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Association between elevated red blood cell distribution width and long-term mortality in acute pulmonary embolism

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Background/aim: The prognostic value of the red cell distribution width (RDW) as a cost-effective and noninvasive test in acute pulmonary embolism (PE) is still unknown. We aimed to investigate the prognostic value of the admission RDW level in the long-term survival of PE patients.

Materials and methods: In this registry-based, prospective cohort study, a total of 378 patients (mean age: 60.4 ± 17.11 years, 47.4% female) who presented with acute PE were enrolled. All the clinical data for each patient were obtained from our institutional PE registry. The follow-up was performed at a median time of 17 months. The primary endpoint was death at follow-up.

Results: The mean RDW in study patients was 14.67 ± 2.13. The all-cause mortality rate during the follow-up was 15.6% (n = 59). After adjustment for potential confounders, the relationship between RDW and long-term mortality showed a trend of a significant level (hazard ratio: 1.109; 95% CI, 0.998–1.232; P = 0.053). We divided patients into 3 groups based on the European Society of Cardiology's classification. As we moved from the low risk to the higher risk categories, the mean RDW increased significantly (P = 0.037).

Conclusion: It seems there may be an independent association between RDW at presentation and PE mortality within 17 months.

Key words: Pulmonary embolism, red cell distribution width, mortality

1. Introduction

Acute pulmonary embolism (PE) is a common life-threatening cardiovascular disease with 15%–20% mortality (1). Complete blood count is a part of routine laboratory tests performed for patients admitted to the emergency department, and red cell distribution width (RDW), as a marker of anisocytosis, reflects the heterogeneity of red blood cell (RBC) size. Recent studies have shown that RDW is associated with the prognosis of many cardiovascular conditions (2). To our knowledge, only a few studies have shown that RDW is not only associated with the risk of PE but is also a predictor of early mortality in acute PE (3-5). However, the prognostic value of RDW as a cost-effective and noninvasive test in acute PE, specifically in the long term, is still unknown. The present study sought to investigate the prognostic value of the admission RDW level in the long-term survival of PE patients.

2. Materials and methods

2.1. Population and study protocol

This is a registry-based, prospective cohort study conducted in a tertiary cardiac center. In total, 378 confirmed acute PE patients were enrolled in the study. Individuals with a previous PE history and end-stage renal disease were excluded. The diagnosis of PE was confirmed either by pulmonary computed tomography angiography or by ventilation-perfusion lung scan. The treatment consisted of heparin or low-molecular-weight heparin in the acute phase. Decision about the need for thrombolytic therapy was made by the physician based on the clinical condition of the patients. Hence, the patients were placed on warfarin at the time of discharge.

The patients, once admitted to the hospital with a diagnosis of PE, were followed up after discharge until death either by outpatient clinic visits or by telephone contacts in 6-month intervals. The median follow-up time available in the registry at the time of this study was 17

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months. All patients admitted to the hospital were asked whether they would give consent for the use of their medical data for research purposes, and they completed the informed consent form. The study design was approved by the hospital ethics committee of the institutional review board.

The simplified Pulmonary Embolism Severity Index (sPESI) was calculated by allocating a score of 1 to any of the following characteristics: age > 80 years, history of cancer, chronic cardiopulmonary disease, heart rate ≥ 110 beats per minute, systolic blood pressure < 100 mm Hg, and arterial oxygen saturation < 90%. A score of ≥1 was considered high.

Study patients were divided into 3 risk groups according to the guidelines of the European Society of Cardiology (ESC) on the diagnosis and management of acute PE (6). According to the ESC guidelines, patients are categorized in 4 groups: 1- low risk, 2- intermediate-low, 3- intermediate-high, and 4- high risk, based on the risk of early (in-hospital or 30-day) outcome. In the present study, because there were only 2 patients in the high risk category, we added them to the intermediate-high risk category and categorized patients into 3 risk groups: 1- low risk, 2- intermediate-low, 3- intermediate-high/high risk patients. This classification was based on 4 risk parameters: shock or hypotension, sPESI ≥ 1, right ventricular dysfunction in imaging, and cardiac biomarkers of myocardial injury or dysfunction. Right ventricular dysfunction was considered to exist if it was present on echocardiography or computed tomography angiography.

