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The impact of complete blood count-derived indices (RDW, PDW and NLR) on 4 years outcomes in patients after PCI with sirolimus-eluting stent, including complex high-risk index procedure (CHIP) patients

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Medical Research Journal 2024;
 Volume 9, Number 1, 11–22
 DOI: 10.5603/mrj.98541
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 ISSN 2451-2591
 e-ISSN 2451-4101

ABSTRACT

Introduction: The authors analysed red cell distribution width (RDW), platelet distribution width (PDW), and the neutrophil-to-lymphocyte ratio (NLR) as potential predicting factors of adverse outcomes in patients after percutaneous coronary intervention (PCI) at 48 months follow-up.

Material and methods: The authors gathered data on subjects who underwent PCI with a sirolimus-eluting Alex Plus stent (Balton, Poland). They characterized the rate of major adverse cardiovascular events (MACE) over a 4-year period, which encompassed cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR) depending on the RDW, PDW, and NLR values.

Results: Included were 218 patients (256 stents), among which were also identified 77 complex, high-risk index procedure (CHIP) patients and 73 high bleeding risk (HBR) patients. The authors identified only RDW as having a significant impact on long-term outcomes and only in the total population and CHIP patients. The total population with RDW > 14.5% was characterized by higher age (67 ± 11 vs. 73 ± 10 years, $p < 0.01$) and higher incidence of chronic kidney disease (14% vs. 39%, $p < 0.01$) as well as chronic obstructive pulmonary disease (4% vs. 15%, $p = 0.024$). Interestingly, this group had a lower rate of ACS (42% vs. 34%, $p = 0.049$). At 48 months in the total population with RDW > 14.5% of patients, the rates of MACE, cardiac death, MI, and TLR were 26.8%, 19.5%, 9.8%, and 12.2%, respectively.

Conclusions: RDW > 14.5% correlated with a higher risk of cardiac death in the total population and CHIP patients.

Keywords: SES, PCI, Alex Plus, target lesion revascularization, thin-strut stent

Med Res J 2024; 9 (1): 11–22

Introduction

Ischemic cardiovascular events represent a major global health burden, and the quest for novel predictors and markers to enhance patient outcomes remains a cornerstone of cardiovascular research [1]. As the intricacies of cardiovascular disease (CVD) continue

to unfold, there is a growing interest in understanding the subtle relationships between complete blood count-derived indices — such as red cell distribution width (RDW), platelet distribution width (PDW), and the neutrophil-to-lymphocyte ratio (NLR)—and the outcomes of ischemic cardiovascular events, specifically after percutaneous coronary interventions (PCI) [2, 3].

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Red blood cell distribution width, which quantifies the variability in red blood cell size, has traditionally been associated with haematological conditions, particularly anaemias. However, emerging data suggests that elevated RDW values might be indicative of poor outcomes in patients with ischemic heart disease. The variability in red cell size could reflect underlying oxidative stress and inflammation, both of which are integral to the progression of atherosclerosis and subsequent ischemic events [4–6]. PDW, conversely, is a reflection of platelet size variability and, consequently, platelet activation. Given the pivotal role platelets play in thrombus formation — a key event in acute coronary syndromes — a heightened PDW might offer insights into platelet-driven pathophysiological processes in ischemic cardiovascular diseases and the post-PCI state [7]. Lastly, the NLR serves as a composite marker, amalgamating the inflammatory response (represented by neutrophils) and the adaptive immune response (indicated by lymphocytes). A skewed NLR, suggestive of heightened inflammation and a compromised immune response, has been implicated in poorer cardiovascular outcomes, particularly in the context of acute coronary events and their management through PCI [8, 9]. In previous research studies, the red blood cell distribution width (RDW) and platelet distribution width (PDW) were reported to be independent negative predictors of many CVDs [10–13].

Simultaneously, PCI stands as one of the cornerstones in managing coronary artery disease, offering symptomatic relief and improved outcomes for a huge number of patients globally. Yet, within the populations undergoing PCI, specific subsets of patients, notably those characterized as complex high risk and index procedure (CHIP) and high bleeding risk (HBR), highlight unique challenges and necessitate a more refined understanding of their prognosis [14, 15]. CHIP patients, by definition, present with complex coronary artery disease, often marked by advanced atherosclerosis, multi-vessel involvement, and other anatomical challenges that render PCI technically demanding and prognostically uncertain. These patients frequently have comorbid conditions or are deemed unsuitable for surgical revascularization, adding another layer of complexity to their management [16, 17]. On the other spectrum are the HBR patients, who, due to various clinical, anatomical, or procedural characteristics, are predisposed to higher bleeding risks, especially when subjected to the antiplatelet regimens essential post-PCI. These bleeding complications, beyond their immediate impact on morbidity and mortality, can have downstream effects, such as non-adherence to

crucial medications, which can subsequently elevate the risk of stent thrombosis and recurrent ischemic events [18].

Therefore, it becomes evident that an in-depth analysis of the prognostic factors for both CHIP and HBR patients undergoing PCI is not just clinically relevant but vital [19]. The aim was to characterize RDW, PDW, and NLR as potential risk factors for adverse outcomes in patients undergoing PCI at 4 years follow-up.

Material and methods

Study design and participants

The data was gathered from the hospital's historical records. Examined was every successive patient who had PCI with the Alex Plus sirolimus-eluting coronary stent (manufactured by Balton, Poland) from July 2015 to March 2016, as mentioned in an earlier study [14]. The Alex Plus stent is made of cobalt-chromium (L605) with 70 μm struts. This stent elutes sirolimus (1.3 $\mu\text{g}/\text{mm}^2$) from a biodegradable polymer over 8 weeks [20, 21]. The final analysis considered patients with available blood count data. Additionally, the analysis was performed in two groups, i.e., CHIP and HBR patients.

