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Red Blood Cell Distribution Width (RDW) and Its Effect on Survival in Patients with Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

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ABSTRACT

Red blood cell distribution width (RDW) has been reported as a predictive value of morbidity and mortality in many cardiovascular diseases. It is, however, unclear what the relationship is between RDW levels and survival in patients with PAH and CTEPH. We aimed to evaluate the RDW level in these patient groups, and to measure its relationship with mortality.

Between 2018 and 2023, 170 patients followed up in a PAH center were retrospectively evaluated. Demographic information of the patients and RDW levels at the time of diagnosis were obtained from the hospital automation system. Blood-brain natriuretic peptide (BNP) levels, functional class level (WHO-FS) and systolic pulmonary artery pressure values were recorded. Patient follow-up times and survival were recorded from the hospital automation system.

Among the patients, 53 were male (31.2%), and 117 were female (68.8%). The number of PAH patients was 116(68.2%), and the number of CTEPH patients was 54(31.7%). During this period, 24.7%(n:42) of the patients died. Statistical significance was found in RDW and BNP values when descriptive statistics were evaluated according to survival. RDW and BNP values were higher in patients who died (RDW: p=0.008, OR:1.006- BNP: p=0.021, OR:0,998). Clinical, functional class values of the patients were also positively correlated with RDW and BNP values ($p<0.002$-$p<0.001$). Patients with high functional class had poor survival (p=0.000).

In addition to known factors such as functional class level and BNP,RDW can be used as a potential biomarker for predicting survival in patients with PAH and CTEPH.

Keywords: Pulmonary Arterial Hypertension, survival, Red blood cell distribution width, chronic thromboembolic pulmonary hypertension

Introduction

Pulmonary hypertension (PH) is a progressive pulmonary vascular disease characterized by remodeling and vasoconstriction of the pulmonary arteries, resulting in elevated pulmonary arterial pressure and consequent right heart failure. Pulmonary hypertension was classified by categorizing diseases with similar physiopathological mechanisms, clinical findings, hemodynamic characteristics, and treatments under the same main headings (1). Group 1 is pulmonary arterial hypertension (PAH), a group of patients whose survival is severely affected due to permanent structural changes in the vasculature. Left heart disease is the most common cause of pulmonary hypertension and constitutes group 2. Pulmonary diseases constitute group 3, chronic thromboembolic pulmonary hypertension (CTEPH) constitutes group 4, and group 5 consists of patients with pulmonary hypertension known to be associated with multifactorial mechanisms. The vast majority of PAH patients are untreatable. Although group 1 and inoperable group 4 patients are followed up in PAH centers with vascular-specific drugs, treatment aims to improve symptoms and slow the rate of deterioration of the clinical picture. Models predicting the 1-year mortality risk are used in the follow-up of these patients. These models include hemodynamic, clinical, functional, and exercise parameters (1). The relationship between RDW

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Table 1. Frequency Distribution of Categorical Variables

	Frequency (n)	Percent (%)
Sex		
Male	53	31,2
Female	117	68,8
Etiology of pulmonary hypertension		
Group 1 (PAH)	116	68,2
GROUP 4(KTEPH)	54	31,7
Survival		
Exitus	42	24,7
Alive	128	75,3
Functional class at the time of diagnosis (WHO-FS)		
1	16	9,4
2	89	52,4
3	59	34,7
4	6	3,5
Pulmonary hypertension subgroups (Group1+Group 4)		
Idiopathic pulmonary hypertension (IPAH)	41	24,1
Collagen tissue disease	16	9,4
Congenital heart diseases	59	34,7
Chronic thromboembolic pulmonary hypertension	54	31,7

levels and cardiovascular and pulmonary diseases has been shown in many studies (2,3,4,5). Although various RDW levels have been reported in group 1 (PAH) and group 4 (CTEPH) patients with pulmonary hypertension (6,7,8), studies with a high number of patients reporting clear results have not been conducted. In this study, we planned to present the relationship of RDW values with survival and other mortality risk assessment parameters in our high number of patients as a single center.

Material and Method

Between 2018 and 2023, 170 patients followed up in a PAH center were retrospectively evaluated. Demographic information of the patients and RDW levels at the time of diagnosis were recorded from the hospital automation system (Table 1). Blood-brain natriuretic peptide (BNP) levels, functional class level (WHO-FS), which is an indicator of dyspnea, and systolic pulmonary artery pressure values, which are routinely evaluated in outpatient clinic evaluation of patients, were recorded. Patient follow-up times and survival were recorded from the hospital automation system. RDW level was a part of the complete blood count and evaluated by flow cytometric method. Patients with a history of transfusion, iron, vitamin B12, or folate deficiency, chronic renal failure, chronic obstructive or parenchymal lung disease, liver failure, and cancer were excluded.

