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Review Article

Clinical utility of red cell distribution width in pulmonary hypertension: A systematic review

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ABSTRACT

Background: Pulmonary hypertension (PH), a disease with a wide range of etiology, refers to the presence of elevated pressure in the pulmonary vasculature. Red cell distribution width (RDW), a measure of anisocytosis of red cells, has gained interest as a biomarker in various disease conditions. This study aimed to review published studies assessing the clinical utility of RDW in PH.

Methods: Restricting ourselves to publications between 2000 and 2019, we systematically searched PubMed, Medline, and Embase using pre-defined search criteria. Studies that evaluated the clinical utility of RDW including prognosis, diagnosis, response to treatment, and correlation to disease severity, in the setting of PH were included in the study.

Results: A total of 88 abstracts were found, of which 43 were reviewed, 25 full texts retrieved, and 16 studies included in the final analysis after applying exclusion criteria. There was a broad range of study designs, study types, and study populations. There was evidence supporting the use of RDW in diagnosing PH, predicting survival in PH, predicting vasodilator reactivity in PH, and measuring disease severity.

Conclusion: RDW appears to correlate with various parameters in PH. Larger studies are needed to elucidate the possible applicability of RDW in the clinical setting.

Keywords: Pulmonary hypertension, Pulmonary arterial hypertension, Chronic thromboembolic pulmonary hypertension, Red cell distribution width; biomarker

INTRODUCTION

Pulmonary hypertension (PH) is a clinical entity with a broad range of etiology and pathophysiology. The condition is evolving, as exemplified by the revision of its definition during the 6th World Symposium on PH held in 2018, and the emergence of newly approved and investigational therapies in the past few years.[1] Due to the different forms of PH, the exact prevalence of PH is unknown, but the prevalence of idiopathic and heritable PAH is about 5–15 per million adult population. A less explored aspect of PH is the area of biomarkers with diagnostic, therapeutic, and prognostic value. Although biomarkers such as brain natriuretic peptide (BNP), WHO functional class, and 6-minute walk test are valuable in PH, there remains a need for more biomarkers.[2]

Red cell distribution width (RDW) is a calculated measure of variability in the size of red blood cells (RBC) and is one of the red cell indices that are commonly reported on complete blood

counts. The normal reference range is 11.5–14.5%. An elevation beyond this range is classically associated with anemia, hemolysis, ineffective erythropoiesis, and blood transfusion. Given the role of RBC in various inflammatory diseases, there has recently been an interest in RDW as a diagnostic and prognostic marker in various conditions, including cirrhosis,[3] acute heart failure,[4] inflammatory bowel disorders,[5] and obstructive sleep apnea.[6] There have been manifold speculated mechanisms behind this phenomenon, including systemic inflammation, hypoxia-induced erythropoiesis, and nutritional deficiency. Given that the pathophysiology of PH, especially pulmonary artery hypertension (PAH), involves microvascular dysfunction and inflammation, the association of RDW with PH is a reasonable hypothesis. As such, the goal of this literature review was to systematically assess the available literature studying RDW in PH and to provide a synthesis of the data regarding the clinical utility of RDW as a potential biomarker in PH.

MATERIALS AND METHODS

Data sources and searches

We searched PubMed, Medline, and EMBASE using our predetermined MeSH terms ("RDW," "Red Cell Distribution" and "Pulmonary Hypertension," "PAH") for abstracts and titles published in English between 2000 and 2020. We also performed author and reference tracking to identify additional articles that may be relevant to the review but did not appear on our preliminary database search.

Study selection

All titles and abstracts were independently screened by two reviewers. We included observational (cohort, case-control, and cross-sectional) and interventional studies (randomized and control trials) involving humans (males and non-pregnant females) over the age of 12, published in English between January 1, 2000, and November 1, 2019. We excluded case reports, case series, review articles, editorials, *in vitro*, and animal studies. The same investigators independently reviewed full texts of selected articles to identify those that met inclusion criteria. Disagreements on inclusion were resolved by a third reviewer. Inter-rater reliability for the abstract selection process and the concurrent decision to include the article in the review were excellent (Cohen $\varkappa$ 0.86).

