

## Evaluating the Prognostic Nutritional Index for Predicting the Clinical Relevance of Angiographically Intermediate Coronary Lesions

### ABSTRACT

**Background:** Coronary artery disease (CAD) is a widespread health issue globally, linked to significant morbidity and mortality. While oxidative stress, dysregulated lipid metabolism, and unhealthy lifestyle choices contribute to CAD, recent research highlights the role of immune responses and inflammation. Malnutrition, a modifiable risk factor, notably impacts CAD prognosis. The prognostic nutritional index (PNI), derived from serum albumin and lymphocyte count, predicts outcomes in various diseases. This study aims to elucidate the relationship between malnutrition, as assessed by the PNI score, and the functional significance of coronary artery stenosis, evaluated by fractional flow reserve (FFR) measurements.

**Methods:** A retrospective analysis involved 232 patients with single intermediate-grade coronary stenosis who underwent FFR measurement between January 2022 and January 2024. Prognostic nutritional index values were calculated from serum albumin and lymphocyte counts. Patients were divided into 2 groups based on FFR values.

**Results:** Patients with hemodynamically significant coronary stenosis ( $FFR \leq 0.80$ ) exhibited higher inflammatory markers and triglycerides, while those with  $FFR > 0.80$  showed elevated albumin and PNI levels. Triglycerides and PNI emerged as independent predictors of significant coronary stenosis.

**Conclusions:** This study demonstrates that PNI is independently associated with the functional significance of coronary artery stenosis as determined by FFR. Since lymphocytes, total protein and albumin values, which are readily available from routine blood tests, form the basis for PNI, this index can be easily used in clinical settings to predict hemodynamically significant coronary artery stenosis. However, the results of this study should be further expanded and validated through studies involving larger samples and prospective designs.

**Keywords:** Prognostic nutritional index, fractional flow reserve, coronary artery disease, coronary angiography

### INTRODUCTION

Coronary artery disease (CAD) is a prevalent disorder impacting millions globally, constituting 32.7% of all heart diseases and 1.7% of the total disease burden.<sup>1</sup> It stands as a leading cause of both morbidity and mortality, imposing substantial medical and economic strains on society.<sup>2</sup> Primarily, CAD onset is linked to oxidative stress, dysregulated lipid metabolism, and unhealthy lifestyle choices predisposing to thrombosis. However, contemporary research underscores the contribution of immune responses and inflammatory processes to CAD progression.<sup>3,4</sup>

Malnutrition is a growing global concern and is recognized as a modifiable risk factor for various diseases. Its detrimental impact extends to the prognosis for individuals with acute coronary syndrome (ACS).<sup>5</sup> Research indicates that over 40% of patients with heart failure suffer from malnutrition, and its presence serves as an independent predictor of mortality.<sup>6</sup> Furthermore, a study revealed that more than 50% of CAD patients exhibit varying degrees of malnutrition, a factor predictive of adverse cardiac events.<sup>7</sup>

### ORIGINAL INVESTIGATION

Can Özkan<sup>1</sup> 

Abdullah Kadir Dolu<sup>2</sup> 

Muhammet Cihat Çelik<sup>3</sup> 

Bekir Demirtaş<sup>4</sup> 

Orhan Karayığit<sup>5</sup> 

<sup>1</sup>Department of Cardiology, Bursa City Hospital, Bursa, Türkiye

<sup>2</sup>Department of Cardiology, İzmir Katip Çelebi University Atatürk Training and Research Hospital, İzmir, Türkiye

<sup>3</sup>Department of Cardiology, Hitit University Erol Olçok Training and Research Hospital, Çorum, Türkiye

<sup>4</sup>Department of Cardiology, Ankara Etilik City Hospital, Ankara, Türkiye

