1. Central and peripheral ground glass opacities and consolidation compatible with COVID-19 pneumonia in thorax CT.

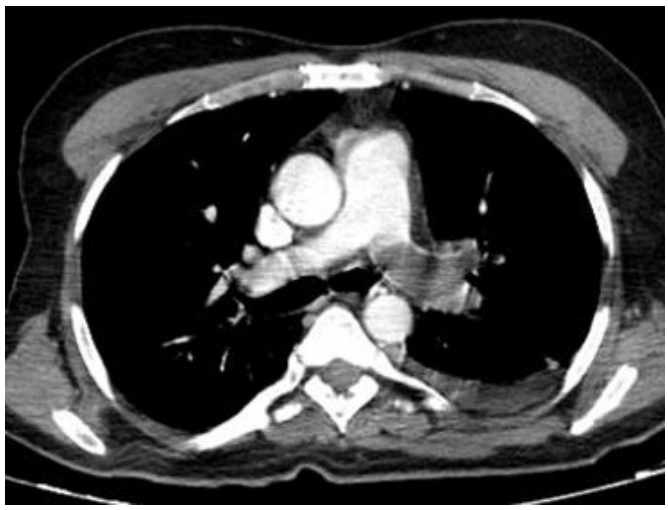


Figure 2. Pulmonary CT angiography of massive pulmonary thrombus in left main pulmonary artery.

Table 1. Results of the pulmonary CT angiography in the hospitalized patients with the diagnosis of COVID-19.

	Positive Pulmonary Embolism in CT Angiography	Negative Pulmonary Embolism in CT Angiography	Total
PCR positive	6	15	21
CT undefined	2	5	7
CT compatible for COVID-19	3	7	10
CT incompatible for COVID-19	1	3	4
PCR negative	17	57	74
CT undefined	3	11	14
CT compatible for COVID-19	10	7	17
CT incompatible for COVID-19	4	39	43
Total	23	72	95

CT: Computerized tomography

DISCUSSION

Routine thrombosis prophylaxis in the treatment of COVID-19 contributes to the clinical course by preventing the development of micro-emboli in the patients. In our hospital, thromboprophylaxis was applied to the patients with COVID-19 depending on the algorithms of the Ministry of Health (6). As a result of routine prophylaxis, pulmonary CT angiography request was found to be quite low due to the suspicion of pulmonary embolism.

COVID-19 might cause arterial and venous thrombosis directly or by causing endothelial damage due to infection, inflammation, immobilization and hypoxia (2-8). The coronovirus might affect many organs, including the lung, heart, vascular system, kidney and intestine through the angiotensin converting enzyme 2 (ACE-2) receptor (2,6,11). COVID-19 activates the renin-angiotensin system (RAS) by binding to ACE-2 receptors. Thus, it increases the tendency to thrombosis by increasing platelet adhesion and aggregation (9). Also, inflammatory cytokines secreted due to the disease might activate the coagulation cascade, causing thrombosis (1). Cytokine storm might play an important role in initiating and promoting thrombosis in arteries and veins (12). Cytokine storm in sepsis might damage monocytes and endothelial cells, causing disseminated intravascular coagulation (DIC) (13). Prevention of cytokine storm might reduce the risk of thrombosis in patients with COVID-19 and alleviate the progression of the disease (12). Thromboprophylaxis with low molecular heparin decrease the risk of embolic events with its anticoagulant effect and might help to decrease the risk of cytokine storm with its anti-inflammatory effect (14).

Acute respiratory distress syndrome (ARDS) is not the only pathology in pulmonary involvement of COVID-19, microvascular thrombosis also plays a role in pathogenesis (2). Complement accumulation in the vascular bed, which is an important feature of many micro thrombotic syndromes such as antiphospholipid antibody syndrome, atypical hemolytic uremic syndrome, purpura fulminant, was also reported in COVID-19. Complement accumulation might be accompanied by septal capillary injury in COVID-19 (14).

Hypercoagulability develops and D-dimer increases in the COVID-19 patients with progressed respiratory infection. Prothrombin time (PT) becomes longer and platelet level decreases as the disease becomes serious. Free thrombin, which is not controlled by natural anticoagulants in circulation, activates platelets and stimulates fibrinolysis. Accordingly, levels of D-Dimer and fibrin degradation products (FDP) increase (13). D-dimer and FDP levels were found significantly elevated in patients who were lost, suggesting a common coagulation activation, irregular thrombin production, impaired natural anticoagulants and fibrinolysis might be effective in the pathogenesis of the disease (15). Early recognition of thrombosis or routine prophylaxis will contribute to improve the clinical outcome of the patients. Thromboprophylaxis in COVID-19 patients is recommended for all hospitalized patients in Turkey country since April with recommendation of scientific committee of Ministry of Health (6). Routine prophylaxis decreases the thrombogenic effect of the virus by preventing deep venous thrombosis and related complications due to immobilization along with microemboli that might develop in the pulmonary system.

In the standard approach to the hospitalized patients, anticoagulant therapy is not routinely recommended for mobile patients. Patients with COVID-19 are at risk for venous thrombosis due to the severity of the infection and immobilization. Risk of venous thrombosis in hospitalized cases with COVID-19 was reported as 40% (8, 17). It has been reported that venous thrombosis was developed in 25% of ICU patients without prophylaxis (1). In the evaluation of 184 patients with COVID-19, thrombosis was detected in 1/3 of intensive care patients despite standard prophylaxis, and segmental or subsegmental pulmonary embolism was found in 80% of venous thrombosis (3).

Anticoagulation to be started early term in COVID-19 patients contributes to prognosis by reducing the risk of micro-thrombus. (11,13). It is suggested that to apply prophylactic anticoagulants to all hospitalized patients with the diagnosis of COVID-19, to perform CT angiography in the patients with suspicion of pulmonary embolism, and to use therapeutic dose of LMWH if CT examination was not possible (2). Thrombophylaxis was applied only to immobile patients, as in other diseases, at the beginning of the fight against COVID-19. Upon the determination of the microthrombosis and microemboli caused by the virus, thromboprophylaxis is recommended to all hospitalized patients in our country since April (6). In Turkey, in the comparison with other European countries, earlier reduction of intensive care unit need, number of hospitalization and COVID-19 patients, might be associated with starting LMWH in all hospitalized patients.

Depending on the risk of transmission and general condition of the patient, the examinations tests to be performed in COVID-19 patients may be restricted. Changes of D-dimer levels might be caused by hypercoagulability or severity of the disease (9). Since the D-dimer levels, which is used for differential diagnosis of thrombosis, might be increased by direct effect of COVID-19, it cannot be used to diagnosis of thrombosis in COVID-19. Therefore, pulmonary CT angiography is appropriate for clinical suspicion of pulmonary embolism. Increasing the anticoagulant dose to the therapeutic dose might prevent progression of the disease in the patients with moderate and severe symptoms. As a result of routine prophylaxis

in our hospital, only 1.4% of our patients required CT angiography with suspicion of pulmonary embolism and only 24% of these patients had pulmonary embolism. Considering that CT angiography was performed only in patients with highly suspicion of pulmonary embolism in order to decrease the risk of transmission during the pandemic period, this rate might be considered as an indication that thromboprophylaxis significantly reduces the risk of pulmonary embolism in COVID-19.

Limitation of the study is data loss due to the nature of the retrospective study. Although LMWH treatment has been routine since April, it was not known how many patients who have undergone CT angiography with the suspicion of pulmonary embolism were used prophylaxis. The cases with pulmonary embolism and severe COVID-19 infection, who were admitted to the emergency department in serious condition and directly transferred to the intensive care unit, might not be diagnosed. However, in the evaluation of the need and results of CT angiography rates, it might be considered that routine prophylaxis with LMWH reduces the clinical suspicion of pulmonary embolism in COVID-19.

CONCLUSION

COVID-19 is a disease, characterized by respiratory system involvement, and severity of the disease is associated with microthrombosis and microembolism in pulmonary artery or other vascular beds. Adding thromboprophylaxis to the treatment of the COVID-19 contributes positively to the clinical course by reducing the risk of venous thrombosis, which might cause pulmonary embolism, and thrombosis that might develop in the pulmonary arteries.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Scientific Researches Ethics Committee of Sancaktepe Sehit Prof. Dr. İlhan Varank Education and Research Hospital (Date: 19.09.2020, Decision No: 2020/1).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 1421-4.
2. Oudkerk M, Büller HR, Kuijpers D, et al. Diagnosis, Prevention, and Treatment of Thromboembolic Complications in COVID-19: Report of the National Institute for Public Health of the Netherlands. Radiology 2020; 297: 216-22.
3. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020; 191: 145-7.
4. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E. Acute pulmonary embolism associated with COVID-19 Pneumonia Detected with Pulmonary CT Angiography. Radiology 2020; 296: E186-E188
5. Whyte MB, Kelly PA, Gonzalez E, Arya R, Roberts LN. Pulmonary embolism in hospitalised patients with COVID-19. Thromb Res 2020; 195: 95-99.
6. COVID-19 (SARS-CoV-2 infection) guide. Science Committee Work. Ministriy of Health, Public Health General Directorate. Ankara, April, 2020.
7. Kuzan TY, Murzoğlu Altıntoprak K, Çiftçi HÖ, et al. A comparison of clinical, laboratory and chest CT findings of laboratory-confirmed and clinically diagnosed COVID-19 patients at first admission. Diagn Interv Radiol. 2020; 10.5152/dir.2020.20270.
8. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art review. J Am Coll Cardiol 2020; 75: 2950-73.
9. Liu X, Li Z, Liu S, et al. Potential therapeutic effects of dipyridamole in the severely ill patients with COVID-19. Acta Pharm Sin B 2020; 10: 1205-15.
10. Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. Intensive Care Med 2020; 46: 586-90.
11. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect 2020; 9: 687-90.
12. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med 2020; 217: e20200652.
13. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-7.
14. Miesbach W, Makris M. COVID-19: Coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost 2020; 26: 1076029620938149.
15. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020; 220: 1-13.
16. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol. 2020; 42: 11-8.
17. Wang T, Chen R, Liu C, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. Lancet Haematol 2020; 7: 362–3.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.888740

Anatolian Curr Med J 2021; 3(3); 192-197

The role of serum red blood cell distribution width level in predicting the short term mortality of community-acguired pneumonia, acute attack chronic pulmonary disease, and acute pulmonary thromboembolism

Semih Aydemir, Derya Hoşgün

Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Department of Intensive Care Unit, Ankara, Turkey

Cite this article as: Aydemir S, Hoşgün D. The role of serum RDW level in predicting the short term mortality of community-acguired pneumonia, acute attack chronic pulmonary disease, and acute pulmonary thromboembolism. Anatolian Curr Med J 2021; 3(3); 192-197.

ABSTRACT

Background: There is a growing concern in inflammatory parameters that are commonly used in routine practice and can be measured cost-effectively for predicting mortality community-acquired pneumonia (CAP), acute-attack chronic obstructive pulmonary disease (COPD), and acute pulmonary thromboembolism (PTE). Red blood cell distribution width (RDW) is a significant parameter indicating the heterogeneity of the size of red blood cells (RBCs). The present study was designed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation, and to investigate the role of RDW in predicting 30-day mortality.

Material and Method: The RDW levels measured on admission in all three groups were evaluated retrospectively.

Results: The 554 patients comprised 320 (57.76%) men and 234 (42.24%) women with a mean age of 67.074±14.73 years. The patients comprised 92 (16.6%) CAP, 265 (47.8%) acute PTE, and 197 (35.6%) acute-attack COPD patients. Mean RDW was 14.42%±2.73% (range, 3.77-28%) while it was 14.88%±3.30% in the CAP group, 13.21%±2.77% in the COPD group, and 15.15%±2.12% in the PTE group. In the COPD, CAP, and PTE groups, RDW levels were significantly higher in patients with 30-day mortality compared to those without mortality ($p=0.008$, $p=0.020$, and $p<0.05$, respectively).

Conclusion: RDW is a practical, inexpensive and automatically reported blood test parameter which can be used along with scoring systems in the prediction of prognosis and ICU requirement and also in the follow-up of patients with diseases that are characterized by persistent inflammation in their pathophysiology.

Keywords: Red blood cell distribution width, community acquired pneumonia, pulmonary thromboembolism

INTRODUCTION

Community-acquired pneumonia (CAP) is an inflammatory disease caused by bacteriologic infection of the lung parenchyma, and pulmonary thromboembolism (PTE) is a disease characterized by clinical manifestations of the blockage of the pulmonary artery (1-3). Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities arising from significant exposure to harmful particles or gases. Acute exacerbations of COPD are diagnosed when specific symptoms including increased sputum volume and dyspnea worsen beyond day-to-day variability. In these diseases, early diagnosis and treatment are of paramount importance for reducing mortality and morbidity. Recently, there is a growing concern in inflammatory parameters that are commonly used in routine practice and can be measured cost-effectively for predicting mortality in CAP, acute PTE, and acute-attack COPD (4).

Red blood cell distribution width (RDW) is a significant parameter indicating the heterogeneity of the size of red blood cells (RBCs) as well as their morphology. RDW is a simple, cost-effective, routinely measured, and automatically reported blood test parameter. RDW elevation has been shown to be associated with the increase in oxidative stress and other inflammatory markers such as C-reactive protein (CRP). Moreover,

Corresponding Author: Derya Hoşgün, deryahosgun@gmail.com

Received: 01.03.2021 **Accepted:** 19.06.2021

in acute PTE, elevated RDW has been associated with mortality and this association has been attributed to acute inflammation and also to alterations in blood viscosity (5). Han et al. (6) evaluated the RDW levels measured on admission and at 24 h after presentation in patients with acute PTE and reported that the group with elevated RDW levels had higher mortality rates. In the CAP requiring hospitalization, RDW levels have been shown to vary significantly among patients and these variations have been associated with prognosis, mortality, and severity of clinical profile. In a retrospective study, the elevated RDW level in CAP was found to be a predictor of intensive care unit (ICU) requirement and mortality (7). Another retrospective study evaluated 442 patients with acute-attack COPD and revealed that increased RDW was independently associated with in-hospital and one-year mortality (8). Another study evaluated a total of 36,532 patients hospitalized in ICU and reported that an elevated RDW level measured on admission was a significant independent risk factor for in-hospital and 4-year mortality (6-9).

The present study was designed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation, and to investigate the role of RDW in predicting 30-day mortality.

MATERIAL AND METHOD

Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ankara Chest Diseases and Chest Surgery Education and Research Hospital (Date:19.12.2019, Decision No:654). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The retrospective study included a total of 554 patients that were hospitalized in our Chest Diseases outpatient clinic and ICU due to CAP, acute-attack COPD or acute PTE within 24 h after admission to emergency service. The 554 patients comprised 92 (16.6%) CAP and 265 (47.8%) PTE patients who were diagnosed and treated based on international guidelines and 197 (35.6%) stable COPD patients who were diagnosed, graded, and treated based on GOLD (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease) guidelines (1-4). Exclusion criteria were as follows: age below 18 years, pregnancy, a diagnosis of diseases other than COPD, PTE, and CAP, history of blood transfusion, intradermal or oral iron, vitamin B12, and folic acid use. The APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of the patients hospitalized in ICU were retrieved from patient records. All the patients included in the study had undergone a complete blood count (CBC) examination within the first 4 h after admission to the clinic or ICU and had been followed up for 30-day mortality. CBC examination was performed photo metrically using a BC-6800 auto analyzer. Normal reference ranges for hemoglobin (HGB), hematocrit (HCT), platelet (PLT) count, and RDW were accepted as 12-16 g/dL, 40-54%,142-424 103/μL, and 11.6-17.2%, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc.; Chicago, IL, USA). Demographic data related to patients and control subjects were expressed as numbers, percentages, median values, and min-max values. Data were presented as mean ± standard deviation (SD) and median (range) for continuous variables and as frequencies (percentiles) for categorical variables. The Shapiro-Wilk test was used to assess the normal distribution of the variables. Nonparametric categorical parameters were analyzed using the Chi-square test, and nonparametric dependent ordinal parameters were analyzed using the Wilcoxon test. Independent nonparametric or parametric values were analyzed using the Mann-Whitney U test or student t test.RDW level affecting the 30-day mortality was determined using logistic regression analyses.ROC curves analysis was used to determine cut-off values in relation to mortality of RDW levels. p value 0.05 was considered statistically significant.

RESULTS

The 554 patients comprised 320 (57.76%) men and 234 (42.24%) women with a mean age of 67.074±14.73years. The patients comprised 92 (16.6%) CAP, 265 (47.8%) acute PTE, and 197 (35.6%) acute-attack COPD patients. Mean age was 69.63±15.44, 71.57±10.54,and 62.79±15.95years in CAP, COPD, and PTE patients, respectively, and no significant difference was found among the three groups with regard to mean age (p=0.831). Of all patients, 133 (24%) patients were hospitalized in ICU and had a mean APACHE II score of 23.79±7.26 (range, 8-44). The median APACHE II score in the CAP group was 29.00 and was significantly higher than the scores in COPD and PTE groups (p<0.001).Thirty-day mortality occurred in 49 (8.84%) patients and the mortality rate in the CAP group (n=36; 6.50%) was significantly higher than that of other groups (p<0.001). **Table 1** presents the demographic characteristics, mortality rates, clinical and ICU hospitalization rates, CURB-65 scores in CAP patients, and GOLD stages in COPD patients.In the CAP group, the 30-day mortality rate increased as the CURB-65 (Confusion Urea Respiratory Rate Blood Pressure-65) score increased (p<0.001). The use of LTOT and NIMV at home and the grading of patients with the new combined GOLD staging had no significant effect on 30-day mortality (p=0.366, p=0.968, and p=0.520, respectively).

Table 1. Demographic and clinical characteristics

	Groups	**Mean±SD**	**Median**
Age (years)	CAP	69.63±15.44	73.00
	Acute-attack COPD	71.57±10.54	71.00
	AcutePTE	62.79±15.95	63.00
	Total	67.07±14.73	69.00
Variables			**n(%)**
Groups	CAP		92 (16.6)
	Acute-attack COPD		197 (35.6)
	AcutePTE		265 (47.8)
	Total		554 (100)
Gender	CAP	Male	55 (59.8)
		Female	37 (40.2)
	Acute-attack COPD	Male	147 (74.6)
		Female	50 (25.4)
	Acute PTE	Male	118 (44.5)
		Female	147 (55.5)
	Total	Male	320 (57.8)
		Female	234 (42.2)
Outpatient hospitalization	CAP		43 (46.7)
	Acute-attack COPD		188 (95.4)
	Acute PTE		190 (71.7)
Comorbidities	CAP		55 (59.7)
	Acute-attack COPD		111 (56.3)
	Acute PTE		70 (26.4)
	Total		236 (42.5)
ICU hospitalization	CAP		49 (53.3)
	Acute-attack COPD		9 (4.6)
	Acute PTE		75 (28.3)
	Total		133 (24)
Mortality	CAP		36 (39.1)
	Acute-attack COPD		5 (2.5)
	Acute PTE		8 (3)
	Total		49 (8.84)
Pneumonia	CURB-65 score	2	22 (23.9)
		3	30 (32.6)
		4	23 (25.0)
		5	17 (18.5)
COPD	GOLD stage	A	33 (16.8)
		B	71 (36.0)
		C	43 (21.8)
		D	50 (25.4)

CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonarythromboembolism, ICU: Intensive care unit, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, GOLD:Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, SD: Standard deviation

Table 2. Red blood cell distribution width levels

Groups	RDW		
	Mean±SD	Median	Min-Max
CAP	14.88±3.30	14.65	10.18-28.00
COPD	13.21±2.77	12.48	3.77-23.10
PTE	15.15±2.12	14.60	9.70-23.50
Total	14.42± 2.73	14.00	3.77-28

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

Table 3. Correlation between GOLD stages, use of LTOT and NIMV and RDW

Variables		**n**	**%**	**RDW (%)**	**p**
GOLD stages	A	33	25	10.86	0.061
			50	11.78	
			75	12.85	
	B	71	25	11.19	
			50	12.49	
			75	14.44	
	C	43	25	12.61	
			50	11.56	
			75	12.61	
	D	50	25	11.76	
			50	12.78	
			75	15.12	
LTOT	Yes	38	25	11.93	0.007
			50	13.43	
			75	15.11	
	No	159	25	11.19	
			50	12.17	
			75	14.44	
NIMV	Yes	17	25	12.05	0.067
			50	13.61	
			75	15.47	
	No	180	25	11.22	
			50	12.24	
			75	14.50	

GOLD: Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, LTOT: Long-term oxygen therapy (LTOT), NIMV: noninvasive mechanical ventilation (NIMV) at home

In the CBC examination performed within the first 4 h after admission, the PLT counts and HGB, HCT levels were normal in 90.8%, 65.16%, and 60.64% patients in the CAP, COPD, and PTE groups, respectively. **Table 2** presents the laboratory parameters of the CAP, COPD and PTE group.RDW was significantly higher in the PTE group compared to other groups (p<0.001). In the CAP group, mortality-associated RDW increased as the CURB-65 score increased (p<0.05). In the COPD group, no significant difference was found between the patients using and not using NIMV at home with regard to RDW (p=0.067), whereas RDW was significantly higher in patients using LTOT at home compared to patients not using it (p=0.007). No significant relationship was found between the new combined GOLD staging and RDW (p=0.061) (**Table 3**).

In the COPD, CAP, and PTE groups, RDW levels were significantly higher in patients with 30-day mortality compared to those without mortality (p=0.008, p=0.020, and p<0.05, respectively) (**Table 4**).When the RDW levels relationship with mortality was evaluated by logistic regression analysis, it was determined that it increased 0.530 times in CAP, 0.731 times in COPD and 0.759 PTE groups (**Table 5**).In the ROC analysis, a RDW value below 15.45 % predicted independent mortality with a sensitivity of 75.5% and specificity of 74.1% (**Table 6**, **Figure 1**).

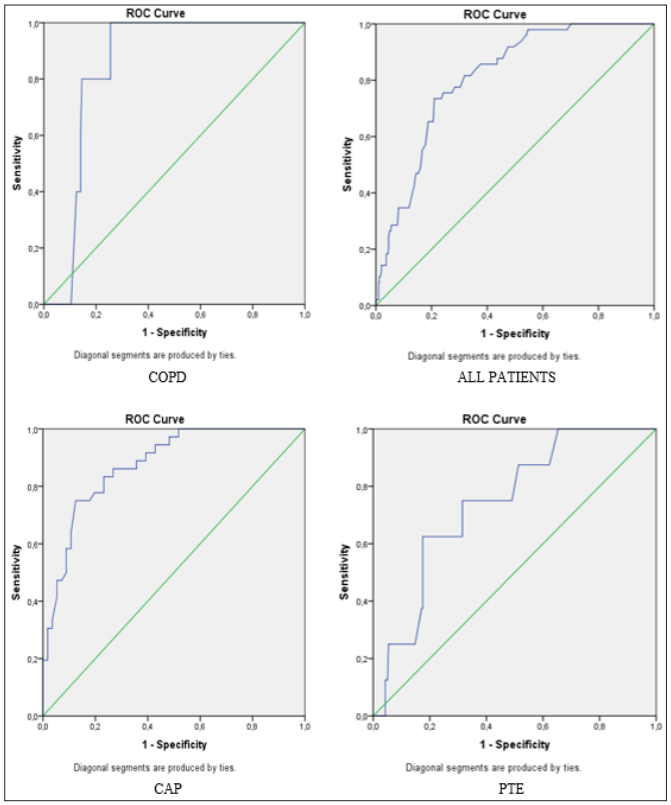


Figure 1. Effect of RDW in predicting 30-day mortality

Table 4. Relationship between RDW and 30-day mortality

Variables			n	%	RDW (%)	p
Acute-attack COPD	Mortality	Yes	5	25 50 75	15.27 16.36 17.00	0.008
		No	192	25 50 75	12.32 11.27 12.32	
Acute PTE	Mortality	Yes	8	25 50 75	14.85 16.80 18.57	0.020
		No	257	25 50 75	13.60 14.60 16.20	
CAP	Mortality	Yes	36	25 50 75	15.47 16.55 19.00	<0.05
		No	56	25 50 75	11.25 12.99 14.95	
Total	Mortality	Yes	49	25 50 75	15.45 16.60 18.95	<0.05
		No	505	25 50 75	12.32 13.80 15.50	

COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism, CAP: Community-acquired pneumonia

DISCUSSION

Community-acquired pneumonia (CAP), acute PTE, and COPD area leading cause of mortality and morbidity in clinical practice of chest diseases. In patients with acute PTE, 1- to 3-month mortality rates range between 5.4-15% and these rates may reach up to 50% in the presence of hypotensive shock (10). Repeated acute exacerbations of COPD lead to reduced lung function as well as repeated hospitalization, and increased mortality and morbidity (11). In-hospital mortality rate has been reported as 6.7% while short-term mortality rates vary between 1.8% and 20.4% (12). In CAP, however, short-term mortality rates vary between 2.4% and 34.6% and may reach up to 30% in patients requiring ICU and in patients with increased CURB-65 scores Scoring systems such as CURB-65 and pneumonia severity index (PSI) are commonly used for assessing disease severity and requirement of hospitalization and ICU admission (13,14). In our study, the overall mortality rate was 8.84% and the CAP group had the highest mortality rate (39.1%) among others. This high rate could be attributed to the high ICU admission rate (53.3%) and the high mean age among our patients. Due to the retrospective nature of our study, only CURB-65 scores were available for our CAP patients. It is commonly known that the severity of CAP increases as the CURB-65 scores increase. In our study, we also found that the mortality rate increased as the CURB-65 scores increased. Nevertheless, the mortality rate in our COPD patients (2.5%) was remarkably lower than those reported in the literature, which could be associated with the lower ICU admission rate in this group as well as the lower prevalence of GOLD C and D stages and the lower rate of patients using LTOT and NIMV at home. However, unlike in other studies, the 30-day mortality in our PTE patients (3%) was remarkably lower than those reported in the literature.

Table 5. Logistic regression analysis and 30-day mortality

	WALD	p	OR	95% CI for EXP(B)	
				Lower	Upper
CAP	22.057	<0.001	0.530	0.406	0.691
COPD	5.074	0.024	0.731	0.557	0.960
PTE	4.131	0.042	0.759	0.582	0.990

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

Table 6. Effect of RDW levels inpredicting 30-day mortality

	AUC	p	95% CI		Cut off	Sensitivity %	Specificity %
CAP	0.885	<0.001	0.819	0.951	15.25	77.8%	76.6%
COPD	0.836	0.010	0.768	0.904	15.00	80.0%	78.8%
PTE	0.746	0.018	0.604	0.887	15.55	75.0%	69.5%
All patients	0.810	0.026	0.759	0.862	15.45	75.5%	74,1%

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

Studies investigating systemic inflammatory diseases have shown elevated RDW levels, which are known to indicate dysregulation of erythrocyte homeostasis and abnormal erythrocyte survival and to occur in response to the underlying mechanism of telomere shortening, oxidative stress, and inflammation (15,16).Recently, there has been a growing interest in the role of RDW in predicting short- and long-term mortality in patients with CAP, acute-attack COPD, acute PTE, and sepsis, all of which have persistent inflammation in their physiopathology (6,17,18). Studies evaluating CAP patients have shown that RDW is associated with the severity of clinical profile and could be an independent risk factor for predicting the prognosis, short-term mortality, and ICU requirement. RDW shows time-dependent variation due to the fact that each RBC circulates for 100-120 days due to in these patients groups, in particular, it has beeb suggested that repeated measurement of RDW durinh hospitalization (7,19,20). A previous study evaluated patients with acute-attack COPD and reported that on-admission RDW levels were significantly higher in patients receiving LTOT and NIMV at home (21). Another study evaluated patients with acute-attack COPD and revealed that increased RDW was a significant independent risk factor for COPD at a cut off value of ≥13.75% (9). Tertemiz et al. (22) revealed that increased RDW levels established a positive correlation with the severity of clinical profile and a negative correlation with pulmonary function tests. A retrospective study evaluated 309 patients with acute PTE and found increased RDW levels in the mortality group.In all the studies abovementioned, the physiology of increased RDW has not been elucidated. Nevertheless, in some studies, this increase has been attributed to neutrophil activation induced by increased oxidative stress in CAP, to intermittent hypoxemia in PTE, and to hypoxemia and reduced lung function in COPD (23,24). In the present study, we aimed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation. The results indicated that the RDW levels were significantly higher in PTE patients compared to other patients (Table 2). The incidence of alterations in blood viscosity and intermittent hypoxemia is higher in acute PTE compared to CAP and acute-attack COPD, which is associated with the physiology of the disease and explains the high mean RDW level. In our COPD patients, RDW was significantly higher in patients using LTOT at home compared to patients not using it (p=0.007) and this finding was considered to be associated with increased erythropoetine secondary to hypoxia and also with oxidative stress (16,21,25). On the other hand, in our study, only a small proportion of our COPD patients (8.6%) were using NIMV at home and no significant difference was found between the patients using and not using NIMV at home with regard to RDW (p=0.067). The absence of a significant difference could be attributed to the fact that patients with hypoxemic or hypercapnic respiratory failure could not be identified since no evaluation could be performed on the arterial blood gas parameters that were measured simultaneously with RDW due to the retrospective nature of our study.In our study, unlike in other studies in the literature, no significant relationship was found between the new combined GOLD staging and RDW in patients with stable COPD (p=0.061). Although the staging procedure was performed in the patients within the last one year, no standardization could be achieved due to the retrospective nature of the study and the absence of standardization was considered to affect the results of the study.

Our study was limited in several ways. First, the study was a single-center and retrospective study. Second, RDW levels were only measured during hospital admission and these measurements were not standardized, baseline RDW levels (i.e. pre-admission levels) were not measured in the patients, and no serial measurement was performed. Third, prediction of mortality was limited to 30 days and no data could be retrieved regarding specific causes of death due to the retrospective nature of the study.

CONCLUSION

Red blood cell distribution width is a practical, inexpensive and automatically reported blood test parameter which can be used along with scoring systems in the prediction of prognosis and ICU requirement and also in the follow-up of patients with diseases that are characterized by persistent inflammation in their pathophysiology.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ankara Chest Diseases and Chest Surgery Education and Research Hospital (Date:19.12.2019, Decision No:654).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Mandell LA, Wunderink RG, Anzuwto A, et al. Infectious Diseases Society of America/America Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44: S27-72.
2. Saar JA, Maack C. Diagnosis and management of acute pulmonary embolism. ESC guidelines 2014. Herz 2015; 40: 1048-54.
3. Konstantinides SV, Meyer G, Becattini C, et al.2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 9: 54.
4. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.
5. Hammons L, Filopel J, Steiger D, Bondarsky E. A narrative review of red blood cell distribution width as a marker for pulmonary embolism. J Thromb Thrombolysis 2019; 48: 638-47.
6. Han YQ, Yan L, Zhang L, et al. Red blood cell distribution width provides additional prognostic value beyond severity scores in adult critical illness. Clin Chim Acta 2019; 498: 62-7.
7. Ge YL, Liu CH, Rana MA, et al. Elevated red blood cell distribution width combined white blood cell in peripheral blood routine have a better sensivity than CURB-65 Scores in Predicting ICU Admission and Mortality in Adult Community-Acguired Pneumonia Patients. Clin Lab 2019; 1: 65.
8. Hu GP, Zhou YM, Wu ZL, et al. Red blood cell distribuiton width is an independent predictor of mortality for an acute exacerbation of COPD. Int J Tuberc Lung Dis 2019; 23: 817-23.
9. Han YQ, Zhang L, Yan L, et al. Red blood cell distribution width predicts long-term outcomes in sepsis patients admitted to the intensive care unit.Clim Chim Acta 2018; 487: 112-6.
10. Zhou XY, Chen HL, Ni SS. Red cell distribution width in predicting 30-day mortality in patients with pulmonary embolism. Journal of Critical Care 2017; 37: 197-201.
11. Park S, Lee SJ, Shin B, et al. The association of delta neutrophil index with the prognosis of acute exacerbation of chronic obstructive pulmonary disease. BMC Pulm Med 2020; 20: 47.
12. Crisafulli E, Manco A, Torres A. How may we improve clinical outcomes for patients hospitalizes with acute exacerabtions of chronic obstructive pulmonary disease? A narrative review about possible therapeutic and preventive strategies.Expert Rev Respir Med 2020; 14: 493-500.
13. Viasus D, Del RP, Simonetti AF, et al. Biomarkers for predicting short-term mortality in community-acguired pneumonia: A systematic review and meta-analysis. J Infect 2016; 72: 273-82.
14. Huang Y, Liu A, Liang L, et al. Diagnostic value of blood parameters for commnutiy-acguired pneumonia. Int Immunopharm 2018; 64: 10-15.
15. Lippi G, Plebani M. Red blood cell distribution width (RDW) and human pathology. One size fits all. Clin Chem Lab Med 2014; 52: 1247-9.
16. Mahmood NA, Mathew J, Kang B, et al. Broadening of the red blood cekk distribution width is associated with increased severity of illness in patients with sepsis. Int J Crit Illn Inj Sci 2014; 4: 278-82.
17. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: A narrative review. Clin Biochem 2010; 77: 1-6.
18. Jiang Y, Jiang FQ, Kong F, et al. Inflammatory anemia-associated parameters are related to 28- day mortality in patients with sepsis admitted to the ICU: a preliminary observational study. Ann Intensive Care 2019; 9: 67.
19. Gorelik O, Izhakian S, Barchel D, et al. Changes in red cell distribution width during hospitalization for community-acguired pneumonia: clinical characteristic and prognostic significance. Lung 2016; 194: 985-95.
20. Orfanu AE, Popescu C, Leuştean A, et al. The Importance of Haemogram Parameters in the Diagnosis and Prognosis of Septic Patients. J Crit Care Med 2017; 3: 105-10.
21. Karampitsakos T, Dimakou K, Papaioannou O, et al. The role of increased red cell distribution width as a negative prognostic marker in patients with COPD. Pulm Pharmacol Ther 2020; 60: 101877.
22. Tertemiz KC, Alpaydın AO, Sevinc C, et al. Could "red cell distribution width" predict COPD severity ?Rev Port Pneumol 2016; 22: 196-201.
23. Grant BJ, Kudalkar DP, Muti P, et al. Relation between lung function and RBC distribution width in a population-based study. Chest 2002; 124: 494-500.
24. Epstein D, Nasser R, Mashiach T, et al. Increased red cell distribution width: A novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. Respir Med 2018; 136: 1-7.
25. Ycas JW, Horrow JC, Horne BD. Persistent increase in red cell size distribution width after acute diseases: A biomarker of hypoxemia? Clin Chim Acta 2015; 448: 107-17.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.890109

Anatolian Curr Med J 2021; 3(3); 198-203

Comparison of hospitalized patients with idiopathic pulmonary fibrosis and obstructive sleep apnea outpatients in terms of general characteristics and polysomnographic features

Bengü Şaylan

[1]Health Sciences University, Sultan 2. Abdulhamid Han Training and Research Hospital, Department of Chest Diseases, Istanbul, Turkey

Cite this article as: Şaylan B. Comparison of hospitalized patients with idiopathic pulmonary fibrosis and obstructive sleep apnea outpatients in terms of general characteristics and polysomnographic features. Anatolian Curr Med J 2021; 3(3); 198-203.

ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a significant comorbidity in patients with idiopathic pulmonary fibrosis (IPF). This study aimed to evaluate the demographic and clinical characteristics of patients with and without IPF, and their polysomnographic features according to the presence and severity of OSA.

Material and Method: A total of 52 cases (29 patients hospitalized for IPF and 23 controls without IPF) admitted to the sleep laboratory with suspicion of OSA were included. Demographic, clinical data and results of polysomnographic studies were recorded from the patients' self-reports and hospital records.

Results: The distribution of sex was similar (p=0.775) between the patient and control groups; however, the patients with IPF were older than the controls (68 vs. 57 years, p=0.003). The rate of current smokers was higher among the controls (p=0.003), whereas dyspnea (p<0.001), headache (p=0.005), congestive heart failure (p=0.013), pulmonary hypertension (p<0.001), number of previous hospitalizations (p<0.001), and dust exposure (p=0.028) were more frequent in the IPF group. The median sleep time with O_2 saturation below 90% was significantly higher in the IPF group (p<0.001). Among overall study population, 40 patients had OSA of whom 10 had mild, 15 had moderate, and 15 had severe OSA.

Conclusions: The co-existence of IPF significantly worsened the polysomnographic features of the patients with OSA. Further studies are needed to clarify the underlying mechanisms and to determine the optimal interventions to increase sleep quality of IPF patients.

Keywords: Idiopathic pulmonary fibrosis, obstructive sleep apnea, polysomnography, severity, hospitalization

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disorder characterized by recurrent collapse of the upper airways during sleep and is seen in about 2-4% of the general population (1) and in about 20% of the elderly (2). The prevalence of OSA is dramatically increased in idiopathic pulmonary fibrosis (IPF), which is the most common type of idiopathic interstitial pneumonia (3). Based on the currently available literature data, about 50-90% of patients with IPF may suffer from OSA (4). It has a progressive course with a poor prognosis; the median survival is approximately three to four years (3). Besides, there is evidence that the severity of OSA is increased in patients with IPF. Previous studies showed that moderate-severe OSA, in which the apnea-hypopnea index is greater than 15 events per hour, was more frequent in IPF patients than that in the individuals without IPF (5,6).

In previous years, professional associations including the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association have declared that OSA is a significant comorbidity for IPF, which has to be treated effectively as a primary goal (5,7,8). Recent studies showed that OSA treatment with continuous positive airway pressure could slow down the progression of IPF (5,9). Nevertheless, despite the accumulating number of studies on the topic, there are still questions yet to be answered, such as whether the exacerbation and hospitalization episodes in IPF affect the severity of OSA. Based on this background, this study aimed to evaluate the demographic and clinical characteristics of patients with and without IPF, and their polysomnographic features according to the presence and severity of OSA.

Corresponding Author: Bengü Şaylan, metebengu@yahoo.com

Received: 03.03.2021 **Accepted:** 23.04.2021

MATERIAL AND METHOD

This study was conducted at the Department of Chest Diseases and Sleep Laboratory of the Sultan 2. Abdulhamid Han Training and Research Hospital, İstanbul, Turkey. The patients who were admitted to the Department of Chest Diseases of our hospital between February and April 2020 due to interstitial lung disease, and who were stable at the time of assessment, were informed about the study. Those who gave consent to participate were included in the study group. Controls were recruited from the patients admitted to the Sleep Laboratory. The ethical committee of the İstanbul Health Sciences University of the Ministry of Health, Ümraniye Training and Research Hospital approved the study protocol (Date: 22/01/2020, Decision No: B.10.1.TKH.4.34.H.GP.0.01/8).

Polysomnographic studies were done with a 32 channel Medcare Embla A device. Electroencephalography, electrooculography, submental and bilateral tibial electromyography, and electrocardiographic recording were taken during polysomnographic sleep recordings. Airflow was measured using a nasal and oral thermistor, thoracoabdominal motion was measured with a piezoelectric belt, and saturation was measured using a pulse oximetry device. Sleep stages, desaturation, and apnea-hypopnea index (AHI) were calculated in polysomnography. The patients with an AHI ≥5 per hour were diagnosed with OSA syndrome. The severity of OSA were defined as mild (AHI ≥5 but <15 per hour), moderate (AHI ≥15 but <30 per hour), and severe (AHI ≥30 per hour).

Demographic and clinical characteristics were recorded from the patient records and hospital database management system. Clinical data included disease-related characteristics, comorbidities, OSA parameters, and sleep test measurements. Sleep tests for the patients with IPF were done after discharge and in the stable phase of IPF.

Statistical Analysis

Descriptive statistics were presented as number and percentage for categorical variables and median, minimum and maximum for continuous variables. Comparisons between independent groups were made using the Chi-square test for categorical data (Fisher's exact test when assumptions were not met) and the Kruskal-Wallis/Mann-Whitney U test for more than two/two groups for continuous data. Post-hoc analyses between independent groups were done with the Mann-Whitney U test with Bonferroni correction for numerical variables. All analyses were performed using PASW 18 (IBM Inc., Chicago, IL, USA), and a type-I error level of 5% was considered the statistical significance threshold.

RESULTS

A total of 52 cases; 29 patients with IPF and 23 controls were included in the study. About one-third of the patients were females in each group (p=0.775). The median age of the patients was higher than the controls (68 vs. 57 years, p=0.003). Comparisons of demographic characteristics revealed that the median BMI (p=0.007) and rate of smokers (p=0.003) were higher in the control group, whereas dyspnea (p<0.001), headache (p=0.005), congestive heart failure (p=0.013), pulmonary hypertension (p<0.001), number of previous hospitalizations (p<0.001) and dust exposure (p=0.028) were more frequent in the patients with IPF (**Table 1**).

