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Association between atherogenic index of plasma and in-hospital mortality in patients with STEMI undergoing primary percutaneous coronary intervention

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ABSTRACT

Aim: Dyslipidemia is an established risk factor for cardiovascular disease. Increased triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) levels, and decreased high lipoprotein cholesterol (HDL-C) levels were associated with increased cardiovascular risk. Recently, comprehensive lipid profile indices derived from these conventional parameters have attracted to attention. Atherogenic index of plasma (AIP) is one of the indices calculated as the logarithm of TG/HDL-C levels and it is accepted as an alternative and simple marker of plasma atherogenicity. Although various studies demonstrated that their relationship with these lipid indices and clinical outcomes in patients with acute coronary syndrome, this situation is not yet clear in acute ST-elevation myocardial infarction (STEMI) patients undergoing primer percutaneous coronary intervention (pPCI). In this study, we aimed to investigate the relationship of AIP with early mortality in STEMI patients undergoing pPCI.

Material and Method: This is a retrospective, single center, hospital-based study carried out between January 2019 and April 2021. A total of 873 consecutive STEMI patients (705 men; median age 59 years), whose undergoing pPCI, were enrolled. The patients were divided into two groups according to in-hospital mortality status namely survivors vs non-survivors. Conventional lipid values were measured and non-traditional lipid indexes including non-HDL-C [Total cholesterol minus HDL-C], Total cholesterol/HDL-C, LDL-C/HDL-C, atherogenic index (AI) [non-HDL-C/HDL-C], lipoprotein combine index (LCI) [Total cholesterol*TG*LDL-C/HDL-C] and atherogenic index of plasma (AIP) [Log(TG/HDL-C)] were calculated. Angiographic images of the patients were evaluated through the hospital automation system.

Results: AIP was significantly higher in non-survivors compared to survivor group (0.59, 0.47, p=0.006, respectively). AI, non-HDL-C, Total cholesterol/HDL-C ratio, LDL-C/HDL-C ratio and LCI measurements were similar between two groups. The cut-off value of the AIP (0.50) was associated with 70% sensitivity and 52% specificity for predicts in-hospital mortality. Multivariate logistic regression model indicated AIP (OR: 3.77, 95% CI: 1.34–10.6, p < 0.012) as independent predictor of in-hospital mortality in STEMI patients undergoing pPCI.

Conclusion: AIP predicts in-hospital mortality in patients with STEMI undergoing pPCI. AIP, which can be calculated easily by complete blood can be beneficial in evaluating the prognosis of these patients.

Keywords: Atherogenic index of plasma, acute myocardial infarction, dyslipidemia

INTRODUCTION

Cardiovascular diseases are among the most common causes of death worldwide and are responsible for 1/3 of all deaths in individuals over the age of 35 (1). Cardiovascular diseases refer to different clinical conditions originating from the cardiovascular system. The incidence and prevalence of atherosclerotic coronary artery disease in this group has increased in recent years (2). Although there are advances in primary and secondary prevention, mortality and morbidity still remain high (3). Atherosclerotic cardiovascular disease, a common condition involving plaque formation on arterial walls, is directly related to high levels of low-density lipoprotein cholesterol (LDL-C) (2-4). Atherosclerosis, a lipid-induced chronic inflammatory disease, is an important mechanism in the pathogenesis of coronary artery disease. This phenomenon facilitates the formation of clinical scenarios such as plaque rupture and erosion occurring in the continuation of intravascular plaque formation. As a result of this pathophysiological change in the coronary arteries, coronary occlusion, which prevents the blood supply to the myocardium, develops and acute coronary syndrome (ACS) clinic emerges (5). ACS may present with different clinical presentations. Situations such as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), unstable angina and sudden cardiac death can be seen. While ACS cause death, they also carry a high risk for recurrence in surviving patients. Although improvements have been

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achieved in the treatment of ACS over time, factors such as diabetes, hypertension, hyperlipidemia, obesity, sedentary life and stress, which are risk factors for cardiovascular diseases, have important effects on prognosis (6, 8). This is associated with both early and long term mortality and morbidity (9). In the Asian population, each 1 mmol/L (39 mg/dl) increase in total cholesterol (TC) causes a 35% increase in the risk of coronary death (10). For this reason, preventive approaches constitute the key point in the treatment of coronary artery disease.