<sup>5</sup>Department of Cardiology, Yozgat City Hospital, Yozgat, Türkiye

#### Corresponding author:

Can Özkan

✉ canozzkan@hotmail.com

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Albumin, a plasma protein crucial for maintaining plasma oncotic pressure, serves as a reliable indicator of nutritional status. Moreover, it possesses anti-inflammatory and anti-oxidative properties, including the binding of various toxins and scavenging free radicals. Lymphocytes, constituents of the white blood cell population, are pivotal during inflammatory processes.<sup>8</sup> Prognostic nutritional index, easily calculable, offers insights into both nutritional and immunological statuses. Derived from serum albumin concentration and total lymphocyte count, it has been commonly utilized to anticipate complication risks post-gastrointestinal surgeries.<sup>9</sup> Recent evidence highlights the prognostic significance of PNI following coronary artery bypass graft procedures, correlating with mortality and adverse events.<sup>10</sup> Notably, in a local study involving patients with unprotected left main coronary artery undergoing percutaneous coronary intervention (PCI), malnourished individuals exhibited higher rates of all-cause mortality and stroke compared to their well-nourished counterparts, findings reflected in their PNI.<sup>11</sup>

Prognostic nutritional index is a biomarker of inflammation beyond nutritional status.<sup>12</sup> Inflammation is recognized as an important risk factor for CAD.<sup>13</sup> Different inflammatory markers have been used to predict hemodynamically severe lesions.<sup>14</sup> However, there is insufficient data on whether PNI can predict hemodynamically significant lesions. A study by Zhang et al<sup>15</sup> reported that malnutrition as assessed by PNI was independently predictive of mortality and major adverse cardiovascular events (MACEs) in CAD patients. In another study, nutritional status assessed by PNI was significantly and strongly associated with adverse cardiac events in patients after elective PCI and was identified as an independent predictor of long-term cardiovascular outcomes in patients with stable CAD after elective PCI.<sup>16</sup>

Intermediate coronary artery stenosis is a common finding in routine coronary angiography.<sup>17</sup> Identifying and managing these moderate coronary lesions may offer potential advantages but presents significant challenges due to heightened procedural and long-term risks.<sup>18</sup>

## HIGHLIGHTS

- Prognostic nutritional index (PNI) correlates independently with functional coronary artery stenosis severity assessed by fractional flow reserve (FFR).
- Elevated triglycerides and lower PNI values are predictive markers of hemodynamically significant coronary lesions.
- Prognostic nutritional index, derived from routine blood tests, offers a cost-effective tool for risk stratification in patients with intermediate coronary artery disease.
- Neutrophil levels and hypoalbuminemia are associated with the severity of coronary artery lesions assessed by FFR.
- Integrating PNI assessment into clinical practice could enhance prognostic evaluation and guide therapeutic strategies effectively.

Nevertheless, it is imperative to mitigate the risk of future MACE associated with culprit intermediate lesions.<sup>19</sup> Fractional flow reserve (FFR), representing the ratio of maximum myocardial blood flow in a diseased artery to the maximum myocardial blood flow under normal conditions,<sup>20</sup> has been substantiated by numerous clinical trials to significantly enhance patient outcomes, particularly when utilized for guiding coronary revascularization. Consequently, strategies informed by FFR have garnered the most robust endorsement in the latest guidelines for PCI. The optimization of this advantage necessitates scrupulous and standardized protocols governing the acquisition, documentation, storage, and transmission of FFR measurements within the realm of clinical investigations.<sup>21</sup>

Fractional flow reserve is the gold standard method used to assess whether lesions are hemodynamically significant. However, its disadvantages include an invasive procedure, possible complications, and increased cost. The PNI serves as a practical, applicable, and prognostic scoring system. In this context, our study aims to investigate the relationship between PNI-assessed malnutrition and FFR assessment in patients with moderate coronary artery stenosis. By investigating this association, our study aims to contribute to the understanding of the role of PNI as a practical, cost-effective biomarker for predicting hemodynamically significant coronary lesions and potentially provide new insights in CAD management.