Table 1. Demographic characteristics of the study groups

	Controls (n=23)	IPF (n=29)	p
Sex, n (%)			**0.775**
Male	15 (65.2)	20 (69.0)	
Female	8 (34.8)	9 (31.0)	
Age, years, median (min-max)	57 (47-75)	68 (42-91)	0.003
BMI, kg/m², median (min-max)	28 (24-32)	27 (22-32)	0.007
Smoking, n (%)			
Current smoker	8 (34.8)	0 (0.0)	0.003
Ex-smoker	8 (34.8)	17 (58.6)	0.087
Dyspnea, n (%)	6 (26.1)	27 (93.1)	<0.001
Headache, n (%)	4 (17.4)	16 (55.2)	0.005
Comorbidities, n (%)			
Coronary artery disease	2 (8.7)	9 (31)	0.086
Atrial fibrillation/ Arrhythmia	3 (13)	3 (10.3)	1.000
Hypertension	9 (39.1)	19 (65.5)	0.058
Diabetes	8 (34.8)	8 (27.6)	0.577
Reflux	6 (26.1)	15 (51.7)	0.061
Congestive heart failure	0 (0.0)	7 (24.1)	0.013
Rheumatoid disease	0 (0.0)	5 (17.2)	0.059
Pulmonary hypertension	1 (4.3)	22 (75.9)	<0.001
Hospitalization in intensive care unit, n (%)	0 (0.0)	1 (3.4)	-
Disease duration, years, median (min-max)	-	2 (1-12)	-
Number of previous hospitalizations, median (min-max)	0 (0-3)	2 (0-8)	<0.001
Dust exposure, n (%)	2 (8.7)	10 (34.5)	0.028
Diagnosis, n (%)			-
Radiological	-	20 (69.0)	
Pathological	-	9 (31.0)	

IPF: Idiopathic pulmonary fibrosis; Q1-Q3: 25th percentile-75th percentile

When the polysomnographic parameters were compared between patients and controls, the median sleep time with O_2 saturation below 90% (20 (0-90) vs. 2 (0-15); p<0.001) was significantly higher in the IPF group. However, the median sleep saturation (93 (92-96) vs. 90 (81-95); p<0.001), the median lowest O_2 saturation (87 (69-92) vs. 80 (8-90); p=0.023), and the median awake O_2 saturation (95 (93-97) vs. 83 (86-96); p<0.001) were higher in the control group (**Table 2**).

Table 2. Polysomnographic features of the study groups

	Controls (n=23)	IPF (n=29)	p
OSA, n (%)	15 (65.2)	25 (86.2)	0.074
Mild	4 (26.7)	6 (24.0)	0.518
Moderate	4 (26.7)	11 (44.0)	
Severe	7 (46.7)	8 (32.0)	
Apnea-hypopnea index, median (min-max)	11 (2-42)	20 (3-38)	0.433
Normal, n (%)	8 (34.8)	4 (13.8)	0.487
Mild, n (%)	4 (17.4)	6 (20.7)	
Moderate, n (%)	4 (17.4)	10 (34.5)	
Severe, n (%)	7 (30.4)	9 (31)	
Obstructive apnea index, median (min-max)	15 (1-150)	18 (2-126)	0.411
Normal, n (%)	10 (43.5)	6 (20.7)	0.077
High, n (%)	13 (56.5)	23 (79.3)	
Periodic leg movement index, median (min-max)	14 (2-52)	9 (2-81)	0.306
Normal, n (%)	14 (60.9)	20 (69)	0.542
High, n (%)	9 (39.1)	9 (31)	
Oxygen use at home, n (%)	-	6 (20.7)	-
Total sleep time, min, n (%)	290 (200-380)	265 (200-360)	0.337
Hypopnea index, median (min-max)	8 (1-32)	15 (1-32)	0.256
Oxygen desaturation index, %, median (min-max)	7 (1-36)	14 (2-33)	0.305
Sleep saturation, %, median (min-max)	93 (92-96)	90 (81-95)	<0.001
Lowest O_2 saturation, %, median (min-max)	87 (69-92)	80 (8-90)	0.023
Sleep time with saturation below 90%, min, median (min-max)	2 (0-15)	20 (0-90)	<0.001
Awake O_2 saturation, %, median (min-max)	95 (93-97)	93 (86-96)	<0.001

AHI: Apnea-hypopnea index; IPF: Idiopathic pulmonary fibrosis; OSA: Obstructive sleep apnea; Min-Max: Minimum-maximum

Among the whole group, 40 patients had OSA, and regarding disease severity, 10 patients had mild, 15 patients had moderate, and 15 patients had severe OSA. **Table 3** summarizes the comparison of basal demographic characteristics between patients with and without OSA and mild-moderate-severe OSA patients. All baseline characteristics were similar according to the presence and severity of OSA. Comparison of polysomnographic features according to the severity of OSA showed a gradual worsening parallel to disease severity except for sleep saturation (p=0.239) and awake O_2 saturation (p=0.268; **Table 4**).

DISCUSSION

Sleep breathing disorders, particularly OSA, possess a significant comorbidity burden for patients with IPF (10). Identifying differences regarding OSA in patients with and without IPF may provide valuable information for determining effective interventions that may improve patients' quality of life and daily living activities (5). This study showed that the polysomnographic parameters that were significantly deteriorated among patients with IPF were sleep saturation, and awake and asleep oxygen saturations. Significant decrease in O_2 saturation, increase in sleep time with O_2 saturation below 90%, and lower awake O_2 saturation are expected results, as all these parameters are associated with the pathophysiology of IPF. Besides decreases in sleep saturation, these parameters indicate a deteriorated quality of sleep and poor quality of life (11) in IPF.

Moreover, OSA is not an essential component for altered sleep quality in patients with IPF since they suffer from nocturnal hypoxia due to decreased lung volume, particularly in the supine position in sleep (12). Nocturnal hypoxia or impaired O_2 saturation both in sleep and awake periods, are associated with the physiological changes in IPF. Still, OSA might also be related to these changes. Although no causative association was clearly shown between these two conditions, it was suggested that they might share common pathways. Previous studies reported that OSA might be a cause of subclinical lung injury through inspiratory resistive loads and forced inspirations against a closed glottis that cause decreased interstitial pressure, alveolar deformation, and proinflammatory capillary responses (13-16).

Polysomnographic features of patients in OSA severity categories were consistent with the grade of OSA. However, periodic leg movement index, total sleep time, sleep saturation, and awake O_2 saturations were not associated with the disease severity in OSA. Among these, similar awake O_2 saturations might be expected since patients with OSA may suffer from daytime fatigue or sleepiness but not decreased saturations. Nevertheless, previous studies reported that periodic leg movements and total sleep time were valuable predictors of disease severity in OSA. Periodic leg movements are involuntary, repetitive, stereotypical, and segmental movements, which may be present in approximately 6% of the general population and 65% of the older adults over 65 years (17,18). Periodic leg movements may also accompany sleep disorders, including OSA (19). Previous studies showed that periodic leg movement in patients with OSA was associated with the disease severity and indicated a more risky subgroup of patients (20). Nevertheless, our results did not support this conclusion, and the periodic leg movement index was similar between OSA severity categories in our study.

Table 3. Characteristics of patients according to the presence and severity of obstructive sleep apnea

	Presence of OSA			OSA severity			
	OSA- (n=12)	OSA+ (n=40)	p	Mild (n=10)	Moderate (n=15)	Severe (n=15)	p
Sex, n (%)							
Male	6 (50.0)	29 (72.5)	0.173	6 (60.0)	11 (73.3)	12 (80.0)	0.597
Female	6 (50.0)	11 (27.5)		4 (40.0)	4 (26.7)	3 (20.0)	
Age, years, median (min-max)	57 (42-83)	63 (43-91)	0.110	59 (43-91)	67 (47-81)	63 (49-89)	0.527
BMI, kg/m², median (min-max)	27 (22-30)	27 (22-32)	0.921	28 (22-32)	26 (23-30)	28 (22-32)	0.205
Smoking, n (%)							
Current smoker	2 (28.6)	6 (30.0)	1.000	3 (75.0)	1 (11.1)	2 (28.6)	-
Ex-smoker	5 (41.7)	20 (50.0)	0.612	6 (60.0)	6 (40.0)	8 (53.3)	0.587
Disease duration, years, median (min-max)	2 (1-4)	2 (1-12)	0.425	4 (1-5)	2 (1-12)	2 (1-4)	0.371
Previous hospitalization, n (%)	4 (33.3)	25 (62.5)	0.102	6 (60.0)	11 (73.3)	8 (53.3)	0.591
Previous "clinical" hospitalization, median (min-max)	0 (0-4)	2 (0-8)	0.033	1.5 (0-6)	2 (0-6)	2 (0-8)	0.616
Hospitalization in intensive care unit, n (%)	0 (0.0)	1 (2.5)	-	0 (0.0)	1 (6.7)	0 (0.0)	1.000
Dyspnea, n (%)	4 (33.3)	29 (72.5)	0.019	7 (70.0)	12 (80.0)	10 (66.7)	0.749
Headache, n (%)	3 (25.0)	17 (42.5)	0.330	4 (40.0)	7 (46.7)	6 (40.0)	0.918
Comorbidities, n (%)							
Coronary artery disease	1 (8.3)	10 (25.0)	0.421	0 (0.0)	5 (33.3)	5 (33.3)	0.161
Atrial fibrillation/Arrhythmia	0 (0.0)	6 (15.0)	0.316	2 (20.0)	2 (13.3)	2 (13.3)	1.000
Hypertension	5 (41.7)	23 (57.5)	0.510	5 (50.0)	10 (66.7)	8 (53.3)	0.653
Diabetes	1 (8.3)	15 (37.5)	0.078	4 (40.0)	6 (40.0)	5 (33.3)	0.915
Gastroesophageal reflux disease	4 (33.3)	17 (42.5)	0.741	3 (30.0)	7 (46.7)	7 (46.7)	0.653
Congestive heart failure	0 (0.0)	7 (17.5)	0.181	0 (0.0)	4 (26.7)	3 (20)	0.244
Rheumatoid disease	0 (0.0)	5 (12.5)	0.578	3 (30.0)	2 (13.3)	0 (0.0)	-
Pulmonary hypertension	2 (16.7)	21 (52.5)	0.046	4 (40.0)	9 (60.0)	8 (53.3)	0.616
Dust exposure, n (%)	0 (0.0)	12 (30.0)	0.047	2 (20.0)	5 (33.3)	5 (33.3)	0.829
Diagnosis, n (%)			0.076				0.307
Radiological	1 (25.0)	19 (76.0)		6 (100.0)	7 (63.6)	6 (75.0)	
Pathological	3 (75.0)	6 (24.0)		0 (0.0)	4 (36.4)	2 (25.0)	

BMI, Body mass index; OSA: Obstructive sleep apnea; Min-Max: Minimum-maximum

Table 4. Polysomnographic characteristics according to the presence and severity of obstructive sleep apnea

	Presence of OSA			OSA Severity			
	OSA- (n=12)	OSA+ (n=40)	p	Mild (n=10)	Moderate (n=15)	Severe (n=15)	p
AHI, median (Q1-Q3)	3 (2-4)	22 (6-42)	<0.001	8 (6-11)	20 (15-30)	35 (31-42)	<0.001
Normal, n (%)	12 (100)	0 (0.0)	<0.001	0 (0.0)	0 (0.0)	0 (0.0)	-
Mild, n (%)	0 (0.0)	10 (25.0)		10 (100.0)	0 (0.0)	0 (0.0)	
Moderate, n (%)	0 (0.0)	14 (35.0)		0 (0.0)	14 (93.3)	0 (0.0)	
Severe, n (%)	0 (0.0)	16 (40.0)		0 (0.0)	1 (6.7)	15 (100.0)	
Obstructive apnea index, median (min-max)	2 (1-4)	24 (2-150)	<0.001	6 (2-20)	22 (5-126)	40 (15-150)	<0.001
Normal, n (%)	12 (100.0)	4 (10.0)	<0.001	4 (40.0)	0 (0.0)	0 (0.0)	-
High, n (%)	0 (0.0)	36 (90.0)		6 (60.0)	15 (100.0)	15 (100.0)	
Periodic leg movement index, median (min-max)	14 (2-30)	9.5 (2-81)	0.974	9 (2-81)	7 (2-48)	12 (2.1-52)	0.773
Normal, n (%)	8 (66.7)	26 (65.0)	1.000	7 (70.0)	11 (73.3)	8 (53.3)	0.481
High, n (%)	4 (33.3)	14 (35.0)		3 (30.0)	4 (26.7)	7 (46.7)	
Oxygen use at home, n (%)	0 (0.0)	6 (24.0)	-	0 (0.0)	4 (36.4)	2 (25.0)	-
Total sleep time, min, median (min-max)	265 (200-380)	273 (200-380)	0.695	283 (200-360)	266 (245-380)	280 (210-360)	0.696
Hypopnea index, median (min-max)	2.5 (1-4)	16 (3-32)	<0.001	6.5 (3-20)	16 (10-22)	21 (8-32)	<0.001
Oxygen desaturation index, median (min-max)	2 (1-5)	17 (3-36)	<0.001	6 (3-8)	16 (5-25)	25 (12-36)	<0.001
Average sleep saturation, %, median (min-max)	93 (90-96)	92 (81-95)	0.024	93 (83-95)	91 (81-95)	90 (82-95)	0.239
Lowest O2 saturation, %, median (Q1-Q3)	90 (85-92)	81 (8-90)	<0.001	88 (77-90)	83 (8-88)	78 (67-87)	0.004
Sleep time with saturation below 90%, min, median (min-max)	1 (0-8)	11 (0-90)	<0.001	3 (0-80)	15 (3-90)	20 (2-90)	0.029
Awake O2 saturation, %, median (min-max)	95 (92-97)	94 (86-96)	0.004	95 (90-96)	93 (89-95)	94 (86-95)	0.268

AHI: Apnea-hypopnea index; OSA: Obstructive sleep apnea; Min-Max: Minimum-maximum

Likewise, total sleep time was also suggested to be associated with the disease severity in OSA. This conclusion was based on the association of total sleep time with the high-sensitivity C-reactive protein, a significant indicator of chronic intermittent hypoxia in patients with OSA. Multivariate analyses showed that total sleep time was a stronger predictor of high-sensitivity C-reactive protein variability than the apnea-hypopnea index, which is the gold-standard indicator of OSA severity (21). Our results were contrary to this evidence, in which the total sleep time was not associated with OSA severity. This might be related to patient selection for the analysis because the OSA group included patients both with and without IPF, which may alleviate the importance of total sleep time to predict OSA's severity.

CONCLUSION

Idiopathic pulmonary fibrosis is a chronic debilitating disease with poor prognosis and a significantly deteriorated quality of life. Patients with IPF and comorbid OSA are at increased risk of severe disease outcomes. OSA is known to impair the quality of life, and this study showed that the co-existing IPF significantly worsens polysomnographic features in these patients. Further comparison studies that includes increased number of patients and healthy individuals are needed. These studies may help to clarify the mechanisms that additively deteriorate these pathways and to determine the optimal interventions to increase sleep quality and subsequent quality of life of IPF patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethical committee of the İstanbul Health Sciences University of the Ministry of Health, Ümraniye Training and Research Hospital approved the study protocol (Date: 22/01/2020, Decision No: B.10.1.TKH.4.34.H.GP.0.01/8).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Ther Adv Chronic Dis 2015; 6: 273-85.
2. Hiestand DM, Britz P, Goldman M, Phillips B. Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005 poll. Chest 2006; 130: 780-6.
3. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018; 198: e44-e68.
4. Schiza SE, Bouloukaki I, Bolaki M, Antoniou KM. Obstructive sleep apnea in pulmonary fibrosis. Curr Opin Pulm Med 2020; 26: 443-8.
5. Mermigkis C, Bouloukaki I, Antoniou K, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath 2015; 19: 385-91.
6. Gille T, Didier M, Boubaya M, et al. Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis. Eur Respir J 2017; 49: 1601934.
7. King C, Nathan SD. Identification and treatment of comorbidities in idiopathic pulmonary fibrosis and other fibrotic lung diseases. Curr Opin Pulm Med 2013; 19: 466-73.
8. Mermigkis C, Bouloukaki I, Antoniou K, et al. Obstructive sleep apnea should be treated in patients with idiopathic pulmonary fibrosis. Sleep Breath 2015; 19: 385-91.
9. Gille T, Didier M, Boubaya M, et al., Natural history of idiopathic pulmonary fibrosis (IPF) associated with obstructive sleep apnea (OSA) with or without continuous positive airway pressure (CPAP), in Idiopathic interstitial pneumonias. Eur Respir J 2018 52: PA2911.
10. Bosi M, Milioli G, Fanfulla F, et al. OSA and prolonged oxygen desaturation during sleep are strong predictors of poor outcome in IPF. Lung 2017; 195: 643-51.
11. Mermigkis C, Bouloukaki I, Schiza SE. Sleep as a new target for improving outcomes in idiopathic pulmonary fibrosis. Chest 2017; 152: 1327-38.
12. Tudorache V, Traila D, Marc M, et al. Impact of moderate to severe obstructive sleep apnea on the cognition in idiopathic pulmonary fibrosis. PLoS One 2019; 14: e0211455.
13. Lederer DJ, Jelic S, Bhattacharya J, Basner RC. Is obstructive sleep apnea a cause of idiopathic pulmonary fibrosis? Arch Pathol Lab Med 2012; 136: 470.
14. Toumpanakis D, Kastis GA, Zacharatos P, et al. Inspiratory resistive breathing induces acute lung injury. Am J Respir Crit Care Med 2010; 182: 1129-36.
15. Ichimura H, Parthasarathi K, Quadri S, Issekutz AC, Bhattacharya J. Mechano-oxidative coupling by mitochondria induces proinflammatory responses in lung venular capillaries. J Clin Invest 2003; 111: 691-9.
16. Glucksberg MR, Bhattacharya J. Effect of alveolar and pleural pressures on interstitial pressures in isolated dog lungs. J Appl Physiol (1985) 1991; 70: 914-8.
17. Al-Alawi A, Mulgrew A, Tench E, Ryan CF. Prevalence, risk factors and impact on daytime sleepiness and hypertension of periodic leg movements with arousals in patients with obstructive sleep apnea. J Clin Sleep Med 2006; 2: 281-7.
18. Bixler EO, Kales A, Vela-Bueno A, Jacoby JA, Scarone S, Soldatos CR. Nocturnal myoclonus and nocturnal myoclonic activity in the normal population. Res Commun Chem Pathol Pharmacol 1982; 36: 129-40.

19. Hornyak M, Feige B, Riemann D, Voderholzer U. Periodic leg movements in sleep and periodic limb movement disorder: prevalence, clinical significance and treatment. Sleep Med Rev 2006; 10: 169-77.

20. Yalın OÖ, Yılmaz İA, Sungur MA, Doğu O. Obstructive sleep apnea syndrome, periodic limb movements and related factors. Turk J Neurol 2015; 21: 90-4.

21. Zhang XB, Zen HQ, Lin QC, Chen GP, Chen LD, Chen H. TST, as a polysomnographic variable, is superior to the apnea hypopnea index for evaluating intermittent hypoxia in severe obstructive sleep apnea. Eur Arch Otorhinolaryngol 2014; 271: 2745-50.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.909312

Anatolian Curr Med J 2021; 3(3); 204-207

Comparison of lesion level and ischemic modified albumin in peripheral artery disease

Cihan Yücel[1], Serkan Ketenciler[1], Aslıhan Tenekecigil[2], Hüseyin Gemalmaz[1], Sevgi Özcan[3], Nihan Kayalar[1]

[1]Prof. Dr. Cemil Taşçıoğlu City Hospital, Department of Cardiovascular Surgery, İstanbul, Turkey
[2]Bağcılar Training and Research Hospital, İstanbul, Turkey
[3]Bağcılar Training and Research Hospital, Department of cardiology, İstanbul, Turkey

Cite this article as: Yücel C, Ketenciler S, Tenekecigil A, Gemalmaz H, Özcan S, Kayalar N. Comparison of lesion level and ischemic modified albumin in peripheral artery disease. Anatolian Curr Med J 2021; 3(3); 204-207.

ABSTRACT

Aim: Research is ongoing to discover biomarkers that can be used to monitor disease progression and predict prognosis in peripheral artery disease (PAD). Ischemia-modified albumin (IMA) is known to predict the risk for PAD. The aim of this study was to investigate whether serum IMA levels were associated with PAD lesions and ankle-brachial index (ABI) values, and to determine the accuracy of IMA levels in predicting PAD prognosis.

Material and Method: Seventy-three patients with PAD who applied to our hospital between July and September 2018 were included in the study. The lesion levels of patients with an ankle-brachial index (ABI) value lower than or equal to 0.9 were determined by computed tomography angiography (CTA). Patients were grouped according to their lesion levels and Fontaine classification. Serum IMA concentrations were measured and compared with regard to lesion levels and ABI values.

Results: Sixty-five of the patients (89%) were male. The mean age of the patients was 62.2±8.8 (43–77) years. The mean serum IMA level was 25.9±26.7 (10–218) ng/ml. Serum IMA levels were found to be lower in patients with bilateral iliac artery lesions (p=0.040). There was no statistically significant relationship between other parameters and serum IMA levels (p >0.05 for all).

Conclusion: There is a need for biomarkers that can predict lesion level and prognosis in patients with PAD. Although no statistically significant relationship was found between lesion level and serum IMA concentrations in this study, further studies involving a higher number of patients may provide more informative data on this subject.

Keywords: Ischemia-modified albumin, peripheral artery disease, ankle-brachial index

INTRODUCTION

Since there is no specific laboratory test for the diagnosis of peripheral artery disease (PAD), imaging techniques remain the only option for diagnosis. Advanced imaging techniques, such as magnetic resonance imaging angiography, computed tomography angiography (CTA) or digital subtraction angiography can be used in the diagnosis of PAD (1).

Ankle-brachial index (ABI) is used in the clinical follow-up of the patients with PAD. ABI measurements have a sensitivity of 95% and a specificity of 99% in patients with angiography-diagnosed PAD, as determined by ABI values lower than or equal to 0.9 which are diagnostic for PAD (reference range: 1.0-1.3) (2). Nevertheless, studies continue to reveal biomarkers that can be used to monitor treatment and predict prognosis in PAD. One of these markers is ischemia-modified albumin (IMA), which is has also been shown to be associated with risk for ischemia, oxidative stress and cardiovascular diseases (3,4). Besides ABI, IMA may be helpful to predict the risk for PAD and could be used in the early diagnosis of PAD (4). Various studies have reported that high serum IMA levels were found in patients with PAD (5,6).

The aim of this study is to investigate IMA concentrations in PAD and its association with PAD lesion level and ABI value. We also sought to assess whether IMA concentrations could predict PAD prognosis.

MATERIAL AND METHOD

Seventy-three patients with PAD who applied to our hospital between July and September 2018 were included in the study. The study was carried out with the permission of Clinical Researches Ethics Committee

Corresponding Author: Cihan Yücel, cihanyucell@hotmail.com

Received: 05.04.2021 **Accepted:** 17.06.2021

of Okmeydanı Training and Research Hospital (Date: 19.06.2018, Decision No: 48670771-514.10). Informed consent was obtained from all patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients with a history of angina pectoris, myocardial infarction or heart failure within the last six months were excluded from the study. None of the patients included in the study had a history of ischemic stroke, transient ischemic attack, coronary artery spasm, or renal failure.

The ABI values of all patients were measured. The lesion levels of the patients with an ankle-brachial index (ABI) value of ≤0.9 was determined by computed tomography angiography (CTA). The patients were grouped according to the Fontaine classification and also lesion levels. Three groups were formed with regard to lesion levels: iliac artery, knee joint and below the knee. In addition, multiple lesions were assessed with regard to their localization (only a single site, two of the defined sites, or three sites), as well as their unilateral or bilateral presence.

Peripheral blood samples of the patients were taken into biochemistry tubes and centrifuged to obtain serum. The serum IMA levels were made with Albumin Cobalt Binding Test. This test is based on the colorimetric measurement of the colored complex formed by dithiothreitol (DTT) and free cobalt (the remaining amount that has not been bound to albumin due to the presence of IMA) (7). The materials used were as follows: cobalt chloride (0.1%), DTT (1.5 mg/ml) and NaCl (0.9%) solutions, glass tubes, a vortex, an adjustable automatic Eppendorf pipette, disposable plastic micro cuvettes and a spectrophotometer. After adding 50 µl of cobalt chloride (0.1%) to 200 µl patient serum, it was vortexed and incubated for 10 minutes to allow albumin-cobalt binding to occur. Then, 50 µl DTT (1.5 mg/mL) was added and incubated for 2 minutes. After the incubation, the reaction was quenched by adding 1 mL of NaCl (0.9%) to the mixture. Distilled water was used instead of DTT for the sample blank. The differences between the absorbance values of patient samples and sample blank read at 470 nm in the spectrophotometer were recorded as serum IMA levels.

The Statistical Package for the Social Sciences (SPSS, IBM, version 20.0) program was used for the analysis of all data. Sociodemographic characteristics of the study groups were presented in descriptive statistical expressions such as, number, percentage and standard deviation. Quantitative data were described with mean, standard deviation and minimum and maximum values. The compliance of quantitative data to normal distribution was determined by the Shapiro-Wilk test. The Mann-Whitney U test and Spearman's correlation coefficient were used for the analyses.

RESULTS

Eight of the patients (11%) were female, and 65 (89%) were male. The mean age of the patients was 62.2±8.8 (43–77) years. Forty-three (58.9%) had comorbid diabetes mellitus. The distribution of demographic characteristics and history of the study groups are presented in **Table 1**.

The present study investigated the relationship between PAD lesion level and serum IMA level. No significant correlation was found between patients' medical histories, demographic or clinical characteristics and serum IMA levels (p>0.05 for all) (**Table 2**).

The mean serum IMA levels of the patients were 25.9±26.7 (10–218) ng/ml. Serum IMA levels were found to be lower in patients with bilateral iliac artery lesions (p=0.040). There was no statistically significant relationship between serum IMA concentrations and ABI values, Fontaine classification (p>0.05 for each) (**Table 3**).

Table 1. Preoperative data of patients

Age (years)	62.2±8.8	43-77
Variable	**n**	**% of total**
Sex		
Male	65	89
Female	8	11
Hypertension	28	38.4
Smoking	59	80.8
Diabetes mellitus	43	58.9
Coronary Artery Disease	29	39.7
Concomitant CABG	8	11
COPD	3	4.1
Hyperlipidemia	19	26
Carotid stenosis	2	2.7

COPD: Chronic obstructive pulmonary disease, CABG: Coronary artery bypass graft

DISCUSSION

High serum IMA levels were found in patients with PAD (5). However, to our knowledge, there are no studies investigating the relationship between PAD lesion level and IMA concentration in the literature. The presence of diffuse lesions in patients with PAD is an indicator of poor prognosis (8).

In a study by Özkan et al. (8), severe ischemia was not observed in patients with iliac artery involvement, whereas severe foot ischemia was observed in patients with below-knee vascular lesions. This result may suggest that ischemia is relatively mild when artery stenosis is anatomically superior, possibly due to the presence of better collateral perfusion in this area. Further studies involving more patients are needed to reach a definitive conclusion on this subject.

Table 2. Distribution of IMA values of the study group according to some variables

	n(%)	Mean IMA(ng/ml)	p
Age (years)			
<65yıl	38 (52.1)	29±36	1.110
>65yıl	35 (47.9)	23±7	0.267
Sex			
Male	65 (89.0)	26±28	0.118
Female	8 (11)	27±10	1.563
Hypertension	28 (38.4)	29±38	0.901
Smoking	59 (80.9)	26±29	0.492
Diabetes mellitus	43 (58.9)	22±8	0.766
Coronary Artery Disease	29 (39.7)	21±7	0.401
Concomitant CABG	8 (11)	22±8	0.839
COPD	3 (4.1)	23±9	0.824
Hyperlipidemia	19 (26)	21±7	0.458
Carotid stenosis	2 (2.7)	16±5	0.129
Iliac artery stenosis (right)	9 (12.3)	19±5	0.182
Iliac artery stenosis (left)	13 (17.8)	28±30	0.449
SFA (right)	27 (37)	22±8	0.775
SFA (left)	32 (43.8)	30±35	0.103
BTK(right)	3 (4.1)	21±4	0.865
BTK(left)	4 (5.5)	22±3	0.861
Only unilateral BTK	7 (9.6)	22±8	0.822
Only bilateral BTK	4 (5.5)	22±3	0.842
Only unilateral iliac artery	8 (11)	34±37	0.578
Only bilateral iliac artery	4 (5.5)	16±3	0.040
Only unilateral SFA	19 (26)	33±46	0.669
Only bilateral SFA	5 (6.8)	20±5	0.824
Iliac artery and SFA	4 (5.5)	22±5	0.752
Iliac artery and BTK	1 (1.4)	12	0.137
SFA and BTK	21 (28.8)	24±8	0.534
Single level lesion	47 (64.4)	28±33	0.708
Lesion on two levels	26 (35.6)	23±8	0.708
Bilateral lesion	24 (32.9)	22±8	0.842
Unilateral lesion	49 (67.1)	28±32	0.842

COPD: Chronic obstructive pulmonary disease, CABG: Coronary artery bypass graft , SFA:Superficial femoral artery, BTK: Below the knee,, IMA: Ischemia-modified albumin

Table 3. Comparison of walking distance, ABI values and IMA values

	IMA	
	r	p
Walking distance	-0.103	0.386
ABI	-0.081	0.498

ABI: Ankle-brachial index , IMA : Ischemia-modified albumin

In this study, patients with iliac artery lesions, those with above-knee and those with below-knee vascular lesions were grouped separately. There was no statistically significant relationship between vascular lesion levels and IMA concentrations (p>0.05 for all). However, the serum IMA levels of patients with bilateral iliac artery lesions were found to be significantly lower (p=0.040). This result may indicate that skeletal muscle ischemia is relatively mild in patients with isolated proximal stenosis, which could again be associated with greater collateral perfusion in this area.

When early diagnosis is not made and appropriate care is not provided, patients with PAD may develop ischemia that ultimately leads to limb amputation and increased morbidity and mortality.

It has recently been reported that the atherosclerotic process in the lower extremities in PAD is not only limited to causing vascular stenosis, but also affects microvascular endothelial cell activity and metabolism along with skeletal muscle microvascular flow reservoir (9). Microvascular endothelial cell activity and skeletal muscle microvascular flow were found to be reduced significantly in patients with PAD in both upper and lower extremities (10,11). The pathophysiological explanation of the relationship between PAD and IMA is that the decrease in lower extremity perfusion and oxygenation in patients with PAD causes microvascular dysfunction and triggers albumin modification.

Transformation of albumin to IMA due to ischemic effects results in decreased binding capacity of cobalt, copper and nickel to the N-terminal region of albumin. Therefore, the change in IMA level in the presence of ischemia has been investigated frequently in recent years.

Various studies reported that serum IMA levels increased in patients with pulmonary embolism, those that underwent cardiopulmonary resuscitation and arthroscopic knee surgery, and subjects with various conditions, including end stage renal disease, cerebrovascular ischemia, acute mesenteric ischemia, systemic sclerosis, post-exercise skeletal muscle ischemia, diabetes mellitus, liver diseases and PAD (5,6).

Zimmerman et al. (12) stated that the response to ischemia in PAD is associated with the affected muscle mass, and a potent systemic response occurs only when there is proximal involvement affecting the entire extremity. In another study, it was found that serum IMA levels in patients with PAD decreased temporarily after exercise and returned to baseline levels within one hour (13).

Debashis et al. (13) found a relationship between post-exercise skeletal muscle ischemia severity and IMA concentration, but stated that ischemia should develop acutely in order to alter IMA concentration. The lack of correlation between ABI values and IMA levels in the present study may be due to the absence of acute ischemia in these patients (p>0.05).

CONCLUSION

The presence of diffuse lesions in patients with PAD is an indicator of poor prognosis. In order to predict the prognosis of these patients, there is a need for biomarkers besides results obtained with radiological techniques. Although no statistically significant relationship was

found between lesion level and serum IMA level in this study, we believe that more comprehensive further studies may provide more informative data on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of Okmeydanı Training and Research Hospital (Date: 19.06.2018, Decision No: 48670771-514.10).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCE

1. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006; 113: e463-e654.
2. Karabay Ö, Karaçelik M, Yılık L, et al. Ischemic peripheral arterial disease: A screening survey. Türk Göğüs Kalp Damar Cerr Derg 2012; 20: 450-7.
3. Küçükşen S, Toker A, Küçük A, et al. Evaluation of ischemia modified albumin levels and carotid intima media thickness in patients with systemic lupus eythematosus. Eur J Basic Med Sci 2014; 4: 77-82.
4. Ma SG, Wei CL, Hong B, Yu WN. Ischemia-modified albumin in type 2 diabetic patients with and without peripheral arterial disease. Clinics 2011; 66: 1677-80.
5. Sbarouni E, Georgiadou P, Voudris V. Ischemia modified albumin changes - review and clinical implications. Clin Chem Lab Med 2011; 49: 177-84
6. Piwowar A, Knapik-Kordecka M, Warwas M. Ischemia-modified albumin level in type 2 diabetes mellitus-Preliminary report. Dis Markers 2008; 24: 311-7.
7. Bar-Or D, Curtis G, Rao N, Bampos N, Lau E. Characterization of the Co2+ and Ni2+ binding amino-acid residues of the N-terminus of human albumin. Eur J Biochem 2001; 268: 42-8.
8. Ozkan U, Oguzkurt L, Tercan F. Atherosclerotic risk factors and segmental distribution in symptomatic peripheral artery disease. J Vasc Interv Radiol 2009; 20: 437
9. Diehm C, Kareem S, Lawall H. Epidemiology of peripheral arterial disease. Vasa. 2004; 33: 183-9
10. Cooke JP, Wilson AM. Biomarkers of peripheral arterial disease. J Am Coll Cardiol 2010; 55: 2017–23.
11. Bragadeesh T, Sari I, Pascotto M, Micari A, Kaul S, Lindner JR. Detection of peripheral vascular stenosis by assessing skeletal muscle flow reserve. J Am Coll Cardiol 2005; 45: 780–5.
12. Zimmerman BJ, Granger DN. Mechanisms of reperfusion injury. Am J Med Sci 1994; 307: 284-92.
13. Roy D, Quiles J, Sharma R, et al. Ischemia-modified albumin concentrations in patients with peripheral vascular disease and exercise-induced skeletal muscle ischemia. Clin Chem 2004; 50: 1656-60.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.915839

Anatolian Curr Med J 2021; 3(3); 208-213

The level of C-erbB-2 in patients with esophageal and gastric cancers

Serkan Cerrah[1], Salim Başol Tekin[2]

[1]Health Sciences University, Erzurum Regional Training and Research Hospital, Department of Gastroenterology, Erzurum, Turkey
[2] Ataturk University, Depertment of Medical Oncology, Erzurum, Turkey

Cite this article as: Cerrah Si Tekin SB. The level of C-erbB-2 in patients with esophageal and gastric cancers. Anatolian Curr Med J 2021; 3(3); 208-213.

ABSTRACT

Aim: In this study, we aimed to reveal the prevalence of c-erbB-2 expression in patients with gastric and esophageal cancers in the Eastern Anatolia Region and their relationships with pathologic parameters.

Material and Method: A total of 50 patients, 25 esophageal cancer and 25 gastric cancer patients, who were diagnosed and operated in three clinics at Atatürk University, School of Medicine (Internal Medicine, General Surgery, and Thoracic Surgery) between 2000-2007, were retrospectively included in the study. The parameters belonging to these cases, such as histologic type, differentiation degree, tumor invasion depth, and lymph node metastasis, were extracted from the pathology reports. We obtained the preparations from pathology laboratory archives and reexamined them. Those suitable for immunohistochemical stain were selected from the paraffin block archive and undergone to immunohistochemical process.

Results: We detected c-erbB-2 positivity in 6 (24%) of 25 patients with esophageal cancer and 7 (%28) of 25 patients with gastric cancer. The relationships between c-erbB-2 expression scores and the selected parameters were evaluated using the Chi-square test. Ultimately, we found no significant relationships between c-erbB-2 positivity and differentiation degree (p=0.447), tumor invasion depth (p=0.067), and lymph node metastasis (p=0.461). Despite no statistical relationships, esophageal cancer cases with positive c-erbB-2 displayed noticeable features, such as lymph node involvement and well-differentiated tumors. In the cases with gastric cancer, there were no statistical relationships between c-erbB-2 positivity and the WHO classification (p=0.748), the Lauren classification (p=0.373), lymph node metastasis (p=0.629), tumor invasion depth (p=0.262), and differentiation degree (p=0.083). However, by the WHO classification, lymph node involvement and tubularity were noticeable features of all cases with c-erbB-2 positivity.

Conclusion: Larger and further studies are needed to more clearly observe the effect of C-erbB-2 expression on clinicopathological outcomes in gastric and esophageal cancers.

Keywords: C-erbB-2, gastric cancer, esophageal cancer

INTRODUCTION

Esophageal cancer is a disease that shows late symptoms and spreads rapidly throughout the esophagus. It is often difficult to be diagnosed early, and patients, unfortunately, apply to a physician late (1,2). There are regional differences in esophageal cancer incidences; it is more prevalent in regions with low socioeconomic levels. Esophageal cancer is seen at a rate of 1.5% -2% among all cancer types and 7% among gastrointestinal cancers. It is frequently encountered in Iran, China, South Africa, the USA, Ceylon, Normandy, Britain, and the Eastern Anatolia Region in Turkey (3,4). Tobacco and alcohol use, nitrosamines, zinc and molybdenum deficiencies, achalasia, tylosis characterized by hyperkeratosis of the palms and soles, caustic strictures, Plummer Winson's syndrome, and human papillomavirus play a role in the etiology of esophageal squamous cell cancer. Among the risk factors of esophageal adenocarcinoma are gastroesophageal reflux and Barrett's esophagus (3,5).

On the other hand, stomach cancer is one of the most prevalent cancers; its incidence varies geographically. It is rather prevalent in Japan, Chile, Finland, Costa Rica, Colombia, Portugal, Russia, and Bulgaria. Western Europe, New Zealand, and Australia are the countries where it is less prevalent. Ranking first among gastrointestinal cancers in Turkey, it is placed fourth among all cancers. According to the Ministry of Health's latest statistics, stomach cancer ranks first in males and

Corresponding Author: Serkan Cerrah, drserkancerrah@hotmail.com

Received: 27.04.2021 **Accepted:** 04.06.2021

second in females in Erzurum (4). Among the reasons triggering gastric cancer development are environmental, genetic, and familial factors as well as helicobacter pylori and nutritional habits (6,8).

So far, many laboratory methods have been investigated in terms of etiology, early diagnosis, prognosis, and follow-up in gastric and esophageal cancers. However, no marker that can be used to determine the diagnosis, follow-up, and prognosis specific for these cancers has yet been identified (9,10). C-erbB-2 (HER-2/neu) is a protooncogene encoding a transmembrane glycoprotein with 185 kDa molecular weight and 1255 amino acids, mapped on chromosome 17q21. Studies generally suggest that gastric cancer patients showing c-erbB-2 overexpression have a lower survival rate compared to patients who do not and that c-erB-2 overexpression is a poor prognostic factor (11,12). In some studies performed with patients with esophageal adenocarcinoma, c-erbB-2 overexpression was suggested to be associated with poor prognosis (13). In another study carried out with esophageal squamous cell cancer patients, c-erB-2 positivity was presented to be a new prognostic factor (14).

Through an immunohistochemical study, we aimed to reveal the frequency of c-erbB-2 expression in esophagus and stomach cancers, which are frequently seen in Erzurum and its nearby regions, and its relationships with pathological parameters. Also, we evaluated its effectiveness as a prognostic factor.

MATERIAL AND METHOD

For the study, we obtained ethical approval from the Ethics Committee of School of Medicine, Atatürk University (Dated 12.15.2006; Session No: 8; Decision No: 40). A total of 50 patients (25 esophageal cancer and 25 gastric cancer patients), who were diagnosed and operated in three clinics at the School of Medicine, Atatürk University (Internal Medicine, General Surgery, and Thoracic Surgery) between 2000-2007, were retrospectively included in the study. We evaluated the demographic information and surgery findings from the case files. We extracted the data, such as histological type and differentiation degree, tumor invasion depth, lymph node metastasis, and presence of distant metastasis, from the pathology reports. We reexamined the ready-made preparations obtained from the preparation archive of the pathology laboratory. They were reclassified and rechecked by the WHO and Lauren classifications, and the results were confirmed. Preparations belonging to the cases were reexamined. Immunohistochemical examinations of those suitable for immunohistochemical staining were performed in the immunopathology unit of the Department of Pathology, School of Medicine, Atatürk University. We used 5-micrometer sections prepared from paraffin blocks for the immunohistochemical study.

We did the evaluation of the immunohistochemically applied c-erbB-2 antibody staining by examining the hematoxylin-Eosin-stained ready-made preparation and the c-erbB-2-stained preparation of each material together. Then, we evaluated positive staining for C-erbB-2 by precise membranous staining. Cytoplasmic staining was evaluated as negative immunoreactivity. While evaluating staining, we considered examining all tumor areas in the section. Membranous staining acuity was assessed by weak or intense complete membranous staining.

Accordingly, no staining in all of the tumoral areas was considered immunoreactivity negative (-) for c-erbB-2. The immunoreactivity for c-erbB-2 was considered +1 (positive) when there was a weak or intense complete membranous immunoreactivity in less than 10% of all tumor-containing areas or a partial (incomplete) immunoreactivity in more than 10% of the areas. When there was weak and complete membranous staining in more than 10% of all tumoral areas, the immunoreactivity was deemed +2 (positive) for c-erbB-2. Finally, immunoreactivity for c-erbB-2 was evaluated as +3 (positive), when more than 10% of all tumoral areas had severe and complete membranous staining.

Statistical Analysis

Data on patients with esophageal and gastric cancers are presented in separate **Table 1** and **Table 2**. The relationships between c-erbB-2 expression scores and the selected parameters were evaluated using the Chi-square test. The cases with non-significant but remarkable results were also recorded. In all statistical analyses, the level of significance was accepted as 0.05.

