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Original Article *Özgün Araştırma*

PREDICTIVE VALUE OF FIBROSIS-4 INDEX FOR HIGHER TROPONIN LEVELS IN ACUTE CORONARY SYNDROME

Akut Koroner Sendromda Fibrozis-4 İndeksinin Yüksek Troponin Düzeyleri için Öngördürücü Değeri

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ABSTRACT

Objective: Non-alcoholic fatty liver disease, a condition that affects nearly one-third of the population, is associated with cardiovascular disease and is the leading cause of death. Studies have found that peak troponin level is a strong predictor of all-cause death and infarct area width in the left ventricle after acute coronary syndrome. The fibrosis-4 (FIB-4) index is a noninvasive clinical tool that combines four laboratory parameters to measure liver fibrosis. The relationship between the FIB-4 index and peak troponin level is unclear. We speculated that a higher FIB-4 index might be associated with higher peak troponin levels, as it is linked to cardiovascular disease. We aimed to explore the relationship between peak troponin levels and the FIB-4 index in patients with acute coronary syndrome.

Material and Methods: This was an observational, cross-sectional cohort study. A total of 302 inpatients with acute coronary syndrome admitted to our clinic between June and September 2023 were enrolled. The FIB-4 index and peak troponin levels were evaluated. The maximum mean troponin level was determined, and two patient groups were formed and compared according to whether it was below or above this level.

Results: We demonstrated for the first time that the FIB-4 index is a strong indicator of peak troponin levels in patients with acute coronary syndrome (odds ratio: 2.301, 95% CI 1.667-3.172, p<0.001).

Conclusion: A higher FIB-4 index in patients with acute coronary syndrome was associated with higher troponin levels. It may be beneficial for clinicians to take more preventive measures in patients with acute coronary syndrome with a higher FIB-4 index.

Keywords: *FIB-4 index, acute coronary syndrome, troponin*

ÖZ

Amaç: Non-alkolik yağlı karaciğer hastalığı nüfusun yaklaşık üçte birini etkiler. Kardiyovasküler hastalıklar, non-alkolik yağlı karaciğer hastalığı olan hastalarda ölümün başlıca nedenidir. Çalışmalar, zirve troponin seviyesinin akut koroner sendrom sonrası tüm nedenlere bağlı ölümün ve sol ventrikül infarkt alanı genişliğinin güçlü bir öngörücüsü olduğunu göstermiştir. Fibrozis-4 (FIB-4) indeksi, karaciğer fibrozunu ölçmek için dört laboratuvar parametresini birleştiren invaziv olmayan bir klinik araçtır. FIB-4 indeksi ile zirve troponin seviyesi arasındaki ilişki bilinmemektedir. Yüksek FIB-4 indeks seviyesinin kardiyovasküler hastalıklar ile bağlantılı olduğu bilindiği için zirve troponin seviyelerinin de FIB-4 indeks ile ilişkili olabileceğini varsaydık. Bu çalışmada akut koroner sendrom hastalarında zirve troponin seviyesi ile FIB-4 indeksi arasındaki ilişkiyi incelemeyi amaçladık.

Gereç ve Yöntemler: Bu çalışma gözlemsel, kesitsel bir kohort çalışmasıydı. Haziran ve Eylül 2023 arasında kliniğimize kabul edilen akut koroner sendrom hastalarından toplam 302 hasta çalışmaya dahil edildi. FIB-4 indeksi ve zirve troponin seviyeleri değerlendirildi. Ortalama zirve troponin seviyesi belirlendi ve hastalar bu seviyenin altında veya üstünde olup olmamasına göre iki gruba ayrıldı ve birbirleriyle karşılaştırıldı.

Bulgular: FIB-4 indeksinin akut koroner sendrom hastalarında zirve troponin seviyelerinin güçlü bir öngörücüsü olduğunu gösterdik (Odds oranı: 2.301, %95 CI 1.667-3.172, p<0.001).

Sonuç: Akut koroner sendrom hastalarında daha yüksek bir FIB-4 indeksi, daha yüksek troponin seviyeleri ile ilişkilidir. Daha yüksek bir FIB-4 indeksi olan akut koroner sendrom hastalarında daha fazla önleyici tedbir almanın klinisyenler için faydalı olabileceği düşünülebilir.