## METHODS

This retrospective study was conducted over the period spanning from January 2022 to January 2024, encompassing a cohort of 232 consecutive patients. Among these, there were 63 female and 169 male individuals diagnosed with single intermediate-grade coronary stenosis (40%-70%, as determined by quantitative coronary analysis), all of whom underwent FFR measurement. The study population consisted of patients who had undergone coronary angiography due to stable angina pectoris. Exclusion criteria encompassed patients with ACS, moderate or severe valvular heart disease, significant arrhythmias, hemodynamic instability, a secondary lesion in the index coronary artery or presence of another coronary artery with  $\geq 40\%$  luminal narrowing, history of prior surgical or percutaneous coronary artery intervention, acute or chronic inflammatory or infectious conditions, anemia, chronic renal failure, or malignancy.

Data were collected from hospital records and files, including patients' demographic, clinical, and angiographic information. Blood samples were obtained from venous sources within 24 hours of hospital admission and analyzed for lipid profile, serum creatinine levels, and complete blood count. Prognostic nutritional index was calculated using the formula:  $PNI = \text{serum albumin level} + (5 \times \text{total lymphocyte count})$ .

Fractional flow reserve assessments were conducted on intermediate-grade lesions exhibiting a stenosis rate ranging between 40% and 70%, as determined at the discretion of cardiologists. Fractional flow reserve records were also obtained from the hospital's registration system.

Fractional flow reserve values of 0.80 or less were considered indicative of hemodynamic significance. Patients were categorized into 2 groups: group I, with FFR values greater than 0.80, and group II, with FFR values of 0.80 or less.

### Artificial Intelligence Statement

Artificial Intelligence-supported technologies were not used in the production of this submitted work.

### Statistical Analysis

The necessary statistical analyses were performed using SPSS software version 20.0 for Windows (SPSS Inc., Chicago, IL, USA), and the distribution shapes of variables were analyzed using the Kolmogorov–Smirnov test. While categorical determinants were given as percentages and numbers, continuous variables were presented as mean  $\pm$  standard deviation or median with interquartile range, depending on the distribution model of the variables. The Mann–Whitney *U*-test was preferred to calculate differences between non-parametric continuous variables, and categorical variables were compared using the Pearson chi-square test. Possible confounding factors for the severity of coronary artery lesions were determined using multiple logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal PNI cutoff value to predict hemodynamically significant coronary artery stenosis. The level of statistical significance was set at  $<0.05$ .

### RESULTS

Based on the presence of significant functional coronary stenosis, the study cohort was divided into 2 groups: group I comprised 120 patients (males: 84 (70%); mean age:  $59 \pm 9.69$  years) without significant stenosis, while group II included 112 patients (males: 85 (75.9%); mean age:  $57.6 \pm 9.18$  years) with significant stenosis.

Table 1 illustrates the baseline characteristics and laboratory findings of the patients. There were no statistically significant differences observed in baseline characteristics, including age, gender, diabetes mellitus, hypertension, stroke, dyslipidemia, history of coronary artery disease, and smoking.

Regarding laboratory parameters, group II demonstrated higher levels of white blood cells [ $9.25$  (7.62–11.1) vs.  $7.93$  (6.83–9.82)  $\times 10^3/\mu\text{L}$ ,  $P = .006$ ], neutrophils [ $5.61$  (4.40–7.18) vs.  $4.83$  (3.95–6.30)  $\times 10^3/\mu\text{L}$ ,  $P = .026$ ], and triglycerides (TG) levels [ $169$  (117–248.3) vs.  $140.5$  (99.3–189.3) mmol/L,  $P = .003$ ]. Conversely, group I exhibited higher levels of total protein [ $69$  (65–71) vs.  $67$  (64–70) mg/dL,  $P = .007$ ], albumin [ $42$  (40.1–44) vs.  $39$  (37.3–42) mg/dL,  $P < .001$ ], and PNI ( $53.08 \pm 4.84$  vs.  $51.20 \pm 5.67$ ,  $P = .007$ ). No significant differences were noted in other laboratory data between the 2 groups. Additionally, the left ventricular ejection fractions were similar between both groups.

