Is obstructive sleep apnea associated with erythrocytosis? A systematic review and meta-analysis

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Abstract

Objective: The aim of this systematic review and meta-analysis was to investigate the association between obstructive sleep apnea (OSA) and erythrocytosis.

Methods: The PubMed, Web of Science, and Cochrane Library databases were searched for articles examining hematocrit values in patients with OSA and control individuals published till September 1, 2021. The pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated, and subgroup analyses were performed.

Results: Eleven eligible studies with a total of 4608 patients with OSA were included in this meta-analysis. Pooled outcomes revealed that hematocrit values were significantly higher in patients with OSA than in controls (SMD, 0.19; 95% CI, 0.08–0.29; p < .01). When studies were stratified by disease severity, the significant differences in hematocrit values between patients and controls were only observed in the severe OSA group (SMD, 0.34; 95% CI, 0.08–0.59; p < .01), but not in the mild and moderate OSA groups. In subgroup analyses according to sex and publication year, significant differences in hematocrit values between patients and controls remained stable in studies with only female patients (SMD, 0.25; 95% CI, 0.12–0.38; p < .01) and in studies published after 2012 (SMD, 0.17; 95% CI, 0.06–0.28, p < .01).

Conclusion: Our meta-analysis revealed that the hematocrit value was significantly increased in patients with OSA, particularly in severe patients, compared with that in controls. However, the elevation was modest, and the hematocrit value is expected to be within the normal range in patients with OSA. These data suggest that OSA leads to slight increases in hematocrit but does not cause clinically significant erythrocytosis.

Keywords
erthrocytosis, hematocrit, obstructive sleep apnea, polycythemia, sleep apnea
1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, causing intermittent hypoxia. The prevalence of OSA in the general population is reported to be 3%–9%, and OSA is a serious health problem associated with various types of morbidities and mortalities, such as cardiovascular and cerebrovascular diseases. Intermittent hypoxia during OSA is largely responsible for oxidative stress, which in turn promotes sympathetic activation and inflammation, leading to endothelial dysfunction, hypertension, and atherosclerosis. However, the exact hematological consequences of OSA and the underlying pathophysiological mechanisms are not fully understood.

Erythrocytosis is characterized by an increase in red cell mass and is classified as primary if there is a defect in the erythroid compartment of the bone marrow or secondary when it occurs due to other erythropoiesis-stimulating factors. Absolute erythrocytosis is defined as a red cell mass > 125% of that predicted according to sex and body mass. Generally, erythrocytosis is suspected when the hematocrit is > 0.52 in men or > 0.48 in women. Chronic hypoxemia caused by a variety of conditions, including cyanotic heart disease, chronic lung disease, and smoking, is a well-described etiology for secondary erythrocytosis. Hypoxemia is a potent stimulus for the release of erythropoietin (EPO), resulting in increased red blood cell production in the bone marrow.

In the work-up for the diagnosis of secondary erythrocytosis, previous guidelines recommend an evaluation for OSA. However, the association between OSA and clinically significant erythrocytosis has not been fully established. Although several studies have investigated the relationship between OSA and secondary erythrocytosis, the results are inconsistent and controversial. Some studies found a significantly increased hematocrit value in patients with OSA compared to that in the control group, whereas others did not.

This discrepancy may be due to several factors, such as the statistical power of the study and differences in the composition of the study populations. In the present study, we aimed to investigate whether patients with OSA are associated with clinically significant erythrocytosis. Therefore, we conducted a systematic review and meta-analysis to examine the difference in hematocrit values between patients with OSA and individuals without OSA.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This study was reported following guidelines of the preferred reporting items for systematic reviews and meta-analyses guidelines. A systematic search for studies published up to September 1, 2021 was conducted in the PubMed, Web of science, and Cochrane library databases using the following MeSH terms and keywords: “sleep apnea syndromes,” “obstructive sleep apnea,” “sleep apnea,” “sleep apnoea,” “erythrocytosis”, “hematocrit”, “polycythemia”, and “polycythaemia.” The full search strategy is presented in Table S1.