Either high-sensitivity troponin T of ≥14 pg/mL or N-terminal pro-BNP of >600 pg/mL was regarded as a positive cardiac biomarker. Red cell indices were analyzed using K_3-EDTA as an anticoagulant in a Lavender-Top Tube. RDW-SD was calculated as the width of the erythrocyte distribution curve at a relative height of 20% above the baseline. According to our automated coulter (SYSMEX KX-21N Hematology Analyzer), the lower and upper limits of the normal laboratory reference range were 11.6% and 14.6%, respectively.

2.2. Statistical analysis

The continuous variables were described through means and standard deviations (SDs) when the data were normally distributed, or medians with 25th and 75th percentiles whenever the data were not normally distributed. The normal distribution of the data was assessed through the aforementioned descriptive measures as well as histogram charts. The continuous variables were compared among the ESC risk classification groups using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test. The categorical variables were presented with frequencies and percentages and were compared between the abovementioned groups applying the chi-square or Fisher exact test, as appropriate. Survival curves were calculated using the Kaplan–Meier method and were compared between the first RDW categories applying the log-rank test. The Cox proportional hazards (PH) model was applied to evaluate the univariate effect of the variables, as well as unadjusted and adjusted effects of first RDW, on the long-term mortality, and the effects were reported through the hazards ratio (HR) with 95% confidence intervals (CIs). Those variables that were associated with long-term mortality with P-value less than 0.1 were considered as potential confounders. PH assumption was assessed through the chi-square test of the correlation coefficient between the scaled Schoenfeld residuals and the transformed survival times (P = 0.121). The method proposed by Heagerty et al. (7) was applied to find a best cut-off for the first RDW predicting long-term mortality at the median follow-up time.

IBM SPSS 23.0 for Windows (IBM Corp., Armonk, NY, USA), Stata release 13 (StataCorp LP, College Station, TX, USA), and the "survivalROC" package in R software (R Foundation for Statistical Computing, Vienna, Austria) were used to conduct the statistical analyses (8,9).

3. Results

The mean age of the study population was 60.4 ± 17.11 years. The study patients consisted of 179 (47.4%) females and 199 (52.6%) males. The most common symptom on admission was dyspnea. Overall, 59.3% of the patients had a high sPESI score and 73% had a positive cardiac biomarker. Additionally, RV dysfunction was detected in 71.4% of the patients. The mean RDW in study patients was 14.67 ± 2.13. The median follow-up duration was 17 months (95% CI: 15.4-18.5) and the all-cause mortality rate in this period was 15.6% (n = 59).

The comparison of baseline characteristics between the dead and surviving patients is depicted in Table 1. Patients in the deceased group were more likely female and older than those in the surviving group. The deceased group also had significantly more history of malignancy, oxygen saturation < 90%, sPESI score ≥ 1, atrial fibrillation rhythm, positive cardiac biomarkers, and higher mean RDW [1.194 (95% CI: 1.101-1.296)] and white blood cell count.

In the next step, the relationship between mean RDW and long-term mortality was adjusted for other confounding factors and the results are outlined in Table 2. According to Table 2, the adjusted hazard ratio for the relationship between RDW and long-term mortality was 1.109 (95% CI: 0.998-1.232). The independent association between RDW and mortality tended to be significant (P = 0.053).

In further analysis we performed a comparison between the 3 risk groups defined based on the ESC classification:

Table 1. Univariate effect of variables on long-term mortality in study patients.

