Association Between Red Blood Cell Distribution Width Levels and Hypertension Development in Patients with Obstructive Sleep Apnea: A Post-print

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Date: 2024-05-10T10:09:58+00:00

Abstract

Background: Hypertension and obstructive sleep apnea (OSA) frequently co-exist, and blood pressure management is challenging in such patients. The availability of reliable, objective indicators to predict the presence of comorbid hypertension and blood pressure control status in OSA patients would facilitate timely identification and enhanced management of these patients.

Objective: To explore the correlation between red blood cell distribution width (RDW) level and the occurrence of hypertension and blood pressure control status in OSA patients.

Methods: A total of 510 patients diagnosed with OSA by polysomnography at the Sleep Center of Peking University International Hospital from January 2019 to September 2022 were retrospectively enrolled. Patients enrolled from 2019 to 2021 were taken as the experimental cohort (n=370), and patients enrolled from January to September 2022 were taken as the validation cohort (n=140). Patients in the experimental cohort were divided into a hypertension group (n=211) and a non-hypertension group (n=159) according to whether they met the definition of hypertension. The hypertension group was further divided into a blood pressure control subgroup (n=107) and an uncontrolled blood pressure subgroup (n=104) based on blood pressure control levels. The clinical characteristics and laboratory test results of patients in the hypertension and non-hypertension groups, as well as the blood pressure control and uncontrolled subgroups, were analyzed. Univariate and multivariate Logistic regression analyses were used to explore the influencing factors of hypertension occurrence in OSA patients and poor blood pressure control in OSA patients with hypertension. Receiver operating characteristic (ROC) curves were plotted

to calculate the sensitivity and specificity of RDW in predicting hypertension in OSA patients, which was validated in the validation cohort.

Results: Multivariate Logistic regression analysis showed that elevated BMI (OR=1.087, 95%CI=1.007~1.174, P=0.032), comorbid diabetes (OR=3.310, 95%CI=1.484~7.380, P=0.003), and decreased RDW (OR=0.598, 95%CI=0.507~0.704, P<0.001) were independent influencing factors for hypertension occurrence in OSA patients; elevated hemoglobin (OR=1.027, 95%CI=1.005~1.050, P=0.016) and decreased RDW (OR=0.804, 95%CI=0.669~0.965, P=0.019) were independent influencing factors for poor blood pressure control in OSA patients with hypertension. ROC curve analysis of the experimental cohort for RDW predicting hypertension in OSA patients showed that the area under the ROC curve was 0.779 (95%CI=0.732~0.826, P<0.001), with an optimal cutoff value of 39.9 fL. Considering clinical usability, with RDW $\leq$ 40 fL as the threshold, the sensitivity and specificity for predicting hypertension in OSA patients were 70.14% and 81.76%, respectively. In the validation cohort, with RDW $\leq$ 40 fL as the threshold, decreased RDW predicted hypertension in OSA patients with a sensitivity of 63.64% and specificity of 80.95%, and the area under the ROC curve was 0.757 (95%CI=0.678~0.835, P<0.001).

Conclusion: Decreased RDW is associated with hypertension occurrence and poor blood pressure control in OSA patients, and OSA patients with decreased RDW have a higher risk of developing hypertension.

Full Text

The Correlation between Red Blood Cell Distribution Width Level and Hypertension in Patients with Obstructive Sleep Apnea

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Abstract

Background Hypertension and obstructive sleep apnea (OSA) often coexist, posing challenges in the management of blood pressure in these patients. A reliable and objective predictor is needed to anticipate the occurrence of hypertension and assess the status of blood pressure control in OSA patients, which would facilitate their blood pressure management.

Objective To explore the correlation between red blood cell distribution width (RDW) and hypertension in patients with OSA.