Anahtar Kelimeler: *FIB-4 indeks, akut koroner sendrom, troponin*

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a significant hepatological condition observed in approximately 30% of the overall population. The incidence of NAFLD increases significantly to 90% in individuals with type 2 diabetes mellitus (DM). Notably, NAFLD patients with a heightened risk of progressive fibrosis are particularly prone to cardiovascular disease (CVD), which is a prominent contributor to morbidity and mortality in this patient population. Coronary atherosclerotic heart disease and NAFLD share several common risk factors, including obesity, hypertension (HT), DM, metabolic syndrome (MS), and dyslipidemia (1). Clinical studies have shown that NAFLD contributes to accelerating the atherogenic process and have proposed that the association between CVD and NAFLD is causative or that both diseases are the result of a common pathogenic origin (1-5). The fibrosis-4 index (FIB-4 index) is a cost-effective and user-friendly noninvasive fibrosis scoring system that encompasses demographic, clinical, and laboratory parameters. Its high sensitivity makes it an invaluable tool for accurately identifying patients with advanced hepatic fibrosis. Furthermore, the FIB-4 index offers the advantage of being readily accessible and affordable in clinical practice (6).

Acute coronary syndrome (ACS) is caused by acute myocardial ischemia, which causes chest pain and electrocardiographic (ECG) changes, as well as myocardial necrosis, which causes elevation of blood markers, such as troponin, resulting in left ventricular (LV) dysfunction and loss of myocardial function with poor future outcomes (7). The gold standard marker for diagnosing myocardial necrosis is troponin elevation, which provides beneficial data for ACS (8). Prior research has indicated a connection between maximum troponin concentrations and unfavorable cardiovascular (CV) consequences, encompassing overall mortality and both long- and short-term morbidity in individuals diagnosed with ACS. Individuals experiencing unstable angina (UA) manifest a clear link between the increased severity of narrowed lesions and the existence of multivessel disease, alongside heightened troponin levels (9). In an extensive meta-analysis involving 25,252 participants, a significant correlation was observed between an elevated FIB-4 index and an increased likelihood of cardiovascular disease (10). A study encompassing a cohort of 13,448 individuals revealed a predictive correlation between heightened FIB-4 levels and the occurrence of new-onset ischemic heart disease over a 10-year follow-up duration (11). The relationship between the maximum troponin level and FIB-4 index is currently unknown. Drawing on the link between an elevated FIB-4 index and atherosclerotic risk factors, our conjecture posits that peak troponin levels might exhibit a positive correlation with the FIB-4 index. In previous studies, although the FIB-4 index has been demonstrated to be closely associated with the atherosclerotic process and CV events (1,3-5,12). Its relationship with troponin levels, particularly, has not been elucidated. This study aimed to clearly demonstrate this association. Elevated troponin levels in patients with ACS may be considered an indicator of poor prognosis (13). Therefore, an association between troponin and the FIB-4 index suggests that a higher FIB-4 index could potentially provide insights into the prognosis of patients with ACS.

MATERIALS AND METHODS

The design of our study was observational and cross-sectional. We prospectively included 302 patients hospitalized for ACS between June and September 2023. ACS was diagnosed based on the ECG findings, cardiac symptoms according to the recommendations of current guidelines and elevation of blood biomarkers of myocardial necrosis, and the typical range of troponin values in our laboratory was 0 to 57 ng/L. Patients with ST-elevation myocardial infarction (STEMI) and those requiring urgent intervention underwent immediate percutaneous coronary intervention (PCI), while others underwent PCI within 24 hours. Prior to conducting the study, we obtained ethical approval from the ethics committee at our institution (Health Directorate Scientific Research Application Review Commission/26.05.2023/E-64960800-799216481811).

Informed consent forms, which were written and signed, were obtained from all participating patients, ensuring their understanding and agreement to be part of the study. Comprehensive data, including basic demographic characteristics, biochemical data, and relevant clinical information, were recorded for each patient as a part of the study protocol.

In our study, we first determined the average troponin level in the patient population and subsequently divided them into two equal groups based on whether their troponin levels were below or above this mean value. This division allowed for a comparison of outcomes between the two groups.