The authors adopted CHIP and HBR definitions as in the previous paper [14]. Shortly, patients with CHIP were identified by having a minimum of one clinical and one anatomical high-risk factor [22, 23]. Clinical criteria included advanced age (≥ 75 years), acute coronary syndrome, diabetes mellitus, previous cardiac surgery, heart failure with left ventricular ejection fraction $\leq 35\%$, advanced chronic kidney disease (estimated glomerular filtration rate $< 30 \text{ mL}/\text{min}/1.73 \text{ m}^2$), peripheral vascular disease, concomitant severe aortic valvulopathy, chronic obstructive pulmonary disease, or severe mitral regurgitation. Anatomical criteria included: unprotected left main disease, severely calcified lesions requiring preparation (e.g., rotational atherectomy), last patent conduit, degenerated saphenous vein grafts, or chronic total occlusion in a patient with multivessel disease.

High-bleeding risk patients were defined according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR) standard. To be classified as HBR, patients needed to meet either one major criterion or two minor criteria [24]. The ARC-HBR guidelines were used because they offer dependable forecasts for significant bleeding in patients with acute coronary syndrome [25], and they perform just as well, if not better, than other metrics like PRECISE-DAPT [26].

Data collection

We sourced data from the hospital's records, focusing on health conditions such as arterial hypertension, dyslipidaemia, diabetes mellitus, previous PCI, past MI, chronic kidney issues (identified by $eGFR < 60 \text{ mL/min/1.73 m}^2$), earlier CABG, peripheral artery disease, past stroke, chronic obstructive pulmonary disease, and smoking habits. Arterial hypertension was defined as a persistent elevation in office systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg, or a 24-hr ABPM average of $\geq 130/80$ mmHg or an HBPM average of $\geq 135/85$ mmHg [27]. Myocardial infarction was defined according to the Fourth Universal Definition of MI [28]. Diabetes mellitus and dyslipidaemia diagnoses were verified according to the latest European Society of Cardiology guidelines and included patients meeting the recommended threshold or already being on treatment [29].

Furthermore, the details of the PCI were recorded, encompassing lesion categories (A, B1, B2, C as per AHA/ACC classification [30]) and complications during the procedure. The authors also computed the SYNTAX (checked on 21–22 Sep 2023 at <https://syntaxscore.org>), SYNTAX II [31], and EuroScore II scores (<https://www.euroscore.org> checked on 12–13 Sep 2023). Echocardiographic parameters like left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter, intraventricular septal diameter, diastolic posterior wall diameter, left atrial diameter, and tricuspid annular plane systolic excursion were examined. Lab results taken upon admission included a complete blood count, CK, CK-MB, creatinine, troponin T, estimated glomerular filtration rate (eGFR), glucose, HbA1c, and lipid levels. For complete blood count-derived indices, the reference upper limits in the laboratory were as follows: RDW $\leq 14.5\%$, PDW ≤ 11 fl, and NLR ≤ 3 . NLR was calculated by dividing the absolute count for neutrophils by the absolute count for lymphocytes.

We also provided the names of medicines given upon discharge (antiplatelets, beta-blockers, Ca-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, hypolipemic drugs, hypoglycaemic drugs, anticoagulants, and nitrates).

Study endpoints

The main focus of the study was to assess the rate of major adverse cardiovascular events (MACE) over a 4-year period, which encompassed cardiac death, MI, and TLR depending on the RDW, PDW, and NLR

values. The secondary endpoints measured rates of overall mortality, cardiac death, MI, and TLR at the 1st, 2nd, 3rd, and 4th year milestones depending on the RDW, PDW, and NLR values. Target lesion revascularization (TLR) was defined as revascularization post-stenting within the stent or the 5-mm borders adjacent to the stent.

Statistical methods

Initially, using the multivariable Cox regression model, the authors assessed whether any of the values (RDW, PDW, NLR — as categorical variables normal vs. abnormal as well as other variables presented in Supplementary Tables S1–S3) influenced the study's outcomes. The multivariable Cox regression model was chosen in stepwise selection with a backward elimination algorithm. Results regarding the hazard ratio (HR) and 95% confidence intervals for HR are presented. Of these, only RDW showed a significant effect. Therefore, subsequent analyses were categorized into two subgroups: normal RDW ($\leq 14.5\%$) and elevated RDW ($> 14.5\%$).

For continuous variables, descriptive statistics are shown as the average, standard deviation, lowest and highest values, median, and interquartile range. For categorical variables, the count and percentage are provided. To compare categorical variables between the RDW $\leq 14.5\%$ and RDW $> 14.5\%$ patient groups, either Pearson's Chi-squared test or Fisher's exact test was employed. Fisher's exact test was chosen when any subgroup had a count of zero. The Wilcoxon rank sum test was used to compare continuous variables between the two patient groups, RDW $\leq 14.5\%$ and RDW $> 14.5\%$. A p-value less than 0.05 was deemed statistically meaningful.

Kaplan-Meier estimates with a 95% confidence interval (CI) was used to contrast 4-year survival curves for different endpoints between the RDW $\leq 14.5\%$ and RDW $> 14.5\%$ groups. If an endpoint happened more than once for a patient over the 4-year observation period, the survival time was considered as the duration of the first incident. Specifically, for MACE (a combined endpoint), survival time was seen as the time to the initial event of cardiac death, MI, or TLR. Additionally, ROC curves were provided.

