VIA MEDICA

ORIGINAL ARTICLE

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The predictive value of complete blood count-derived indices for major adverse cardiovascular events in MINOCA patients at 5-year follow-up

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ABSTRACT

Introduction: The authors analysed the potential of red blood cell and platelet indices such as red cell distribution width (RDW), mean corpuscular volume (MCV), and mean platelet volume (MPV) as predicting factors in myocardial infarction with non-obstructive coronary arteries (MINOCA) patients of 5-year outcomes.

Material and methods: Between 2010–2015 were identified 112 patients who had final MINOCA diagnosis and available laboratory findings. The primary endpoint was the 5-year major adverse cardiovascular events rate, defined as cardiac death, myocardial infarction, or hospitalization due to angina.

Results: Only RDW had a significant impact on long-term outcomes. 93 (83%) patients had RDW ≤ 14.5 (group 1), and 19 (17%) patients had RDW > 14.5 (group 2). The mean RDW value was 13.58 ± 1.11%. In group 1 and group 2, mean RDW values were 13.18 ± 0.55%, and 15.54 ± 1.06% ($p < 0.001$), respectively. Patients with abnormal RDW values (group 2) characterized lower value of left ventricular eject fraction (60 ± 8% *vs.* 53 ± 13%, $p = 0.024$), and higher NT-proBNP values (3,170 ± 5,285 pg/mL *vs.* 6,200 ± 4,223 pg/mL, $p = 0.013$) as well as troponin levels (501–2500 ng/mL: 31% *vs.* 53%, $p = 0.02$). A statistically significant difference was observed only for all-cause death. All-cause death rates for no RDW ≤ 14.5% *vs.* RDW > 14.5% were 2.2% *vs.* 21.1% (HR 5.09, 95% CI 1.03–25.2, $p = 0.046$), respectively.

Conclusions: RDW was significantly associated with the increased risk of all-cause mortality in MINOCA patients at 5 years.

Key words: acetylcholine, chronic coronary syndrome, clinical outcomes, INOCA

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Introduction

Myocardial infarction with the non-obstructive coronary arteries (MINOCA) is a heterogeneous disorder [1, 2]. Recently, it has become acknowledged that MINOCA is not a rare entity, and it affects 5–15% of patients presenting with acute MI [1, 3–5]. However, MINOCA was deemed as a non-serious disorder with favourable outcomes; nevertheless, from very recently, it has been perceived that MINOCA is associated with a worse prognosis and higher incidence of future cardiovascular events than the general population [6–8]. For example, at 4 years, Lindahl et al. reported a major adverse cardiovascular event (MACE) rate of 23.9%, an all-cause death rate of 13.4%, MI of 7.1%, and heart failure hospitalization of 6.4% [9]. As a result, a comprehensive understanding of MINOCA-evoking factors is crucial to introduce personalized management that could decrease mortality as well as improve the quality of life [10].

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 cardiovascular diseases (CVD) [11–14]. The exact underlying mechanisms still must be elucidated. However, some research papers highlighted the

interaction between endothelium with impaired function, oxidative stress, and inflammatory response [1, 15, 16].

At the same time, few studies investigated the role of complete blood count-derived markers in patients with ischaemia and non-obstructive coronary arteries. Research studies were identified assessing the role of RDW in cardiac syndrome X [17], vasospastic angina [18], or slow flow phenomenon [19]. In addition, Lee et al. disclosed the positive correlation between neutrophil-to-lymphocyte ratio and index of microcirculatory resistance in ST-segment elevation MI patients undergoing primary percutaneous coronary intervention [20].

Earlier, it was shown that PDW and RDW correlated with coronary microcirculation spasms in patients undergoing provocative acetylcholine tests. The female sex (odds ratio [OR] = 1.199), PDW (OR = 2.891), and RDW (OR = 1.567) were identified as the independent risk factors for coronary microcirculation spasm diagnosis [21]. To the authors' knowledge, there is also no data on the association between complete blood count indices and long-term outcomes in MINOCA patients. The present study analyses various red blood cell and platelet indices such as RDW, mean corpuscular volume (MCV), and mean platelet volume (MPV), assessing their potential as predicting factors in MINOCA patients at 5-year outcomes.