Parameters identified as significant in the univariate logistic regression analysis were subsequently included in the multivariate logistic regression analysis to determine the predictors of hemodynamically significant coronary artery stenosis. TG (OR: 1.005, 95% CI: 1.002–1.008;  $P = .002$ ) and PNI

**Table 1. Comparison of Baseline Characteristics and Laboratory Findings of the Groups**

Variables Baseline Characteristics	Significant FFR		P
	Insignificant FFR (n = 120)	(n = 112)	
Age (years)	$59 \pm 9.69$	$57.6 \pm 9.18$	.266
Gender (male), n (%)	84 (70)	85 (75.9)	.313
Diabetes mellitus, n (%)	38 (31.7)	42 (37.5)	.350
Hypertension, n (%)	64 (53.3)	62 (55.4)	.757
Stroke, n (%)	1 (0.8)	6 (5.4)	.058
Dyslipidemia, n (%)	24 (20)	27 (24.1)	.450
History of CAD, n (%)	45 (37.5)	34 (30.4)	.251
Smoking, n (%)	44 (36.7)	43 (38.4)	.786
Urea (mg/dL)	17.6 (13–28.8)	15.2 (12–23.7)	.069
Creatinine (mg/dL)	0.87 (0.72–1)	0.87 (0.76–0.98)	.870
GFR (mL/dk/1.73 m <sup>2</sup> )	90 (82.3–99.8)	93.5 (81.3–101)	.429
Total protein (mg/dL)	69 (65–71)	67 (64–70)	<b>.007</b>
Albumin (mg/dL)	42 (40.1–44)	39 (37.3–42)	<b>&lt; .001</b>
WBC ( $\times 10^3/\mu\text{L}$ )	7.93 (6.83–9.82)	9.25 (7.62–11.1)	<b>.006</b>
Neutrophil ( $\times 10^3/\mu\text{L}$ )	4.83 (3.95–6.30)	5.61 (4.40–7.18)	<b>.026</b>
Lymphocyte ( $\times 10^3/\mu\text{L}$ )	2.14 (1.67–2.60)	2.17 (1.80–2.90)	.338
RBC (M/ $\mu\text{L}$ )	$4.77 \pm 0.60$	$4.89 \pm 0.65$	.144
Hemoglobin (g/dL)	13.9 (12.6–15.3)	14.4 (12.7–15.5)	.430
HTC (%)	$40.9 \pm 5.19$	$41.2 \pm 5.56$	.745
MCV (fL)	86 (83–89)	84.8 (81–88.7)	.059
RDW (%)	13.1 (12.6–13.9)	13.3 (12.5–14.2)	.429
Platelets ( $\times 10^3/\mu\text{L}$ )	250.5 (205–291.5)	267.5 (223–310.8)	.071
MPV (fL)	10.4 (9.9–11)	10.2 (9.7–10.8)	.079
Fasting blood glucose level (mg/dL)	102 (92–137.5)	108 (92.3–149.8)	.303
AST (U/L)	20 (14–25)	18 (14–25)	.571
ALT (U/L)	19 (15–25)	19 (14.3–26.8)	.777
Total cholesterol (mmol/L)	$172.5 \pm 42.9$	$182.2 \pm 44.9$	.095
LDL-C (mmol/L)	$102.5 \pm 37.5$	$108.1 \pm 41.9$	.277
HDL-C (mmol/L)	40 (35–48.8)	38 (33–45.8)	.140
Triglyceride (mmol/L)	140.5 (99.3–189.3)	169 (117–248.3)	<b>.003</b>
Calcium (mg/dL)	9.20 (9–9.50)	9.20 (9–9.60)	.894
Sodium (mEq/L)	140 (138–141)	139 (137–141)	.109
Potassium (mmol/L)	4.30 (4.09–4.50)	4.28 (4.04–4.60)	.711
hs-CRP (mg/dL)	4 (2–6.74)	4 (2–6.85)	.507
LVEF (%)	60 (55–60)	60 (55–60)	.187
PNI	$53.08 \pm 4.84$	$51.20 \pm 5.67$	<b>.007</b>