All statistical procedures were conducted using R software, version 4.2.1 (dated 2022-06-23 ucrt) titled "Funny-Looking Kid", credited to The R Foundation for Statistical Computing and used on a x86_64-w64-mingw32/x64 (64-bit) platform.

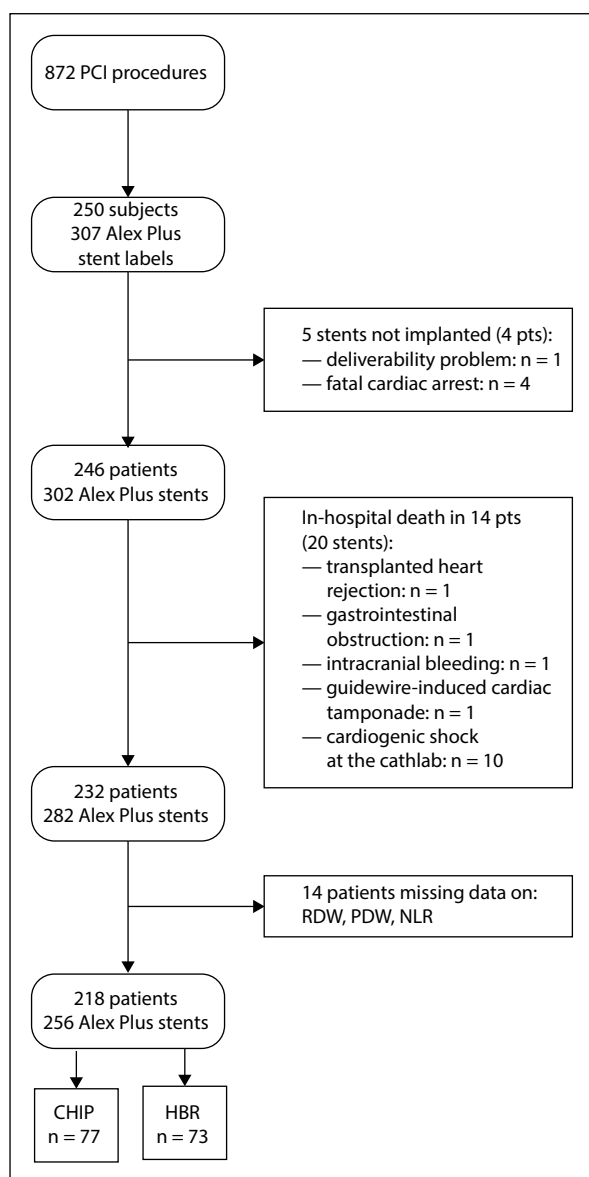


Figure 1. Study flow chart; CHIP — complex high-risk index procedure; HBR — high bleeding risk; NLR — neutrophil-to-lymphocyte ratio; PCI — percutaneous coronary intervention; PDW — platelet distribution width; RDW — red cell distribution width

Results

In the analysed period, identified were 872 PCI procedures. For the final analysis, 218 patients were included (256 stents) for whom lab tests with complete blood count-derived indices were available. Additionally, 77 CHIP patients and 73 HBR patients were identified (Fig. 1).

Analysis of complete blood count-derived indices

Initially, Cox regression analysis was performed, checking the influence of RDW, PDW, and NLR values in multivariable models on MACE, cardiac death, MI and TLR in the whole population, CHIP subgroup and HBR subgroup. As a result, only RDW was identified as having a significant impact on long-term outcomes and only in the total population and CHIP patients. Therefore further, presented was the analysis for patients with $RDW \leq 14.5\%$ and $RDW > 14.5\%$ in the total population and CHIP subgroup. In the total population as well as in CHIP patients, the increased RDW value correlated with cardiac death at 4 years, HR 1.45 (95% CI 1.19–2.73, $p < 0.001$) and HR 1.49 (95% CI 1.11–2.73, $p = 0.002$), respectively. The multivariable models for cardiac death are presented in Table 1. Supplementary Tables S1–S3 show the results of univariable analyses for cardiac death. Data for MACE, MI, and TLR as not statistically significant were not shown.

Baseline characteristics

The total population was characterized previously [14]. The total population with $RDW > 14.5\%$ characterized by higher age (67 ± 11 vs. 73 ± 10 years, $p < 0.01$) and higher incidence of chronic kidney disease (14% vs. 39%, $p < 0.01$) as well as chronic obstructive pulmonary disease (4% vs. 15%, $p = 0.024$). Interestingly, in this group, there was a lower rate of ACS (42% vs. 34%, $p = 0.049$). CHIP patients with $RDW > 14.5\%$ characterized higher age (69 ± 12 vs. 78 ± 5 years, $p = 0.011$) and higher rates of prior MI (45% vs. 91%, $p = 0.005$), chronic kidney disease (15% vs. 55%, $p = 0.008$) and chronic obstructive pulmonary disease (4.5% vs. 27%, $p = 0.046$) (Tab. 2). Laboratory results are presented in Table 3. There were statistically significant differences between normal and increased RDW groups regarding red blood cell count, lipid profile, kidney function and cardiac necrosis markers.