Material and methods

Study design and participants

It was a retrospective, non-interventional study. Initially, all patients undergoing coronary angiography due to MI were identified. Then, only patients with coronary angiography with non-obstructive coronary arteries (lesions < 50% of diameter stenosis) and with MINOCA as a final diagnosis were separated. In the final analysis, patients for whom blood count recordings were available were included.

Data collection

Demographic, clinical, periprocedural, and laboratory data from the hospital database were collected. Retrieved was information on arterial hypertension, dyslipidaemia, diabetes mellitus, peripheral artery disease, atrial fibrillation, chronic kidney disease (defined as eGFR < 60 mL/min/1.73 m^2), prior percutaneous coronary intervention (PCI), prior MI, prior coronary artery bypass grafting, and clinical data associated with MI: type, disease advancement, treatment strategy, and periprocedural complications. Additionally, data on echocardiographic parameters (left ventricular ejection fraction) and laboratory findings assessed at admission were obtained. The upper reference limits were as follows: RDW — 14.5%, MCV — 92 fL, and MPV — 9 fL. Also, information on medications at discharge was gathered.

Study endpoints

The primary study endpoint was the 5-year rate of major cardiovascular adverse events (MACE) defined as joined rates of cardiac death, MI, and recurrent hospitalization due to angina. The secondary endpoints included all-cause death, cardiac death, MI, and recurrent hospitalization due to angina rates at 5-year follow-up.

Statistical methods

Initially, in the multivariable Cox regression model, it was checked if any of these values (RDW, MCV, MPV) according to the upper limit of the reference range as the threshold impacted the study endpoints. Only RDW had a significant impact, and further analyses were performed in subgroups: normal RDW (≤ 14.5%) *vs.* increased RDW value (> 14.5%).

Descriptive statistics were presented: mean, standard deviation, minimum, 25% centile, median, 75% centile, and maximum for continuous variables; count and per cent for categorical variables. Pearson's Chi-squared test or Fisher's exact test was performed to compare categorical variables between two groups (e.g., normal RDW vs. increased RDW value). Fisher's exact test was used when at least one of the subgroups had count = 0. Wilcoxon rank sum test was performed to compare continuous variables between two groups (e.g., normal RDW vs. increased RDW value). P-value < < 0.05 was statistically significant. Kaplan-Meier estimators with a 95% confidence interval (CI) were calculated to compare 5-year survival curves for various endpoints between groups (e.g., normal RDW *vs.* increased RDW value). If a given endpoint occurred for a particular patient more than once in a 5-year follow-up period, then survival time was assumed as the time to the first occurrence of this endpoint. Notably, in the case of MACE (a composite endpoint), survival time was assumed as the time to the first occurrence of either cardiac death, myocardial infarction, or angina pectoris hospitalization. Statistical analyses were performed using R software version 4.2.1 (2022-06-23 ucrt) — "Funny-Looking Kid" Copyright (C) 2022 The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit).

Results

Between 2010–2015 were identified 3171 coronary angiography procedures performed due to acute coronary syndrome, from which 153 had working MINOCA

Table 1. Analysis of complete blood count-derived indices (multivariable Cox regression)

Characteristic	Hazard ratio [HR]	95% Confidence interval [CI]	P-value
All-cause death			
RDW	5.09	1.03–25.2	0.046
MPV	0.67	0.28–1.64	0.384
MCV	0.80	0.15–4.38	0.799
Cardiac death			
RDW	0.32	0.01–10.7	0.523
MPV	0.70	0.08–5.96	0.746
MCV	0.99	0.70–1.39	0.940
Myocardial infarction			
RDW	1.13	0.46–1.56	0.6
MPV	1.13	0.51–2.53	0.763
MCV	0.97	0.82–1.16	0.766
Hospitalization due to angina			
RDW	1.53	0.32–7.36	0.597
MPV	1.38	0.86–2.22	0.183
MCV	0.98	0.87–1.11	0.773
MACE			
RDW	1.73	0.67–4.32	0.2
MPV	1.40	0.92–2.14	0.119
MCV	0.90	0.26–3.07	0.866