Methods A retrospective study was conducted at the Sleep Center of Peking University International Hospital, involving 510 patients who were diagnosed with OSA using polysomnography between January 2019 and September 2022. The derivation cohort comprised 370 enrolled patients between January 2019 and December 2021, while the validation cohort included the remaining 140 patients enrolled between January and September 2022. Within the derivation cohort, patients were categorized into two groups based on their adherence to the definition of hypertension: hypertension group (n=211) and non-hypertension group (n=159). Subsequently, the hypertension group was further divided into two subgroups: blood pressure control subgroup (n=107) and blood pressure uncontrolled subgroup (n=104). The clinical characteristics and laboratory examination results of patients in the hypertension group and non-hypertension group, as well as those in the blood pressure control subgroup and blood pressure uncontrolled subgroup, were analyzed. Univariate and multivariate Logistic regression analyses were employed to investigate the predictors of hypertension in OSA patients and the status of blood pressure control in OSA patients with combined hypertension. The receiver operating characteristic (ROC) curve was plotted to evaluate the sensitivity and specificity of RDW in predicting the occurrence of hypertension among OSA patients, with its validity confirmed in the validation cohort.

Results The multivariate Logistic regression analysis revealed that an increased BMI (OR=1.087, 95%CI=1.007-1.174, P=0.032), diabetes (OR=3.310, 95%CI=1.484-7.380, P=0.003), and a decreased RDW (OR=0.598, 95%CI=0.507-0.704, P<0.001) were independent predictors of hypertension in OSA patients. Furthermore, an increased hemoglobin level (OR=1.027, 95%CI=1.005-1.050, P=0.016) and a decreased RDW (OR=0.804, 95%CI=0.669-0.965, P=0.019) were identified as independent predictors of poor blood pressure control status in OSA patients with combined hypertension. The results of ROC curve analysis for RDW in predicting hypertension in OSA patients showed that the area under the ROC curve was 0.779 (95%CI=0.732-0.826, P<0.001), with an optimal cut-off value identified at 39.9 fL. Considering the clinical usability, when using an RDW $\leq$ 40 fL as the threshold value, the sensitivity and specificity for predicting hypertension in OSA patients were 70.14% and 81.76%, respectively. The validation cohort, utilizing an RDW cutoff value of $\leq$ 40 fL, demonstrated that RDW predicted hypertension in OSA patients with a sensitivity of 63.64% and a specificity of 80.95%. The area under the ROC curve was 0.757 (95%CI=0.678-0.835, P<0.001).

Conclusion The reduction of RDW is associated with the occurrence of hypertension and poor blood pressure control status in patients with OSA. OSA patients exhibiting decreased RDW level are at an elevated risk for hypertension.

Keywords Sleep apnea, obstructive; Hypertension; Red cell distribution width; Forecast; Correlation

Obstructive sleep apnea (OSA) is a clinical syndrome characterized by recurrent upper airway obstruction during sleep. Epidemiological studies abroad have shown that the incidence of OSA in adults exceeds 4%[1]. Data from Shanghai in the early 2000s indicated that the prevalence of OSA was estimated at 3.62%, and with the increasing number of overweight and obese individuals, its prevalence continues to rise globally, becoming a significant public health concern[2]. Hypertension and OSA often coexist—50% of OSA patients have concurrent hypertension, and 30% of hypertensive patients have OSA[3]. When hypertension is combined with OSA, antihypertensive medications often fail to achieve ideal efficacy, making blood pressure management more challenging for these patients[4]. Clinically, the diagnosis and management of hypertension primarily rely on blood pressure measurements, but measurement accuracy can be affected by equipment precision and patient technique, while variations in patient compliance may lead to delayed diagnosis and ineffective control. Uncontrolled hypertension significantly increases the risk of cardiovascular, cerebrovascular, and renal diseases[5-6]. If reliable and objective biomarkers could predict hypertension occurrence and blood pressure control status in OSA patients, clinicians could identify these patients early and intensify management, thereby more effectively reducing related complications.