All patients included in the study underwent thorough evaluation by a cardiologist who recorded their medical history, functional capacity, vital signs, and baseline characteristics. The recorded baseline features encompassed previous cerebrovascular accidents (CVA), peripheral artery disease (PAD), smoking habits, family history of early coronary artery disease (CAD), prior revascularization procedures, and the presence of HT and DM. The determination of HT and DM was made in accordance with the prevailing guidelines in the field.

KÜ Tıp Fak Derg 2024;26(1):34-41
Doi: 10.24938/kutfd.1400280

Exclusion Criteria

Patients with acute or chronic renal failure, active inflammatory disease, myocarditis, cardiomyopathy, cardiogenic shock, liver shock, ischemic or toxic hepatitis, sepsis, secondary HT, severe heart valve disorders, endocrinological conditions, electrolyte imbalances, pulmonary thromboembolism, malignancy, cirrhosis, or acute/chronic liver disease with other known causes (acute/chronic viral hepatitis, hemochromatosis, or alcohol consumption) were excluded from the study.

Laboratory assays

Blood samples were obtained from the veins of the forearm for routine blood tests upon admission to the emergency room. Troponin levels were measured twice daily within 3 days period from admission to obtain peak troponin levels. Biochemical parameters were measured using standard methods. For the measurement of complete blood count, we employed a self-directing cell counter known as the Coulter Gen-S, manufactured by COULTER Corp in Miami, USA. This device was utilized to obtain accurate and automated measurements of various blood parameters.

FIB-4 index

In our study, the FIB-4 index was calculated using the formula [Age (years)×aspartate aminotransferase (AST)] / [platelets (PLT) x√alanine aminotransferase (ALT)].

Statistical analysis

In our study, all statistical analyses were conducted using the Statistical Program for Social Sciences (SPSS, version 19.0; SPSS, Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD), while nominal variables were represented as percentages indicating the number of cases. This standardized approach allowed for appropriate data representation and facilitated comparisons and interpretations of the study results. For normally distributed parameters, we utilized Student's t-test to compare the means between two groups. A significance level of $p<0.05$ was considered statistically significant, indicating a significant difference between the compared groups. This widely accepted threshold allowed us to determine the presence of statistically significant results for normally distributed variables in our study. Categorical variables of different patient populations were compared using the chi-squared test. In order to ascertain the predictive impact of the FIB-4 index, Receiver Operating Characteristic (ROC) analysis was conducted. For multivariate analysis, potential robust factors were identified using univariate analyses.

RESULTS

In the present study, 117 men (38.7%) and 302 patients were enrolled in the analysis. A total of 126 patients had STEMI; 137 patients underwent urgent PCI, while the other patients underwent PCI within 24 hours. The initial and maximum median troponin levels of the 302 patients were calculated by taking the average of initial and maximum troponin values. The study group had a median initial troponin level of 24 ng/L, ranging from 0 to 17.857 ng/L (range of normal values, 0-57 ng/L). The maximum troponin level reached a median of 21.352 ng/L, with a range of 0 to 52.477 ng/L. Based on this median maximum troponin value, the patients were then categorized into two distinct groups: the higher troponin group and the lower troponin group. This information is summarized in Table 1, which presents the distribution of patients across these two groups. No significant differences were observed between the peak troponin level group and the other groups in terms of age, sex, systolic and diastolic blood pressure, presence of HT, DM, hyperlipidemia (HL), PAD, history of CVA, previous coronary artery bypass graft surgery (CABG), coronary stent history, and other medications, except aldosterone antagonists. The two groups, based on peak troponin levels, did not demonstrate any statistically significant differences in serum creatinine, low-density lipoprotein (LDL) cholesterol, total cholesterol, high-density lipoprotein (HDL) cholesterol, or HbA1c values. As expected, in the group with high troponin level, STEMI (12.6% vs. 70.9%, $p<0.001$), Killip functional class 3-4 (2% vs. 8%, $p=0.015$), FIB-4 index (1.76±1.01 vs. 3.05±2.6, $p<0.001$), current smoking (%35.8 vs. 48.3%, $p=0.018$), aldosterone antagonist use (1.3% vs. 9.3%, $p=0.002$), glucose (142±77.1 vs. 162.2±73, $p=0.023$) and white blood cell (WBC) (9.1±2.8 vs. 11.2±3.6, $p<0.001$) were statistically significantly higher, while LV ejection fraction (EF) (55.8±8.5 vs. 49.3±11.5, $p<0.001$) and triglyceride levels (173.1±131 vs. 139.2±91.8, $p=0.010$) were lower (Table 1). In our analysis, we examined the parameters that exhibited statistical differences between the two groups, as presented in Table 2. Initially, univariate analysis was performed, followed by multivariable analysis using the backward method. The results indicated that several factors independently predicted peak troponin levels in patients with ACS. Specifically, a diagnosis of STEMI (OR: 0.056, 95% CI 0.028-0.110, $p<0.001$), current smoking (OR: 0.494, 95% CI 0.255-0.958, p:0.037), WBC (OR: 1.185, 95% CI 1.068-1.314, p:0.001), and the FIB-4 index (OR: 2.301, 95% CI 1.667-3.172, $p<0.001$) were identified as independent predictors of peak troponin levels in ACS patients. The detailed results are summarized in Table 2. ROC analysis showed that a higher FIB-4 index predicted the maximum median troponin values, with an AUC of 0.669 ($p<0.001$) (Figure 1).