RESULTS

The mean age of the cases with esophageal cancer was 54.1±12.7 (16-82) years. Among the cases, 16 (64%) were males and 9 (36%) were females. Neighboring tissues and distant metastases were not detected in any of the patients included in the study. It was found that 6 cases (24%) had no lymph node metastasis of the tumor (stage N0), while 19 cases (76%) had lymph node metastasis (stage N1) (**Table 1**). Ultimately, we found no significant relationships between c-erbB-2 positivity and differentiation degree (p=0.447), tumor invasion depth (p=0.067), and lymph node metastasis (p=0.461) (**Table 1**). Although there was no relationship between differentiation degree and the intensity of c-erbB-2 antibody staining, +2 and +3 (positive immunoreactivity)

staining were seen only in well-differentiated tumors. Besides, c-erbB-2 positive immunoreactivity was seen only in cases with lymph node involvement despite no significant relationships. According to the intensity of staining assessed based on the membranous properties of the immunohistochemically applied c-erbB-2 antibody in the cases diagnosed with esophageal squamous cell carcinoma, 16 cases (64%) were scored as 0 (negative), 3 cases (12%) as +1 (negative), 5 cases (20%) as +2 (positive), and 1 case (4%) as +3 (positive) (**Figures 1**-**4**).

The mean age of patients with gastric cancer was 60±7.19 (50-77) years. Eighteen (72%) of the cases were males and 7 (28%) were females. Of tumors, 6 (24%) were corpus-located, 9 (36%) were antrum-located, 6 (24%) were cardia-located, 2 (8%) were corpus+cardia-located, and 2 (8%) were corpus+antrum-located. By the Lauren classification, 2 of the patients (8%) were with diffuse-type cancer, 19 (76%) were with intestinal-type cancer, and 4 (16%) were with mixed-type cancer. According to the WHO classification, 22 (88%) cases were tubular and 3 (12%) cases were considered as mucinous type as histopathological type. Distant metastasis was not detected in any of the patients included in the study. Subtotal removal was performed in 6 (24%) patients, and total gastrectomy was performed in 19 (76%) patients. According to the intensity of staining assessed based on the membranous properties of the immunohistochemically applied c-erbB-2 antibody in the cases diagnosed with gastric adenocarcinoma, 15 cases (60%) were scored as 0 (negative), 3 cases (12%) as +1 (negative), 2 cases (8%) as +2 (positive), and 5 cases (10%) as +3 (positive) (**Figures 5-8**).

We could not reach significant relationships between c-erbB-2 positivity and differentiation degree (p= 0.083), tumor invasion depth (p=0.262), lymph node metastasis (p=0.629), the Lauren classification (p= 0.373), and the WHO classification (p=0.748). There was also no significant relationship between histopathological subtype and c-erbB-2 antibody staining intensity. However, +2 and + 3 (positive immunoreactivity) staining were seen only in tubular-type cancers by the WHO classification and only in intestinal-type cancers by the Lauren classification. Although there were no statistically significant relationships, c-erbB-2 positive immunoreactivity was found only in cases with lymph node involvement.

Table 1. The relationships between C-erbB-2 staining intensity and pathological parameters in cases with esophageal cancer

Pathological parameters	Groups	Number of cases	%	C-erbB-2 staining intensity, number of cases, and percentages								p value
				-	%	1+	%	2+	%	3 +	%	
Differentiation degree	Poor	1	4	1	4	0	0	0	0	0	0	0.447
	Moderate	13	52	10	40	2	8	1	4	0	0	
	Good	11	44	5	20	1	4	4	16	1	4	
Tumor invasion depth	T1	4	16	4	16	0	0	0	0	0	0	0.067
	T2	7	28	4	16	2	8	1	4	0	0	
	T3	14	56	8	32	1	4	4	16	1	4	
	T4	0	0	0	0	0	0	0	0	0	0	
Lymph node metastasis	None	6	24	3	12	2	8	1	4	0	0	0.461
	Present	19	76	13	52	1	4	4	16	1	4	

Table 2. The relationships between C-erbB-2 staining intensity and pathological parameters in cases with gastric cancer

Pathological parameters	Groups	Number of Cases	%	C-erbB-2 staining intensity, number of cases, and percentages								p value
				-	%	1+	%	2+	%	3 +	%	
Differentiation degree	Poor	11	44	6	24	2	8	1	4	2	8	0.083
	Moderate	8	32	6	24	0	0	0	0	2	8	
	Good	6	24	3	12	1	4	1	4	1	4	
Tumor invasion depth	T1	5	20	5	20	0	0	0	0	0	0	0.262
	T2	3	12	1	4	0	0	1	4	1	4	
	T3	17	68	9	36	3	12	1	4	3	12	
	T4	0	0	0	0	0	0	0	0	0	0	
Lymph node metastasis	None	2	8	2	8	0	0	0	0	0	0	0.629
	Present	23	92	12	48	3	12	2	8	8	5	
Lauren classification	Diffuse	2	8	1	4	1	4	0	0	0	0	0.373
	Intestinal	19	76	10	40	2	8	2	8	5	20	
	Mix	4	16	4	16	0	0	0	0	0	0	

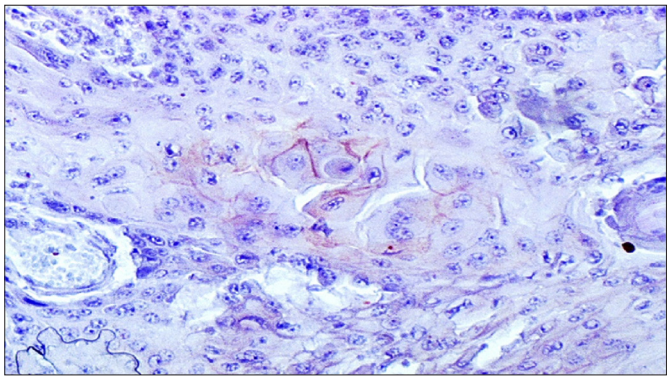


Figure 1. Negative immunoreactivity in the esophageal tumor area for C-erbB-2; Score 0 (x100)

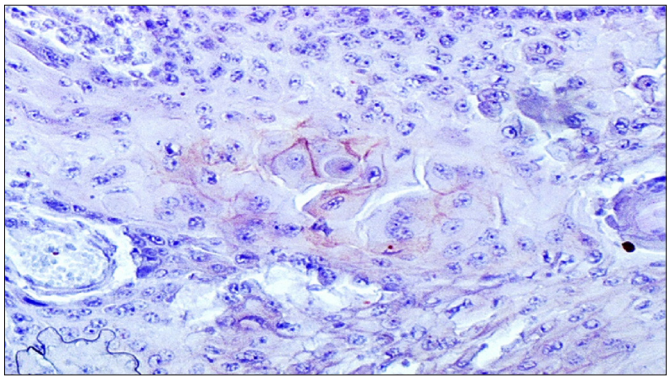


Figure 2. Incomplete membranous staining of more than 10% of the esophageal tumor area for C-erbB-2; Score 1 (x200)

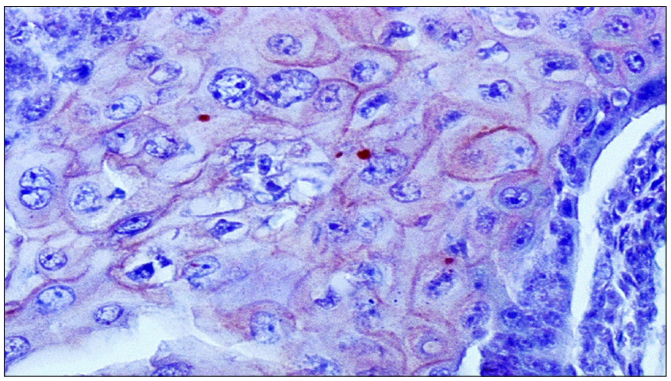


Figure 3. Weak complete membranous staining of more than 10% of the esophageal tumor area for C-erbB-2; Score 2 (x200)

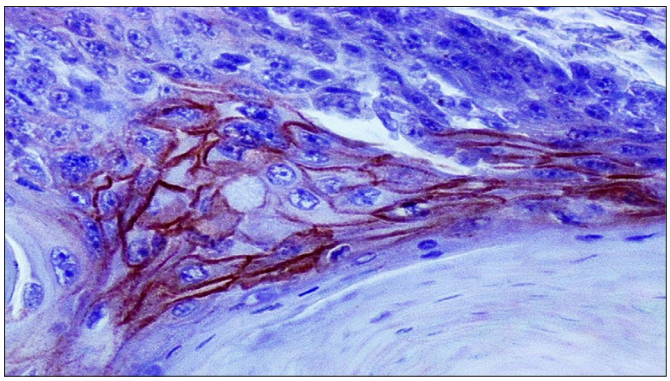


Figure 4. Intense complete membranous staining of more than 10% of the esophageal tumor area for C-erbB-2; Score 3 (x200)

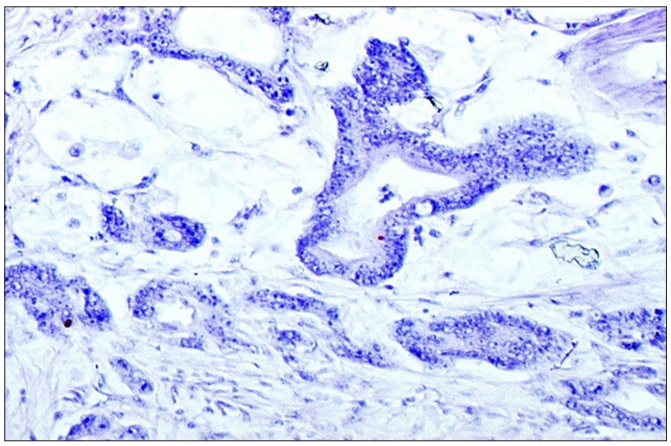


Figure 5. Negative immunoreactivity in the gastric tumor area for C-erbB-2; Score 0 (x100)

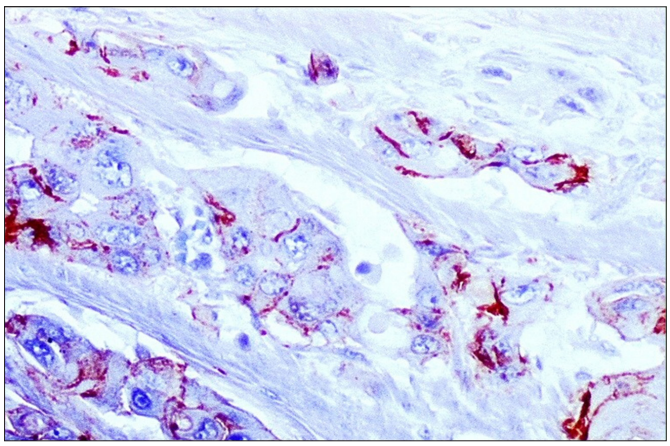


Figure 6. Incomplete membranous staining of more than 10% of the gastric tumor area for C-erbB-2; Score 1 (x200)

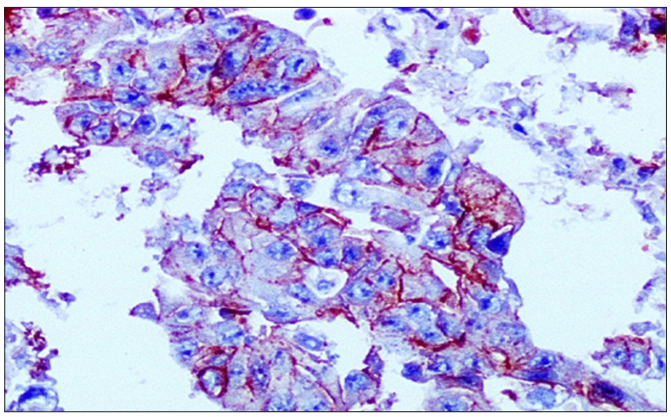


Figure 7. Weak complete membranous staining of more than 10% of the gastric tumor area for C-erbB-2; Score 2 (x200)

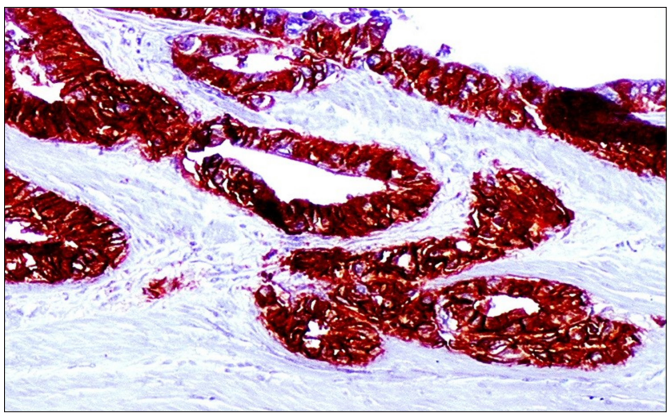


Figure 8. Intense complete membranous staining of more than 10% of the gastric tumor area for C-erbB-2; Score 3 (x200)

DISCUSSION

C-erbB-2 overexpression was previously found to be associated with the stage and tumor grade in prostatic adenocarcinoma cases (15). In lung adenocarcinoma cases, the researchers also determined that patients with CerbB-2 overexpression had shorter survival compared to those not expressing this protein (16). C-erbB-2 overexpression and gene amplitude were discovered to be linked with poor prognosis in breast cancer patients (17). It was reported that C-erbB-2 overexpression occurred in 25-30% of breast carcinomas and that it was expressed at higher rates in ductal carcinoma in situ, especially in those with less differentiation, hormone receptor-negative, lymph node-positive, and increased proliferation (18). C-erbB-2 overexpression varied in immunohistochemical studies performed in esophageal cancers. Studies indicated that this rate ranged from 0% to 60%. In our study, we detected that c-erbB-2 expression rates in gastric and esophageal cancers were similar to in breast cancer cases. In the study, we could not reach significant relationships between the intensity of c-erbB-2 staining and differentiation degree, lymph node involvement, and tumor invasion depth in gastric and esophageal cancers. C-erbB-2 positivity was found to be 24% in 25 cases with esophageal cancer. Possible reasons for obtaining different results in terms of C-erbB-2 positivity may depend on tumor histology, methodological differences, immunohistochemical methods, and tumor stages. The reason why other studies found the frequency of c-erbB-2 overexpression up to 60% may be due to the fact that cytoplasmic staining was also accepted as positive in these studies. However, cytoplasmic staining is accepted as non-specific in the contemporary c-erbB-2 scoring system, routinely used in breast carcinomas. In their immunohistochemical study, Lam et al. (22) investigated patients with esophageal squamous cell carcinoma retrospectively and found that c-erbB-2 overexpression was positive in 10 patients (10%). Moreover, tumors with c-erbB-2 overexpression were found to be superficially well-differentiated tumors, and, therefore, it was concluded that c-erbB-2 overexpression was not associated with the biological behavior of the tumor. It was also suggested that c-erbB-2 overexpression might play an important role in identifying early-stage tumors.

The stage is an essential prognostic factor in esophageal cancer and provides the basis for treatment decisions. Studies comparing c-erbB-2 expression with TNM staging and other prognostic parameters have varied results. Sauter et al. (23) suggested that c-erbB-2 overexpression might disappear in the normal epithelium during tumor development in patients with esophageal adenocarcinoma. In a retrospective study with 62 cases, Dursun et al. (24) found c-erbB-2 positivity in 11 (17.7%) cases. In the study, c-erbB-2 positivity was found as 24.3% in intestinal-type carcinomas and 4.76% in diffuse-type carcinomas. In the same study, c-erbB-2 positivity was found in one of 9 (11.1%) early-stage gastric cancer cases and 10 (18.8%) of 53 advanced gastric cancer cases. In this study, we found no significant relationships between c-erbB-2 positivity and tumor invasion depth, lymph node metastasis, and tumor location, which led us to conclude that c-erbB-2 was not a prognostic marker.

We could also found no significant relationships between the c-erbB-2 staining intensity scores (0, +1, +2, +3) and tumor invasion depth, lymph node metastasis, and the histopathological subtype. Despite the insignificant findings, all cases with c-erbB-2 positivity had lymph node involvement. The different results in other studies may have stemmed from different evaluations of immunohistochemical staining, sample differences, variations in the number of early and advanced gastric cancer cases, and the use of archive paraffin blocks. Tanner et al. (25) conducted a study, where 131 cases of gastric cancer and 100 cases with gastroesophageal junction tumors were included, and determined that there was c-erbB-2 positivity in 16 (12.2%) of gastric cancer patients and 24 (24%) of gastroesophageal junction tumors. They also found that c-erbB-2 positivity in gastric cancer cases was 21.5% in intestinal-type tumors and 2% in diffuse and mixed-type tumors. In the same study, cases with c-erbB-2 overexpression were shown to be associated with lower survival rates. In another study conducted to determine the frequency of c-erbB-2 expression in patients who underwent gastrectomy for gastric cancer, it was reported that c-erbB-2 expression could be used to differentiate a patient group who would benefit from targeted treatment approaches (26).

The limitations of our study are that it was conducted with few patients and the relationship between C-erbB-2 results and clinical data has not been researched.

CONCLUSION

In conclusion, larger and further studies are needed to more clearly observe the effect of C-erbB-2 expression on clinicopathological outcomes in gastric and esophageal cancers.

ETHICAL DECLARATIONS

Ethics Committee Approval: For the study, we obtained ethical approval from the Ethics Committee of School of Medicine, Atatürk University (Date: 12.15.2006, Session No: 8; Decision No: 40).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma I: a critical review of surgery. Br J Surg 1980; 67: 381-90.
2. King RM, Pairolero PC, Trastek VF. Ivor Lewis esophagastrectomy for carcinoma of the esophagus: early and late functional results. Ann Thorac Surg 1987; 44: 119-22.
3. Klumpp T, Macdonald JS, Esophageal cancer: epidemiology and pathology. In Ahlgreen J, Macdonald J. (ed)s. Gastrointestinal Oncology. Philadelphia: JB Lippincott Company 1992; 71-80.
4. Kanserle Savaş Politikası ve Kanser Verileri (1995-1999), T.C Sağlık Bakanlığı Kanserle Savaş Dairesi Başkanlığı, Ankara 2002: 12-6.
5. Peters JH, De Meester TR, Essophagus and dipragmatic hernia. Ed: Schwartz Sl, Shires TG, Spencer FC, et al. Principles of Surgery. 7th ed. McGraw-Hill, 1999:1081-180.
6. Becker KF, Keller G, Hoefler. The use of molecular biology in diagnosis and prognosis of gastric cancer. Surg Oncol 2000; 9: 5-11.
7. Truszkowski JA, Summers RW. Colorectal Neoplasms. Postgraduate Med 1996; 98: 20-5.
8. Başaran N.Tıbbi Genetik. Eskişehir, Bilim Teknik Yayınevi 1196: 357-68.
9. Sherman CD. Klinik Onkoloji. Türk Kanser Araştırma ve Savaş Kurumu yayınları, Ankara 1190: 3-9.
10. AOO Chan, SK Lam, KM Chu, et al. Soluble Ecadherin is a valid prognostic marker in gastric carcinoma. Gut 2001; 48: 808-11.
11. David N L, Klaus JL. Malignant: adenocarcinoma, stomach. In: Weidner N, Cote RJ, Suster S, Weiss LM, (ed)s. Modern Surgical Pathology Fist ed. Saunders; 2003: 672-80.
12. Yonemura Y, Ninomiya I, Yamaguchi A. Evalution of immünreactivity for c-erbB-2 protein as a marker of poor short term prognosis in gastric cancer. Cancer Res 1991; 51: 1034-8.
13. Flejou JF, Paraf F, Muzeau F, et al. Expression of c-erbB-2 oncogene product in Barrett's adenocarcinoma: Pathological and prognostic correlations. J Clin Pathol 1994; 47: 23-6.
14. Ueda M. New prognostic factors in patients with esophageal squamaus carcinoma. Gan To Kagaku Ryoho 1992; 19: 20-5.
15. Ross JS, Sheean C, Hayner Buchan AM, et al. HER-2/neu gene amplication status in prostate cancer by flourescence insutu hybridization. Hum Pathol 1997; 28: 827-33.
16. Kern JA, Schwartz DA, Nordberg JE. P185/neu expression in human lung adenocarcinomas predicts shortened survival. Cancer Res 1990; 50: 5184-9.
17. Ross JS, Fletcher JA. C-erbB-2 gene and protein in breast cancer. Am J Clin Pathol 1999; 112: 53-7.
18. Yarden Y. Biology of HER2 and it's importance in breast cancer. Oncology 2001; 61: 1-13.
19. Yoshida K, Kuniyasu H, Yasui W, et al. Expression of growth factors and their receptors in human esophageal carcinomas: Regulation of expression by epidermal growth factor and transforming growth factor alpha. J Cancer Res Clin Oncol 1993; 119: 401–7.
20. Dreilich M, Wanders A, Brattstrom D. HER-2 overexpression (3+) in patients with squamous cell esophageal carcinoma correlates with poorer survival. Dis Esophagus 2006;19: 224–31.
21. Suo Z, Su W, Holm R. Lack of expression of c-erbB-2 oncoprotein in human esophageal squamous cell carcinomas. Anticancer Res 1995; 15: 2797–8.
22. Lam KY, Tin L, Ma L. C-erbB-2 ptotein expression in a esophageal squamous epithelium from esophageal squamous cell carcinoma with special reference to histological grade of carcinoma and pre-invasive lesions. Eur J Surg Oncol 1998; 24: 431-5.
23. Sauter ER, Keller SM, Erner S. HER-2/neu: A differentiation marker in adenocarcinoma of the esophagus. Cancer Lett 1993; 75: 41–4.
24. Dursun A, Poyraz A, Çelik B, Akyol G. Expression of c-erbB-2 Oncoprotein in gastric carcinoma: correlation with histopathologic charesteristic s and analysis of Ki-67. Pathol Oncol Res 1999; 5: 104-6.
25. Tanner M, Hollmen M, Junntilla T, et al. Amplication of HER-2 in gastric carcinoma: assosiacion with Topoisomerase 2 gene amplification, intestinal type, poor prognosis and sensitivity to transtuzumab. Ann Onc 2005; 16: 273-8.
26. Yıldırım S, Dandin O, Durmuş M, et al. C-erb-B2 (Her2/neu) expression rate and its association with clinicopathologic parameters in gastric cancer. Int J Hematol Oncol 2012: 3: 156-62.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.916262

Anatolian Curr Med J 2021; 3(3); 214-219

The role of thiol-disulfide and ischemia-modified albumin levels in the diagnosis of childhood appendicitis

Ahmet Ertürk[1], Süleyman Arif Bostancı[1], Rabia Demir[2], Gökhan Demirtaş[1], Doğuş Güney[3], Cüneyt Karagöl[4], Emine Feyza Yurt[5], Özcan Erel[5], Can İhsan Öztorun[6], Müjdem Nur Azılı[6], Emrah Şenel[6]

[1]Ankara City Hospital, Pediatric Surgery Clinic, Ankara, Turkey
[2]Şırnak State Hospital, Pediatric Surgery Clinic, Şırnak, Turkey
[3]Ankara Yıldırım Beyazıt University, Department of Pediatric Surgery, Ankara, Turkey
[4]Ankara City Hospital, Pediatric Clinic, Ankara, Turkey
[5]Ankara Yıldırım Beyazıt University, Department of Biochemistry, Ankara, Turkey
[6]Ankara Yıldırım Beyazıt University, Department of Pediatric Surgery, Ankara, Turkey

Cite this article as: Ertürk A, Bostancı S, Demir R, et al. The role of thiol-disulfide and ischemia-modified albumin levels in the diagnosis of childhood appendicitis. Anatolian Curr Med J 2021; 3(3); 214-219.

ABSTRACT

Aim: The accurate diagnosis of acute appendicitis can be achieved by a combination of evaluation of clinical symptoms, physical examination findings and history taking, but is still challenging for the clinician. Some biochemical markers have been evaluated for the purpose of increasing the diagnostic accuracy rate for appendicitis. In this study, our aim is to evaluate the diagnostic value of thiol-disulfide levels and IMA, in pediatric patients with suspected acute appendicitis.

Material And Method: The children (1-17 years age) who were admitted to our clinic for suspected acute appendicitis between March 2017 and September 2017 were evaluated. A total of 238 children are enrolled in the study; 119 were operated for suspected acute appendicitis and the 119 children who did not have appendicitis constituted the control group. Serum levels of native thiol (-SH), total thiol (SH+SS), dynamic disulfide (SS), dynamic disulfide (SS)/total thiol (SH+SS) ratio, albumin, ischemic modified albumin (IMA) and WBC levels were obtained and compared within groups.

Results: The mean age of the patients was 10.9 years (±3.7, 3-17 years) and 9.1 years (±3.7, 1-17 years) in the operation and the control groups, respectively. The SH, SH+SS, SS and albumin levels and SS/SH+SS ratio were significantly lower and IMA levels were significantly higher in the operation group than the control group. Among the operated patients, IMA and dynamic disulfide levels were significantly higher and WBC levels were significantly lower in patients with non-perforated appendicitis than patients with perforated appendicitis. A significant decrease in serum levels of IMA was observed in the postoperative 1st day when compared with the preoperative values.

Conclusion: Measuring the IMA levels with thiol/disulfide homeostasis may increase the diagnostic accuracy rate when evaluating the patients with suspected appendicitis. However, it appears that these evaluations fail to distinguish the patients with perforated and non-perforated appendicitis, thus further studies are necessary.

Keywords: Appendicitis, oxidative stress, children, thiol-disulfide

INTRODUCTION

Acute appendicitis (AA) is one of the most common cause of surgical intervention in children (1). The establishment of diagnosis requires a combination of evaluating the clinical symptoms, physical examination and patients' history. However, as findings commonly overlap with many other conditions, accurate diagnosis is still challenging. In the English literature, negative appendectomy and perforated appendicitis rates are reported around 12.2% and 3.4%, respectively (2,3). Imaging modalities (plain X-rays, ultrasonography, computerized tomography) and laboratory tests (WBC, C-reactive protein) may be helpful. WBC and CRP levels may help but not highly specific for the condition. Many scoring systems were proposed (like Alvarado) in an effort to increase the preoperative diagnostic accuracy (4).

Corresponding Author: Ahmet Ertürk, drahmeterturk@hotmail.com

Received: 15.04.2021 **Accepted:** 04.06.2021

During the process of acute appendicitis, the integrity of the mucosal barrier is damaged due to obstruction of the appendiceal lumen and the resultant inflammatory response increases the tissue levels of neutrophils and other inflammatory cells. These cells release soluble mediators such as proinflammatory cytokines like (IL-1, IL-6 and IL-8), tumor necrosis factor-α (TNF-α), interferon-gamma (INF-Ɣ), and anti-inflammatory cytokines (IL-4 and IL-10). Increased serum levels of interleukins like IL-6, IL-8 and IL-10 are proposed to be helpful in the diagnosis of AA (5,6). Nevertheless, a specific test for accurate diagnosis of AA is still lacking.

Oxidative Stress

Free radicals are highly reactive molecules that contain one or more unpaired electrons which emerge during cellular metabolism. The balance between the production of free radicals and antioxidant defense is regulated by delicate mechanisms which are essential in the physiology and for the survival of living organisms (7). A trend to oxidative process results in oxidative stress (OS) producing increased production of free oxygen radicals (FOR) and consequently damages the cellular structures, nucleic acids, lipids and proteins (8).

During the inflammatory process, OS is accelerated due to neutrophil and macrophage activation and over-production of FORs (9-11). FORs released by the polymorphonuclear leucocytes cause peroxidation of the lipids of the cellular membrane. Microvascular permeability increases consequently resulting in edema, infiltration by the inflammatory cells, neutrophil activation and finally cellular death (10).

Thiol/Disulfide Balance

Thiols, also known as mercaptans, are organic compounds composed of a central carbon atom attached with a sulfur and a hydrogen atoms that contain a sulfhydryl (-SH) group (12). Thiol compounds in the plasma act as antioxidants by binding free radicals for scavenging (13). Thiols (RSH) react with free radicals forming disulfide (RSSR) bonds. Resultant disulfide bonds are degraded back to thiol groups in order to maintain the dynamic thiol-disulfide homeostasis of the organism (12).

Disturbances in the dynamic thiol-disulfide homeostasis and resultant oxidative stress are accused to play a role in the pathogenesis of many disease processes like diabetes, cardiovascular diseases, cancer, Rheumatoid Arthritis, chronic kidney disease, AIDS, Parkinson's Disease, Alzheimer's Disease, Friedrich's ataxia, multiple sclerosis, amyotrophic lateral sclerosis, and liver diseases (12,14). Accordingly, determination of the dynamic thiol/disulfide balance may provide valuable information about various normal or pathological biochemical processes (12).

Evaluation of oxidative stress in humans can be performed by either analyzing the products that emerged during oxidative damage or by determining the defensive antioxidant capacity of the organism (15). Erel et al. (12) developed a novel method that measures thiol/disulfide homeostasis in order to evaluate the oxidative stress level of the body, and the validity of the technique as a reliable indicator of OS is confirmed by many others (16-20).

Ischemia-Modified Albumin (IMA)

Ischemia-modified albümin is a novel cardiac marker approved by the FDA (21). The principle of the test is to measure the cobalt binding capacity of the albümin which is altered by the oxidative free radicals that emerged during the process of ischemia that leads to chemical alterations on the albumin itself. This altered albumin molecule loses its cobalt binding capability and is an early marker of ischemia (22). Recent research provided new perspectives that cardiac ischemia marker IMA may also provide useful information in various conditions (23-25). In this study, we aimed to evaluate if the disturbances in thiol-disulfide homeostasis can be a useful marker for the diagnosis of AA in children.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Researches Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Date: 27.03.2017, Decision No: 2017-005). The study was designed prospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 238 patients are enrolled in the study and 2 groups were formed; Appendicitis Group (n=119) and Control Group (n=119). The 119 children (0-18 years of age) who underwent appendectomy between March 2017 and September 2017 are enrolled in the Appendicitis Group. A gender and age-matched cohort of 119 children who underwent circumcision without preputial inflammation and inguinal herniorrhaphy without incarceration are enrolled in the Control Group. Informed consent was obtained from the patients' parents or legal guardians.

For the patients with appendicitis, 2 mL blood samples were drawn into tubes with yellow cap and gel (BD Vacutainer plastic SST II tube ®) before the procedure, on the first day after surgery; an additional sample was taken on the postoperative day 5 if the patient had perforated appendicitis. Samples were centrifuged 10 minutes with 3600 rpm and 2 cc serum is extracted which was stored at -800 temperature. All the samples were defrozen at the same time and blood thiol-sulfide measurements were performed by a novel automatic method developed by Erel and Neselioglu (12), and IMA levels were measured

by a colorimetric method developed by Bar-Or et al. (26) with Roche Hitachi Cobas c501 automatic analyzer device in the Biochemistry Laboratory of Ankara Atatürk Education And Research Hospital. With this technique, disulfide levels can also be measured together with thiol levels (which is also referred to as native thiol). The sum of the native thiol and disulfide levels is called total thiol (27). The serum levels of native thiol (-SH), total thiol (SH+SS), dynamic disulfide (SS), % dynamic disulfide (SS)/total thiol (SH+SS), albümin, IMA and WBC were measured. Statistical analyses are performed between the groups, and between the subgroups of patients with perforated and nonperforated appendicitis in the Appendicitis Group.

Statistical Analysis

Statistical analyses were performed with the SPSS ((Statistical Package for Social Sciences) software version 17 (Chicago, USA). On evaluation of normality of the numerical variables, native thiol (SH), total thiol (SS+SH), dynamic disulfide (SS), % dynamic disulfide (SS)/total thiol, İMA, albumin and WBC values are found not normally distributed. Descriptive analyses of the numerical variables that do not distribute normally were performed with the Mann-Whitney U test by mean values. Categorical variables were compared Chi-square test. Preoperative, postoperative 1st and 5th days values of dynamic disulfide (SS), native thiol, total thiol, % dynamic disulfide (SS)/total thiol (SS+SH), IMA ve albümin values were analyzed with paired correlation test. A $p<0.05$ value is considered statistically significant.

RESULTS

In the Appendicitis Group, 36% (n=43) of the patients had perforated and 64% (n=76) had non-perforated appendicitis. Appendectomy was performed with laparoscopic technique in 12.5% (n=16) and open technique in 87.5% (n=103).

The Demographic Results

The rates and numbers of girls and boys were the same in both groups with 40.3% (n=48) girls and 59.7% (n=71) boys. The mean age of the patients was 11,51 years (Min-Max=7.0–17.0, Std Dev=2.86) and 12,34 years (Min-Max=6.0-17.0, Std. Dev=3.35) in the control and study groups, respectively. the gender and age of the patients were not significantly different between the groups (p=0.30 and p=0.59, respectively) (**Table 1**).

Laboratory Results

SH, SS+SH, SS, SS/ SH+SS %, IMA, albumin and WBC levels of the groups and statistical analyses are given in **Table 2**.

The SH ($p<0.001$), SH+SS ($p<0.001$), dynamic thiol ($p<0.001$) levels, calculated SS/ SH+SS ratio ($p<0.001$), and albumin ($p<0.001$) were found significantly lower in the Appendicitis Group, whereas IMA levels ($p<0.001$) were found significantly higher (**Table 2**). WBC levels were significantly higher in the Appendicitis Group ($p<0.001$)

The comparison of the laboratory findings between the patients with perforated (n=43) and non-perforated (n=76) appendicitis in the Appendectomy Group are given in **Table 3**.

Only IMA, dynamic disulfide and WBC were significantly different between the groups. On subgroup evaluation, WBC levels were found significantly lower in patients with non-perforated appendicitis while IMA and dynamic disulfide levels were significantly higher in patients with perforated appendicitis (p=0.03, p=0,001, and p=0,038, respectively).

The details about the comparison of SH, SS+SH, SS, SS/ SH+SS %, IMA, and albumin levels on the preoperative and the 1st day after the operation in the Appendicitis Group are given in **Table 4**. A significant decrease in the IMA levels is found (p=0.028). When native thiol (SH), total thiol (SS+SH), dynamic disulfide (SS), % dynamic disulfide/ total thiol, IMA, and albümin levels on preoperative and 5th day after the operation were compared, no significant change was found ($p>0.05$).

Table 1. The demographic variables of the appendicitis and control groups

Variables	Appendicitis group n=119	Control group n=119	p value
Age (years)*	10.9 (3-17;3.7)	9.1 (1-17; 3.7)	0.72†
Gender, n (%)			
Male	71 (59.7)	71 (59.7)	1.00‡
Female	48 (40.3)	48 (40.3)	

*: Mean (Year) (Min-Max; Std. Dev.), †: Student t test, ‡: Pearson chi-square test,

Table 2. Comparison of test results of control group and appendectomy group

Variables	Appendicitis (n=119) Mean (Min-Max; SD)	Control (n=119) Mean (Min-Max; SD)	P value*
Native thiol (SH)	341.54 (171.9-574.8; 67.93)	408.25 (259.3-673.2; 63.62)	< 0.001
Total thiol (SS+SH)	370.27 (181.8-632; 74.41)	448.21 (279.6-742.5; 69.35)	< 0.001
Dynamic disulfide (SS)	14.35 (5-29; 3,67)	19.97 (10-35; 4.41)	< 0.001
Dynamic disulfide/Total thiol, %	3.85 (2.55-5.24; 0.50)	4.46 (3.11-7.77; 0.77)	< 0.001
Ischemia-modified albumin	0.82 (0.38-1.43; 0.20)	0.62 (0.26-1.31; 0.17)	< 0.001
Albumin	4.19 (1.9-6.1; 0.69)	4.53 (3.7-6; 0.42)	< 0.001
White blood count (WBC)	14.77 (4.3-34.2; 5.29)	9.42 (4.10-13.76; 4.56)	< 0.001

*: Mann-Whitney U test, SD: standard deviation,

Table 3. The comparison of laboratory results in non-perforated (n=76) and perforated (n=43) appendisitis subjects

Variables	Non-perforated Appendicitis (n=76) Mean (Min-Max; SD)	Perforated Appendicitis (n=43) Mean (Min-Max; SD)	P value*
Native thiol (SH)	350.78 (212.9-574.8; 59.18)	352.22 (171.9-463.7; 79.26)	0.110
Total thiol (SS+SH)	380.74 (227-632; 65.13)	351.76 (181.8-504.3; 86.21)	0.09
Dynamic disulfide (SS)	14.96 (7-29; 3.48)	13.28 (5-20; 3.78)	0.038
Dynamic disulfide/Total thiol, %	3.90 (2.55-5.24; 0.49)	3.75 (2.75-5.13; 0.51)	0.100
Ischemia-modified albumin	0.77 (0.38-1.35; 0.18)	0.90 (0.45-1.43; 0.21)	0.001
Albumin	4.32 (1.9-6.1; 0.21)	3.96 (2-5.2; 0.79)	0.27
White blood count (WBC)	13.46 (4.9-25; 4.64)	17.09 (4.3-34.2; 5.63)	< 0.001

*: Mann-Whitney U testi, SD: standard deviation,

Table 4. Pre-operative and post-operative first day laboratory findings in the acute appendicitis group (n =119)

Variables	Pre-op levels Mean (Min-Max; SD)	Post-op 1st day level Mean (Min-Max; SD)	P value*
Native thiol (SH)	341.54 (171.9-574.8; 67.93)	408.25 (259.3-673.2; 63.62)	0.063
Total thiol (SS+SH)	370.27 (181.8-632; 74.41)	352.88 (177.8-466.5; 50.98)	0.068
Dynamic disulfide (SS)	14.35 (5-29; 3.67)	13.62 (5-18; 2.81)	0.254
Dynamic disulfide/Total thiol, %	3.85 (2.55-5.24; 0.50)	3.83 (2.81-5.17; 0.50)	0.959
Ischemia-modified albumin	0.82 (0.38-1.43; 0.20)	0.74 (0.45-1.36; 0.20)	0.028
Albumin	4.19 (1.9-6.1; 0.69)	4.26 (2.3-5.4; 0.57)	0.587

*: Wilcoxon Signed Rank Test, SD: standard deviation

DISCUSSION

Findings of this study support that antioxidant representatives (including SS+SH, SH and albumin and oxidative side substrates as SS and SS/ SH+SS ratios) have crucial roles on the thiol/disulfide homeostasis, and are found to decrease significantly in patients with acute appendicitis. Additionally, IMA levels demonstrated a significant increase in patients with acute appendicitis. IMA has become a significant molecule in the diagnosis of appendicitis (28). Yeniocak et al. (29) and Demir et al. (30) stated that serum IMA levels can be used as a diagnostic marker in patients with suspected acute appendicitis. These results indicate that the thiol/disulfide balance in the AA group shifts towards the oxidative side, resulting in increased OS levels.

Although some authors claim a contribution of increased OS in the etiology of AA, some others attribute the increased OS as a result of the inflammation process initiated by the AA (31). The relationship between AA and OS has been investigated in several experimental and clinical studies (3,11,32).

The data in children is quite limited (33). Dumlu et al. (3) demonstrated increased oxidative stress markers in the plasma and the appendiceal tissue in children with AA compared to the controls, suggesting that OS is higher in patients with acute appendicitis. they also hypothesized that OS might have a role in the pathogenesis of AA and OS might positively be correlated with the severity of the disease. Özyazıcı et al. (18) demonstrated a trend towards the oxidant side in the thiol/disulfide balance in adult patients with AA. Yildirim et al. (5) found decreased SS+SH levels in adult patients with AA when compared to controls. These findings support the hypothesis of elevated oxidative stress in adults and children with AA, which is also supported by the results of our current study.

OS is reported to be higher in patients with perforated AA than patients with non-perforated AA (2,32-33). Koltuksuz et al. (34) demonstrated significantly higher OS in patients with perforated AA than patients with non-perforated AA and claimed that excessively elevated OS may indicate an advanced stage of AA. However, we could not demonstrate any significant difference in the thiol/disulfide balance between patients with perforated and non-perforated appendicitis, except SS. IMA levels of the patients with non-perforated AA were found significantly lower than the patients with perforated AA and SS levels were higher. Based on these findings, thiol /disulfide balance is not a useful laboratory marker for discrimination of the non-perforated and perforated acute appendicitis in children. The preoperative and postoperative 1st day SH+SS, SH, SS, SS/ SH+SS ratio, albumin, and IMA levels were not significantly different.

In line with the current literature, we found significantly increased WBC levels in patients with AA (35,36). We found decreased albumin and increased IMA levels in patients with AA than controls. IMA has been widely accepted as a marker of OS in various pathological processes. Increased IMA levels related to AA have been reported by many others (3,34,36,37). Kılıç et al. (38) found significantly increased IMA levels in adult patients with AA and concluded that IMA can be used as an indicator of the severity of AA. Similarly, many other authors conclude that IMA can be used as a marker for the diagnosis of AA (39,40).

Compatible with the current literature, we found higher IMA levels in patients with AA than controls.

CONCLUSION

The differential diagnosis of AA in children is challenging due to the lack of a reliable laboratory test or imaging method. The development of a specific test for the diagnosis of AA may prevent unnecessary negative appendectomy rates and reduce the morbidity and mortality related to perforated appendicitis.

