ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J)

April 2024;11(1):33-48

ARAŞTIMA MAKALES/ RESEARCH ARTICLE

DOI: 10.56941/odutip.1414180

Evaluation of Single/Multiple Joint Effects of Lipid Profiles on Hypertension, Diabetes Mellitus and Obesity Accompanying Coronary Artery Disease

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Received: 04 January 2024, Accepted: 13 April 2024, Published online: 30 April 2024

Abstract

Objective: Although cardiovascular diseases are among the most prominent causes of mortality/morbidity in the world, they are even more important together with comorbidities. This study aims to reveal the single/multiple effects of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglyceride (TG) on hypertension (HT), type 2 diabetes mellitus (T2DM) and obesity accompanying coronary artery disease (CAD).

Method: The data were retrospectively achieved from the records of CAD patients undergoing coronary bypass surgery at the Department of Cardiovascular Surgery, Medical Center, University. The medical knowledge discovery process (MKDP) was applied to the data concerning HT, DM, obesity, TC, HDL-C, LDL-C, and TG variables. Different methods were used to determine the optimal cut-off points of lipid profiles. Logistic regression analysis (LRA) was examined the single/multiple effects of lipid profiles on HT, T2DM, and obesity.

Results: TC, LDL-C, TG, and HDL-C lipid profiles categorized according to the cut-off points determined in the current study were analyzed with LRA models. LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) in HT and TC (>190 mg/dL)*TG (>197) mg/dL)*HDL-C (>36.3 mg/dL) in T2DM interaction terms had a moderate effect size. LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) interaction terms in T2DM and TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TK (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) interaction terms in obesity were reported as having a high effect size.

Conclusion: In conclusion, it is recommended to use the approach that analyzes the cut-off points proposed in this study for lipid profiles in predicting HT, T2DM, and obesity.

Keywords: Coronary artery disease, Risk factors, Lipids, Knowledge discovery.

Lipid Profilinin Hipertansiyon, Diabetes Mellitus ve Obezite ile Birlikte Gelen Koroner Arter Hastalığı Üzerindeki Tekli/Çoklu Etkilerinin Değerlendirilmesi

Özet

Amaç: Kardiyovasküler hastalıklar dünya genelindeki önde gelen ölüm/morbidite nedenleri arasında olmasına rağmen, eşlik eden hastalıklarla birlikte daha da önemlidirler. Bu çalışma, total kolesterol (TK), yüksek dansiteli lipoprotein-kolesterol (HDL-C), düşük dansiteli lipoprotein-kolesterol (LDL-C) ve trigliserit (TG)'nin hipertansiyon (HT), tip 2 diabetes mellitus (T2DM) ve obezite üzerindeki tekli/çoklu etkilerini ortaya çıkarmayı amaçlamaktadır.

Yöntem: Üniversitesi Tıp Merkezi … Kardiyovasküler Cerrahi Bölümü'nde koroner bypass cerrahisi geçiren koroner arter hastalarının kayıtlarından retrospektif olarak elde edilmiştir. Hipertansiyon, DM, obezite, TK, HDL-C, LDL-C ve TG değişkenlerine ilişkin veriler için tıbbi bilgi keşfi süreci (TBKS) uygulanmıştır. Lipid profillerinin optimal kesme noktalarını belirlemek için farklı yöntemler kullanılmıştır. Tekli/çoklu etkilerini belirlemek için lojistik regresyon analizi (LRA) lipid profilleri incelenmiştir.

Bulgular: Bu çalışmada belirlenen kesme noktalarına göre kategorize edilen TK, LDL-C, TG ve HDL-C lipid profilleri LRA modelleri ile analiz edilmiştir. HT'de LDL-C (>117 mg/dL)*TK (>191 mg/dL)*HDL-C (>37.2 mg/dL) ve T2DM'de TK (>190 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) etkileşim terimleri orta etki büyüklüğüne sahipti. T2DM'de LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) etkileşim terimleri ve obezitede TK (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TK (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) ve LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) etkileşim terimleri yüksek etki büyüklüğü olarak rapor edilmiştir.

Sonuç: Sonuç olarak, HT, T2DM ve obeziteyi öngörmede lipid profilleri için bu çalışmada önerilen kesme noktalarını analiz eden bir yaklaşımın kullanılması önerilir.