KÜ Tıp Fak Derg 2024;26(1):34-41
Doi: 10.24938/kutfd.1400280

Table 1: Comparison of basal charac teristics, biochemical param eters and FIB-4 index

Variable	Troponin < Median (n=151)	Troponin≥Median (n=151)	p
Gender (Male) n (%)	117 (77.5)	128 (84.8)	0.070
Age (year)	62.6±11.6	62.8±11.6	0.921
BMI (kg/m^2)	29.6±4.8	29.1±4.8	0.407
SBP (mmHg)	133.7±20.1	131.6±24.1	0.421
DBP (mmHg)	76.11±11.9	78.7±14.9	0.096
HT n (%)	93 (61.6)	88 (58.3)	0.319
DM n (%)	52 (34.3)	46 (30.5)	0.269
HPL n (%)	67 (44.4)	55 (36.4)	0.098
Current smoking n (%)	**54 (35.8)**	**73 (48.3)**	**0.018**
PAD n (%)	5 (3.3)	9 (6.0)	0.206
CVA n (%)	9 (6)	7 (4.6)	0.399
STEMI n (%)	**19 (12.6)**	**107 (70.9)**	**<0.001**
Previous CABG n (%)	11 (7.3)	8 (5.3)	0.318
Previous stent n (%)	27 (17.9)	30 (19.9)	0.384
Killip class III-IV n (%)	**3 (2.0)**	**12 (8.0)**	**0.015**
ASA n (%)	151 (100)	150 (99.3)	0.500
Beta blocker n (%)	127 (84.1)	130 (86.1)	0.373
ACE/ARB n (%)	132 (88)	139 (92.1)	0.163
Statin n (%)	149 (98.7)	149 (98.7)	0.689
CCB n (%)	23 (15.2)	21 (13.9)	0.435
Aldosterone antagonist n (%)	**2 (1.3)**	**14 (9.3)**	**0.002**
Insulin n (%)	14 (9.3)	9 (6.0)	0.202
OAD n (%)	39 (25.8)	37 (24.5)	0.447
LVEF (%)	**55.8±8.5**	**49.3±11.5**	**<0.001**
Glucose (mg/dL)	**142±77.1**	**162.2±73**	**0.023**
Se Cr (mg/dL)	0.96±0.28	1.01±0.33	0.119
Total cholesterol (mg/dL)	198.8±49.1	193.2±43.1	0.300
TGL (mg/dL)	**173.1±131**	**139.2±91.8**	**0.010**
HDL (mg/dL)	38.7±9.1	40.3±9.3	0.133
LDL (mg/dL)	126.5±41.8	125.7±37	0.808
GFR mL/dk/m^2	79.8±21.3	77.1±21.1	0.257
HbA1c (%)	6.67±1.7	6.66±1.51	0.869
WBC (10^3/µL)	**9.1±2.8**	**11.2±3.6**	**<0.001**
Hemoglobin (g/dL)	14.1±1.9	14.3±1.8	0.278
Albumin (g/dL)	4.1±0.34	4.1±0.35	0.565
FIB-4 index	**1.76±1.01**	**3.05±2.6**	**<0.001**

