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ORIGINAL ARTICLE

Red Blood Cells Distribution Width as a Potential Prognostic Biomarker in Patients With Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

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Background Red blood cells distribution width (RDW) predicts survival in cardiovascular diseases. Little is known about the variability of RDW level over time among patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). To our knowledge, RDW has never been analysed as a marker of response to specific treatment.

Materials and Methods We retrospectively analysed 77 patients for: i) RDW measured during the last hospitalisation before death or during the last follow-up (RDWlast); ii) mean RDW from all hospitalisations during the entire follow-up of the patient (RDWmean); iii) maximum RDW of all hospitalisations of each patient (RDWmax). In order to assess response to specific treatment and association with prognosis, we compared RDW levels (obtained from 56 patients) before and three to six months after introduction or intensification of treatment in both the alive and deceased group.

Results Twenty-eight of 77 patients died, whereas in specific drugs treatment response analysis, 22 of 56 patients died during follow-up. The cut-off values derived from the ROC analysis and assessed using the log-rank test were significant for RDWlast ($p < 0.0001$), RDWmean ($p < 0.001$) and RDWmax ($p = 0.02$). A decrease in RDW levels after introduction or intensification of specific treatment was significant ($p = 0.015$) in survivors, whereas there was no significance ($p = 0.29$) in decrease in RDW levels in non-survivors after change of therapy.

Conclusions Red blood cells distribution width might be a potential prognostic biomarker in patients with PAH and inoperable CTEPH. The decrease in RDW level after introduction or escalation of PAH-targeted and CTEPH-targeted drugs is associated with a good treatment response and better prognosis.

Keywords Red blood cell distribution width • Pulmonary arterial hypertension • Chronic thromboembolic pulmonary hypertension • Treatment • Prognosis

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Introduction

Q6 Red blood cells distribution width (RDW), a laboratory biomarker routinely measured in standard blood analyses, predicts survival in cardiovascular diseases, such as chronic heart failure [1], coronary artery disease [2], acute pulmonary embolism [3], and many more. In addition, RDW is associated with morbidity in a wide range of cardiovascular and pulmonary diseases: it predicts adverse clinical outcomes in patients with paroxysmal atrial fibrillation [4], acute decompensated heart failure [5], coronary artery disease [6], com-
Q7 munity-acquired pneumonia [7], and many more.

Previously, RDW has been identified as an independent prognostic marker in patients with pulmonary hypertension (PH) of mixed aetiology [8], idiopathic arterial pulmonary hypertension [9] as well as Eisenmenger syndrome [10]. However, little is still known about variability of RDW level over time among patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). In addition, to the best of our knowledge, RDW has never been analysed as a marker of a response to a specific treatment.

Therefore, we aimed to investigate the predictive value of RDW in patients with PAH and CTEPH and to examine whether the introduction or intensification of specific pulmonary hypertension treatment is associated with a decrease in RDW.

Subjects and Methods

Study Subjects

We retrospectively collected RDW results from 77 patients (70% of whom were females) with PAH and inoperable CTEPH, treated in the 1st Department of Cardiology, Poznan, Poland, between October 2008 and October 2016. The mean age was 52.15 ± 17.49 years. Forty-five per cent of the patients were diagnosed with idiopathic pulmonary arterial hypertension (IPAH), 25% with pulmonary arterial hypertension associated with congenital heart defect (PAH CHD), 16% with pulmonary arterial hypertension associated with connective tissue disease (PAH CTD), 1% with portopulmonary arterial hypertension (PAH PoP), and 13% with CTEPH. The mean pulmonary arterial pressure (PAPm) was 53 millimetres of mercury (mmHg), the mean 6-minute walking test was 305 metres and 67% of the patients were in World Health Organization Functional Class (WHO FC) III (Table 1). The median follow-up was 65 months. The primary endpoint was all-cause death. For further analysis we took RDW measurements from 56 patients of the whole cohort of 77 patients who had complete data to evaluate the response to the treatment (77% of whom were females). Blood samples to assess the RDW level were obtained at two time points: before and three to six months after introduction or intensification of specific drug treatment. The mean age of this group was 54.45 ± 15.18 years. Forty-one per cent of the patients were diagnosed with IPAH, 25% with PAH CHD, 20% with PAH CTD, 2% with PAH PoP, and 12% with CTEPH. The PAPm was 53 mmHg, the mean 6-minute walking test (6-MWT) was 303 metres and 64% of the patients were in WHO functional class III. The median follow-up was 57 months (Table 1). The secondary endpoint was response to treatment with specific drugs. The diagnosis of pulmonary hypertension was made based on right heart catheterisation (RHC). The PAH-targeted drugs were as follows: sildenafil, bosentan, ambrisentan, macitentan, treprostinil, iloprost, and the CTEPH-targeted drug was riociguat. The first-line treatment was oral monotherapy (sildenafil or bosentan in PAH CHD, and riociguat or sildenafil in CTEPH). When disease worsening occurred or a patient was in WHO functional class IV at the time of diagnosis, dual therapy was introduced (sildenafil with one of the PAH-targeted drugs mentioned above). Follow-up data were collected during scheduled visits every three to six months and during unscheduled hospitalisations due to all-cause sudden clinical worsening/deterioration. The time period of follow-up visits was

Q1 **Table 1 Patient demographics.**

Characteristics	Analysis of RDW as a prognostic marker	Analysis of RDW as a marker of response to specific treatment
Total number of patients	77	56
Gender		
F	54 (70%)	43 (77%)
M	23 (30%)	13 (23%)
Age (years)	52.15 ± 17.49	54.45 ± 15.18
Aetiology:		
IPAH	35 (45%)	23 (41%)
PAH CHD	19 (25%)	14 (25%)
PAH CTD	12 (16%)	11 (20%)
PAH PoP	1 (1%)	1 (2%)
CTEPH	10 (13%)	7 (12%)
WHO FC		
I	2 (3%)	0
II	12 (16%)	9 (16%)
III	52 (67%)	36 (64%)
IV	11 (14%)	11 (20%)
PAPm (mmHg)	53	53
6MWT (meters)	305	303

Patient age, PAPm, 6MWT are presented as mean.
Abbreviations: IPAH: idiopathic pulmonary arterial hypertension, PAH CHD pulmonary arterial hypertension associated with congestive heart defect, pulmonary arterial hypertension associated with connective tissue disease, PAH PoP: portopulmonary arterial hypertension, CTEPH: chronic thrombembolic pulmonary hypertension, WHO FC: World Health Organization Functional Class, PAPm: mean pressure in pulmonary artery, 6MWT: 6-minute walking test.

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