2.2 | Eligibility criteria, study selection, and quality assessment

The population, intervention, comparator, outcome, and study design (PICOS) approaches were utilized to define study eligibility. (1) P: adult patients with OSA (determined by sleep study); (2) I: assessment of hematocrit; (3) C: control individuals without OSA; (4) O: the hematocrit value; and (5) S: randomized controlled trials or observational studies including cross-sectional studies, cohort studies, case-control studies, or case series. In addition, articles were eligible if they were written in English and full-text publications.

Abstracts of retrieved studies were screened independently by two investigators to examine the relevance of the studies. If relevant, two authors independently reviewed the full articles. The references of the retrieved articles were searched to identify additional studies. Any disagreement between the reviewers was resolved by a third investigator.

The quality of each study was assessed using the modified Newcastle-Ottawa scale (NOS), with a maximum of seven points for observational studies based on the following components: patient selection, comparability, and outcome. Two researchers independently evaluated the quality of each study. Disagreements between the researchers were resolved through consensus. Studies with five or more stars were considered high-quality studies.

2.3 | Data extraction

The following information was extracted from the included studies: authors, publication year, study design, geographic location of studies, number of study subjects, age, sex composition of the cohort, mean body mass index (BMI), OSA severity, and hematocrit value. OSA severity was determined by the apnea hypopnea index (AHI) or respiratory disturbance index (RDI): mild [5 ≤ AHI (RDI) < 15], moderate [15 ≤ AHI (RDI) < 30], and severe [30 ≤ AHI (RDI)].

2.4 | Statistical analysis

A meta-analysis of the included studies was performed using R 4.1.1 version statistical software (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). The difference in hematocrit values between patients with OSA and controls was assessed using the standardized mean difference (SMD). For interpreting the effect size calculated by SMD, we used the benchmark values suggested by Cohen (0.2, small effect; 0.5, medium effect; 0.8, large effect). Significance was set at p < .05. Heterogeneity between the included studies was calculated using the I2 test: I2 > 50% indicated significant heterogeneity across studies. In these cases, a random-effects model was used to generate pooled outcomes. In contrast,
studies that did not present a significant value of heterogeneity ($I^2 < 50$) were analyzed using the fixed-effects model. Subgroup analysis was performed to evaluate the impact of disease severity, sex, and publication year of the studies on the outcomes. In addition, we conducted a meta-regression analysis to identify possible sources of heterogeneity. Funnel plots and Egger’s test were used to detect publication bias. Sensitivity analyses were performed to estimate the influence of each study on the overall results.

3 | RESULTS

3.1 | Literature search and study characteristics

The database search retrieved a total of 459 articles, of which 88 articles were excluded due to duplication. After title and abstract screening, we excluded 320 articles and assessed the full texts of 51 articles. In addition, two articles from the reference lists of retrieved articles were assessed. Finally, 11 articles with a total of 4608 patients with OSA and 1484 individuals without OSA were included in the meta-analysis. A flowchart of the study selection process is shown in Figure 1.

The publication year of the included studies ranged from 1994 to 2021. All included studies were hospital-based cross-sectional studies. Among the 11 studies, six divided patients with OSA into subgroups according to disease severity, sex, and both severity and sex, respectively. The characteristics of the included studies and patient data from the included studies are presented in Tables 1 and 2, respectively. Table 3 presents the quality assessment of the included studies. The NOS scores of all the included studies were 6, indicating that all studies were high-quality.

### TABLE 1 Summary of included studies

| Study           | Year | Country | Study design | OSA assessment | Inclusion criteria                      |
|-----------------|------|---------|--------------|----------------|-----------------------------------------|
| Hoffstein et al.| 1994 | Canada  | Cross-sectional | PSG            | 10 < AHI                                |
| Choi et al.     | 2006 | USA     | Cross-sectional | PSG            | 5 ≤ RDI                                 |
| Dikmenoglu et al.| 2006 | Turkey  | Cross-sectional | PSG            | 30 < AHI                                |
| Sinnapah et al. | 2015 | France  | Cross-sectional | PSG and type 3 sleep study | 5 ≤ AHI                                |
| Nguyen et al.   | 2017 | USA     | Cross-sectional | PSG or type 3 sleep study | 5 ≤ AHI                                |
| Fan et al.      | 2018 | China   | Cross-sectional | PSG            | 5 ≤ AHI                                |
| Li et al. (1)   | 2019 | China   | Cross-sectional | PSG            | 5 ≤ AHI                                |
| Xie et al.      | 2020 | China   | Cross-sectional | PSG            | 5 ≤ AHI                                |
| Li et al. (2)   | 2020 | China   | Cross-sectional | PSG            | 5 ≤ AHI                                |
| Waltz et al.    | 2021 | Canada  | Cross-sectional | Type 3 sleep study | 15 ≤ ODI & SaO2 < 90% (≥12% of total time) |
| Cummins et al.  | 2021 | Canada & Malaysia | Cross-sectional | PSG or type 3 sleep study | 5 ≤ AHI                                |