Statistical Analysis: While descriptive statistics for continuous variables are expressed as Mean, Standard Deviation, Minimum and Maximum values, categorical variables are expressed as numbers and percentages. Indenependent t test was used to compare group means in terms of continuous variables. Kaplan-Meier and Cox regression analyses were performed to determine the effect of the variables on survival times. Statistical significance level was considered as 5%, and SPSS (ver: 21) statistical package program was used for all statistical calculations.

Results

Of the patients, 53 were male (31.2%), and 117 were female (68.8%). The number of PAH patients (Group 1) was 116 (68.2%), and the number of CTEPH patients (Group 4) was 54 (31.7%). During this period, 24.7% (n:42) of the patients died. When the descriptive statistics were

Table 2. Descriptive Statistics and Comparison Results By Survival

		N	Mean	St. Dev.	Min.	Max.	p*
Age	Living	128	56,64	17,493	21	93	0,055
	Ex	42	62,95	20,766	22	90	
sPAB	Living	128	73,30	23,096	30	130	0,066
	Ex	42	80,83	22,452	30	125	
Follow-Up Period (Month)	Living	128	65,48	118,239	12	984	0,255
	Ex	42	44,36	31,490	2	108	
	Ex	42	9,355	1,1456	6,8	11,6	
RDW	Living	128	15,448	3,1467	1,8	27,0	0,001
	Ex	42	18,710	4,5955	1,4	30,0	
BNP	Living	128	176,65	232,139	10	1800	0,005
	Ex	42	297,62	256,540	20	1040	

*: Independent t test

Table 3. Examination of Risk Factors Affecting Mortality

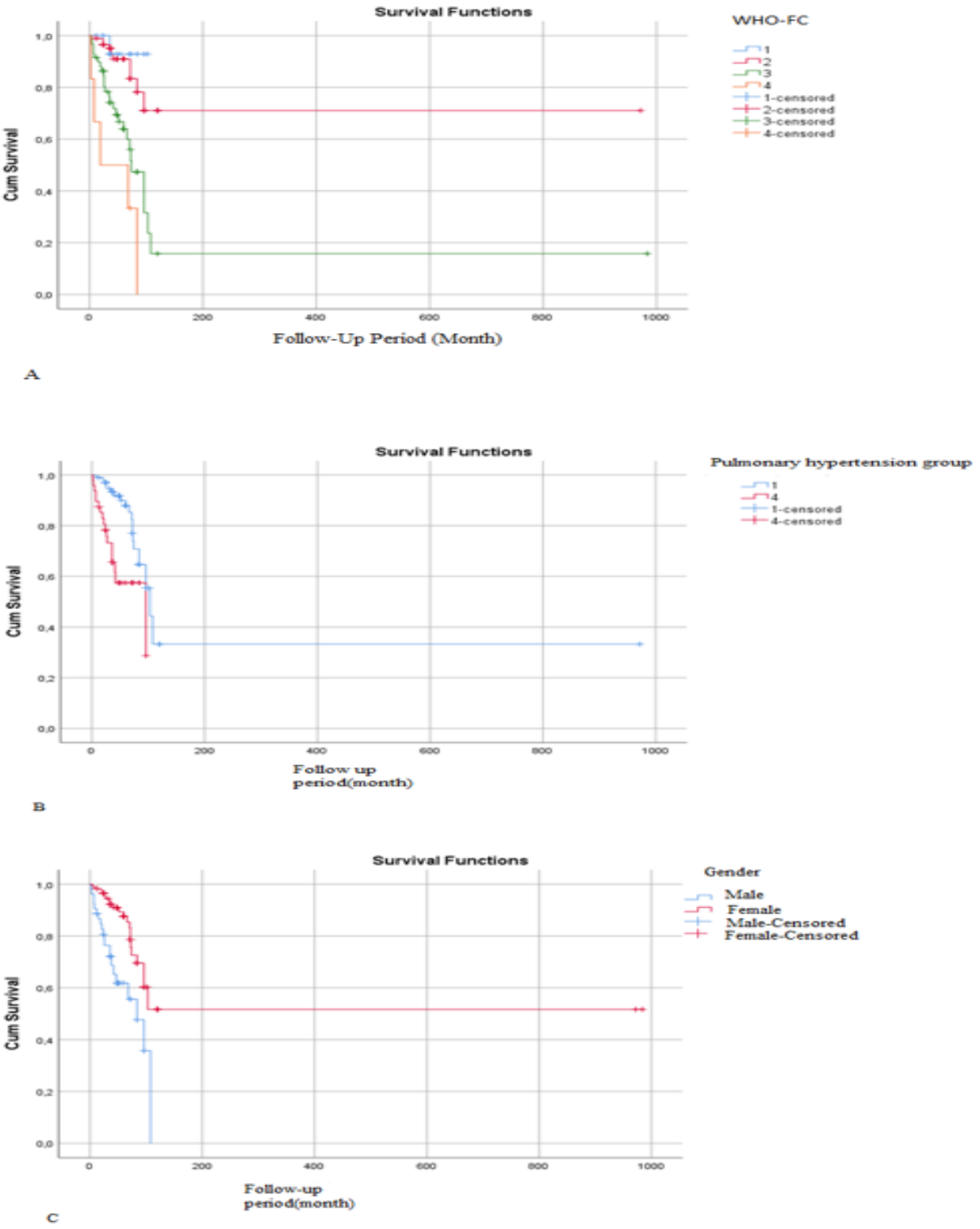
	OR (95% CI)	p
Age (years)	1,040 (1,016 – 1,066)	0,001
Gender	7,683 (3,260- 18,103)	0,001
RDW(%)	1,006 (1,038 – 1,284)	0,008
BNP (pg/mL)	0,998 (0,997 - 1,000)	0,021
Pulmonary hypertension group (Group1/Group4)	0,316 (0,139 – 0,722)	0,006