To date, different parameters, biomarkers and indices have been proposed to assess cardiovascular disease (CVD) risk and to administer preventive drugs. Therefore, low-cost, rapid and specific tools are used to identify high-risk cases. In this context, individual lipid risk factors such as triglyceride (TG), , high-density lipoprotein cholesterol (HDL-C), TC, LDL-C and non-HDL cholesterol are used. It has been shown that indices based on lipid profile over time can be used as better predictors for CVD (6). Atherogenic index of plasma (AIP) is one of the indices calculated as the logarithm of TG/HDL. Based on the significant positive association of AIP with cholesterol levels, it is considered an alternative and simple marker of plasma atherogenicity. Epidemiological studies have shown that AIP is significantly associated with diabetes mellitus (DM), hypertension (HT) and other risk factors for coronary artery disease (CAD) (11,12). In addition, there is strong evidence that AIP is a superior predictor of other lipid profile indicators in predicting all-cause mortality in CVD (13).

ACS are a group of diseases with high mortality. The prognosis of the disease is affected by the patient's current risk factors and angiographic findings. Treatment approaches vary according to the patient's presentation. In STEMI patients, the mainstay of the treatment approach is primary percutaneous coronary intervention (pPCI) or immediate reperfusion with fibrinolytic therapy if it cannot be performed on time (14). Evaluating the risk factors after coronary intervention in this patient group and developing a treatment strategy accordingly may affect the early and late prognosis of the patient. This study was planned to investigate the association of AIP with early mortality in STEMI patients undergoing pPCI.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: E1-21/1571). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This is a retrospective, single-center, hospital database-based study. From the hospital data system, a total of 873 consecutive patients who were diagnosed with STEMI and underwent pPCI between January 2019 and April 2021 were included in the study. The criteria for inclusion in the study were used for the diagnosis of STEMI and the STEMI guideline criteria published in 2017 by the European Society of Cardiology for the indication of pPCI (15). Electrocardiography (ECG), clinical data and laboratory values of the study patients were obtained by scanning the hospital data system and patient files. The patient population to be included in the study was created by examining the available data. Patients with familial hypercholesterolemia, systemic inflammatory diseases, metabolic diseases, malignancies, renal failure requiring hemodialysis, pulmonary edema, cardiogenic shock and patients requiring inotropic support and/or mechanical circulatory support were excluded from the study

Age, gender, medical history, cardiovascular risk factors, medications and all other demographic data of all participants included in the study were recorded. Complete blood count, routine biochemical parameters and cholesterol panel data of the patients were examined and recorded. Calculated indices were calculated based on these data. ECG data required for diagnosis were evaluated through the system. The 12-lead ECG data of all patients taken within 10 minutes of admission were analyzed. Percutaneous coronary intervention procedures were viewed and examined through the hospital data system, and patient procedure reports were evaluated. The clinical follow-up and mortality data of the patients in the hospital were obtained by using data from the patient file and hospital automation system.

Study Design

Routine blood samples were taken for examination during the first admission to the patient for complete blood count, cardiac markers and routine biochemical parameters. Whole blood samples are made with Symex K-1000, Kobe, Japan device. Separate blood samples are taken for follow-up for detailed biochemical and hormonal examinations. These samples are studied with the COBAS C-501 (Roche, Manheim, Germany) device. Another sample is taken for the cholesterol panel, such as TC, TG, fasting blood glucose (FG), HDL-C and LDL-C after 10-12 hours of fasting, and these data were used in the study. The lipid panel measurements and the calculated indices with the values to be obtained from it were calculated as indicated. AIP was calculated as log10 of the ratio of plasma concentration of triglycerides to HDL-C. Coronary angiographic procedures of the patients were performed with General Electric (GE) INNOVA IGS 620, Rye de la Miniere, France and GE OPTIMA IGS 320 001, Milwaukee, Wisconsin model devices in the catheter laboratory. Image data were analyzed through the hospital automation system. Comorbid conditions were defined as