		Survived	Died	HR	CI (95%)	P-value
Female		143 (44.8)	36 (61)	1.786	1.057-3.019	0.030
Age		58.81 ± 17.1	69.25 ± 14.35	1.038	1.019-1.058	<0.001
Dyspnea		279 (88)	51 (86.4)	0.966	0.455-2.053	0.929
Syncope		34 (12.3)	3 (5.4)	0.509	0.159-1.634	0.257
Chest pain		130 (48.1)	24 (43.6)	0.853	0.498-1.461	0.562
Heart rate ≥ 110 bpm		66 (34.6)	15 (35.7)	1.310	0.769-2.234	0.321
Systolic blood pressure < 100 mmHg		13 (4.1)	3 (5.1)	0.978	0.291-3.285	0.972
Respiratory rate		24.07 ± 6.3	25.12 ± 8.76	1.028	0.988-1.070	0.169
O_2Sat < 90%		55 (17.3)	17 (28.8)	2.122	1.201-3.748	0.010
sPESI ≥ 1		176 (55.2)	48 (81.4)	3.547	1.833-6.864	<0.001
Diabetes mellitus		55 (17.2)	13 (22)	1.292	0.697-2.393	0.417
Hypertension		124 (38.9)	26 (44.1)	1.241	0.742-2.076	0.411
Smoking		68 (21.3)	9 (15.3)	0.731	0.358-1.490	0.389
Chronic pulmonary disease		11 (3.4)	1 (1.7)	0.533	0.074-3.853	0.533
Immobility ≥ 3 days		82 (25.7)	22 (37.3)	1.423	0.834-2.425	0.195
Surgery within previous 4 weeks		45 (14.1)	7 (11.9)	0.705	0.317-1.567	0.391
Malignancy		11 (3.4)	8 (13.6)	2.871	1.325-6.219	0.007
Electrocardiographic findings						
	Complete RBBB	20 (6.3)	6 (10.3)	1.345	0.566-3.197	0.502
	S1Q3T3	97 (30.7)	18 (30.5)	1.104	0.633-1.928	0.727
	T inversion in precordial leads	104 (32.9)	24 (41.4)	1.516	0.897-2.564	0.121
	Atrial fibrillation	12 (3.8)	7 (12.1)	2.555	1.017-6.417	0.046
Positive cardiac biomarkers		224 (74.2)	52 (92.9)	4.509	1.625-12.512	0.004
Right ventricular dysfunction		227 (71.2)	43 (72.9)	1.393	0.761-2.550	0.283
Complete blood count findings						
	RDW (%)	14.44 ± 1.87	15.95 ± 2.93	1.194	1.101-1.296	<0.001
	WBC (per 10^3 increase)	10,690 ± 3552	11,509 ± 3888	1.070	1.010-1.130	0.032
	Hemoglobin (g/dL)	13.74 ± 2.29	13.59 ± 2.31	0.980	0.875-1.099	0.734
Mean corpuscular volume (fL)		85.56 ± 7.67	85.05 ± 7.21	0.993	0.961-1.026	0.658
Platelet count (number)		22,4083 ± 91,850	21,5261 ± 77,566	0.999	0.996-1.002	0.514

Categorical variables are presented as numbers (percent), and continuous variables are presented as mean ± standard deviation. sPESI, Simplified Pulmonary Embolism Severity Index; RBBB, right bundle branch block; RDW, red cell distribution width; WBC, white blood cells.

Table 2. Unadjusted and adjusted association between RDW and long-term mortality of patients with pulmonary embolism.

		HR	95.0% CI		P
Unadjusted					
	RDW	1.194	1.101	1.296	<0.001
Adjusted					
	RDW	1.108	0.999	1.229	0.053
	Sex	1.805	1.027	3.173	0.040
	Age	1.026	1.005	1.048	0.016
	O_2Sat < 90	1.254	0.668	2.353	0.481
	sPESI ≥ 1	2.152	0.931	4.971	0.073
	Malignancy	1.313	0.490	3.516	0.588
	Atrial fibrillation	1.377	0.586	3.238	0.463
	Positive cardiac biomarkers	2.309	0.790	6.753	0.126
	WBC (per 10^3 increase)	1.000	1.000	1.000	0.247

Proportional hazard assumption; P = 0.121.
RDW, Red cell distribution width; sPESI, Simplified Pulmonary Embolism Severity Index; WBC, white blood cells.

low, low-intermediate, and high-intermediate + high. Mortality was 3% in the low risk, 12.4% in the intermediate, and 21.9% in the high risk patients (P < 0.001). As we moved from low risk towards the higher risk categories, the mean RDW increased significantly (P = 0.037; Table 3). Similar trends of increase from low to high risk groups were also significant in the mean age and white blood cell count (Table 3).

4. Discussion

Based on the results of our study, it seems there may be an independent association between RDW at presentation and PE mortality within 17 months. To our knowledge, the present study is one of the first of its kind to evaluate the association between RDW and long-term mortality of patients with acute PE.