Cox regression OR:

evaluated according to survival, the difference between the living and the deceased patient groups in terms of RDW and BNP values was statistically significant, and it was observed that the RDW and BNP values of the deceased patients were higher. Furthermore, Odds ratios of RDW and BNP values ((RDW: p=0.008, OR:1.006- BNP: p=0.021, OR:0,998) were also statistically significant. Accordingly, it can be said that an increase of 1 unit in the RDW values of the patients may increase the risk of exiting 1.15 times. Similarly, it was observed that the clinical, functional class values of the patients were positively correlated (positive correlation) with RDW and BNP values (p=0.008 and p=0.021, respectively). There was no statistically significant difference between male and female patients regarding age, systolic pulmonary artery pressure, RDW, BNP, and follow-up period. According to the pulmonary hypertension group, the difference between the groups was statistically significant only in terms of age (the age of the patients in group 1 was higher), while no significant difference was found regarding other characteristics. The difference between the two groups was statistically significant in terms of RDW and BNP values according to survival (living and exited patients) (Table 2). Accordingly, RDW (p=0.001) and BNP (p=0.005) values of the dying patients were higher than those of the living patients. RDW (p=0.001) and BNP (p=0.005) values tended to increase as the functional class increased. Survival was low in male patients and patients in the 4th group (graphs 1, 2, 3). In male patients, the mortality risk was 7.6 times higher than in female patients (OR:7.68- p=0,001). Similarly, for a 1 unit increase in age (years), the mortality risk was 1.04 times higher (OR:1.04 p=0,001). For a 1-unit increase in RDW, the risk of mortality increased 1.006-fold (OR: 1.1 p=0,008), while for each unit increase in BNP, the risk of mortality increased 0.99-fold (OR: 0.998 p=0.021) (Table 3).

Discussion

In our study, a positive relationship was observed between RDW levels and mortality in patients with PAH and CTEPH, and a significant positive relationship was also found between RDW levels and other known risk factors. RDW is a parameter showing the morphology of erythrocytes and is a cheap and easily accessible test. It has been reported in many studies that it can be used as a



Graph 1. A. Kaplan Meier curve showing the relationship between functional class and survival B. Kaplan Meier curve showing the relationship between pulmonary hypertension group and survival C. Kaplan Meier curve showing the relationship between gender and survival (Log rank test)

predictor of mortality in many diseases, such as cardiovascular diseases, pulmonary diseases, cancer, sepsis, and kidney diseases (9). It has been suggested that increased RDW is associated with impaired erythropoiesis due to metabolic abnormalities such as inflammation, impaired iron metabolism, oxidative stress, renal dysfunction, malnutrition, erythrocyte fragmentation, and

impaired erythropoietin disorder (9). There is evidence of pulmonary perivascular inflammation in the early stages of pulmonary arterial hypertension and other groups of pulmonary hypertension patients. It has been shown in experimental models in PAH patients that there is a variable degree of perivascular inflammatory infiltration in the pulmonary arteries. Conditions like inflammatory status, iron metabolism disorders, and oxidative stress secondary to hypoxia (10,11,12) may increase RDW. However, the role of RDW in the detailed pathogenesis of PH and its impact on the development and prognosis of PH remains unclear.