MCV — mean corpuscular volume; MPV — mean platelet volume; RDW — red blood cell distribution width

diagnosis, and the final diagnosis of MINOCA was ascribed to 112 (5.8%) patients. All patients had required laboratory results available.

Analysis of complete blood count-derived indices

The authors performed Cox regression analysis, checking the influence of RDW, MPV, and MCV values (Tab. 1). As a result, only RDW as having a significant impact on long-term outcomes were identified. Further, the analysis for patients with RDW ≤ 14.5% (group 1) and RDW > 14.5% (group 2) was presented.

Baseline characteristics

All patients had required laboratory results available, and among them, 93 (83%) had RDW ≤ 14.5 (group 1), and 19 (17%) patients had RDW > 14.5 (group 2) (Fig. 1). The mean RDW value was 13.58 ± 1.11% (min. 12.10%, max. 18.8%). In group 1 and group 2, mean RDW values were 13.18 ± 0.55% (min. 12.10%, max. 14.40), and 15.54 ± 1.06% (min. 14.70, max. 18.80; p < 0.001), respectively.

Baseline characteristics are presented in Table 2. Patients did not differ in terms of sex (females: group 1 *vs.* group 2: 59% *vs.* 63%, p = 0.7) or age (62 ± 14 years *vs.* 66 ± 16 years, p = 0.3). Patients with

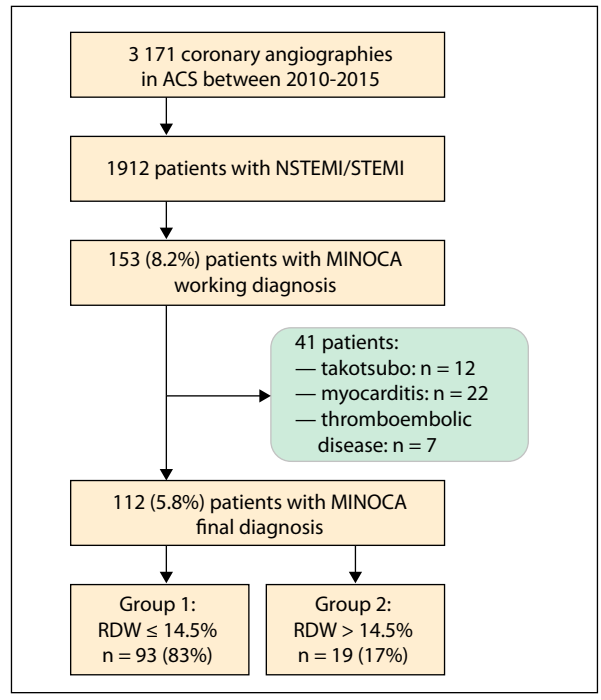

Figure 1. Study flowchart
ACS — acute coronary syndrome; MINOCA — myocardial infarction with non-obstructive coronary arteries; NSTEMI — non-ST-elevation myocardial infarction; RDW — red cell distribution width; STEMI — ST-elevation myocardial infarction

