

ORIGINAL ARTICLE

Platelet Distribution Width as a Marker for Severity and Extent of Coronary Artery Disease in Acute Coronary Syndrome

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Abstract

Background: Previous studies have demonstrated an association between larger platelet volume and coronary thrombus formation in acute coronary syndrome (ACS).

Objectives: We aimed to investigate the association of platelet distribution width (PDW) levels with both the clinical severity and the extent of coronary artery disease (CAD) in patients diagnosed with ACS.

Methods: A retrospective evaluation was conducted on 1043 consecutive patients diagnosed with ACS. Patients were stratified into two groups based on their PDW values: group 1 (PDW > 11.8 fL) and group 2 (PDW ≤ 11.8 fL). For each patient, Global Registry of Acute Coronary Events (GRACE) score, SYNTAX score, Thrombolysis in Myocardial Infarction (TIMI) flow grade, thrombus grades of culprit lesions, and neutrophil-lymphocyte ratio (NLR) were calculated, and their associations with PDW were examined.

Results: The mean age of the patients was 60.1 ± 12.4 years, with the majority being male (78.5%). The mean PDW was 11.8 fL (range: 8.9 to 22.0). Patients in group 1 exhibited higher NLR (3.21 versus 2.13, $p < 0.05$) and higher GRACE scores (139 versus 126, $p < 0.05$) compared to group 2. Group 1 patients also showed lower TIMI flow grades (0 and 1). A positive correlation was observed between PDW and GRACE score ($R: 0.304$, $p = 0.01$), but not with the SYNTAX score.

Conclusion: Elevated PDW levels in patients with ACS were associated with more severe disease, as indicated by higher GRACE scores and reduced TIMI flow grades.

Keywords: Blood Platelets; Coronary Artery Disease; Acute Coronary Syndrome.

Introduction

Acute coronary syndrome (ACS) encompasses a diverse array of clinical presentations resulting from either partial or complete acute obstruction of a coronary vessel. Its well-established pathophysiology is rooted in the rupture of a vulnerable atherosclerotic plaque and subsequent thrombus formation. The clinical spectrum of ACS ranges from unstable angina pectoris to sudden cardiac death.¹ Platelets play a pivotal role in the pathogenesis of ACS, participating not only in thrombus formation but also contributing to inflammation and modulation of the immune system.² Upon activation,

platelets undergo enlargement, and two laboratory parameters, namely, mean platelet volume and platelet distribution width (PDW), serve as indicators of platelet size or, equivalently, their activity in circulation.³

Previous investigations have established a link between coronary thrombus formation and larger platelet volume in cases of ACS.⁴ Additionally, studies have demonstrated an association between PDW and major adverse cardiac events, further underscoring the clinical relevance of platelet parameters in ACS.⁵

The primary objective of our study is to explore the association between PDW levels and both the clinical

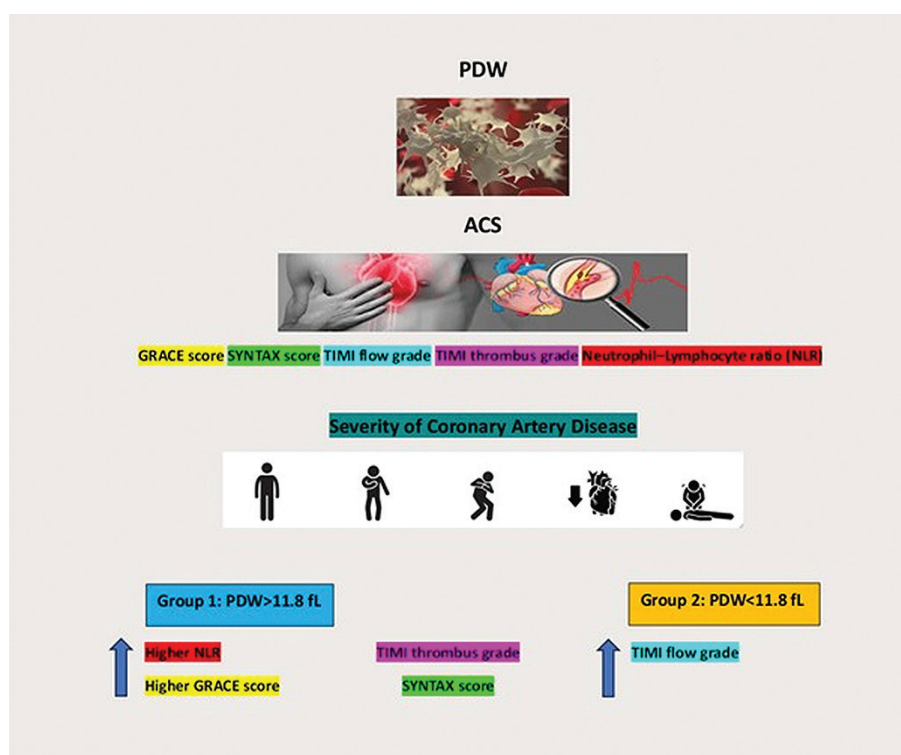
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Central Illustration: Platelet Distribution Width as a Marker for Severity and Extent of Coronary Artery Disease in Acute Coronary Syndrome