indicated. HT was defined as systolic blood pressure ≥ 140 mmHg on at least three office measurements or diastolic blood pressure ≥ 90 mmHg or receiving antihypertensive therapy. DM was defined as a fasting blood glucose level of ≥126 mg/dl or a glucose level of ≥200 mg/dl measured at any time or concomitant use of antidiabetic medication. Body mass index (BMI) was calculated as body weight (kg)/height(m)2. Regardless of the amount, those who smoked actively in the last 6 months were defined as smokers. Dyslipidemia was defined as triglyceride>150 mg/dl and/or total cholesterol (TC)>200 mg/dl and/or low-density lipoprotein cholesterol (LDL-C)>130 mg/dl and/or high-density lipoprotein cholesterol (HDL-C) <40 mg/dl according to the adult treatment panel III (NCEP ATP III) criteria of the national cholesterol education program.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics for Macintosh, Version 25.0 (IBM Corp., Armonk, New York, USA). Kolmogorov-Smirnov (K-S) test was used in order to determine the distribution of continuous variables. Chi-square test was used for categorical variables and presented as percentages. The Mann-Whitney-U test was used for the abnormal distributed variables and the findings were presented as median with interquartile range. Receiver operating characteristic (ROC) curve analyses were carried out in order to determine the cut-off values for the sensitivity and specificity of AIP for predicting in hospital mortality. The area under the ROC curve (AUC) was given with 95% confidence interval (CI) in addition to sensitivity, specificity value. The multivariate logistic regression analyses were used in order to identify independent predictors of mortality. Variables, which might be a possible confounding factor for mortality such as age, gender, diabetes mellitus, hemoglobin, creatinin and AIP were included in multivariate analysis. A p value <0.05 was considered statistically significant in all analyses.

RESULTS

A total of 873 patients diagnosed with STEMI and undergoing pPCI were included in this study. The basic demographic, comorbid diseases and procedural data of the patients included in the study are given in **Table 1**. The median age of the patients was 59 (51-67) years and the number of male patients in the group was 705 (81%). Demographic characteristics of the patients were evaluated. When the non-survivors and survivor groups were compared, the mean age of the non-survivor group was found to be higher [69 / 58 years, p<0.05] and the rate of previous cerebrovascular disease (13% / 2%, p<0.05) was different, respectively. Considering the laboratory findings of the patients, creatinine (mg/dl) value was higher [1.29 (0.83-1.71), 0.83 (0.72-0.99) mg/dl, p<0.05] and GFR (ml/min) value was lower [59 (32-95), 95 (79-104) ml/min, p<0.05], in the non-surviving group respectively. The clinical diagnoses of the patients, the localization of the infarction and the ratio of infarct-related arterial distributions were found to be similar in both groups. Similarly, there was no significant difference between the groups in the stent length and diameter values used during percutaneous coronary intervention.

When traditional and non-traditional lipid values were examined, total cholesterol levels [177 (154-207), 162 (135-180) mg/dl, p=0.05] and HDL-C values [34 (29-40), 31 (25-38) mg/dl, p<0.005] were found to be statistically significant in the survivor group, respectively. LDL-C and triglyceride levels were similar between both groups. When non-traditional lipid parameters were examined, AIP [0.47 (0.26-0.72), 0.59 (0.46-0.83), p=0.005] was found to be higher in the non-survivor group. Other parameters such as atherogenic index, total cholesterol/HDL-C, LDL-C/HDL-C and non-HDL cholesterol were not significantly different between two groups. These data are shown in **Table 2**. Comparison of median AIP values between nonsurvivor and survivor groups are shown in **Figure 1**.

