Original Article

Hematological indices as simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome: a meta-analysis

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Background: Clinical detection of inflammatory markers is useful to assess the degree of nocturnal hypoxia and predict the presence of complications in obstructive sleep apnea syndrome (OSAS) patients. Nowadays, some researchers proposed that hematological parameters could be substituted for novel disease-specific biochemical markers (such as C-reactive protein) because they were comparatively cheap, simple and practical. But there was a contradiction whether the hematological parameters were positively correlated with the OSAS severity.

Methods: Medical databases were searched included PubMed, Web of Science, Scopus, Cochrane Library, Clinical Trial, Embase and Google Scholar (up to March 29, 2018). We used weighted mean differences (WMDs) with 95% confidence intervals (CIs) from random-effects model.

Results: Seventeen studies were included in this meta-analysis and results were presented by different hematological parameters. Pooled analysis showed that OSAS was associated with a high level of WBC (white blood cell, 11 studies, 2,206 subjects, WMD: 0.58; 95% CI: 0.31 to 0.85; P<0.0001), NLR (neutrophil-to-lymphocyte ratio, 5 studies, 1416 subjects, WMD: 0.46; 95% CI: 0.13 to 0.80; P=0.007), MPV (mean platelet volume, 8 studies, 1,854 subjects, WMD: 0.63; 95% CI: 0.29 to 0.98; P=0.0004), PDW (platelet distribution width, 6 studies, 1,911 subjects, WMD: 0.76; 95% CI: 0.47 to 1.06; P<0.00001), PLR (platelet-to-lymphocyte ratio, 3 studies, 998 subjects, WMD: 21.76; 95% CI: 8.54 to 34.99; P=0.001), RDW (red cell distribution width, 5 studies, 1,701 subjects, WMD: 0.31; 95% CI: 0.11 to 0.51; P=0.002) and HCT (hematocrit, 3 studies, 662 subjects, WMD: 1.58; 95% CI: 0.52 to 2.64; P=0.003). But OSAS was associated with a low level of LYM (lymphocyte, 5 studies, 1,285 subjects, WMD: −0.27; 95% CI: −0.49 to −0.06; P=0.01). There was a gradual rising trend from mild OSAS to severe OSAS existed in all subgroups.

Conclusions: Hematological indices are comparatively Simple, Inexpensive and Practical Severity Markers of OSAS including WBC, LYM, NLR, MPV, PDW, PLR, RDW and HCT.

Keywords: Hematological indices; meta-analysis; obstructive sleep apnea syndrome (OSAS); severity; biomarker

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disease with a prevalence of moderate to severe sleep apnea in 6% to 13% of the adults population which affecting more than 20 million Americans (1). It is characterized by recurrent obstruction of partial or total upper airway and subsequent paroxysmal nocturnal hypoxia which leads to intermittent arousals from sleep, excessive daytime sleepiness and so on (2).

Although the etiologies and pathophysiological mechanisms are still not thoroughly understood, OSAS can lead to some complications such as cardiovascular disorders (CVDs), cancer and diabetes (3). And CVD occupies a large part in complications (4-6). Several evidences proposed that the predisposition to CVD of OSAS patients may be associated with endothelial dysfunction, excessive oxidative stress, increased systemic inflammation and sympathetic excitation (7-11).

The chronic systematic inflammation of OSAS may play an important role in the progression of CVD (12). Recent studies suggest that both WBC and NLR are good indicators of inflammation (13-17). Neutrophils (NEU) mainly mediate innate immune response by secreting mediators while LYM mediate adaptive immune response by regulating inflammation (18). Besides, some studies reported platelet was activated and aggregated in patients with OSAS, which was also relevant in inflammation (19,20). MPV and PDW are both useful markers of platelet activity. Recently, studies introduce PLR as a novel inflammatory marker to predict the adverse outcomes of CVD (14-17,21). Third, in view of hypoxemic states, HCT was elevated in OSAS patients that might be called secondary erythrocytosis (22). What's more, red cell distribution width (RDW), which assessed the variability of erythrocyte, was also reported to be increased in relation to inflammation in OSAS (23).