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severity and extent of coronary artery disease (CAD) in patients diagnosed with ACS. Furthermore, we endeavor to elucidate the relationship between PDW levels and intracoronary thrombus grade, as well as the Thrombolysis in Myocardial Infarction (TIMI) flow rate. Through these investigations, we aim to contribute valuable insights into the role of platelet indices in characterizing the severity and extent of ACS, as well as their potential utility as prognostic markers in this clinical context.

Methods

This retrospective study involved a comprehensive analysis of clinical, angiographic, and laboratory data obtained from a consecutive cohort comprising 1043 patients diagnosed with ACS. The patient population comprised a heterogeneous mix, consisting of 119 individuals presenting unstable angina pectoris, 252 cases of non-ST-segment elevation myocardial infarction, and 672 instances of ST-segment elevation myocardial infarction. To ensure the integrity of calculations

concerning CAD complexity, patients with a history of prior coronary artery bypass grafting surgery were meticulously excluded from the study cohort.

Patients were categorized into two distinct groups based on their PDW values: group 1 (comprising patients with $PDW > 11.8$ fL) and group 2 (encompassing patients with $PDW \leq 11.8$ fL). The Global Registry of Acute Coronary Events (GRACE) score, serving as a reflection of pertinent clinical and laboratory parameters, was meticulously calculated for each patient.⁶ To ensure an objective assessment, an independent interventional cardiologist, blinded to patients' clinical and demographic data, thoroughly evaluated all angiographic records. The SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) score, serving as an indicator of CAD complexity, alongside the TIMI flow grade and thrombus grade of the culprit coronary arteries were diligently determined for each participant.⁷⁻¹⁰

The SYNTAX scoring system, encompassing a set of 12 main questions, facilitated the assignment

of individual scores to each lesion, culminating in the derivation of a comprehensive total SYNTAX score.⁷⁻¹⁰ Regarding TIMI flow grades, meticulous categorization was employed, encompassing TIMI 0 flow (denoting the absence of contrast penetration beyond stenosis or occlusion), TIMI 1 flow (indicating contrast penetration beyond stenosis with no perfusion of the distal vessel), TIMI 2 flow (reflecting contrast reaching the distal vessel with a decreased filling rate or clearance compared to other coronary arteries), and TIMI 3 flow (where contrast reaches the distal bed and clears at a rate comparable to other coronary arteries).⁸ On the other hand, TIMI thrombus grades spanned from grade 0 (characterized by the absence of thrombus) to grade 5 (indicative of complete thrombotic occlusion of a vessel).⁹ Notably, instances where TIMI thrombus grade 5 was initially diagnosed underwent meticulous reclassification via angiographic reassessment subsequent to the removal of total occlusion facilitated by guidewire advancement during balloon angioplasty.¹¹ Furthermore, the neutrophil-lymphocyte ratio (NLR) was calculated for each patient.

Statistical analyses were conducted employing SPSS 17.0 software. Spearman's rank correlation test facilitated the exploration of associations between PDW, GRACE, and SYNTAX scores. Additionally, the Kruskal-Wallis test was employed to examine differences in PDW values among TIMI flow grades and thrombus grade subclasses. Continuous variable differences between the two PDW groups were evaluated by means of t test and Mann-Whitney tests, while chi-square tests explored differences in categorical variables. Ethical approval for the study was obtained from the local ethics committee, ensuring adherence to the principles outlined in the Helsinki Declaration of 1975, as revised in 2008, concerning ethical standards for human experimentation.