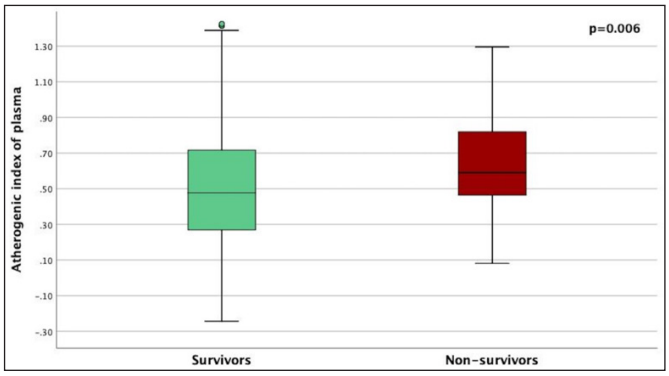

Figure 1. Comparison of median AIP values between survivor and non-survivor groups. P values are given according to Mann-Whitney U test.

Table 2. Traditional and non-traditional lipid parameters of the patients with STEMI

Variables	Non-survivor (n= 53)	Survivors (n= 820)	P Value
Traditional lipid profiles			
TC, mg/dL	162 (135-180)	177 (154-207)	.005
TG, mg/dL	144 (83-165)	103 (70-164)	.033
HDL-C, mg/dL	31 (25-38)	34 (29-40)	.007
LDL-C, mg/dL	104 (81-135)	118 (93-143)	.123
VLDL-C, mg/dL	24 (15-32)	21 (14-33)	.300
Non-traditional lipid profiles			
AIP	0.59 (0.46-0.83)	0.47 (0.26-0.72)	.006
Atherogenic index	4.71 (3.11-5.84)	4.13 (3.19-5.22)	.168
Non-HDL-C, mg/dL	130 (109-173)	143 (119-170)	.125
TC / HDL-C ratio	5.5 (4.1-6.5)	5.1 (4.2-6.2)	.533
LDL-C/HDL-C ratio	3.59 (2.60-4.67)	3.42 (2.68-4.21)	.519
Lipoprotein combine index, $\times 10^3$, mg/dL	649 (430-1121)	632 (335-1139)	.567

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL: very low-density lipoprotein cholesterol. TC: Total cholesterol, TG: Triglyceride,

Table 1. Baseline demographic, comorbid, laboratory characteristics and procedural features