Clinical detection of inflammatory markers is useful to assess the degree of nocturnal hypoxia and predict the presence of complications in OSAS patients. Nowadays, clinical scientists usually use the novel disease-specific biochemical markers to measure the overall inflammatory status of human body. However, there is an obvious drawback that such markers, such as C-reactive protein and interleukin-6, are always expensive and time-consuming, especially in developing countries. Besides, blood routine examination is used more frequently than disease-specific biochemical markers in primary hospital. Hence, we proposed the hematological parameters mentioned above could be alternative markers to evaluate the inflammation in OSAS population because they were comparatively cheap, readily-measurable, easy and practical laboratory markers.

Nevertheless, there was a contradiction whether the hematological parameters were positively correlated with the OSAS severity. Therefore, we conducted the meta-analysis to solve this problem and assessed the values of hematological indices to be Severity Markers of OSAS. To the best of our knowledge, this is the first meta-analysis in this academic field.

Methods

Our study was performed according to The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (24).

Data sources and search strategy

Medical databases were searched included PubMed, Web of Science, Scopus, Cochrane Library, Clinical Trial, Embase and Google Scholar. Each database was searched from inception through March 29, 2018. The following terms were used in the search: ("hematology" or "white blood cell count" or "neutrophil count" or "lymphocyte count" or "neutrophil-to-lymphocyte ratio" or "NLR" or "platelet count" or "platelet-to-lymphocyte ratio" or "PLR" or "mean platelet volume" or "MPV" or "platelet distribution width" or "PDW" or "red cell count" or "Hematocrit" or "HCT" or "red cell distribution width" or "RDW") and ("obstructive sleep apnea syndrome" or "OSAS"). Meanwhile, we scanned the reference list of included studies and relevant scientific meetings.

Selection criteria

Inclusion criteria for this meta-analysis: (I) *patients*: adults who had OSAS and were categorized into three OSAS severity groups as mild, moderate and severe according to the apnea-hypopnea index (AHI) values of 5–14, 15–29 and more than 30, respectively (25); (II) *outcomes*: clinical hematological parameters including white blood cell, neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio, platelet, platelet-to-lymphocyte ratio, mean platelet volume, platelet distribution width, erythrocyte, hematocrit and RDW; (III) *study language*: only English language; (IV) *data*:

all the data was based on means and standard deviations or medians and ranges.

Exclusion criteria: studies didn't have available data and control group.

Quality assessment

Two reviewers (M Wu and L Zhou) used the Effective Public Health Practice Project tool (EPHPP) (26) to assess the methodological quality of included studies in this review. We graded key component assessments as strong, moderate, or weak: Selection bias, Study design, Data collection methods and Confounders. From the component-specific assessments, we derived an overall quality assessment according to each component assessment of no weak rating, one weak rating and two or more weak ratings. Any discrepancies were resolved by discussion or a third reviewer.

Data extraction

Two authors (M Wu and L Zhou) independently evaluated all the studies that were retrieved from the databases and bibliography and determined the final included studies according to inclusion criteria described above. Any disagreements were resolved via consensus or third reviewer when necessary. For each included study, we extracted data using two data extraction forms.

Statistical analysis

We used weighted mean differences (WMDs) with 95% confidence intervals (95% CIs) for the meta-analysis to analyze the association between hematological parameters and OSAS severity. The I^2 statistic was used to assess the heterogeneity across the studies. Heterogeneity was defined as low, moderate and high heterogeneity according to I^2 statistic values of 25%, 50% and 75%. When heterogeneity was found, we performed a sensitivity analysis to determine which studies contributed most significantly to the heterogeneity. The respiratory disturbance index (RDI) was combined data with AHI. If a study only reported median (Q25–Q75), then the data was calculates as an estimate of mean and SD according to the Cochrane Handbook (27). The Egger's test and Begg's test were used to assess publication bias. All analyses were performed with Review Manager (Version 5.3, The Cochrane Collaboration) and Stata (Version SE12.0, Stata Corporation, USA). A P value of <0.05 was considered to be statistically significant.