Procedure characteristics

No significant differences were observed in the total population between $RDW \leq 14.5\%$ and $RDW > 14.5\%$ subgroups, taking into consideration lesion location as well as lesion type (both in the total population as well as in CHIP patients). In the total population, most lesions were located in the right coronary artery ($RDW \leq 14.5\%$ and $RDW > 14.5\%$: 39% vs. 39%, $p = 0.265$), followed

Table 1. Cox regression for red cell distribution width, platelet distribution width and neutrophil-to-lymphocyte ratio

Variable	Multivariable analysis for cardiac death		
	HR	95% CI	P-value
Total population (n = 218)			
Lesion in left main	12.1	3.91, 32.2	< 0.001
Calcification	3.12	0.89, 8.89	0.061
Second stent	4.17	1.71, 9.12	0.021
RDW (above normal vs. normal)	1.45	1.19, 3.78	< 0.001
PDW (above normal vs. normal)	1.01	0.81, 1.12	0.981
NLR (above normal vs. normal)	1.09	0.99, 1.56	0.454
CHIP (n = 77)			
Prior CABG	3.24	1.12, 12.7	0.031
RDW (above normal vs. normal)	1.49	1.11, 2.73	0.002
PDW (above normal vs. normal)	0.97	0.79, 1.78	0.967
NLR (above normal vs. normal)	1.05	0.92, 1.32	0.455
HBR (n = 73)			
Male sex	0.14	0.03, 0.78	0.015
Postdilatation	4.23	0.97, 19.9	0.074
Smoking	4.21	1.04, 26.7	0.034
Alpha-adrenolytic	5.09	1.34, 19.1	0.034
RDW (above normal vs. normal)	1.18	0.98, 1.67	0.063
PDW (above normal vs. normal)	0.96	0.71, 1.35	0.891
NLR (above normal vs. normal)	1.06	0.91, 1.65	0.251

CHIP — complex high risk index procedure; HBR — high bleeding risk; NLR — neutro-phil-to-lymphocyte ratio; PDW — platelet distribution width; RDW — red cell distribution width; HR — hazard ratio; CI — confidence interval; CABG — coronary artery bypass grafting

by the left anterior descending artery (28% vs. 37%) and left circumflex artery (27% vs. 22%). Lesions undergoing PCI were quite complex. Type B2/C lesions were treated in 56% of cases in the RDW \leq 14.5% subgroup and 49% of cases in the RDW $>$ 14.5% subgroup ($p = 0.373$). Coronary bifurcations were treated in 9.6% and 12% of RDW \leq 14.5% and RDW $>$ 14.5% cases, respectively ($p = 0.572$). The mean SYNTAX II PCI score was higher in RDW $>$ 14.5% of patients (32 ± 10 vs. 40 ± 13 , $p < 0.01$). Comparable observations were reported when the CHIP subgroup was analyzed (Tab. 4).

In the total population, lesions were less frequently predilated in the RDW \leq 14.5% group (58% vs. 73%, $p = 0.076$ — trend), and postdilations were performed at similar rates (37% vs. 37%, $p = 0.991$). The mean nominal parameters of the Alex Plus stent did not differ significantly between groups. Device success was 100% in the RDW \leq 14.5% group and 97.6% in the RDW $>$ 14.5% group (1 case, heavy calcifications). Additional stents were deployed in 41% of RDW \leq 14.5% cases and 27% of RDW $>$ 14.5% cases ($p = 0.078$). Coronary dissections were comparable between groups (6.2 vs. 4.9%, $p = 0.887$). Comparable observations were reported when the CHIP subgroup was analyzed (Tab. 4).

Medications at discharge are presented in Table 5. All patients received acetylsalicylic acid and P2Y12 inhibitors. In the total population, RDW \leq 14.5% of patients received less frequent diuretics (50% vs. 71%, $p = 0.023$) and more frequently — angiotensin receptor blockers (17% vs. 2.4%, $p = 0.028$). In the CHIP subgroup, RDW $>$ 14.5% of patients received more frequently diuretics (59% vs. 91%, $p = 0.049$) and nitrates (6.1% vs. 36%, $p = 0.009$).

48-month outcomes

The rates of MACE, death, cardiac death, MI, and TLR at 12, 24, 36, and 48 months for the total population were published previously [14]. At 48 months in the total population with RDW $>$ 14.5% patients, the rates of MACE, cardiac death, MI, and TLR were 26.8%, 19.5%, 9.8%, and 12.2%, respectively (Tab. 6). The reasons for cardiac death were heart failure deterioration ($n = 5$), cardiogenic shock due to MI ($n = 1$), and sudden cardiac death ($n = 1$). No stent thrombosis cases were reported. Figure 2 shows statistically significant differences between RDW \leq 14.5% and RDW $>$ 14.5% subgroups for cardiac death in the total population and CHIP patients.