Previous studies reported the prognostic value of RDW at admission in the short-term follow-up of patients with PE. Zorlu et al. (5) concluded that high RDW was associated with worse short-term outcome and suggested that RDW seems to aid in risk stratification of patients with acute PE. Ozsu et al. (3) studied 702 acute PE patients and concluded that high RDW level was an independent predictor of short-term mortality. In the study by Sen

Table 3. Comparison of baseline characteristics and blood count indices in different risk groups based on the European Society of Cardiology risk classification.

	Low risk n = 33	Low-intermediate risk n = 185	High-intermediate plus high risk n = 160	P-value
Age	47.6 ± 13.65	58.9 ± 16.60	64.8 ± 16.78	<0.001
RDW† (percent)	14.14 ± 1.96	14.50 ± 2.06	14.98 ± 2.21	0.037
WBC (n/mm^3)	9770 ± 2846	10,470 ± 3123	11,437 ± 4157	0.010
Hb (g/dL)	12.98 ± 2.54	13.94 ± 2.17	13.59 ± 2.34	0.062
Platelets (n/mm^3)	256,000 (181,700, 298,000)	204,500 (160,550, 277,750)	198,500 (160,250, 259,750)	0.112

WBC: White blood cells; Hb: hemoglobin; RDW: red cell distribution width.
Data are presented as mean ± standard deviation or median (25th, 75th percentile).

et al. (4), among 208 patients with acute PE, RDW was associated with a 4.08-fold increase in PE mortality in the first 100 days. In the present study we investigated the relationship between RDW and long-term mortality in such patients and observed that after adjustment for other factors there was a trend of a significant association between RDW at admission and long-term mortality after a mean follow-up of 17 months (P = 0.053). The reason for not reaching a significant level may be the small number of deceased patients. Further studies including larger sample sizes are needed to confirm the results.

We also classified our PE patients into 3 risk groups according to the ESC guidelines. We observed that in addition to white blood cell count, RDW increased significantly as the risk of worse outcome increased. The significant correlation of RDW with the ESC risk groups suggests that increased RDW not only foresees long-term mortality but also might augment the efficiency of the baseline risk assessment of patients with confirmed PE at admission.

The pathophysiology of anisocytosis and elevated RDW levels in PE is still a matter of debate. Some evidence shows that RDW acts quite similar to well-known inflammatory markers such as leukocytosis and elevated C-reactive protein (10). Nonetheless, this seems to be an oversimplification of the role of RDW. Others have hypothesized that RDW is associated with increased prothrombotic effects of RBCs and even some genetic factors (11). Some recent studies showed that RDW increases in many acute conditions related to decreased oxygen saturation and hypoxemia, including acute hemorrhage, pneumonia, pneumothorax, and atelectasis (12). Hypoxia could augment bone marrow erythropoiesis by upregulating erythropoietin production by the kidneys, which in turn results in the release of variably sized RBCs into the circulation (12). The correlation between higher RDW and higher long-term PE mortality may reflect its direct association with the severity of PE. Patients with more severe PE experience lower oxygen saturation and poorer hemodynamics. This condition produces much more inflammatory cytokines and oxidative stress. Also, the activation of sympathetic and other neurohormonal mediators such as angiotensin II is more prevalent in severe PE. All of these mechanisms may affect the RBC formation process, which might provide some explanation for the increased RDW in high risk PE patients.

There are some limitations in the present study that need to be addressed. Although in our study RDW was shown to be independent of other factors, such as hemoglobin levels and malignancy, some probable confounders, such as iron deficiency anemia, recent treatment by iron supplements, and megaloblastic anemia, might have inadvertently affected the results; however, being an acute disease process, it seems improbable for PE mortality to be directly affected by the hemoglobin level. In addition, the PE-related inflammatory state may confound the relationship between RDW and long-term mortality (10). Further studies designed to control for these factors from the beginning of the patient selection process are suggested for a more robust confirmation of the observed association between RDW and long-term PE mortality. Additionally, the confirmation of the present association needs further assessment with a larger study group. On the other hand, this study benefits from the advantage of introducing a novel association between RDW and long-term PE mortality. Being a readily available and low-cost technique, the calculation of RDW might be an interesting test to help physicians stratify the risk category of PE patients in the emergency room and guide treatment selection of ambiguous cases.

In conclusion, in the current study, we observed evidence showing possible independent association between RDW at admission and long-term mortality in PE patients; however, further studies are necessary to confirm whether this simple, inexpensive test can be used by physicians for risk stratification in patients with acute PE.

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