For this purpose, evaluating the thiol/disulfide homeostasis and demonstrating the elevated oxidative stress may be helpful for the differential diagnosis in patients with suspected AA. Although measuring the IMA levels and demonstrating the alterations in the thiol/disulfide homeostasis appear to be promising for increasing the specificity of the differential diagnosis process, discrimination of perforated and non-perforated AA do not look reliable, currently. Further clinical studies with prospective design and increased number of patients are necessary for validation of these results.

ETHICAL DEVCLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (Date: 27.03.2017, Decision No: 2017-005).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Vahdad M.R, Nissen M, Semaan A, et al. Experiences with LESS-appendectomy in Children. Arch Iran Med 2016; 19: 57.
2. Park JS, Jeong JH, Lee JI, Lee JH, Park JK, Moon HJ. Accuracies of diagnostic methods for acute appendicitis. Am Surg 2013; 79: 101-6.
3. Dumlu EG, Tokaç M, Bozkurt B, et al. Correlation between the serum and tissue levels of oxidative stress markers and the extent of inflammation in acute appendicitis. Clinics 2014; 69: 677-82
4. Mohammed AA, Daghman NA, Aboud SM, Oshibi HO. The diagnostic value of C-reactive protein, white blood cell count and neutrophil percentage in childhood appendicitis. Saudi Med J 2004; 25: 1212-5.
5. Yıldırım O, Solak C, Koçer B, et al. The role of serum inflammatory markers in acute appendicitis and their success in preventing negative laparotomy. J Invest Surg 2006; 19: 345-52.
6. Paajanen H, Mansikka A, Laato M, Ristamäki R, Pulkki K, Kostiainen S. Novel serum inflammatory markers in acute appendicitis. Scand J Clin Lab Invest 2002; 62: 579-84.
7. Saugstad OD. Mechanisms of tissue injury by oxygen radicals: implications for neonatal disease. Acta Paediatr 1996; 85: 1-4.
8. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007; 39: 44-84.
9. Bolukbas C, Bolukbas FF, Horoz M, Aslan M, Celik H, Erel O. Increased oxidative stress associated with the severity of the liver disease in various forms of hepatitis B virus infection. BMC Infect Dis 2005; 5: 95.
10. Ozdogan M, Devay AO, Gurer A, et al. Plasma total anti-oxidant capacity correlates inversely with the extent of acute appendicitis: a case control study. World J Emerg Surg 2006; 1: 6.
11. Serefhanoglu K, Taskin A, Turan H, Timurkaynak FE, Arslan H, Erel O. Evaluation of oxidative status in patients with brucellosis. Braz J Infect Dis 2009; 13: 249-51.
12. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014; 47: 326-32.
13. Hu M.L. Measurement of protein thiol groups and glutathione in plasma. Methods Enzymol 1994; 233: 380-5.
14. Abuja P.M, Albertini R. Methods for monitoring oxidative stress, lipid peroxidation and oxidation resistance of lipoproteins. Clin Chim Acta 2001; 306: 1-17.
15. De Oliveira Machado SL, Bagatini MD, Da Costa P, et al. Evaluation of mediators of oxidative stress and inflammation in patients with acute appendicitis. Biomarkers 2016; 21: 530-7.
16. Karadag-Oncel E, Erel O, Ozsurekci Y, et al. Plasma oxidative stress and total thiol levels in Crimean-Congo hemorrhagic fever. Jpn J Infect Dis 2014; 67: 22-6.
17. Dinc ME, Ozdemir C, Ayan NN, et al. Thiol/disulfide homeostasis as a novel indicator of oxidative stress in obstructive sleep apnea patients. Laryngoscope 2017; 127: 244-50.
18. Ozyazici S, Karateke F, Turan U, et al. A Novel oxidative stress mediator in acute appendicitis: thiol/disulphide homeostasis. Mediators Inflamm 2016:6761050.
19. Elmas B, Erel Ö, Ersavaş D, Yürümez Y. Thiol/disulfide homeostasis as a novel indicator of oxidative stress in children with simple febrile seizures. Neurol Sci 2017; 38: 1969-75.
20. Elmas B, Karacan M, Dervişoğlu P, Kösecik M, İşgüven ŞP, Bal C. Dynamic thiol/disulphide homeostasis as a novel indicator of oxidative stress in obese children and its relationship with inflammatory-cardiovascular markers. Anatol J Cardiol 2017; 18: 361-9.
21. Wudkowska A, Goch J, Goch A. Ischemia-modified albumin in differential diagnosis of acute coronary syndrome without ST elevation and unstable anginapectoris. Kardiol Pol 2010; 68: 431-7.
22. Aran T, Unsal MA, Güven S, Kart C, Cetin E, Alver A. Carbon dioxide pneumoperitoneum induces systemic oxidative stres: a clinical study. Eur J Obstet Gynecol Reprod Biol 2012; 161: 80-3.
23. Ma SG, Wei CL, Hong B, Yu WN. Ischemia-modified albumin in type 2 diabetic patients with and without peripheral arterial disease. Clinics 2011; 66: 1677-80.
24. Mastella AK, Moresco RN, da Silva DB, et al. Evaluation of ischemiamodified albumin in myocardial infarction and prostatic diseases. Biomed Pharmacother 2009; 63: 762-6.
25. Lippi G, Montagnana M. Ischemia Modified Albumin in Ischemic Disorders. Ann Thorac Cardiovasc Surg 2009; 15: 137
26. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt–albumin binding and its potential as a marker for myocardial ischemia a preliminary report. J Emerg Med 2000; 19: 311-5.
27. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci 2020; 50.SI-2: 1728-38.

28. Ulusoy E, Çitlenbik H, Akgül F, et al. Is ischemia-modified albumin a reliable marker in accurate diagnosis of appendicitis in children? World J Surg 2020; 44: 1309-15.
29. Yeniocak S, Saraç F, Yazıcıoğlu M, et al. The diagnostic values of ischemia-modified albumin in patients with acute abdominal pain and its role in differentiating acute abdomen. Emerg Med Int 2020; 2020: 7925975.
30. Demir S, Dere Günal Y, Özmen İ, Dindar Badem N, Neşelioğlu S, Erel Ö. Can thiol/disulphide homeostasis help in the differential diagnosis of appendicitis in children?. Türkiye Çocuk Hast Derg 2020; 14: 236-43.
31. Kaya M, Boleken ME, Kanmaz T, Erel O, Yucesan S. Total antioxidant capacity in children with acute appendicitis. Eur J Pediatr Surg 2006; 16: 34-8.
32. Nazik S, Avci V, Kiraz KZ. Ischemia-modified albumin and other inflammatory markers in the diagnosis of appendicitis in children. Ulus Travma Acil Cerrahi Derg 2017; 23: 317-21.
33. Boshnak N, M Boshnaq, Elgohary H. Evaluation of platelet indices and red cell distribution width as new biomarkers for the diagnosis of acute appendicitis. J Invest Surg 2017; 31: 1-9.
34. Koltuksuz U, Uz E, Özen S, Aydinç M, Karaman A, Akyol Ö. Plasma superoxide dismutase activity and malondialdehyde level correlate with the extent of acute appendicitis. Pediatr Surg Int 2000; 16: 559-61.
35. Fan Z, Pan J, Zhang Y, et al. Mean platelet volume and platelet distribution width as markers in the diagnosis of acute gangrenous appendicitis. Dis Markers 2015: 542013.
36. Reddy VS, Perugu B, Garg MK. Ischemia-modified albumin must be evaluated as an oxidative stress marker together with albumin and bilirubin in individuals with acute appendicitis. Clinics 2015; 70: 531-2.
37. Reddy VS, Sethi S, Agrawal P, Gupta N, Garg R. Ischemia modified albumin (IMA) and albumin adjusted-IMA (AAIMA) as biomarkers for diabetic retinopathy. Nepal J Ophthalmol 2015; 7: 117-23.
38. Kılıç MÖ, Güldoğan CE, Balamir İ, Tez M. Ischemia-modified albumin as a predictor of the severity of acute appendicitis. Am J Emerg Med 2017; 35: 92-5.
39. Hakkoymaz H, Nazik S, Seyithanoğlu M, et al. The value of ischemia-modified albumin and oxidative stress markers in the diagnosis of acute appendicitis in adults. Am J Emerg Med 2019; 37: 2097-101.
40. Ayengin K, Alp HH, Avci V, Huyut Z. The effect of laparoscopic and open surgery on oxidative DNA damage and IL-37 in children with acute appendicitis. Ir J Med Sci 2021; 190: 281-9.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.928198

Anatolian Curr Med J 2021; 3(3); 220-226

Comparative analysis of the anaesthesia management of gynecological operations between the normal period and COVID-19 pandemic

Esra Uyar Türkyılmaz, Nihan Aydın Güzey

Ankara City Hospital, Department of Anaesthesiology and Reanimation, Ankara, Turkiye

Cite this article as: Uyar Türkyılmaz E, Aydın Güzey N. Comparative analysis of the anaesthesia management of gynecological operations between the normal period and COVID-19 pandemic. Anatolian Curr Med J 2021; 3(3); 220-226.

ABSTRACT

Aim: In the novel coronavirus (2019-nCoV/SARS-CoV-2) disease 2019 (COVID-19) pandemic period, one of the major objectives of the anaesthesia team was providing quality care for patients whose procedures cannot (or can no longer) be postponed while limiting the risk of contamination of these patients and healthcare professionals. The aim of this study is to analyse and document the changes in anaesthesia management of gynecological operations in accordance with this objective during the pandemic period.

Material and Method: A retrospective observational study was conducted on patients who had gynecological operation from 01.09.2019 to 31.12.2020. Anaesthetic management of gynecological operations corresponding to the pandemic process (After Pandemic Group) were compared with anaesthetic management of gynecological operations from the before the pandemic process (Before Pandemic Group) . Anaesthesia records of the patients were examined. The following parameters are recorded: Surgery type, indication of the surgery, urgency of the surgery and anaesthesia method performed, airway management of the patients, used medications for the anaesthesia management.

Results: There was an increment in the percentage of operations performed with regional anaesthesia after the start of the pandemic. There was a statistically significant decrement in the percentage of operations performed with laparoscopic technique after the start of the pandemic. There was an increment in the percentage of operations with oncologycal or suspected oncologycal indications after the start of the pandemic; there was no difference in the percentage of urgent surgeries while there was a decrement in the percentage of operations with elective indications.

Conclusion: By taking alterations and fluctations in community prevalence into consideration, decisions about cancellation of surgeries must be made dynamically. Possibility of COVID-19 infection must be considered in every patient. In anaesthesia management, regional anaesthesia methods may be considered in appropriate cases. Proper PPE must be used if airway manipulations are needed.

Keywords: COVID-19, gynecological operations, anaesthesia management

INTRODUCTION

The novel coronavirus (2019-nCoV/SARS-CoV-2) disease 2019 (COVID-19) began in Wuhan, China, at the end of 2019 and spread rapidly across the country and worldwide, which was declared to be a pandemic by the World Health Organization (WHO) (1). The virus, has been identified in respiratory tract specimens one to two days before the onset of symptoms (2), and mainly spread through respiratory droplets or direct contact. It may also be transmitted through aerosols with prolonged exposure to high concentrations of aerosol in an enclosed environment (3). Aerosol generating procedures (AGPs), involve intubation, extubation, chest tube insertion, bronchoscopy, gastrointestinal endoscopy, laparoscopy, and the use of energy devices such as electrocautery, are associated with an increased risk of infection to the healthcare professionals (4). Anaesthesia practise, based on its nature, is obliged to either perform or exist together with the teams performing most of these procedures. This situation puts healthcare professionals working in anaesthesia and criticalcare departments and anaesthesia units in an elevated risk of COVID-19 exposure (5,6). In this pandemic period, one of the major objectives of the anaesthesia team was providing quality care for patients whose procedures can not (or can no longer) be postponed

Corresponding Author: Esra Uyar Türkyılmaz, esrauyarturkyilmaz@yahoo.com

Received: 26.04.2021 **Accepted:** 04.07.2021

while limiting the risk of contamination of these patients and healthcare professionals. For this purpose, there had been some changes in anaesthesia practise. There is not adequate information to evaluate the effects of the COVID-19 pandemic on anaesthesia management of gynecologic operations. The aim of this study is to analyse and document the changes in anaesthesia management of gynecological operations in accordance with this objective during the pandemic period.

MATERIAL AND METHOD

A retrospective observational study was conducted on patients who had gynecological operation from 01.09.2019 to 31.12.2020 comparatively, in Ankara City Hospital as a pandemic hospital, after ethical approval was taken from both local ethics committee (Ankara City Hospital-E1-1-21-1732-14.04.2021, and the Ministry of Health (2021-03-09T23_29_08). That is, anaesthetic management of gynecological operations after the beginning of the the pandemic period (After Pandemic Group) was compared with anaesthetic management of gynecological operations before the pandemic period (Before Pandemic Group) .

From the hospital records, all the patients who had gynecological operations at the determined period were identified. As our hospital has begun to provide service since September 2019, the operation records has been kept from that date. Anaesthesia records of the patients were examined. The following parameters are recorded: Surgery type, indication of the surgery, urgency of the surgery and anaesthesia method performed, airway management of the patients, used medications for the anaesthesia management

Also, the indications for surgery was grouped as Group 1 (Surgery indications-Group 1): Oncologycal or suspected oncologycal indications (adnexial mass, ovarian carcinoma, endometrial carcinoma, cervical carcinoma, high grade cervical intraepithelial neoplasia, vulvar carcinoma, postmenopausal bleeding, endometrial hyperplasia) Group 2 (Surgery indications-Group 2): Morbidities with increment bleeding but not urgent (myoma uteri, endometrial polyps, menometrorrhagia) Group 3 (Surgery indications -Group 3): Urgent surgeries (extra uterine pregnancy; ovarian cyste rupture/torsion, tubo ovarian abscess; wound infection debridement; postoperative bleeding or complications requiring surgery, molar pregnancy termination) Group 4 (Surgery indications -Group 4): Indications for pelvic organ prolapse (uterine prolapse, cystocele, rectocele etc.). Group 5 (Surgery indications - Group 5): Indications for endometriosis and ovarian cysts. Group 6 (Surgery indications -Group 6): Fertility/infertility related indications (tube ligation, lost intrauterine device, uterine septum resection)

Statistical analyses were performed using SPSS Software (Version 21.0, SPSS Inc., IL, USA). Categorical data are expresses as counts and percentages. Chi-square test was used for qualitative data. Z test and post hoc tests for the chi-square independence test was used to detect the different group. $p<0.05$ was considered significant.

RESULTS

The total number of gynecological and gynecologic oncological operations between the period 01.09.2019 to 31.12.2020 was 2973; of which 1683 (56.6%) were before and 1290 (43.4%) were after covid 19 pandemic period.

There was an increment in the percentage of operations performed with regional anaesthesia while there was a decrement in the percentage of operations performed with general anaesthesia after the start of the pandemic. (**Table 1**)

Table 1. The indications, anaesthesia type, laparoscopy and emergency situation of operations before and after start of pandemic

	Before pandemic group n(%)	After pandemic group n(%)	p
Surgery indications			<0.001*
Group1	519 (30.8)*	553 (42.5)*	
Group2	559 (33.2)*	374 (29.0)*	
Group3	169 (10.0)	158 (12.2)	
Group4	209 (12.4)	115 (8.9)	
Group5	153 (9.1)*	54 (4.2)*	
Group6	74 (4.4)*	36 (2.8)*	
Total	1683 (100)	1290 (100)	
Anaesthesia and airway management method			<0.001*
GA-EI	1067 (63.4)*	876 (67.9)*	
GA-LMA	404 (24.0)*	30 (2.3)*	
RA-CSE/Epidural	69 (4.1)*	75 (5.8)*	
RA- Spinal	116 (6.9)*	292 (22.6)*	
MAC	27 (1.6)	17 (1.3)	
Total	1683 (100)	1290 (100)	
Anaesthesia type			p<0.001
GA	1498 (89.0)	923 (71.6)	
RA	185 (11.0)	367 (28.4)	
Total	1683 (100)	1290 (100)	
Surgery method types			p<0.001
Laparoscopic	364 (21.6)	193 (15.0)	
Non-laparoscopic	1391 (78.4)	1097 (85.0)	
Total	1683 (100)	1290 (100)	
Emergency of surgery			p=0.134
Emergency	127 (7.5)	117 (9.1)	
Non-emergency	1556 (92.5)	1173 (90.9)	
Total	1683 (100)	1290 (100)	

Chi-square test was used for detecting the difference between surgery indications, anaesthesia and airway management method, anaesthesia type, surgery method types and emergency of surgery before and after pandemic period. Z test and post hoc tests for the chi-square independence test was used to detect the different group in surgery indications, anaesthesia and airway management method before and after pandemic period. $p<0.001$ for the parameters indicated with * GA-EI: General anaesthesia, endotracheal intubation for airway management, GA-LMA: General anaesthesia, LMA for airway management; RA-CSE/Epidural: Regional anaesthesia with combined spinal-epidural or only epidural technique; RA-Spinal: Regional anaesthesia with intrathecal technique; MAC: Monitorised anaesthesia care

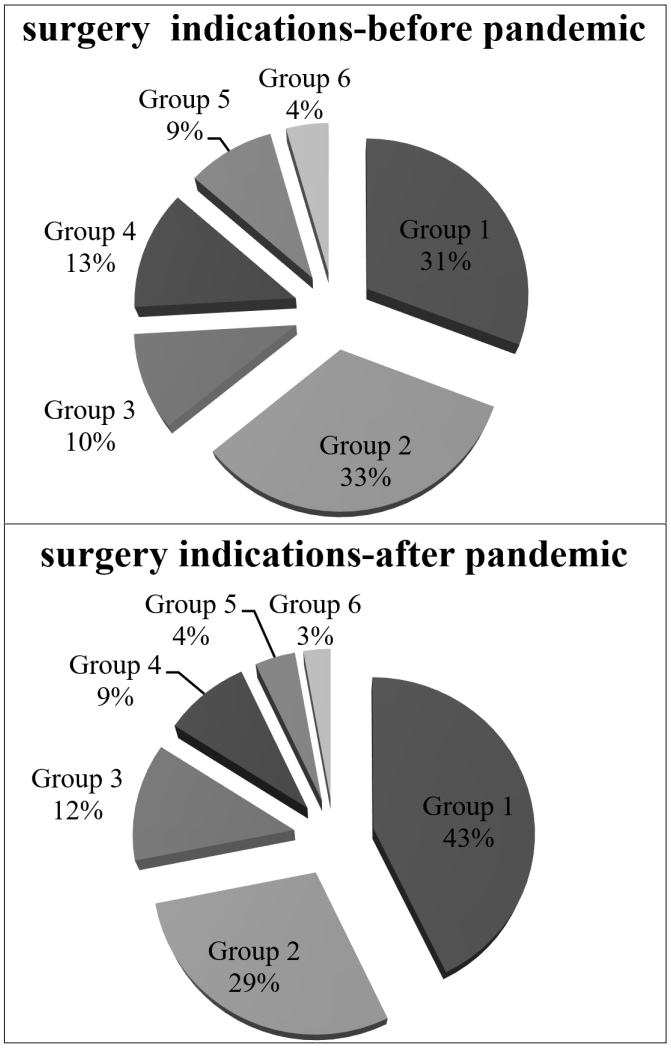
The number and the percentage of operations grouped according to the surgical indications and start of pandemic period are shown in **Table 1** and **Graphic 1**. There was an increment in the percentage of operations with Surgery indications -Group 1 after the start of the pandemic (30.8 % to 42.5%); while there was a decrement in percentage of operations with Surgery indications -Group 2, Surgery indications -Group 4, Surgery indications -Group 5 and Surgery indications -Group 6. There was no difference in the percentage of operations with Surgery indications -Group 3 before and after start of the pandemic.

The number and percentage of operations grouped according to anaesthesia and airway management methods and start of the pandemic period are also shown in **Table 1** and **Graphic 2**. There was an increment in the percentage of patients who had general anaesthesia and airway management by endotracheal intubation (GA-EI), who had regional anaesthesia with spinal anaesthesia technique (RA-Spinal) and regional anaesthesia with combined spinal-epidural or only epidural technique (RA-CSE/Epidural) after the start of the pandemic. There was a decrement in the percentage of patients who had general anaesthesia and airway management by supraglottic airway devices (GA-LMA) after the start of the pandemic. There was no difference in percentage of patients who had monitorised anaesthesia care and sedo-analgesia(MAC). 85.4% of intubations were was facilitated with non depolarising and 14.6 of intubations were facilitated with depolarising neuromusculary blocking agents after the start of the pandemic while 99% of intubations were facilitated with non depolarising neuromusculary blocking agents before the start of the pandemic

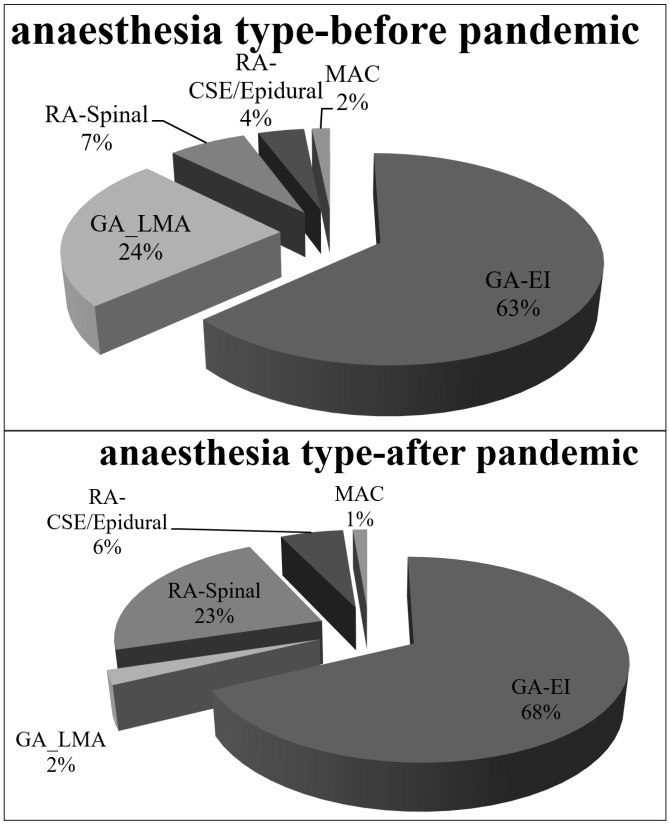
There was a decrement in the percentage of operations performed with laparoscopic technique while there was an increment in the percentage of operations performed with non laparoscopic technique after the start of the pandemic.(**Table 1**).

The percentage of emergency operations did not change before and after the start of the pandemic (**Table 1**)

The percentage of operations performed for extra uterine pregnancy, ovarian cyste rupture/torsion, tubo ovarian abscess and ovarian cysts with laparoscopic technique decreased after the start of pandemic when compared with the period before the start of the pandemic (**Table 2**)



Graphic 1. Surgery indications before and after the start of COVID-19 pandemic



Graphic 2. The percentage of operations grouped according to anaesthesia and airway management methods before and after the start of COVID-19 pandemic.

The anaesthesia and airway management method of operations classified according to operation site and surgery method before and after the start of pandemic is shown in **Table 3** and **Graphic 3**. There was an increment in the percentage of hysteroscopic operations performed with RA-Spinal after the start of the pandemic period. All the laparoscopic operations were performed with GA-EI before and after the start of the pandemic period. There was an increment in the percentage of vaginal operations performed with RA-Spinal and RA-CSE/Epidural after the start of the pandemic period. There was a an increment in the percentage of abdominal operations performed with RA-Spinal after the start of the pandemic period.

Table 2. Some operations which could either be done laparoscopic or non laparoscopic technique

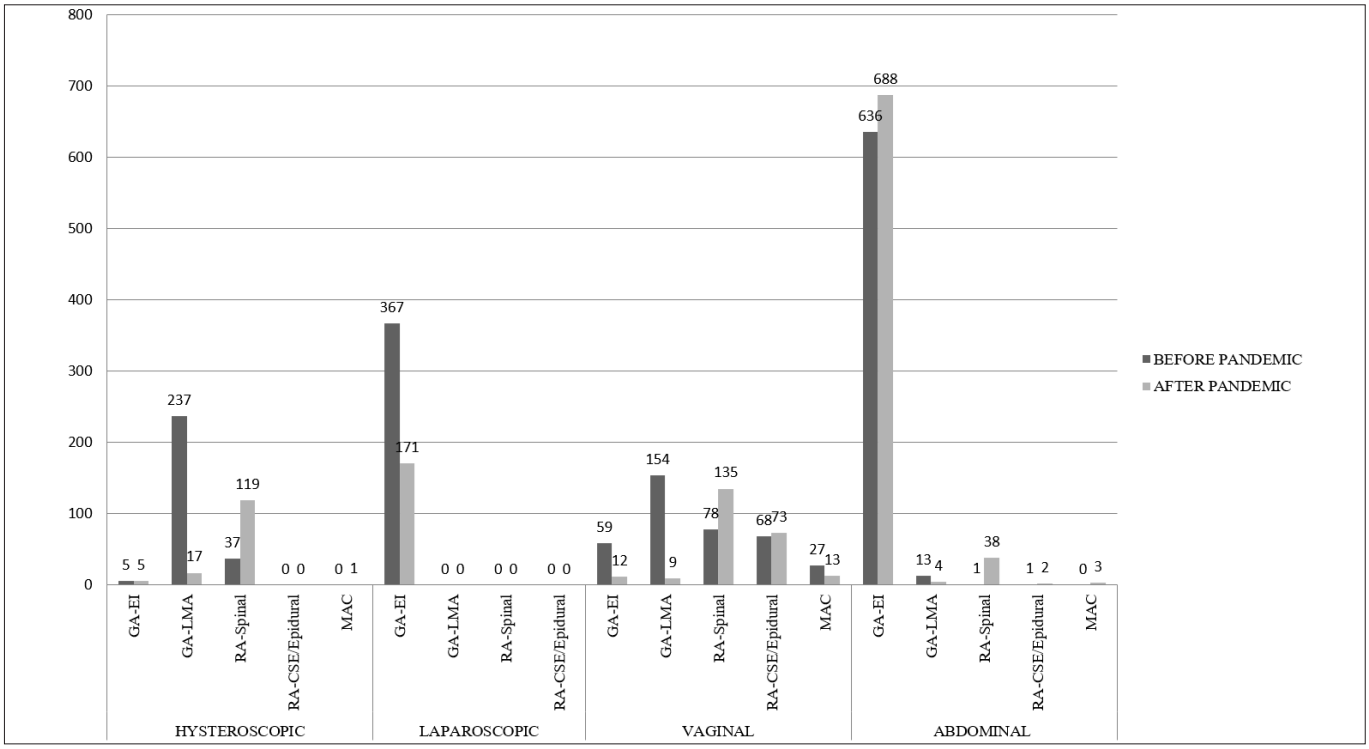
	Before pandemic group n (%)	After pandemic group n (%)	p
Extra uterine pregnancy			<0.001
Laparoscopic	70 (92.1)	45 (62.5)	
Non-laparoscopic	6 (7.9)	27 (37.5)	
Total	76 (100)	72 (100)	
Ovarian cyste rupture/torsion, tubo ovarian abscess			0.002
Laparoscopic	52 (66.7)	27 (41.5)	
Non-laparoscopic	26 (33.3)	38 (58.5)	
Total	88 (100)	65 (100)	
Ovarian cysts			0.008
Laparoscopic	109 (81.3)	25 (61.0)	
Non-laparoscopic	25 (18.7)	16 (39.0)	
Total	134 (100)	41 (100)	

Chi-square test was used for detecting the difference between laparoscopic or non laparoscopic technique before and after pandemic period.

Table 3. The anaesthesia and airway management method of operations classified according to operation site and surgery method before and after start of pandemic.

	Before pandemic group n (%)	After pandemic group n (%)	p
HYSTEROSCOPIC			<0.001
GA-EI	5 (1.8)	5 (3.5)	
GA-LMA	237 (84.9)*	17 (12.0)*	
RA-Spinal	37 (13.3)*	119 (83.8)*	
RACSE/Epidural	-	-	
MAC	-	1 (0.7)	
LAPAROSCOPIC			<0.001
GA-EI	367 (100)	171 (100)	
GA-LMA	-	-	
RA-Spinal	-	-	
RA-CSE/Epidural	-	-	
VAGINAL			<0.001
GA-EI	59 (15.3)*	12 (5.0)*	
GA-LMA	154 (39.9)*	9 (3.7)*	
RA-Spinal	78 (20.2)*	135 (55.8)*	
RA-CSE/Epidural	68 (17.6)*	73 (30.2)*	
MAC	27 (7.0)	13 (5.4)	
ABDOMINAL			<0.001
GA-EI	636 (97.7)*	688 (93.6)*	
GA-LMA	13 (2.0)*	4 (0.5)*	
RA-Spinal	1 (0.2)*	38 (5.2)*	
RA-CSE/Epidural	1 (0.2)	2 (0.3)	
MAC	-	3 (0.4)	

Chi-square test and Z test and post hoc tests for the chi-square independence test was used to detect the different group in anaesthesia and airway management method before and after pandemic period classified according to operation site and surgery method. p<0.001 for the parameters indicated with *
GA-EI: General anaesthesia, endotracheal intubation for airway management, GA-LMA: General anaesthesia, LMA for airway management; RA-CSE/Epidural: Regional anaesthesia with combined spinal-epidural or only epidural technique; RA-Spinal: Regional anaesthesia with intrathecal technique; MAC: Monitorised anaesthesia care



Graphic 3. The anaesthesia type of operations classified according to operation site before and after start of COVID-19 pandemic

DISCUSSION

In the context of the COVID-19 pandemic, the resumption of surgical activity is subject to several major limitations. The first case of Covid-19 in Turkey was detected on March 10, 2020; soon after this, our hospital was converted to a 'pandemic hospital'. During the period between March 15,2020 and the end of May 2020, Ministry of Health has issued regulations on the need to postpone elective surgical procedures as much as possible. During this period, elective cases were delayed and only emergency and cancer surgeries were performed. Also operating room and postoperative follow-up procedures, were updated for pandemic conditions. The main rationale for this measure was minimizing the redundance in health institutions and reducing the burden on health personnel, managing the change in hospitalisation capacities. During the period between June 2020 and end of September 2020 elective surgical procedures for elective cases had been resumed. During the period between October 2020 and December 2020 elective surgical procedures not totally postponed but limited to decreased numbers.

Similarly, elective surgical procedures has been ceased in most of countries. In the UK, it is announced by NHS in March that all non-urgent elective surgery would be suspended for at least 3 months. (7). The same decision was taken in Washington, regarding non-urgent medical procedures in order to reserve critical equipment for COVID-19 healthcare professionals (8). Many countries have recently resumed elective cases by early summer 2020, in response to dramatic reductions in medical care unrelated to COVID-19.

According to a global predictive modeling in May 2020 CovidSurg Collaborative (9), 28 404 603 operations will have been canceled or postponed worldwide during the peak 12 weeks of disruption due to COVID-19. During the COVID-19 pandemic, Oui L et al (3), classified each operation into 3 types according to urgency, as emergency surgery, "time-limited" surgery, and elective surgery. They defined emergency surgery as life-threatening circumstances requiring immediate surgical treatment such as ectopic pregnancy, ovarian torsion, uncontrollable uterine bleeding from cancer, pelvic mass causing severe symptoms; time-limited surgery as procedures whose time can be delayed, but should not be delayed for too long, for example, operations on malignant tumors; and elective surgery as neither emergency nor time-limited for example, excision of pelvic masses withouthigh suspicion of malignancy, hysterectomy for benign diseases.

Our surgery indications were consistent with this classification. There was an increment in percentage of operations with oncologycal or suspected oncologycal indications after the start of pandemic; there was no difference in the percentage of urgent surgeries while there was a decrement in the percentage of operations with elective indications. Keles et al, reported to perform surgeries for major gynecologic operations including malignant cases and associated this situation with being a non-pandemic speciality hospital (10). Cancer patients are vulnerable to COVID- 19 and also, their oncologic outcome is based on the type and timing of treatment (11). Hospitals, are postponing or canceling clinic visits and treatment to protect cancer patients from COVID-19, according to cancer acuity (12). This results in stress and anxiety in patients. According to conducted a survey, patients were found to be more fearful of cancer progression (70.9%) than developing COVID-19. Many patients had a high level of anxiety that COVID-19 pandemic would lead to a change of planned cancer treatment (13).

For providing quality care for patients while limiting the risk of contamination of these patients and healthcare professionals, a thorough preoperative examination and epidemiologic investigation is essential for all surgical patients to assess suspected COVID-19 patients. The European Society for Gynaecological Endoscopy recommendations highlight the importance of screening for SARS-CoV-2 before gynaecological procedures (14). Especially in non-emergency situations this seems to be a very logical approach. In our institution, preoperative the reverse transcriptase – polymerase chain reaction (RT-PCR) testing for screening COVID 19 for patients schuled for surgery were not performed until the end of May 2020. After June 2020, RT-PCR testing were performed for all the patients whether or not having any symptoms before 48-72 hours from the surgery. Owing to reported false negative rates of 47-70% for RT-PCR tests (15), still all cases were presumed to be potential COVID-19 positive and FFP2/N95 respirators were brought into use of all anaesthesia and surgical team for all operations after June 2020. Access to personal protective equipment (PPE) for health professionals is an important concern while providing anaesthesia because of the high risk of COVID-19 transmission of anaesthesia team as mentioned in above sections. Applying RT_PCR testing to patients for screening of Sars-Cov-2 and using PPE, lead to a safer setting for patients and anaesthesia and surgery team in our institution.

In the context of COVID-19 pandemic, choosing regional anaesthesia for appropriate operations is seems to be more advantageous. General anaesthesia exposes to the risk of contamination during periods of upper airway management (16). According to a systematic review that analyzed the transmission risk of acute respiratory infections to healthcare workers for aerosol-generating procedures, the odds ratio of tracheal

intubation have been reported to be 6.6 (17). Peripheral and central regional anaesthesia techniques reported to have a favourable risk/benefit ratio (18) and allow for the maintenance of patient protection measures (mask use) and decreased caregiver exposure during anaesthesia and surgical procedures (19). The American Society of Regional Anesthesia and Pain Medicine and European Society of Regional Anesthesia and Pain Therapy (20) have made practice recommendations on neuraxial anesthesia and during the COVID- 19 pandemic. In their joint statement, regional anesthesia is not contraindicated for COVID-19-positive patients and should be preferred for providing anesthesia care wherever possible. The choice of anaesthesia method in our institution was consistent with the recommendations about regional anaesthesia. There was a statistically significant increment in the percentage of operations performed with regional anaesthesia (11% to 28%, $p<0.001$) after the start of the pandemic. Many gynecological procedures can be performed under regional anaesthesia without intubation or supraglottic airway device insertion, minimising the hazard to the operating team. In our institution, there was a decrement in the percentage of hysteroscopic operations performed with GA-LMA and increment in the percentage of hysteroscopic operations performed with RA-Spinal after the start of the pandemic period. Although there is no adequate literature about safety of supraglottic airway devices, they seem to be more insecure in context of COVID-19 transmission because of the possible continuous leakege from the airway.

There is no consensus in the literature regarding whether laparoscopy or laparotomy is superior under pandemic conditions. In laparoscopic surgery, the technique-pneumoperitoneum brings about the risk of aerosol exposure to the operating team (14). Aerosol exposure is reported to occur during the release of CO2 which occurs mostly during the procedures involving ports and removal of pneumoperitoneum at the end of surgery. Risks of smoke inhalation to operation room staff during laparoscopic surgery has also been documented (21).

Abstaining general anaesthesia can not be carried out for laparoscopic surgery but certain emergency gynaecological procedures such as ruptured ectopic pregnancy or ovarian torsion can be performed via minilaparotomy under regional anaesthesia. In our institution, the percentage of operations performed for extra uterine pregnancy, ovarian cyste rupture/ torsion, tubo ovarian abscess and ovarian cysts with laparoscopic technique had decreased after the start of pandemic when compared with the period before the start of the pandemic. Addition to this, total percentage of laparoscopic operations had also decreased after the start of COVID-19 pandemic.

CONCLUSION

By taking alterations and fluctations in community prevalence into consideration, decisions about cancellation of surgeries must be made dynamically. It is a great challenge to make the arrangements between the need to maintain surgical treatment and the risk to patients who may experience worse outcomes if they contract COVID-19. Possibility of COVID-19 infection must be considered in every patient. In anaesthesia management, regional anaesthesia methods may be considered in appropriate cases. Proper PPE must be used if airway manipulations are needed

ETHICAL DEVCLARATIONS

Ethics Committee Approval: After ethical approval was taken from both local ethics committee (Ankara City Hospital-E1-1-21-1732-14.04.2021, and the Ministry of Health (2021-03-09T23_29_08).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Mahase E. Covid-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ 2020; 368: 1036.
2. Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis 2020; 6: 656-7.
3. Lin Q, Abraham M, Wen D, et al. Management of gynecology patients during the coronavirus disease 2019 pandemic: Chinese expert consensus. Am J Obstet Gynecol 2020; 223: 3-8.
4. Wang J, Du G. COVID-19 may transmit through aerosol. Ir J Med Sci 2020; 189: 1143-4.
5. Greenland JR, Michelow MD, Wang L, London MJ. COVID-19 infection: implications for perioperative and critical care physicians. Anesthesiology 2020; 132: 1346-61.
6. Chang D, Xu H, Rebaza A, Sharma L, Dela Cruz CS. Protecting healthcareworkers from subclinical coronavirus infection. Lancet Respir Med 2020; 8: 13.
7. Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three monthsin England. BMJ 2020 Mar 18; 368: m1106.
8. Inslee orders halt to elective surgeries and dental services to reserve critical equipment for COVID-19 health care workers. Washington Governor Jay Inslee; 2020. Accessed,https://www.governor.wa.gov/news-media/inslee-ordershalt-elective-surgeries-and-dental-services-reserve-critical-equipment. [Accessed 3 April 2020].

9. Fowler AJ, Dobbs TD, Wan YI, Laloo R, Hui S. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg 2021; 108: 97-103.
10. Keles E, Akis S, Öztürk UK, Özyürek EŞ, Api M. Gynecological surgeries during the COVID-19 pandemic in Turkey. Int J Gynecol Obstet 2020; 151: 141–62.
11. Xia Y, Jin R, Zhao J, et al. Risk of COVID-19 for cancer patients. Lancet Oncol 2020; 21: 181.
12. Thomakos N, Pandraklakis A, Bisch SP, et al. Int J Gynecol Cancer 2020; 30: 728–9.
13. The European Network of Gynaecological Cancer Advocacy Groups. ESGO-ENGAG e-survey: perspective of gynecological cancer patients during COVID-19 pandemia, 2020. Available: https://engage.esgo.org/esgo-engage-survey perspectivegynecological-cancer-patients-covid-19-pandemia. [Accessed 26 May 2020].
14. ESGE. Recommendations on gynaecological laparoscopic surgery during covid-19 outbreak. https://esge.org/wpcontent/ uploads/2020/03/ Covid19 Statement ESGE .pdf; 2020.
15. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46: 854-87.
16. World Health Organization. Coronavirus disease (COVID-19) technical guidance: infection prevention and control.https:// www.who.int/emergencies/ diseases/novel-coronavirus-2019/ technical-guidance/infection-prevention-and-control.
17. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS ONE 2012; 7: e35797.
18. Lie SA, Wong SW, Wong LT, Wong TGL, Chong SY. Practical considerations forperforming regional anesthesia: lessons learned from the COVID-19 pandemic. Can J Anesth Can Anesth 2020; 67: 885-92.
19. Zhong Q, Liu YY, Luo Q, et al. Spinal anaesthesia for patients with coronavirus disease 2019 and possible transmission rates in anaesthetists:retrospective, single-centre, observational cohort study. Br J Anaesth 2020; 124: 670-5.
20. Uppal V, Sondekoppam RV, Lobo CA, Kolli S, Kalagara HKP. Practice recommendations on neuraxial anesthesia and peripheral blocks during the COVID-19 pandemic, ASRA/ESRA COVID-19 Guidance for Regional Anesthesia March 31, 2020 www.asra.com/covid-19/radguidance
21. Zheng MH, Boni L, Fingerhut A. Minimally invasive surgery and the novel coronavirus outbreak: lessons learned in China and Italy. Ann Surg 2020; 272: 5-6

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.946296

Anatolian Curr Med J 2021; 3(3); 227-233

A new grading system for evaluation of uroflowmetry-EMG results (Gülhane Grading System)

Burak Köprü[1], Hasan Cem Irkılata[2], Giray Ergin[1], Turgay Ebiloğlu[3], Bahadır Topuz[3], Yusuf Kibar[1], Murat Dayanç[4]

[1]Koru Ankara Hospital, Urology Clinic, Ankara, Turkey
[2]Isparta Private Davraz Life Hospital, Urology Clinic, Isparta, Turkey
[3]Gülhane Training and Research Hospital, Department of Urology, Ankara, Turkey
[4]Private Pediatric Urology Center, Ankara, Turkey

Cite this article as: Köprü B, Irkılata HC, Ergin G, et al. A new grading system for evaluation of uroflowmetry-EMG results (Gülhane Grading System). Anatolian Curr Med J 2021; 3(3); 227-233.

ABSTRACT

Aim: It is recommended that dysfunctional voiding diagnosis should made by the repeated uroflowmetry simultaneously pelvic floor electromyography (UF-EMG) + post-void residual measurements. However, there is no evaluation system for UF-EMG parameters regarding the clinical diagnosis, follow up and treatment of these patients. In our study, we aimed to create a new grading system for the diagnosis of dysfunctional voiding by using UF-EMG parameters.

