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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Platelet distribution width predicts left ventricular dysfunction in patients with acute coronary syndromes treated with percutaneous coronary intervention

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Abstract

Background: The role of platelets in the pathophysiology of acute coronary syndromes (ACS) is undeniable, but precise relationships between platelet activity and treatment outcomes are a matter of continuant investigation. Among platelet indices, mean platelet volume (MPV) has proven to be a valuable predicting factor in cardiac patients. However, platelet distribution width (PDW) is reported to be a more specific marker of platelet reactivity. Thus, application of PDW in risk stratification of ACS treatment is an up-to-date subject of research. PDW values in the assessment of left ventricular (LV) function have not been previously studied.

Aim: The aim of the study was to evaluate whether admission PDW can predict LV systolic function in patients with ACS treated with stent implantation.

Methods: On-admission PDW was measured in 278 consecutive patients with diagnosis of ACS, who underwent stent(s) implantation. Echocardiogram with LV ejection fraction (LVEF) estimation was performed within 24 h of percutaneous coronary intervention. Additionally, patients were under one-year follow-up, and one-year all-cause mortality was assessed.

Results: According to receiver-operating characteristics (ROC) analysis, a PDW value greater than 12.8 fL could predict LVEF ≤ 35% with sensitivity of 81% and specificity of 39% (AUC 0.614; p = 0.0177). Only a trend was noted in ROC for PDW and one-year mortality (AUC 0.608; p = 0.0815). Multivariate logistic regression analysis has shown that the PDW parameter correlates independently with both systolic heart failure with LVEF ≤ 35% (PDW cut-off: 12.8 fL, OR 2.8107, CI 1.1401–6.9293, p = 0.0248) and one-year mortality (PDW cut-off: 16 fL, OR 2.6750, CI 1.0190–7.0225, p = 0.0457).

Conclusions: Admission PDW may serve as a simple and widely available predictor of impaired LV function in patients with ACS. Association between PDW and mortality needs to be confirmed in larger studies.

Key words: platelet distribution width, left ventricular ejection fraction, percutaneous coronary intervention

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INTRODUCTION

Platelets play a key role in the development of acute thrombotic events; therefore, the possibilities of applying platelet indices in risk stratification for cardiac patients were the subject of numerous studies. Mean platelet volume (MPV) has been shown to be an independent risk factor for myocardial infraction (MI) [1]. Furthermore, MPV values may also predict unfavourable outcomes of primary percutaneous coronary intervention (PCI) [2]. Lately the introduction of platelet distribution width (PDW) as a predicting factor has been studied extensively in consideration of its greater reliability in comparison to MPV [3]. PDW was reported to have prognostic value in PCI-treated acute MI [4]. No relationship between PDW and the prevalence of coronary artery disease (CAD) was discovered; however, PDW was related to CAD severity in patients with acute coronary syndrome (ACS) [5–8]. Because simple

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and rapidly available predictors of prognosis in ACS are still in demand, we sought to determine the association between PDW and left ventricular (LV) function in patients treated with PCI with stent implantation. Additionally, all-cause mortality was assessed for one year after ACS.

METHODS

Study design

It was a single-centre, retrospective, observational study with one-year follow-up. The population of the present study was previously included in the international BleeMacs registry designed for the development and validation of a risk score for prediction of major bleeding during follow-up of patients diagnosed with ACS, who received PCI [9]. We analysed 278 consecutive patients in whom primary percutaneous intervention with at least one stent implantation — either bare-metal stent (BMS) or drug-eluting stent (DES) — was performed for ACS. Thrombocytopaenia (PLT < 100,000/μL) was an exclusion criterion.

The study was performed at the First Department of Cardiology, Medical University of Warsaw. Analysed data was entirely from in-hospital records and information obtained directly from the patients by telephone interview and/or outpatient clinic visits.

Written informed consent was obtained from all participating patients before inclusion in the study. The local ethics committee granted permission for the study.