Variables	All (n=873)	Non-survivors (n= 53)	Survivors (n= 820)	P Value
Demographic and comorbid features				
Age, years	59 (51-67)	69 (61-76)	58 (51-66)	<.001
Gender, male	705 (81%)	45 (85%)	660 (80%)	.429
Diabetes mellitus	224 (26%)	21 (40%)	203 (25%)	.016
Hypertension	329 (38%)	27 (51%)	302 (37%)	.040
Prior coronary artery bypass grafting	36 (4%)	4 (8%)	32 (4%)	.196
Prior percutaneous coronary intervention	135 (15%)	11 (21%)	124 (15%)	.272
Prior cerebravascular disease	27 (3%)	7 (13%)	20 (2%)	<.001
Atrial fibrillation	34 (4%)	5 (9%)	29 (4%)	.031
Laboratory findings				
Urea, mg/dL	34 (28-43)	45 (39-75)	34 (28-41)	<.001
Creatinin, mg/dL	0.84 (0.73-1.00)	1.29 (0.83-1.71)	0.83 (0.72-0.99)	<.001
Glomerular filtration rate, ml/min	94 (76-104)	59 (32-85)	95 (79-104)	<.001
Albumin, mg/dL	41 (38-43)	37 (33-42)	41 (38-43)	<.001
Alanin aminotransferase, U/L	35 (24-58)	49 (25-170)	34 (24-59)	.003
Aspartate aminotransferase, U/L	99 (44-243)	150 (52-525)	97 (43-237)	.007
Hemoglobin, g/L	14.2 (13.0-15.3)	13.2 (11.5-15.1)	14.2 (13.0-15.3)	.011
Hematocrit, %	42 (39-46)	42 (35-46)	42 (39-46)	.360
White blood cells, $\times 10^3$	11.8 (9.6-14.5)	15.6 (11.1-20.8)	11.8 (9.5-14.3)	<.001
Neutrophils, $\times 10^3$	9.5 (7.0-12.1)	12.5 (8.9-18.1)	9.4 (6.9-11.8)	<.001
Lymphocyte, $\times 10^3$	1.5 (1.1-2.1)	1.4 (0.7-2.3)	1.5 (1.1-2.1)	.116
Monocytes, $\times 10^3$	0.5 (0.4-0.7)	0.6 (0.4-0.9)	0.5 (0.4-0.7)	<.001
Platelets, $\times 10^3$	256 (215-303)	285 (213-346)	255 (216-302)	.071
Procedural features				
Infarct location				.341
Anterior	398 (46%)	26 (49%)	372 (45%)	
Inferior	428 (49%)	25 (47%)	403 (49%)	
Isolated posterior	16 (2%)	2 (4%)	14 (2%)	
Isolated lateral	31 (4%)	0	31 (4%)	
Infarct-related artery				.992
Left anterior descending artery	420 (48%)	26 (49%)	393 (48%)	
Circumflex artery	105 (12%)	6 (11%)	99 (12%)	
Right coronary artery	348 (%40)	21 (40%)	327 (40%)	
Total stent length, mm	30 (23-43)	33 (28-48)	29 (23-41)	.057
Stent diamater, mm	3.0 (2.75-3.0)	3.0 (2.75-3.0)	3.0 (2.75-3.0)	.576
Hospital stay duration, days	3 (2-5)	2 (1-5)	3 (2-5)	.001

ROC analysis for the AIP to predict inpatient hospital mortality showed an AUC of 0.61 (95% CI: 0.55-0.68, P=0.006). The cutoff value of AIP (0.50) was associated with 70.0% sensitivity and 52% specificity. It is shown in **Figure 2**.

AIP (OR: 3.77, 95% CI: 1.34–10.6, p <0.012), age (OR: 1.07, 95% CI: 1.03–1.10, p <0.001) in multivariate analysis as an independent predictor of inpatient clinic mortality found by logistic regression analysis, creatinine (OR: 2.02, 95% CI: 1.26–3.24, p < 0.005) was found to be statistically significant. Logistic regression analysis and mortality predictors are given in **Table 3**. In addition, when we evaluated in terms of AIP, the mortality rate was significantly higher in patients with high AIP values compared to patients with low AIP values (28% vs. 72%, p=0.001).

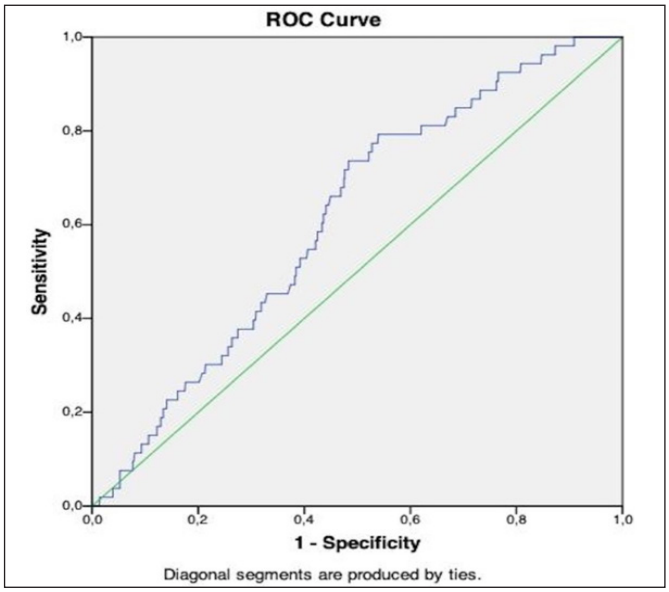

Figure 2. ROC curve analysis for AIP to predict in-hospital mortality demonstrated an AUC value 0.61 (95% CI: 0.55–0.68, p=0.006). The cutoff value of AIP (0.50) was associated with 70.0% sensitivity, 52% specificity.