Table 2. Baseline characteristics

Parameter	Group 1 N = 93	Group 2 N = 19	P-value
Females	55 (59%)	12 (63%)	0.7
Age [years]	62 ± 14	66 ± 16	0.3
Body mass index [kg/m^2]	27.5 ± 5.0	30.0 ± 8.7	0.2
Myocardial infarction type at presentation			
NSTEMI	12 (13%)	5 (26%)	0.3
STEMI	80 (86%)	14 (74%)	
Arterial hypertension	49 (53%)	10 (53%)	> 0.9
Diabetes type 2	12 (13%)	3 (16%)	0.7
Dyslipidaemia	27 (29%)	1 (5.3%)	0.039
Chronic kidney disease	3 (3.2%)	1 (5.3%)	0.5
Atrial fibrillation	19 (20%)	6 (32%)	0.4
Peripheral artery disease	1 (1.1%)	0	> 0.9
Smoking	10 (11%)	3 (16%)	0.5
LVEF [%]	60 ± 8	53 ± 13	0.024
Coronary lesions			
No lesions	46 (49%)	5 (26%)	
< 30%	31 (33%)	10 (53%)	0.2
30–50%	16 (18%)	4 (21%)	

CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; NSTEMI — non-ST-elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-elevation myocardial infarction

abnormal RDW values (group 2) characterized the statistically significant lower risk of dyslipidemia (29% *vs.* 5.3%, p = 0.039) and lower value of left ventricular ejection fraction (60 ± 8% *vs.* 53 ± 13%, p = 0.024). Table 3 presents laboratory findings at admission. Group 2 patients characterized higher NT-proBNP values (3,170 ± 5,285 pg/mL *vs.* 6,200 ± 4,223 pg/mL, p = 0.013) and higher troponin levels (501–2500 ng/mL 31% *vs.* 53%, p = 0.02).

Management at discharge

All included patients were discharged. Table 4 presents medications prescribed at discharge. All patients received similar treatment.

Outcomes at five years

Survival rates at five years are presented in Table 5, and Kaplan-Meier curves for all-cause death are shown in Figure 2. A statistically significant difference was observed only for all-cause death. All-cause death rates for no RDW ≤ 14.5% *vs.* RDW > 14.5% were 2.2% *vs.* 21.1% (HR 5.09, 95% CI 1.03–25.2, p = 0.046), respectively.

Discussion

To the authors' knowledge, this study is the first to verify the predictive value of complete blood count indices in MINOCA patients in the long-term follow-up. RDW was significantly associated with all-cause death at five years.

The RDW is a parameter characterizing erythrocyte volume variations (i.e., anisocytosis) and is readily available in a complete blood count result [22]. Several research papers reported that RDW was linked with CVDs and increased RDW values were predicting factors of poor outcomes not only in patients with ischaemic heart disease but also in other populations such as subjects with arterial hypertension [23], hypertrophic cardiomyopathy [24], undergoing carotid endarterectomy [25], congenital heart disease [26] or aortoiliac disease [27].

But coming back to RDW, it is definitely a predictor of poor outcomes in patients with obstructive coronary artery disease. Dai et al. showed that RDW was an independent predictor of MI type 4a [28]. Zhang et al. showed that RDW was linked with increased risk of MACE (HR 1.75), all-cause mortality (HR 1.58), and any revascularization (HR 2.10) [29] at long-term follow-up. In the research by Wu et al., RDW was an independent predictor of cardiac death (HR 1.33) but not all-cause mortality or MACE at 3 years [30]. The interesting concept was developed by Xiao et al. [31], who proposed to measure the change of RDW (ΔRDW) before PCI and 16 weeks after PCI. The ΔRDW showed the potential to predict MACE. The range of HR values was slightly lower than in the current study, i.e., HR 5.09 for all-cause mortality at 5 years. However, this can be explained by the fact that the authors assessed the population with MI and had the most extended follow-up. In patients undergoing PCI, also other factors had a substantial impact, such as PDW in subjects undergoing PCI within coronary bifurcation lesions [14].

Some studies also showed that patients with increased RDW value characterized unfavourable prognosis after acute MI (OR 2.2 for MACE) [32]. This was also confirmed in other studies [33–35]. In one of these studies, similar to the current one, the association between increased RDW value and increased NT-proBNP was confirmed [33]. Interestingly, subanalysis from the ODYSSEY OUTCOMES study showed that despite heavy treatment of dyslipidaemia with alirocumab, RDW remained an independent predictor of MACE after acute coronary syndrome [36].