Blood sampling

For all the study participants, venous peripheral blood samples were collected at admission at the Emergency Department. Subsequently, samples were investigated for platelet indices — particularly PDW. Blood samples were taken into standardised tubes containing ethylenedinitro tetraacetic acid (EDTA) at room temperature and were processed within 30 min on a SYSMEX XN-2000, which applies optical flow cytometry and electric current interference analysis on suspended in EDTA platelets passing through a detection chamber.

Echocardiographic analysis

Early assessment of LV ejection fraction (LVEF) was performed within 24 h after PCI. LVEF was evaluated using the Simpson method. All the examinations were performed by a skilled echocardiographer who was blinded to platelet indices results.

Data collection and endpoints definition

All clinical events and follow-up data were registered and entered into a central database. The primary end-point was LVEF, in particular systolic heart dysfunction with LVEF ≤ 35%. The secondary end-point was a one-year mortality — this information was collected by both direct telephonic information and via general hospital database.

Statistical analysis

Baseline characteristics were composed according to median values of PDW. A normality of distribution was assessed by Kolmogorov-Smirnov test. Continuous variables with normal distribution were compared by t-Student test, whereas those without normal distribution — by U-Mann-Whitney test. Categorical variables were summarised as numbers and percentages and compared with the χ^2 test. Receiver-operating characteristics (ROC) curve for PDW categorised by LVEF ≤ 35% and one-year follow-up mortality was performed in order to assess the predictive role of PDW in systolic heart failure (LVEF< 35%) and one-year mortality. In multivariate logistics regression analysis PDW in relation to decreased LVEF was adjusted for age, sex, prior MI, prior heart failure hospitalisation, kidney failure, diabetes, dyslipidaemia, hypertension, haemoglobin, platelet count, and more than one vessel affected in coronary angiography. A PDW parameter in relation to one-year follow-up mortality was adjusted for age, sex, dyslipidaemia, diabetes, hypertension, kidney failure, more than one vessel affected in coronary angiography, DES implantation, more than one stent implantation, and in-hospital complications (bleeding requiring transfusion, acute heart failure, reinfarction). A p value < 0.05 was considered statistically significant and confidence intervals (CI) were 95%. All statistic calculations were performed with MedCalc™ Software (Mariakerke, Belgium).

RESULTS

Baseline characteristics

Baseline characteristics of the population (n = 278) and population divided according to median PDW values are presented in Table 1. Patients with PDW above the median differ from those with PDW below the median only in platelet count value (for PDW below median — median PLT is 200 × 10^3/μL, for PDW above median — 234 × 10^3/μL; p < 0.0001). In addition, the number of secondary end-points (i.e. death in one-year follow-up) was 24 (8.6%).

Receiver-operating characteristics

Left ventricular ejection fraction values were categorised as non-continuous variables — LVEF ≤ 35% and LVEF > 35%. The ROC curves were constructed for PDW values categorised for one-year mortality (Fig. 1A) and systolic heart dysfunction with LVEF ≤ 35% (Fig. 1B). Parameters describing ROC curves are presented in Table 2. ROC analysis showed that PDW for a cut-off of 12.8% can predict systolic heart dysfunction with LVEF ≤ 35% with sensitivity of 81% and specificity of 39% (area under the curve [AUC] 0.614, p = 0.0177). An ROC curve for PDW categorised by one-year mortality is described by optimal cut off of 16%, with sensitivity 42% and specificity 80% (AUC 0.608, p = 0.0815).