*P* < .05 shows statistical significance. Statistically significant values are indicated in bold. ALT, alanine transaminase; AST, aspartate transaminase; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; HTC, hematocrit; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricle (LV) ejection fraction; MCV, mean corpuscular volume; MPV, mean platelet volume; PNI, prognostic nutritional index; RBC, red blood cell.

**Table 2. Multiple Logistic Regression Analysis of Potential Predictor Factors for Hemodynamically Significant Coronary Artery Stenosis**

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Total protein	0.944	0.896-0.993	<b>.027</b>	0.972	0.913-1.035	.374
Albumin*	0.811	0.743-0.884	<b>&lt;.001</b>			
WBC	1.092	0.993-1.201	<b>.007</b>	1.100	0.993-1.219	.067
Neutrophil	1.064	0.959-1.182	.242			
Triglyceride	1.004	1.001-1.007	<b>.007</b>	1.005	1.002-1.008	<b>.002</b>
PNI	0.933	0.887-0.982	<b>.008</b>	0.922	0.865-0.983	<b>.013</b>

P < .05 shows statistical significance. \*This parameter was not entered into the model in order to prevent multicollinearity. Statistically significant values are indicated in bold.

OR, odds ratio; PNI, prognostic nutritional index; WBC, white blood cell.

(OR: 0.922, 95% CI: 0.865-0.983;  $P = .013$ ) were established as independent predictors of hemodynamically significant coronary artery stenosis (refer to Table 2).

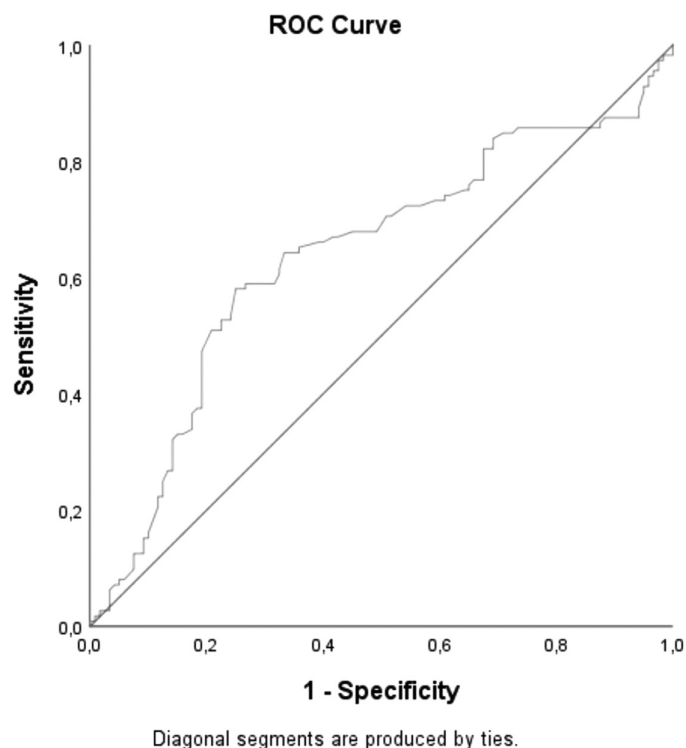
Receiver operating characteristic analysis revealed that a threshold value of 51.9 exhibited a sensitivity of 65.2% and a specificity of 64.2% in predicting hemodynamically significant coronary artery stenosis (AUC: 0.637, 95% CI: 0.564-0.710,  $P < .001$ ) (Figure 1).