Red blood cell distribution width (RDW) is a common, inexpensive, and readily available laboratory parameter that quantitatively measures the variability in circulating red blood cell size, reflecting the heterogeneity of red blood cell volume (commonly known as anisocytosis). RDW is measured by automated hematology analyzers as part of the complete blood count. Traditionally, RDW has been used in hematology for the differential diagnosis of anemia, often in combination with mean corpuscular volume (MCV), with elevated RDW commonly seen in erythropoietic disorders (such as iron deficiency, folate deficiency, and hemoglobinopathies) and increased red blood cell destruction (such as hemolysis). Increasing research indicates that abnormal RDW is common in other diseases, including cardiovascular disease, pulmonary hypertension, cancer, community-acquired pneumonia, chronic obstructive pulmonary disease, liver and kidney failure, and other chronic conditions[7]. Some studies have found that RDW is elevated in OSA patients compared to healthy populations, and in severe OSA patients, elevated RDW is associated with increased hypertension risk[8]. Mansoori et al.[9] found that elevated RDW was associated with hypertension occurrence in women and elderly individuals. However, a Sudanese study found no association between RDW and hypertension[10]. Whether RDW level correlates with hypertension occurrence and blood pressure control status in OSA patients remains unclear. This study aims to explore the correlation between RDW level and hypertension occurrence and blood pressure control status in OSA patients.

1. Methods

1.1 Study Population and Inclusion/Exclusion Criteria

The study population consisted of patients aged 18-65 years who visited the Sleep Center of Peking University International Hospital between January 2019 and September 2022 and were diagnosed with OSA through overnight polysomnography (PSG). Patients enrolled between 2019-2021 served as the derivation cohort to evaluate the predictive value of RDW for hypertension and blood pressure control status in OSA patients, while those enrolled between January-September 2022 served as the validation cohort to verify conclusions from the derivation cohort. Inclusion criteria were: (1) age 18-65 years, regardless of gender; (2) no previous sleep breathing monitoring or treatment for OSA. Exclusion criteria were: (1) severe cardiopulmonary disease, such as severe heart failure [NYHA class III-IV], atrial fibrillation, myocardial infarction within 3 months, chronic obstructive pulmonary disease, cor pulmonale, pulmonary embolism within 3 months; (2) chronic liver or kidney disease, such as hepatic insufficiency, chronic viral hepatitis, glomerulonephritis, nephrotic syndrome, renal insufficiency; (3) autoimmune disease; (4) anemia; (5) malignancy; (6) infectious disease; (7) patients undergoing continuous positive airway pressure or oxygen titration during their first PSG. This was a retrospective study, and all patient data were kept strictly confidential.

1.2 Data Collection and Measurement Methods

1.2.1 General Data Collection Demographic and clinical data were obtained from electronic medical records, including gender, date of birth, height, weight, age at PSG, smoking history, alcohol consumption history, comorbidities, complete blood count (CBC), serum biochemical tests (creatinine, uric acid, homocysteine, C-reactive protein, blood lipids), and PSG results. Blood pressure before sleep and upon morning awakening during PSG recording were documented, and patient medical history and medication history were verified.

1.2.2 Sleep Monitoring Methods All patients underwent PSG at the Sleep Center (Sandman Elite, Natus Medical Incorporated; Alice6, Philips Respironics). Patients could sleep in any comfortable position without discontinuing long-term medications. PSG signals were recorded according to the American Academy of Sleep Medicine (AASM) recommended methods, including electroencephalography (F3M2, F4M1, C3M2, C4M1, O1M2, O2M1), bilateral electrooculography, submental electromyography, oronasal thermal signals, nasal pressure airflow, thoracoabdominal respiratory movements, electrocardiography, snoring sounds, body position, bilateral anterior tibialis electromyography, pulse oximetry, and heart rate. All sleep study data were manually scored by internationally registered polysomnographic technologists using AASM scoring criteria[11]. Total sleep time in PSG was calculated through electroencephalographic signal analysis. The apnea and hypopnea index (AHI) and oxygen desaturation index (ODI) were calculated based on total sleep time. OSA was diagnosed at

AHI ≥ 5 events/hour, with moderate and severe OSA defined as AHI ≥ 15 and ≥ 30 events/hour, respectively.