Table 1. Baseline characteristics with procedural data for all patients and comparison between baseline characteristics of patients with platelet distribution width (PDW) values below or above median (PDW median value: 13.6%, PDW above median: > 13.6%, PDW below median: ≤ 13.6%)

Baseline characteristics	Total cohort (n = 278)	PDW below median	PDW above median	Significance p
Age [year]; median (CI)	65 ± 12	62.5 (60–65)	63.5 (61–66)	0.5292
Female	68 (24.5%)	40 (28.2%)	28 (20.6%)	0.1423
Hypertension	193 (69.4%)	102 (71.8%)	91 (66.9%)	0.3744
Dyslipidaemia	136 (48,9%)	74 (52.1%)	62 (45.6%)	0.2775
Diabetes	66 (23.7%)	32 (22.5%)	34 (25.0%)	0.6298
Previous coronary artery bypass grafting	12 (4.3%)	6 (4.2%)	6 (4.4%)	0.9392
Previous myocardial infarction	58 (20.9%)	23 (16.2%)	35 (25.7%)	0.0508
Prior percutaneous coronary intervention	43 (15.5%)	20 (14.1%)	23 (16.9%)	0.5154
Peripheral arterial disease	11 (4.0%)	3 (2.1%)	8 (5.9%)	0.1077
Stroke	17 (6.1%)	7 (4.9%)	10 (7.4%)	0.4001
Previous bleeding	10 (3.6%)	3 (2.1%)	7 (5.1%)	0.1752
Malignant neoplastic disease	17 (6.1%)	10 (7.0%)	7 (5.1%)	0.5105
Prior heart failure admission	29 (10.4%)	14 (9.9%)	15 (11.0%)	0.7501
Increased creatinine level (> 1.3 mg/dL]*	35 (12.6%)	19 (13.4%)	16 (11.8%)	0.6853
Haemoglobin on admission [g/dL]; median (CI)	14.0 ± 1.6	14.2 (13.9–14.4)	14.2 (13.9–14.4)	0.9851
Platelet count [10^6/L]; median (CI)	225 ± 62	234 (225.5–243)	200(192–209)	< 0.0001
Killip-Kimball class ≥ 2	35 (12.6%)	14 (9.9%)	21 (15.4%)	0.1615
ACS–STEMI	156 (56.1%)	77 (54.2%)	79 (58.1%)	0.5172
Transfemoral access	46 (16.5%)	19 (13.4%)	27 (19.9%)	0.1473
No. of vessel affected ≥ 2	145 (52.5%)	74 (52.1%)	71 (52.2%)	0.9876
Patients with DES implanted	67 (24.1%)	39 (27.5%)	28 (20.6%)	0.1810
More than 1 stent	72 (25.9%)	30 (21.1%)	42 (30.9%)	0.0639
Glycoprotein IIb/IIIa inhibitors	113 (40.6%)	54 (38.0%)	59 (43.4%)	0.3645

*Creatinine concentration value 1.3 mg/dL according to Mayo Clinic protocol; CI — confidence interval; ACS — acute coronary syndrome; DES — drug-eluting stent; STEMI — ST segment elevation myocardial infarction