## DISCUSSION

In this study, PNI levels were independently associated with functionally significant coronary artery lesions evaluated by FFR measurement. Additionally, triglycerides remained one

of the independent determinants of functional significance in the multivariable analysis. The concept of FFR has been developed as an index of the functional severity of coronary artery stenoses determined invasively.<sup>22</sup> It represents the ratio of hyperemic myocardial blood flow in the stenotic region to hyperemic myocardial blood flow in the same region without narrowing.<sup>23</sup> It is used when the severity of stenoses seen by coronary angiography cannot be clearly assessed qualitatively.<sup>24</sup> Fractional flow reserve-guided PCI improves patient outcomes, reduces stent implantations, and lowers costs.<sup>25</sup> Studies have found FFR to be superior to angiography when used to guide revascularization strategies and have shown that routine FFR measurement in patients with multivessel coronary artery disease reduces the rate of major adverse cardiac events.<sup>26,27</sup> Therefore, in this study, FFR measurement was used to determine the functional significance of coronary lesions and their relationship with PNI levels. We found that in patients with hemodynamically significant lesions evaluated by FFR ( $FFR \leq 0.80$ ), PNI levels were significantly lower.

The PNI emerges as an indicator of poor prognosis in individuals with cardiovascular disease.<sup>28</sup> Initially utilized to monitor the nutritional status of postoperative patients, over time, PNI has been employed to predict outcomes in malignant tumors and coronary artery disease, with it being thought to reflect the systemic inflammatory state to a certain extent.<sup>29</sup> Coronary artery disease develops on an atherosclerotic background, which involves lipid metabolism and specific inflammatory cytokines and processes.<sup>30</sup> Therefore, inflammation is considered one of the most significant factors in the development of atherosclerosis.<sup>31</sup> Furthermore, studies have reported an association between low PNI values and increased risk of MACE and cerebrovascular events.<sup>32</sup> In a cohort study examining the relationship between diabetes, PNI, and the prognosis of coronary artery disease, Li et al<sup>33</sup> demonstrated that patients with low PNI levels had a higher risk of all-cause mortality. Additionally, Ling et al<sup>34</sup> showed in their study that PNI was an independent risk factor for all-cause mortality in patients who underwent PCI following acute myocardial infarction. In another study, it was found that low PNI values increased in-stent restenosis by activating inflammatory processes.<sup>35</sup> Furthermore, a meta-analysis revealed that in patients with heart failure, PNI was



**Figure 1. The receiver-operating characteristic curve analysis for PNI in predicting functionally significant coronary stenosis in FFR measurements (AUC: 0.637, 95% CI: 0.564-0.710,  $P < .001$ ).**

identified as an independent predictor of all-cause mortality and/or readmission to the hospital.<sup>36</sup> A study by Tolunay et al<sup>37</sup> found that PNI was significantly associated with the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, and PNI was associated with cardiovascular mortality and rehospitalization within 6 months of ACS diagnosis. In another study supporting our study, the severity of coronary lesions was found to be closely associated with PNI.<sup>38</sup> In a study by Güzel et al<sup>11</sup> examining long-term outcomes after left main coronary artery revascularization, a statistically significant relationship was found between PNI values and SYNTAX score. Another study investigated the relationship between nutritional status and prognosis in ST-elevation myocardial infarction (STEMI) patients and the main finding was that a controlling nutritional status score of  $\geq 5$  predicted an increased risk of MACE in STEMI patients at long-term follow-up. It has been suggested that scores used to estimate the degree of malnutrition may be more effective than parameters used alone, such as body mass index or serum albumin levels.<sup>39</sup> All these studies show a correlation between the degree of coronary artery disease and PNI. In our study, FFR measurement was used to determine the functional significance of coronary lesions and their relationship with PNI levels. We found that patients with hemodynamically significant lesions, as assessed by FFR (FFR  $\leq 0.80$ ), had significantly lower PNI levels. In another respect, our study also shows that hemodynamically significant stenoses, as measured by FFR, are statistically significantly associated with PNI.