Results

The study cohort was predominantly constituted by male patients, comprising 78.5% of the total participants. The age distribution of the majority fell within the sixth decade, with a mean age of 60.1 ± 12.4 years. Among the diverse clinical presentations, ST-segment elevation myocardial infarction emerged as the most prevalent, representing 64.5% of cases. Table 1 displays a comprehensive delineation of the demographic, clinical, laboratory, and angiographic characteristics.

Table 1 – Demographic, clinical, laboratory, and angiographic data of patients

Patient characteristics	
Age (years, mean \pm SD)	60.1 \pm 12.4
Sex (male, %)	819 (78.5%)
Diabetes mellitus	196 (18.8%)
Current smokers	245 (33.5%)
Creatinine (mg/dl)	0.86 (0.44-3.08)
PDW (fL)	11.8 (8.9-22.0)
Neutrophil-lymphocyte ratio	2.55 (0.36-18.0)
UAP	119 (11.4%)
NSTEMI	252 (24.1%)
STEMI	672 (64.5%)
GRACE score	134.4 (68-334)
SYNTAX score	11.0 (2.0-44.5)
TIMI thrombus grade	
0	252 (24.2%)
1	189 (18.1%)
2	259 (24.8%)
3	280 (26.8%)
4	63 (6%)
TIMI flow grade	
0	364 (34.9%)
1	91 (8.7%)
2	259 (24.8%)
3	329 (31.5%)
GRACE: Global Registry of Acute Coronary Events; NSTEMI: non-ST-segment elevation myocardial infarction; PDW: platelet distribution width; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction; SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery; TIMI: Thrombolysis in Myocardial Infarction; UAP: unstable angina pectoris.	

Upon comparative analysis of the demographic, clinical, laboratory, and angiographic features between the two groups, significant distinctions were observed, as elucidated in Table 2. Specifically, group 1 patients exhibited an elevated mean age, with a notable predominance of females within the subset displaying increased PDW values. Further scrutiny revealed that patients in group 1 manifested heightened NLR and

Table 2 – Demographic, clinical, laboratory, and angiographic characteristics of high-PDW and low-PDW groups

Patient Characteristics	Low PDW (n = 546)	High PDW (n = 497)	P value
Age	57.5 ± 12.4	62 ± 11.8	<0.01
Sex (male, %)	476 (87.1%)	343 (69.0%)	<0.01
Diabetes mellitus	91 (16.6%)	105 (21.1%)	0.057
UAP	56 (10.3%)	63 (12.6%)	0.39
NSTEMI	119 (21.8%)	133 (26.8%)	0.27
STEMI	37 (6.9%)	301 (60.6%)	0.31
Creatinine (mg/dl)	0.7 (0.44 – 0.87)	1 (0.87 – 3.08)	0.93
Neutrophil-lymphocyte Ratio	2.13 (0.36 - 13.91)	3.21 (0.45 – 18.0)	0.032
GRACE score	126 (68 – 192)	139 (75 – 334)	0.025
SYNTAX score	11.0 (2.0 - 36.0)	11.0 (2.0 - 44.5)	0.96
TIMI thrombus grade			
0 and 1	252 (46.2%)	189 (38.1%)	0.087
2, 3, and 4	294 (53.8%)	308 (61.9%)	0.082
TIMI flow grade			
0 and 1	231 (42.4%)	273 (54.1%)	0.039
2 and 3	315 (57.6%)	224 (45.9%)	0.045

GRACE: Global Registry of Acute Coronary Events; NSTEMI: non-ST-segment elevation myocardial infarction; PDW: platelet distribution width; STEMI: ST-segment elevation myocardial infarction; SYNTAX: SYNERgy between percutaneous coronary intervention with TAXus and cardiac surgery; TIMI: Thrombolysis in Myocardial Infarction; UAP: unstable angina pectoris.

GRACE scores, suggestive of an elevated risk profile. Moreover, a distinct association emerged between TIMI flow grades and PDW values, with higher PDW values correlating with lower TIMI flow grades (0 and 1). However, no significant disparities in TIMI thrombus grades were identified between the two groups.

A correlation analysis provided insightful findings, demonstrating a positive relationship between PDW and GRACE score ($R: 0.34$, $p = 0.01$), thereby highlighting a potential linkage between PDW and the GRACE scoring system. Interestingly, no such correlation was discerned when scrutinizing the SYNTAX score.