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, ASA: Acetyl salicylic acid, BMI: Body mass index, CAD: Coronary artery disease, CCB: Calcium channel blocker, CVA: Cerebrovascular accident, DBP: Diastolic blood pressure, DM: Diabetes mellitus, GFR: Glomerular filtration rate, HDL: High-density lipoprotein, HPL: Hyperlipidemia, HT: Hypertension, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, OAD: Oral antidiabetic, PAD: Peripheral arterial disease, SBP: Systolic blood pressure, Se Cr: Serum creatinine, STEMI, ST-elevation myocardial infarction, TGL: Triglyceride, WBC: White blood cell.

Table 2: Univariate and multivariate logistic regression analysis

	Univariate			Multivariate		
Variable	OR	95% CI	p	OR	95% CI	p
STEMI	**0.059**	**0.033-0.107**	**<0.001**	**0.056**	**0.028-0.110**	**<0.001**
Killip class III-IV	4.290	1.185-15.52	**0.026**			
LVEF	0.931	0.906-0.958	**<0.001**			
Glucose	1.004	1.001-1.007	**0.026**			
TGL	0.997	0.995-0.999	**0.013**			
WBC	**1.240**	**1.140-1.349**	**<0.001**	**1.185**	**1.068-1.314**	**0.001**
FIB-4 index	**1.634**	**1.335-2.001**	**<0.001**	**2.301**	**1.667-3.172**	**<0.001**
Current smoking	**1.681**	**1.060-2.666**	**0.027**	**0.494**	**0.255-0.958**	**0.037**
Aldosterone antagonist	7.669	1.712-34.361	**0.008**			

LVEF: Left ventricular ejection fraction, TGL: Triglyceride, WBC: White blood cell

KÜ Tıp Fak Derg 2024;26(1):34-41
Doi: 10.24938/kutfd.1400280

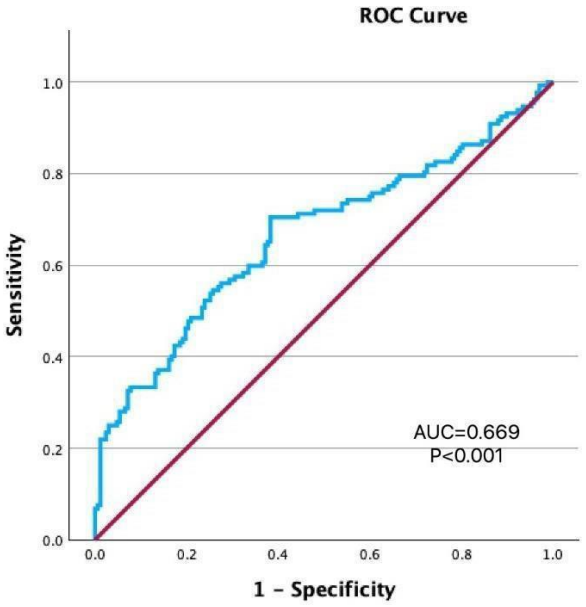

Figure 1: ROC analysis showed that a higher FIB-4 index predicted the maximum median troponin values, with an AUC of 0.669 (p<0.001)

DISCUSSION

The present study has yielded several significant findings. To the best of our knowledge, this study represents the initial investigation furnishing evidence that substantiates the predictive potential of the FIB-4 index in discerning peak troponin levels among patients diagnosed with ACS. With these results, the hypothesis we initially posited at the commencement of the study has been confirmed; higher FIB-4 index values in ACS may indeed correspond to higher peak troponin levels in these patients. This novel association implies that the FIB-4 index could function as a valuable instrument for risk stratification and prognostic evaluation in ACS patients. The identification of this relationship opens new avenues for future research and clinical applications, potentially enhancing the management and outcomes of ACS patients. Second, STEMI, current smoking status, and WBC count were strong predictors of peak troponin levels. In addition, the LVEF was lower in this group.