Anahtar kelimeler: Koroner arter hastalığı, Risk faktörleri, Lipitler, Bilgi keşfi

Suggested Citation: Çolak C, Arslan AK, Erdil N, Tekin S, Akça B, Sahin İ, Çolak MC, Parlakpınar H. Evaluation of Single/Multiple Joint Effects of Lipid Profiles on Hypertension, Diabetes Mellitus and Obesity Accompanying Coronary Artery Disease. ODU Med J, 2024;11(1): 33-48

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INTRODUCTION

Cardiovascular diseases, including coronary artery disease (CAD), have increasing importance in terms of being one of the most prominent causes of mortality and morbidity worldwide. In addition, hypertension (HT), type 2 diabetes mellitus (T2DM), obesity, hyperlipidemia, cancer, etc., diseases accompanying CAD can further increase mortality and morbidity. Thence, it is predicted that there will be more than 22 million deaths due to cardiovascular diseases worldwide in 2030 (1). According to the 12-year follow-up data of the heart disease and Risk Factors in Turkish Adults (TEKHARF) study, which has been conducted since 1990 under the leadership of the Turkish Society of Cardiology, it is estimated that there are approximately 2 million coronary heart patients in Turkey and almost 160 thousand people died from coronary heart disease. Approximately 260 thousand coronary events occur throughout the country, and when 85,000 of them are immediately fatal, 175 thousand patients with non-fatal coronary events remain candidates for treatment. Of the 2 million coronary patients, approximately 75-80 thousand additionally die. Thus, the total number of coronary heart patients increases by 90-100 thousand per year. The TEKHARF study found the annual mortality of coronary heart disease in our adults to be 5.2 per thousand in men and 3.2 per thousand in women. Nevertheless, the cause of one out of every eight deaths could not be determined. Among those with known causes, deaths from coronary heart disease were the highest at 42.5%, followed by cancer at a rate of 24% and cerebrovascular event-related deaths at a rate of 12% (2, 3).

When these essential data of TEKHARF (3) and other related studies (4-6) conducted in Turkey are evaluated, it is inferred that preventive medicine practices that can be carried out for the prevention of cardiovascular diseases such as CAD are of great importance to reduce the risk of mortality and morbidity. Lipid profiles are a test that can be used to screen those at risk of developing CAD. Thanks to evaluating these test results, medical information can be obtained to prevent possible risky situations such as heart attack, stroke, etc., in individuals. Lipid profile tests, mainly including total cholesterol (TC) test,

high-density lipoprotein-cholesterol (HDL-C) assay, low-density lipoprotein cholesterol-cholesterol (LDL-C) assay, and triglyceride (TG), are performed for lipids (7). LDL-C plays an important role in developing CAD (8, 9). However, the content of LDL-C particles may show individual variations, and CAD may develop in individuals with normal LDL levels (10). T2DM is a heterogeneous disease and can lead to acute, micro/macro-vascular chronic complications (CAD, stroke, peripheral vascular diseases, etc.). Therefore, it has been reported that the risk of developing CAD in this disease increases 2-4 times (11, 12). T2DM is also defined by several lipid and lipoprotein abnormalities. These abnormalities increased TG level, decreased HDL-C level, increased trim dense LDL-C level, etc., situations (13).

The clinical information, relationships, patterns, and predictive models developed from the existing medical data in the database with data mining/machine learning methods can significantly contribute to clinicians' medical decision-making processes. The medical knowledge discovery process (MKDP) has been used frequently in recent years, especially in medicine and health sciences, because it can extract meaningful and vital information from massive databases and records. MKDP is a process that includes data selection from databases, data pre-processing, transformation, performing data mining methods, and evaluation/interpretation of obtained patterns/relationships (14, 15). MKDP can help physicians make medical decisions by revealing clinically meaningful information from very high-dimensional medical data. Clinical decision support systems are knowledge-based software that support physicians in making the most appropriate medical decisions for patients (16).

The current study aims to reveal the single/multiple effects of TC, HDL-C, LDL-C, and TG on CAD risk factors of HT, T2DM, and obesity, develop an open-source web-based decision support software, and determine the most appropriate cut-off points of the lipid profiles examined.

METHODS

Research sample and characteristics

The present research protocol was approved by the İnönü University Clinical Research Ethics Committee (Research protocol no: 2016/159). The material of this retrospective case-control study consisted of medical records taken from the database of approximately 2400 coronary artery patients who underwent coronary bypass surgery between January 1, 2002, and September 1, 2018, in Inönü University Faculty of Medicine, Turgut Ozal Medical Center, Department of Cardiovascular Surgery. Individuals who had more than 50% stenosis angiographically in at least one of the major epicardial arteries and underwent coronary bypass surgery were included in the study. However, individuals with

less than 50% stenosis in at least one of the epicardial arteries or less than 40% stenosis in the left main coronary artery were excluded from the study. Data collected on coronary artery patients in this study were collected as follows.

- Gender (male/female),
- Age (years),
- HT (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg),
- T2DM,
- Obesity (body mass index (BMI)>30),
- TC (mg/dL),
- HDL-C (mg/dL),
- LDL-C (mg/dL),
- TG (mg/dL).

The current research was evaluated in accordance with the STROBE guideline (17).

