

The importance of mean platelet volume to lymphocyte ratio in predicting atrial fibrillation after coronary bypass operations

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Ethics Committee Approval

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All procedures in this study involving human
participants were performed in accordance with
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Conflict of Interest

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Abstract

Background/Aim: The rate of postoperative atrial fibrillation (PoAF) after coronary artery bypass graft (CABG) operations ranges between 25-40%. Inflammation plays an important role in the pathogenesis of PoAF, and mean platelet volume and lymphocyte count are important inflammatory parameters. This study aimed to investigate the importance of the mean platelet to lymphocyte ratio (MPVLR) in predicting PoAF after CABG operations.

Methods: Three hundred and eighty consecutive patients who underwent on-pump CABG in our clinic between August 2016 and August 2020 were included in this retrospective observational cohort study. Patients with a known history of atrial fibrillation, reoperations, emergency operations, patients who had acute coronary syndrome within the last month, combined surgeries, those with systemic inflammatory disease, chronic autoimmune disease, chronic liver/kidney disease, and hematological diseases, and patients under steroid therapy were excluded from the study. Patients who did not develop postoperative PoAF were included in Group 1, while those who did were included in Group 2.

Results: There were 319 patients in Group 1 with a median age of 59 (32-83) years, and 61 patients in Group 2, with a median age of 66 (38-86) years ($P<0.001$). There was no difference between the groups in terms of gender distribution, hypertension (HT), diabetes mellitus (DM), smoking, body mass index, hyperlipidemia, ejection fraction, and current medical treatments (such as Angiotensin-converting enzyme inhibitor and beta-blocker therapy). The rate of chronic obstructive pulmonary disease ($P=0.017$), as well as MPV, MPVLR, intensive care unit stay and total hospitalization times were significantly higher ($P<0.001$ for all) in Group 2, while lymphocyte levels were significantly lower ($P=0.006$). Based on multivariate analysis, being over 70 years old (OR: 2.432, CI 95%: 1.966-3.723, $P<0.001$), having an ejection fraction below 35% (OR: 1.325, CI 95%: 1.190-1.1894, $P=0.021$) and MPVLR (OR: 1.821, 95%CI: 1.645-2.1592, $P<0.001$) were independent predictors of PoAF.

Conclusion: We found that the preoperative MPVLR value, which can be obtained from a simple hemogram test, is an important predictor of PoAF in patients who underwent CABG. MPVLR value can be a marker in determining risky groups preoperatively.

Keywords: Inflammation, Platelets, Coronary artery disease, Coronary artery bypass grafting, Postoperative term

Introduction

Although endovascular procedures have come to the fore with the developing technology today, coronary artery bypass graft (CABG) surgery is still the most important treatment method for coronary artery disease (CAD) [1]. These technological advances have also improved cardiopulmonary bypass (CPB) systems, and CABG operations can be performed with low mortality and morbidity rates. However, apart from mortality, morbid conditions such as renal failure, atrial fibrillation, and cerebrovascular accident may occur after these operations [2-4]. Postoperative atrial fibrillation (PoAF), one of these cases, can be seen at a rate of 25-40%. This prolongs hospitalizations, increases treatment costs, and may lead to workforce loss [3, 4].

Inflammation not only plays a role in the pathogenesis of cardiovascular diseases, but also affects their progression. Many hemogram and routine biochemical parameters were used to predict prognosis after CABG operations because they are inexpensive and easily available [5, 6]. The most important of these parameters are related to lymphocyte count and mean platelet volume (MPV). In a recent study, preoperative high MPV value was an independent predictor of PoAF after CABG operations [7]. Preoperative low lymphocyte counts were also associated with PoAF in several studies [8]. In the light of all this information, mean platelet to lymphocyte ratio (MPVLR) seems a valuable prognostic marker in predicting PoAF.

This study aimed to investigate the importance of MPVLR in predicting postoperative atrial fibrillation after CABG operations performed with CPB.

