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Predictive impact on medium-term mortality of hematological parameters in Acute Coronary Syndromes: added value on top of GRACE risk score

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Abstract

Background: Red Cell Distribution Width (RDW) prognostic value in patients with Acute Coronary Syndrome (ACS) has been well validated whereas that of Platelet Distribution Width (PDW) is less well known.

Objectives: Investigate the incremental prognostic value, on top of GRACE risk score, of a new variable resulting from the combination of RDW and PDW.

Methods: Consecutive patients with ACS. Complete blood count, with RDW and PDW, was obtained. Primary endpoint was one-year all-cause mortality and Cox regression models were used to measure the influence of RDW and PDW on patients' survival time. A new combination categorical variable (RDW/PDW) was created with both discretized RDW and PDW and logistic regression models were used. Predictive value and discriminative ability of the model with GRACE risk score alone and of the model with inclusion of RDW/PDW was assessed.

Results: We included 787 patients. Hospital and one-year mortality rates were 5.1% and 7.8%, respectively. Both continuous RDW and PDW were independent predictors of death. The best cut-off for RDW was 13.9%, and 14.5% for PDW. Inclusion of RDW/PDW in a model with GRACE risk score improved the AUC from 0.81 (95% CI 0.75–0.86) to 0.84 (95% CI 0.79–0.90) (p=0.024) with an improvement in total NRI (56%) and IDI (0.048).

Conclusions: Simple markers such as RDW and PDW can be useful in risk stratification of death after ACS. Combining both markers with GRACE risk score improved the predictive value for all-cause mortality and reduced the estimated risk of those who did not die.

Keywords

Acute coronary syndromes, GRACE risk score, platelet distribution width, prognosis, red blood cell distribution width

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Introduction

Red Blood Cell Distribution Width (RDW) represents the coefficient of variation of the red blood cell volume distribution width and can be considered an index of heterogeneity, the equivalent of anysocitosis observed in the peripheral blood smear. It is routinely reported as part of the complete blood count, but its use is generally restricted to narrowing the differential diagnosis of anaemia. Higher RDW is associated with mortality in patients with heart failure, stable coronary artery disease, acute coronary syndromes (ACS),

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in patients undergoing percutaneous coronary revascularization and also in the general population.[1–7]

Platelet Distribution Width (PDW) represents a similar measurement applied to platelets. Platelets have been implicated in the pathogenesis of cardiovascular disorders, including atherosclerosis and its complications, such as ACS.[8,9] However, the evidence for mortality prediction is scarce when compared to RDW, with very few bibliographic references on the subject.

The Global Registry of Acute Coronary Events (GRACE) risk score is a validated and established score for risk stratification of patients with ACS, obtained from a multicentre registry.[10] This score is based on several clinical and laboratorial variables and is used worldwide with a very good predictive value.

We sought to investigate the predictive value of each haematological marker individually, as well as the potential incremental prognostic value, on top of GRACE risk score, of a new variable that resulted from a combination of both markers (RDW/PDW), because the prognostic information from both variables might potentiate prognostic predictiveness.

Population and methods

This is a cohort study of consecutive patients admitted to our Intensive Care Unit with ACS (with and without ST-segment elevation) during the years 2008 through 2010. Data was collected prospectively and recorded on a computer database of ACS patients admitted to our institution's Intensive Care Unit. Inclusion criteria were a history of chest pain at rest or other symptoms suggestive of an ACS, with the most recent episode occurring within 24 hours of admission. This could be associated with new or presumed new significant ST-segment – T wave changes/new left bundle branch block or elevated levels of biomarkers of myocardial damage (cardiac troponin I and creatinine kinase). Myocardial infarction was defined by a rise and/or fall of cardiac troponin I with at least one value above 0.06 ng/mL. We evaluated demographic characteristics of the patients, risk factors for coronary artery disease, previous cardiac history and vital signs on admission as well as in-hospital treatment. Blood samples were obtained on admission. We used automated laboratory equipment (Beckman Coulter Automated CBC Analyzer – LH 750™) for haematological evaluation. Normal reference range for RDW in our laboratory is 11.5%–15.5% and for PDW is 9.0%–17.0%. Patients with increased RDW and PDW were defined by a cut-off obtained with the statistical analysis described below.