Abbreviations: AHI, apnea-hypopnea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PSG, polypsomnography; RDI, respiratory disturbance index.
### Table 2: Characteristics of patients

| Study | OSA severity | n | Age (mean) | Sex (M/F) | BMI (mean) | Hct (%) |
|-------|--------------|---|------------|-----------|------------|---------|
| Hoffstein (male)a | 28 ≤ AHI < 12 | 113 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Hoffstein (female)a | 12 ≤ AHI ≤ 120 | 110 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Choi (mild to moderate)b | Mild | 25 | n/a | n/a | 42.0 ± 5.0 | n/a |
| Choi (severe)b | Severe | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Dikmenoglu | Severe | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Sinnapah (mild)b | Mild | 25 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Sinnapah (moderate)b | Moderate | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Sinnapah (severe)b | Severe | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Nguyen (mild)b | Mild | 467 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Nguyen (moderate)b | Moderate | 355 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Nguyen (severe)b | Severe | 418 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Fan (mild)b | Mild | 185 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Fan (moderate)b | Moderate | 171 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Fan (severe)b | Severe | 59 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (male, mild to moderate)a,b | Mild to moderate | 110 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (male, severe)a,b | Severe | 220 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (female, mild to moderate)a,b | Mild to moderate | 88 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, mild)a,b | Mild | 59 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, moderate)a,b | Moderate | 76 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, severe)a,b | Severe | 7 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, mild to moderate)a,b | Mild to moderate | 10 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, moderate)a,b | Moderate | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, severe)a,b | Severe | 1 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Xie (mild to moderate)b | Mild to moderate | 32 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Xie (severe)b | Severe | 59 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (male, mild to moderate)ab | Mild to moderate | 110 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (male, severe)ab | Severe | 220 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (1) (female, mild to moderate)ab | Mild to moderate | 88 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, mild)ab | Mild | 59 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, moderate)ab | Moderate | 76 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (male, severe)ab | Severe | 7 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, mild to moderate)ab | Mild to moderate | 10 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, moderate)ab | Moderate | 11 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Li (2) (female, severe)ab | Severe | 1 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Waltz | All | 23 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Cummins (mild)p | Mild | 294 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Cummins (moderate)p | Moderate | 223 | n/a | n/a | 44.0 ± 5.0 | n/a |
| Cummins (severe)p | Severe | 180 | n/a | n/a | 44.0 ± 5.0 | n/a |

Note: Data are presented as mean ± SD.

Abbreviations: Hct, hematocrit; n/a, not available; OSA, obstructive sleep apnea.

These articles divided patients into subgroups according to sex: male and female.

These articles divided patients into two (mild (≤ AHI < 30) and severe (≥ AHI ≥ 30)) or three (mild (≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe (≥ AHI ≥ 30)) subgroups according to disease severity.

Abbreviations: Hct, hematocrit; n/a, not available; OSA, obstructive sleep apnea.

These articles divided patients into subgroups according to sex: male and female.

These articles divided patients into two (mild (≤ AHI < 30) and severe (≥ AHI ≥ 30)) or three (mild (≤ AHI < 15), moderate (15 ≤ AHI < 30), and severe (≥ AHI ≥ 30)) subgroups according to disease severity.
3.2 | Association between OSA and elevation of hematocrit

We examined whether patients with OSA had higher hematocrit values than control individuals. Because there was significant heterogeneity across the included studies ($I^2 = 78\%$), the random-effects model was used. We found a significant difference in the hematocrit value between patients with OSA and controls (SMD, 0.19; 95% CI, 0.08–0.29; $p < .01$; Figure 2).

3.3 | Publication bias

Visual inspection of the funnel plots suggested the existence of asymmetry (Figure S1). However, Egger's regression test did not show evidence of publication bias in the analysis of hematocrit values ($t = 0.92$, $p = .36$).