Materials and methods

Patients who underwent CPB-guided isolated coronary bypass between January 2016 and January 2020 were included in this retrospective observational cohort study. The study was initiated after approval was granted by the ethics committee of Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital (2011-KAEK-25-2021/02-19). Demographic data of the patients (age, gender, chronic disease conditions such as hypertension, diabetes mellitus, etc.), preoperative blood parameters (hematocrit, white blood cell, neutrophil, lymphocyte, platelet count, MPV), operative data (perfusion times), and postoperative data (hospital and intensive care unit length of stay, drainage amounts, etc.) were obtained from the hospital registry. Patients with a known history of atrial fibrillation, reoperations, emergency operations, patients who had acute coronary syndrome within the last month, combined surgeries, those under steroid therapy, those with chronic autoimmune diseases, systemic inflammatory diseases, chronic liver/kidney diseases, and hematological diseases were excluded from the study. The implementation of these criteria left 380 consecutive patients to be included in the study. The primary endpoint of the study was the development of in-hospital PoAF after the operation. Patients who did not develop postoperative PoAF were included in Group 1, and those who did, made up Group 2.

Blood parameter analysis

All blood samples were obtained from peripheral venous structures during hospitalization. Hemogram (Beckmann Coulter LH 780) and biochemical (Cobas 6000, Mannheim) measurements were performed using automatic analyzers. The MPVLR value was calculated as follows:

$$\text{MPVLR} = \text{Mean platelet volume (fl)} / \text{lymphocyte count } 10^3/\mu\text{L}$$

Surgical technique

All patients underwent CABG with median sternotomy and standard CPB. All operations were performed by the same surgical team. Following the induction of anesthesia, a cardioplegic arrest was achieved after median sternotomy followed by aorta-two stage venous cannulation. All operations were performed in mild hypothermia (32 degrees Celsius). First, distal anastomoses were performed after aortic cross-clamping. When the distal anastomoses were done, the patient was warmed, and the heart was operated on by giving hot shot cardioplegia. Proximal anastomoses were performed with partial clamps. When sufficient hemodynamic status was obtained, the patient was weaned from the CPB, and the surgical incisions were closed. All patients were taken to the intensive care unit with close follow-up after the operation.

Postoperative Atrial Fibrillation Follow-up and Definition

Continuous electrocardiography (ECG) follow-ups were performed in all patients during their intensive care follow-up. Daily 12-lead ECG recordings were obtained from all patients followed up in the ward and the intensive care unit, as well as from those who had palpitation, sweating, and chest pain at the time of the complaint. PoAF was defined as the absence of P waves before QRS waves, and an irregular rhythm, lasting longer than five minutes.

Statistical analysis

SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) was used for data analysis. For continuous and ordinal data, mean and standard deviations were calculated using descriptive methods. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of distribution. For normally distributed data, the Student's t-test was used and the data were shown as mean (SD). The Mann-Whitney U test was used for non-normally distributed data, which were expressed as median (minimum-maximum). Frequency and percentile analyses were performed for the nominal data, which was compared with the Chi-Square test. Multivariate logistic regression analysis was used to assess the predictors of postoperative atrial fibrillation. A P value of less than 0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve analysis was performed for preoperative MPVLR to predict PoAF and the area under the curve was calculated.

Results

A total of 380 patients were included in the study, and the preoperative characteristics and demographic data of the patients are presented in Table 1. There were 319 patients in Group 1 with a median age of 59 (32-83) years, and 61 patients in Group 2, with a median age of 66 (38-86) years ($P < 0.001$).

The groups were similar in terms of gender, hypertension (HT), diabetes mellitus (DM), smoking, body mass index, hyperlipidemia, ejection fraction, and current medical treatments (such as Angiotensin-converting enzyme inhibitor and beta-blocker therapy). The rate of chronic obstructive pulmonary disease was significantly higher in Group 2 ($P= 0.017$).