Data extraction and quality assessment

For each included study, investigators collected information on study design, study population, age and gender distribution, RDW values, and results. We assessed the risk of bias (ROB) using variants of the Newcastle-Ottawa scale as suitable for the study designs.[7,8] Two investigators independently rated study quality as low, moderate, or high ROB. Disagreements were resolved by consensus. Studies with a higher ROB tended to be rated that way because of small or non-representative samples or a deficiency of control for confounding factors.

Data synthesis and analysis

We performed a qualitative assessment of the included studies due to the lack of reportable effect size and wide heterogeneity of the included studies. We reported the results in terms of hazard ratios (HR), odds ratios (OR), correlation coefficients (r) with confidence intervals (CI), and P-values, as applicable, and provided a narrative synthesis of the results.

RESULTS

Study characteristics

Out of 43 reviewed abstracts, 25 were selected for a full-text review. Nine studies were subsequently excluded from the study, and a total of 16 studies were included in this review [Figure 1]. Given the high degree of variability in study populations and endpoints, a decision was made to organize studies based on the group of PH that was assessed. Ten studies involved WHO Group 1 PH [Table 1], of which four evaluated PAH in connective tissue diseases (CTD). There were three studies of PH in chronic obstructive pulmonary disease (COPD) [Table 2], and three studies assessed chronic thromboembolic PH (CTEPH) [Table 3].

Association of RDW with group 1 PH

Three studies revealed elevated RDW values in patients with the WHO Group 1 PH. Bellan *et al.* (low ROB)[9] demonstrated that patients with CTD and PH had a higher RDW compared to CTD patients without PH (14.9% vs. 13.8%, $P = 0.02$). Zhao *et al.* (low ROB)[10] demonstrated similar findings in patients with systemic sclerosis (SSc); patients with SSc and PH had higher RDW values than those without pulmonary involvement (15.7 ± 2.2% vs. 13.7 ± 1.0%, $P < 0.001$). The same study showed that among patients with SSc and interstitial lung disease, patients with PH had higher RDW than those without PH (16.3 ± 2.2% vs. 14.0 ± 1.5%, $P < 0.001$). RDW was an independent risk factor for the presence of PH in SSc patients on multivariate analysis (OR 3.314, 95% CI 1.038–10.580, $P = 0.043$). Fox *et al.* (low ROB)[11] found higher RDW measurements in PH patients compared to healthy controls (15.2% vs. 12.8%, $P < 0.0001$).

RDW for the diagnosis of group 1 PH

The diagnostic utility of RDW for PH was demonstrated in two studies; Bellan *et al.* calculated an AUC of 0.666 (95% CI 0.581–0.783, $P = 0\ 015$) on receiver operator curve (ROC)

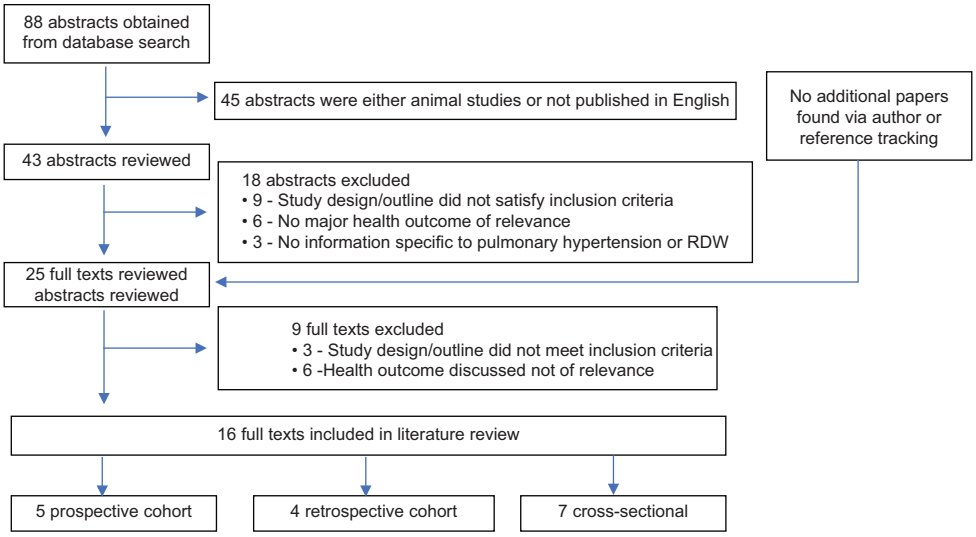

Figure 1: Flow chart representing selection of studies in the review process.