Hypertension, diabetes and hyperlipidemia were defined as either previously known or on specific therapy. Patients that smoked during the previous six months were classified as smokers and were self-reported. Estimated glomerular filtration rate (GFR) was calculated according to the Cockcroft-Gault formula.[11] For each patient, a numerical classification according to the previously described GRACE risk score was calculated from the initial clinical history, electrocardiogram and laboratory values collected at admission.[10]

Follow-up was obtained for every patient that survived to discharge by reviewing the medical records and/or by telephone interview with the patient or family members at 30 days and one year after admission. Follow-up information was obtained in 99.8% of the patients. The study primary endpoint was all-cause mortality at the one-year follow-up.

The study complies with the Declaration of Helsinki and informed consent was obtained from all the subjects.

Statistical analysis

Continuous variables were presented as mean or median, standard deviation or inter-quartile range (25th–75th percentile), as required. Normality and homogeneity of variances were tested by Kolmogorov-Smirnov test and Levene test, respectively. Groups were compared with ANOVA or with the non-parametric Kruskal-Wallis test whenever appropriate. Categorical data were presented as frequencies and percentages and Pearson's Chi-squared test or Fisher's exact test, were used.

The primary endpoint was one-year all-cause mortality and univariable and multivariable Cox proportional hazards regression models were used to measure the individual influence of RDW and PDW on the survival time. To test for proportional hazards assumption, Schoenfeld's global test was used. A global measure of concordance was also calculated.

Moreover, considering death within one-year follow-up, the best cut-off points of both parameters (RDW and PDW) were selected by maximizing the sum of sensitivity and specificity. A code was given for each variable: 0 = below cut-off; 1 = above or equal to cut-off. A new categorical variable RDW/PDW with three groups was obtained by summing these two binary variables. Two logistic regression models were then fitted to the data, with GRACE risk score alone and with the new variable RDW/PDW included. Predictive and discriminative abilities were assessed by the Hosmer-Lemeshow goodness of fit test and by the area under the Receiver Operating Characteristic curve (AUC), respectively. To compare the AUC from each of these models, the method described by DeLong et al. was used.[12] The Akaike Information Criterion was also used to compare the two models.

The incremental predictive value resulting from adding RDW/PDW variable to GRACE risk score was analysed with Continuous Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI). The net proportion of patients who died (with events) with higher probabilities of death (NRI_{events}) and of patients who did not

Table 1. Univariable and multivariable Cox proportional hazards regression analysis.

Variable	Univariable analysis	*p* value	Multivariable analysis	*p* value
	HR (95% CI)		HR (95% CI)	
Age (per 10 years increase)	2.04 (1.63–2.57)	<0.001	1.98 (1.55–2.52)	<0.001
Male gender	0.43 (0.26–0.71)	0.001	–	–
Smoking	0.42 (0.23–0.77)	0.005	–	–
Diabetes	2.22 (1.33–3.69)	0.002	1.70 (1.00–2.90)	0.051
Heart rate (per 10 bpm increase)	1.30 (1,15–1.48)	<0.001	1.26 (1.22–1.42)	<0.001
SBP (per 10 mmHg increase)	0.85 (0.77-0.93)	0.001	0.80 (0.72–0.88)	<0.001
ACEI	0.40 (0.23–0.71)	0.002	0.51 (0.28–0.95)	0.033
Beta-blocker	0.39 (0.23–0.68)	0.001	0.45 (0.25–0.81)	0.008
Killip class > 1	3.23 (1.95–5.37)	<0.001	–	–
eGFR < 60	3.33 (2.00–5.55)	<0.001	–	–
PCI	0.54 (0.31–0.92)	0.022	–	–
RDW	1.24 (1.12–1.37)	<0.001	1.17 (1.03–1.32)	0.012
PDW	1.20 (1.08–1.35)	0.001	1.14 (1.02–1.28)	0.022

ACEI: angiotensin converting enzyme inhibitor; PCI: percutaneous coronary intervention; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure.

die (without events) with lower probabilities of death ($NRI_{nonevents}$), were calculated considering both models. The NRI is the sum of NRI_{events} and $NRI_{nonevents}$ and quantifies the correctness of upward and downward movement of predicted probabilities as a result of adding a new marker.[13] The IDI is a measure of the improvement in prediction and may be viewed as the difference between improvement in average sensitivity and average 1-specificity.[13]

For all comparisons, a p value < 0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CI) were calculated.