Table 3. Independent predictor of in-hospital mortality by logistic regression analysis

Variables	Multivariate analysis		
	Odds Ratio	95%CI	P value
Age	1.07	1.03-1.10	<.001
Gender	0.88	0.39-1.98	.752
Diabetes mellitus	1.43	0.71-2.90	.316
Hemoglobin	0.99	0.91-1.10	.988
Creatinin	2.02	1.26-3.24	.004
AIP	3.77	1.34-10.6	.012

DISCUSSION

Atherosclerosis may present with variable clinical presentations as a result of different pathophysiological processes such as intravascular plaque formation, plaque erosion and plaque rupture. It is known that CAD is generally associated with dyslipidemia,HT, DM, sedentary life, obesity, stress and chronic proinflammatory conditions (6,8).

Various risk factors and indices are used to assess cardiovascular risk and implement preventive treatments. Therefore, efforts are being made to find low-cost, rapid, specific, non-invasive and predictive tools to identify high-risk cases. In this context, lipid parameters such as TG, TC, HDL-C, LDL-C have been suggested. However, indices that are better predictors of CVD based on lipid profile have also been used (6).

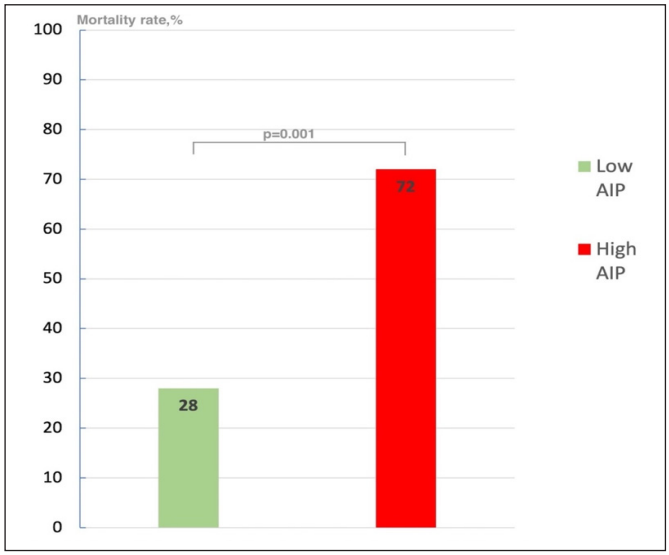

Figure 3. Comparison of mortality rate according to AIP value of study patients. It was significantly higher in patients with high AIP as compared to those with low AIP (28% vs 72%, p=0.001)

AIP is one of the indexes calculated as the logarithm of TG/HDL. Epidemiological studies show that AIP is significantly associated with obesity, HT, DM and other risk factors for CAD (11,12). Similarly, it has been suggested to be a valuable marker for the prediction of atherogenicity and CAD (16,17). In addition, it is claimed that AIP is a predictor of all-cause mortality in CVD and is superior to other lipid indices (13).

When the studies investigating the relationship between AIP with CVD and risk factors are examined, it is seen that there is a positive relationship in general. Considering all these data, we investigated the relationship between AIP and early mortality in patients with STEMI who underwent pPCI. ACS are diseases with high mortality and early diagnosis, treatment planning and risk determination are important in these patients. Especially identifying high-risk groups and planning treatment strategies are important in terms of prognosis.