analysis of RDW as a diagnostic marker for PH.[9] A cutoff of ≥16% had a sensitivity and specificity of 40% and 88.3% for the diagnosis of PAH. For diagnosing PH in SSc patients, the AUC for RDW was 0.816 (95% CI 0.744–0.889, $P < 0.001$) in the study by Zhao *et al*., with an optimal cutoff of 14.3% (78.6% sensitive and 69.9% specific).[10]

RDW versus measures of severity and hemodynamic parameters in group 1 PH

The association between RDW and markers of disease severity commonly employed in PH, including 6-min, walk distance (6MWD), and WHO functional class (WHO FC), was found to be inconsistent. Three studies indicated a correlation between the degrees of elevation in RDW and 6MWD[9,12,13] while three did not.[10,14,15] However, there was a correlation between RDW and WHO FC in four studies.[10,12,14,16]

There was inconsistency in correlations between RDW and several hemodynamic parameters in PH. Four studies determined significant correlations with pulmonary artery pressures[9,12,13,15] while two did not.[14,16] Similarly, two studies established a significant correlation between RDW and pulmonary vascular resistance (PVR),[13,14] while three did not.[12,14,16]

RDW and survival in group 1 PH

Xi *et al*. (low ROB)[16] demonstrated a significantly worse survival rate among idiopathic PAH patients with elevated RDW, on Kaplan-Meier survival analysis (Log-rank $P = 0.007$). In patients with idiopathic PAH, Rhodes *et al*. (low ROB) calculated an AUC of 0.82 for mortality prediction, which outperformed other markers of survival, including 6MWD. An RDW cutoff of 15.7% had a sensitivity of 82.4% to predict mortality.[14]

Similar results were observed in patients with Eisenmenger syndrome (low ROB) were subjects with RDW ≥13.9% had a significantly lower survival rate than subjects with RDW < 13.9% ($P < 0.001$). In the same study, a higher RDW was found in non-survivors compared with survivors (16.9% ± 4.4% vs. 14.3% ± 2.3%, $P = 0.015$). The AUC for RDW as a predictor for survival was 0.735 ($P < 0.001$), with an optimal cutoff of 13.9%.[13]

Hui *et al*. (moderate ROB) found that elevated baseline RDW was a significant risk factor for poor overall survival and clinical outcomes (HR 1.79, 95% CI 1.14–2.80, $P = 0.012$) in patients with PH and primary Sjogren's syndrome. High RDW was associated with worse 3-year overall survival and expected overall survival than normal RDW (59.5% vs. 88.7%, log-rank test, $P = 0.015$ and 132.7 vs. 52.7 months, log-rank test, $P = 0.015$, respectively).[12] However, Li *et al*. (moderate ROB) did not find a significant difference in RDW between survivors and non-survivors in PH subjects with hereditary hemorrhagic telangiectasia ($n = 9$).[17]

In a multi-etiology PAH cohort, Smukowska-Gorynia *et al*. (moderate ROB) found that RDW was predictive of death. Survivors had a statistically significant ($P = 0.015$) decrease in RDW levels after introduction or intensification of specific treatment, while there was no statistically significant ($P = 0.29$) decrease in RDW levels in non-survivors after the change of therapy.[18]

RDW as a predictor of vasodilator reactivity

Xi *et al*. (low ROB) found that RDW had prognostic value for predicting vasodilator reactivity in PAH (OR 18.453, 95% CI 2.279–149.391, $P = 0.006$). The optimal RDW value for predicting a positive response in acute pulmonary vasodilator testing was 13.65% (AUC 0.747, 95% CI 0.632–0.861, 89.5% sensitive, and 52.7% specific).[16]

Table 1: Studies that examined RDW in Group 1 pulmonary hypertension.