Surgical Technique

All surgical operations were performed under cardiopulmonary bypass (CPB) with the aid of a membrane oxygenator (Dideco D 708 Simplex, 41037 Mirandola-Italy), a roller pump (Cobe Cardiovascular INC, Arvada CO 80004-3599 USA) and a non-pulsatile flow. Antegrade and retrograde blood cardioplegia were used for myocardial protection (Medtronic CardioTermTM CT 400 BR CA 92807 USA). All patients were systemically cooled to 28-32 ˚C. Distal anastomoses were performed using 7.0 prolene sutures under a cross-clamp in all surgical operations. Proximal anastomoses were applied to the proximal aorta using 6.0 or 7.0 prolene sutures. After completing the proximal anastomoses, retrograde warm blood cardioplegia was given. In cases with left ventricular aneurysm and left ventricular thrombus, aneurysm repair, thrombectomy, and proximal anastomoses under cross-clamp were performed before distal anastomoses. Cardiopulmonary bypass was performed with moderate hypothermia (28-30°C) and high perfusion pressure (60-70 mmHg). Surgical strategies were exiting cardiopulmonary bypass at low body temperature (35 °C), striving to shorten the times of cross-clamping and CPB, and avoiding hypotension in the intraoperative and early postoperative periods. In the intraoperative evaluation, great attention was paid to the cannulation area in cases with plaques in the ascending aorta. No narcotic analgesics or deep sedative drugs were administered to the operated patients after they were admitted to the intensive care unit. All patients were extubated as early as possible. After the drainage tubes were removed from the patients, antiaggregant treatment was applied with acetylsalicylic acid at a dose of 300 mg/day. The patients were contacted to come in for the normal outpatient controls on the 10th postoperative day, in the second and sixth months, and then once a year (18).

Biochemical Analysis

The lipid profiles discussed in this study are studied with the Abbott brand Architect C16000

model device (in the same device) in the central laboratory of Inonu University Turgut Ozal Medical Center. Comprehensive information on the determination of relevant lipid profiles is presented below.

TC determination: TC determination is studied by the enzymatic method (cholesterol esterase and cholesterol oxidase) (Ref no: 7D62-21). The system can measure up to 705 mg/dL directly, and for higher results, the sample can be diluted 1:4 initially with automatic or manual dilution, and the result can be obtained automatically by multiplying its concentration with the appropriate dilution factor. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external quality control (Biorad EQAS External Quality Assurance Service) is performed once a month. Interassay values were 2.5% for control 1 and 2.7% for control 2. Intraassay values are 2.1% CV for control 1 and 2.3% for control 2.

TG determination: TG determination is made by the enzymatic method (lipase, glycerol kinase, and glycerol phosphate oxidase) (Ref no: 7D74-21). The system can measure up to 1420 mg/dL directly, and for higher values, the sample can be diluted 1:4 initially with automatic or manual dilution, and the result can be obtained automatically by multiplying its concentration with the appropriate dilution factor. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external control quality control (Biorad EQAS External Quality Assurance Service) is performed once a month. Interassay values are 2.9% CV for control 1 and 3.1% CV for control 2. Intraassay values are 2.2% CV for control 1 and 2.5% CV for control 2 (19).

HDL-C determination: This procedure is performed by the colorimetric endpoint reaction technique (Ref no: 02R06-31, 02R06-21). The method is linear up to 200 mg/dL. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external control is performed once a month. Interassay values were 3.8% CV for control 1 and 4.1% for control 2. Intraassay values are 2.3% CV for control 1 and 2.2% CV for control 2.

Determination and calculation of LDL-C: The colorimetric method is carried out (Ref no: 02R05-31, 02R05-21). The method is linear up to 600 mg/dL. The calibration process is repeated at least every 20 days, and internal quality control is performed every day. The normal value is <100 mg/dL. Interassay values are 4.3% CV for control 1 and 4.5% for control 2. Intraassay values are 2.4% CV for control 1 and 2.8% CV for control 2. Friedewald's formula (20) calculates LDL-C according to the following equation when TG<400 mg/dL (21).

LDL-C= TC – (HDL-C + TG/5)

Sample Size

In patients with CAD, a priori power analysis revealed a minimum of 515 in each group (1030 individuals in total) considering the estimated difference in HT rate between the two groups of 0.10, type I error (α) of 0.05, Type II error (β) of 0.10 (power=0.90), and the assumed effect size of 0.20 (22). In this research study, to increase the validity and reliability of the research findings, all data on 2831 CAD patients were obtained from the records of the cardiovascular surgery department.

Medical Knowledge Discovery Process (MKDP)

In this research, MKDP, which is explained in Figure 1, 2 and the details given below, was applied for the selection, pre-processing, transformation, data mining, and evaluation of the data.

I. Data selection: Absence or presence of CAD risk factors of HT, T2DM, and obesity were dependent/output/outcome variables (binary categorical features), and TC, HDL-C, LDL-C, and TG lipid profiles were explanatory/independent/input variables.