The elevation of serum AST levels in patients with acute myocardial infarction (AMI) was first demonstrated in 1954 (14). AST exhibits an increase in blood approximately 3–4 h post-AMI, attaining its peak value within 15–28 h, and subsequently returning to baseline levels within a span of 5 days (15). Recent studies, particularly focusing on patients with ACS, have indicated that maximum AST levels can escalate up to threefold of the upper limit (16). However, in the present study, we computed the FIB-4 index from blood samples obtained in the emergency room. Notably, our findings revealed a correlation between FIB-4 index and the maximum troponin concentration in the patient, providing valuable insights into the interplay of these parameters. Based on our study, the elevation of AST levels especially during the initial presentation in patients with ACS may have prognostic significance. A study conducted by Moon et al. demonstrated that the examination of AST levels in the emergency department predicted future mortality in patients with STEMI following successful PCI, in alignment with our present study (17).

The primary cause of mortality among individuals with NAFLD, particularly in those experiencing progressing fibrosis, is attributed to CVD. Extensive research, including numerous studies and meta-analyses, has consistently demonstrated various cardiovascular complications associated with NAFLD. These include a heightened carotid intima-media thickness (CIMT), an elevated risk of AMI, impaired endothelial function, cardiomyopathy, arrhythmias, and elevated arterial stiffness. These findings underscore the importance of recognizing and addressing the cardiovascular implications of NAFLD to optimize patient care and outcomes (18). Considering the wealth of existing research, it is plausible to claim that FIB-4 index may indeed serve as a subclinical indicator of atherosclerosis. The FIB-4 index, encompassing PLT, ALT, AST, and age, has been significantly enhanced to predict liver fibrosis (19). In a study by Shah et al., other noninvasive fibrosis markers were found to be inferior to the FIB-4 index in patients with NAFLD (20). Several studies have shown that the FIB-4 index is a good predictor of advanced liver fibrosis in several studies (21). Although the accuracy of this score is moderate for differentiating advanced liver fibrosis, especially in primary care population screening, the negative predictive value of FIB-4 is high. A lower FIB-4 predicted a lower risk of liver and non-liver diseases in recent studies (22). Myocardial ischemia results in necrosis of the heart muscle, which leads to cardiac muscle destruction and causes troponin release, resulting in the deterioration of myocardial function and development of left ventricular dysfunction (23). The gold standard marker for diagnosing ACS is elevated troponin levels, which also provides beneficial information for the prognosis of ACS. Adverse CV events, all-cause mortality, and long- and short-term mortality in patients with ACS have been associated with peak troponin levels in previous studies (24,25). In a recent investigation, a positive correlation was noted between the peak troponin level and the magnitude of LV infarction, whereas a negative correlation was observed with LV EF in STEMI patients (26). Furthermore, higher peak troponin levels in patients presenting with chest pain were found to be associated with unfavorable outcomes (27). Consistent with these findings, the peak troponin level group exhibited a significantly lower LV EF compared to the

KÜ Tıp Fak Derg 2024;26(1):34-41
Doi: 10.24938/kutfd.1400280

other groups. Another meta-analysis involving a large cohort of over 280,000 individuals demonstrated a robust correlation between NAFLD and an increased risk of LV diastolic dysfunction (28). In a study by Schonmann et al., FIB-4 index of 8511 individuals was determined and a higher FIB-4 index showed a higher CVD risk (29). In a study by Barbosa et al. involving 67,273 patients, the FIB-4 index was identified as a potent predictor of major adverse cardiovascular outcomes (12). In a study by Xiong et al., liver fibrosis scores, including the FIB-4 index, were found to be associated with CVD in hypertensive patients (30). It is known that NAFLD is a manifestation of MS in the liver, and its involvement exacerbates the pathogenesis and complications associated with MS (31). In a study conducted by Lee et al., a higher FIB-4 index was associated with a higher risk of coronary artery calcification progression (32). In a prospective study conducted by Liu et al. involving 4003 patients, it was demonstrated that liver fibrosis scores, including the FIB-4 index, had predictive capabilities for an unfavorable prognosis in stable angina pectoris patients undergoing percutaneous coronary intervention (5). In previous studies, no direct association was reported between an increased FIB-4 index and peak troponin level. However, this study revealed for the first time that a higher FIB-4 index independently predicts peak troponin levels in patients with ACS. Patients with NAFLD are more likely to develop atherosclerosis, cardiomyopathy, and arrhythmia, all of which can lead to increased cardiovascular morbidity and mortality. This may be due to various mechanisms, such as low-grade systemic inflammation, oxidative stress, cytokines, and insulin resistance, that can promote atherosclerosis (1,33). As known, the elevation of troponin levels in ACS patients has been associated with in-hospital mortality, arrhythmias, development of heart failure, and an increase in post-discharge bleeding (13,25). Therefore, the correlation between the FIB-4 index and peak troponin levels suggests that the FIB-4 index may also contribute to risk stratification in ACS patients. Furthermore, an elevated FIB-4 index is generally indicative of an increased risk of severe liver fibrosis. A comprehensive review conducted by Targher et al. emphasized that the severity of NAFLD correlates with the risk of CV events and has a substantial long-term impact on both all-cause mortality and CV outcomes among individuals with NAFLD. The review emphasized that in patients with NAFLD, the stage of liver fibrosis is a more significant prognostic marker for CV outcomes compared to other histological features of NAFLD (34).