Table 2. Baseline characteristics

Variable	Total population			CHIP subgroup		
	RDW ≤ 14.5% N = 177 (%)	RDW > 4.5% N = 41 (%)	P	RDW ≤ 14.5% N = 66 (%)	RDW > 14.5% N = 11 (%)	P-value
Females	48 (27)	12 (29)	0.779	19 (29)	2 (18)	0.722
Age [years]	67 ± 11	73 ± 10	< 0.01	69 ± 12	78 ± 5	0.011
Comorbidities						
ACS at presentation	75 (42)	14 (34)	0.049	39 (59)	3 (27)	0.443
Cardiogenic shock	4 (2.3)	2 (4.9)	0.322	2 (3.0)	1 (9.1)	0.369
Arterial hypertension	162 (92)	39 (95)	0.754	61 (92)	11 (100)	0.991
Diabetes type 2	72 (41)	20 (49)	0.344	34 (52)	8 (73)	0.335
Dyslipidaemia	132 (75)	33 (80)	0.426	55 (83)	11 (100)	0.348
Prior MI	80 (45)	26 (63)	0.045	30 (45)	10 (91)	0.005
Prior PCI	97 (55)	22 (54)	0.891	37 (56)	9 (73)	0.353
Prior CABG	15 (8.5)	5 (12)	0.551	9 (14)	1 (9.1)	0.991
Chronic kidney disease	25 (14)	16 (39)	< 0.01	10 (15)	6 (55)	0.008
Prior stroke	11 (6.2)	5 (12)	0.188	5 (7.6)	1 (9.1)	0.994
Peripheral artery disease	16 (9.0)	7 (17)	0.163	8 (12)	3 (27)	0.192
Chronic obstructive pulmonary disease	7 (4)	6 (15)	0.024	3 (4.5)	3 (27)	0.046
Echocardiographic parameters						
LVEDd [mm]	50 ± 9	52 ± 8	0.214	51 ± 7	59 ± 9	0.003
IVSd [mm]	11 ± 2	12 ± 1	0.491	12 ± 3	11 ± 1	0.491
PWDd [mm]	10 ± 2	11 ± 1	0.178	10 ± 2	11 ± 2	0.480
LA [mm]	40 ± 6	43 ± 6	0.004	40 ± 6	44 ± 4	0.043
TAPSE [mm]	22 ± 4	22 ± 5	0.763	22 ± 5	22 ± 5	0.786
LVEF [%]	50 ± 10	46 ± 13	0.102	50 ± 9	40 ± 13	0.026

ACS — acute coronary syndrome; CABG — coronary artery bypass grafting; CHIP — complex, high-risk index procedure; IVSd — intraventricular septal diameter; LA — left atrium; LVEDd — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; PWDd — posterior wall diastolic diameter; RDW — red cell distribution width; TAPSE — tricuspid annular plane systolic excursion; MI — myocardial infarction

Table 3. Laboratory test findings

Variable	Total population			CHIP subgroup		
	RDW ≤ 14.5% N = 177 (%)	RDW > 14.5% N = 41 (%)	P	RDW ≤ 14.5% N = 66 (%)	RDW > 14.5% N = 11 (%)	P-value
White blood cells [10 ⁹ /L]	8.59 ± 2.80	8.31 ± 2.09	0.783	8.64 ± 2.31	8.39 ± 2.39	0.734
Hemoglobin [g/dL]	13.7 ± 1.4	12.0 ± 1.99	< 0.001	13.36 ± 1.49	11.55 ± 2.17	0.008
Red blood cells [10 ¹² /L]	4.50 ± 0.48	4.21 ± 0.70	0.035	4.40 ± 0.47	3.98 ± 0.77	0.073
Platelets [10 ⁹ /L]	218 ± 60	244 ± 81	0.113	214 ± 64	225 ± 55	0.572
Glucose [mg/dL]	138 ± 68	129 ± 44	0.912	155 ± 79	153 ± 56	0.752
HbA1c [%]	7.67 ± 0.7	6.61 ± 0.8	0.973	8.69 ± 2.74	6.48 ± 0.49	0.541
Total cholesterol [mg/dL]	168 ± 52	143 ± 41	0.009	167 ± 63	134 ± 41	0.081
HDL [mg/dL]	46 ± 15	45 ± 12	0.681	44 ± 12	42 ± 11	0.694
LDL [mg/dL]	93 ± 41	73 ± 34	0.007	86 ± 44	65 ± 30	0.087
Triglycerides [mg/dL]	148 ± 44	119 ± 66	0.281	177 ± 73	138 ± 42	0.544
Creatine [mg/dL]	1.07 ± 0.63	1.39 ± 0.98	< 0.001	1.18 ± 0.96	1.51 ± 0.88	0.004
eGFR [mL/min/1.73 m ²]	73 ± 23	58 ± 21	< 0.001	70 ± 24	50 ± 14	0.002
TnI at admission [ng/mL]	54 (23–217)	117 (15–1706)	0.202	50 (36–311)	222 (28–3,406)	0.284
TnI max [ng/mL]	376 (34–2,191)	1389 (53–15,560)	0.090	218 (41–2,484)	2925 (112–17,766)	0.084
CK at admission [IU/L]	91 (76–132)	170 (89–408)	0.006	85 (65–127)	220 (91–409)	0.043
CK max [IU/L]	106 (76–176)	201 (98–621)	0.004	84 (65–164)	230 (115–477)	0.042
CK-MB at admission [IU/L]	15 (13–22)	18 (14–30)	0.179	13 (13–18)	21 (14–36)	0.131
CK-MB max [IU/L]	17 (13–30)	24 (15–64)	0.035	14 (13–22)	36 (17–77)	0.069

Results presented as mean ± standard deviation or median (interquartile range). CHIP — complex high-risk index procedure; CK — creatine kinase; HDL — high-density lipoprotein; LDL — low-density lipoprotein; RDW — red cell distribution width; TnI — troponin I; CK-MB — creatine kinase myocardial band