Statistical analysis was carried out using the IBM SPSS Statistics, Version 21.0 (IBM Corp., North Castle, New York, USA) and the R software.[14]

Results

A total of 787 consecutive patients were included in the study, with a mean age of 64 ± 13 years, 70% males. The majority of the patients were admitted with an ST-segment elevation acute myocardial infarction (STEMI) (62%). In our sample, median GRACE risk score was 139 (P_{25}: 114–P_{75}: 161). The in-hospital, 30-day and one-year mortality rates were 5.1%, 5.8% and 7.8%, respectively. RDW correlated with haemoglobin values (r=−0.34, p<0.001) and PDW correlated with platelet numbers (r=−0.15, p<0.001). Patients with Non-STEMI or unstable angina were elderly, had more risk factors for coronary artery disease (except for smoking), more frequent previous cardiac history and medications compared to patients with STEMI (Supplemental Table). Patients with STEMI or non-STEMI had higher heart rate, systolic blood pressure, GRACE risk score and lower GFR compared to patients with unstable angina. No differences were found in haematological parameters according to admission diagnosis, with the exception of PDW. There were also no statistically significant differences in outcome, although there were no deaths in the unstable angina group.

The concordance index obtained for the Cox regression model with only the continuous RDW as an independent variable was 0.67 (95% CI: 0.60–0.74). For PDW, the obtained concordance was 0.63 (95% CI: 0.56–0.70). In the univariable analysis, age, gender, smoking, diabetes, heart rate, systolic blood pressure, angiotensin-converting enzyme inhibitors and beta-blockers use, Killip class, estimated glomerular filtration rate, PCI, RDW and PDW were significant predictors of outcome. In the multiple Cox proportional-hazards regression model, RDW and PDW remained as independent predictors of all-cause mortality after adjusting for age, diabetes, heart rate, systolic blood pressure, angiotensin-converting enzyme inhibitor and beta-blocker (Table 1). Proportional hazards assumption was met (p=0.277) and the global concordance of the final model was 0.83 (95% CI: 0.75–0.90). Anaemia is also an important predictor of mortality in ACS. In our study, in univariable analysis, anaemia showed an OR of 2.79 (95% CI 1.64–4.73, p<0.001) for all-cause mortality. Since anaemia could influence outcome and RDW values, we checked it in multivariable analysis. RDW remained as an independent predictor of outcome after adjustment for the presence of anaemia (OR 1.22, 95% CI 1.05–1.42, p=0.010) or after adjustment for haemoglobin values as a continuous variable (OR 1.22, 95% CI 1.04–1.43, p=0.013). This confirmed that although important for outcome, RDW does not lose its predictive ability after adjustment for the presence of anaemia.

Before studying how much RDW and PDW add to the predictive and discriminative ability of GRACE risk score and, due to the known usefulness of cut-off points in clinical practice, RDW and PDW were discretized by

maximizing the sum of sensitivity and specificity. RDW had an AUC of 0.672 (95% CI 0.603–0.741) and PDW an AUC of 0.635 (95% CI 0.567–0.703). The best cut-off for RDW was 13.9%, with a sensitivity of 62.3% (95% CI: 49.0–74.4) and a specificity of 62.0% (95% CI: 58.3–65.5); the best cut-off for PDW was 14.5%, with a sensitivity of 73.8% (95% CI: 60.9–84.2) and a specificity of 49.4% (95% CI: 45.8–53.2). A new variable RDW/PDW was then constructed as explained above. Patients with increases in both RDW and PDW (Group 2) were older and less often males. No significant associations were observed for coronary artery disease, diabetes, smoking, previous history, other initial presentation data and treatment (Table 2).