Material and Method: We have retrospectively obtained UF-EMG and lower urinary tract symptom score results that performed to the children whom applied to our clinic with the symptoms of dysfunctional voiding between 2010 and 2015. A total of 856 reports were included into this retrospective cohort analysis. The proper 610 UF-EMG tests were graded according to our grading system. The UF-EMG grading system is divided into 6 grades: Grade 0: No EMG activity and normal uroflowmetry, Gradenon-EMG: Disturbed flow pattern with no EMG activity, Grade 1: EMG activity with no disturbed flow pattern, Grade 2: EMG activity with minimally disturbed flow pattern, Grade 3: EMG activity with moderately disturbed flow pattern, Grade 4: EMG activity with extremely disturbed flow pattern.

Results: There was no statistically significant difference between the demographic data of patient and control groups ($p>0.05$). According to grading system, day and nighttime incontinence were statistically significant increases as the grades increases (respectively, $p<0,001$, $p=0,023$). According to grading system we created as the grades increased the UF-EMG parameters and the questions of lower urinary tract dysfunction symptom score which evaluated the voiding phase results were statistically significant ($p<0.05$).

Conclusion: Grading system will be helpful to interpreting the results of the UF-EMG, which considered to be relatively difficult and thus, the diagnosis of the patients can be easier to evaluate and respond to the treatment by urologist.

Keywords: Lower urinary tract dysfunction, dysfunctional voiding, uroflowmetry-EMG, grading system

INTRODUCTION

Dysfunctional voiding (DV) is defined as habitually contractions of the external urethral sphincter during urination in children (1). Formerly, obtaining staccato patterns at repeated uroflowmetry (UF) tests or invasive urodynamic investigation were suggested for the diagnosis of DV (2.3). However, recent guidelines have suggested to perform repeated UF and electromyography (EMG) of pelvic floor muscles (UF-EMG) for the diagnosis and follow-up of DV which also led us to move away from invasive techniques for the evaluation of lower urinary tract dysfunction (LUTD) (4-6).

Uroflowmetry is a simple and non-invasive test which evaluates the voiding phase of lower urinary tract (LUT). The integration of UF results with pelvic floor EMG recordings increases the adequacy of DV diagnosis (3-5). Several nomograms were defined by using UF rates according to gender among healthy children, which aimed to establish normal UF references (7,8).

UF-EMG has already been proven as a reliable method for the diagnosis of the voiding disorders in children (4-6,9). The flow curve pattern, UF parameters and pelvic floor activity during voiding can concomitantly be evaluated

Corresponding Author: Burak Köprü, dr_burak83@yahoo.com

Received: 01.06.2021 **Accepted:** 10.06.2021

by UF-EMG. However, there is no definitive nomogram that leads to stages for voiding dysfunction by UF-EMG findings. The aim of this study to develop a new simple, understandable grading system [Gülhane Grading System (GGS)] which might lead us to reach easy decision of therapies for DV based on the data of EMG activities among 610 patients who performed UF-EMG.

MATERIAL AND METHOD

This retrospective study was approved by the Ethical Committee of Gülhane Military Medical Academy (Date: September 2012, Decision No: 1491-99-12/1648.4-4950) and followed the Institution's Review Board of Human Subject Guidelines. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. We have retrospectively obtained a total of 856 UF-EMG tests performed children without any neurological or anatomical deficit between September 2010 to October 2015. All performed UF-EMG studies were analyzed by two different pediatric urologists. Children with LUTS were evaluated by lower urinary tract dysfunction symptom score (LUTDSS) defined by Akbal et al. (10) along with UF-EMG analysis. The data of the patients including physical examination, 3-day bladder diary, urine analysis, urine culture, urinary ultrasonography, post-void residual urine (PVR) was also obtained.

In our center, standard urotherapy, voiding training, regulation of daily fluid, stay away from colorful liquids (coke, fruit juice etc.) and fiber rich diet for the prevention of constipation were recommended to children with DV.

LUTDSS is a diagnostic tool for the diagnosis of LUTD in children with a score of 8.5 or greater had voiding abnormalities, with 90% sensitivity and 90% specifity (10). The questionnaire was composed of the following items: daytime urinary incontinance (Q1,2), nighttime urinary incontinance (Q3,4), frequency (Q5), voiding habits as strain, pain during voiding, intermittency (Q6,7,8,9), bladder habits as urgency and urge incontinance (Q10,11,12), constipation (Q13) and quality of life.

UF-EMG studies were performed by the expert nurse (MMS 5000, Medical measurement system 5000, USA) in our urodinamy study center. In our clinic, all patients were informed about UF-EMG procedure for reduce the anxiety as a routine clinical practice. Bladder volume was assessed by ultrasonography (Bladder Scan BVI 6100, Bothell, WA) to ensure expected bladder capacity (EBC) is enough to perform for UF. EBC was calculated using Koff's formula (11). Superficial surface electrodes used for recording the external sphincter EMG activity were placed at 3 and 9 o'clock positions at the perineum and third electrode placed to left thigh. PVR was measured by ultrasonography (Bladder Scan BVI 6100) immediately after voiding. We have included into our analysis the following parameters recorded by UF-EMG: expected bladder capacity, voided volume (VV), voiding time (VT), average flow rate (Qave), maximum flow rate (Qmax), maximum flow rate time (T-Qmax), EMG activity and PVR.

Gülhane Grading System (GGS)

The reports with any artefact were not graded. The stratification of EMG activities that reflects the voiding pattern was the key parameter for our new scale.

GGS was defined in to 6 grades as Grade 0: Patients with bell curve type voiding curve and without EMG activity (**Figure 1A**), Grade 1: EMG activity with not disrupt the voiding curve (**Figure 1B**), Grade 2: EMG activity that does not disrupt the voiding curve minimally, EMG activity that does not cause deep notches in the voiding curve during voiding (**Figure 1C**), Grade 3: moderately disrupted voiding curve, patients with EMG activity leading to staccato or plateau type voiding curve (**Figure 1D**), Grade 4: Patients with EMG activity leading to intermittent voiding curve (**Figure 1E**), Grade non-EMG: the disrupt voiding curve without EMG or delayed activity was determined (**Figure 1F**).

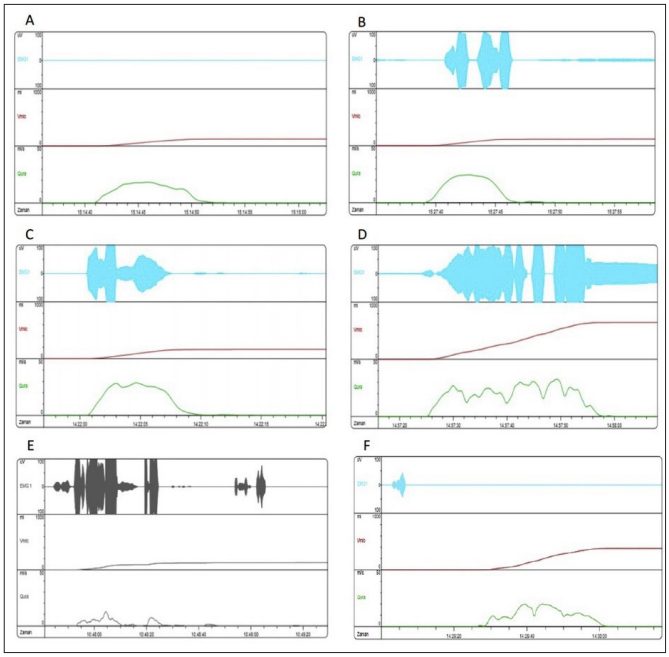


Figure 1. A: Grade 0 UF-EMG sample image according to GGS, **B:** Grade 1 UF-EMG sample image according to GGS, **C:** Grade 2 UF-EMG sample image according to GGS, **D:** Grade 3 UF-EMG sample image according to GGS, **E:** Grade 4 UF-EMG sample image according to GGS, **F:** Gradenon-EMG UF-EMG sample image according to GGS

After analyzing the reports and demographical data of the patients we have excluded the children with anatomical abnormality, acute or chronic urinary tract infection, urolithiasis, neurologic lesions, chronic constipation and any records with artefacts due to the wet skin or cross talking of the electrodes. Among 729

reports, a total 610 patient data were included into the statistical analysis (**Figure 2**). After completion of retrospective data obtaining, we also have performed LUTDSS and UF EMG to 119 healthy children to demonstrate the normal values of UF-EMG.

The children with any LUTS and LUTDSS > 8.5 were assigned as patient group, whereas the children with LUTS and LUTDSS score as 0 in control group. Study flow chard was given in **Figure 2**.

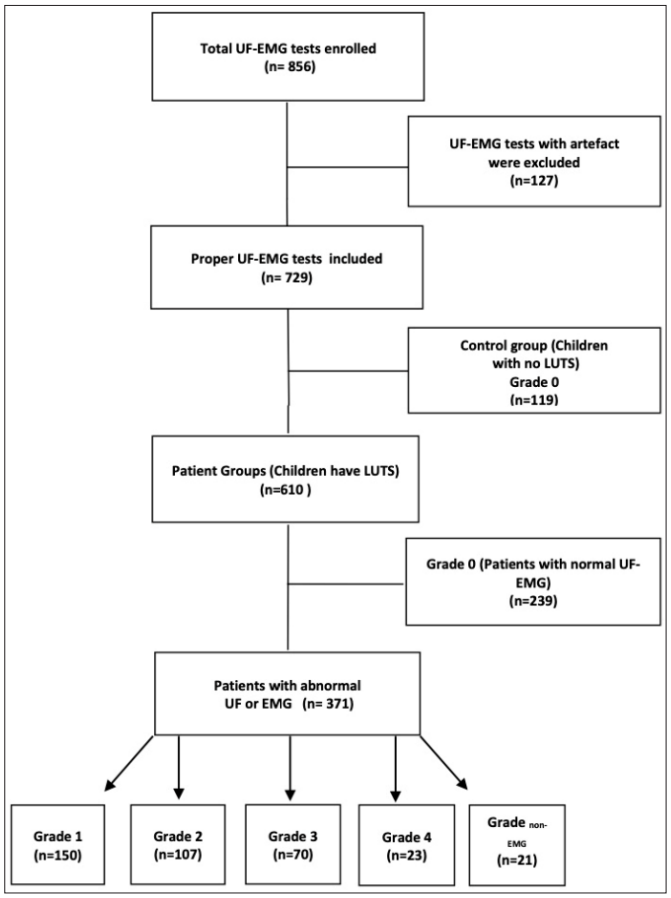


Figure 2. Study flow-chart

Statistical Analysis

The statistical analysis was using the Statistical Package for Social Sciences 15.0 software (SPSS 15.0 package program, Collage Station, TX, USA). Descriptive statistic was calculate using number, percentage, standard deviation, minimum and maximum as proper. In comparisons between groups, Mann Whitney-U test was used for advanced paired comparisons. Student-T test was used in the comparison of 2 groups. The Chi-Square test was used to compare discrete variables. Log formation was used for the abnormally distributed data for the reach normality. Spearmen Correlation test was used to evaluate the linear relationship between variables. p<0.05 level was considered statistically significant.

RESULTS

A total 610 UF-EMG (433 female, 177 male) patients and 119 UF-EMG (75 female, 44 male) control (p=0.188) have been included to our study. The mean age was 8.90±2.91 for patient group and 9.02±2.86 for control group (p=0.168). There was no statistically significant difference between patient and control groups regarding age and gender. The analysis of patient and control groups' with GGS grades, mostly grade 0 was detected in the patient group (39%) and no grade 4 was detected in control group (**Table 1**).

Table 1. UF-EMG results of the patient and control group according to GGS

Group		Patient (n=610)		Control (n=119)	
		n	%	n	%
Grade	0	239	39	90	76
	1	150	25	17	15
	2	107	18	9	7
	3	70	12	3	2
	4	23	3.7	0	0
	non-EMG	21	3.3	0	0

There was a statistically significant positive correlation between the mean age and GGS grades (r=0.128, p=0.002) and negative correlation between the mean age and LUTDSS total score (r=-0.208 p<0.001). The comparison analysis showed that the mean age was sequentially increasing by increase in GGS grades (**Table 2**). The female patients had statistically significantly higher GGS grades compared to male patients (p<0.001) (**Table 2**).

When we further analyzed the LUTDSS questionnaire by GGS scale; there was a statistically significantly increase in presence and the severity of incontinence (Q1, Q2) by increasing GGS grade (p<0.001). The comparison of nighttime symptom questions (Q3, Q4) showed statistically significant difference by increase in GGS grade (p<0.001 for Q3 and P=0.023 for Q4). No significant difference was found regarding the Q5 which reflects the voiding frequency of the patient (p=0.26). The analysis of Q6,7,8,9 that examine the voiding habits and voiding phase, only straining (Q6) and intermittency (Q8) showed statistically significant differences between GGS grades (p<0,001). The questions that reflect the bladder habits (Q10, 11) showed no difference by GGS grades except Q12 which indicates bladder storage (p=0.016). All the results were depicted in **Table 3**.

When we analyzed all UF parameters results according to GGS scale, all the parameters showed significant deterioration by GGS grade. The results were summarized in **Table 4**. The spearmen correlation analysis showed that there was a statistically significant positive correlation between GGS grades and EBC, VV, VT, TQmax and PVR. The Qwave and Qmax values did not show statistically significant correlation with GGS scores (**Table 5**).

Table 2. Patients' demographic data and LUTSS questions according to GGS

Grup		Grade 0 n= 239		Grade 1 n=150		Grade 2 n=107		Grade 3 n= 70		Grade 4 n=23		Grade non-EMG n=21		p
Age	Mean±SD (Min-max)	8.29± 2.79 (5-17)		8.60±2.82 (5-17)		9.41±3.15 (5-19)		9.58±2.93 (5-16)		9.78±2.53 (6-15)		9.95±2.68 (5-17)		0.012
		n	%	N	%	n	%	n	%	n	%	n	%	
Gender	Female	147	61.3	105	70.1	88	82.2	61	87	23	100	12	57.1	<0.001
	Male	92	38.6	45	29.9	19	17.8	9	13	0	0	9	42.8	
LUTSS	Mean±SD (Min-max)	11.04±6.40 (1-31)		12.02±6.56 (1-33)		12.90±6.78 (1-32)		14.31±6.89 (1-35)		14.52±5.62 (4-27)		14.19±6.21 (5-24)		0.50
	Sometimes	87	14.2	63	10.3	37	6.6	24	4.0	8	1.3	11	1.8	
	Mostly	80	13.1	33	5.4	39	6.4	18	3.0	3	0.5	7	1.1	
	Seriously	18	2.9	20	3.2	7	1.1	12	2.0	1	0.1	2	0.3	

LUTSS: Lower urinary tract dysfunction symptom score

Table 3. The Comparison of LUTSS questionnaire by GGS

Group		Grade 0 n=239		Grade 1 n=150		Grade 2 n=107		Grade 3 n=70		Grade 4 n=23		Grade non-EMG n=21		p
Q1: Does your child have urinary incontinence during the day?	No	87	14.3	57	9.3	26	4.2	9	1.5	3	0.4	3	0.5	<0.001
	Sometimes	114	18.8	78	12.8	60	9.8	41	6.7	11	1.8	13	2.1	
	1-2 times/day	27	4.6	10	1.6	7	1.1	12	2.0	8	1.3	5	0.8	
	3 or more times/day	11	1.9	5	0.8	14	2.2	8	1.3	1	0.1	0	0	
Q2: How wet is your child during the day?	A few drops	78	12.7	43	7.0	50	8.2	37	6.0	5	0.8	10	1.6	<0.001
	Only underwear wet	64	10.5	41	6.7	22	3.6	19	3.1	14	2.3	8	1.3	
	Pants soaking wet	10	1.6	9	1.5	8	1.3	4	0.6	1	0.1	0	0	
Q3: Does your child have urinary incontinance during the night?	No	75	12.2	41	6.7	51	8.4	28	4.6	10	1.6	10	1.6	<0.001
	1-2 nights/week	107	17.7	83	13.6	31	5.0	26	4.3	11	1.8	11	1.8	
	3-5 nights week	39	6.4	14	2.3	8	1.3	6	9.8	2	3.0	0	0	
	6-7 nights/week	18	3.0	12	19.6	17	2.8	10	1.6	0	0	0	0	
Q4: How wet is your child during the night?	Underwear wet	67	10.9	43	7.0	17	2.8	20	3.2	6	9.8	8	1.3	0.023
	Bed wet	97	15.9	66	10.8	39	6.4	23	3.8	7	1.1	3	0.5	
Q5: How many times does your child void?	1-7/Day	134	21.9	93	15.2	69	11.3	50	8.2	13	2.1	11	1.8	0.263
	More than 7/Day	105	17.2	57	9.4	38	6.2	20	3.3	10	1.6	10	1.6	
Q6: My child has to strain to pee.	No	203	33.2	126	20.6	67	10.9	46	7.5	12	2.0	14	2.3	<0.001
	Yes	36	5.9	24	3.9	40	6.5	24	3.9	11	1.8	7	1.1	
Q7: My child feels pain during voiding	No	203	32.1	120	19.6	84	13.7	51	8.4	21	3.4	19	3.1	0.103
	Yes	36	5.9	30	5.0	23	3.7	19	3.1	2	0.3	2	0.3	
Q8: My child pees intermittently when on the toilet.	No	186	30.4	106	17.3	63	10.3	41	6.7	10	1.6	12	1.9	<0.001
	Yes	53	8.6	44	7.2	44	7.2	29	4.8	13	2.1	9	1.4	
Q9: My child has to go to revisit the toilet to pee soon after his/her pee.	No	184	30.1	117	19.1	83	13.6	48	7.9	13	2.1	16	2.6	0.133
	Yes	55	9.2	33	5.4	24	3.9	22	3.6	10	1.6	5	0.8	
Q10: My child has to run to the toilet when s/he feels the need to pee.	No	53	8.8	43	7.0	34	5.5	20	3.2	9	1.5	4	0.6	0.223
	Yes	167	27.3	107	17.5	73	12.0	50	8.2	14	2.3	17	2.8	
Q11: My child can hold his/her pee by crossing his/her legs, squatting, or doing the "pee dance."	No	115	18.9	85	14.0	63	10.3	35	5.7	14	2.3	9	1.4	0.336
	Yes	124	20.3	65	11.1	44	7.2	35	5.7	9	1.5	12	2.0	
Q12: My child wets his/her clothes before reaching the toilet.	No	106	17.3	84	13.7	69	11.3	42	6.9	11	1.8	11	1.8	0.016
	Yes	133	21.8	66	10.8	38	6.2	28	4.6	12	2.0	10	1.6	
Q13: My child does not pass stool every day.	No	196	32.2	133	21.8	85	14.0	49	8.0	19	3.1	14	2.2	0.113
	Yes	43	7.1	17	2.8	22	3.6	21	3.4	4	0.6	7	1.1	
Quality of life:Does this affect his/her family life or social life?	No	54	9.0	34	5.5	24	4.0	16	2.6	11	1.8	1	0.01	0.011
	Sometimes	87	14.2	63	10.3	37	6.6	24	4.0	8	1.3	11	1.8	
	Mostly	80	13.1	33	5.4	39	6.4	18	3.0	3	0.5	7	1.1	
	Seriously	18	2.9	20	3.2	7	1.1	12	2.0	1	0.1	2	0.3	

LUTSS: Lower urinary tract dysfunction symptom score; Q: Question

Table 4. Patient group's uroflowmetry parameters analysis according to grading system

Group		Grade 0 n= 239	Grade 1 n=150	Grade 2 n=107	Grade 3 n= 70	Grade 4 n=23	Gradenon-EMG n=21	P
EBC (ml)	Mean±SD (Min-max)	287.85±83.93 (150-540)	288.2±84.77 (180-540)	312.33±94.77 (180-600)	317.57±88.09 (180-510)	323.47±76.19 (210-480)	328.57±81.22 (210-540)	0.012
VV (ml)	Mean±SD (Min-max)	195.80±167 (36-660)	195.62±104.00 (43-530)	261.90±171.33 (30-980)	315.44±203.31 (75-1100)	269.43±151.43 (55-571)	320.52± 98.56 (122-660)	<0.001
VT (sec)	Mean±SD (Min-max)	18.18±13.6 (6-108)	19.64±10.71 (7-77)	25.84±22.56 (8-231)	29.32±11.46 (11-57)	48.43±25.99 (14-116)	33.52±11.32 (13-57)	<0.001
Qave (ml/sec)	Mean±SD (Min-max)	13.95±4.68 (5-30)	12.35±4.45 (5-25)	11.24±6.20 (4.33)	10.72±4.37 (3-21)	6.82±3.33 (3-16)	11.61±5.57 (6-18)	<0.001
Qmax (ml/sec)	Mean±SD (Min-max)	21.9±9.57 (8-57)	22.31±9.84 (5-66)	24.55±11.48 (3-62)	25.02±9.55 (7-48)	17.52±7.82 (7-33)	26.52±6.45 (16-48)	0.002
T-Qmax (sec)	Mean±SD (Min-max)	6.80±6.06 (1-65)	6.19±4.48 (1-27)	8.35±5.92 (2-37)	9.55±5.87 (1-38)	22.00±37.23 (2-172)	9.61±5.68 (4-26)	<0.001
PVR (ml)	Mean±SD (Min-max)	22.98±15.50 (0-225)	21.92±11.62 (0-190)	42.85±19.02 (0-339)	54.52±15.91 (0-277)	64.95±20.60 (0-142)	60.04±12.36 (0-225)	<0.001

EBC: Expected bladder capacity, VV: voided volume, VT: Voiding time, Qave: Average flowrate, Qmax: Peak flowrate, T-Qmax: Peak flowrate time, PVR: Post voiding residua

Table 5. The statistical correlation between grades and UF-EMG parameters

		EBC	VV	VT	Qvave	Qmax	T-Qmax	PVR
GGS Grade	r *	0.140	0.261	0.288	-0.016	0.05	0.227	0.117
	p *	0.001	<0.001	<0.001	0.697	0.216	<0.001	0.004

* Pearson correlation test, EBC: Expected bladder capacity; VV: voided volume; VT: Voiding time; Qave: Average flowrate; Qmax: Peak flowrate; T-Qmax: Peak flowrate time; PVR: Post voiding residua

DISCUSSION

Uroflowmetry is the main important evaluation test that analysis the voiding phase of LUT. Simultaneous assessment of UF with pelvic floor EMG along with PVR test gives much valuable information about LUTD diagnosis and severity (4). The aim of this study was to create a new simple grading system depends on UF-EMG findings by the presence of EMG activity for to determine the severity of DV.

LUTDSS is a non-invasive questionnaire including the day and night incontinence with filling-phase symptoms and voiding-phase symptoms (10). In our study, there was no significant differences between GGS grades regarding LUTDSS, although correlation showed mild significance. This result led us to suggest that LUTDSS evaluates the voiding and storage phase of bladder at the same time, however GGS was designed according to UF-EMG test which evaluate the voiding phase of bladder.

The bell-shaped curve defined in healthy child is regardless from gender, age and voided volume (6). In our study, the most common patient group was grade 0 patients with a bell-shaped curve. Although the LUTDSS of those patients was higher than 8.5, their UF-EMG findings were similar with the control group. Samijn et al. (12) reported 50-60% of children with LUTS void on the bell-shaped curve and suggested that initiation to the procedure with a UF alone and followed by a measurement of UF with EMG. Similar with this study, we have found the rate of Grade 0 and Grade 1 which were bell shaped curve in 54% of the patient.

This complex situation might be due to the incorrect interpretation of LUTDSS questions by families of the patients whom might have nocturnal enuresis. Nocturnal enuresis is common clinical disorder which has primary or mono symptomatic types and has a deep impact on affected children and their families (13,14). Furthermore, repeated UF-EMG tests in those patients would help to make the definitive diagnosis.

The urgency symptom is a predominant symptom in the overactive bladder and a silent pelvic floor or minimal EMG activity during voiding, which does not affect the voiding curve is a guide for the diagnosis of overactive bladder in children (2,15). In our study, the incidence of urgency symptom (Q10) decreased as the grades increased. That results might be due to the low grade GGS patients have more profoundly overactive bladder also GGS gives information about the voiding phase.

ICCS suggested that to perfom repeated UF-EMG tests for the diagnosis of DV. Mostly, in DV uroflow pattern show staccato pattern and interrupted pattern with EMG activity due to the lack of the sphincter relaxation during voiding (16).

A staccato or fluctuating uroflow pattern is considered representative for DV. Additionally, interrupted-shaped flow pattern might be seen in patients with DV. Wenske et al. (17) reported that staccato or interrupted flow curve was associated with a 40.7% incidence of an active pelvic floor EMG during voiding at DV. In this study, the rate of DV is 41.6% among only staccato pattern.

Remaining 59.3% of patients with staccato, interrupted or mixed uroflow pattern had a quiet pelvic floor EMG during voiding. These patients were ultimately diagnosed as primary bladder neck dysfunction (PBND) in 27.9%, detrusor underactivity in 15.2%, and idiopathic detrusor overactivity disorder in 16.1%. Therefore, majority of staccato or interrupted flow patterns were not associated with DV in this study (17). According to them, EMG positivity during voiding is vital for the diagnosis of DV. Increased pelvic floor muscle activity can cause staccato or interrupted, and sometimes depressive (plateau-like) voiding patterns. Rarely, a bell voiding pattern might be seen during positive EMG. We believe that the most of Grade 3 patients have DV and Grade 4 patients have DV with under active bladder.

PBND is a disease characterized by weak voiding flow due to delay or incomplete opening of the bladder neck during voiding. The EMG lag time is defined in the UF-EMG test is also a peciluar finding to PBND (6,9,18). Plateau voiding flow is a low-amplitude voiding pattern due to the bladder outlet obstruction and in UF-EMG mostly does nothave EMG activation during voiding (6). Taken all these together, Gradenon-emg indicates the primary bladder neck dysfunction and bladder outlet obstruction in patient groups.

The abnormal contractions of sphincter during voiding could lead to negative effect on uroflowmetry parameters like Qave, VT, Qmax, T-Qmax and PVR. The contracts of external urethral sphincter during voiding causes decrement in Qave, Qmax and increment in VT, T-Qmax and PVR.

In our study we have found the statistically significant decrease in Qave and increase in VT, Qmax, T-Qmax and PVR by GGS grades. Also, the mean age of patients showed statistically significant increase with increasing of grades. We also determined the statistically significant increases of EBC and VV by GGS grades. We believed that the increment of Qmax along with the increase in grades depends on this situation because in DV we expected decreases of Qmax while increase the severity of disease. The positive correlation between UF parameters and GGS finding is supportive for the conclusion regarding increasing grade of GGS is reflective for severity of LUTD.

Dysfunctional voiding is more common and has severe clinical manifestation in females (19,20) then males. In our study, girls showed a statistically significant higher grade of GGS.

Here, this new grading system developed by the presence of EMG activity of UF-EMG test which performed in the initial evaluation of the DV might be very informative for the diagnosis of severity of the disease and decision of treatment type. We believe that the easy interpretation of UF-EMG results with our new grading system provides clear and effortless practice at outpatient urology clinics.

The main limitations of our study are the retrospective design and single center analysis which limits the generalization of the data. Our findings might shed light on the future larger sample sized, prospective validation studies.

CONCLUSION

For both diagnosis and follow-up of DV is a complex and our new GGS grading system is easy technique in this field for routine urology practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gülhane Military Medical Academy (Date: September 2012, Decision No: 1491-99-12/1648.4-4950).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Wenke S, Van Batavia JP, Combs AJ, Glassberg KI. Analysis of uroflow patterns in children with dysfunctional voiding. J Pediatr Urol 2014; 10: 250-4.
2. Norgaard JP, van Gool JD, Hjalmas K, Djurhuus JC, Hellstrom AL. Standardization and definitions in lower urinary tract dysfunction in children. International Children's Continence Society. Br J Urol 1998; 81: 1-16.
3. Neveus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006; 176: 314-24.
4. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: update report from the Standardization Committee of the International Children's Continence Society. J Urol 2014; 191: 1863-5.
5. Chase J, Austin P, Hoebeke P, McKenna P. The management of dysfunctional voiding in children: a report from the Standardisation Committee of the International Children's Continence Society. J Urol 2010; 183: 1296-302.

6. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society Neurourol Urodyn 2016; 35: 471-81.
7. Kajbafzadeh AM, Yazdi CA, Rouhi O, Tajik P, Mohseni P. Uroflowmetry nomogram in Iranian children aged 7 to 14 years. BMC Urol 2005; 16: 5-3.
8. Gupta DK, Sankhwar SN, Goel A. Uroflowmetry nomograms for healthy children 5 to 15 years old. J Urol 2013; 190: 1008-13.
9. Combs AJ, Grafstein N, Horowitz M, Glassberg KI. Primary bladder neck dysfunction in children and adolescents I: pelvic floor electromyography lag time--a new noninvasive method to screen for and monitor therapeutic response. J Urol 2005; 173: 207-10
10. Akbal C, Genc Y, Burgu B, Ozden E, Tekgul S. Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. J Urol 2005; 173: 969-73.
11. Koff SA. Estimating bladder capacity in children. Urology 1983; 21: 248.
12. Samijn B, Van Laecke E, Vande Walle J, et al. Uroflw measurement combined with electromyography testing of the pelvic floor in healthy children. Neurourol Urodid 2019; 38: 231-8.
13. Kılıç A, Hacıhamdioğlu DÖ, Tural E, Karademir F. Evaluation of neuropsychological development of children diagnosed with primary monosymptomatic nocturnal enuresis: A pilot study. Turk J Urol 2020; 46: 320-5
14. Ferrara P, Franceschini G, Mercurio S, Del Vescovo E, Ianniello F, Petitti T. The adverse effects of oral desmopressin lyophilisate (MELT): personal experience on enuretic children. Turk J Urol 2018; 44: 51-5.
15. Abrams P, Cardoso L, Fall M, et al. The standardization of terminology in lower urinary tract function: report from the standardisation subcommittee of the International Continence Society. Urology 2003; 61: 37-49
16. Sinha S. Dysfunctional voiding: A review of the terminology, presentation, evaluation and management in children and adults. Indian J Urol 2011; 27: 437-47.
17. Wenske S, Combs AJ, Van Batavia JP, et al. Can staccato and interrupted/fractionated uroflow patterns alone correctly identify the underlying lower urinary tract condition? J Urol 2012; 187: 2188-93.
18. Sharifi-Rad L, Seyedian SL, Fatemi-Behbahani SM, Lotfi B, Kajbafzadeh A. Impact of transcutaneous interferential electrical stimulation for management of primary bladder neck dysfunction in children J Pediatr Urol 2020; 16: 36.
19. Corcos J, Schick E. Prevelence of overactive bladder and incontinence in Canada. Can J Urol 2004; 11: 2278-84.
20. Ergin G, Kibar Y, Ebiloğlu T, et al. The role of urinary nerve growth factor for the diagnosis and assessment of the biofeedback success in children with dysfunctional voiding. J Pediatr Urol 2016; 12: 118.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.950216

Anatolian Curr Med J 2021; 3(3); 234-238

Evaluation of YouTube videos related to intubation in the pandemic process in terms of quality and content in Turkish and English

Münire Babayiğit[1], Mustafa Alparslan Babayiğit[2]

[1]Keçiören Training and Research Hospital, Department of Anesthesiology and Reanimation, Ankara, Turkey
[2]Public Health Consultant, Ankara, Turkey

Cite this article as: Babayiğit M, Babayiğit MA. Evaluation of YouTube videos related to intubation in the pandemic process in terms of quality and content in Turkish and English. Anatolian Curr Med J 2021; 3(3); 234-238.

ABSTRACT

Aim: YouTube videos, which are used as sources of information, can also be an essential resource in intubation training. For this reason, we aimed to investigate the content, adequacy, and reliability of the training videos on intubation in our searches in Turkish and English.

Material and Method: This study was carried out between8 May to 9 May 2021by searching Youtube in Turkish and English with 'entübasyon' and 'intubation.' Forty four videos that met the inclusion criteria were included. Intubation indication, explanation of complications, number of views, number of likes, video power index (likes ratio*view rate/100) were recorded in the video content. Ten items were scored over ten total points after the subject content was evaluated.

Results: Although the number of views, the number of likes, and the power index values were higher in English videos, the difference was not statistically significant ($p>0.05$). No significant difference was found between Turkish and English videos in the quality evaluation ($p>0.05$). Although it was seen that the approach to the patient diagnosed with Covid-19 (30.4% vs. 9.5%) and the pediatric approach (8.7% vs. 0.0%) were mentioned at higher rates in the English videos, no significant difference was detected ($p>0.05$).

Conclusions: Video sharing on endotracheal intubation in Turkish and English has similar features. Educational videos are shared in Turkish, especially by academic institutions.

Keywords: Intubation, internet, video, YouTube

INTRODUCTION

Avicenna (980-1037) described the first endotracheal intubation practice. Curry performed the first human cadaver intubation in 1792. Magill first applied intubation in 1920 to give anesthesia. It was used for the first time in Turkey by Dr Burhaneddin Toker and Dr. Sadi Sun in 1949 (1). The intubation process provides keeping the airway open, controlling the airway and breathing, relieving the respiratory burden, and preventing aspiration.

It is crucial to make the necessary preparations for intubation, position the head and neck appropriately, and place the laryngoscope correctly. In addition, it is an intubation procedure that is desired to select the proper size tube, provide sedation and remove secretions, and then advance the tube between the vocal cords as soon as possible with non-traumatic movement (2,3). When done correctly and quickly, without causing morbidity, intubation is life-saving by providing a reliable airway. It is an essential part of in-service training for every healthcare worker to acquire intubation skills (1-4).

Millions of videos are shared on YouTube, the video-sharing site established in February 2005, and the number of shared videos is increasing day by day. There are also many videos on health-related topics on the site where almost every subject is shared (5). It is thought that online information sharing and search for education and health issues have increased, especially during the pandemic. However, the fact that video sharing is free and professional competence is not sought raises doubts about the reliability of the information (6-9).

Corresponding Author: Münire Babayiğit, mnroksuz@hotmail.com

Received: 09.06.2021 **Accepted:** 28.06.2021

In the Covid-19 pandemic caused by the SARS-COV-2 virus, significant changes and restructurings have occurred in the health system. In this process, in-service training was organized, and the training of intubation, which is one of the primary duties of health workers, was repeated. However, there may be difficulties in conducting this training face-to-face. During the pandemic process, it is seen that educational videos for health professionals have been published along with the videos published on subjects such as the transmission routes of the disease and prevention. When the literature is examined, no study has been found that evaluates intubation videos on YouTube as a source of information. For this reason, we aimed to investigate the content, adequacy, and reliability of the training videos on intubation in our searches in Turkish and English.

MATERIAL AND METHOD

This observational study was carried out on Youtube between 8 May to 9 May 2021 by searching in Turkish and English with entübasyon and intubation. In the study, 44 of the elective endotracheal and rapid serial endotracheal intubation videos, in Turkish and English, with a duration of 2-20 minutes, were included. Videos in other languages containing other topics, repetitive, containing advertisements, non-educational, non-audio narration, and advanced airway applications such as nasotracheal intubation, fiberoptic intubation, retrograde intubation were excluded study. Two researchers analyzed the videos. Due to nature of this study, ethics committee approval was not obtained.

Intubation indication, explanation of complications, number of views, number of likes, video power index (likes ratio*view rate/100) were recorded in the video content. It was recorded whether the intubation application was shown on the patient, on a model, or as an animation. Subject content-preparation, tools, 2-Preoxygenation, 3-Anesthesia, paralysis, 4-Ventilation, 5-Difficult ventilation, 6-Intubation phase, 7-Difficult intubation, 8-Confirmation, 9-Post-intubation management, 10-Management in the case of failed intubation , the explanation of management issues were evaluated. The content was scored over ten total points.

Intubation expression was recorded in pediatric and adult patients. In the video content, the features of intubation in patients with a diagnosis of Covid-19 or suspected were examined. In addition, the video tutorial was evaluated by a public health specialist and an experienced anesthesiologist as 1: little, 2: moderate, 3: very useful for healthcare professionals who have no experience with intubation, and it was recorded.

Statistical Analysis

Continuous variables, median (minimum-maximum), categorical data were expressed as numbers and percentages. In the intergroup analysis of continuous variables, normality analyzes were performed with the Kolmogorov-Smirnov Goodness of Fit Test. Mann Whitney U Test was used for comparisons between groups as the data were not suitable for normal distribution. Chi-square test (Fisher's exact test when necessary) was used to compare categorical data. Analyzes were performed with IBM SPSS Package Program version 22.0 (IBM Corporation, Armonk, NY, USA). Cases where the type 1 error level was below 5% were considered statistically significant.

RESULTS

The median video length of Turkish videos is 7.2 (2.1-19) minutes, the content is 6 (1-11), the number of views is 11.662 (14-4.160.600), the number of likes is 143 (7-36.000), the number of dislikes is 6 (0-1200) and power index median value is 10.917 (10 – 1.497.816.000), while median video length of English videos is 6.5 (2-19) minutes, content is 6 (2-9), number of views is 28.336 (764 -972.269), the number of likes was 173 (0-11.000), the number of dislikes was 7 (0-292), and the median value of the power index was 19.818 (0 - 96.605.410). Although the number of views, the number of likes and the power index values were higher in English videos, the differences were not statistically significant (p>0.05) (**Table 1**).

Table 1. Comparison of Turkish and English intubation videos published on YouTube according to some features

	Turkish videos [Median (min-max)] (n=21)	English videos [Median (min-max)] (n=23)	p
Video length	7.2 (2.1-19)	6.5 (2-19)	0.689*
Content	6 (1-10)	6 (2-9)	0.487*
Number of views	11.662 (14-4.160.600)	28.336 (764-972.269)	0.142*
Number of likes	143 (7-36.000)	173 (0-11.000)	0.613*
Number of dislikes	6 (0-1200)	7 (0-292)	0.612*
Powerindex	10.917 (10–1.497.816.000)	19.818 (0–96.605.410)	0.549*

* Mann Whitney U Test

While the rate of finding indications in English videos (43.5%) was higher than in Turkish videos (28.6%), the difference was not significant (p>0.05). The complication rate was found to be statistically significantly higher in Turkish videos (28.6%) than in English (4.3%) videos (p=0.042). It has been observed that no wrong,

incorrect or misleading information was given in any of the videos. While the application rates were higher in Turkish videos (76.2% vs. 47.8%), the application rates were higher in English videos on the patient (21.7% vs. 4.8%), but there was no significant difference (p>0.05).). No significant difference was found between Turkish and English videos in the quality evaluation (p>0.05). Although it was seen that the approach to the patient diagnosed with Covid-19 (30.4% vs. 9.5%) and the pediatric approach (8.7% vs. 0.0%) was mentioned at higher rates in the English videos, no significant difference was detected (p>0.05) (**Table 2**).

Table 2. Comparison of Turkish and English intubation videos published on YouTube according to features such as application content and quality

	Turkish Videos (n=21)	English Videos (n=23)	p
Indication expression (n,%)			0.360*[a]
No	15 (71.4%)	13 (56.5%)	
Yes	6 (28.6%)	10 (43.5%)	
Complication expression (n,%)			0.042*[a]
No	15 (71.4%)	22 (95.7%)	
Yes	6 (28.6%)	1 (4.3%)	
Video uploader (n,%)			0.232*
Academic Institution	13 (61.9%)	16 (69.6%)	
Individual	8 (38.1%)	5 (21.7%)	
Unknown	0 (0.0%)	2 (8.7%)	
Contents of application (n,%)			0.150*
No	1 (4.8%)	4 (17.4%)	
Patient	1 (4.8%)	5 (21.7%)	
Mannequin	16 (76.2%)	11 (47.8%)	
Animation	3 (14.3%)	3 (13.0%)	
Instructiveness (n,%)			0.953*
Little	4 (19.0%)	5 (21.7%)	
Middle	11 (52.4%)	11 (47.8%)	
Very	6 (28.6%)	7 (30.4%)	
Application in Covid-19 (n,%)			0.137*[a]
No	19 (90.5%)	16 (69.6%)	
Yes	2 (9.5%)	7 (30.4%)	
Patient population (n,%)			0.384*
Pediatric patient	0 (0.0%)	2 (8.7%)	
Adult patient	20 (95.2%)	20 (87.0%)	
Pediatric and adult patient	1 (4.8%)	1 (4.3%)	

* Chi-square test ([a]Fisher's exact test)

DISCUSSION

Every healthcare worker should know about intubation and cardiopulmonary resuscitation. Even though in-service training was organized on these subjects at regular intervals, face-to-face training was interrupted during the pandemic process, and online training was primarily organized via the internet. Therefore, YouTube videos are of great importance as an educational tool in that they can be accessed anywhere, anytime, even via phones. In particular, the need for training on intubation has increased. Giving intubation training primarily on models is preferred as a safe method (10). Our study observed that the applications mainly were made on models in video types in both languages. There was no statistically significant difference between the two groups regarding application demonstrations on the model or the patient. Unlike our study, it was stated in other studies on intubation that the practices were more frequently demonstrated on patients. Because our study was carried out during the pandemic process, it is thought that the applied videos on the model may have been shared more.