Author, year	Study design	Study population	Subject age (mean±SD)	Results	Risk of Bias
Smukowska -Gorynia *et al*., 2018	Prospective cohort	77 patients with PH and inoperable CTEPH	Prognostic: 52.15±17.49; Rx response: 54.45±15.18	On Cox regression analysis, RDW predicted death: RDW last (HR 1.21; 95% CI 1.06–1.39, *P*<0.01), RDW mean (HR 1.47; 95% CI 1.19–1.82, *P*<0.001) and RDW max (HR 1.14; 95% CI 1.00–1.29, *P*=0.04) Decrease in RDW levels after introduction or intensification of specific treatment was statistically significant (*P*=0.015) in survivors, but not in non-survivors (*P*=0.29)	Low
Bellan *et al*., 2018	Cross-sectional	CTD without PH: 121; CTD with PH: 20, PH of other etiology: 59	CTD without PH: 62 (52–72); CTD with PH: 74 (69–79), PH of other etiology: 73 (64––79)	CTD patients with PH had higher RDW (14.9, 95% CI 13.5–17.2) compared to those without PAH (13.8, 95% CI 13.1–15.0) (*P*=0.02) RDW had an AUC of 0.666 (95% CI 0.581–0.783, *P*=0.015) for the diagnosis, with a cut-off value of ≥16% being 40.0% sensitive and 88.3% specific RDW directly correlated to PASP (r=0 381, *P*=0.0008)	Moderate
Li *et al*., 2019	Prospective cohort	HHT-PH: 9; IPAH: 18	HHT-PH: 33.89±10; IPAH: 32.06±9.18	HHT-PH patients had higher RDW than IPAH patients (14.88±2.93 vs. 13.19±0.83, *P*=0.031)	Low
Zhao *et al*., 2018	Cross-sectional	SSc patients; RDW <13.6%: 54; 13.6–14.6%: 39; >14.6%: 52	RDW <13.6%: 43.0 (SD 12.2); 13.6–14.6%: 44.6 (SD 11.8); >14.6%: 43.3 (SD 10.9)	SSc patients with PH had significantly higher RDW compared to SSc patients without pulmonary disease (15.7±2.2% vs. 13.7±1.0%, *P*<0.001) AUC of the RDW to indicate PAH in SSc was 0.816 (95% CI 0.744–0.889) with an optimal RDW cutoff point of 14.3% with a sensitivity and specificity of 78.6% and 69.9%	Low
Fox *et al*., 2012	Cross-sectional	PH: 40; Controls: 30	PH: 52 (CI 47–56); Controls: 41 (31–45)	PH patients were found to have higher RDW (15.2%, 95% CI 14.6–15.9) than the control group (12.8% 95% CI 12.6–13.0; *P*<0.0001)	Low
Decker *et al*., 2011	Cross-sectional	Sleep apnea PH: 4; IPAH: 19; Asthma: 14; Controls: 12	Sleep apnea PH: 57±6; IPAH: 48±3; Asthma: 40±3; Controls: 36±3	All patients with PH had significantly higher RDW than controls and asthmatics RDW was proportional to PASP on TTE (r=0.47, *P*=0.01), mPAP (r=0.51, *P*=0.01), RAP (r=0.62, *P*=0.002) and PVR (r=0.61, *P*=0.02) RDW correlated with 6MWD (r=−0.52, *P*=0.01)	Low
Yang *et al*., 2014	Retrospective cohort	Patients with Eisenmenger syndrome. Survivors: 88; Non-survivors: 21	Survivors: 32±11; Non-survivors: 28±9	RDW was shown to be significantly higher in non-survivors compared with survivors (16.9±4.4% vs. 14.3±2.3%, *P*=0.015) RDW significantly correlated with mixed venous oxygen saturation (r=−0.286, *P*=0.003), arterial oxygen saturation (r=−0.423, *P*<0.001), mPAP (r=0.271, *P*=0.004), TPR (r=0.465, *P*<0.001)	Low
Xi *et al*., 2015	Prospective cohort	Patients with IPAH. RDW ≤13.65%: 87; RDW > 13.65%: 80	RDW≤13.65%: 33±11; RDW>13.65%: 33±11	AUC for RDW predicting a positive response to acute pulmonary vasodilator reactivity testing was 0.747 (95% CI 0.632–0.861), with an optimal cutoff of 13.65% (89.5% sensitive, 52.7% specific) RDW predicted vasodilator reactivity on multivariate analysis (OR 18.453, CI 2.279–149.391, *P*=0.0006)	Low