3.4 | Sensitivity analysis

The stability of the results of the hematocrit value was evaluated through a sensitivity analysis. The corresponding pooled SMD (range, 0.153–0.202) was not substantially altered when single studies were sequentially removed, suggesting that the results of the meta-analysis were stable (Figure S2).

3.5 | Subgroup analysis

Subgroup analysis was performed according to disease severity, sex, and publication year. Only studies for which detailed information on each parameter was available were included in the subgroup analyses. When studies were stratified according to disease severity ("mild", "moderate", and "severe"), the hematocrit value of patients with "mild" and "moderate" OSA did not significantly differ from that of controls ($p = .06$ and $p = .19$, respectively; Figure 3A,B). In contrast, a significant difference in hematocrit values was found between patients with "severe" OSA and controls (SMD, 0.34; 95% CI, 0.08–0.59; $p < .01$; Figure 3C). In the subgroup analysis according to sex, the difference in hematocrit values between patients and control individuals was not significant in studies including only men ($p = .12$; Figure 4A), whereas it was significant in studies including only women (SMD, 0.25; 95% CI, 0.12–0.38; $p < .01$; Figure 4B). As the American Academy of Sleep Medicine (AASM) criteria for scoring hypopnea was substantially revised in 2012, we divided the studies into two subgroups based on publication year: "pre-2012" and "post-2012." A significant difference in the hematocrit value between patients and controls was observed in the post-2012 group (SMD, 0.17; 95% CI, 0.06–0.28, $p < .01$), but not in the pre-2012 group ($p = .28$) (Figure S3A,B).

3.6 | Meta-regression analysis

We conducted a meta-regression analysis to assess the effects of confounding factors on differences in hematocrit values between patients with OSA and controls. The outcome variable was the SMD, and the covariates included differences in the mean values of age (years), BMI, and the proportion of male patients (%) between patients with OSA and controls. We found that differences in mean age ($p = .77$), mean BMI ($p = .09$), and the proportion of male patients (%) ($p = .10$) showed no significant effect (Figure S4).

4 | DISCUSSION

OSA is traditionally considered to be one of the causes of secondary erythrocytosis. However, evidence showing an association between OSA and secondary erythrocytosis is largely anecdotal. In addition,
whether erythrocyte values are elevated in patients with OSA is controversial. In the present study, we comprehensively analyzed the results of 11 studies through a meta-analysis and found that hematocrit values were significantly higher in patients with OSA than in controls. Although we found significant increases in hematocrit, the value in patients with OSA was estimated to remain within the normal range.