Table 1: Demographic data and preoperative features of the patients

Parameters	Group 1 (n=319)	Group 2 (n=61)	P-value
Age(years)	59 (32- 83)	66 (38-86)	<0.001
Female gender, n (%)	86 (26.9)	17(27.8)	0.879
COPD, n (%)	50 (15.6)	18 (29.5)	0.017
Hypertension, n (%)	186 (58.3)	38 (62.2)	0.518
Hyperlipidemia, n (%)	108 (33.8)	22 (36)	0.710
BMI (kg/m ²)	28.7 (23- 36)	29.3 (22.4-35.8)	0.226
Diabetes mellitus, n (%)	66 (20.6)	17 (27.8)	0.312
Smoking, n (%)	75 (23.5)	16 (26.2)	0.619
Beta blocker use, n (%)	140 (43.8)	23 (37.7)	0.412
ACEI/ ARB use, n (%)	161 (50.4)	28 (45.9)	0.541
EF (%)	50 (30- 65)	50 (25-65)	0.092
Left atrial diameter (cm)	3.5 (3.2- 4.4)	3.6 (3.3-4.8)	0.194

COPD: Chronic obstructive pulmonary disease, PCI: Percutaneous coronary intervention, CVA: Cerebrovascular accident, BMI: Body mass index, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, EF: Ejection fraction

Preoperative laboratory parameters and perioperative data of the patients are presented in Table 2. There was no difference between the groups in terms of white blood cell (WBC), hematocrit (Htc), platelet (PLT) count, neutrophil counts, urea, creatinine, C-reactive protein (CRP) values, drainage amounts, and perfusion times. In Group 2, MPV, MPVLR, intensive care, and total hospitalization times were significantly higher (for all parameters $P<0.001$), while lymphocyte levels were significantly lower ($P=0.006$).

Table 2: Preoperative laboratory variables and perioperative features of the patients

Variables	Group 1 (n=319)	Group 2 (n=61)	P-value †
White blood Cell (10 ³ /μL)	8.4 (4.5- 14.9)	8.7 (4.2- 14.3)	0.178
Hematocrit (%)	41.4 (33.6- 52.3)	40.2 (33- 51.5)	0.276
Platelet (10 ³ /μL)	252 (136- 496)	254 (130- 472)	0.189
MPV (fl)	8.4 (7.8- 10.2)	9.8 (8.9- 12.2)	<0.001
Neutrophil (10 ³ /μL)	4.4 (1.8- 8.8)	4.6 (2.2- 9.1)	0.094
Lymphocyte(10 ³ /μL)	2.3 (0.8- 4.4)	1.9 (0.7- 3.9)	0.006
Creatinine, mg/dL	0.99 (0.7- 2)	0.97 (0.8- 2)	0.494
Urea, mg/dL	20 (14- 40)	18 (16- 44)	0.256
C Reactive protein (mg/dL)	8.9 (0.6- 49.4)	9.2 (0.5- 44.9)	0.208
MPVLR	2.98 (2.61- 3.32)	4.71 (2.75- 6.48)	<0.001
Total perfusion time	90 (62- 196)	96 (55- 178)	0.128
Cross-clamp time	35 (21- 78)	38 (30- 75)	0.321
Total chest tube drainage (ml)	700 (200- 1600)	750 (300- 1500)	0.219
Total ICU stay (days)	2 (1- 9)	4 (2-16)	<0.001
Total hospital stay (days)	7 (5- 18)	111 (9- 28)	<0.001

† Mann Whitney U test, MPVLR: Meal platelet volume to lymphocyte ratio, TSH: Thyrotropin-stimulating hormone, T3: Triiodothyronine, T4: thyroxine.

Logistic regression analysis was performed to evaluate predictive parameters in predicting PoAF after CABG operations performed with cardiopulmonary bypass (Table 3). In univariate analysis, being over 70 years of age (odds ratio (OR): 3.945, confident interval (CI) 95%: 2.196-5.671, $P<0.001$), having an EF below 35% (OR:2.192, CI 95%:1.658-3.1690, $P=0.005$), COPD (OR: 0.889, CI 95%: 0.694-0.912, $P=0.0020$), low lymphocyte count (OR: 1.428 CI 95%: 1.212-1.894, $P=0.008$), MPV elevation (OR: 1.696, CI 95%: 1.422-1.987, $P<0.001$) and MPVLR elevation (OR: 2.874, CI 95%: 1.968-3.418 $P<0.001$) were significantly correlated with PoAF development. Based on multivariate analysis, being over 70 years old (OR: 2.432, CI 95%: 1.966-3.723, $P<0.001$), having an EF below 35% (OR: 1.325, CI 95%: 1.190-1.1894, $P=0.021$), and MPVLR elevation (OR:1.821, 95%CI: 1.645-2.1592, $P<0.001$) were independent predictors of PoAF.