We built prediction models with GRACE risk score alone and after including the new RDW/PDW variable. AUC increased significantly after the inclusion of this variable in the model, although with a decrease in the goodness of fit (Figure 1, Table 3). However, Akaike Information Criterion also improved with the lowest value attained by the model with RDW/PDW variable, indicating a better model. Overall, the inclusion of RDW/PDW in a model with GRACE risk score was associated with a NRI of 56%, suggesting correct upward and downward movement of predicted probabilities of death. However, these movements occurred more effectively in the non-events group. In fact, the new model reduced the estimated probability of death in 58% of those without events. That is, the new model may better identify those patients who did not die. The IDI again showed that the model diagnostic performance was significantly improved by adding RDW/PDW to the GRACE risk score (IDI = 0.048) (Table 3).

Discussion

RDW reflects variability in circulating red blood cell size. It is based on the width of red blood cell volume distribution curve, with larger values indicating greater variability. Conditions of ineffective red cell production (such as iron deficiency, B12 of folate deficiency, and haemoglobinopathies), increase red cell destruction (such as haemolysis), and blood transfusion increase RDW.

RDW is an independent predictor of all-cause mortality in different patient populations and it gives valuable information for short-term risk stratification of ACS.[1–7] RDW is also an independent predictor of major bleeding in patients with non-ST-segment elevation myocardial infarction.[15] Anaemia has been shown to be a powerful and independent predictor of adverse cardiovascular outcomes.[16–18] Adjustment for multiple potential confounders (including anaemia) attenuated, but did not eliminate, the association between higher RDW levels and the adverse clinical outcomes.[16] In our sample, the same was observed. A study analysed both baseline and discharge RDW in patients with acute myocardial infarction.[19] They concluded that an increase in RDW during hospitalization shifted patients to a higher level of risk. On the contrary, decreasing RDW had a favourable outcome. Thus RDW is a dynamic marker of risk. RDW levels were significantly increased in patients with inadequate ST-segment resolution after primary PCI and baseline levels predicted no-reflow.[20] It was also an independent predictor of 6-month cardiovascular mortality, even after adjustment for multiple confounders including anaemia.[20]

The mechanisms by which elevated values of RDW are associated with adverse outcome in patients with cardiovascular disease have yet to be fully clarified but are probably multifactorial. In the context of ACS, we have an increase in inflammatory cytokines, oxidative stress, activation of neurohumoral pathways and adrenergic activation, all implicated in adverse outcome after ACS, and all these mechanisms seem to be involved in bone marrow response and erythroid cell poiesis.[21–32] In ACS, there is usually an infarct-related inflammatory response with excess cytokine production. Proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation, allowing juvenile erythrocytes to enter into circulation and leading to an increase in size heterogeneity.[27,28] Plasma erythropoietin levels increase in the early phase of acute myocardial infarction independently of haemoglobin levels.[29] Oxidative stress also causes damage which reduces cell survival, and it enhances the release of juvenile erythrocytes to circulation.[30] Activation of neurohumoral pathways with elevated circulating levels of neurohumoral mediators can affect erythropoiesis.[31,32]

Platelet hyper-reactivity and local platelet activation have been suggested to play a causal role in ACS.[33] Platelet size reflects platelet activity, with larger platelets being metabolically and enzymatically more active than small platelets. Large platelets are denser, aggregate more rapidly upon collagen challenge, produce larger amounts of thromboxane A2, release more serotonin and β-thromboglobulin, and express more Ib and IIb/IIIa glycoproteins.[34,35] Platelet activation causes morphologic changes, from discoid to spherical shape and pseudopodia formation with increased PDW.[36,37] Patients with ACS (compared to control patients and patients with stable angina) have raised platelet volume indices.[8] The increase in platelet consumption at the site of coronary atherosclerotic plaque causes larger platelets to be released from the bone marrow and the increase persists even after hospital discharge.[8] Erythropoietin and thrombopoietin have considerable structural homology and erythropoietin may also increase platelet reactivity.[38]

Several studies showed that Mean Platelet Volume (MPV) is an independent risk factor in myocardial infarction with aggravated clinical outcomes and higher mortality.[39,40] In a meta-analysis, an increased MPV was associated with acute myocardial infarction, mortality following myocardial infarction, and restenosis following PCI.[41] It is also

Table 2. Clinical characteristics by each RDW/PDW group.