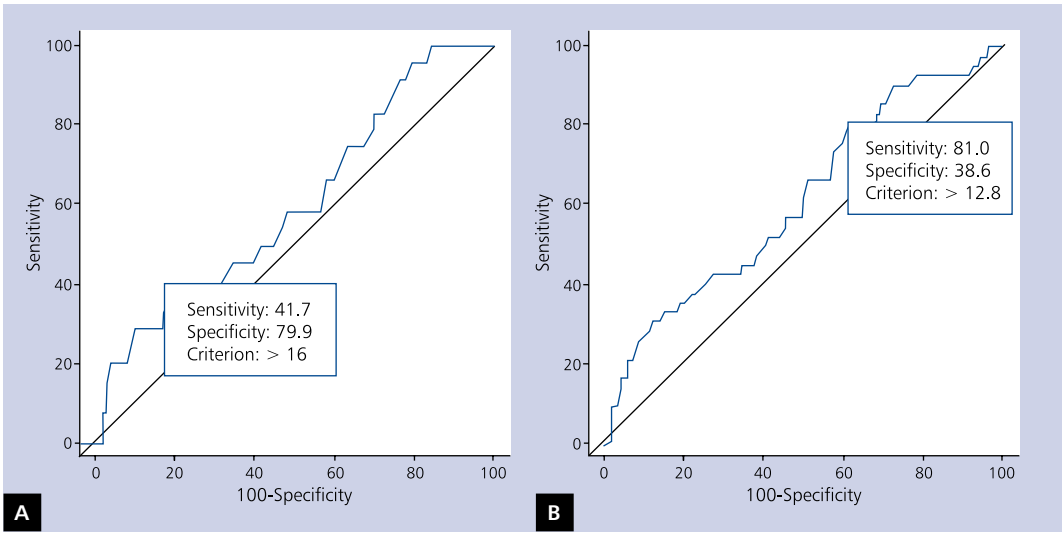

Figure 1. **A.** Receiver-operating characteristics (ROC) curve for platelet distribution width (PDW) categorised by one-year mortality; **B.** ROC for PDW categorised by systolic heart dysfunction with left ventricular ejection fraction ≤ 35%

Table 2. Receiver operating characteristics curve parameters for platelet distribution width categorised by one-year mortality and systolic heart dysfunction with left ventricular ejection fraction (LVEF) ≤ 35%

	AUC	95% CI	Cut-off	P	Sensitivity (%)	Specificity (%)
One-year mortality	0.608	0.548–0.665	16.0	0.0815	41.7	79.9
LVEF ≤ 35%	0.614	0.554–0.672	12.8	0.0177	81.0	38.6

AUC — area under the curve; CI — confidence interval

Table 3. Univariate analysis — platelet distribution width (PDW) in relation to one-year mortality and systolic heart dysfunction with left ventricular ejection fraction (LVEF) ≤ 35%.

Variable and type of analysis	Adjusted odds ratio (confidence interval)	P significance
Univariate analysis[1]		
1-year mortality	2.8571 (1.1999–6.8033)	0.0177
LVEF ≤ 35%	2.6672 (1.1823 to 6.0172)	0.0181
Multivariate logistic regression analysis[2]		
1-year mortality	2.6750 (1.0190–7.0225)	0.0457
LVEF ≤ 35%	2.8107 (1.1401–6.9293)	0.0248

[1]PDW in correlation with LVEF ≤ 35% — cut off value: 12.8%. PDW in correlation with one-year mortality — cut off value: 16%.
[2]PDW in correlation with LVEF ≤ 35% adjusted for: age, sex, hypertension, diabetes, dyslipidaemia, prior myocardial infarction, prior heart failure admission, haemoglobin on admission, platelet count on admission, high creatinine level, more than one vessel affected. PDW in correlation with one-year mortality adjusted for: age, sex, hypertension, diabetes, dyslipidaemia, high creatinine level, more than one vessel affected, drug eluting stent implanted, more than one stent implanted and in-hospital complications.

Univariate analysis

The univariate analysis demonstrated that the PDW value correlates with systolic heart dysfunction with LVEF ≤ 35% (cut-off 12.8%) and one-year follow-up mortality (cut-off 16%) (Table 3).

Multivariate analysis

The multivariate analysis also confirmed the hypothesis that the PDW value correlates independently with one-year mortality (cut-off 16%, OR 2.6750, CI 1.0190–7.0225, p = 0.0457) and in-hospital systolic heart dysfunction (cut-off 12.8%, OR 2.8107, CI 1.1401–6.9293, p = 0.0248) (Table 3).

DISCUSSION

The present study showed that systolic heart dysfunction in patients with ACS, who underwent PCI with stent implantation, is related to PDW. Furthermore, PDW may serve as an independent factor predicting one-year mortality in the above-mentioned group.

Platelet distribution width measures the variability in platelet size, which increases during platelet activation. PDW is proposed as a more specific indicator of platelet reactivity than MPV because PDW remains unaffected by the single platelet distention caused by platelet swelling. PDW is used to detect fractions of larger platelets that are more active, both enzymatically and metabolically [3]. The relationship between the platelet volume and ACS course results from multiple mechanisms, which have not yet been completely characterised [10].