Table 4. Lesion and procedure characteristics

Variable	Total population			CHIP subgroup		
	RDW ≤ 14.5% N = 177 (%)	RDW > 14.5% N = 41 (%)	P-value	RDW ≤ 14.5% N = 66 (%)	RDW > 14.5% N = 11 (%)	P-value
Lesion location						
LM	8 (4.5)	0	0.265	7 (11)	0 (0)	0.134
LAD	49 (28)	15 (37)		14 (21)	5 (45)	
LCx	48 (27)	9 (22)		13 (20)	1 (9.1)	
RCA	69 (39)	16 (39)		29 (44)	4 (36)	
VG	5 (2.8)	1 (2.4)		5 (7.6)	1 (9.1)	
Lesion type						
A/B1	77 (44)	21 (51)	0.373	23 (35)	5 (45)	0.525
B2/C	100 (56)	20 (49)		43 (65)	6 (55)	
Heavy calcification	14 (7.9)	3 (7.3)	1.000	7 (11)	1 (9.1)	0.992
Coronary bifurcation	17 (9.6)	5 (12)	0.572	10 (15)	2 (18)	0.678
SYNTAX	14 ± 8	14 ± 10	0.453	16 ± 9	14 ± 6	0.519
SYNTAX II PCI	32 ± 10	40 ± 13	< 0.01	34 ± 9	45 ± 11	0.003
SYNTAX II CABG	30 ± 11	26 ± 10	0.114	30 ± 11	28 ± 9	0.546
EuroScore II	2.87 ± 4.6	5.3 ± 2.2	0.006	3.7 ± 4.6	8.4 ± 10.3	0.061
Lesion predilatation	103 (58)	30 (73)	0.076	37 (56)	6 (55)	0.994
Stent diameter [mm]	3.15 ± 0.50	3.17 ± 0.52	0.891	3.27 ± 0.54	3.12 ± 0.49	0.293
Stent length [mm]	22 ± 11	19 ± 8	0.152	27 ± 14	23 ± 12	0.464
Stent pressure [atm]	15 ± 3	16 ± 2	0.557	16 ± 3	15 ± 2	0.393
2 nd stent implantation	73 (41)	11 (27)	0.078	57 (86)	10 (91)	0.991
Stent postdilatation	65 (37)	15 (37)	0.991	26 (39)	6 (55)	0.512
Coronary dissection	11 (6.2)	2 (4.9)	0.887	9 (14)	1 (9.1)	0.993

CABG — coronary artery bypass grafting; CHIP — complex high-risk index procedure; LAD — left anterior descending artery; LCx — left circumflex artery; LM — left main; PCI — percutaneous coronary intervention; RCA — right coronary artery; RDW — red cell distribution width; VG — vein graft

Table 5. Medications at discharge

Variable	Total population			CHIP subgroup		
	RDW ≤ 14.5% N = 177 (%)	RDW > 14.5% N = 41 (%)	P-value	RDW ≤ 14.5% N = 66 (%)	RDW > 14.5% N = 11 (%)	P-value
Acetylsalicylic acid	177 (100)	41 (100)	1.000	66 (100)	11 (100)	1.000
P2Y12						
Clopidogrel	161 (91)	39 (95)	0.534	59 (89)	11 (100)	0.582
Prasugrel	1 (0.6)	0		1 (1.5)	0	
Ticagrelor	15 (8.5)	2 (4.9)		6 (9.1)	0	
Beta-blocker	172 (97)	39 (95)	0.623	66 (100)	10 (91)	0.129
Ca-blocker	42 (24)	7 (17)	0.35	19 (29)	0	0.01
Angiotensin-converting enzyme inhibitor	146 (82)	37 (90)	0.221	55 (83)	9 (82)	0.991
Angiotensin receptor blocker	30 (17)	1 (2.4)	0.028	11 (17)	1 (9.1)	0.991
Diuretic	89 (50)	29 (71)	0.023	39 (59)	10 (91)	0.049
Mineralocorticoid receptor antagonist	35 (20)	12 (29)	0.177	10 (15)	6 (55)	0.008
Nitrates	8 (4.5)	5 (12)	0.068	4 (6.1)	4 (36)	0.009
Vitamin K antagonist	12 (6.8)	5 (12)	0.334	4 (6.1)	0	0.994
Novel oral anticoagulant	8 (4.6)	1 (2.4)	0.991	3 (4.5)	1 (9.1)	0.473
Statin	175 (99)	41 (100)	0.994	66 (100)	11 (100)	1.000
Hypoglycaemic medications	47 (27)	13 (32)	0.514	21 (32)	6 (55)	0.184
Insulin	22 (12)	10 (24)	0.058	14 (21)	5 (45)	0.128

CHIP — complex high-risk index procedure; RDW — red cell distribution width

Table 6. Study endpoints at 4 years based on the red cell distribution width value

Total population				
Endpoint	RDW ≤ 14.5% N = 177 (%)	RDW > 14.5% N = 41 (%)	HR, 95% CI	P-value
MACE	42 (23.7)	11 (26.8)	1.13, 0.87–1.44	0.686
Cardiac death	7 (3.9)	8 (19.5)	3.90, 1.18–4.92	0.005
Myocardial infarction	11 (6.2)	4 (9.8)	1.33, 0.79–2.56	0.485
Target lesion revascularization	28 (15.8)	5 (12.2)	0.75, 0.67–2.13	0.343
CHIP population				
Endpoint	RDW ≤ 14.5% N = 66 (%)	RDW > 14.5% N = 11 (%)	HR, 95% CI	P-value
MACE	18 (27.3)	6 (54.5)	2.48, 0.96–5.13	0.091
Cardiac death	5 (7.6)	4 (36.3)	4.2, 1.45–5.02	0.024
Myocardial infarction	5 (7.6)	1 (9.1)	1.28, 0.81–2.19	0.487
Target lesion revascularization	13 (19.7)	2 (18.2)	0.87, 0.55–3.44	0.523