	Group 0	Group 1	Group 2	*p* value
	n=243	*n*=362	*n*=182	
Age (years)	61 (13)	64 (13)	66 (14)	0.001†
Male gender (%)	77.0	67.1	65.4	0.012
Risk factors (%)				
Hypertension	63.0	66.9	70.9	0.228
Hyperlipidemia	53.9	49.7	51.1	0.599
Diabetes	23.9	23.2	27.5	0.535
Smoking	38.3	40.9	35.7	0.492
Previous history (%)				
Myocardial infarction	16.0	19.1	20.3	0.485
PCI	11.1	13.5	11.0	0.571
CABG	4.9	4.4	7.7	0.262
Stroke / TIA	3.7	8.3	6.6	0.080
Initial presentation				
STEMI n (%)	56.8	63.8	63.2	0.191
Killip class >1 (%)	18.9	19.3	21.4	0.793
HR (bpm)	78 (66–90)	80 (65–88)	80 (66–94)	0.302
SBP (mmHg)	130 (117–150)	131 (117–153)	132 (120–157)	0.621
Laboratory data				
eGFR < 60 ml/min/1.73m2 (%)	32.5	28.7	34.1	0.383
Haemoglobin (g/dL)	13.9 (1.6)	13.6 (1.8)	13.2 (2.1)	<0.001
Anemia (%)	18.9	27.9	38.5	<0.001
RDW	13.0 (12.7–13.4)	13.5 (13.0–14.0)	14.4 (14.0–15.1)	<0.001‡
PDW	12.5 (11.7–13.4)	15.6 (13.28–16.6)	16.5 (16.2–17.2	<0.001‡
Platelets (x10^3)	214 (185–248)	203 (169–242)	210 (168–256)	0.055
GRACE risk score	140 (117.0–159.0)	137 (112.0–160.0)	139.5 (114.8–162.5)	0.544
LVEF < 35% (%)	3.3	7.2	7.1	0.106
Treatment (%)				
ASA	99.2	98.6	98.9	0.817
Clopidogrel	96.7	96.4	96.2	0.953
ACEI	87.2	86.2	86.8	0.930
Beta-blocker	86.9	84.5	84.6	0.870
Statin	93.8	94.8	91.2	0.276
PCI	80.2	78.7	76.9	0.709
CABG	2.1	1.1	0.5	0.362
All-cause mortality (%)				
In-hospital mortality	1.6	4.1	11.5	<0.001
30-day mortality	2.9	4.1	13.2	<0.001
One-year mortality	3.3	6.4	16.5	<0.001

Continuous variables are presented as mean (*SD*) or median (P_{25}–P_{75}), as appropriate.
CABG: coronary artery bypass grafting; CK: creatinine kinase; ASA: acetil-salicilic acid; ACEI: angiotensin converting enzyme inhibitor; eGFR: estimated glomerular filtration rate; TIA: transient ischemic attack; HR: heart rate; SBP: systolic blood pressure; LVEF: left ventricular ejection fraction.
Multiple comparisons:
†Group 0 vs. Group 2, $p<0.001$; Group 1 vs. Group 2, $p=0.044$.
‡Group 0 vs. Group 1, $p<0.001$; Group 0 vs. Group 2, $p<0.001$; Group 1 vs. Group 2, $p<0.001$.

associated with no ST-segment resolution after treatment with streptokinase and no-reflow after primary PCI.[42,43] In fact, large platelets are younger platelets and this is a sign of increased platelet turnover. In diabetic patients, MPV is a strong predictor of the thromboxane B2 recovery slope after acetylsalicylic acid administration, suggesting that the diabetic milieu may account for the faster *de novo* synthesis of cyclooxygenase-1 in the bone marrow progenitors or their accelerated turnover, increasing risk.[44]

Although MPV has been extensively evaluated, novel platelet indices such as PDW have been less well investigated as platelet activation markers. PDW is significantly increased in patients with STEMI and is an independent predictor of STEMI.[45] More recently, it was demonstrated