To our knowledge, this is first study to describe the association of PDW with LV dysfunction in patients with ACS. Acar et al. [11] previously reported a relationship of MPV with impaired LVEF in primary PCI of anterior ST-segment elevation MI patients. The current study complements the above results in some respects. Firstly, while their study evaluated MPV, we used PDW — a more novel approach to platelet indices — which is believed to be more authoritative than MPV. Secondly, the number of patients enrolled in our study was nearly threefold greater [11]. Both studies support the findings of Fujita et al. [12], who associated MPV and PDW with LV systolic function in a group of 1241 consecutive patients admitted to the cardiology department due to a wide spectrum of cardiovascular causes including arrhythmia, cardiomyopathies, peripheral arterial disease, and valvular heart disease.

The outcomes of our study suggest that raised platelet reactivity, manifested with increased values of PDW, adversely affects the function of myocardium after ACS, resulting in depressed LVEF. We assume that fractions of larger platelets wielding greater thrombotic potential by reason of higher expression of granules, glycoprotein Ib, and glycoprotein IIb/IIIa receptors may cause recurrent thrombosis in an environment of microcirculation injured due to ischaemic reperfusion [13]. Impairment of microvascular circulation seems to represent a primary link in sequence leading to LV systolic dysfunction.

Research on the no-reflow phenomenon, where intravascular plugging by platelets was identified as one of responsible factors, support this hypothesis. In light of these findings, the necessity of further investigation of platelet function in LV remodelling is legitimised.

For PDW and one-year mortality only a trend was noted in ROC. We previously found that MPV, measured on admission, is a strong and independent factor of six-month mortality in patients with ST-segment elevation MI, who received coronary stenting [2]. The current study confirms the role of PDW in mortality prediction and suggests its reliability in longer-term follow-up. However, application of PDW in risk stratification should be re-evaluated within a larger ACS population.

Limitations of the study

The main limitation of the present study is the relatively low number of primary events (one-year mortality), which may be a limiting factor for statistical power to detect significant differences. Secondly, multivariate logistic regression analysis has been restricted to a certain limited number of confounders. Furthermore, the evaluation of LV function was performed only once — within 24 h after PCI. Changes in LVEF after revascularisation, however, may extend beyond this time period as the result of myocardial stunning caused by ACS.

CONCLUSIONS

Platelet distribution width is an affordable and reliable predictor of LV systolic dysfunction. Also, outcomes suggest that platelet reactivity might impact remodelling of LV. Association between PDW and mortality needs to be confirmed in larger studies.

Conflict of interest: *none declared*

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Wskaźnik zmienności objętości płytek krwi pozwala przewidzieć dysfunkcję lewej komory u pacjentów poddawanych przezskórnej interwencji wieńcowej

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Streszczenie

Wstęp: Płytki krwi odgrywają istotną rolę w patofizjologii ostrego zespołu wieńcowego (ACS), dlatego też wiele badań poświęcono możliwości zastosowania wskaźników płytkowych w przewidywaniu wyników jego leczenia. Stwierdzono, że średnia objętość płytek krwi (MPV) jest niezależnym czynnikiem ryzyka zawału serca. Ponadto udowodniono, że wartości MPV mogą posłużyć do przewidywania niekorzystnych wyników przezskórnych interwencji wieńcowych (PCI), w tym upośledzonej reperfuzji miokardium. Wskaźnik zmienności objętości płytek krwi (PDW), podobnie jak MPV, odzwierciedla reaktywność płytek krwi. PDW jest jednak uważany za bardziej miarodajny parametr pozwalający na identyfikowanie frakcji płytkowych o większej objętości, które są aktywniejsze zarówno enzymatycznie, jak i metabolicznie. Dotychczasowe wyniki badań wykazały wartość prognostyczną PDW u pacjentów z zawałem serca oraz korelację ze stopniem zaawansowania choroby wieńcowej. Wskaźniki płytkowe okazują się więc być tanim i ogólnodostępnym narzędziem w stratyfikacji ryzyka u pacjentów z ACS. Jednak mimo dużego zainteresowania nimi użyteczność PDW w ocenie funkcji lewej komory (LV) dotychczas nie została zbadana.