To further elucidate angiographic characteristics, patients were stratified into two distinct groups based on the size of the angiographic thrombus. Group A comprised patients devoid of apparent angiographic thrombus (TIMI thrombus grade 0) and those with a suspected angiographic thrombus (TIMI thrombus grade 1). Conversely, group B encompassed patients presenting

with an apparent thrombus (TIMI thrombus grades 2, 3, and 4). Intriguingly, PDW values exhibited no significant disparities between these two groups (11.6 versus 11.9, $p = 0.40$). Nonetheless, when evaluating PDW values in relation to angiographic TIMI flow grades, a noteworthy observation emerged; patients with TIMI flow grade 3 consistently displayed lower PDW values compared to counterparts with different TIMI flow grades (Figure 1).

Discussion

Beyond their established role in thrombus formation, platelets play crucial roles in inflammation and the immune system. During acute myocardial infarction, platelets assume an active role in leukocyte activation by releasing inflammatory mediators and forming aggregates with leukocytes.^{12,13} Platelets exhibit heterogeneity in size, reflecting their reactivity, with a decrease in volume during circulation.¹⁴⁻¹⁶ Under stress conditions, platelet production is stimulated,

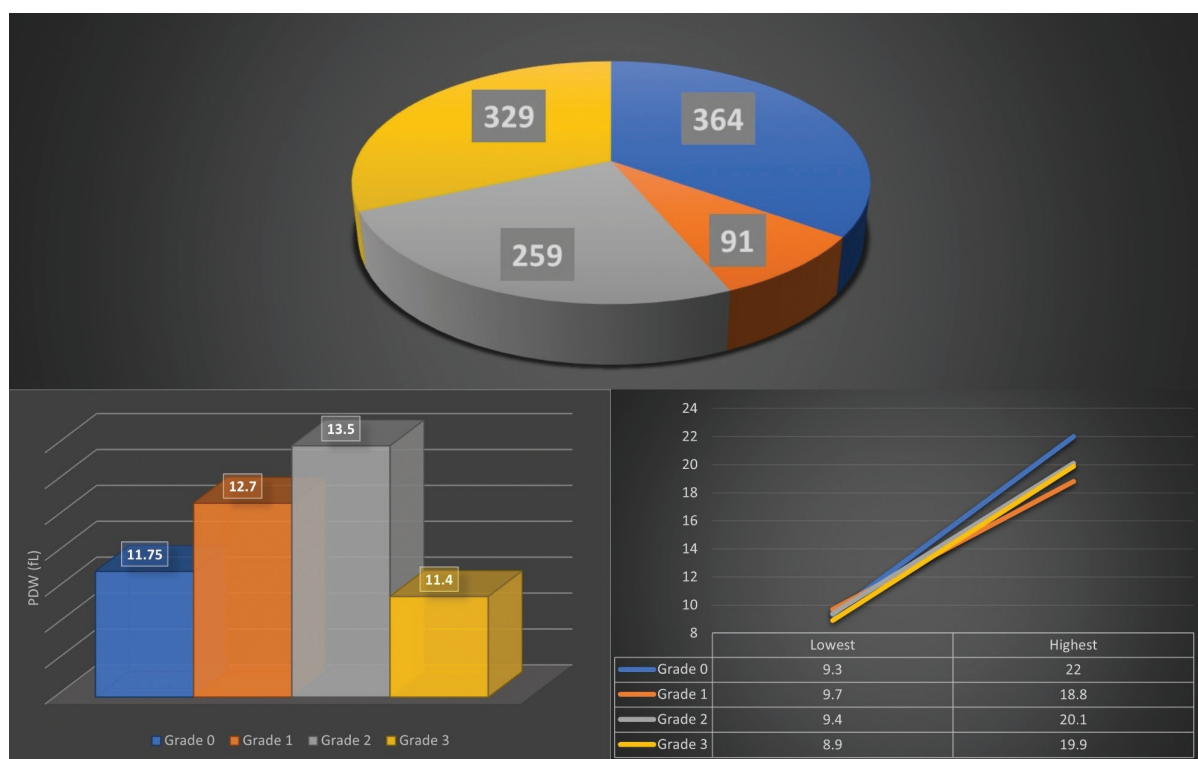


Figure 1 – PDW values according to angiographic TIMI flow grades.
PDW: platelet distribution width

leading to the release of larger and more active “stress platelets” into circulation.¹⁷ These stress platelets are notably increased during ACS, potentially indicating heightened thrombopoietic activity in the bone marrow.¹⁸ The observed enlargement of platelets in ACS may be indicative of increased thrombopoietic activity driven by proinflammatory cytokines, particularly interleukin-6.¹⁹ Numerous reports have associated the presence of large platelets with adverse outcomes in patients with ACS, and the increased megakaryocyte heterogeneity resulting from heightened thrombotic activity in the bone marrow contributes to elevated PDW in peripheral blood counts.^{20,21} Consequently, elevated PDW in patients with ACS may serve as a marker for increased thrombopoietic activity driven by heightened cytokine levels.