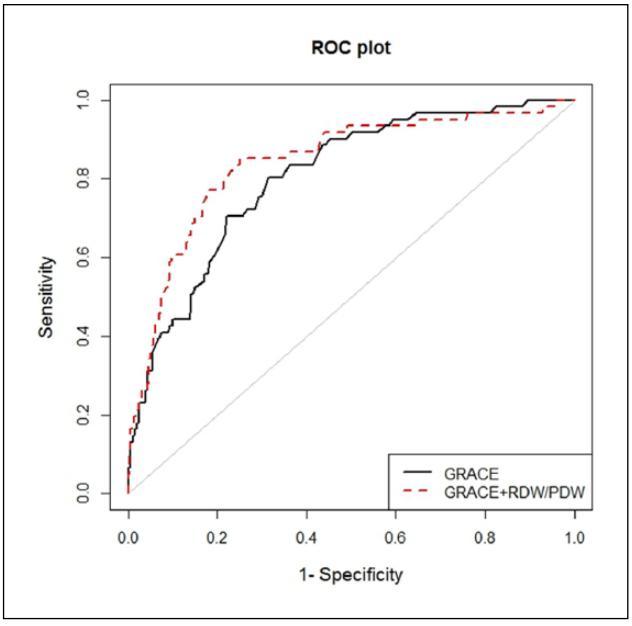

Figure 1. ROC curve analysis comparing the GRACE risk score and the new model with the inclusion of RDW/PDW (p=0.024).

Table 3. Statistics for model improvement with the addition of RDW/PDW.

Events, *n* (%)	61 (7.8)
Nonevents, *n* (%)	726 (92.2)
Continuous NRI (%)	
$cNRI_{events}$	−2 (−27–24)
$cNRI_{nonevents}$	58 (30–83)
cNRI	56 (51–65)
IDI statistics	
IDI_{events}	0.044
$IDI_{nonevents}$	0.004
IDI	0.048 (0.022–0.073)
AIC	
GRACE risk score	359.47
GRACE + RDW/PDW	341.25
AUC	
GRACE risk score	0.81 (0.75–0.86)
GRACE + RDW/PDW	0.84 (0.79–0.90)
Difference (*p* value)	0.024
Goodness of fit (GRACE risk score)*	0.559
Goodness of fit (GRACE + RDW/PDW)*	0.052

95% confidence intervals are shown in parenthesis.
*Hosmer-Lemeshow goodness of fit test *p* value.

that admission PDW correlated to platelet activation, no-reflow, in-hospital and long-term major acute coronary events (in-stent thrombosis, non-fatal myocardial infarction, coronary revascularization and in-hospital mortality) amongst patients with STEMI undergoing thrombolysis or primary PCI.[35,42,45,46] The prognostic value of PDW was even stronger than that previously reported for MPV.

Currently, automated cell counters enable routine availability of an extended panel of platelet volume indices beyond MPV (including PDW) routinely available in most clinical laboratories. RDW is also widely available to clinicians as part of the complete blood count and, therefore, incurs no additional costs, in contrast to other novel markers of cardiovascular risk.

Our results in medium-term follow-up in a population with the whole spectrum of ACS confirmed the independent association between RDW and PDW and survival time, after adjustment for relevant variables. They also showed some benefit in risk stratification after the inclusion in a model with GRACE risk score.

To better assess the improvement in outcome risk prediction we did a prediction/discrimination-oriented study which showed a significant AUC increase after including RDW/PDW in the model with GRACE risk score alone. The Akaike Information Criterion, a measure that considers both the goodness of fit and complexity of the model, also showed that this last model was the best. Considering the other new statistical metrics, recently proposed to quantify the degree of correct reclassification, the inclusion of RDW/PDW in a model with GRACE risk score was associated with a NRI of 56%. However, the new model identifies better those who do not have events than those who do. We also have found an IDI compatible with a favourable result after adding RDW/PDW to the GRACE risk score. Our results showed that adding RDW/PDW to a model with GRACE risk score could mainly better identify patients at low risk. The identification of 'truly low-risk' patients, instead of focusing mainly on identification of high-risk patients, may allow a better selection of patients avoiding unnecessary interventions that might increase costs as well as the risk of intervention-related adverse events, such as intensive anti-platelet or anti-thrombotic therapy. It can also help in the selection of patients for early discharge.