When examining the basal characteristic features of patients in the study, it was observed that in the group with hemodynamically significant FFR results, statistically significant hypoalbuminemia and elevated neutrophil counts were detected. Neutrophils significantly influence the onset and progression of notable atherosclerotic lesions.<sup>40</sup> Therefore, high neutrophil levels may be associated with the hemodynamically significant FFR group. Acute-phase reactants are proteins that indirectly measure the inflammatory state. Albumin is one of the most well-known acute-phase reactants.<sup>41</sup> Serum albumin levels serve as reliable predictors of cardiovascular diseases.<sup>42</sup> Albumin has been associated with coronary artery disease through the response mechanism to inflammation. Numerous studies have reported the relationship between low serum albumin levels and increased risks of cardiovascular disease and heart failure. It has been suggested that serum albumin levels are inversely proportional to the incidence of ischemic heart disease. Low serum albumin levels are associated with platelet aggregation, impaired endothelial function, and thrombocyte-derived luminal narrowing in coronary arteries.<sup>43</sup>

In our study, we also observed that TG levels were significantly higher in the group with significant FFR results. Previous studies support the critical role of alterations in specific lipid or lipoprotein levels in the development of atherosclerosis. The importance of local vascular wall and systemic inflammation in the development of atherosclerosis has been clearly demonstrated. While dyslipidemia was previously

considered predominant in the development of atherosclerosis, it is now accepted that inflammation and dyslipidemia are integrated.<sup>44</sup> Elevated TG levels lead to the formation of TG-rich lipoproteins enriched with apolipoprotein C-III, which affect signaling pathways influencing nuclear factor kappa B and contribute to inflammation, leading to the development of fatty streaks and advanced atherosclerosis. Moreover, it has been shown that the cholesterol content in TG-rich lipoproteins predicts CAD risk better than low-density lipoprotein-cholesterol.<sup>45</sup> High TG levels have been identified as an independent risk factor for the development of coronary artery disease and acute cardiovascular events.<sup>46</sup>

Our study underscores the value of the PNI as a tool to assess the functional significance of coronary lesions. Our research showing an independent association between low PNI levels and hemodynamically significant coronary stenosis highlights the potential role of PNI in improving risk stratification and guiding management strategies for CAD. This approach may improve patient outcomes by identifying those at higher risk for adverse cardiovascular events, thereby enabling more targeted interventions.

### Study Limitations

This study has several limitations. Firstly, it is characterized by a retrospective design with a limited number of patients. Secondly, many other important inflammatory markers were not included in this study. Lastly, our analyses are based on a single PNI value; thus, we did not track changes over time and variations in PNI.

### CONCLUSION

In conclusion, this study demonstrates that PNI is independently associated with the functional significance of coronary artery stenosis as determined by FFR. Given the accessibility and low cost of PNI derived from routine blood tests such as serum albumin and total lymphocyte count, it offers a practical and effective tool to predict significant coronary artery stenosis in clinical practice. Integrating PNI assessment into clinical practice may aid in the management of CAD patients with intermediate coronary lesions. Future research should further investigate the utility of PNI in various CAD contexts and its potential to complement existing diagnostic methods.

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**Ethics Committee Approval:** The research protocol received approval from the Local Ethics Committee (Ankara Etlik City Hospital) and was executed in accordance with the principles outlined in the Declaration of Helsinki. Due to the retrospective nature of the study, written informed consent from patients was unattainable (Institutional Ethics Committee, decision number: 2024-140, date: 14.02.2024).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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B.D.; Data Collection and/or Processing – O.K., B.D.; Analysis and/or Interpretation – A.K.D., C.Ö.; Literature Search – C.Ö., B.D.; Writing – C.Ö., A.K.D.; Critical Review – M.C.Ç., B.D.

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