Values presented as n (%). CHIP — complex high-risk index procedure; CI — confidence interval; HR — hazard ratio; MACE — major adverse cardiovascular events; RDW — red cell distribution width

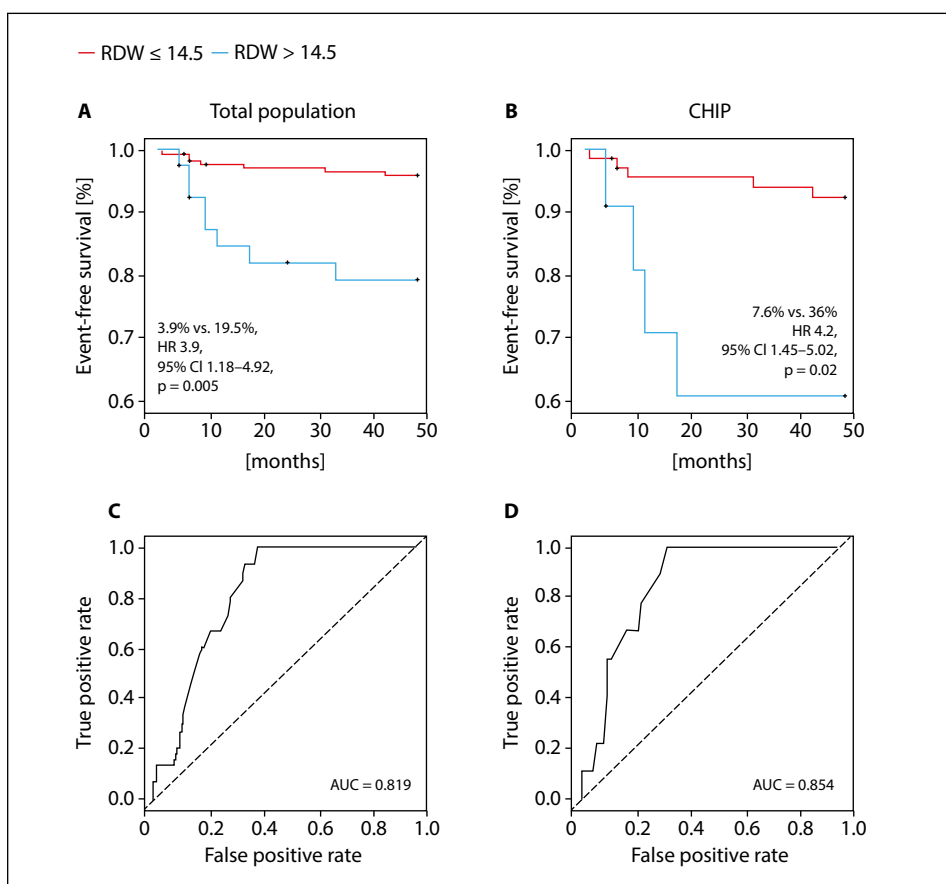


Figure 2. A.B. Cardiac death. Kaplan-Meier curves showing event-free survival in the total population and CHIP; **C. D.** ROC curves for cardiac death in the total population and CHIP subgroup

Additionally, the ROC curve for the univariable logistic regression model with the probability of cardiac death in 4-year follow-up as the response variable and continuous RDW as the explanatory variable was prepared. In the total population, the AUC was 0.819, with sensitivity for RDW threshold equal to 14.5% was 0.533, and specificity for RDW threshold equal to 14.5% –0.837. Similarly, in CHIP patients, AUC was 0.854, with sensitivity for RDW threshold equal to 14.5% was 0.444 and specificity for RDW threshold equal to 14.5% –0.897 (Fig. 2).

Discussion

The following study is the first to show the impact of RDW on outcomes in CHIP patients as well as one of the few showing the impact of RDW long-term outcomes (48 months). The study findings showed that patients with RDW > 14.5% in the total population, as well as in the CHIP subgroup, were characterized by a higher risk of MACE, especially cardiac death at 4 years after undergoing PCI with Alex Plus stent deployment. Interestingly, in the present study, cardiac death or MI rates were higher in the group with increased RDW values, but TLR rates were not. This might suggest that RDW value is more associated with further de novo ischemic events, like sudden plaque rupture outside the target lesion leading to MI or sometimes to ventricular arrhythmia and cardiac arrest. PDW and NLR did not show to impact statistically significant on long-term outcomes.

Red cell distribution width, a measure of the variability in red blood cell size, has long been used in haematology to differentiate types of anaemia. However, in recent years, its potential prognostic role in various cardiovascular conditions, including post-PCI, has garnered significant attention [32]. This was also shown in a recent meta-analysis by Bao et al. [33]. The analysis included twelve studies (spanning 13 articles) with a total of 17,113 patients. When comparing the groups with the highest and lowest RDW, the combined risk ratio (RR) was found to be 1.77 (with a 95% CI of 1.32 to 2.37) for overall mortality, 1.70 (95% CI 1.25 to 2.32) for deaths due to cardiovascular issues, and 1.62 (95% CI 1.21 to 2.18) for MACEs. Notably, the risk of all-cause mortality associated with increased RDW was more pronounced in patients without anaemia (RR 4.59; 95% CI 3.07 to 6.86) compared to those with anaemia.