A study shows that internet users perceive themselves as more competent and in control due to accessing information found on a website (11). The presence of visual expression in addition to theoretical knowledge increases interest and learning. Especially in medical interventions, visual representation is preferred by healthcare professionals. However, the reliability of the videos on the narration of medical practices is questioned, and academic studies are carried out on this subject. Pant et al., in their study, examined Youtube videos about acute myocardial infarction. They reported that the reliability of the posts on this life-threatening issue is low, that video recordings of traditional associations are not available on this site, and that some information given to patients is risky (5). Our study determined that most of the videos in both languages were prepared by academic institutions. It has been observed that no wrong, incorrect or misleading information was given in any of the videos. In these videos, in which a specific medical application is explained, it is seen that the narrators are health professionals and provide reliable information.

Endotracheal intubation is an important procedure that must be done meticulously and risky in transmission, since it is a procedure with high viral load, upper respiratory tract secretions and aerosol release. The healthcare worker performing the endotracheal intubation is close to the patient's airway before, during, and after the procedure (11).

Some protective measures and protocols are recommended for the intubation of patients diagnosed with COVID-19 (11-13). Using intubation boxes to prevent droplet spread, performing procedures in isolation rooms suitable for airborne infections, performing intubation practices with a separate special team, and only necessary personnel enter the operation room, cleaning and disinfection of the room after the procedure and the use of personal protective equipment (PPE) are some of these (11,12). In particular, the use of WCE and the participation of a limited number of personnel in the procedure are important, and it was observed that these precautions were explained in all videos that talked about intubation in a patient with COVID-19.

In a study evaluating the content and quality of information about intubation videos on YouTube, the posts were insufficient and unsafe in terms of content (15). Akça et al., in their study, examined the videos published in English in which rapid serial intubation was explained and found that the majority of the videos did not comply with the ACLS-RSI (Advanced Cardiac Life Support-Rapid Sequence Intubation) guideline (16). In our study, ten items were created by adding additional criteria to these criteria, and evaluation was made over ten points. The median values of the content of the videos in both languages were found to be similar, with 6/10. In general, every step of the intubation application was not explained, and in some videos, only endotracheal tube placement was explained. However, when the researchers on endotracheal intubation examined the videos, it was determined that half of the videos were helpful as a learning tool and one-third were very useful.Two studies evaluate YouTube videos as a general information source for tonsillectomy and ventilation tube placement specific to otolaryngology. Both studies found that the percentage of correct and valuable videos was less than 25% (17,18). Compared to these studies, in which videos of patients and their relatives are shared, it is seen that there is a more reliable and helpful information rate in our study since health professionals share the technique of applying a medical skill.

Airway management and intubation attempt are some of the essential medical skills for healthcare professionals. Intubation and mechanical ventilation may be required to ensure adequate oxygenation in respiratory failure. Respiratory failure due to diffuse lung involvement may also develop in the COVID-19 clinic. In many countries, the number of patients has exceeded the health system's capacity due to the pandemic. In these extraordinary conditions, while anesthesiologists and health personnel with intensive care experience were assigned to intensive care units, the number and capacity increasing day by day, all elective health practices were terminated, and other health workers were assigned to pandemic services. Therefore, intubation practices were sometimes performed by healthcare professionals other than anesthesiologists or intensive care physicians.

CONCLUSION

In our age, online content that can be found anytime and anywhere on laptops, tablets, and smartphones is replacing the use of traditional textbooks. It is seen that video sharing for medical applications such as endotracheal intubation is an important learning tool, and useful videos are shared in Turkish, especially by academic institutions.

ETHICAL DECLARATIONS

Ethics Committee Approval: Due to nature of this study, ethics committee approval was not obtained.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Relationship between Financial Support and Interest: There is no person/organization that supports the study financially and the authors do not have any interest-based relationship

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Luckhaupt H, Brusis T. History of intubation. Laryngologie, Rhinologie, Otologie 1986; 65: 506-10.
2. Wang HE, Yealy DM. How many attempts are required to accomplish out-of-hospital endotracheal intubation? Acad Emerg Med 2006; 13: 372-7.
3. Asai T, Marfin AG. Ease of insertion of the laryngeal tube during manual-in-line neck stabilisation. Anaesthesia 2004; 59: 1163-6.
4. Lim M, Celaschi DA. Rapid sequence intubation: how do we define success? Can J Anaesth 2004; 51: 858.
5. Pant S, Deshmukh A, Murugiah K, et al. Clinical investigations assessing the credibility of the ‘‘ YouTube approach ’’ to health ınformation on acute myocardial ınfarction. Clinical Cardiology 2012; 285: 281-5.
6. Yuksel B, Cakmak K. Healthcare information on YouTube : Pregnancy and COVID - 19. Int J Gynaecol Obstet 2020; 150: 189-93.
7. Li HO, Bailey A, Huynh D, Chan J. YouTube as a source of information on COVID-19: a pandemic of misinformation? BMJ Glob Health 2020; 5: e002604.
8. Ramirez MG, Rojas Travesedo RG, Martinez AA. YouTube and coronavirus : analysis of video consumption on the COVID-19 pandemic YouTube y coronavirus : análisis del consumo de vídeos sobre la. Rev Lat Comun Soc 2020; 78: 121-53.
9. Ataç Ö, Özalp YC, Kurnaz R, Güler OM, İnamlık M, Hayran O. Youtube as an Information Source During the Coronavirus Disease (COVID-19) Pandemic: Evaluation of the Turkish and English Content. Cureus 2020; 12: e10795.
10. Yüksel EM, İzdeş S. Safe intubation, sedation and neuromuscular block in COVID-19. In: Yamanel HL (Ed). Critical Care and COVID-19. 1st edition. Ankara: Türkiye Klinikleri 2020; 21-6.
11. Lemire M, Sicotte C, Paré G. Internet use and the logics of personal empowerment in health. Health Policy 2008; 88: 130-40.
12. Duggan LV, Mastoras G, Bryson GL. Tracheal intubation in patients with COVID-19. CMAJ 2020; 192: E607.
13. Matava CT, Kovatsis PG, Summers JL, et al. Pediatric airway management in covıd-19 patients - consensus guidelines from the society for pediatric anesthesia's pediatric difficult ıntubation collaborative and the Canadian Pediatric Anesthesia Society. Anesth Analg 2020; 13: 10.
14. Brewster DJ, Chrimes N, Do TB, et al. Consensus statement: Safe Airway Society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group. Med J Aust 2020; 212: 472-81.

15. Ocak U. Evaluation of the content, quality, reliability and accuracy of YouTube videos regarding endotracheal intubation techniques. Niger J Clin Pract 2018; 21: 1651-5.
16. Akça AH, Şaşmaz Mİ. YouTube for Rapid Sequence Intubation Learning , Is It Reliable ? Van Tıp Derg 2018; 25: 207-12.
17. Sorensen JA, Pusz MD, Brietzke SE. International Journal of Pediatric Otorhinolaryngology YouTube as an information source for pediatric adenotonsillectomy and ear tube surgery. Int J Pediatr Otorhinolaryngol 2014; 78: 65-70.
18. Strychowsky JE, Nayan S, Farrokhyar F, Maclean J. International Journal of Pediatric Otorhinolaryngology YouTube : A good source of information on pediatric tonsillectomy ? Int J Pediatr Otorhinolaryngol 2013; 77: 972-5.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.951923

Anatolian Curr Med J 2021; 3(3); 239-245

Real-life data of tenofovir disoproxil fumarate and tenofovir alafenamide fumarate in the patients with chronic hepatitis B: a single-center experience

Mustafa Akar

Health Sciences University, Bursa Yüksek İhtisas Training and Research Hospital, Department of Gastroenterology, Bursa, Turkey

Cite this article as: Akar M. Real-life data of tenofovir disoproxil fumarate and tenofovir alafenamide fumarate in the patients with chronic hepatitis B: A single-center experience. Anatolian Curr Med J 2021; 3(3); 239-245.

ABSTRACT

Aim: Chronic hepatitis B (CHB) infection can cause liver cirrhosis and hepatocellular carcinoma. In this study, it was aimed to evaluate the efficacy of tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF) on clinical parameters, glomerular filtration rate (GFR), and phosphorus metabolism in the patients with CHB.

Material and Method: Eighty one patients with CHB treated with TDF were included in the study retrospectively. Twenty seven of them switched from TDF to TAF during the follow-up were considered as TAF group. Fifty four patients continued TDF were evaluated as TDF group.

Results: The mean ages of the patients were 45±12 and 48±15 years, and the mean durations of TDF treatment were 31±20 and 52±32 months in the TDF and TAF groups, respectively. The mean duration of TDF treatment was significantly higher in the TAF group (p: 0.01). The mean GFR and serum phosphorus levels of the patients before/after the TDF treatment were 99/103 ml/min and 2.9/3.1 mg/dl in the TDF group, respectively. The mean GFR and serum phosphorus levels of the patients before the TDF treatment/at the time of the switch/after the TAF treatment were 90/100/102 ml/min and 2.8/2.3/2.9 mg/dl in the TAF group, respectively. Increase in the mean level of phosphorus after the switch were found significant ($p < 0.05$). The mean GFR levels of the patients switched due to low GFR showed a significant decrease under the TDF treatment and a significant increase after the TAF treatment. A significant improvement was observed in the total hip and spine T score of the patients who were switched to TAF due to osteoporosis.

Conclusion: TAF used in the treatment of CHB has a similar efficacy with TDF, and it has more positive effects on creatinine clearance, bone mineral density, and phosphorus metabolism than TDF.

Keywords: Chronic hepatitis B, hypophosphatemia, osteoporosis, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate.

INTRODUCTION

It is estimated that approximately 257 million people worldwide are chronically infected with hepatitis B virus, which is one of the major causes of chronic liver disease, liver cirrhosis, and hepatocellular carcinoma (HCC) (1-3). In these patients, the level of viral load in the serum and the risk of developing liver cirrhosis, HCC, and other liver-related complications are directly related (4). Therefore, it is a necessity of suppressing the viral load at undetectable levels with treatment in patients with chronic hepatitis B (CHB).

There are 6 oral nucleos(t)ide analogue antiviral agents that have been approved by the Food and Drug Administration (FDA) so far in the treatment of CHB (5). Lamivudine was the first oral antiviral agent to be approved for this purpose in 1998. One of the most important disadvantages of using lamivudine is the development of resistance at a rate of 60-70% in 5 years (6,7). By 2005, entecavir, which has a higher resistance barrier compared to lamivudine, was introduced, especially in naive patients. However, in 5 years with entecavir, the resistance rate found in naive patients was 1.2%, while this rate was 51% in lamivudine-resistant patients (8,9). For this reason, drugs with higher resistance barriers have been developed over time. Tenofovir disoproxil fumarate (TDF), which has been used for CHB since 2008, has a very high resistance barrier and no resistance has been

Corresponding Author: Mustafa Akar, ms-akar@hotmail.com

Received: 13.06.2021 **Accepted:** 28.06.2021

reported in 8 years of period (10). However, some of the patients using TDF have reported the risk of developing renal tubular dysfunction and osteopenia/osteoporosis in the long term (11).

Tenofovir alafenamide fumarate (TAF), which is a prodrug just like TDF and contains tenofovir, received FDA approval in the treatment of CHB in 2016 (5,12). It has been reported that TAF, which contains about 90% lower tenofovir concentration than TDF, has a high resistance barrier like TDF and excellent efficiency, and also has more positive effects on renal functions, serum phosphorus levels, and bone metabolism (13-16). At the same time, no resistance has been reported in the 3-year use of TAF (17).

Phosphorus is involved in cell membrane integrity, nucleic acid formation, ATP production, cell signaling, buffering of acid-base balance, and bone mineralization. Therefore, keeping serum phosphorus levels within normal limits is crucial (18). With the change in the national reimbursement guideline for about the last 2 years, the use of TAF in CHB patients in Turkey has been approved with the established rules. In this study, it was aimed to evaluate the efficacy of TDF and TAF on clinical parameters, GFR, and phosphorus metabolism in the patients with CHB.

MATERIAL AND METHOD

Ethics committee approval of the study was obtained from Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee (Date: 17.02.2021, Decision No: 2011-KAEK-25 2021/02-03) The study was conducted in accordance with the Declaration of Helsinki ethical standards.

The patients with CHB treated with TDF in the gastroenterology outpatient clinic, Bursa Yüksek İhtisas Training and Research Hospital, between March 2016 and March 2021 were evaluated retrospectively. Demographic and clinical data of the patients were obtained from the outpatient follow-up files. The patients who were switched from TDF to TAF aligned with the national reimbursement guideline during the follow-up were considered as TAF group. The remaining patients continued on TDF treatment were considered as TDF group. The patients who have not completed the first 3 months of TAF use and did not attend regular follow-up were excluded. In addition, patients with less than 6 months of TDF use were also excluded from the study. TDF to TAF switch criteria were defined as follows: Hypophosphatemia; serum phosphorus level <2.5 mg/dl, osteoporosis; T score <-2.5 on BMD, low GFR; creatinine clearance <60 ml/min, and detectable HBV DNA; HBV DNA level > 20 IU/ml. Abnormal alanine aminotransferase (ALT) was defined according to the reference laboratory (for male >41 U/L, for female >33 U/L). GFR is calculated with modification of diet in renal disease (MDRD) formula (19). Hepatic fibrosis staging and histological activity index (HAI) score were assessed according to the Modified Ishak Scoring System (20).

Statistical Analyses

The data were analysed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, Illinois, USA). Conformity to normal distribution was evaluated with the "Kolmogorov-Smirnov" test. The data that could be measured and provided the parametric condition were given as mean±standard deviation. For data that could be measured and did not meet the parametric condition, the distribution was defined as median (min.-max.). Categorical variables were shown as numbers and percentages. Comparison of laboratory parameters during treatment was performed with repeated measures analysis of variance (ANOVA) test. Bonferroni test was used in multiple comparisons. In all statistical evaluations, $p < 0.05$ was considered significant.

RESULTS

In total 115 patients with CHB treated with TDF were evaluated retrospectively. 29 patients were excluded (22 had not regular follow-up, seven had a follow-up time < 6 months). Thirty two of the remaining 86 patients were switched from TDF to TAF during the follow-up. The reasons for the switch were as follows; 25 (78%) hypophosphatemia, three (9.4%) low GFR, two (6.3%) osteoporosis, and two (6.3%) detectable HBV DNA under the TDF treatment. Five patients switched from TDF to TAF were excluded in the hypophosphatemia group (four did not complete the 3-month TAF usage period and one left the treatment voluntarily). Thus, 27 patients were evaluated as the TAF treatment group. Fifty four patients who continued the TDF treatment were evaluated as the TDF group (**Figure 1**).

In the TDF group: The mean age of the patients was 45±12 years, 36 of them (67%) were male. The mean duration of TDF treatment was 31±20 (range: 6-96) months. Four (7%) of the patients had HBeAg positivity and 11 (20%) had a diagnosis of cirrhosis. As a comorbid disease; eight (15%) patients had hypertension and six (11%) patients had diabetes mellitus. The median HBV DNA level before the TDF treatment was 10.2x103 IU/ml. The mean HAI and fibrosis values were 8 (±2.4) and 2.8 (±1.5), respectively (**Table 1**). The mean aspartate aminotransferase (AST), ALT, GFR, and serum phosphorus level of the patients before/after the TDF treatment were 48/23 U/L, 67/25 U/L, 99/103 ml/min, and 2.9/3.1 mg/dl, respectively. Decrease in the mean

values of transaminases after the TDF treatment was significant (p<0.001). There were no significant changes in the mean GFR value and serum phosphorus level under the TDF treatment. Detectable HBV DNA was detected in two (4%) patients under the TDF treatment. The mean duration of TDF use in the patients with detectable HBV DNA was 17 months. Abnormal ALT level was detected in five (9%) patients under the TDF treatment. Three of these patients had grade-2 hepatosteatosis on ultrasonography. The other two patients had liver cirrhosis. No HBsAg loss or HBeAg seroconversion was observed during the treatment course (**Table 2**).

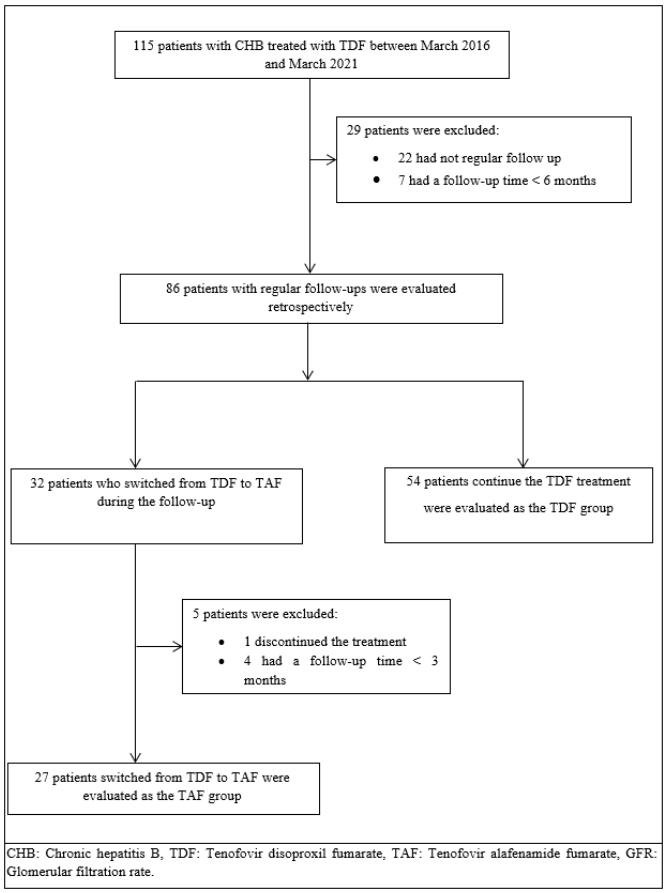


Figure 1. Flow diagram of the current study

Table 2. Changes in laboratory parameters of the patients continuing the TDF treatment (n: 54)

Variables	Baseline (before TDF)	The latest follow up (after TDF)	p
AST* (U/L)	48 (±50)	23 (±10)	<0.001
ALT* (U/L)	67 (±80)	25 (±14)	<0.001
Prevalence of abnormal ALT***, n (%)	23 (43)	5 (9)	0.002
Serum phosphorus* (mg/dl)	2.9 (±0.5)	3.1 (±0.7)	0.4
GFR*, ml/min	99 (±13)	103 (±16)	0.5
HBsAg loss, n	-	0	-
HBeAg seroconversion, n	-	0	-
Detectable HBV DNA, n (%)	54 (100)	2 (4)	-

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, GFR: Glomerular filtration rate
*: Mean (±Standard deviation)
**: Median (min-max)
***: Normal ALT cutoffs for male 41 U/L, female 33 U/L according to the reference laboratory

Table 1. Comparison of the baseline demographic, clinical, and laboratory characteristics between the groups (n: 81)

Characteristics	TDF group (n: 54)	TAF group (n:27)	p
Age* (years)	45±12	48±15	0.3
Gender (M), n (%)	36 (67)	16 (59)	0.5
HBeAg positivity, n (%)	4 (7)	3 (11)	0.3
Cirrhosis, n (%)	11 (20)	6 (22)	0.6
HBV DNA** (×10³ IU/ml)	10.2 (0.46-98026)	9.4 (0.47-82018)	0.1
HAI*	8 (±2.4)	8 (±1.7)	0.8
Fibrosis*	2.8 (±1.5)	3 (±2)	0.5
Duration of TDF (months)*	31 (±20) (min-max: 6-96)	52 (±32) (min-max: 6-120)	0.01
Duration of TAF (months)*	-	12 (±6) (min-max: 3-23)	-
AST* (U/L)	48 (±50)	42 (±34)	0.5
ALT* (U/L)	67 (±80)	51 (±51)	0.4
Prevalence of abnormal ALT***, n (%)	23 (43)	11 (41)	0.7
Serum phosphorus* (mg/dl)	2.9 (±0.5)	2.8 (±0.3)	0.5
GFR*, ml/min¶	99 (±13)	90 (±15)	0.02
Comorbid diseases			
HT, n (%)	8 (15)	5 (19)	0.6
DM, n (%)	6 (11)	3 (11)	0.9
CKD, n (%)	-	3 (11)	-

M: Male, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, HAI: Histologic activity index, GFR: Glomerular filtration rate, DM: Diabetes mellitus, HT: Hypertension, CKD: Chronic kidney disease
*: Mean (±Standard deviation)
**: Median (min-max)
***: Normal ALT cutoffs for male 41 U/L, for female 33 U/L according to the reference laboratory
¶: Three patients with chronic kidney disease in the TAF group were not included in the statistical analysis

In the TAF group: The mean age of the patients was 48±15 years, 16 of them (59%) were male. The mean durations of TDF and TAF treatment were 52±32 (range: 6-120) and 12±6 (range: 3-23) months, respectively. Three (11%) of the patients had HBeAg positivity and six (22%) had a diagnosis of cirrhosis. As a comorbid disease; five (19%) patients had hypertension, three (11%) patients had diabetes mellitus, and three (11%) patients had chronic kidney disease (CKD). One of these patients with CKD was receiving TDF from a renal dose, once in every other day (her GFR level was 43 ml/min). The median HBV DNA level before the TDF treatment was 9.4×103 IU/ml. The mean HAI and fibrosis values were 8 (±1.7) and 3 (±2), respectively (**Table 1**). The mean AST, ALT, GFR, and serum phosphorus level of the patients before the TDF treatment/at the time of the switch/after the TAF treatment were 42/22/21 U/L, 48/23/22 U/L, 90/100/102 ml/min, and 2.8/2.3/2.9 mg/dl, respectively. Decrease in the mean values of transaminases and serum phosphorus level after the TDF treatment, and increase in the mean serum phosphorus level after the switch were significant (p: 0.01 and 0.05, and 0.01, respectively). There was a significant increase in GFR values under the TDF treatment (p: 0.03). While detectable HBV DNA was detected in two (7%) patients under the TDF treatment, this was not observed in any patient after the TAF treatment. Abnormal ALT levels were detected in two (7%) patients in both the TDF and TAF groups. One of these patients had grade-2 hepatosteatosis on ultrasonography. The other patient had liver cirrhosis. No HBsAg loss or HBeAg seroconversion was observed during the treatment course (**Table 3**).

When the baseline demographic, clinical, and laboratory characteristics were compared between the groups, there was no significant difference except for the duration of TDF treatment and the mean GFR levels. The duration of TDF use was significantly higher in the TAF group (p: 0.01). The mean GFR level was significantly lower in the TAF group (p: 0.02) (**Table 1**).

In addition, the mean GFR values of three patients switched due to low GFR showed a significant decrease from 56 to 49 ml/min under the TDF treatment and a significant increase from 49 to 62 ml/min after the TAF treatment (**Figure 2**). A significant improvement was observed in the total hip and spine T score of the patients who were switched to TAF due to osteoporosis (-1.8 & -1.1 and -2.7 & -1.4, respectively) (**Figure 3**). No side effects that could discontinue the treatment were observed either under the TDF treatment or during the TAF treatment.

Table 3. Changes in laboratory parameters of the patients switched from TDF to TAF (n: 27)

Variables	Baseline (before TDF)a	At the time of the switch (before TAF)b	The latest follow up (after TAF)c	p
AST* (U/L)	42 (±34)	22 (±6)	21 (±7)	**a-b: 0.01** b-c: 0.9 **a-c: 0.01**
ALT* (U/L)	48 (±43)	23 (±12)	22 (±10)	**a-b: 0.01** b-c: 0.9 **a-c: 0.01**
Prevalence of abnormal ALT***, n (%)	11 (41)	2 (7)	2 (7)	**a-b: 0.003** b-c: 1 **a-c: 0.003**
Serum phosphorus* (mg/dl)	2.8 (±0.3)	2.3 (±0.4)	2.9 (±0.6)	**a-b: 0.05** **b-c: 0.01** a-c: 0.8
GFR*, ml/min¶	90 (±15)	100 (±14)	102 (±15)	**a-b: 0.03** b-c: 0.6 **a-c: 0.01**
HBsAg loss, n	-	0	0	
HBeAg seroconversion, n	-	0	0	
Detectable HBV DNA, n (%)	27 (100)	2 (7)	0	

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, GFR: Glomerular filtration rate
*: Mean (±Standard deviation)
**: Median (min-max)
***: Normal ALT cutoffs for male 41 U/L, female 33 U/L according to the reference laboratory
¶: Three patients with chronic kidney disease were not included in the statistical analysis

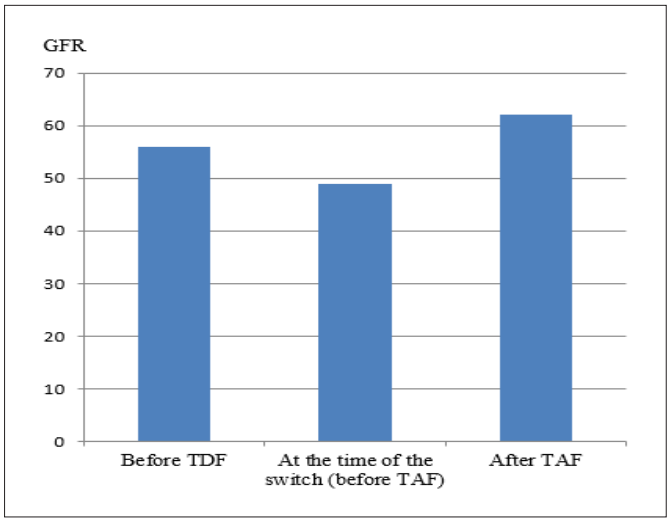


Figure 2. Mean changes in GFR in patients who are switched to TAF due to GFR <60 ml/min (n: 3)

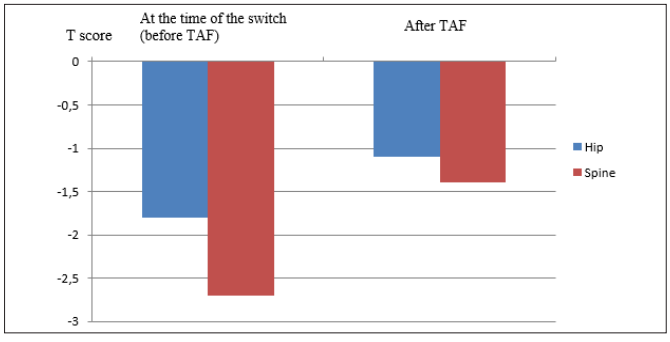


Figure 1. Mean changes in T score in patients who are switched to TAF due to osteoporosis (n: 2)

DISCUSSION

Only very few studies have been carried out worldwide on real-life data of TAF in the treatment of CHB. In addition, when the published literature is searched, only one study has yet been reported from Turkey (21). In this respect, this study is valuable in that it contains the second real-life data of Turkey, even it has a small patient group.

Sustained suppression of viral replication with treatment in CHB, reduces the level of liver inflammation, liver fibrosis, and the risk of HCC (22-24). Oral anti-virals, which are nucleos(t)ide analogs used in CHB treatment, are well tolerated and patient compliance is better the pegile interferon (25,26). In the long-term use of oral antiviral agents, resistance development and some side effects have been encountered (27). TAF has recently started to be used in the treatment of CHB and has a very high resistance barrier (12). Free serum tenofovir, which is mainly responsible for the systemic side effects of TDF, is eliminated from the urinary system via the proximal tubules. This can cause proximal tubular damage, hypophosphatemia, proteinuria, and decreased GFR (28-31).

Long-term use of TDF in HIV-positive patients has been shown to have negative effects on renal functions and BMD (28-30,32). In phase 3 studies, it has been shown that TAF used in the treatment of CHB in recent years has a similar anti-viral activity to TDF and, it has more positive effects on renal functions and bone metabolism than TDF (14-16). Lampertico et al. (16) have demonstrated that TAF has a similar anti-viral activity with TDF in patients with CHB. In addition, TAF was superior to TDF in terms of ALT normalization (according to the 2018 American Association for the Study of Liver Diseases criteria) and improved GFR and BMD. In a study, Kaneko et al. (33) conducted on patients with CHB, it was found that the use of TDF and TAF has similar anti-viral effects. However, it has been shown that there is a significant decrease in GFR as a result of using TDF for 48 weeks, and in patients who have switched from TDF to TAF, this decrease has been shown to improve significantly from the 4th week. In addition, no significant change was detected in serum phosphorus levels in patients with 48 weeks of TDF use or switched from TDF to TAF, while a significant improvement was observed in the urinary β2 microglobulin/creatinine ratio showing improved proximal renal tubular function in the switched group. In another 96-week study comparing TDF and TAF in patients with CHB, it was shown that TDF and TAF had similar anti-viral activity, but TAF's effects on both ALT normalization and BMD and GFR were more positive (34).

As a result of the 24-week follow-up of 75 CHB patients who were switched from TDF to TAF, a significant improvement was detected in BMD and some proximal renal tubular functions, while no change was detected in the mean GFR value (35). In another multi-center study, it has been revealed that TAF has more positive effects on BMD than TDF in the 2-year follow-up of patients with CHB (36). In a recent study, significant improvement was observed in proximal renal tubular functions (urinary beta2-microglobulin / creatinine and retinol-binding protein/creatinine ratios) and BMD in the 72-week follow-up of 61 CHB patients who were switched from TDF to TAF. However, it was determined that there was a decrease in the initial GFR values over time (96 & 90 ml/min). No significant change was found in serum phosphorus levels (3.2 & 3.1 mg/dl). They attributed this decrease in GFR to the basal chronic renal failure ground in some of the patients in the study (37).

In this study, similar to the literature, it has been shown that TAF has similar anti-viral activity with TDF. While there was no negative effect of TDF use on creatinine clearance, there was a significant increase in GFR level in the patients switched to TAF (**Table 2 and 3**). However, it was determined that the mean GFR value in three patients who switched to TAF due to low GFR (<60 ml/min) decreased significantly under the TDF treatment and increased significantly after the TAF treatment (**Figure 2**). It was noteworthy that the mean GFR values (56 ml/min) of these three patients at the beginning of treatment (before the TDF treatment) were significantly lower than the general average (99 and 90 ml/min) of all the patients. This situation suggested that TDF treatment causes a decrease in creatinine clearance only in the patients with low baseline GFR. However, long-term prospective studies involving large patient groups are needed to confirm this situation. In this study, it was found that serum phosphorus levels were significantly improved after the switch from TDF to TAF. This result showed that TAF had more positive effects on phosphorus metabolism. Similar to the literature, the total hip and spine T score values in our two patients who were diagnosed with osteoporosis while under the TDF treatment showed a significant improvement with the TAF treatment (**Figure 3**).

In TAF's pivotal phase 3 studies, it has been shown that TDF is superior to TAF in terms of HBsAg loss in patients with CHB (in the TDF group; 5/245, in the TAF group; 0/243). During the treatment, detectable HBV DNA (> 20 IU/ml) was detected in one patient in both groups. There was no significant difference between the two groups in terms of HBeAg seroconversion (16). In this study, HBsAg loss or HBeAg seroconversion was

not observed in any of the patients. The reason for this may be the small number of the patients in our study and the short duration of our treatment follow-up. It was remarkable that in the current study, measurable levels of HBV DNA (> 20 IU/ml) were detected under TDF treatment in two patients. When these patients were questioned for adherence retrospectively about whether they took their medicines every day, the patients stated that they were compliant and used their medicines regularly. In addition, it was found that the mean duration of TDF use of these patients was shorter than all the patients (17 & 31-52 months). This may explain the presence of detectable HBV DNA in these patients.

Limitations of the study: The most important limitation of this study is that is being a retrospective study. In addition, the study contains a small number of patients.

CONCLUSIONS

It has been found that TAF, which has recently been used in the treatment of CHB in our country as well as in the world, has a similar anti-viral activity to TDF and, it is superior in terms of its effects on serum phosphorus levels, GFR, and BMD. In patients with CHB in whom TDF is initiated, serum phosphorus levels should be checked regularly before and after the treatment. At the same time, BMD annual follow-up is required during the TDF treatment, especially in individuals at risk for osteoporosis. In addition, it is thought that TDF does not effect creatinine clearance in patients with normal basal GFR levels. Prospective and long-term studies involving large patient groups are needed to reveal the real-life data of TAF in patients with CHB more clearly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the ethics committee of Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital (Date: 17.02.2021, Decision No: 2011-KAEK-25 2021/02-03).

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that he has participated in the design, execution, and analysis of the paper, and that he has approved the final version.

REFERENCES

1. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Available at: http://apps.who.int/iris/handle/10665/255016. Accessed April 23, 2021.
2. Karagoz E, Tanoglu A. Clinical usefulness of HBsAg quantification in patients with chronic hepatitis B infection. Hepat Mon 2017; 17: e12293.
3. Hyun Kim B, Ray Kim W. Epidemiology of hepatitis B virus infection in the United States. Clin Liver Dis (Hoboken) 2018; 12: 1-4.
4. Konerman MA & Lok AS: Epidemiology, Diagnosis, and Natural History of Hepatitis B. In Sanyal AJ, Boyer TD, Lindor KD & Terrault NA (Eds.), Zakim and Boyer's Hepatology: A textbook of liver disease, 7th edition, Philadelphia; Saunders/Elsevier; 2018: pp. 474-84.
5. Abdul Basit S, Dawood A, Ryan J, Gish R. Tenofovir alafenamide for the treatment of chronic hepatitis B virus infection. Expert Rev Clin Pharmacol 2017; 10: 707-16.
6. Wright TL. Clinical trial results and treatment resistance with lamivudine in hepatitis B. Semin Liver Dis 2004; 24: 31–6.
7. Liaw YF. The current management of HBV drug resistance. J Clin Virol 2005; 34: 143–6.
8. Tenney DJ, Rose RE, Baldick CJ, et al. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virüs patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob Agents Chemother 2007; 51: 902-11.
9. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleosidenaïve patients is rare through 5 years of therapy. Hepatology 2009; 49: 1503-14.
10. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. J Viral Hepat 2017; 24: 68-74.
11. Gara N, Zhao X, Collins MT, et al. Renal tubular dysfunction during long-term adefovir or tenofovir therapy in chronic hepatitis B. Aliment Pharmacol Ther 2012; 35: 1317–25.
12. Liu Y, Chang S, Martin R, Flaherty J, Mo H, Feierbach B. Characterization of hepatitis B virus polymerase mutations A194T and CYEI and tenofovir disoproxil fumarate or tenofovir alafenamide resistance. J Viral Hepat 2021; 28: 30-9.
13. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol 2015; 62: 533–40.
14. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 185–95.
15. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol 2016; 1: 196–06.
16. Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol 2020; 5: 441-53.
17. Chan HLY, Marcellin P, Pan CQ, et al, editors. No Resistance to Tenofovir Alafenamide Detected Through 144 Weeks of Treatment in Patients With Chronic Hepatitis B [Poster 386]. AASLD: The Liver Meeting® 2018; 2018 09-13 November; San Francisco, CA.

18. Amanzadeh J, Reilly RF Jr. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. Nat Clin Pract Nephrol 2006; 2: 136-48.
19. Levey AS, Coresh J, Greene T, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247-54.
20. Ishak KG, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995; 22: 696-9.
21. Karasahin O, Akdemir Kalkan I, Dal T, et al. Real-life data for tenofovir alafenamide fumarate treatment of hepatitis B: the pythagoras Cohort. Hepat Mon 2021 21: e104943.
22. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010; 53: 348–56.
23. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010; 52: 886–93.
24. Lin CL, Kao JH. Risk stratification for hepatitis B virus related hepatocellular carcinoma. J Gastroenterol Hepatol 2013; 28: 10–7.
25. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261–83.
26. Jafri SM, Lok AS. Antiviral therapy for chronic hepatitis B. Clin Liver Dis 2010; 14: 425–38.
27. Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. Gastroenterology 2012; 142: 1360–8.
28. Casado JL. Renal and bone toxicity with the use of tenofovir: understanding at the end. AIDS Rev 2016; 18: 59-68.
29. Hall AM, Hendry BH, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV – infected patients: a review of the evidence. Am J Kidney Dis 2011; 57: 773-80.
30. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat 2011; 2011: 354908.
31. Koklu S, Gulsen MT, Tuna Y, et al. Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B. Aliment Pharmacol Ther 2015; 41: 310-9.
32. Haskelberg H, Hoy JF, Amin J, Ebeling PR, Emery S, Carr A; STEAL Studey Group. Changes in bone turnover and bone loss in HIVinfected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. PLoS ONE 2012; 7: e38377.
33. Kaneko S, Kurosaki M, Tamaki N, et al. Tenofovir alafenamide for hepatitis B virus infection including switching therapy from tenofovir disoproxil fumarate. J Gastroenterol Hepatol 2019; 34: 2004-10.
34. Agarwal K, Brunetto M, Seto WK, et al. GS-US-320-0110; GS-US-320-0108 Investigators. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol 2018; 68: 672-81.
35. Fong TL, Lee BT, Tien A, et al. Improvement of bone mineral density and markers of proximal renal tubular function in chronic hepatitis B patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. J Viral Hepat 2019; 26: 561-7.
36. Seto WK, Asahina Y, Brown TT, et al. Improved Bone Safety of Tenofovir Alafenamide Compared to Tenofovir Disoproxil Fumarate Over 2 Years in Patients With Chronic HBV Infection. Clin Gastroenterol Hepatol 2018: S1542-3565(18)30633-5.
37. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 weeks after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open 2020; 5: 258-63.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.959167

Anatolian Curr Med J 2021; 3(3); 246-250

Investigation of the potential use of VCAM-1, TNF-α, IL-10 and IL-6 as biomarkers of nickel exposure

Özgür Oztan[1], Vugar Ali Türksoy[2], Serdar Deniz[3], Engin Tutkun[2]

[1]HLC Medical Center, Department of Medical Management, Ankara, Turkey
[2]Yozgat Bozok University Faculty of Medicine, Department of Public Health, Yozgat, Turkey
[3]Malatya Turgut Ozal University Faculty of Medicine, Department of Public Health, Malatya, Turkey

Cite this article as: Oztan Ö, Türksoy VA, Deniz S, Tutkun E. Investigation of the potential use of VCAM-1, TNF-α, IL-10 and IL-6 as biomarkers of nickel exposure. Anatolian Curr Med J 2021; 3(3); 246-250.

ABSTRACT

Objectives: Industrial and agricultural activities such as mining, smelting, and the discharging of industrial and domestic wastewater have increased the severity of heavy metal pollution in environments. Nickel poisoning continues to be an important occupational health problem in many branches of industry, especially coating. Occupational exposure to nickel can occur through skin contact or inhalation of nickel-containing aerosols, dust, or fumes. As a result of the toxic effect of nickel, it can cause various health problems, including respiratory and dermatological effects.

Material and Method: The study included 56 male workers exposed to nickel in a coating factory (Ni-exposed group) and 44 non-exposed male workers (control group). Vascular Cell Adhesion protein (VCAM)-1, Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-10, and IL-6 levels of serum were analyzed using enzyme-linked immunosorbent assays (ELISA). Ni levels were determined using inductively coupled plasma mass spectrometry (ICP-MS) in urine samples.

Results: Significant intergroup differences were observed in the levels of all inflammatory parameters such as VCAM-1, TNF-α, IL-10 and IL-6 ($p<0.01$ for all).

Conclusions: The correlations between increased inflammatory biomarkers levels and exposed/control groups suggest a close relationship between inflammation and toxicity. This relationship provides a clinical model for the early diagnosis of nickel toxicity.

Keywords: Nickel exposure, coating workers, inflammation parameters, early diagnosis

INTRODUCTION

Heavy metals such as nickel are highly conservative and refractory elemental pollutants that produce irreversible physiological and biochemical changes in organisms. Industrial and agricultural activities such as mining, smelting, and the discharging of industrial and domestic wastewater have increased the severity of heavy metal pollution in environments (1). The International Agency for Research on Cancer classified nickel compounds as group 1, carcinogenic to humans (2). Occupational exposure to nickel can occur through skin contact or inhalation of nickel-containing aerosols, clouds of dust, or fumes. (3). Nickel poisoning continues to be an important occupational health problem in many branches of industry (4). Nickel toxicity may result with various health problems, including respiratory and dermatological effects (2). Nickel is not metabolized and poorly absorbed through the skin, which is eliminated via the urine (3). Nickel at a low level in biological and environmental specimens has become a critical research topic in terms of community health (5).

The advances achieved with biological-analytical techniques in the field of biomarkers accelerate the studies on the effectiveness of exposure to chemical agents, individual or population susceptibility, risk assessments, the dose-response relationship for chemicals and treatments (6). Tumor Necrosis Factor (TNF-α) is one of the pro-inflammatory cytokines mediating immune regulation (7,8). TNF-alpha has also been suggested to be an endogenous tumor promoter (9). Like TNF- α, Interleukin (IL)-6 plays an important pathophysiological role not only in inflammatory diseases but also in cancers. However, Vascular Cell Adhesion protein (VCAM-1), TNF-α, IL-10 and IL-6 especially play an important role in the interpretation of systemic inflammatory responses (7–11).

Corresponding Author: Vugar Ali Türksoy, draliturksoy@gmail.com

Received: 29.06.2021 **Accepted:** 11.07.2021

The correlations between increased inflammatory biomarkers levels and exposed/control groups suggest a close relationship between inflammation and toxicity. This relationship provides a clinical model for the early diagnosis for nickel toxicity. We aimed to evaluate the toxicity of nickel in Turkish coating workers. The research investigated the potential use of VCAM-1, TNF-α, IL-10 and IL-6 as biomarkers of nickel exposure and provides a clinical model for the inflammation that can be caused by nickel toxicity among the exposed workers in the coating industry.