Models predicting the 1-year mortality risk are used in the follow-up of patients with pulmonary hypertension. These models include hemodynamic, clinical, functional, and exercise parameters (1). WHO-FS, patient symptoms, clinical signs of right heart failure, syncope, 6-minute walk tests, cardiopulmonary exercise tests, echocardiography and right heart catheterization, blood BNP, NT-proBNP levels are used in monitoring (REVEAL, COMPERA)(1). Although some models have fewer parameters (1,13,14,15), all evaluations are conducted at 3-month intervals in the follow-up of PH patients. These assessments are used in treatment planning and follow-up during initial diagnosis. These risk assessment criteria were obtained from retrospective studies. ESC also admits this limitation. In our study, we planned to measure the mortality risk of patients by evaluating RDW in hemogram, which is a cheap and accessible test. We only took measurements at the initial diagnosis, which is a limitation of our study. We found that RDW value was associated with mortality risk as in Functional class and BNP values. Anna et al. showed that RDW value was associated with mortality and poor prognosis in groups 1 and 4 patients(9). In this study, unlike us, the mean RDW values obtained at the time of initial diagnosis and subsequent outpatient clinic visits were evaluated. In this study, it was observed that RDW values decreased after pah-specific treatment. In our study, the number of patients was higher, and the exclusion criteria were more clearly stated. In a meta-analysis by Jiu Liu et al., 1236 publications on pulmonary HT were analyzed (16). In this meta-analysis, retrospective studies in 7 eligible publications showed that RDW might predict a worse prognosis in PH (HR=1.27), but no evidence was obtained in prospective studies. Further analysis in this study showed that the prognostic value of RDW was affected by patient age and follow-up. Our study found no relationship between RDW and age and follow-up period. In the same meta-analysis, it was observed that there was no relationship between RDW and PH in Asia compared to Europe, and this was attributed to high altitude (17). High altitude may be a reason that increases RDW. In our study, all patients were followed up in the same center, and this did not pose a problem because all patients were evaluated as unit increase rather than cut off. Anemia may be a cause of increased RDW. Anemia is present in 40% of PD patients, and studies show that anemia is associated with mortality. (1) Although patients with anemia were not included in our study, it was a good result that RDW alone was associated with mortality. In patients with pulmonary hypertension, the inflammatory process, especially secondary to hypoxia or initiated by the cause of pulmonary hypertension, leads to increased hemotopoiesis and a subsequent increase in iron demand. Disruption of iron balance causes mitochondrial damage, increased reactive oxygen radicals, increased inflammatory processes, and contributes to increased pulmonary vascular endothelial damage (18,19). Despite these mechanistic relationships, it is not yet clear whether anemia is a consequence of pulmonary hypertension, but erythropoiesis disorders are well known. There is a need for more sensitive tests that test for erythropoiesis abnormalities in PH patients at an early stage.

Wang et al. found that increased RDW has a diagnostic value in CTEPH(20). Another study reported that RDW is an important prognostic biomarker in IPAH(21,22), indicating the severity of CTEPH and poor prognosis(23). All these results support our study.

However, one study involving only nine patients with IPAH found that baseline total bilirubin, but not RDW, was significantly associated with adverse outcomes (24). Nickel et al. found that RDW had little predictive value in IPAH patients (25). These different results may be due to differences in pathogenesis and study design. When we look at these studies, it is noteworthy that the number of patients was small, and the population was inadequate.

Limitation: The retrospective nature of the study and the lack of RDW values before and after PAH-specific treatment can be considered limitations of the study.

The study results showed that RDW could be used as a potential mortality risk assessment biomarker

in patients with PAH and inoperable CTEPH. RDW can be used to assess clinical prognosis in PH patients as a cheap and easily obtained parameter. However, large-scale prospective studies should be conducted to confirm these results.

Conflict of Interest: The author(s) declare that there is no conflict of interest.

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