II. Data pre-processing: The missing data were completed with the help of the assignment approach based on the Random Forest method. Extreme/outlier observations were detected with the local outlier factor (LOF). LOF values were calculated according to the k=5 neighborhood value, and the extreme value threshold was determined as 2.5.

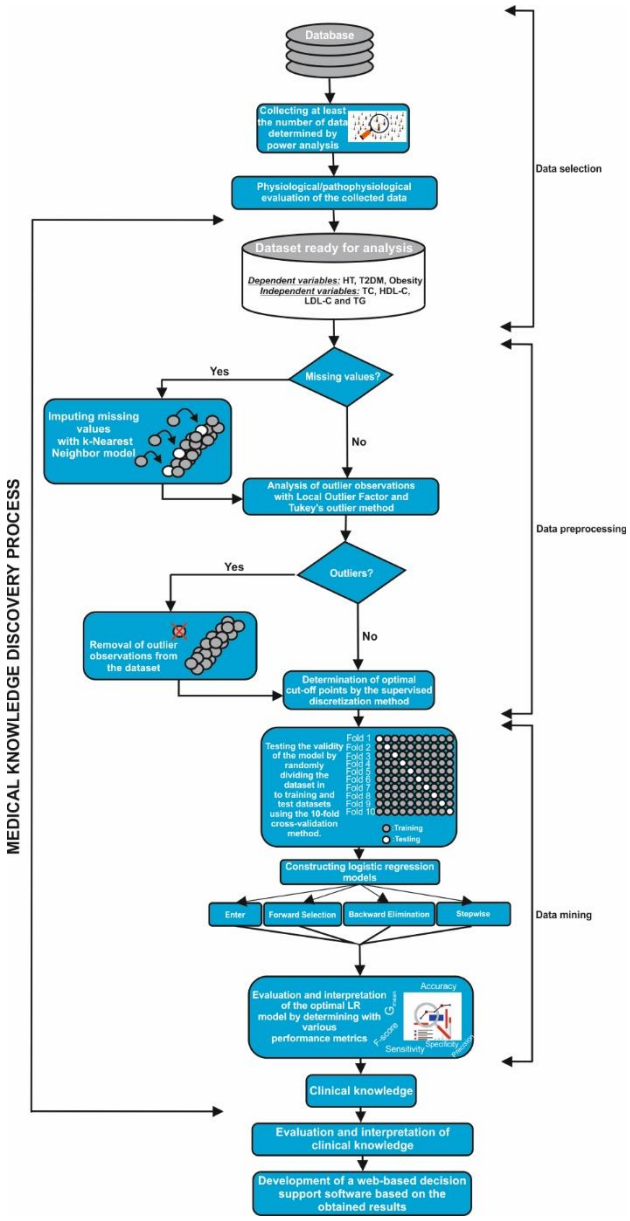

Figure 1. Graphical abstract

III. Data transformation: No transformation techniques were applied to quantitative data.

IV. Data mining: In the modeling stage, multiple logistic regression (LR) analysis (LRA) was used for the relationships between the absence or presence of CAD risk factors of HT, DM, and obesity (dependent/output/outcome variable) and

lipid profiles of TC, HDL-C, LDL-C and TG (explanatory/independent/input variables. The most appropriate (optimal) LR model was selected by applying the Akaike Information Criterion (AIC) based stepwise feature selection. The 10-fold cross-validation method was used to examine the accuracy of the models. LRA models were obtained by stepwise feature selection techniques. AIC statistics were used in selecting the variables that could be included in the models. In this stage, single and multiple joint effects of TC, HDL-C, LDL-C, and TG lipid profiles on HT, DM, and obesity were investigated for risk assessment.

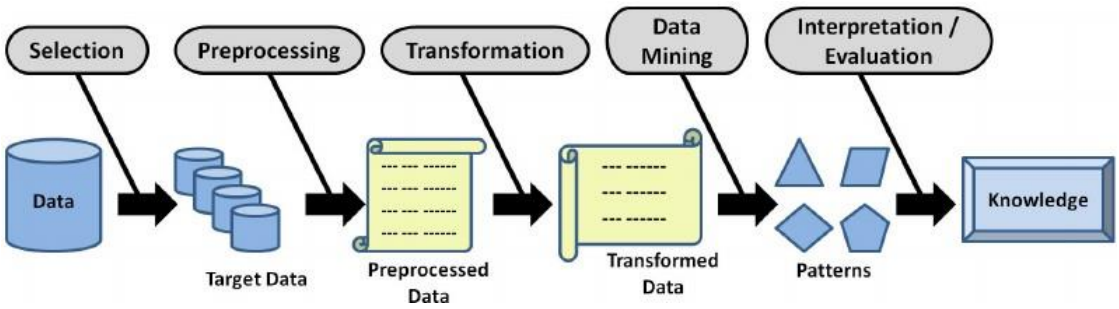

Figure 2. Detailed stages for the MKDP approach

The goodness of the fit of the established LR models was examined by the Hosmer-Lemeshow test and the Akaike Information Criterion (AIC). In addition, McFadden, Nagelkerke, and Cox-Snell summary statistics were given for the LR models. Interpretations for OR with 95% confidence intervals, the measure of effect size (ES) in this study, were made according to the relevant reference study (23).