| Study | OSA | Control | SMD | 95% CI | Weight |
|-------|-----|---------|-----|--------|--------|
| Hoffstein et al. (male) | 113 | 44.0 | 118 | 44.0 | 5.0 | 0.00 [-0.26; 0.26] | 3.8% |
| Hoffstein et al. (female) | 43 | 40.0 | 38 | 40.0 | 3.0 | 0.00 [-0.42; 0.42] | 2.8% |
| Choi et al. (mild-moderate) | 91 | 41.0 | 61 | 39.0 | 3.0 | 0.35 [0.02; 0.67] | 3.3% |
| Choi et al. (severe) | 111 | 43.5 | 61 | 39.0 | 3.0 | 0.98 [-0.65; 1.31] | 3.3% |
| Dikmenoglu et al. | 11 | 40.6 | 11 | 42.3 | 0.0 | 0.41 [-1.25; 0.44] | 5.0% |
| Sinnapah et al. (mild) | 25 | 43.0 | 50 | 41.4 | 5.0 | 0.39 [0.14; 0.14] | 36.7% |
| Sinnapah et al. (mild-moderate) | 467 | 42.7 | 364 | 42.7 | 3.9 | 0.00 [-0.34; 0.34] | 3.4% |
| Sinnapah et al. (severe) | 11 | 41.4 | 50 | 41.4 | 4.8 | 0.39 [0.14; 0.14] | 36.7% |
| Nguyen et al. (mild) | 467 | 42.7 | 364 | 42.7 | 3.9 | 0.00 [-0.34; 0.34] | 3.4% |
| Nguyen et al. (mild-moderate) | 355 | 42.6 | 304 | 42.7 | 3.9 | 0.03 [-0.12; 0.17] | 4.4% |
| Nguyen et al. (severe) | 418 | 42.2 | 364 | 42.7 | 3.9 | 0.17 [-0.26; 0.02] | 4.5% |
| Fan et al. (mild) | 185 | 43.9 | 135 | 42.9 | 3.2 | 0.32 [0.09; 0.55] | 4.0% |
| Fan et al. (mild-moderate) | 171 | 43.9 | 135 | 42.9 | 3.2 | 0.33 [0.10; 0.56] | 4.0% |
| Fan et al. (severe) | 506 | 46.7 | 135 | 42.9 | 3.2 | 0.70 [0.66; 1.04] | 4.2% |
| Liu et al. (1) (male, mild-moderate) | 110 | 43.8 | 2.7 | 53 | 43.7 | 3.1 | 0.04 [-0.29; 0.36] | 3.3% |
| Liu et al. (1) (male, severe) | 220 | 44.9 | 3.3 | 53 | 43.7 | 3.1 | 0.37 [0.07; 0.67] | 3.5% |
| Liu et al. (1) (female, mild-moderate) | 88 | 39.4 | 2.7 | 102 | 39.1 | 2.6 | 0.11 [-0.17; 0.40] | 3.6% |
| Liu et al. (1) (female, severe) | 32 | 40.0 | 4.3 | 102 | 39.1 | 2.6 | 0.29 [-0.11; 0.69] | 2.9% |
| Xie et al. (mild) | 48 | 42.0 | 5.0 | 34 | 43.0 | 5.0 | 0.20 [-0.04; 0.44] | 2.6% |
| Xie et al. (severe) | 59 | 46.0 | 4.0 | 34 | 43.0 | 5.0 | 0.45 [0.02; 0.88] | 2.7% |
| Liu et al. (2) (male, mild) | 97 | 47.0 | 3.0 | 85 | 47.0 | 3.0 | 0.00 [-0.29; 0.29] | 3.5% |
| Liu et al. (2) (male, moderate) | 84 | 46.0 | 4.0 | 85 | 47.0 | 3.0 | 0.26 [-0.58; 0.02] | 3.5% |
| Liu et al. (2) (male, severe) | 341 | 47.0 | 4.0 | 85 | 47.0 | 3.0 | 0.00 [-0.24; 0.24] | 3.5% |
| Liu et al. (2) (female, mild) | 76 | 41.0 | 5.0 | 186 | 40.0 | 3.0 | 0.33 [-0.06; 0.75] | 3.7% |
| Liu et al. (2) (female, moderate) | 54 | 41.0 | 5.0 | 186 | 40.0 | 3.0 | 0.33 [-0.02; 0.64] | 3.4% |
| Liu et al. (2) (female, severe) | 71 | 41.0 | 5.0 | 186 | 40.0 | 3.0 | 0.33 [-0.05; 0.61] | 3.6% |
| Watanabe et al. | 23 | 46.0 | 3.3 | 14 | 46.9 | 3.5 | 0.32 [-0.37; 1.00] | 1.6% |
| Cummins et al. (mild) | 294 | 39.7 | 5.0 | 224 | 39.6 | 5.0 | 0.17 [0.05; 0.30] | 2.7% |
| Cummins et al. (moderate) | 223 | 40.5 | 5.0 | 244 | 39.6 | 5.0 | 0.19 [-0.19; 0.57] | 4.2% |
| Cummins et al. (severe) | 180 | 40.7 | 5.0 | 244 | 39.6 | 5.0 | 0.22 [0.03; 0.41] | 4.2% |

**FIGURE 2** Comparison of hematocrit values between patients with OSA and controls. Forest plots comparing hematocrit values between patients with OSA and controls. Results are expressed as the SMD with 95% CI. The calculation is based on a random-effects model. CI, confidence interval; OSA, obstructive sleep apnea; SMD, standardized mean difference.

**FIGURE 3** Subgroup analysis of hematocrit values based on disease severity of OSA. The studies were divided into three subgroups according to disease severity: (A) mild (5 ≤ AHI < 15), (B) moderate (15 ≤ AHI < 30), and (C) severe (30 ≥ AHI). Forest plots comparing hematocrit values between patients with OSA and controls. The results are expressed as SMD and 95% CI. AHI, apnea hypopnea index; CI, confidence interval; OSA, obstructive sleep apnea; SMD, standardized mean difference.
These results suggest that OSA may lead to minor increases in hematocrit, but rarely causes clinically significant erythrocytosis.