Cel: Celem pracy było zbadanie, czy wartość PDW oznaczanego podczas przyjęcia do szpitala może zostać wykorzystana jako predyktor dysfunkcji skurczowej LV u pacjentów poddawanych implantacji stentu z powodu ACS.

Metody: Analizą retrospektywną objęto 278 pacjentów (214 mężczyzn, 64 kobiety) poddawanych wszczepieniu stentu (metalowego lub uwalniającego lek) z powodu ACS (STEMI u 156 osób). Średnia wieku wynosiła 65 ± 12 lat, zgon w ciągu jednego roku odnotowano w sumie u 24 (8,6%) osób. Badana grupa była również włączona w rejestr BleeMACS. Pacjentom pobierano krew żylną do probówki z kwasem wersenowym (EDTA) podczas przyjęcia do szpitala, a następnie w ciągu 30 min oznaczano wartości PDW przy użyciu systemu SYSMEX XN-2000. Echokardiogram z oceną frakcji wyrzutowej lewej komory (LVEF) wykonywał w ciągu 24 h od PCI doświadczony echokardiografista nieświadomy wartości PDW u badanego pacjenta. Na podstawie szpitalnej bazy danych oraz informacji uzyskanych drogą telefoniczną od pacjentów lub ich rodziny okres obserwacji wynosił 1 rok. Pierwszorzędowym punktem końcowym była wartość LVEF, w szczególności LVEF ≤ 35% rozumiana jako dysfunkcja skurczowa LV. Jednoroczna śmiertelność stanowiła drugorzędowy punkt końcowy. Zgon w okresie wewnątrzszpitalnym i trombocytopenia (liczba płytek we krwi < 100 000/μl) były kryteriami wykluczającymi.

Wyniki: Analiza krzywej ROC (*receiver-operating characteristics*) wykazała, że optymalny punkt odcięcia dla PDW wynoszący 12,8% charakteryzuje się 81% czułością i 39% specyficznością (pole pod krzywą 0,614; p = 0,0177) w prognozowaniu LVEF ≤ 35%. Analiza jednoczynnikowa dowiodła, że wartość PDW koreluje niezależnie z LVEF ≤ 35% i śmiertelnością jednoroczną. Wielomianowa regresja logistyczna potwierdziła hipotezę, że wartości PDW korelują niezależnie zarówno z upośledzeniem skurczowej funkcji serca wyrażonej wartością LVEF ≤ 35% (punkt odcięcia PDW: 12,8%; OR 2,8107; CI 1,1401–6,9293; p = 0,0248), jak i śmiertelnością jednoroczną (punkt odcięcia PDW: 16%; OR 2,6750; CI 1,0190–7,0225; p = 0,0457).

Wnioski: Wartość PDW mierzonego podczas przyjęcia do szpitala jest ogólnodostępnym i tanim współczynnikiem pozwalającym przewidzieć dysfunkcję skurczową LV w grupie pacjentów leczonych PCI z implantacją stentu z powodu ACS. Ponadto powyższa korelacja sugeruje niekorzystny wpływ zwiększonej aktywności płytek krwi na przebudowę mięśnia sercowego po przebytym zawale, który może wynikać z upośledzenia mikrokrążenia serca spowodowanego zakrzepami tworzonymi przez frakcje płytkowe o większej reaktywności. Zaobserwowany związek między wartością PDW a śmiertelnością wymaga potwierdzenia w badaniu obejmującym większą grupę pacjentów.

Słowa kluczowe: wskaźnik zmienności objętości płytek krwi, frakcja wyrzutowa lewej komory, przezskórne interwencje wieńcowe

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