V. Interpretation and evaluation: In the performance evaluation of the models estimated in this study, accuracy, sensitivity, specificity, positive/negative predictive values, F-score and Gmean were calculated. The 95% confidence intervals of the relevant performance criteria were performed using the 1000 repetitive bootstrap technique, one of the non-parametric methods.

Biostatistical Data Analysis

Quantitative data are summed up as mean and standard deviation or median and interquartile range, and numbers and percentages summarize qualitative data. In data analysis, controls and necessary actions were taken to prevent missing and erroneous data and excessive variability problems. Normality assessment of the variables was performed by the Kolmogorov-Smirnov test. Since the normality assumptions were not met, the differences between the classes of qualitative variables in terms of lipid profiles were examined

with the help of the Mann-Whitney U test. The effect size (ES) for the Mann-Whitney U test is the square of epsilon (ε2) was interpreted as low for values of 0.01 to <0.08, moderate for values of 0.08 to <0.26, and high for values ≥ 0.26 (24). Correlations between quantitative variables were calculated using the Spearman rho technique as the data did not show normal distribution. The effect size for correlations was evaluated as low for 0.10 - <0.30, moderate for 0.30 - <0.50, and high for ≥ 0.50 (25). All p<0.05 values were considered statistically significant. The optimal cut-off points of the lipid profiles examined according to the risk factors for CAD, HT, T2DM, and obesity were determined with the help of an approach based on the logistic regression model with the supervised/supervised discretization method. In all analyses and models, R software and IBM SPSS Statistics Premium version 26.0 for Windows package program were used where appropriate.

Risk Calculation Tool

A web-based open-source "Risk Calculation Tool" was developed using the significant coefficients from the multiple LR analysis for the relevant tasks. Shiny (26), a package available in R, was utilized throughout the development of the tool. In addition, the following packages – shinyWidgets (27), shinyLP (28), shinythemes (29), and shinydashboard (30)- were employed to design the graphical user interface. The proposed web-based software is freely available at the internet address: http://161.9.167.247/RiskCalcTools/. Figure 3 provides a perspective on the relevant portions of the tool and descriptions.

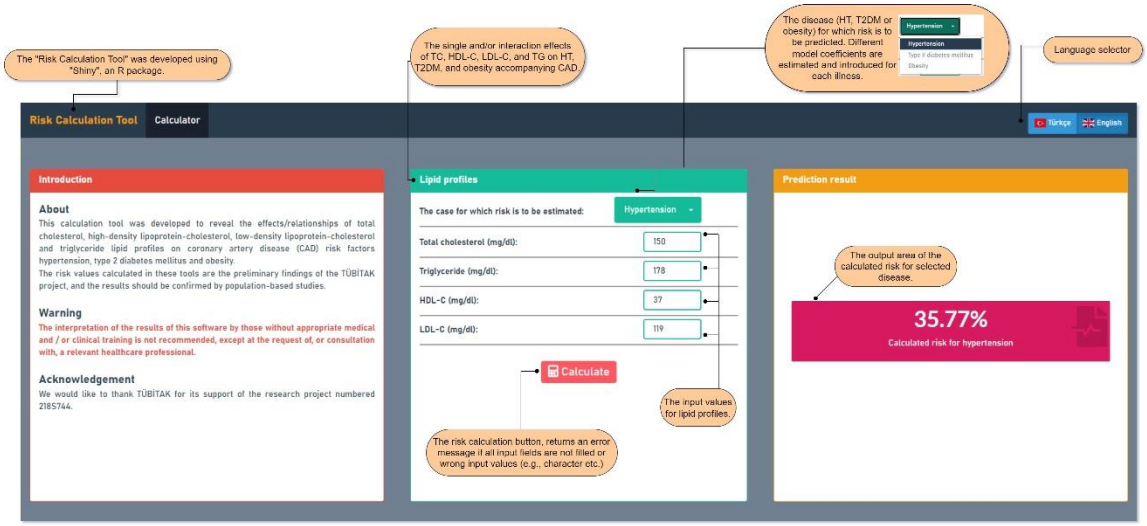

Figure 3. A perspective on the relevant portions of the tool and descriptions

RESULTS

The study consisted of 2828 people, 2137 men (75.6%) and 691 women (24.4%). The mean age

of the individuals is 60.84±9.71 years, the mean age of men is 60.12±9.77 years, and the mean age of women is 63.07±9.15 years.

In this study, the lipid profiles examined for coronary artery patients were classified according to the optimal cut-off points determined by the supervised discretization method. Optimal cut-off points determined in this study for HT accompanying CAD were given below:

• > 191 mg/dL for TC,

• > 117 mg/dL for LDL-C,

• > 181 mg/dL for TG,

• > 37.2 mg/dL for HDL-C.