(Contd...)

Table 1: *(Continued)*.

Author, year	Study design	Study population	Subject age (mean±SD)	Results	Risk of Bias
Rhodes *et al*., 2011	Prospective cohort	IPAH: 139; Controls: 40	IPAH: 47.6 (± 15.8); Controls: 39.7 (± 9.3)	RDW was a significant, independent prognostic factor for PH, with an AUC of 0.82 for predicting survival on ROC analysis A cutoff of 15.7% had a sensitivity of 82.4% to predict mortality. In addition, RDW correlated with WHO functional class (P<0.01) and 6MWD (r=−0.250, P=0.008)	Low
Hiu, 2019	Retrospective cohort	Patients with pSS, PH. RDW ≤15%: 33; RDW > 15%: 22	RDW ≤15%: 40.82 (SD 8.09); RDW >15%: 40.82 (SD 8.09)	Patients with RDW>15% had a significantly worse 3-year overall survival those with RDW≤15% (59.5 vs. 88.7%, log rank test, P=0.015)	Moderate

6MWD: 6-minute walk distance, AUC: Area under curve, CTD: Connective tissue disorders, CTEPH: Chronic thromboembolic pulmonary hypertension, HHT: Hereditary hemorrhagic telangiectasia, IPAH: Idiopathic pulmonary artery hypertension, mPAP: Mean pulmonary artery pressure, PASP: Pulmonary artery systolic pressure, PH: Pulmonary hypertension, pSS: Primary Sjogren's syndrome, PVR: Pulmonary vascular resistance, RAP: Right atrial pressure, RDW: Red cell distribution width, Ssc: Systemic Sclerosis

Table 2: Studies that examined RDW in PH associated with COPD.

Author, year	Study design	Study population	Subject age (mean±SD)	Results	Risk of Bias
Yang *et al*., 2019	Cross-sectional	COPD with PH: 39; COPD without PH: 174	COPD with PH: 70.95±6.36; COPD without PH: 70.95±6.82	COPD patients with PH had higher RDW than those without PH (15.10±1.72 vs. 13.70±1.03, P<0.001) RDW was an independent risk factor for PH (OR 1.521, 95% CI 1.001–2.313, P=0.050) on multivariate analysis The AUC for RDW for the diagnosis of PH was 0.749±0.054 (P<0.001) with an optimal cutoff of 14.65% (69.2% sensitive, 82.8% specific) RDW positively correlated with pulmonary artery systolic pressure (r=0.390, P=0.014), BNP (r=0.513, P=0.001)	Low
Ozgul, 2016	Cross-sectional	COPD: 175; Healthy controls: 210	COPD: 61±7.4. Healthy controls: 57.4±11	Patients with high RDW (>15.5%) were more likely to have PH (P=0.004) RDW positively correlated with the presence of PH (r=0.1, P=0.02)	Low
Seyhan, 2013	Retrospective cohort	COPD with RDW >15.5%: 108; COPD with RDW ≤15.5%: 162	COPD with RDW >15.5%: 61.8±7.2; COPD with RDW ≤15.5%: 60±7.4	Patients with high RDW (>15.5%) were more likely to have PH (61% vs. 40%, P=0.02) RDW positively correlated with PH (r=0.16, P=0.03)	Low