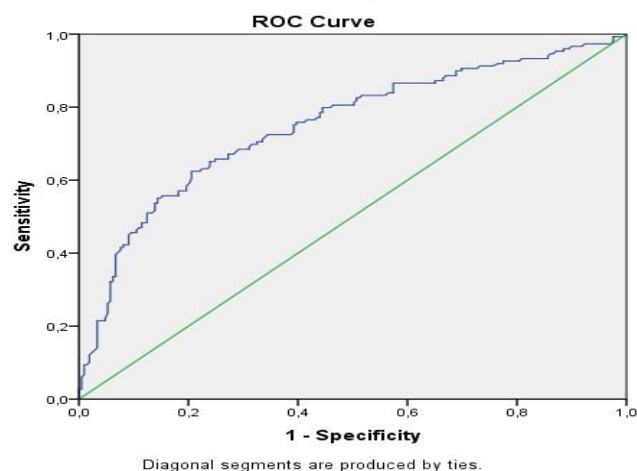
In the ROC curve analysis, the cut-off value for preoperative MPVLR was 4.96 (AUC: 0.749, $P<0.001$, 69.1% sensitivity, and 70.7% specificity) (Figure 1).

Table 3: Logistic regression analysis to identify factors affecting development of postoperative atrial fibrillation

Variables	Univariate analysis			Multivariate analysis		
	P-value	Exp(B) Odds Ratio	95% CI Lower - Upper	P-value	Exp(B) Odds Ratio	95% CI Lower - Upper
Age>70	<0.001	3.945	2.196-5.671	<0.001	2.432	1.966-3.723
EF<35	0.005	2.192	1.658-3.190	0.021	1.325	1.190-1.894
Hypertension	0.498	1.145	0.968-1.541	--	--	--
Diabetes Mellitus	0.298	0.786	0.696-1.110	--	--	--
COPD	0.020	0.889	0.694-0.912	0.246	1.114	0.965-1.237
Total perfusion time	0.130	1.022	0.954-1.326	--	--	--
Lymphocyte	0.008	1.428	1.212-1.894	--	--	--
MPV	<0.001	1.696	1.422-1.987	--	--	--
MPVLR	<0.001	2.874	1.968-3.418	<0.001	1.821	1.645-2.592

COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, MPV: Mean platelet volume, MPVLR: Mean platelet volume to lymphocyte ratio

Figure 1: ROC (Receiver operation characteristics) curve and AUC (Area under the curve) for mean platelet volume to lymphocyte ration (MPVLR) for predicting PoAF. (Cut off:4.96, AUC: 0.749, $P<0.001$, 69.1% sensitivity and 70.7% specificity)



Discussion

Today, coronary bypass operations can be performed with low mortality and morbidity. Postoperative atrial fibrillation is an important postoperative condition that prolongs hospitalizations and poses thromboembolic risks. The mechanism of PoAF formation depends on many factors and the reason for its occurrence is not fully understood [9]. Therefore, revealing the risk factors before the operation maintains its importance. This study investigated the predictive value of the relationship between platelet volume and lymphocyte count for PoAF, both of which are inflammatory parameters that can be obtained from simple hemogram values. In addition to known risk factors such as advanced age and low ejection fraction, we found that MPVLR value was an independent predictor of PoAF after CABG operations.

Inflammation plays a role in the pathogenesis of atherosclerotic coronary artery disease and may also affect the poor outcomes after CABG operations. PoAF is an important condition that can occur after CABG operations, and inflammation plays a vital role in its formation. Therefore, many inflammatory parameters have been investigated on this subject [8]. It is also important that an inflammatory parameter is as easily available as its predictive value. For this reason, the values that can be obtained from routine hemogram and biochemical parameters are important. MPV and NLR values are important

parameters in this respect. Platelets are important blood cells that play a role in the hemostatic process. It is known that platelet size is more effective for platelet functions than its numerical multiplicity. Large platelets contain denser granules and are more metabolically active [10, 11]. Accordingly, a high MPV value was reported as a risk factor for cardiac and cerebrovascular events [12]. Neutrophils play a prominent role in the inflammatory process because they secrete inflammatory parameters and lymphocytes regulate the inflammatory response [13]. NLR elevation, which occurs because of lymphocyte reduction, is used as an important inflammatory marker.