Contrary to expectations, there were no differences in BMI, HT, DM, or HPL between the two groups. Obesity or a higher BMI, DM, and HPL are essential components of MS and are strongly correlated with NAFLD. Nevertheless, our study did not reveal any apparent association between a higher BMI and elevated troponin levels. The reason for this inconsistency is currently unknown but may be related to individuals with non-obese or lean NAFLD. In a meta-analysis conducted by Ye et al., approximately 19.2% of NAFLD patients were categorized as lean, whereas 40.8% were classified as non-obese (35). The small size of our study population may have played a role in producing this outcome. In fact, considering that these CV risk factors serve as confounding factors, and despite their similarity in both patient groups, the study's value is heightened by the observation that a higher FIB-4 level predicts an elevated troponin level.

In the present study, STEMI diagnosis, current smoking status, and WBC count were strong indicators of peak troponin levels. High peak troponin levels in STEMI patients are an expected outcome due to trans-mural infarction. In a study by Bhatt et al., a high SYNTAX score with STEMI was associated with a high troponin level and previous aspirin use was associated with a low troponin level, supporting our results (36). In line with our study's findings, Guasti et al. conducted a systematic analysis that demonstrated the predictive power of neutrophils, in combination with other inflammatory markers such as WBC and C-reactive protein, in determining cardiovascular (CV) outcomes (37). Additionally, data from the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) provided further evidence supporting the notion that targeting pro-inflammatory biomarkers with anti-inflammatory medication can reduce the risk of CV events. These findings collectively underscore the importance of inflammation in the pathogenesis of CV diseases and highlight the potential benefits of anti-inflammatory interventions in improving CV outcomes (38). Lifestyle changes that are essential in CAD risk control, including smoking cessation, physical exercise, maintaining appropriate body weight, and a healthy diet, are recommended for the treatment of CAD according to current guidelines (39). In our study, we observed an association between smoking and peak troponin levels.

Our study has several limitations that need to be considered. Firstly, the study was conducted at a single center, which may limit the generalizability of the findings to a wider population. The sample size was also relatively small, which could affect the statistical power of the study and limit the ability to detect smaller effect sizes. Another limitation is that blood samples were collected at admission without fasting, which may have influenced the accuracy of lipid profile analysis, as fasting status can impact lipid levels. Furthermore, the study design was observational, which prevents us from establishing causality or determining the temporal

relationship between variables. Future studies with larger sample sizes, multi-center designs, and consideration of fasting status are needed to further validate and generalize the findings of our study. Moreover, we did not utilize imaging modalities or other fibrosis scores, apart from the FIB-4 index, to evaluate patients with NAFLD. Future studies incorporating a larger and more diverse patient population, along with comprehensive assessments of NAFLD using various diagnostic techniques, are warranted to validate and expand upon our findings.

Higher troponin levels in patients with ACS were strongly predicted by a higher FIB-4 index. Owing to its low cost and ease of use, the presence of a higher FIB-4 index may alert clinicians to more preventive actions in patients with ACS.

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

*Researchers' Contribution Rate Statement***:** Concept/Design: HD, EE; Analysis/Interpretation: HD, EE; Data Collection: HD, EE; Writer: HD; Critical Review: HD, EE; Approver: HD, EE

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