MATERIAL AND METHOD

This study was conducted with the approval of Bozok University Ethics Committee (Date: 2.10.2016; Decision No: 69). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 56 male workers exposed to nickel in coating factories (Ni-exposed group) and 44 non-exposed male workers (control group). Nickel-exposed workers were selected among workers who are under risk of various toxic metals, including arsenic and cadmium. The exclusion criteria for all groups were acute infections (physical examination and/or imaging), chronic lung disease, diabetes mellitus, diagnosed coronary vascular disease, hypertension, rheumatic diseases, or cancer.

Collection of Serum Samples and VCAM-1, TNF-α, IL-10 and IL-6 Analysis

The serum was separated from blood samples by centrifugation at 1500 rpm for 10 min and then transferred to 2 mL Eppendorf tubes and frozen to -20 °C until analysis. For VCAM-1, TNF-α, IL-10 and IL-6 analyses were used in the respective ELISA kits and prepared the samples following manufacturer's instructions for each kit. The samples were then placed on microplates and analyzed using enzyme-linked immunosorbent assays (ELISA-BMG LABTECH, CLARIOstar model). The wavelength was set at 450 nm and r2 values, TNF-α, IL-10 and IL-6 of the calibration curves were obtained for VCAM-1 0.9993, for TNF-α 0.9998, for IL-10 0.9993 and for IL-6 0.9995 (11).

Collection of Urine Samples and Ni Analysis

For nickel analysis, 1 mL amounts of the urine samples were added to the Teflon tubes and then 5 ml 65% nitric acid and 5 ml ultra-pure water added to the tubes. For digestion sample was used Milestone microwave digestion system. After digestion, samples were transferred to 50 mL polypropylene tubes, added ultra-pure water to obtain the total volume of 20 mL, and stored at +4 °C until analysis (11). Ni levels were determined using inductively coupled plasma mass spectrometry (ICP-MS). The operating parameters of ICP-MS were set as follows: RF power 1550 W, nebulizer gas 0.90 L/min, plasma gas 0.80 L/min, nebulizer pressure 2.9 bar, dwell time 0.01 and spray chamber temperature 3.0°C. The sampler probe was washed between injections by rinsing with ultrapure water for 30 s, followed by washing with 2% HNO3 for 45 s then rinsing with ultrapure water for 45 s. After the wash steps, the instrument automatically ran the next sample. The r2 value of the calibration curve was calculated as 0.9998 and the interval of the calibration was set at 0.1–1000 µg/L nickel. Sample and standard of measurements were repeated three times. Method validations were performed with CRM-Seronorm™

Trace Elements Whole Blood L-2. CRM was measured 5 times on the same day and on different days. Moreover, the average of the repeated measurements was used for the validation of the method whereby the relative standard deviation (RSD) of the values did not exceed 5%. Coefficient of variation (CV) and recovery was found as %3.58 and %103.32, respectively. On the other hand, ICP-MS method for Ni analysis provided limit of detection (LOD) and lowest limit of quantification (LOQ) equal to 0.022 and 0.137, respectively.

Statistical Analysis

The SPSS 20.0 software was used in statistical analysis. The suitability of the parameters to the normal distribution was evaluated with the Kolmogorov Smirnov test. It was observed that the data were normally distributed and parametric tests were applied. Continuous variables were presented with their mean and standard deviations. The difference between the two means was evaluated with the t-test, and the relations of the variables with each other were evaluated with Pearson Correlation analysis.

RESULTS

This study included 100 male subjects, who were stratified into a control group of 44 subjects and a Ni-exposed group of 56 subjects. The mean age and BMI values of the control group and the exposure group were similar ($p>0.05$). Significant intergroup differences were observed in the levels of all inflammatory parameters such as VCAM-1, TNF-α, IL-10 and IL-6 ($p<0.01$ for all). Nickel levels in VCAM-1, TNF-α, IL-10 and IL-6 parameters were significantly higher in the exposure group. The relationships between the main parameters in all groups are presented in **Table 1**.

The positive correlations were found between Ni and VCAM-1 ($r=0.704$), TNF-α ($r=0.697$), IL-10 ($r=0.640$), and IL-6 ($r=0.268$) ($p<0.01$ for all). Among them, the strongest association was found between Ni and VCAM-1 ($p<0.01$). The IL-6 level also negatively correlated with the hemoglobin (HGB) ($r= -0,257$, $p<0.01$) and

Table 2. Pearson correlation coefficients of all tested parameters.

	BMI	WBC	HGB	HCT	PLT	ALT	AST	Ni Levels	VCAM-1	TNF-a	IL-10	IL-6
Age	0,333**	-0,065	0,013	-0,04	0,045	-0,11	-0,085	0,042	-0,091	-0,085	-0,092	-0,330**
BMI	1	-0,133	-0,003	-0,01	-0,101	0,177	0,104	0,007	0,084	0,17	0,182	-0,072
WBC		1	0,107	0,1	0,279**	0,036	0,004	0,024	0,004	-0,044	-0,08	0,063
HGB			1	0,913**	-0,028	0,235*	0,156	0,095	0,009	-0,011	-0,028	-0,257**
HCT				1	-0,16	0,239*	0,131	0,058	-0,029	-0,092	-0,09	-0,238*
PLT					1	0,18	0,147	-0,065	0,088	-0,065	-0,134	0,04
ALT						1	0,707**	0,137	0,113	0,097	0,027	-0,009
AST							1	0,138	0,032	0,046	0,035	-0,082
Ni Levels								1	0,704**	0,697**	0,640**	0,268**
VCAM-1									1	0,798**	0,577**	0,420**
TNF-a										1	0,888**	0,418**
IL-10											1	0,408**

Table 1. Differences in parameters between control and Ni-exposed groups (n=100).

	Groups	N	Mean	Std. Deviation	t	p
Age (years)	Control	44	36.57	10.05	0.724	0.471
	Ni-Exposed	56	38.00	9.64		
BMI (kg/m^2)	Control	44	26.85	2.59	1.303	0.196
	Ni-Exposed	56	27.61	3.09		
WBC (µl/ml)	Control	44	7.62	1.92	0.416	0.678
	Ni-Exposed	56	7.78	1.81		
HGB (g/dL)	Control	44	15.11	1.48	0.663	0.509
	Ni-Exposed	56	15.32	1.64		
HCT (%)	Control	44	45.31	3.83	0.335	0.738
	Ni-Exposed	56	45.57	3.76		
PLT (10^3/µL)	Control	44	243.25	49.66	1.182	0.240
	Ni-Exposed	56	230	59.92		
ALT (IU/L)	Control	44	22.48	12.23	1.656	0.101
	Ni-Exposed	56	27.48	16.85		
AST (IU/L)	Control	44	19.84	4.93	0.872	0.385
	Ni-Exposed	56	20.86	6.37		
Ni (µg/L)	Control	44	1.35	0.83	19.145	<0.001*
	Ni-Exposed	56	5.86	1.49		
VCAM-1 (ng/mL)	Control	44	4.41	1.91	10.545	<0.001*
	Ni-Exposed	56	12.21	5.1		
TNF-a (pg/mL)	Control	44	2.96	1.36	9.832	<0.001*
	Ni-Exposed	56	5.21	0.76		
IL-10 (pg/mL)	Control	44	30.67	8.69	7.972	<0.001*
	Ni-Exposed	56	41.8	3.62		
IL-6 (pg/mL)	Control	44	25.57	12.4	3.114	0.002*
	Ni-Exposed	56	34.49	16.24		

hematocrit (HCT) levels (r= -0,238, p<0.01) (**Table 2**).

DISCUSSION

As a very common metal used in alloys, nickel can be found in many forms such as metallic nickel, nickel alloy, oxidic nickel, soluble nickel, sulfidic nickel and nickel carbonyl. The major route of occupational nickel intake is oral, inhalation and dermal absorption. The contamination of nickel among workers depends upon several factors: aerodynamic size of particles, the concentration of nickel that is inhaled, ventilation rate of worker, the proper use of personal protective equipment, and the safety awareness of the worker. While the acute effects of nickel exposure are mostly associated with nickel carbonyl, chronic effects can be seen in all nickel forms, especially metallic nickel, and the most prominent chronic effects are lung and sinonasal cancers (12,13).

Nickel-induced carcinogenesis was found to be related to epigenetic changes, inflammation and generation of reactive oxygen species in many studies (14,15). In a study with nickel oxide nanoparticles, it was demonstrated that inflammation is triggered in lung epithelial cells and genotoxic effects may occur accordingly (16). In another study, 0.2 mg of nickel oxide were given intratracheally and rats were sacrificed from three days to six months. A persistent increase of macrophage inflammatory protein (MIP-1α) and a transient expression increase of interleukin-1α (IL-1α), interleukin-1β (IL-1β) and macrophage inflammatory protein-1 (MIP-1) were observed (17). As a representative of the β- or C-C chemokines, MIP-1 is induced by inflammation, IL-1 and TNF-α. MIP-1 has an important modulating role in the development of inflammatory response especially during infection by regulating cytokine production and recruiting mononuclear cells (18). In an experimental study with male Sprague-Dawley rats, Ni Cl2 were found to make immunologic effects, but suppressed IL-10 dose- and time-dependently (19).

In our study, a positive correlation was found between Ni and VCAM-1, TNF-α, IL-10, and IL-6. **Figures 1,**

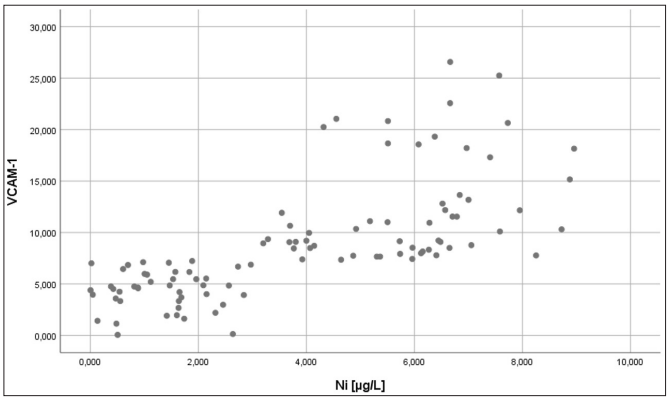


Figure 1. The scatter plot of the correlation between nickel (Ni) and VCAM-1 levels.

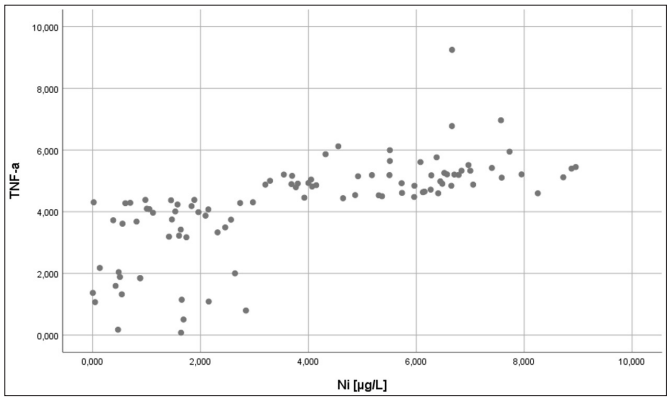


Figure 2. The scatter plot of the correlation between nickel (Ni) and TNF-α levels.

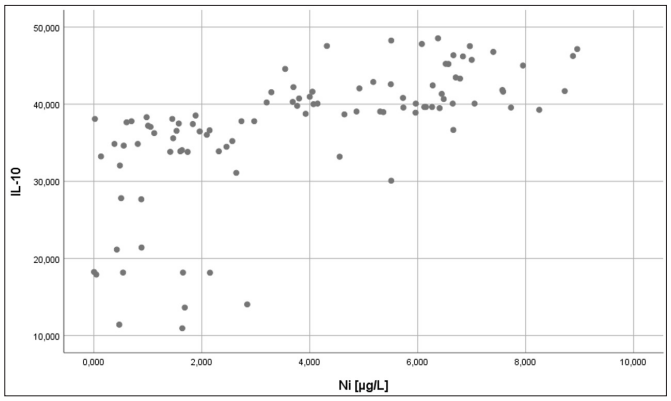


Figure 3. The scatter plot of the correlation between nickel (Ni) and IL-10 levels.

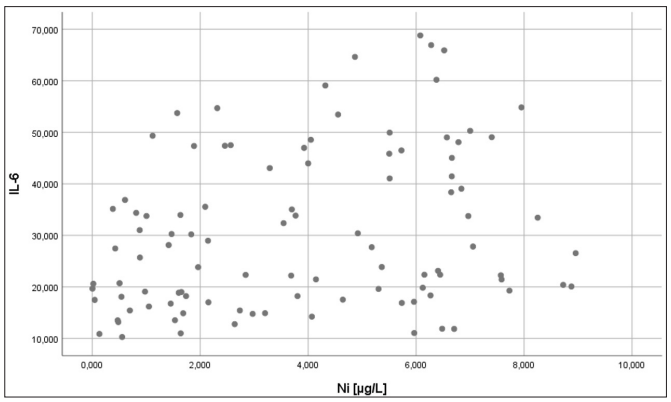


Figure 4. The scatter plot of the correlation between nickel (Ni) and IL-6 levels.

2, 3, and **4** shows the relationships between VCAM-1, TNF-α, IL-10 and IL-6 with corresponding graphs, respectively.

Among them, the strongest association was found between Ni and VCAM-1. In tumor promotion and progression, TNF-α, IL-1 and IL-6 have an important role as pro-inflammatory mediators (20). On the other hand, VCAM-1 adhesion molecule is known to induce tumor cells (21). The changes in the biomarker levels we used in our study are compatible with the studies in the literature (8,10,15) and it is one of the rare studies conducted among workers exposed to nickel. The results obtained allow these biomarkers to be used to detect both inflammation and cancer risk in annual periodic follow-ups of workers exposed to nickel. From this point of view, they are promising biomarkers in routine use.

CONCLUSIONS

The correlations between increased inflammatory biomarkers levels and exposed/control groups propose a close relationship between inflammation and toxicity. This relationship provides a clinical model for the early diagnosis of toxicity of nickel. VCAM-1, TNF-a, IL-10 and IL-6 are promising biomarkers in routine use.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was conducted with the approval of Bozok University Ethics Committee (Date: 2.10.2016; Decision No: 69).

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: No financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and approved the final version.

REFERENCES

1. Sun Z, Gong C, Ren J, et al. Toxicity of nickel and cobalt in Japanese flounder. Environ Pollut 2020; 263.
2. El Safty AMK, Samir AM, Mekkawy MK, Fouad MM. Genotoxic effects due to exposure to chromium and nickel among electroplating workers. Int J Toxicol 2018; 37: 234–40.
3. ATSDR. Toxicokinetics and Biomarkers/Environmental Sources of Exposure Normal Human Levels Levels ToxGuide TM General Populations Toxicokinetics Biomarkers 2002; 2. Available from: www.atsdr.cdc.gov
4. ATSDR. Toxicology Profile for Nickel. Toxicol Profile Nickel 2005; 1–397.
5. Yüksel B, Arica E, Söylemezoglu T. Assessing Reference Levels of Nickel and Chromium in Cord Blood, Maternal Blood and Placenta Specimens from Ankara, Turkey. J Turk Ger Gynecol Assoc 2021; 10.4274/jtgga.galenos.2021.2020.0202.
6. World Health Organization. Biological monitoring of chemical exposure in the workplace: Guidelines. Vol. 1. 1996. 300 p.
7. Klagsbrun M, D'Amore PA. Vascular endothelial growth factor and its receptors. Vol. 7, Cytokine and Growth Factor Reviews. Elsevier Ltd; 1996. p. 259–70.
8. Ozgur O, Vugar Ali T, Iskender Samet D, et al. Pro-inflammatory cytokine and vascular adhesion molecule levels in manganese and lead-exposed workers. Int J Immunother Cancer Res 2019; 5: 001–7.
9. Komori A, Yatsunami J, Suganuma M, et al. Tumor Necrosis Factor Acts as a Tumor Promoter in BALB/3T3 Cell Transformation. Cancer Res 1993; 53: 1982–5.
10. López P, Gutiérrez C, Suárez A. IL-10 and TNFalpha genotypes in SLE. J Biomed Biotechnol 2010; 2010: 838390.
11. Turksoy VA, Tutkun L, Iritas SB, Gunduzoz M, Deniz S. The effects of occupational lead exposure on selected inflammatory biomarkers. Arh Hig Rada Toksikol 2019; 70: 36–41.

12. Grimsrud TK, Berge SR, Haldorsen T, Andersen A. Exposure to different forms of nickel and risk of lung cancer. Am J Epidemiol 2002; 156: 1123–32.
13. Pavela M, Uitti J, Pukkala E. Cancer incidence among copper smelting and nickel refining workers in Finland. Am J Ind Med 2017; 60: 87–95.
14. Wataha JC, O'Dell NL, Singh BB, Ghazi M, Whitford GM, Lockwood PE. Relating nickel-induced tissue inflammation to nickel release in vivo. J Biomed Mater Res 2001; 58: 537–44.
15. Wang Z, Yang C. Metal carcinogen exposure induces cancer stem cell-like property through epigenetic reprograming: A novel mechanism of metal carcinogenesis. Semin Cancer Biol 2019; 57: 95-104.
16. Capasso L, Camatini M, Gualtieri M. Nickel oxide nanoparticles induce inflammation and genotoxic effect in lung epithelial cells. Toxicol Lett 2014; 226: 28–34.
17. Morimoto Y, Ogami A, Todoroki M, et al. Expression of inflammation-related cytokines following intratracheal instillation of nickel oxide nanoparticles. Nanotoxicology 2010; 4: 161–76.
18. O'Grady NP, Tropea M, Preas HL, et al. Detection of macrophage inflammatory protein (MIP)-1α and MIP-1β during experimental endotoxemia and human sepsis. J Infect Dis 1999; 179: 136–41.
19. Harkin A, Hynes MJ, Masterson E, Kelly JP, O'Donnell JM, Connor TJ. A Toxicokinetic Study of Nickel-Induced Immunosuppression in Rats. Immunopharmacol Immunotoxicol 2003; 25: 655–70.
20. Wang PC, Weng CC, Hou YS, et al. Activation of VCAM-1 and its associated molecule CD44 leads to increased malignant potential of breast cancer cells. Int J Mol Sci 2014; 15: 3560–79.
21. Bogiatzi SI, Fernandez I, Bichet J-C, et al. Cutting edge: proinflammatory and Th2 cytokines synergize to induce thymic stromal lymphopoietin production by human skin keratinocytes. J Immunol 2007; 178: 3373–7.

Review

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.892326

Anatolian Curr Med J 2021; 3(3); 251-255

Aging and geriatric palliative care

Orkun Sarıçam[1], Kadriye Kahveci[2]

[1]Pursaklar State Hospital, Department of Internal Medicine Clinic, Ankara, Turkey
[2]Ankara City Hospital, Department of Anesthesology and Reanimation, Ankara, Turkey

Cite this article as: Sarıçam O, Kahveci K. Aging and geriatric palliative care. Anatolian Curr Med J 2021; 3(3); 251-255.

ABSTRACT

The rise in the prevalence of chronic diseases and the growing number of persons, who cannot continue living alone, emerge as a serious problem in parallel to the increased life expectancy around the globe. Geriatrics and palliative care overlap in many ways, although they are different medical specialties. Both are multidisciplinary fields aiming to improve the patient's quality of life, personal abilities, and participation in social activities through patient and family-centered activities. We think that the synergy generated by the collaboration between these two specialties will become a model for interdisciplinary collaboration in healthcare and improve the quality of life of patients.

Keywords: Geriatrics, palliative care, systemic changes

INTRODUCTION

The World Health Organization (WHO) defines individuals aged 65 and over as old persons. Old age is the accumulation of a series of cellular and molecular damages that leads to a decline in physiological capacity and an increase in the risk of developing various diseases (1). Gerontology is a medical specialty which deals with the health problems, social and functional lives, and the quality of life of patients over 65 years of age. Furthermore, preventive medicine practices in the geriatric population and the aging society are other fields of gerontology. The average life expectancy of people has increased throughout the world and the geriatric population is growing day after day (2). Such changes are invoking serious problems along with the increases in the prevalence of chronic diseases and the rise in the number of people, who cannot continue to live alone. The increased life expectancy is associated with aging-associated significant problems that affect the quality of life.

Geriatrics and palliative care (PC) overlap in many ways, although they are different medical specialties (3). Both are multidisciplinary fields aiming to improve the patient's quality of life, personal abilities, and social participation through both patient-centered and family-centered activities (4). To achieve improvements in the quality of life is the common purpose in geriatrics and PC. The aims of both specialties are remarkable because they evaluate the individual not only from the medical aspect but evaluate the individual's social environment as well while taking the individual's values, preferences, and needs into account (5). Olden et al. showed that the majority of the patients referred to palliative care were 65 years old and that, especially, those aged 85 and over were consulted more frequently for end-of-life care (6). The increased prevalence of dementia in old persons adds to the complexity and complications of patient management issues, especially in individuals over 80 years of age (7).

In geriatric palliative care, the aim is to improve the quality of life and alleviate pain through the treatment and prevention of symptoms rather than diseases during the process of the provision of care to old persons suffering from serious and life-threatening diseases (3). The incidences of life-threatening diseases such as cardiac, cerebrovascular, and respiratory diseases, and cancer increase in the geriatric age group (8). Of individuals at 65 years of age or over, approximately two-thirds have two or more chronic diseases and one-third have more than three diseases. Disease factors, symptoms, and signs, too, occur differently in geriatric patients. Furthermore, the co-existence of multiple pathologies and the administration of polypharmacy are common in this age group (9). As the number of older adults living with multiple chronic illnesses continues to increase, so too does the need to develop targeted screening, referral processes and geriatrics palliative cares for managing these patients' often complicated symptom presentations (10)

Corresponding Author: Orkun Sarıçam, orkunsar@hotmail.com

Received: 06.03.2021 **Accepted:** 07.05.2021

Table 1. Systemic changes in old individuals
1. Cardiovascular system
2. Respiratory system
3. Genitourinary system
4. Nervous system
5. Gastrointestinal system
6. Metabolic and endocrine system
7. Musculoskeletal system
8. Skin changes and sensory functions
9. Immune system

SYSTEMIC CHANGES IN OLD INDIVIDUALS

Cardiovascular System

The World Health Organization states that 39% of 40 million people with cardiovascular diseases need PC each year but, of those individuals, 86% cannot have access to such care (11). Cardiovascular diseases in the geriatric population are the most significant causes of morbidity and mortality. The loss and degeneration of muscle cells, increases in connective tissue proportions, reduced vascular elasticity, and increased fibrosis and calcification in cardiac valves are common changes observed during the aging process (12,13). Therefore; the incidence and prevalence of cardiac diseases such as coronary heart disease, atherosclerosis, arrhythmias, and valvular heart diseases are found high in the geriatric population (14).

Geriatric cardiology practices have recently come to the forefront aiming to combine the goals of improving and advancing the provision of care to old persons and to adapt such practices to the needs of individual patients in large healthcare institutions (15). Geriatric cardiology combines cardiovascular perspectives with multimorbidity, polypharmacy, frailty, cognitive decline, and other clinical, social, financial, and psychological dimensions of aging. At the same time, it aims to facilitate the coordination across clinicians from various specialties, including specialists and subspecialists from medical and surgical fields along with physiotherapists and palliative care specialists in order to improve the provision of care to old persons (16).

Respiratory System

Functional and anatomical deformations occur over time and the lung capacity decreases with advancing age. The structures of collagen and elastin in the lung undergo alterations leading to significant progressive decreases in the forced vital capacity, diffusing capacity, gas exchange, ventilation, and respiratory sensitivity (17). The prevalence of chronic obstructive pulmonary disease (COPD) in older individuals increases two-to-three folds. Pneumonia is an important cause of death in older individuals and susceptibility to respiratory system infections increases in this population because of immune system alterations (18).

Patients with chronic lung disease have a high symptom burden and their symptom burden is even higher compared to patients with cancer and other chronic diseases (19). Palliative care aims for symptom alleviation in old individuals with chronic lung disease through the management of dyspnea and the combination of pharmacological and non-pharmacological interventions (20).

Genitourinary System

Along with aging; functional kidney tissue is lost, the blood supply to the kidneys decreases, the glomerular filtration rate slows down, the secretion and absorption capacities of the kidneys decrease, and progressive loss of nephrons occurs. Kidneys' capacity to concentrate urine and retain sodium decreases leading to electrolyte imbalance due to impairments in the perception of thirst. Bladder capacity decreases and the incidence of urinary tract infections increases resulting from the weakening of the bladder muscles causing an increased residual volume of urine (21).

Pharmacokinetic changes occur in the absorption, distribution, metabolism, and excretion of anesthetic drugs in geriatric patients. The incidence of chronic kidney disease (CKD) rises (22). Complaints such as the enlargement of the prostate gland, difficulties in bladder emptying, and frequent urination in small volumes develop in men along with advancing age. Vaginal atrophy, decreased uterine volume, and atrophy of mammary glands occur due to low levels of estrogen and progesterone in women in advanced ages. Besides, the incidence of stress incontinence is found to increase. The quality of life is impaired in urinary incontinence and with the limitation of physical activity. Furthermore; the incidences of hypertension, osteoporosis, coronary heart disease, and psycho-social problems increase in this age group (23).

Despite ongoing efforts to improve the quality of care; patients with progressed CKD continue to experience significant physical, emotional, and mental suffering. In the last months of their lives, many elderly patients undergoing dialysis face many disease complications. Palliative care for these patients focuses on optimizing disease management and addressing the needs of patients and caregivers broadly (24).

Nervous System

The blood supply to the brain decreases, meninges thicken, and ventricles expand with aging. Continuing neuron loss accompanied by the degeneration of the vessels providing blood supply to the brain causes the occurrence of symptoms in association with aging (25). Natural cognitive changes associated with aging are observed; including mild impairments, particularly in

memory planning and processing speed, and learning capacity. However, such functional impairments are not significant enough to interfere with daily life. Breakdown of knowledge, loss of vocabulary, and communication and perception disorders are not anticipated in old individuals without dementia (26). Leading neurological diseases with increasing incidences in parallel to the aging process are neurodegenerative disorders including Alzheimer's disease, Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia (LCD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), and stroke (27).

The density of brain vessels changes in each decade of life. A decrease in areas with dense capillaries and an increase in the degree and number of micro-vessel deformities start to occur with advancing age (28). Advanced age is one of the unmodifiable risk factors for both hemorrhagic and ischemic stroke. The risk of stroke doubles every 10 years in men and women after 55 years of age (29). Palliative care professionals (in inpatient, outpatient, or residential service settings) interacting with patients and families affected by neurological diseases need to comprehend basic principles of care specific to neurological disorders, including prognosis, prognostic uncertainty, and unique aspects of impacts of the disease (30).

Gastrointestinal System

In advanced ages, peristaltic movements slow down and swallowing reflexes become impaired due to the loss of elastic tissue around the oropharynx. The decreased population of gustatory cells in the tongue and the oral cavity and changes in salivary functions are observed. Tooth loss occurs due to physiological erosions in the tooth enamel and the reduced density of blood vessels, nerves, and lymphatic vessels entering the pulp (31). Esophageal muscles start losing tonus. The stomach loses its elasticity resulting in slowing down gastric emptying. Secretion of gastric acid and the intrinsic factor is reduced in the stomach (32). Consequent to such changes in the gastrointestinal system; gastrointestinal bleeding, progressive constipation leading to ileus, atrophic gastritis, peptic ulcer, duodenal ulcer, loss of appetite, and malnutrition are frequently seen in the geriatric age group. In the aging process, the hepatic blood flow decreases along with the volume loss in the liver. The total capacity of the liver to metabolize drugs decreases, too (21).

Metabolic and Endocrine System

Aging causes reductions in endocrine functions, tissue sensitivity, and hormone secretion from peripheral glands. The circadian hormonal rhythm slows down along with increasing age (33). Diabetes prevalence in older adults is more than twice that of middle-aged adults (34). Risk of cardiovascular events, loss of skeletal mass, vasomotor instability, psychological symptoms, and atrophy of estrogen-sensitive tissue increase in parallel to reductions in estrogen levels in women. Male gonadal steroid production changes with aging and that condition is called andropause. Furthermore, total serum testosterone concentrations start to decrease in men along with aging (33).

Musculoskeletal System

Bone density decreases and poor body posture develops with aging. Bone density starts to decrease and bone remodeling increases around 40-50 years of age on average, causing reductions in body height in both sexes (35). About half of the muscle mass is lost in individuals around 75 years of age. The isometric muscle contraction strength decreases besides the reduction in the muscle mass (36).

Skin Changes and Sensory Functions

Fibrous proteins such as collagen and elastin decrease in quantity in old individuals. Quantities of glycosaminoglycan and proteoglycan and similar substances decrease, too. Thinning of the epidermis is observed due to the deceleration of cell renewal. Loss of connective tissue elasticity is observed in old persons. For this reason, the skin of old individuals is thin and fragile. In old age, the sensitivity of touch receptors is reduced and heat, cold, and pressure sensations in hands and feet become poor (37). The protection capacity of the skin against ultraviolet (UV) light is reduced as the number of melanocytes decreases (38).

Sensorial perception decreases with aging. The ability to focus on close objects decreases and the visual acuity and peripheral vision become less sharp. Tear secretion decreases, the conjunctiva becomes thinner and acquires a yellowish tint, and cataracts develop. Old persons start to have difficulty in hearing high-frequency sounds. Taste and smell sensations may become less sharp, too. Furthermore, stimuli may be perceived differently (39).

Immune System

The balance between protective and pathogenic immune responses is impaired with aging. Reduction in T-cell functions leads to a reduction in cellular and humoral immunity. Changes in B-cell functions appear to be less important. Susceptibility to infections develops and responses to vaccination and defenses against cancer lose strength. Advanced age increases the risk of autoimmunity. Autoantibody formation increases in old individuals (40).

CONCLUSION

The last stages of life are characterized by changes in individuals of aging societies in a way that traditional care services in geriatrics and PC cannot meet the emerging needs. To meet such unmet needs, both specialties should act in close collaboration and geriatric palliative care should be conceptualized as an interdisciplinary care and research field based on care ethics. Increased life expectancy and changes associated with end-of-life morbidity predict major challenges for healthcare. For most old individuals, the last two decades of life are characterized by the increased burden of functional and chronic multimorbidity with a potential to cause an emerging need for geriatric care because of the occurrence of dependency, frailty, and often cognitive decline (41,42). At the same time, the end-of-life period may represent a long and challenging process complicated by difficulties in symptom management, complex treatment decisions, easily overlooked psychological distress, and a wide range of psychosocial problems.

Geriatrics is a medical specialty focusing on the provision of healthcare to old persons. The specialty of geriatrics has been evolved to increase functional abilities and solve physical, mental, social, and moral problems of old individuals; thus aiming to increase the quality of life and social participation in order to counteract the unfavorable effects of multimorbidity in the growing population of geriatric patients. Geriatrics and PC are overlapping medical specialties. Both are professional and interdisciplinary fields administering patient and family-centered activities to improve the quality of life, personal abilities, and social inclusion. We strongly believe that the synergy that will be generated through the collaboration of these two interrelated specialties will serve as a model for cross-specialty collaboration in healthcare.

ETHICAL DECLARATION

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declare that no funds were received.

Author Contributions: All of the authors declare that they all participated in the design and the conduct of the study. All authors have approved the final version.

REFERENCES

1. Global Health and Aging, National Institute of Aging, NIH, WHO, 2011
2. Department of Economic and Social Affairs, Population Division, United Nations. World Population Ageing 2015. New York: United Nations; 2015. 164 p.
3. Voumard R, Truchard ER, Benaroyo L, Borasio GD, Büla C, Jox RJ. Geriatric palliative care: a view of its concept, challenges and strategies. BMC Geriatr 2018; 18: 220.
4. Albers G, Froggatt K, Block LV, et al. A qualitative exploration of the collaborative working between palliative care and geriatric medicine: barriers and facilitators from a European perspective. BMC Palliat Care 2016; 15: 47.
5. Şahin S. Geriatride Palyatif Bakım. Türkiye Klinikleri J Anesthesiol Reanimat Spec Topics 2017; 10: 36-41.
6. Olden AM, Holloway R, Ladwig S, Quill TE, van Wijngaarden E. Palliative care needs and symptom patterns of hospitalized elders referred for consultation. J Pain Symptom Manag 2011; 42: 410–8.
7. Evers MM, Meier DE, Morrison RS. Assessing differences in care needs and service utilization in geriatric palliative care patients. J Pain Symptom Manage 2002; 23: 424–32.
8. Sanford AM, Morley JE, Weger MB, et al. High prevalence of geriatric syndromes in older adults. PLoS One 2020; 15: e0233857.
9. Marengoni A, Angleman S, Meinow B, et al. Coexisting chronic conditions in the older population: variation by health indicators. Eur J Intern Med 2016; 31: 29–34.
10. Kapo J, Morrison LJ, Liao S. Palliative care for the older adult. J Palliat Med 2007; 10: 185–209.
11. Connor SR, Bermedo MCS. Worldwide Palliative Care Alliance. World Health Organization. Global Atlas of Palliative Care at the End of Life. London: Worldwide Palliative Care Alliance; 2014.
12. Fox CS, Vasan RS, Parise H, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: The Framingham Heart Study. Circulation 2003; 107: 1492–6.
13. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: A community-based study. Circulation 2005; 112 :2254–62.
14. Alagiakrishnan K, Banach M, Mah D, Ahmed A, Aronow WS. Role of geriatric syndromes in the management of atrial fibrillation in older adults: a narrative review. J Am Med Dir Assoc 2019; 20 :123-30
15. Wu Q, Li LF, Chen YD. Advances in Journal of Geriatric Cardiology over the course of a decade. J Geriatr Cardiol 2020; 17: 733–9.
16. Bell SP, Orr NM, Dodson JA, et al. What to expect from the evolving field of geriatric cardiology. J Am Coll Cardiol 2015; 66: 1286–99.
17. Thannickal VJ, Murthy M, Balch WE, et al. Blue Journal Conference. Aging and susceptibility to lung disease. Am J Respir Crit Care Med 2015; 191: 261–9.
18. Boe DM, Boule LA, Kovacs EJ. Innate immune responses in the ageing lung. Clin Exp Immunol 2017; 187: 16–25.
19. Walke LM, Byers AL, Tinetti ME, Dubin JA, McCorkle R, Fried TR. Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure. Arch Intern Med 2007; 167: 2503–08
20. Mularski RA, Rocker G. Managing dyspnea in advanced chronic obstructive pulmonary disease: Balancing all the evidence. Ann Am Thorac Soc 2015; 12: 978–80
21. Alvis BD, Christopher G. Hughes, physiology considerations in the geriatric patient. Anesthesiol Clin 2015; 33: 447–56.
22. Ptasinska AP, Materkowska DD, Bartczak A, et al. Kidney disease in the elderly: biopsy based data from 14 renal centers in Poland. BMC Nephrol 2016; 17: 194.
23. McDaniel C, Ratnani I, Fatima S, Abid MH, Surani S. Urinary incontinence in older adults takes collaborative nursing efforts to improve. Cureus 2020; 12: e9161.
24. O'Hare AM, Song MK, Tamura MK, Moss AH. Research priorities for palliative care for older adults with advanced chronic kidney disease. J Palliat Med 2017; 20: 453–60.

25. Nicaise AM, Willis CM, Crocker SJ, Pluchino S. Stem cells of the aging brain. Front Aging Neurosci 2020; 12: 247.
26. Gallagher M, Okonkwo OC, Resnick SM, Jagust WJ, Benzinger TLS, Rapp PR. What are the threats to successful brain and cognitive aging? Neurobiol Aging 2019; 83: 130–4.
27. Sarıcam G, Kahveci K, Akdoğan D. Palliative care requirement in neurologic diseases. Turk J Neurol 2020; 26: 153-9
28. Xu X, Wang B, Ren C, et al. Age-related impairment of vascular structure and functions. Aging Dis 2017; 8: 590–610.
29. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003; 2: 43–53
30. Sarıcam G, Akdogan D, Kahveci K. Palliative care after stroke. Acta Neurologica Belgica 2019; 119: 69–75.
31. Mioche L, Bourdiol P, Peyron MA. Influence of age on mastication: effects on eating behaviour. Nutr Res Rev 2004; 17: 43–54
32. Funk MC, Zhou J, Boutros M. Ageing, metabolism and the intestine EMBO Rep 2020; 21: e50047.
33. Beld AW, Kaufman JM, Zillikens MC, Lamberts SWJ, Egan JM, Lely AJ. The physiology of endocrine systems with ageing. Lancet Diabetes Endocrinol 2018; 6: 647–58.
34. Kalyani RR, Egan JM. Diabetes and altered glucose metabolism with aging. Endocrinol Metab Clin North Am 2013; 42: 333–47.
35. Russo CR, Lauretani F, Bandinelli S, et al. Aging bone in men and women: beyond changes in bone mineral density. Osteoporos Int 2003; 14: 531-8.
36. Novotny SA, Warren GL, Hamrick MW. Aging and the muscle-bone relationship. Physiology (Bethesda) 2015; 30: 8–16
37. Eckhart L, Tschachler E, Gruber F. Autophagic control of skin aging. Front Cell Dev Biol 2019; 7: 143.
38. Sator PG, Schmidt JB, Rabe T, Zouboulis CC. Skin aging and sex hormones in women- clinical perspectives for intervention by hormone replacement therapy. Exp Dermatol 2004; 13: 36-40
39. Çivi S, Tanrıkulu Z. Yaşlılarda bağımlılık ve fiziksel yetersizlik düzeyleri ile kronik hastalıklar prevelansını saptamaya yönelik epidemiyolojik çalışma. Türk Geriatri Derg 2000; 3: 85-90.
40. Jones E, Sheng J, Carlson J, Wang S. Aging-induced fragility of the immune system. J Theor Biol 2021; 510: 110473.
41. Finucane TE, Nirmalasari O, Graham A. Palliative care in the ambulatory geriatric practise. Clin Geriatr Med 2015; 31: 193-206
42. Voumard R, Rubli Truchard E, Benaroyo L, Borasio GD, Büla C, Jox RJ. Geriatric palliative care: a view of its concept, challenges and strategies BMC Geriatrics 2018; 18: 22

Case Report

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.896361

Anatolian Curr Med J 2021; 3(3); 256-258

A rare case: acute ischemic stroke that developed in a case with severe COVID-19 pneumonia

Özlem Ertan, Esma Sevil Akkurt, Tuğçe Şahin Özdemirel, Berna Akıncı Özyürek

University of Health Sciences Ankara Atatürk Chest Diseases and Chest Surgery Training and Research Hospital, Department of Chest Disease, Ankara, Turkey

Cite this article as: Ertan Ö, Akkurt ES, Şahin Özdemirel T, Akıncı Özyürek B. A rare case: acute ischemic stroke that developed in a case with severe COVID-19 pneumonia. Anatolian Curr Med J 2021; 3(3); 256-258.

ABSTRACT

The COVID-19 infection causes involvements in many such as the central nervous system and causes prothrombotic complications. Viral neurotropism, endothelial dysfunction, coagulopathy, and inflammation are suggested mechanisms in the development of acute cerebrovascular disease in COVID-19 patients. The development of a neurological complication is a risk factor for mortality. Patients with high inflammatory markers need to be closely followed-up, because of the risk of the development of complications. It should be kept in mind that there may be neurological involvement in patients with symptoms such as headache, impaired consciousness, vertigo, drowsiness, and loss of strength. In this case, we aimed to present our patient who developed ischemic stroke while under treatment for severe COVID-19 pneumonia.

Keywords: COVID-19, pneumonia, ischemic stroke

INTRODUCTION

Coronavirus disease-2019 (COVID -19) is caused by SARS-COV-2 virus and its systemic and neurological complications are known better today. Characteristically, along with the respiratory system related symptoms (1), neurological symptoms such as headache, impaired consciousness, and vertigo may also develop (2). Especially in the case of severe pneumonia due to COVID-19 infection, the probability of observing neurological symptoms was found to be higher (3). In literature, neurological complications such as acute cerebrovascular disease (CVD), intracranial hemorrhage, seizures, encephalitis, and Guillain Barré syndrome have been reported (4,5). In COVID-19 patients, neurological involvement is a risk factor for mortality (6). We aimed to present a patient in our clinic who developed acute ischemic stroke during follow-up for severe pneumonia.

CASE

A 62-year-old male patient was admitted to the emergency department with complaints of dyspnea and weakness for two days. Upon admission his vital signs were as fever: 38.2°C arterial blood pressure (TA): 120/80 mmHg, pulse: 89/min, oxygen saturation 82% at room air. His history revealed he had epilepsy, but he had not used antiepileptic drugs for 3 years and worked as a shoe repairer. On his chest radiography, bilateral increased nonhomogeneous density areas were observed. Laboratory findings were detected as white blood cell 15.910×10^3/µl, lymphocyte count 0.44×10^3/µl, Na: 127 mEq/L, C-reactive protein (CRP): 286.82 mg/L, D-dimer: 0.68 mg/L, ferritin 537.4 ng/ml and cardiac troponin was normal. COVID-19 reverse-transcriptase polymerase chain reaction (RT-PCR) test was found positive. Due to the detection of bilateral multilobar ground-glass infiltration and consolidation areas in thoracic computed tomography (CT), the patient was considered as severe pneumonia and was hospitalized in the COVID clinic of our hospital. His hypoxemia regressed with oxygen therapy given by nasal cannula. Dexamethasone, low molecular weight heparin (LMWH) (1×0.6 ml), favipiravir, and nonspecific antibiotherapy were started. On the sixth day of his hospitalization, the loss of strength developed in distal right hand of the patient. On physical examination, he was conscious, and the distal of right upper extremity was weakness and hypoesthesia. During the follow-up of the patient, right central facial paralysis developed and an epileptic seizure for a short duration was observed. The neurology department was

Corresponding Author: Berna Akıncı Özyürek, drberna_1982@yahoo.com

Received: 13.03.2021 **Accepted:** 15.05.2021

consulted. On cranial CT, intracranial hemorrhage was not detected. The patient was referred to another hospital with a pre-diagnosis of acute ischemic stroke. From the E-Nabız system database, it was learned that the cranial diffusion magnetic resonance (MR) imaging taken in the hospital where he was transferred revealed areas showing diffusion restriction in the left cerebral hemisphere and them markers d-dimer (>80 mg/L, reference values: 0-0.5 mg/L) and IL-6 (10.6 pg/mL) were significantly increased.