In relation to T2DM accompanying CAD, the following optimal cut-off values were identified:

• > 190 mg/dL for TC,

• > 115 mg/dL for LDL-C,

• > 197 mg/dL for TG,

• > 36.3 mg/dL for HDL-C.

Similarly, the optimal threshold points below were calculated for obesity concomitant with CAD:

• > 192 mg/dL for TC,

• > 117 mg/dL for LDL-C,

• > 193 mg/dL for TG,

• > 36.8 mg/dL for HDL-C.

Statistics from multiple LRA models regarding the possible effects of clinically categorized lipid profiles on HT, T2DM, and obesity are summarized in Table 1. According to the modeling results, the goodness of fit criteria of the models established to evaluate the multiple effects of categorized lipid profiles on HT, T2DM, and obesity were statistically significant (Hosmer & Lemeshow test; $p>0.05$).

Considering the values given in Table 1, in the model for the HT response variable, TC (>191 mg/dL)*HDL-C (>37.2 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) and LDL-C (>117 mg/dL)*TC (≥191 mg/dL)*HDL-C (>37.2 mg/dL) interactions were statistically significant ($p<0.05$). Other coefficients in the model were insignificant ($p>0.05$). LDL-C (>115 mg/dL), TG (>197 mg/dL), HDL-C (>36.3 mg/dL), and TC (>190 mg/dL)*LDL-C (the terms >115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) were statistically significant ($p<0.05$).

In the model equation estimated for obesity, TG (>193 mg/dL), LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (> 36.8 mg/dL), TG (>193 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and LDL-C (>117 mg/dL)*TG (> 193

mg/dL)*HDL-C (>36.8 mg/dL) terms were found to be significant ($p<0.05$).

While the ES levels of the OR were "Low" for TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) and LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) interactions for the HT dependent variable, the ES values were "Moderate" for LDL-C (>117 mg/dL)*TC (≥191 mg/dL)*HDL-C (>37.2 mg/dL).

In the equation established for the T2DM output variable, the ES levels for OR were also obtained as "Low". For LDL-C (>115 mg/dL), TG (>197 mg/dL), HDL-C (>36.3 mg/dL), TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL).

In the multiple LR equation estimated for obesity, ES was calculated at "High" levels for TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*TG (>193 mg/dL)* HDL-C (>36.8 mg/dL), and was determined to be "Moderate" for TG (> 197 mg/dL). in the same way, the ES level was found to be "Low" for LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)). The coefficients of determination for each model for all dependent variables were calculated as small degrees

Table 1. Statistics from multiple LRA models on the effects of lipid profiles classified by optimal cut-off points from this study on HT, T2DM, and obesity

HT	TC (>191 mg/dL)*TG (?181 mg/dL)*HDL-C (>37.2 mg/dL)	-0.5708	0.3528	2.6175	1	0.1057	0.5651	0.28-1.1195	Low	NPV	0.644 (0.626-0.661)
	LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL)	0.8329	0.3628	5.2714	1	**0.0217**	2.3001	1.1382-4.7314	Moderate	F-score	-
										G_{Mean}	-
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	0.018	8	1	3685.2				2.38E-03	4.26E-03		3.10E-03
	Statistics on coefficients									***Performance metrics***	***Values (95% CI)***
	Variables	**ß**	**SE**	**Wald**	**DF**	***p***	**OR**	**95% CI**	**ES**		
	Constant	-1.0596	0.0814	169.5454	1	**<0.0001**	0.3466	-	-	Accuracy	0.742 (0.727-0.76)
	LDL-C (>115 mg/dL)	-0.3816	0.1886	4.0912	1	**0.0431**	0.6828	0.4661-0.9782	Low	Specificity	0.005 (0-0.01)
	TG (>197 mg/dL)	0.4023	0.1131	12.6596	1	**0.0004**	1.4953	1.1971-1.8652	Low	Specificity	0.998 (0.996-1)
	HDL-C (>36.3 mg/dL)	-0.2147	0.1027	4.3726	1	**0.0365**	0.8068	0.6594-0.9862	Low	PPV	0.500 (0.091-0.875)
	TC (>190 mg/dL)*LDL-C (>115 mg/dL)	0.3102	0.1963	2.499	1	0.1139	1.3638	0.9369-2.0257	Low	NPV	0.743 (0.727-0.759)
	TC (>190 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)	0.5735	0.308	3.4681	1	0.0626	1.7745	0.9627-3.235	Moderate	F-score	0.011 (0.001-0.019)
T2DM	**LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)**	1.2535	0.7427	2.8487	1	0.0914	3.5027	0.7783-15.7846	High	G_{Mean}	0.052 (0.014-0.105)
	TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)	-1.7372	0.813	4.566	1	**0.0326**	0.176	0.0344-0.8999	Low		
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	2.32	8	0.969385	3199.7				1.37E-02	2.28E-02		1.55E-02
	Statistics on coefficients									***Performance metrics***	***Values (95% CI)***
	Variables	**ß**	**SE**	**Wald**	**DF**	***p***	**OR**	**95% CI**	**ES**		
	Constant	-1.6778	0.0899	348.677	1	**<0.0001**	0.1868	-	-	Accuracy	0.817 (0.803-0.832)
	TG (>193 mg/dL)	0.6017	0.1611	13.9484	1	**0.0002**	1.8251	1.3268-2.4967	Moderate	Specificity	0.000 (0.000-0.001)
	HDL-C (>36.8 mg/dL)	0.2587	0.1479	3.0601	1	0.0802	1.2953	0.967-1.7277	Low		
	TC (>192 mg/dL)*HDL-C (>36.8 mg/dL)	-1.1199	0.6105	3.365	1	0.0666	0.3263	0.0776-0.9277	Low	Specificity	1.000 (0.999-1.000)
	LDL-C (>117 mg/dL)*TG (>193 mg/dL)	-0.4205	0.2123	3.9228	1	**0.0476**	0.6567	0.4309-0.992	Low		
	LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)	-0.7531	0.3709	4.1236	1	**0.0423**	0.4709	0.2132-0.9278	Low	PPV	-
	TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	-0.9927	0.4111	5.8293	1	**0.0158**	0.3706	0.157-0.7987	Low		
Obesity	**TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)**	1.7271	0.7169	5.8036	1	**0.016**	5.6245	1.5627-27.8208	High	NPV	0.817 (0.802-0.830)
	TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	1.6448	0.7747	4.5074	1	**0.0337**	5.18	1.2501-27.9009	High	F-score	-
	LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	2.7606	0.8729	10.0023	1	**0.0016**	15.8094	2.7805-89.6744	High	G_{Mean}	-
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	3.45E-13	8	1	2684.2				1.15E-02	1.77E-02		1.09E-02