1.2.3 Blood Pressure Measurement Methods Blood pressure was measured at two time points: at night before PSG recording (20:00-21:00) and in the morning after PSG recording (6:00-7:00). Measurements were taken in the supine position after at least 10 minutes of rest using an electronic sphygmomanometer (Omron, HEM-7136) with an accuracy of $\pm 3 mmHg, which was calibrated monthly against a mercury sphygmomanometer by staff. Nighttime and morning 2×$DBP)/3. The patient' s average SBP, average DBP, and average MAP were calculated as (nighttime blood pressure + morning blood pressure)/2 to determine blood pressure status.

Hypertension was diagnosed by either: (1) average DBP ≥ 90 mmHg and/or average SBP ≥ 140 mmHg (1 mmHg = 0.133 kPa)[12]; or (2) prior diagnosis of hypertension by a cardiology specialist with current regular antihypertensive medication use. Patients meeting either criterion were classified into the hypertension group, while those meeting neither criterion were classified into the non-hypertension group. Based on measured average blood pressure values, hypertensive patients were further divided into uncontrolled blood pressure subgroup (average DBP ≥ 90 mmHg and/or average SBP ≥ 140 mmHg) and controlled blood pressure subgroup (average DBP < 90 mmHg and average SBP < 140 mmHg).

1.2.4 CBC Parameters CBC parameters included white blood cells, neutrophils, lymphocytes, eosinophils, platelets, MCV, and RDW, which were measured using the Coulter LH analyzer.

1.3 Statistical Methods

Statistical analysis was performed using SPSS 22.0 software. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using Mann-Whitney U test. Categorical variables were analyzed using chi-square test. Univariate and multivariate Logistic regression analyses were used to explore influencing factors for hypertension occurrence in OSA patients and poor blood pressure control in OSA patients with hypertension. ROC curve of RDW predicting hypertension in OSA patients was plotted. $P < 0.05$ was considered statistically significant.

2. Results

2.1 General Data

During the study period, 632 OSA patients visited the Sleep Center, of which 122 were excluded due to severe cardiopulmonary disease, anemia, autoimmune

disease, malignancy, infectious disease, or missing data, leaving 510 patients included. The average age of enrolled OSA patients was (48.0 ± 11.9) years; 123 were female (24.1%); 288 met hypertension diagnostic criteria (56.5%). Among OSA patients with hypertension, 49.7% (143/288) had uncontrolled blood pressure. Three hundred seventy patients enrolled between 2019-2021 served as the derivation cohort, and 140 patients enrolled between January-September 2022 served as the validation cohort. The study flow chart is shown in [Figure 1: see original paper].

2.2 Clinical Characteristics and Laboratory Findings in the Derivation Cohort

In the derivation cohort, patients were divided into hypertension group (n=211) and non-hypertension group (n=159) based on hypertension definition. There were no statistically significant differences between groups in age, gender, smoking history, or alcohol consumption ($P > 0.05$). However, BMI, hyperlipidemia, coronary heart disease, diabetes, SBP, DBP, and MAP were all significantly higher in the hypertension group than in the non-hypertension group ($P < 0.05$), as shown in Table 1 .

There were no significant differences between groups in white blood cell count, lymphocyte count, monocyte count, platelet count, creatinine, uric acid, lactate dehydrogenase, total cholesterol, total sleep time, sleep latency, REM latency, sleep efficiency, N1, N2, N3, REM, NREM-AHI, arousal index, or mean heart rate ($P > 0.05$). The hypertension group had significantly higher neutrophil count, hemoglobin, high-sensitivity C-reactive protein, total triglycerides, homocysteine, AHI, REM-AHI, ODI3, and time with SpO2 < 90% compared to the non-hypertension group ($P < 0.05$). Meanwhile, mean corpuscular volume, red blood cell distribution width, mean SpO2, and minimum SpO2 were significantly lower in the hypertension group ($P < 0.05$), as shown in Table 2 .

2.3 Risk Factors for Hypertension in OSA Patients

Variables showing statistical differences between hypertension and non-hypertension groups in Tables 1 and 2 were initially evaluated using univariate Logistic regression analysis (Table 3). Multivariate Logistic regression model was further applied to variables associated with hypertension in OSA patients from univariate analysis. The results showed that increased BMI (OR=1.087, 95%CI=1.007-1.174, P=0.032), diabetes (OR=3.310, 95%CI=1.484-7.380, P=0.003), and decreased RDW (OR=0.598, 95%CI=0.507-0.704, P<0.001) were independent predictors of hypertension in OSA patients.