There are various studies in the literature investigating the effects of MPV values on PoAF. In a recent article by Cayir et al., the effect of MPV value on PoAF after CABG operations was investigated among 227 patients. PoAF was observed in 23.3% of the patients, and age, MPV, and total drainage amount were independent predictors of PoAF (OR=1.080, OR=1.371, OR=1.001; $P<0.001$, $P<0.001$, $P=0.024$, respectively) [7]. Erdem et al. investigated the relationship between MPV and PoAF in patients who underwent CABG, and 208 patients were included. Atrial fibrillation rate was 22%, and MPV, NLR, and CRP values were significantly higher in patients who developed atrial fibrillation (8.9 [1.4] vs. 7.9 [1.2], $P<0.001$, 3.2 1.9 etc. 2.6 1.2, $P=0.005$ and 8.9 [19.6] etc. 5.3 [8.7], $P=0.025$, respectively) [14]. In a recent study, MPV elevation was an independent predictor of PoAF (OR: 2.103, 95% CI: 1.324-3.339, $P=0.002$) in patients aged 65 years and over who underwent CABG [15]. In our study, MPV values were significantly associated with the development of PoAF.

Low lymphocyte count is an important indicator of general ill-health and physiological stress and constitutes a risk for atrial fibrillation in the general population [16, 17]. In a study by Erdolu et al. [5], low lymphocyte level was also a predictor of PoAF after off-pump CABG operations. A recent meta-analysis investigating the development of PoAF after cardiac surgery was published in mid-2020. As a result of a meta-analysis including 9,262 patients and 12 studies, the authors showed that the increase in NLR, which is also due to the preoperative low lymphocyte level, is associated with PoAF [18].

With all this literature information, MPVLR value seems an important parameter. The prognostic significance of MPVLR value in patients with diabetes mellitus who had acute myocardial infarction was investigated by Hudzik et al. [19]. The authors identified MPVLR as an independent risk factor for early and late mortality. In another study by Chen et al., the importance of MPVLR value in patients with acute ischemic stroke was investigated. MPVLR values at admission and 18-24 hours after intravenous thrombolysis, and the elevation of MPVLR at both times were predictors for poor outcomes [20]. In another recent study, high MPVLR values were associated with symptom development in patients with 50-79% carotid artery stenosis [21]. In our study, we determined the MPVLR value as an independent predictor for the development of PoAF, which is closely related to inflammation.

Being over 70 years old and having a left ventricular ejection fraction below 35% were other independent predictors of PoAF in our study. Advanced age not only causes the formation of many diseases but also affects their progression.

With increasing age, fibrosis may occur in cardiac conduction pathways and atrial structures, which increases the risk of atrial fibrillation [22]. In addition, elderly patients may experience mobilization problems after cardiac operations, thus increasing the risk of PoAF [23]. In many studies, advanced age was associated with PoAF [3, 24]. Low ejection fraction also causes dilatation in the heart chambers of patients. Thus, changes occur in myocardial structures and conduction path problems increase. In one study, atrial fibrillation was found in 25% of patients with heart failure [25]. It is known to increase the risk of PoAF after cardiac surgery [5, 9, 22].

The most important limitations of our study include its single-center, retrospective nature and the small number of patients. In addition, due to the retrospective design of the study, continuous ECG monitoring could not be performed in the service follow-up of the patients. Atrial fibrillation episodes may have been missed in some patients who did not report any complaints in the service follow-ups.

Conclusion

Coronary bypass surgery is the most valuable treatment method for atherosclerotic heart disease. It is especially important to predict risky groups to increase the success rates of these operations. In this study, we determined that the preoperative MPVLR value, which can be obtained from a simple hemogram test, is an important predictor of PoAF in patients who underwent CABG. MPVLR values can be a marker in determining preoperative risk groups. Our study needs to be supported by multicenter prospective studies.

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