SE: Standard error, DF: Degrees of freedom, OR: Odds ratio, CI: Confidence interval, ES: Effect Size; HT: Hypertension, T2DM: Type 2 diabetes mellitus, TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TG: Triglyceride; AIC: Akaike Information Criterion; PPV: Positive predictive value; NPV: Negative predictive value

DISCUSSION

Atherosclerotic cardiovascular diseases are a substantial cause of death in developed and

developing countries. Dyslipidemia is one of the most important preventable risk factors that increase the risk of atherosclerotic cardiovascular diseases. Dyslipidemia is the main factor in the pathogenesis of atherosclerosis. According to clinical studies, approximately 80% of the adult population in Turkey is exposed to dyslipidemia. Thanks to early diagnosis and timely measures, cardiovascular disease risk can be reduced. Since blood lipids can be measured easily, quickly, inexpensively, and reliably, screening for dyslipidemia can accurately calculate the future risk of atherosclerotic cardiovascular disease. Although the incidence of diseases such as obesity, T2DM, and HT is increasing worldwide, it also leads to a gradual increase in the incidence of dyslipidemia. Dyslipidemia is not only a lifestyle disorder; but also has a genetic background such as familial hypercholesterolemia, which is an autosomal dominant single-gene disease. Familial cases of hypercholesterolemia develop with increased high cholesterol levels and progression of early atherosclerotic cardiovascular diseases, regardless of lifestyle. In a part of familial dyslipidemia, LDL-C and TG elevation are present together, while in some others, only TG is present (31, 32). In light of these data, the possible single/multiple effects of TC, LDL-C, TG, and HDL-C lipid profiles on obesity, T2DM, HT, etc., illnesses can be evaluated in planning, rearranging, and improving preventive/curative health services.

Many studies have shown that disorders in the lipid profile are risk factors in atherosclerotic diseases. In large-scale screening studies, the critical cut-off value(s) was/were determined as an atherosclerotic risk factor for lipid levels (33). The risk of atherosclerotic disease increases when the single and multiple analyses of the values that make up the lipid profile are above the critical value. However, changes in lipid profile and single/multiple relationships between them may show differences, especially in those with different diseases such as DM, obesity, and HT, which are other risk factors of atherosclerosis. Establishing these differences is very important in determining the type, duration, and dose of dyslipidemia treatment, especially in individuals with atherosclerotic risk factors who have not had the disease and in patients who have the disease and whose treatment is ongoing. In patients with atherosclerosis risk factors, instead of evaluating the lipid profiles individually, single/multiple examinations of the accompanying risk factors and the values that make up the lipid profile are of great importance both in the prevention of atherosclerosis and in demonstrating the success of the treatment of patients with atherosclerotic cardiovascular disease. Also, determining these lipid profile values, and their interrelationships will help determine the targeted lipid profile level(s) in

those with additional risk factors such as DM, HT, and obesity and determine the single/multiple dose and duration of the medical treatment to be given to these patients.