In the context of our study, the observed relationship between the GRACE risk score and PDW is postulated to stem from increased thrombopoietic activity influenced by heightened cytokine levels, particularly in response to the physical stress associated with ACS. This finding aligns with previous studies reporting

correlations between GRACE score and inflammatory biomarkers.^{22,23} Notably, we did not observe any association between the extent of CAD and PDW levels, a deviation from prior research.^{24,25} This discrepancy may be attributed to the chronic and progressive nature of CAD, with our results reflecting a broader clinical spectrum in our patient cohort. Additionally, the use of the Gensini scoring system by Bekler and coauthors in their analysis of CAD extent may offer a more nuanced evaluation of the functional severity of coronary lesions, potentially contributing to the disparate results observed.

In our investigation of the association between intracoronary thrombus load and PDW, a weak inverse correlation was found between TIMI flow grade and PDW, rather than with TIMI thrombus grades. This result may reflect a connection between lower TIMI flow grades and the severity of ACS. The release of “stress platelets” from the bone marrow under stress conditions, mediated by proinflammatory cytokines, may provide an explanation for this observation.¹⁷

Notably, patients with elevated PDW values in our study exhibited older age, higher GRACE scores, elevated NLR, and lower TIMI flow grades. We posit that these findings underscore the association of these large stress platelets with the severity of ACS. Furthermore, the preponderance of female patients in group 1 aligns with established knowledge that female patients with ACS tend to be older and exhibit a greater number of major coronary risk factors than their male counterparts.²⁶ The observed higher cytokine levels in these female patients, presenting with more severe ACS, may contribute to an increased release of stress platelets into circulation from the bone marrow, potentially influencing prognosis.

While our study provides valuable insights into the association between PDW and various parameters in patients with ACS, several limitations must be acknowledged. Firstly, the retrospective nature of the study introduces inherent biases and limits the establishment of causal relationships. The exclusion of patients with a history of prior coronary artery bypass grafting surgery aimed to ensure the accuracy of calculations related to CAD complexity; however, it may have introduced a selection bias, thus limiting the generalizability of our findings. Additionally, the study's reliance on a single-center cohort may impact the external validity, and broader multicenter studies are warranted to validate our observations across diverse populations. Furthermore, the cross-sectional design hinders the exploration of temporal relationships, and prospective studies are needed to elucidate the dynamic changes in platelet indices over time. The use of the GRACE score as a representation of clinical severity may not capture the full spectrum of individual patient characteristics. Despite these limitations, our study offers a foundation for future investigations to delve deeper into the intricate interplay between platelet dynamics and ACS pathophysiology.

Conclusion

In conclusion, our comprehensive investigation into the association between PDW levels and various clinical, angiographic, and laboratory parameters in patients diagnosed with ACS has revealed intricate connections with the severity and extent of this cardiovascular condition. The study elucidates the potential role of PDW as a valuable marker for

heightened thrombopoietic activity, influenced by proinflammatory cytokines, particularly in response to the physical stress associated with ACS. The observed correlations with GRACE score, NLR, and TIMI flow grade underscore the multifaceted involvement of platelets in the pathophysiology of ACS (Central Illustration). Interestingly, our findings did not establish a significant association between PDW levels and the extent of CAD, deviating from previous research, possibly due to the chronic and progressive nature of CAD. This study contributes novel insights into the intricate interplay between platelet indices and the clinical manifestations of ACS, emphasizing the potential of PDW as a prognostic marker and supporting further research to enhance our understanding of platelet dynamics in cardiovascular diseases.

Author Contributions

Conception and design of the research and analysis and interpretation of the data: Ploaf F; acquisition of data and statistical analysis: Polat F, Kaya Z; obtaining financing: Kaya Z, Yanikoglu A

Writing of the manuscript: Kaya Z, Polat F, Yanikoglu A; critical revision of the manuscript for intellectual content: Kaya Z, Yanikoglu A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any graduation program.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Yeni Yüzyıl University under the protocol number 693906709-300-00-1001-1. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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