The RDW threshold differed in various studies for outcomes in patients with ischaemic heart disease and/or hypertension. It ranged from 12.6% to 14.8% [23, 28, 30, 34, 35]. In the present study, the authors applied the threshold of 14.5% as this was the upper reference limit in the laboratory. However, when the authors also applied the median (13.2%) as the threshold, it did not impact long-term outcomes (data not shown).

Table 3. Laboratory findings at admission

Parameter	Group 1 N = 93	Group 2 N = 19	P-value
White blood cells [109/L]	9.5 ± 3.8	11.4 ± 4.9	0.063
Haemoglobin [g/dL]	13.97 ± 1.37	13.23 ± 1.81	0.12
Red blood cells [10^{12}/L]	4.58 ± 0.45	4.38 ± 0.61	0.2
Platelets [10^9/L]	244 ± 65	278 ± 128	0.4
RDW [fL]	13.18 ± 0.55	15.54 ± 1.06	< 0.001
MPV [fL]	8.32 ± 1.06	8.59 ± 1.34	0.4
MCV [fL]	90.6 ± 4.7	92.0 ± 9.8	0.6
Glucose [mmol/L]	7.31 ± 2.42	8.02 ± 2.81	0.3
HbA1c [%]	5.91 ± 0.41	5.90 ± 0.28	0.8
NT-proBNP [pg/mL]	3.170 ± 5.285	6.200 ± 4.223	0.013
C-reactive protein	1.9 ± 2.8	10.3 ± 20.5	0.7
AST [U/L]	40 (29–59)	49 (31–56)	0.8
ALT [U/L]	32 (26–50)	27 (15–68)	0.7
Total cholesterol [mmol/L]	4.78 ± 1.14	4.81 ± 0.88	0.9
HDL [mmol/L]	1.55 ± 0.55	1.81 ± 1.12	0.9
LDL [mmol/L]	2.62 ± 1.05	2.36 ± 0.99	0.4
Triglycerides [mmol/L]	1.37 ± 0.58	1.40 ± 0.72	0.8
Creatine [μmol/L]	84 ± 24	97 ± 55	0.8
TSH [μU/mL]	1.49 ± 1.13	1.96 ± 2.40	0.7
Maximal troponin T [ng/mL]			
0–500	59 (63%)	8 (42%)	0.02
501–2500	29 (31%)	10 (53%)	
2501–10000	5 (5.4%)	1 (5.3%)	
10000+	0 (0%)	0 (0%)	

Results presented as mean ± SD or median (IQR). MCV — mean corpuscular volume; MPV — mean platelet volume; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RDW — red cell distribution width

In coronary microcirculation dysfunction, often is observed coronary slow flow (CSF) phenomenon, defined as a delayed distal coronary artery opacification without significant stenosis on coronary angiography. The CSF mechanism remains somewhat unclear, although an inflammatory state, endothelial dysfunction, or hampered rheological blood properties play an essential part [37]. In a large patient population of 17,315 cases, Akpinar et al. [19] reported that increased RDW and PDW values correlated with microvascular blood flow resistance. Nevertheless, in the authors' previous research, it was not observed that CSF had a negative impact on outcomes in MINOCA patients at 5 years [38].

Ultimately, the white blood cell count issue should be raised in our population. In group 2 with RDW > 14.5%, was observed an increased white blood cell value above the upper reference level. This observation and an elevated RDW value might suggest that a subclinical inflammatory condition may be one of the potential underlying mechanisms of

Table 4. Medications at discharge

Parameter	Group 1 N = 93	Group 2 N = 19	P-value
ASA	87 (93.5%)	18 (94.7%)	> 0.9
Clopidogrel	68 (73.1%)	13 (68.4%)	0.6
Beta-blocker	73 (78.5%)	15 (78.9%)	> 0.9
Ca-blocker	22 (23.6%)	6 (31.6%)	0.6
ACE inhibitor	66 (70.9%)	15 (78.9%)	0.5
Angiotensin receptor blocker	5 (5.3%)	0	0.6
Diuretic	19 (20.4%)	6 (31.6%)	0.4
Trimetazidine	2 (2.2%)	0	> 0.9
Nitrates	50 (53.7%)	11 (57.9%)	0.8
Vitamin K antagonist	10 (10.8%)	3 (15.8%)	0.7
Novel oral anticoagulant	3 (3.3%)	1 (5.3%)	0.5
Statin	84 (90.3%)	17 (89.5%)	0.7