The prevalence of obesity and T2DM continues to increase worldwide, particularly in low-income and developing countries, with the increasing adoption of lifestyles associated with low energy expenditure and high-calorie intake. Although easily diagnosed, T2DM and HT are complex and heterogeneous phenotypes associated with an increased risk of life-threatening cardiovascular disease. Their common presence in the same individual can be attributed to the pathophysiology of obesity and insulin resistance. HT and T2DM are common comorbidities, and the most important cause of morbidity and mortality in diabetes is cardiovascular disease exacerbated by HT. In this regard, T2DM and HT are intimately connected due to similar risk factors such as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity. There is also significant overlap in the cardiovascular complications of T2DM, HT, and obesity, mainly associated with micro/macro-vascular disease(s) (34). TG and LDL-C levels at the start of the Helsinki Heart Study trial group (n = 4,081) were examined concerning the occurrence of cardiac endpoints in the 5-year randomized coronary primary prevention study among dyslipidemic middle-aged men. The related study concluded that serum TG concentration had predictive significance in measuring coronary heart disease risk and predicting the effect of gemfibrozil therapy, particularly when combined with HDL-C and LDL-C (35).

Lipid profiles are a common test that can be used to screen those at risk of developing CAD. Thanks to the evaluation of these test results, information can be obtained to prevent possible risky situations such as heart attack, stroke, and stroke in individuals. Lipid profile tests are mainly; total TC is performed for lipids such as HDL-C, LDL-C, and TG (7). Single and multiple joint effects of lipid profiles on HT, T2DM, and obesity are discussed in the current study. Based on the related analyses for obesity, the most significant interaction was LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) term (OR=15.8094; 95% CI: 2.7805-89.6744), followed by TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL) interaction (OR=5.6245; 95% CI: 1.5627-27.8208), TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) (OR=5.18; 95% CI: 1.2501-27.9009) and TG (>193 mg/dL) (OR=1.8251; 95% CI: 1.3268-2.4967), respectively. The reported factors had high and moderate ES for the estimated model concerning obesity, and the other three interactions (i.e., LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL) and TG

(>193 mg/dL)*HDL-C (>36.8 mg/dL)) were also significant and had low ES levels. In relation to T2DM, the estimated model suggested the most significant factors/interaction of TG (>197 mg/dL) (OR=1.4953; 95% CI: 1.1971-1.8652), LDL-C (>115 mg/dL) (OR=0.6828; 95% CI: 0.4661-0.9782) and TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) (OR=0.176; 95% CI: 0.0344-0.8999), respectively. As for HT, LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) interaction was the most prominent factor having moderate ES level (OR=2.3001; 95% CI: 1.1382-4.7314), pursued by TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) (OR=1.6465; 95% CI: 1.0254-2.6907; ES: Low) and LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) (OR=0.5507; 95% CI: 0.3407-0.8688; ES: Low), consecutively. In this research, single and joint effects of the lipid profiles on T2DM, HT, and obesity are relied on the estimated optimal cut-off points based on supervised learning. As far as known, the current clinical research puts forth the preliminary results of single and joint effects of the categorized lipid profiles on T2DM, HT, and obesity accompanying CAD for the first time, and proposes a "Risk Calculation Tool" available for free with a web-based approach using Shiny in R programming language.

The present paper has a few limitations. Initially, though the sample size was calculated based on the priori power analysis, multicenter studies, which are the update of this research and include more patients, may provide more clinically reliable results. Secondly, even though internal validation was completed on the proposed tool's accessible data in this research, external validation should be undertaken on separate and larger patient groups in the later stages of this study.

In conclusion, it is recommended to use the approach that analyzes the cut-off points proposed in this study for lipid profiles in predicting HT, T2DM, and obesity clinically accompanying CAD. However, there is a need for a comprehensive evaluation of the results by applying the proposed model to independent datasets. The developed web-based decision support tool can be accessed as open access at http://161.9.167.247/RiskCalcTools/

Ethics Committee Approval: The present research protocol was approved by the Malatya Clinical Research Ethics Committee (Research protocol no: 2016/159).

Peer-review: Externally peer-reviewed

Author Contributions: Concept: CC, AKA, NE, ST, BA, Design: CC, AKA, NE, ST, BA, İS, CÇ, HP, Literature search: CC, AKA, NE, ST, BA, İS, CÇ, HP, Data Collection and Processing: CC, AKA, CÇ, HP, Analysis or Interpretation: CC, AKA, NE, ST, BA, İS, CÇ, HP, Writing: CC, AKA, NE, ST, BA, İS, CÇ, HP,

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: This study was financially supported by TÜBİTAK for our 1001 project numbered 218S744.

Acknowledgments

We would like to thank TÜBİTAK for its support in our 1001 project numbered 218S744.

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