Limitations

This is a single-centre study which might limit the conclusions. It is also a retrospective and non-randomized study. It might not be applicable to other populations with different baseline characteristics. Particularly, our population has a predominance of STEMI patients, explained by the fact that we are a tertiary centre which receives many patients, from other hospitals for primary percutaneous coronary intervention. However, this does not reflect the distribution in other cohort studies of ACS and some caution should be taken when extending our results to other cohorts.

There might be some confounding factors such as erythropoietin levels, iron, folic acid and vitamin B12 that were not measured. Other known or unknown comorbidities that

could influence RDW and PDW were not specifically analysed because they were not part of the registry.

Conflict of interest

None declared.

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References

1. Felker GM, Allen LA, Pocock SJ, et al. on behalf of CHARM Investigators. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke databank. *J Am Coll Cardiol* 2007; 50: 40–47.
2. Tonelli M, Sacks F, Arnold M, et al. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary diseases. *Circulation* 2008; 117: 163–168.
3. Uyarel H, Ergelen M, Cicek G, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coron Artery Dis* 2011; 22: 138–144.
4. Azab B, Torbey E, Hatoum H, et al. Usefulness of red cell distribution width in predicting all-cause long-term mortality after non-ST-elevation myocardial infarction. *Cardiology* 2011; 119: 72–80.
5. Nabais S, Losa N, Gaspar A, et al. Association between red blood cell distribution width and outcomes at six months in patients with acute coronary syndromes. *Rev Port Cardiol* 2009; 28: 905–924.
6. Poludasu S, Marmur JD, Weedon J, et al. Red cell distribution width (RDW) as a predictor of long-term mortality in patients undergoing percutaneous coronary intervention. *Thromb Haemost* 2009; 102: 581–587
7. Cavusoglu E, Chopra V, Gupta A, et al. Relation between red blod cell dsitribution width (RDW) and all-cause mortality at two years in an unselected population referred for coronary angiography. *Int J Cardiol* 2010; 141: 141–146.
8. Khandekar MM, Khurana AS, Deshmukh SD, et al. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. *J Clin Pathol* 2006; 59: 146–149.
9. Vagdatli C, Gourari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and psecific marker of activation of coagulation. *Hippokratia* 2010; 14: 28–32.
10. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006; 333: 1091–1094.
11. Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
12. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic cruves: a nonparametric approach. *Biometrics* 1988; 44: 837–845.
13. Pencina MJ, D'Agostino RB and Steyerberg EW. Extension of net reclassification improvement calculations to measure usefulness of new biomarkers. *Statistics in Medicine* 2011; 30: 11–21.
14. R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2013. Vienna, Austria. ISBN: 3-900051-07-0, http://.R-project.org/
15. Gonçalves S, Ferreira Santos J, Amador P, et al. Impact of red blood cell distribution width on risk for bleeding events in patients with non-ST elevation acute coronary syndrome. *Rev Port Cardiol* 2013; 32: 27–33.
16. Cavusoglu E, Chopra V, Gupta A, et al. Usefulness of anemia in men as an independent predictor of two-year cardiovascular outcome in patients presenting with acute coronary syndrome. *Am J Cardiol* 2006; 98: 580–584.
17. Lee PC, Kini AS, Ahsan C, et al. Anemia is an independent predictor of mortality after percutaneous coronary intervention. *J Am Coll Cardiol* 2004; 44: 541–546.
18. O'Meara E, Clayton T, McEntegart MB, et al, on behalf of CHARM Investigators. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the CHARM Program. *Circulation* 2006; 113: 986–994.
19. Dabbah S, Hammerman H and Markiewicz W. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. *Am J Cardiol* 2010; 105: 312–317.
20. Isik T, Kurt M, Ayhan E, et al. The impact of admission red cell distribution width on the development of poor myocardial perfusion after primary percutaneous intervention. *Atherosclerosis* 2012; 224: 143–149.
21. Tsimikas S, Willerson JT and Ridker PM. C-reactive protein and other emerging blood biomarkers to optimize risk stratification of vulnerable patients. *J Am Coll Cardiol* 2006; 47: C19–C31.
22. Weiss G and Goodrough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011–1028.
23. Pierce CN and Larson DF. Inflammatory cytokine inhibition of erythropoesis in patients implanted with a mechanical circulatory assist device. *Perfusion* 2005; 20: 85–90.
24. Ridker PM, Rifai N, Clearfield M, et al. Measurement of C-reactive protein for the targeting of ebatin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344: 1959–1965.
25. Lippi G, Targher G, Montagnana M, et al. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med* 2009; 133: 628–632.
26. Forhecz Z, Gombos T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythopoiesis, inflammation, renal function, and nutritional state. *Am Heart J* 2009; 158: 659–666.
27. Pascual-Figal DA, Bonaque JC, Redondo B, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. *Eur J Heart Fail* 2009; 11: 840–846.
28. Al-Najjar Y, Goode KM, Zhang J, et al. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. *Eur J Heart Fail* 2009; 11: 1155–1162.