In the specific context of post-PCI, RDW might play a predictive role in several ways. Elevated RDW levels pre-PCI could signal a heightened inflammatory state, potentially predisposing patients to stent restenosis,

thrombosis, or even microvascular complications post-procedure. Furthermore, given that PCI, especially in complex lesions or in patients categorized as CHIP, can be a trigger for inflammatory responses, RDW might serve as a valuable marker to stratify patients who would benefit from more aggressive or tailored post-procedural care [34]. Dai et al. [34] explored the connection between RDW value and the occurrence of periprocedural myocardial infarction (PMI) in patients scheduled for elective PCI. Out of 1,723 patients undergoing elective PCI, 230 (or 13.3%) were diagnosed with PMI. Patients with higher RDW levels ($\geq 12.6\%$) showed a higher tendency for PMI (15.4% compared to 11.2%, $p = 0.010$). Additionally, a high RDW was notably linked to an increased risk of MACE during the follow-up period.

However, while the association between RDW and adverse post-PCI outcomes seems robust in multiple studies, it is essential to view RDW as part of a broader clinical picture. RDW is one of many potential biomarkers and should be interpreted alongside other clinical and laboratory parameters. Its exact role in guiding clinical decision-making post-PCI, whether in terms of medication adjustments or follow-up intensity, remains to be fully elucidated [35, 36]. Ling et al. [37] showed that RDW > 13.9% was significantly correlated with residual SYNTAX score, and increased RDW levels were independent predictors of high residual SYNTAX score. Moreover, RDW value > 14.3% is included in the Mayo Cardiac Intensive Care Unit Admission Risk Score (M-CARS). Breen et al. [38] disclosed that patients with M-CARS value < 2 rarely required critical-care resources and characterized extremely low mortality. Interestingly, Zhang et al. [39] showed that older patients with ischemic cardiomyopathy and those taking angiotensin receptor blockers (ARBs) faced a greater MACE risk when they had elevated RDW levels. Similarly, patients with high cholesterol or those not suffering from anaemia also experienced an increased risk of MACE.

The prognostic role of RDW in the context of post-PCI outcomes represents an intriguing intersection of haematology and cardiology. As the authors' understanding of this marker deepens, it holds promise not just as a predictive tool but potentially also as a therapeutic target. Continued research is essential to elucidate its precise role and optimize its integration into cardiovascular care paradigms [40, 41].

Machado et al. [42] showed the negative impact of RDW > 13.4% in STEMI patients undergoing primary PCI at 3 years. Wu et al. [43] disclosed RDW > 13.1% value as a predictor of poor outcomes in coronary

artery disease patients at 3 years. Similarly to the present study, they showed that the cardiac death rate increased by 33% in the high RDW group (HR, 1.33; 95% CI, 1.01–1.76, $P = 0.043$), but there was no impact on total MACE. And Isik et al. [44] presented 4-year results. They showed that the $RDW \geq 13.85\%$ characterized 80% sensitivity and 64% specificity in long-term MACE predicting in STEMI patients. The RDW value on admission was the only independent predictor of long-term MACE (HR 5.3, 95% CI 1.7–16.1; $p = 0.004$).

Ultimately, it is worth stressing that although not proved in the present study, PDW and NLR were also associated with poor outcomes in patients undergoing PCI [13, 45–47]. Moreover, some studies showed the potential of other markers like RDW-to-albumin ratio or haemoglobin-to-RDW ratio. The RDW-to-albumin ratio was an independent predictor of all-cause mortality in patients after PCI at 90 days [48]. Whereas the haemoglobin-to-RDW ratio was a risk factor for post-PCI mortality in patients with coronary artery disease at 36 months [49]. Interestingly, recent studies showed that certain drugs like SGLT2 inhibitors might lead to a decrease in the inflammatory complete blood count-derived indices markers [50]

Study limitations

This research has the typical constraints associated with observational studies, where the treatment decision was primarily driven by the operator's discretion. The absence of randomization could introduce selection bias, though this effect might be somewhat lessened by enrolling patients consecutively. Additionally, the study's relatively modest sample size and potential gaps in follow-up data collection might have affected the outcomes, compounded by the absence of a structured sample size determination. Therefore, also it should be treated as a hypothesis-generating study.

Conclusions

Our study is the first to show the potential impact of RDW on outcomes in CHIP patients as well as one of few showing the impact of RDW long-term outcomes (48 months). The study findings showed that patients with $RDW > 14.5\%$ in the total population, as well as in the CHIP subgroup, were characterized by a higher risk of MACE, especially cardiac death at 4 years after undergoing PCI with Alex Plus stent deployment. More research is needed to refine RDW utility and establish clear guidelines for its use in the context of PCI with

sirolimus-eluting stent implantation. Nevertheless, it represents a potentially valuable addition to the armamentarium of tools available to clinicians for risk stratification and personalized treatment decisions in cardiovascular care. PDW and NLR did not show to impact statistically significant on long-term outcomes.

Article information

Acknowledgements: None.

Author contributions: *Conceptualization — MT and JB; methodology — MT and JB; investigation — PB, MT, AK; data curation — JB, RG; writing (original draft preparation) — MT and JB; writing (review and editing) — MT; supervision — RG. All authors have read and agreed to the published version of the manuscript.*

Funding: None.

Conflict of interest: None.

Ethics statement: *The study protocol was reviewed and approved by the Independent Ethics Committee of the Central Clinical Hospital of the Ministry of Interior and Administration in Warsaw (No 64/2020 of April 22, 2020).*

Data availability statement: *Data are available on request from the corresponding author.*

Informed consent statement: *Patient consent was waived due to the retrospective nature of the study.*

Statement of competing interests: *The authors declare no conflict of interest.*

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