AUC: Area under curve, BNP: Brain natriuretic peptide, COPD: Chronic obstructive pulmonary disease, PH: Pulmonary hypertension, RDW: Red cell distribution width

RDW- and COPD-associated PH

Three studies (all with low ROB) [Table 2] examined the association between RDW and PH in the setting of COPD. A retrospective study by Yang *et al*. demonstrated a higher RDW among COPD patients with PH than those without PH (15.10 ± 1.72 vs. 13.70 ± 1.03, P < 0.001). RDW positively correlated with pulmonary artery systolic pressure (r = 0.390, P = 0.014) and BNP (r = 0.513, P = 0.001). On multivariate analysis, RDW was an independent risk factor for PH (OR 1.521, 95% CI 1.001–2.313, P = 0.050). On ROC analysis, the AUC for RDW was 0.749 ± 0.054 (P < 0.001) with an optimal cutoff of 14.65% for diagnosing PH (69.2% sensitive and 86.8% specific).[19] Ozgul *et al*. and Seyhan *et al*. found a

Table 3: Studies that examined RDW in CTEPH.

Author, year	Study design	Study population	Subject age (mean±SD)	Results	Risk of Bias
Wang *et al*., 2016	Cross-sectional	CTEPH: 56; Matched controls: 56	CTEPH: 52.79±11.38; Matched controls: 52.93±12.62	CTEPH patients had higher RDW values than healthy controls (13.82±1.14% vs. 12.75±0.49%, *P*=0.000) RDW was a significant, independent parameter for the diagnosis of CTEPH on multivariate regression analysis (HR 6.265, 95% CI 2.866–13.698, *P*=0.000) The AUC for RDW was 0.815 (95% CI 0.734–0.895, *P*=0.000) with an optimal cutoff of 13.05% (82.1% sensitive, 71.4% specific) for CTEPH diagnosis RDW positively correlated with PVR (r=0.292, *P*=0.029) and WHO functional class (r=0.450, *P*=0.001)	Low
Xi *et al*., 2014	Prospective cohort	Subjects divided into 2 groups based on RDW. RDW >15: 12; RDW ≤15: 202	RDW >15: 59±14; RDW ≤15: 61±15	Patients with elevated RDW levels had a significant increased risk for CTEPH than those without (50% vs. 6.5%, *P*=0.002) RDW had significant predictive value for CTEPH on univariate (OR, 14.417, 95% CI 3.203–64.892, *P*=0.001) and multivariate logistic regression analysis (OR 7.916, 95% CI 1.474–42.500, *P*=0.016) AUC was 0.730 for RDW (95% CI 0.622–0.839, *P*=0.002)	Low
Abul *et al*., 2014	Retrospective cohort	Pts with PE and CTEPH: 16; Pts with PE without CTEPH: 187	PE with CTEPH: 69±13; PE without CTEPH: 64±15	CTEPH patients had higher RDW at the time of diagnosis of PE than those without CTEPH (17.04+3.46%, 14.64+1.82%; *P*≤0.015); RDW was also higher in the CTEPH patients at the time of diagnosis of CTEPH during follow-up compared with the baseline RDW level of CTEPH patients at the time of initial PE diagnosis (18.63+3.58, 17.02+3.59, respectively; *P*=0.014 A multivariate regression analysis showed that RDW, hazard ratio (HR): 1.58 (95% CI: 1.09–2.30), was a predictor of CTEPH (*P*≤0.016) The AUC for RDW for the diagnosis of CTEPH was 0.735 (95% CI: 0.600–0.869), with an optimal cutoff of 14.65% being 62% specific and 75% sensitive	Low

6MWD: 6-minute walk distance, AUC: Area under curve, CTEPH: Chronic thromboembolic pulmonary hypertension, PE: Pulmonary embolism, RDW: Red cell distribution width

higher likelihood of PH in patients with high RDW (>15.5%) compared to those with non-elevated RDW (≤15.5%) (P = 0.004 and 0.02, respectively), as well as a positive correlation between RDW and PH (r = 0.1, P = 0.02 and r = 0.16, P = 0.03, respectively).[20,21]