29. Ferrario M, Massa M, Rosti V, et al. Early haemoglobin-independent increase of plasma erythropoietin levels in patients with acute myocardial infarction. *Eur Heart J* 2007; 28: 1805–1813.
30. Semba RD, Patel KY, Ferrucci L, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: the Women's Health and Aging Study I. *Clin Nutr* 2010; 29: 600–604.
31. Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J Card Fail* 2010; 16: 230–238.
32. Masson S, Latini R, Anand IS, et al. On behalf of Val-HeFT Investigators. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol* 2008; 52: 997–1003.
33. Trip MD, Cats VK, van Capelle FL, et al. Platelet hyperreactivy and prognosis in survivors of myocardial infarction. *N Engl J Med* 1990; 322: 1549–1554.
34. Thompson CB, Eaton KA, Princiotta SM, et al. Size-dependent platelet subpopulation: relationship of platelet volume to ultrastructure, enzymatic activity and function. *Br J Haematol* 1982; 50: 509–520.
35. Celik T, Kaya M, Akpek M, et al. Predictive value of admission platelet volume indices for in-hospital major adverse cardiovascular events in acute ST-segment elevation myocardial infarction. *Angiology* 2013 Dec 3. (Epub ahead of print). PMID: 24301422. DOI: 10.1177/0003319713513493.
36. Jagroop IA, Clatworthy I, Lewin J, et al. Shape change in human platelets: measurement with a channelyzer and visualization by electron microscopy. *Platelets* 2000; 11: 28–32.
37. Vagdatli E, Gounari E, Lazaridou E, et al. Platelet distribution width: a simple, practical and specific marker of activation of coagulation. *Hippokratia* 2010; 14: 28–32.
38. Stohlawetz PJ, Dzirlo L, Hergovich N, et al. Effects of erythropoietin on platelet reactivity and thrombopoiesis in humans. *Blood* 2000; 95: 2983–2989.
39. Huczek Z, Kochman J, Filipiak KJ, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2005; 46: 284–290.
40. Massberg S, Schulz C and Gawaz M. Role of platelets in the pathophysiology of acute coronary syndrome. *Semin Vasc Med* 2003; 3: 147–162.
41. Chu SG, Becker RC, Berger PB, et al. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J Thromb Haemost* 2010: 8: 148–156.
42. Varastheh-Ravan HR, Ali-Hassan-Sayegh S, Shokraneh S, et al. Relationship of admission mean platelet volume platelet distribution width and white blood cells with ST resolution in patients with acute ST segment elevation myocardial infarction treated with streptokinase without history of previous cardiovascular surgery. *Prespect Clin Research* 2013; 4: 125–129.
43. Michaels AD, Gibson CM and Barron HV. Microvascular dysfunction in acute myocardial infarction: focus on the roles of platelets and inflammatory mediators in the no-reflow phenomenon. *Am J Cardiol* 2000; 85(5A): 50B–60B.
44. Rocca B, Santilli F, Pitoco D, et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. *J Thromb Haemost* 2012; 10: 1220–1230.
45. Rechcinski T, Jasinska A, Forys J, et al. Prognostic value of platelet indices after acute myocardial infarction treated with primary percutaneous coronary intervention. *Cardiol J* 2013; 20: 491–498.
46. Cetin M, Bakirci EM, Baysal E, et al. Increased platelet distribution width is associated with ST-segment elevation myocardial infarction and thrombolysis failure. *Angiology* 2014 Feb 12. (Epub ahead of print). PMID: 24526792. DOI: 10.1177/0003319713520068.