Two main findings from our study are (a) AIP values were found to be higher in STEMI patients who underwent pPCI who died in-hospital (b) AIP was an independent predictor of mortality determined by multivariate regression analysis. It is considered an alternative and simple marker of plasma atherogenicity. Positive correlation observed between AIP and cholesterol levels. Recently, it has been shown that AIP is associated with cardiovascular outcomes in the general population and in different patient groups (18,19). TG and HDL-C are two lipid parameters routinely measured in clinical practice, but neither are markers that consistently reflect plasma atherogenicity. HDL-C is associated with anthropometric indices such as weight, BMI, waist and hip circumference, and metabolic indices including glycemic status (20).

A new lipid index defined as AIP is accepted as a better indicator for atherosclerosis (21). In our study, it was observed that TC, LDL-C and HDL-C levels were lower in the mortality group. There are contraversies in the data here and in their relationship with CVD in general. Different results have been suggested in studies on this subject. A number of large population-based studies from Scandinavian countries have shown that hyperlipidemia is inversely related with mortality, especially in older adults (22,23). A prospective observational study found that low LDL-C at admission was associated with a lower 3-year survival in patients admitted to hospital for non-ST-elevation myocardial infarction (24). Another study suggests that the risk of death from hyperlipidemia decreases with increasing age (25). However, when the AIP value between groups is considered, it is seen that it is more consistent in showing cardiovascular adverse outcomes. LDL-C has been used for a long time as a target for prevention and treatment of cardiovascular diseases. However, the importance of other conventional lipid parameters in atherosclerotic patients with normal LDL-C levels has been understood. Because of this contradiction, indices calculated from these parameters have come prior to conventional lipid parameters.

In a prospective cohort study including 2676 middle-aged adults, it was reported that the group with high AIP significantly predicted the probability of CAD determined by age, in both genders especially in women

(26). AIP has been shown to be associated with mortality in elderly patients and dialysis patients. Edwards MK et al. (13) showed that AIP was positively and independently associated with mortality risk and was a better predictor for mortality than individual cholesterol risk factors. Bendzala M et al. (17) they also found that AIP was positively associated with the risk of all-cause mortality in older women with hypertension. The predictive value of AIP was also investigated in ACS patients. Cai G et al. (29) they divided the patients into 2 groups in a study that included 1478 patients who had retrospectively undergone coronary angiography. They showed that AIP was independently associated with the presence and severity of ACS in a gender-dependent manner, and as the AIP quartiles increased, the prevalence of ACS, acute myocardial infarction, unstable angina pectoris and Gensini score also increased. Qin Z et al. (30) retrospectively enrolled 2356 patients with DM who underwent percutaneous coronary intervention and were followed up for 4 years. They found that AIP was an independent predictor of major cardiovascular and cerebrovascular adverse events, including cardiac death, myocardial infarction, repeated revascularization and stroke, regardless of clinical presentation.

In a study showing that AIP is associated with adverse cardiovascular events, it was shown that the AIP formula consisted of HDL-C and triglycerides. Low HDL-C and high triglyceride levels were associated with adverse cardiovascular events after ACS, independent of diabetic status (31,32). In addition, moderate-to-vigorous physical activity, increased duration of aerobic exercise and decreased sedentary life have been reported to be inversely correlated with AIP, meaning that a healthy lifestyle helps to reduce the risk of cardiovascular disease (33,34). When the results of these studies are examined, it can be argued that AIP is a similar but stronger predictor of the relationship between conventional lipid parameters and CVD. In our study, the results obtained in logistic regression analysis showed that AIP is a strong independent predictor of mortality and supports these studies.

CONCLUSION

AIP may be a good predictor of early mortality in patients with STEMI undergoing pPCI. AIP can be a good marker with its advantages like inexpensive, accessible and easy to apply to reduce mortality in STEMI patients, to categorize risk and to determine treatment strategy and intensity in the early period. It would be more appropriate to support these results with larger-scale studies and a prospective study in which other factors that may affect mortality in acute coronary syndromes are taken into account.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 09.06.2021, Decision No: E1-21/1571).

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 author has no conflicts of interest to declare.

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

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

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