DISCUSSION

COVID-19 infection, which was first defined in December 2019 and affected the whole world, causes many complications. The most common of these are acute respiratory distress syndrome (ARDS), arrhythmia, acute coronary syndrome, and acute renal failure (7). Neurological complications can be observed in hospitalized COVID-19 patients at a rate ranging from 6% to 36% (3). In a study of 1683 COVID-19 patients from Spain, the reported CVD rate was 1.4% (8). Another study found a 2.5-fold increased risk for the development of CVD in COVID 19 infection (9). It has been shown that neurological symptoms such as headache, impaired consciousness, and paresthesia developed in 36.4% of patients with COVID-19 (3). Additionally, dizziness, confusion, epileptic seizures, ataxia, anosmia, aging, and muscle pain may be observed in patients (10). Our patient had no neurological symptoms initially when he was admitted, eight days after his positivity, central facial paralysis, epileptic seizure, weakness and hypoesthesia distal of right upper extremity developed due to ischemic stroke. During COVID-19 infection, multiple mechanisms are emphasized in he emergence of these neurological symptoms. In case of severe disease, neurological symptoms may occur as a result of cerebral hypoxia due to respiratory failure (11). Besides, central nervous system (CNS) invasion due to trans-synaptic spread by the involvement of the olfactory neurons and epithelium is another proposed mechanism (5). In brain biopsies taken from patients with a diagnosis of COVID 19 who developed CVD, thrombotic microangiopathy and endothelial damage have been shown (8). Severe COVID-19 patients may be at risk of thrombogenesis and cerebral ischemia because of both biochemical hypercoagulability and direct vascular endothelial damage (12). In addition to direct CNS involvement, the systemic inflammatory response that occurs with SARS-Cov-2 infection may disrupt the blood-brain barrier and cause peripheral cytokines to pass into the CNS (13). Characteristically, COVID-19 coagulopathy manifests itself with significantly increased d-dimer levels, mild thrombocytopenia, and prolonged prothrombin time (10). Hyperactivation of inflammatory factors causes d-dimer and platelet abnormalities by disrupting the coagulation system (2). Increased IL-6 as a response to systemic inflammation has been associated with an increased risk of CVD (14, 15, 16). In the studies have, it has been shown that there are higher d-dimer and CRP levels in COVID-19 patients in whom CVD developed than patients whom it did not (17). Also, patients with severe CNS involvement present with higher blood urea nitrogen levels as well as lower lymphocyte and platelet counts, while laboratory findings may not be useful in patients with peripheral nervous system involvement or patients with non-severe CNS involvement (11). Our patient did not have a significant increase in the d-dimer levels upon admission, however, the CRP value was significantly higher. After the development of CVD, d-dimer (>80 mg/L) and IL-6 (10.6 pg/ml) values were observed to increase significantly.

Besides observing that cerebral ischemia due to COVID-19 was a risk factor for mortality, it has also been found that COVID-19 patients who had an acute ischemic stroke during infection had significantly lower survival rates compared to those who did not (6).

CONCLUSION

SARS-CoV-2 infection is related to prothrombotic events. It should be kept in mind that in patients with high inflammatory markers, persistent headache, newly developed impaired consciousness and conditions such as agitation and paresthesia may be signs of neurological involvement.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. Zhonghua Liu Xing Bing Xue Za Zhi 2020; 41: 145-51.
2. Niazkar HR, Zibaee B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. Neurol Sci 2020; 41: 1667-71.

3. Mao L, Wang M, Chen S, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. JAMA Neurol 2020; 77: 683-90.
4. Bridwell R, Long B, Gottlieb M. Neurologic complications of COVID-19. Am J Emerg Med 2020; 38: 1549.e3-1549.e7.
5. Bodro M, Compta Y, Sánchez-Valle R. Presentations and mechanisms of CNS disorders related to COVID-19. Neurol Neuroimmunol Neuroinflamm 2020; 8: e923.
6. Annie F, Bates MC, Nanjundappa A, Bhatt DL, Alkhouli M. Prevalence and outcomes of acute ischemic stroke among patients ≤50 years of age with laboratory confirmed COVID-19 infection. Am J Cardiol 2020; 130: 169-70.
7. Vakili K, Fathi M, Pezeshgi A, et al. Critical complications of COVID-19: A descriptive meta-analysis study. Rev Cardiovasc Med 2020; 21: 433-42.
8. Hernández-Fernández F, Sandoval Valencia H, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. Brain 2020; 143: 3089-103.
9. Aggarwal G, Lippi G, Michael Henry B. Cerebrovascular disease is associated with an increased disease severity in patients with coronavirus disease 2019 (COVID-19): a pooled analysis of published literature. Int J Stroke 2020; 15: 385-9.
10. Tsivgoulis G, Palaiodimou L, Zand R, et al. COVID-19 and cerebrovascular diseases: a comprehensive overview. Ther Adv Neurol Disord 2020; 13: 1756286420978004.
11. Azhideh A. COVID-19 Neurological manifestations. Int Clin Neurosci J 2020; 7; 2: 54.
12. Goldberg MF, Goldberg MF, Cerejo R, Tayal AH. Cerebrovascular disease in COVID-19. Am J Neuroradiol 2020; 41; 1170-2.
13. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. Neurology 2020; 95: 1060-70.
14. Reddy ST, Garg T, Shah C, et al. Cerebrovascular disease in patients with COVID-19: a review of the literature and case series. Case Rep Neurol 2020; 12; 199-209.
15. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22.
16. Wang F, Nie J, Wang H, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). MedRxiv 2020: 2020.02.10.20021832.
17. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol 2020; 5: 279-84.

Case Report

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.930047

Anatolian Curr Med J 2021; 3(3); 259-261

Mortal disseminated intravascular coagulopathy and cutaneous involvement in a COVID-19-positive patient: a case report

Muharrem Bayrak, Kenan Çadırcı

Health Sciences University, Erzurum Regional Training and Research Hospital, Department of Internal Medicine, Erzurum, Turkey

Cite this article as: Bayrak M, Çadırcı K. Mortal disseminated intravascular coagulopathy and cutaneous involvement in a COVID-19-positive patient: a case report. Anatolian Curr Med J 2021; 3(3); 259-261.

ABSTRACT

Coronavirus 2019 disease (COVID-19) is a highly deadly disease that hascaused 77 million cases and 1.6 million deaths worldwide. Many cutaneous manifestations are seen withCOVID-19. Cutaneous pathologies, such as vascular endothelial damage, prothrombotic conditions, haemorrhagic cutaneous lesions, vasculitis, disseminated intravascular coagulopathy (DIC), ecchymotic skin lesions, purpura and dry gangrene, are seen in patients with COVID-19. While our 84-year-old male patient was being treated for COVID-19-related pneumonia in the infection ward, DIC developed on the ninthday of his treatment and widespread petechia, purpura, ecchymosis, necrosis, gangrene and bullous skin lesions were observed onhis left arm related to this. Here, we aimed to present a case of DIC that developed as a complication of a COVID-19 infection and hada mortal course with cutaneous involvement, to the literature.

Keywords: DIC, coronavirus-19, cutaneous involvement, infection, mortality.

INTRODUCTION

Coronavirus 2019 disease (COVID-19) is a highly fatal disease that has caused over 77 million cases and 1.6 million deaths worldwide (1). COVID-19 causes microvascular thromboses as well as respiratory problems in patients (2). A D-dimer elevation with a COVID-19 infection is associated with coagulopathy from theinfection. D-dimer occurs after the degradation of stabilized fibril polymers by the plasmin and leads to coagulation. D-dimer elevations are associated with a prognosis in a COVID-19 infection other than coagulopathy (3). At the onset of a COVID-19 infection, disturbances in coagulation tests do not usually lead to active bleeding. Changes in coagulation can result in sepsis-induced coagulopathy or DIC over time (4). The exaggerated inflammation that occurs in host cells with a COVID-19 infection can also lead to DIC (5). An exaggerated inflammation triggered in the host cell after an infection leads to the activation of pro-inflammatory cytokines and causes consumption coagulopathy. While DIC develops in only 0.6% of survivors, there is a 71.4% development rate in those who died of a COVID-19 infection (6). Previous studies have reported that pathologies, such as cutaneous involvement, vasculitis, livedo reticularis, and multiorgan failure, may be observed with the development of DIC in a COVID-19 infection (7,8).

In our case, we aimed to contribute to the literature by presenting the development of mortal complications and associated cutaneous involvement with DIC and multiorgan failure in a patient undergoing treatment with COVID-19 lung involvement.

CASE

An 84-year-old male patient presented with coronary artery disease and hypertension for the past 12 years. He had been taking various medications, including metoprolol (50 mg/day), ramipril/hydrochlorothiazide (5–12.5mg) and acetylsalicylic acid (81 mg/day). A fever, which started duringthe previousthree days, was 38.3°C. Thepatientalsohadapulseof94beats/minute,arespiratory rate of 23 breaths/minute, a blood pressure of 136/94 mmHg and an oxygen saturation, measured by pulse oximetry, of 91%. A physical examination of the patient revealed crepitations and rales in respiratory sounds in the middle lobes of both lungs. Laboratory findings on

Corresponding Author: Muharrem Bayrak, muhabayrak@hotmail.com

Received: 29.04.2021 **Accepted:** 15.06.2021

the first day in the ward were: haemoglobin: 12.8 g/dL (14.1–17.8); white blood cell (WBC): 8.8×10^3 ($3.91–10.9\times10^3$); platelets (PLT): 165×10^3 ($152–383\times10^3$); neutrophil: 72.8% (40%–74%); lymphocyte percentage: 17.2% (17%–47%); lymphocyte count: $1.1x10^3$ µL ($1.21–3.77\times10^3$); serum creatine: 1.52 (0.7–1.7 mg/dL); urea: 28 (9–23 mg/dL); C-reactive protein (CRP): 121.2 mg/L (0–5 mg/L); D-dimer: 765 mg/L (0–500 mg/L); procalcitonin: 0.01 ng/ml (0–0.05 ng/ml); fibrinogen: 738 mg/dL (200–400); prothrombin time (PT): 8.2 seconds (5–15); activated partial thromboplastin time (APTT): 24 seconds (22–31); international normalized ratio (INR): 1.03 (08–1.2); ferritin: 175 ng/ml (22–232); aspartate aminotransferase (AST): 16 IU/L (0–40); alanine transaminase (ALT): 19 U/L (7–40); lactate dehydrogenase (LDH): 258 U/L (230–500); and albumin: 3.9 mg/dL (3.2–4.8). In thoracic tomography, ground-glass opacities accompanied by an increased in terlobular septal thickening were observed in the middle-lower zones of both lungs (**Figure 1a**). The arterial blood gas test results were pH: 7.38; PO_2: 84.4; PCO_2: 35.9; HCO_3: 24.5; BE: -1; and SpO_2: 89. Since the COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR) test performed in our patientwas positive, the antiviral treatment included a favipiravir loading dose (2×1600 mg) followed by a maintenance dose (2×600 mg), which was administered for 10 days. Additionally, 3–4 L/min of oxygen therapy with a nasal cannula, subcutaneous enoxaparin (60 mg/day), dexamethasone (8 mg/day), acetylcysteine (900 mg/day) and levofloxacin (500 mg/day) treatments were started. Metoprolol (50 mg/day) and ramipril/hydrochlorothiazide (5–12.5 mg) were continued. Lopinavir/ritonavir, meropenem and a three-day treatment of methylprednisolone (250 mg/day) was started because of the cytokine storm and since the oxygen saturation was only 84% and the CRP was158 mg/L on the thirdday in the ward. On the sixthday in the ward, when the CRP was 167 mg/L and the oxygen saturation was 82%, tocilizumab (400 mg/day) was given intravenously for two days. On the eighthday in the ward, the patient had a sudden onset of haematuria, accompanied by petechiae and purpura on the left arm. Fresh frozen plasma and an erythrocyte suspension were given. On the ninthday, the ecchymotic lesion on the left arm became prominent in the form of necrosis and haemorrhagic bullous lesions up to the left armpit (**Figure 2a, b**). The patient's laboratory results at this point were haemoglobin: 6.2 g/dL; WBC: 24.2×10^3; PLT: 33×10^3; neutrophil: 76.8%; lymphocyte: 0.5×10^3 µL; CRP: 112.2 mg/L; D-dimer: 3,697 mg/L; procalcitonin: 4.82 ng/ml; fibrinogen: 75 mg/dL; PT: 38.9 seconds; aPTT: 152 seconds; INR: 2.08 (08–1.2); ferritin: 1,268 ng/ml; LDH: 1,126 U/L; AST: 416 IU/L; ALT: 347 U/L; albumin: 2.6 mg/dL; serum creatine: 5.7 mg/dL; urea: 162 mg/dL; and fibrin degradation products: 148 µg/ml (<10 µg/ml). The arterial blood gas test results were pH: 7.22; PO_2: 58.7; PCO_2: 35.9; HCO_3: 8.6; BE: -12; and SpO_2: 81. There were bilateral infiltrates on the posterior chest radiograph (**Figure 1b**). On the 10th day in the ward, our patient had a 24-hour urine output of 120 ml, and when metabolic acidosis, uremic encephalopathy, and creatine increased, the patient was transferred to the intensive care unit. The patient was then placed on haemodialysis with a central dialysis catheter and connected to an invasive mechanical ventilator. Arterial and venous Doppler ultrasonography for the left arm revealed echogenic thrombus images in the cephalic and basilic veins that did not respond to compression. Fresh frozen plasma, vitamin K, and erythrocyte suspension treatments were continued with heparin. Positive inotrope therapy was initiated since the arterial blood pressure of our patient was 72/35 mmHg. Unfortunately, our patient, who did not respond to medical treatments, had a cardiac arrest and was exitus on the 15th day of his follow-up in the intensive care unit.

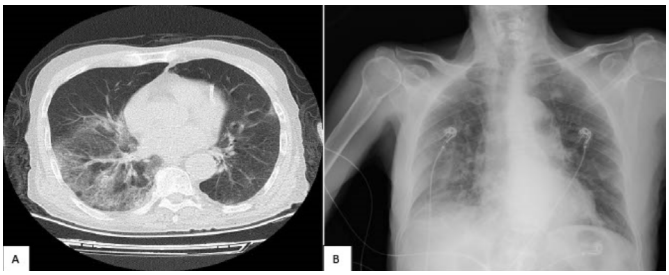


Figure 1. These radiological images show the days during which the patient was hospitalized and DIC developed.

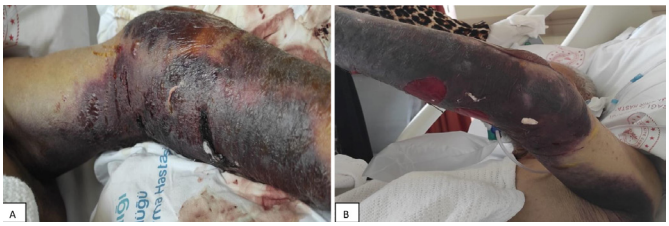


Figure 2. This figure shows the skin lesions during the period when the patient developed DIC.

DISCUSSION

Coagulation disorders, microvascular complications, DIC and thromboembolisms can be seen in cases with more severe courses of COVID-19 infection. Microthrombi, mainly in the lungs, are observed in autopsy studies (6,9). Cutaneous involvement and ecchymoses have been observed in some COVID-19 cases. Ecchymosis lesions on the skin of COVID-19 patients can occur by different mechanisms. Diffuse microvascular thrombi, perivascular neutrophilia and leukocytoclastic vasculitis were observed in skin biopsies performed with the first mechanism. In thrombogenic vasculopathy, an

accumulation of C5b-9, C4d in the complement system, and COVID-19 spike protein (S) in the microvascular area were commonly observed in the entire lesion and dermis layer. Activation in the complement system leads to damage and inflammation in microvascular endothelial cells, resulting in fibrin deposits and thrombi (7). During the second mechanism, COVID-19 enters the cell by binding to the ACE-2 receptor. ACE-2 is an effective component inthe transformation of bradykinin, which is part of the kinin-kallikrein system, and its metabolite, DABK (desArg973 the active metabolite of bradykinin). A decreased activation of ACE-2 with a COVID-19 infection may lead to an increased DABK and the formation of reactive oxygen species, increased NOX2, eNOS and an activation of the complement system, causing vasodilation, microvascular endothelial damage, multiorgan failure and ARDS. The third mechanism leads to procoagulation by activating platelets and antiphospholipid antibodies in endothelial cells by causing the antiphospholipid antibody syndrome secondary to a COVID-19 infection (7,10). In our case, we think that all three mechanisms may have beeninvolvedin the development of ecchymosis and DIC. We think that our patient with COVID-19 pneumonia had increased D-dimer, CRP level, coagulopathy and DIC formation, and with findings in the lungs and cutaneous involvement and multiorgan failure, these were serious complications of severe COVID-19 infection.

We found few cases similar to our case in the literature. Takahashi et al. (11) reported that a 65-year-old patient with COVID-19 and pneumonia developed DIC complications. While the presence of CRP, a high D-dimer level and lung involvement in their case was similar to our case, there were additional severe cutaneous findings in our case. Novara et al. (12) reported a case of DIC and dry gangrene of the hands ofa 78-year-old patient with COVID-19 pneumonia. Our case had many similar symptoms, such as the development of DIC, an advanced age, cutaneous involvement and mortality.

CONCLUSION

In our case, we consider the lack of a skin biopsy in cutaneous involvement as a limitation of the study. In conclusion, our case was an advanced-age patient withcoronary artery disease, hypertension and high CRP and D-dimer levels, whichwere prognostic factors for a COVID-19 infection. Simultaneously, these were important predisposing factors for the development of DIC. Our aim with this case study was to contribute to the literature by presenting a DIC case, which is a mortal complication of COVID-19 infections, and its associated skin involvement.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. JHU, Coronavirus resource center. Medicine 2020.
2. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 2020; 18: 1559-61.
3. Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol 2021; 113: 45-57.
4. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135: 2033-40.
5. Iba T, Levy JH, Thachil J, Wada H, Levi M, Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis. The progression from coagulopathy to disseminated intravascular coagulation in representative underlying diseases. Thromb Res 2019; 179: 11-4.
6. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-7.
7. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res 2020; 220: 1-13.
8. Widysanto A, Wahyuni TD, Simanjuntak LH, et al. Ecchymosis in critical coronavirus disease 2019 (COVID-19) patient in Tangerang, Indonesia: a case report. J Thromb Thrombolysis 2020; 1-5.
9. Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, et al. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. J Thromb Haemost 2020; 18: 1517-9.
10. Iba T, Levy JH, Connors JM, Warkentin TE, Thachil J, Levi M. The unique characteristics of COVID-19 coagulopathy. Crit Care 2020; 24: 360.
11. Takahashi W, Yoneda T, Koba H, et al. Potential mechanisms of nafamostat therapy for severe COVID-19 pneumonia with disseminated intravascular coagulation. Int J Infect Dis 2021; 102: 529-31.
12. Novara E, Molinaro E, Benedetti I, Bonometti R, Lauritano EC, Boverio R. Severe acute dried gangrene in COVID-19 infection: a case report. Eur Rev Med Pharmacol Sci 2020; 24: 5769-71.

Letter to the Editor

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.955678

Anatolian Curr Med J 2021; 3(3); 262-263

Tigecycline induced acute pancreatitis: Suspicion is the first step in diagnosis

Alpaslan Tanoğlu[1], Eylem Çağıltay[2]

[1]Health Sciences University, Sancaktepe Sehit Prof. Dr İlhan Varank Training and Research Hospital, Department of Internal Medicine and Gastroenterology, İstanbul, Turkey

[2]Health Sciences University, Sultan Abdulhamid Han Training and Research Hospital, Department of Endocrinology and Metabolism, İstanbul, Turkey

Cite this article as: Tanoğlu A, Çağıltay E. Tigecycline induced acute pancreatitis: Suspicion is the first step in diagnosis. Anatolian Curr Med J 2021; 3(3); 262-263.

Dear Editor,

Acute pancreatitis is an inflammatory event of the pancreas which may affect seriously all other tissues and organ systems (1-3). Generally, acute pancreatitis is induced by alcoholism or gallstones. However pathogenetic mechanisms of drug induced pancreatitis are not clearly understood (4). A minocycline derivative, tigecycline is a glycylcycline class of antibiotic which is structurally similar to the tetracyclines. It has perfect tissue and organ distribution and favorable microbial coverage, including many kind of Gram-positive and Gram-negative bacteria and also anaerob agents (5,6). Tigecycline's side-effect profile is similar to the tetracyclines (7). Pancreatitis is a well-known adverse effect of tetracyclines (8). However, tigecycline-induced pancreatitis is an uncommon side-effect. We report here a rare case of tigecycline-induced pancreatitis during the treatment of a diabetic food infection.

A 64-year-old man was admitted to hospital because of diabetic food infection requiring glisemic control and antibiotheraphy. He had a history of cholecystectomy operation nearly 5 years ago. His medical history consisted of no alcohol consumption for five years. At the beginning of his diabetic food treatment, teicoplanin 400 mg one per day and imipenem 500 mg four times per day intravenous (iv) injection began empirically. Repetitive diabetic food wound culture was taken and they revealed acinotobacter spp. enfection that was sensitive to colistin, ceftasidime and doxycycline. The antibioteraphy was switched to tigecycline 100 mg iv infusion, then 50 mg iv twice a day and colistin iv 150 mg twice a day. 9 days after the beginning of this therapy, gastro-intestinal symptoms, such as severe epigastric abdominal pain, loss of appetite, nausea and vomiting, were started. Serum amylase (761 U/L, 17-115 normal range) and lipase (426 U/L, 7-60 normal range), aspartate aminotransferase (251 U/L, normal <40), alanine aminotransferase (263 U/L, normal <40) levels and leucocytes (11.9×10^3/mm^3, 4.0–10.5 normal range) counts were increased. Abdominal ultrasonography revealed enlarged edematous pancreas and he was diagnosed as 'acute pancreatitis'. Oral nutrition was stopped, he was hydrated intravenously and fed with parenteral nutrition. Computed tomography imaging could not be performed because of chronic renal failure and elevated creatinine levels. Tigecycline-induced pancreatitis was suspected and the drug was ceased. Then cefoperazone sulbactam and colistin therapy continued. Abdominal pain and vomiting resolved allowing the patient to receive oral alimentation after few days. Amylase and lipase values were decreased to normal levels within a few days. After few days with successful medications, the patient was discharged in a safe condition.

Acute pancreatitis is an important life-threatening pancreatic disease (1,3) Many kind of drugs or toxins may cause acute pancreatitis (4). In the way to exact diagnosis of drug-induced acute pancreatitis, the first step is being suspicious from the currently used drugs. Tigecycline is a globally used wide spectrum antibiotic which is used for many kinds of infectious circumstances (8). It has generally has a safe side effect profile and its side-effect range is similar to the tetracyclines (7). In this current case, we used Naranjo adverse drug reaction probability scale for estimating the probability of adverse effect and a score of 5 was reached. Thus we suggest that a probable relationship between tigecycline and acute pancreatitis is existing (9).

Corresponding Author: Eylem Çağıltay, eylem723@yahoo.com

Received: 21.06.2021 **Accepted:** 28.06.2021

Drug induced acute pancreatitis is an important and sometimes life threatening condition which should be diagnosed early and treated properly. Attention should be given to stop the treatment with tigecycline in patients with acute pancreatitis since it can cause life-threatening consequences.

Keywords: Tigecycline, acute pancreatitis, advers effect

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Tanoglu A, Yazgan Y, Kaplan M, et al. Trimetazidine significantly reduces cerulein-induced pancreatic apoptosis. Clin Res Hepatol Gastroenterol 2015; 39: 145-50.
2. Hançerli Y, Kaplan M, Tanoğlu A, et al. Efficacy of tocilizumab treatment in cerulein-induced experimental acute pancreatitis model in rats. Turk J Gastroenterol 2017; 28: 485-91.
3. Kaplan M, Yazgan Y, Tanoglu A, et al. Effectiveness of interleukin-1 receptor antagonist (Anakinra) on cerulein-induced experimental acute pancreatitis in rats. Scand J Gastroenterol 2014; 49: 1124-30.
4. Tanoglu A, Cagiltay E, Beyazit Y. Spiramycin-associated Acute Pancreatitis: Cause or Coincidence? Med Sci 2015; 4: 2352-5.
5. Giamarellou H, Poulakou Pharmacokinetic and pharmacodynamic evaluation of tigecycline. Expert Opin Drug Metab Toxicol 2011; 7: 1459-70.
6. Barbour A, Schmidt S, Ma B, Schiefelbein L, et al. Clinical pharmacokinetics and pharmacodynamics of tigecycline. Clin Pharmacokinet 2009; 48: 575-84.
7. Brink AJ, Bizos D, Boffard KD, et al. Guideline summary: appropriate use of tigecycline. S Afr J Surg 2012; 50: 20-1.
8. Lipshitz J, Kruh J, Cheung P, Cassagnol M. Tigecycline-induced pancreatitis. J Clin Gastroenterol 2009; 43: 93.
9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.

PUBLICATION RULES, PUBLICATION POLICY, GENERAL PRINCIPLES AND SUBMISSION RULES

AUTHOR GUIDELINES

Anatolian Current Medical Journal (ACMJ) is a refereed, open access and periodical publication. The articles published according to the journal's writing rules are accepted through the **DergiPark** system. All numbers are available at our https://dergipark.org.tr/en/pub/acmj/archive web address and **Dergipark** web page for free. Our purpose is to provide high-quality scientific articles for diseases' diagnosis and treatment having appropriate innovations internationally. It is a scientific medical journal published four times (**January, April, July, October**) a year. The articles coming as a refereed journal are primarily evaluated in terms of common rules conformity with the standard requirements defined by the **Committee of International Medical Journal Editors** (www.icmje.org) in biomedical articles. You can access all of the articles published in our journal electronically, read and download from our web site (https://dergipark.org.tr/en/pub/acmj). Our goal is to make sure that your colleagues send the decision and publishing process of publications that we send to you in the shortest possible time. We would like to emphasize that we are always open to suggestions and constructive criticisms to raise the quality of our publication, and that we will show the necessary sensitivity to the statements in this regard. The **English** name of the journal will be used in the article operating system and citations.

Anatolian Current Medical Journal (ACMJ) It is a scientific, internationally refereed journal that publishes retrospective/prospective clinical and laboratory studies, interesting case presentations, invited collections, editorial letters, original images, short reports and surgical technical articles about every branch of medicine. The language of the journal is **English**. Articles are accepted in English. Sent for evaluation to be published or published articles in another journal or not written in accordance with the journal's rules are not accepted for evaluation. The editor, co-editor and publisher do not take any responsibility for the articles published in the journal.You can access all of the articles published in our journal electronically, read and download from our web site: https://dergipark.org.tr/en/pub/acmj.

JOURNAL NAME

Anatolian Current Medical Journal

ABBREVIATION OF JOURNAL NAME

Anatolian Curr Med J / ACMJ

CORRESPONDENCE ADDRESS

Manuscripts should be sent by e-mail by the responsible author, after registering with **DergiPark**, by going to https://dergipark.org.tr/en/journal/2384/submission/step/manuscript/new.

ARTICLE GENERAL WRITING RULES

All scientific responsibility of the manuscripts belongs to the author (s). The editor, co-editor and publisher do not accept any responsibility for the articles published in the journal.

EDITORIAL PRE-CONTROL EVALUATION

Manuscripts sent to the **Anatolian Current Medical Journal (ACMJ)** are evaluated in terms of format and plagiarism. Manuscripts that do not conform to the format are sent back to the author responsible for evaluation. Spelling rules should be reviewed to avoid such a waste of time. All manuscripts submitted for publication are evaluated by two or more domestic/foreign referees. The evaluation of the articles is made considering the scientific importance and originality. Manuscripts that are accepted for publication can be rearranged by the editorial board without informing the authors. After the article is submitted to the journal or accepted for publication, the order of names cannot be changed, author name cannot be added or removed.

SCIENTIFIC AND ETHICAL RESPONSIBILITY

The editorial and the publication processes of **Anatolian Current Medical Journal (ACMJ)** are shaped in accordance with the guidelines of the World Association of Medical Editors (**WAME**), the Committee on Publication Ethics (**COPE**), the International Council of Medical Journal Editors (**ICMJE**), the Council of Science Editors (**CSE**), the European Association of Science Editors (**EASE**) and National Information Standards Organization (**NISO**). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The protocol for clinical research articles must be approved by the **Ethics Committee**. In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the **Helsinki Declaration of Principles** (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). It should be stated in the text that all persons included in the study signed the Informed Consent Form. The articles submitted to the **Anatolian Current Medical Journal (ACMJ)** will be deemed to have been conducted in accordance with the **Helsinki Declaration of Principles**, and have received ethical and legal permissions and will not be held responsible. If "Animal" was used in the study, the authors stated in the Materials and Methods section of the article that they protect animal rights in accordance with the principles of the **Guide for the Care and Use of Laboratory Animals** (www.nap.edu/catalog/5140.html), and that they have received approval from the ethics committees of their institutions. it is difficult. In case reports Informed Consent an should be obtained from patients regardless of the identity of the patient. If the **Ethics Committee Approval** is required in the article; the received document should be sent with the article. The article should be passed by the authors for **academic plagiarism prevention program**. It is the authors' responsibility to ensure that the article complies with the ethical rules.

All manuscript submissions should be scanned for plagiarism research and then uploaded to the journal system. In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act in accordance with the **COPE** guidelines. See **Guidance from the Committee on Publication Ethics** (**COPE**).

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE- www.icmje.org). The ICMJE recommends that authorship should be based on the following 4 criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) Drafting the work or revising it critically for important intellectual content; (3) Final approval of the version to be published; (4) Agreement to be accountable of all aspects of the work in ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she had done, an author should be able to identify which co-authors are responsible for the specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all of the four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged and thanked on the title page of the article. If the editorial board suspects that someone who does not meet the authorship requirements has been added as a writer, the article will be rejected without further investigation.

Anatolian Current Medical Journal (ACMJ) requires and encourages the authors and the individuals who involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to the potential bias or a conflict of interest. Any financial grants or other supports received for the submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the **ICMJE Potential Conflict of Interest Disclosure Form** should be filled in and submitted by all of the contributing authors. Cases of the potential conflict of interest of the editors, authors, or reviewers are being resolved by the journal's Editorial Board within the scope of **COPE** and **ICMJE** guidelines. The Editorial Board of the journal handles all of the appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office to regard their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all of the appeals and complaints. When submitting a manuscript to the **Anatolian Current Medical Journal (ACMJ)**, authors should accept to assign the copyright of their manuscript to the **Anatolian Current Medical Journal (ACMJ)**. If authors rejected for publication, the copyright of the manuscript will be assigned back to the authors. When using previously published content including figures, tables, or any other material in both of the print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s). Statements or opinions expressed in the manuscripts published in the **Anatolian Current Medical Journal (ACMJ)** reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

ARTICLE IS NOT PUBLISHED ELSEWHERE

Each author should indicate to the editor on the presentation page that part or all of the manuscript is not published elsewhere and is not in the process of being evaluated in another journal at the same time. Oral or poster presentations presented at congresses should be indicated on the title page with the name of the congress, place and date. All responsibility for the articles published in the journal (ethics, scientific, legal, etc.) belongs to the authors.

COPYRIGHT TRANSFER FORM

Copyright Transfer Form (https://dergipark.org.tr/en/journal/2384/file/3854/download) can be obtained from the link. In the native language of the manuscript should be filled in must be sent on-line when loading. According to the 1976 Copyright Act, all kinds of publication rights of articles accepted for publication belong to the publisher.

WRITING LANGUAGE CONTROL

The publication language of the journal is **English**. English articles and Abstract should be checked by a professional linguist before being submitted. The spelling and grammatical errors in the manuscript are corrected by our English language consultant and editorial committee.

STATISTICS EVALUATION

All prospective, experimental and retrospective research articles should be evaluated in terms of statistics (if required by the statistical expert) and indicated by appropriate planning, analysis and reporting.

ACCEPTANCE OF PUBLISHING

After the approval of the editors and referees, the publication date of the article is taken into consideration. A Doi number is obtained for each post.

ARTICLE WRITING RULES

Manuscripts are double-spaced with Microsoft Word, and title titles (Abstract, Abstract, Introduction, Materials and Methods, Results, Discussion, References, etc.) are written in 12 pt. 2.5 cm space should be written at the top and bottom. The writing style should be Times New Roman. "System International" (SI) units should be used. Figures, tables and graphs should be referenced in the text. Abbreviations should be given in parentheses where the word first appears. Review should not exceed 4000 words, research articles 2500, case reports 1500, letters to the editor should not exceed 500 words. Pages should be numbered from the abstract page.

SECTIONS OF MANUSCRIPT

1. Presentation to the Editor

This is the article that the author of the article sends to the editor of the journal. In this section, it should be noted that part or all of the article is not published elsewhere and is not in the process of being evaluated in another journal at the same time, "**Material Support and Interest Relationship**" status, language and statistical checks are made.

2. Title Page

The category of the article submitted at the beginning of the page should be indicated (clinical analysis, research article, experimental study, case report, review, etc.). The names and surnames of all authors should be numbered after the superscript and numbered from 1, and they should be added under the names of the institutions, clinics, cities and countries. On the title page, each author's **Orcid ID** should be his/her e-mail address. This page should include the Authorized Author (s), name, full address, telephone and **e-mail** (address information should be indicated in English. Oral or Poster presentations presented at congresses should be indicated on the title page by giving the name, place and date of the congress.

3. Article File

There should be no names of authors and institutions, only this information should be on the title page.

Title: There should be a short and clear title. It should not contain abbreviations. Abstract: English abstracts should be written. In research articles; It should be divided into sections of Aim, Material, Method, Results and Conclusion and should not exceed 400 words. In the review, case reports and the like.

Keywords: A minimum of 3 and a maximum of 6 should be written. Words should be separated by semicolons. Keywords should be submitted in accordance with Subject **Medical Subject Headings (MESH)** (www.nlm.nih.gov/mesh/MBrowser.html).

Figures, Photographs, Tables and Graphics: It should be indicated at the end of the sentence where it is mentioned in the text, should not be placed in the text, and should be added to the end of the text after the references. Abbreviations used should be indicated in the description below. If previously printed figures, pictures, tables and graphics are used, written permission must be obtained and this permission should be stated in the description of figures, pictures, tables and graphics. The article should be passed by the authors for academic plagiarism prevention program. The picture/photo should be in jpeg and at least 300 dpi resolution.

Text Sections: The text samples to be sent for publication are as follows.

Editorial Comment/Discussion: It is the evaluation of the original research articles published by the expert other than the authors. It is published before the articles in the journal.

Research Article: Prospective-retrospective and all kinds of experimental studies can be published. Introduction, Materials and Methods, Results, Discussion, Conclusion. Abstract (approximately 200-250 words; aim, material and method, findings and conclusion sections), Introduction, Material and Method, Results, Discussion, Conclusion, Acknowledgments, References.

Review: Can be prepared by invited authors or directly. It can be prepared to include the latest medical literature for any subject that has medical characteristics. Abstract (about 200-250 words, unpartitioned), titles, references.

Case Report: These are rare or different articles in diagnosis and treatment. It should be supported with sufficient number of photographs and diagrams. Abstract (about 100-150 words; no section), Introduction, Case report, Discussion, Conclusions.

Letter to the Editor: The articles that are published in the journal within the last year include a maximum of 500 words containing various opinions, experiences and questions of the readers. There are no Title and Abstract sections. The number of references is limited to 5. It should be indicated which article (number, date) is dedicated and at the end there should be the name, institution and address of the author. The answer to the letter is given by the editor or the author (s) of the article and published in the journal.

Education: Scientific articles supported by the latest clinical and laboratory applications that send messages to readers on current issues within the scope of the journal. Abstract (about 200-250 words; no section), related titles, references.

Book Evaluations: Evaluations of national or internationally accepted books of current value within the scope of the journal.

WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

ETHICAL CONSIDERATIONS

Ethics Committee Approval: The study was carried out with the permission of ……... Ethics Committee of ……. (permission granted: ……., decision no: ……).

Informed Consent: All patients signed the free and informed consent form. (If retrospective study; **Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.)

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: If any, it should be written before references.

References: References should be written according to the order of arrival. If the number of authors in the source is 6 or less, all authors (surname and first name should be the first letter, the names of the authors should be separated by commas) should be specified; (”et al ”), the name of the article (only the first letter of the sentence and the first letter of the special names will be capitalized), short journal name, year, volume, short page number (15-8, not 15-18) and a space between the punctuation marks. The format used for the manuscript submission should be as specified in Index Medicus (www.icmje.org). The list of references should only include studies that have been published or accepted for publication or have a Doi number. Journal abbreviations should follow the style used in **Cumulated Index Medicus** (http=//www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). The number of references should be limited to 40 in research articles, 60 in reviews, 20 in case reports and 10 in letter to the editor. References should be given in parentheses at the end of the sentence just before the period. For example (4,5). The author (s) is responsible for the accuracy of the references. Importance should be given to the synthesis of domestic and foreign sources.

4. Figures and Table Titles

Titles should be written after the references. Each must be submitted as a separate image file (at least 300 dpi resolution, jpg).

After the article is accepted for publication, the first copy of the string will be sent to the responsible author by e-mail. In this text, only the spelling errors will be corrected and no additions or substitutions will be made. The responsible author will notify the editorial center by e-mail of the corrections within 2 days.

SOURCE WRITING EXAMPLES

Excerpt from journals;

Cesur S, Aslan T, Hoca NT, Cimen F, Tarhan G, Cifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (not 15-18).

Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD / Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

Eder I hereby declare that all or part of the material in this study has not previously been published in any place and is not currently being evaluated elsewhere for publication. electronic submissions and all kinds of pre-declarations.

Sponsorship Statement

Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

CHECKLIST / CONTROL LIST

The checklist must be complete.

What should be in the article;

—Editor to Presentation Page

—Title Page

- Ethical Status,
- "Conflict of Interest"
- Orcid numbers and author information should be on this page.

—Main Text

—Copyright Transfer Form

1. **Presentation page to the Editor:** It should be written by the responsible author addressed to the editor. Phone and E-mail must be added. The title, short name of the submitted article, 'this work has not been sent to any journal and it is not under consideration and it is authors' own work' should be written in a Conflict of Interest statement'
2. **Title page:** Article titles/Short titles, Authors and Institutions, Corresponding Author's postal address and telephone, **Orcid no** (mandatory since 2019) and **E-mail** addresses of all authors. **Special names and lowercase letters should be used in the title.**
3. **Main pages of the article:** Article Titles/Short Titles, Abstract and Keywords, Article Text, References, Table and Figure Titles, Tables. **This page will not contain author names or institution information.**
4. **Font:** Titles should be "Times New Roman 12 and 12 pt, with 11 pt, double-spaced line spacing and 2.5 cm indentation in all areas.
5. **Abstract**: Abstract should begin with the title ABSTRACT and include the sections "**Introduction/Aim, Material and Method, Findings/Results, Conclusion"**.
6. **Keywords** should be added under the abstract in "**Keywords**", under "**Abstract**". Keywords should be at least 3, at most 6 words, separated by commas, and should be MeSH-compliant.
7. **M**aterial and Method section should indicate the approval of the **Ethics Committee** (it is recommended to include the place, date, ethics committee number). In articles that do not require Ethics Committee Approval, it should be stated that the Approval/Permission of the Institution has been obtained (in order to avoid Conflict of Interest). Related documents should be sent on request. It should be noted that the author (s) is responsible for ethical problems.
8. **S**tatistical terms (such as p, r, α) should **not** be used in the discussion.
9. **"Financial Support/Conflict of Interest Status";** should be stated before the bibliography and "***Acknowledgment***" should be written before the bibliography.
10. **References Representation;** should be as detailed in the spelling rules. Journal's number number "(2)" **is not** in bibliography. In articles with up to six authors, the names of all authors should be written (with the first letter of surname and first name), and for articles with seven or more authors, the first three authors should be cited as et al (et al.). The name of the manuscript should be in the form of sentence usage (**except for special names and first letter**). **The journal should be given a short name.** A space must be left between the punctuation marks after the journal name.
11. **T**ables, Graphs, Pictures and Figures should be placed under a separate title after the bibliography. **Figures/ Images** (at least 300 dpi resolution, must be **jpeg** file) and **Table**s should be submitted as one or more separate files.
12. **Copyright Transfer Form:** Must be filled in the original language of the manuscript. It must be signed by all authors. In the absence of the signature of all authors, the **Corresponding Author** may take responsibility and sign on behalf of all authors.