ACE — angiotensin-converting enzyme; ASA — aspirin

poor outcomes and may predict ischaemic events in the coronary microcirculation. As a consequence, in the follow-up, one can observe a relatively benign situation as recurrent chest pain diminishing quality of life. Nevertheless, acute coronary syndromes or malignant ventricular arrhythmias can also be observed and be responsible for death cases in MINOCA patients at long-term follow-up.

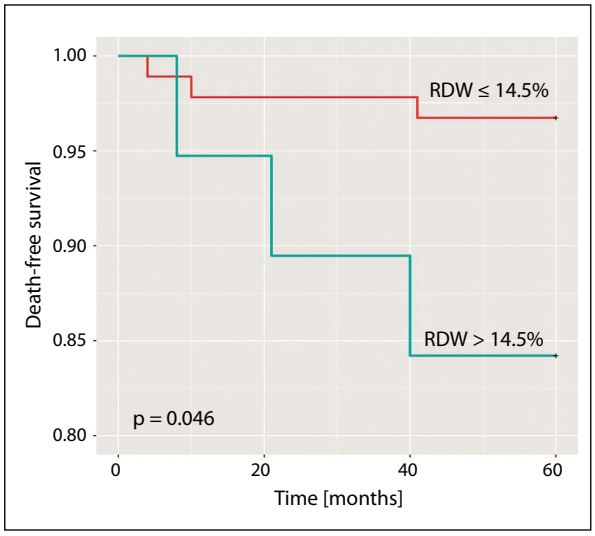

Figure 2. Kaplan-Meier curves for all-cause death at 5 years for MINOCA patients with RDW ≤ 14.5% and RDW > 14.5%; RDW — red blood cell distribution width

Study limitations

This study has several limitations. Firstly, this is a single-centre retrospective study with a relatively small size, and the number of some outcomes is small. Secondly, the indices taken into consideration were somewhat limited, with only three. Finally, all indices were measured only at one point, not repeated during the hospital or the follow-up period. Therefore, this study's findings require confirmation in a multicentre, prospective, large sample size study with more inflammatory biomarkers and dynamic markers changes to validate these findings and elucidate more comprehensively the role of inflammatory response in MACE predicting.

Conclusions

To the best of the authors' knowledge, this study is the first to investigate the predictive value of complete blood count indices in MINOCA patients in long-term follow-up. RDW was significantly associated with all-cause death at five years.

Conflict of interest: *None.*

Funding: *None.*

Ethical approval: *The study protocol was reviewed and approved by the Institutional Review Board (or Ethics Committee) of the District Physician Chamber in Plock (No 1/2020 of 20.11.2020). Patient consent was waived due to the retrospective nature of the study.*

Table 5. Study population 5-year outcomes

Parameter	Group 1 N = 93	Group 2 N = 19	HR	95% CI	P-value
All-cause death	2 (2.2%)	4 (21.1%)	5.09	1.03–25.2	0.046
Cardiac death	1 (1.1%)	0	0.32	0.01–10.7	0.523
Myocardial infarction	3 (3.2%)	1 (5.3%)	1.13	0.46–1.56	0.6
Percutaneous intervention	1 (1.1%)	1 (5.3%)	1.23	0.84–2.34	0.4
Hospitalization due to angina	6 (6.5%)	3 (15.8%)	1.53	0.32–7.36	0.597
MACE	9 (9.7%)	4 (21.1%)	1.73	0.67–4.32	0.2

MACE — major adverse cardiovascular event

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