2.4 Risk Factors for Poor Blood Pressure Control in OSA Patients with Hypertension

In the hypertension subgroup of the derivation cohort, there were 107 patients in the controlled blood pressure subgroup and 104 in the uncontrolled blood

pressure subgroup. There were no significant differences between subgroups in age, gender, smoking history, alcohol consumption, diabetes, coronary heart disease, or hyperlipidemia ($P > 0.05$). However, BMI, hemoglobin, and high-sensitivity C-reactive protein were significantly higher in the uncontrolled subgroup, while MCV and RDW were significantly lower compared to the controlled subgroup ($P < 0.05$), as shown in Table 4 . Further univariate and multivariate Logistic regression analyses revealed that increased hemoglobin (OR=1.027, 95%CI=1.005-1.050, P=0.016) and decreased RDW (OR=0.804, 95%CI=0.669-0.965, P=0.019) were independent predictors of poor blood pressure control in OSA patients with hypertension.

2.5 Predictive Value of Decreased RDW for Hypertension in OSA Patients

The ROC curve of RDW predicting hypertension in OSA patients showed an area under the curve of 0.779 (95%CI=0.732-0.826, P<0.001) (Figure 2 [Figure 2: see original paper]), with an optimal cutoff value of 39.9 fL. Considering clinical practicality, using the lower limit of normal RDW value of 40 fL as the threshold, the sensitivity and specificity for predicting hypertension in OSA patients were 70.14% and 81.76%, respectively.

2.6 Validation of Predictive Value of Decreased RDW

There were no statistically significant differences in clinical characteristics or laboratory findings between the validation cohort and derivation cohort ($P > 0.05$), as shown in Table 5 . Using RDW $\leq$ 40 fL as the cutoff value, the sensitivity, specificity, and area under the ROC curve for decreased RDW predicting hypertension in OSA patients in the validation cohort were 63.64%, 80.95%, and 0.757 (95%CI=0.678-0.835, P<0.001), respectively, as shown in Figure 3 [Figure 3: see original paper] and Table 6 .

3. Discussion

Hypertension is one of the common risk factors for chronic cardiovascular and cerebrovascular diseases, affecting approximately 31% of the global population[13]. Recent studies have found a close association between OSA and hypertension, with OSA prevalence reaching 70%-85% in patients with resistant hypertension[14]. The 2017 hypertension guidelines formally defined OSA-induced secondary hypertension and recommended OSA screening for patients with resistant hypertension[15]. The Wisconsin Sleep Cohort Study demonstrated a strong dose-response relationship between OSA and hypertension, estimating that mild OSA patients have twice the risk of developing hypertension compared to normal populations, while moderate-to-severe OSA patients have three times the risk[16]. The pathophysiological link between OSA and hypertension is complex. Current understanding suggests that recurrent upper airway obstruction during sleep in OSA patients causes varying degrees of SpO2 de-

saturation, and intermittent hypoxic stimulation triggers hypertension through complex pathophysiological mechanisms including oxidative stress, autonomic nervous dysfunction, systemic chronic inflammation, and endothelial dysfunction[2], with multiple shared predisposing factors promoting their co-occurrence. In this study, 288 of 510 OSA patients had concurrent hypertension, a prevalence of 56.5%, consistent with other epidemiological findings[3], and nearly 50% of these hypertensive patients had inadequately controlled blood pressure. Using objective laboratory results to predict hypertension occurrence and control status in OSA patients could enable adequate screening and early intervention, reducing adverse outcomes.