CTEPH

There were three studies (all with low ROB) [Table 3] on RDW in Group IV PH or CTEPH. Wang *et al*. found that CTEPH patients had higher RDW values than healthy controls (13.82 ± 1.14% vs. 12.75 ± 0.49%, P = 0.000). RDW was a significant parameter for the detection of CTEPH on multivariate regression analysis (OR 6.265, 95% CI 2.866–13.698, P = 0.000). The AUC for RDW was 0.815 (95% CI 0.734–0.895, P = 0.000), with an optimal cutoff of 13.05% (82.1% sensitive and 71.4% specific). RDW correlated positively with PVR (r = 0.292, P = 0.029) and WHO functional class (r = 0.450, P = 0.001).[22] The other two studies evaluated the applicability of RDW in predicting CTEPH in patients with acute pulmonary embolism. Xi *et al*. found that patients with elevated RDW levels (>15%) at the time of PE were more likely to develop symptomatic CTEPH compared with those with normal RDW (50% vs. 6.5%, p = 0.002).[23] Abul *et al*. noted a higher RDW at the time of PE diagnosis in symptomatic CTEPH patients than in those without CTEPH (17.04 ± 3.46% vs. 14.64 ± 1.82%, P = 0.015), as well as a higher RDW at the time of diagnosis of CTEPH compared to baseline RDW at the time of PE (18.63 ± 3.58, 17.02 ± 3.59, P = 0.014). RDW was a significant

predictor of CTEPH on multivariate analysis in both studies (OR 7.916, 95% CI 1.474–42.500, $P = 0.016$ and HR 1.58, 95% CI 1.09–2.30, $P = 0.016$, respectively). AUC values for the prediction of CTEPH were 0.730 (95% CI 0.622–0.839, $P = 0.002$) and 0.735 (95% CI 0.600–0.869), with an optimal cutoff of 14.65% (75% sensitive and 62% specific) in the latter study. Elevated baseline RDW values were associated with an increased risk of all-cause death (HR 7.370, 95% CI 1.291–42.066, $P = 0.025$), with a significant difference in survival rate between patients with elevated, and those with normal RDW ($P < 0.001$).[24]

DISCUSSION

This review demonstrates that RDW correlates with various parameters of PH including diagnosis, survival, severity, and vasodilator response.

RDW is an integrative measure of ineffective erythropoiesis, subclinical hemolysis, malnutrition, systemic inflammation, oxidative stress, and renal dysfunction.[25] However, RDW is increased in relation to diagnostic, therapeutic, and prognostic parameters associated with PH. Several mechanisms can explain the association between RDW and PH. First, RDW may reflect levels of inflammatory cytokines, including tumor necrosis factor α, interleukin-1 (IL-1), and IL-6, therefore, implying that the prognostic value of RDW is tied to its relationship to the severity of chronic inflammatory states.[26] Inflammatory cytokines can affect erythropoiesis through inhibition of erythropoietin and an alteration of erythrocyte membrane deformability, contributing to anisocytosis.[22,27] An inflammatory component can be attributed to PH; one study demonstrated increased expression of C-reactive protein (CRP) receptor lectin-like oxidized low-density lipoprotein receptor-1 on cells isolated from pulmonary vasculature of CTEPH patients.[28] Several of the studies that we reviewed demonstrated a significant correlation between RDW and markers of inflammation, including erythrocyte sedimentation rate and CRP. Second, RDW reflects the development and extent of hypoxia, which is known to stimulate the secretion of erythropoietin and consequent erythrocytosis. Bellan *et al*. did find a trend, although non-significant, of higher RDW values in PAH patients with chronic respiratory failure.[9] In the study by Yang *et al*., RDW negatively correlated with mixed venous and arterial oxygen saturation.[13] Third, RDW may be an indicator of subclinical hemolysis in PAH. Fox *et al*. demonstrated a significant correlation between erythrocyte creatine (EC), a measure of hemolysis, and various measures of disease severity.[11] However, EC did not correlate with sPAP or right heart dysfunction on transthoracic echocardiogram, suggesting that subclinical hemolysis may be a modifier of disease severity independent of any effects on pulmonary vascular hemodynamics. Free hemoglobin released from hemolyzed erythrocytes promotes the depletion of nitric oxide (NO), with subsequent endothelial dysfunction, inflammation, thrombosis, vasoconstriction, and capillary smooth muscle proliferation.[11] Fourth, anisocytosis is a manifestation of functional iron deficiency. Zinc-protoporphyrin, which is formed when zinc is inserted into the protoporphyrin ring in lieu of iron in conditions of iron deficiency or defective iron metabolism, was found to be elevated in PAH patients compared to controls in the study by Decker *et al*.[15] Iron-containing proteins are important components in several processes including mitochondrial function and synthesis of NO by NO synthetases, abnormalities of which may be a component of the pathophysiology of PH.