Mechanisms underlying the elevation of hematocrit in patients with OSA may involve increased erythropoiesis driven by intermittent hypoxia. It has been shown that exposure to hypoxia stabilizes hypoxia-inducible factors, resulting in gene transcription and production of EPO, a glycoprotein that stimulates red blood cell production. This hypothesis is supported by a recent study showing that intermittent hypoxia can upregulate serum EPO values in healthy individuals. Similarly, a meta-analysis of nine studies showed that EPO values in patients with sleep apnea were significantly higher than those in the control group. Another possible mechanism explaining the elevation of erythrocyte measures in patients with OSA is a reduction in plasma volume resulting from fluid shift from the intravascular to the extravascular bed. This fluid shift may be caused by increased atrial natriuretic peptide release, which is reduced after treatment with continuous positive airway pressure.

In the subgroup analysis according to disease severity, we found that compared with controls, a significant difference in hematocrit value was observed only in patients with severe OSA, but not in patients with mild or moderate OSA. Although the SMD between severe patients and controls was 0.34, which would be considered a small effect size, these findings indicate that the elevation of erythrocyte measures is more exaggerated in patients with severe disease. As the severity of OSA is determined by the frequency of apnea/hypopnea, more frequent hypoxia in patients with severe OSA induces significant EPO production, which subsequently stimulates erythropoiesis. Indeed, a previous study reported that 8-cycle intermittent hypoxia, but not 5-cycle intermittent hypoxia, increased serum EPO levels in healthy individuals, suggesting that a sufficient frequency of intermittent hypoxia is needed to induce erythropoiesis.

An increase in hematocrit is associated with cardiovascular mortality and morbidity. A previous study reported significant correlations between erythrocyte measures and markers associated with cardiovascular risk, such as BMI and blood pressure, in patients with OSA. In addition, it has been shown that mice with excessive EPO-induced erythrocytosis showed elevated endothelin-1, a potent vasoconstrictor that is increased upon chronic intermittent hypoxia. Given that endothelin-1 promotes elevation of blood pressure through vasoconstriction, it seems plausible that erythrocytosis is associated with adverse cardiovascular events. Further studies would be required to assess the potential contribution of increased erythrocyte measures to the development of cardiovascular diseases in patients with OSA, particularly in patients with severe OSA.

Since OSA is more prevalent in men, the participants in most previous studies were predominantly men. However, considering that men and women have different normal ranges of hematocrit values, the sex composition of study cohorts may be a confounding factor for the analysis of the association between erythrocyte measures and OSA. Furthermore, it has been suggested that the relationship between erythrocyte measures and cardiovascular disease risk differs by sex. Intriguingly, we found significantly elevated hematocrit values compared to controls in women, but not in men, suggesting a sex-specific association between OSA and hematocrit elevation. Therefore, it would be of interest to investigate whether response to intermittent hypoxia is different in men and women. In addition, as the definition and scoring rule for hypopnea by AASM was remarkably changed in 2012, we separately analyzed the pre-2012 and post-2012 groups. The significant elevation of hematocrit values in patients with OSA remained stable in the subgroup analysis of the post-2012 group, indicating that the results were preserved when the current scoring rule was applied.

This study had several limitations. First, there might be a selection bias because all the studies included in this meta-analysis were hospital-based studies. Population-based studies may provide more accurate information on the general population. Second, we excluded articles in languages other than English, which may have biased the results.
results. Third, co-morbidities such as hypertension and smoking history of patients with OSA were unknown, which may be uncontrollable confounding factors in our analysis. However, the strength of this meta-analysis is that it included the largest number of studies to investigate the association between OSA and hematocrit.

5 | CONCLUSION

In summary, the current meta-analysis showed that patients with OSA, particularly severe patients, had significantly higher hematocrit values than controls. However, the elevation of hematocrit was modest and the value was estimated to be within the normal range. These data suggest that OSA is associated with a slight increase in hematocrit but does not cause clinically significant erythrocytosis. Therefore, evaluation of OSA may not be mandatory for the diagnostic work-up of secondary erythrocytosis without cardiovascular diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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