This study found that decreased RDW was an independent risk factor for hypertension and poor blood pressure control in OSA patients, suggesting that decreased RDW is associated with hypertension occurrence and poor control in OSA patients. During sleep, OSA patients experience recurrent intermittent hypoxemia due to upper airway obstruction. Hypoxia stimulates hypoxia-inducible factors to promote erythropoietin (EPO) production and secretion in renal and hepatic cells to cope with tissue hypoxia. On one hand, EPO binds to EPO receptors on vascular endothelial and smooth muscle cells, causing vasoconstriction and increased renal vascular resistance, leading to elevated blood pressure[17]; on the other hand, EPO enhances erythropoiesis by regulating iron metabolism and promotes splenic macrophage clearance of senescent red blood cells. This may explain why hemoglobin was higher in the hypertension group in this study. Vega et al.[18] found in pregnant women that EPO gradually increased and RDW gradually decreased during the second and third trimesters. Alparslan et al.[19] suggested in a study of 2,771 COPD patients that decreased RDW was associated with severity of acute exacerbations. Additionally, Sokucu et al.[20] found that RDW showed an increasing trend after 6 months of CPAP treatment in 36 severe OSA patients. These studies indicate that decreased RDW is associated with hypoxia and elevated EPO, while RDW increases after correction of hypoxia in OSA patients. However, other research suggests RDW is higher in OSA patients with hypertension than in those with OSA alone[21], which is inconsistent with our findings and may be related to sample size and age factors, requiring further prospective validation.

Multivariate Logistic regression analysis in this study also showed that increased BMI and diabetes were independent risk factors for hypertension in OSA patients. Epidemiological surveys have shown that BMI positively correlates with the severity of OSA-associated hypertension[22]. Palma et al.[23] demonstrated that in obesity, adipocytes secrete increased pro-inflammatory factors (such as interleukin-6), which aggravate OSA progression; meanwhile, adipocytes actively produce angiotensinogen and aldosterone, promoting hypertension development. Additionally, studies have shown increased incidence of diabetes and diabetic complications in OSA patients[24], often manifested through shared risk factors such as obesity and hypertension[25-26]. In metabolic syndrome patients, OSA is independently associated with increased levels of inflammatory markers and arterial stiffness markers, suggesting that OSA, diabetes, and

obesity collectively increase cardiovascular disease risk[27]. Furthermore, OSA, hypertension, and diabetes share certain genetic associations, with the tumor necrosis factor G308A gene confirmed as a common susceptibility gene for OSA, hypertension, and diabetes[28]. This indicates that hypertension, obesity, and diabetes share common predisposing factors and may have underlying mechanisms that mutually promote each other' s development, with these risks being more pronounced in OSA patients. This study found that increased BMI and diabetes were no longer independent risk factors for poor blood pressure control, supporting the existence of common predisposing factors and mutual promotion mechanisms among hypertension, obesity, and diabetes.

This study also found no statistical difference in area under the ROC curve between validation and derivation cohorts for decreased RDW predicting hypertension in OSA patients. Therefore, this study suggests that decreased RDW can predict hypertension occurrence in OSA patients.

This study has several limitations. First, it is a retrospective, single-center study, and results may be confounded by unmeasured variables. Second, the lack of patient EPO levels and iron metabolism parameters limits interpretation of findings. Finally, all OSA patients were from a sleep center population with often severe OSA and multiple comorbidities; whether these findings apply to all OSA populations requires further large-scale validation. However, RDW is clinically convenient and readily available, and more aggressive hypertension screening and management for OSA patients with abnormally decreased RDW would not add substantial clinical burden. Therefore, this study has practical clinical significance. Future research will explore the relationship between decreased RDW and EPO, iron metabolism, and erythropoiesis to clarify the specific mechanisms of decreased RDW in OSA patients with hypertension.

In conclusion, decreased RDW is associated with hypertension occurrence and poor blood pressure control in OSA patients, with decreased RDW indicating higher risk. Enhanced hypertension screening and management should be considered for these patients.

Author Contributions: Chang Yuan was responsible for manuscript writing; Gao Yinghui and Zhang Wei were responsible for data collection and processing; Liu Shuang and Han Fang jointly formulated the overall research objectives and revised the manuscript.

Conflict of Interest: None declared.

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Received: November 12, 2023; Revised: March 23, 2024
Edited by: Jia Mengmeng

Note: Figure translations are in progress. See original paper for figures.