Our review suggests a possible correlation between RDW and PH, not merely as a diagnostic marker, but also as a marker for predicting its onset in at-risk patients, response to treatment, and prognosis. Patients with PH tended to have a higher RDW, and patients with higher RDW were more likely to have PH. This held true across the various PH-WHO groups. Petrauskas *et al*. found that RDW was uniformly elevated among the various subtypes of PH, indicating that the relationship between RDW and PH might be independent of etiology.[29] RDW was found to have value as an independent diagnostic marker for PH, with a ROC ranging from 0.666 to 0.816 on AUC analysis. Similarly, Hampole *et al*. demonstrated that RDW was an independent predictor of mortality across various groups of PH.[30] There was a wide variation in the optimum cutoff RDW value for the diagnosis of PH (13.05–16%), which is perhaps reflective of the wide heterogeneity of study populations and study designs encountered. However, the elevation of RDW across all groups of PH may suggest a lack of pulmonary vascular specificity.

The correlation between RDW and various markers of disease severity, including 6MWD and WHO functional class, as well as hemodynamic parameters such as pulmonary artery pressures and PVR, was inconsistent. This discrepancy may be attributed to study heterogeneity and a lack of power to detect significant correlations.

Acute pulmonary vasodilator reactivity is an important component in the evaluation of patients with PH and has therapeutic implications. Xi *et al*. found a significant association between RDW and vasodilator reactivity that was independent of mPAP and PVR, indicating that this association might be based on non-hemodynamic mechanisms.[16] This corresponds to the findings by Grignola *et al*. who showed that patients with a positive reactivity test did not necessarily have vasodilatation as evaluated by intravascular ultrasound.[31]

RDW may also be a marker of response to treatment and prognosis. Smukowska-Gorynia *et al*. demonstrated that

patients who underwent treatment and survived (with a median follow-up period of 65 months) had a significant decrease in RDW following initiation or intensification of treatment, while those who died did not.[18] In addition, following initiation or intensification of treatment, survivors had a lower RDW than non-survivors. Kaplan-Meier survival analysis in various studies indicated significantly higher mortality in association with higher RDW.

Furthermore, RDW may predict the risk of CTEPH in patients with acute pulmonary embolism. Xi *et al*. and Abul *et al*. demonstrated that a higher RDW at the time of diagnosis of PE correlated with an increased probability of CTEPH on follow-up.[23,24] The latter study found an optimal cutoff value of 14.65% for the prediction of CTEPH. If validated, this may be valuable in risk stratification for PE patients in assessing risk for CTEPH.

Our systematic review exposed a few gaps in the body of available evidence. The elevation of RDW across different PH groups may be interpreted as a lack of specificity but could also present an opportunity for precision medicine. The 6th World Symposium revised the definition of PH to include mPAP of >20 mmHg may also change our findings since all the studies that we reviewed used the older definition of mPAP P25 mm Hg. A robust study design that incorporates the revised definition of PH and is appropriately powered would be better suited to elucidate the diagnostic and prognostic value of RDW for PH.

CONCLUSION

In summary, there may be a relationship between RDW and PH in its various forms, with consequent utility in diagnosis, prognosis, and disease monitoring, among others. Further studies are required to define the clinical utility of this relationship.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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