Results

Studies identification and characteristic

A total of 2,479 studies were identified from searching the electronic database. After screening, 35 studies were full-text reviewed for eligibility. Finally 17 studies (19,20,22,23,28-40) met the inclusion criteria and were included in this meta-analysis. The detailed steps of the study identification process are shown in *Figure 1*. The characteristic of each study were summarized in *Table 1* and *Table S1*. *Table 1* mainly included general characteristics: author, year, country, outcomes, characteristic of OSAS patients and quality assessment. *Table S1* presented the demographic data: total sample size of each eligible study, detailed demographic data of each severity group (AHI, sample size, age, BMI and male proportion). The methodological quality was assessed according to the EPHPP tool (*Table S2*).

Results of meta-analysis

A total of 4,518 cases were selected from 17 studies, of which 1,013 were control subjects, 896 were mild OSAS subjects, 832 were moderate OSAS subjects and 1,588 were severe OSAS subjects. In terms of different hematological indices, we made eight subgroup meta-analyses. We analyzed WBC, lymphocyte, NLR, MPV, PDW, PLR, RDW and HCT of the mild, moderate and severe OSAS group versus control group respectively. *Figures 2-4* were generated by Stata and the detail values were reconfirmed by Review Manager. Figures from Stata only provided WMDs and 95% CIs, therefore the P values of WMDs showed in the following results were provided by Review Manager (not showed in the figures).

WBC

A total of 2,206 subjects were enrolled from 11 studies (20,22,30,32-34,36-38,40,41), of which 421 were allocated to the mild OSAS group, 448 to the moderate OSAS group, 805 to the severe OSAS group and 532 to the control group. Mean WBC counts were 6.874, 7.159, 6.968 and 7.586 ($\times 10^9$/L) in control, mild, moderate and severe OSAS groups (*Table S3*). Total pooled analysis result showed that OSAS was associated with a higher level of WBC (WMD:

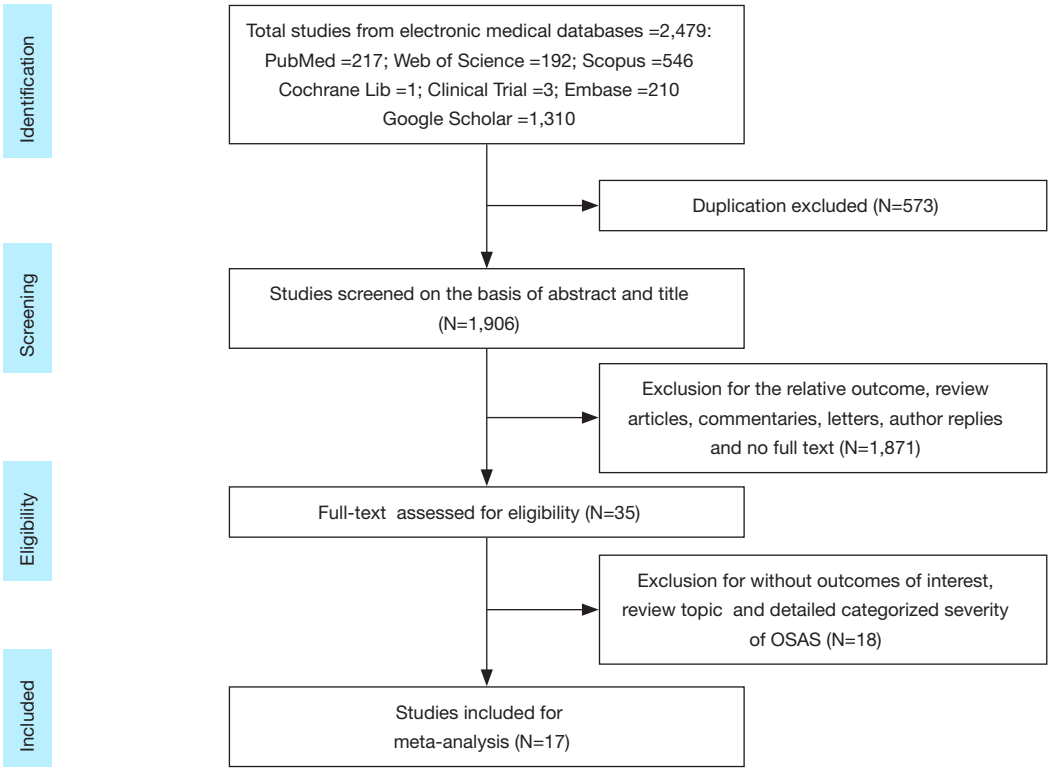

Figure 1 Flow diagram.

0.58; 95% CI: 0.31 to 0.85; P<0.0001). And increased WBC counts of severe OSAS (WMD =0.79, 95% CI: 0.35 to 1.23, P=0.0005) was little higher than the mild OSAS (WMD =0.52, 95% CI: 0.10 to 0.94, P=0.01). All of them showed high heterogeneity: I^2=87.3% and 78.4% respectively (*Figure 2A*).

LYM

A total of 1,285 subjects were included from 5 studies (30-32,37,40), of which 278 were enrolled in the mild OSAS group, 263 to the moderate OSAS group, 430 to the severe OSAS group and 314 to the control group. Mean lymphocyte counts were 2.714, 2.666, 2.419 and 2.222 ($\times 10^9$/L) in control, mild, moderate and severe OSAS group (*Table S3)*. Total pooled analysis result suggested that OSAS was associated with a lower level of LYM (WMD: −0.27; 95% CI: −0.49 to −0.06; P=0.01). And lymphocyte counts gradually decreased with regard of OSAS severity and it was statistically significant until it developed to severe OSAS (WMD =−0.49, 95% CI: −0.88 to −0.09, P=0.02). But a considerable heterogeneity was observed among the severe OSAS groups (I^2=90.2%, P=0.000) (*Figure 2B*).

NLR

A total of 1,416 subjects were selected from 5 studies (30-32,36,37), of which 348 were assigned to the mild OSAS group, 339 to the moderate OSAS group, 405 to the severe OSAS group and 324 to the control group. Mean neutrophil-to-lymphocyte ratios were 1.769, 1.874, 2.17 and 2.676 in control, mild, moderate and severe OSAS groups (*Table S3*). Total pooled analysis result showed that OSAS was associated with a higher level of NLR (WMD: 0.46; 95% CI: 0.13 to 0.80; P=0.007). And there was a gradual rising trend from mild OSAS to severe OSAS which ultimately significant increased (WMD =0.90, 95% CI: 0.04 to 1.76, P=0.04) but was with significant heterogeneity (I^2=98.3%, P=0.000) (*Figure 2C*).

MPV

A total of 1,854 patients were included from 8 studies (19,20,31,32,35,38-40), of which 354 were recruited in the

Table 1 General characteristics of included studies

Author, year*	Study period	Country	Outcomes	Characteristics of OSAS patients	Quality assessment
OSAS subjects with/without CVD					
Sunnetcioglu, 2018	201301–201510	Turkey	HGB, RDW	OSAS w/wo diabetes, hypertension, smoking and CVD	Strong
Song, 2016	201001–201412	Korea	WBC, NEU, LYM, RBC, HGB, HCT, RDW, PLT, PLR, PDW	OSAS w/wo diabetes, smoking, primary hypertension, and hyperlipidemia	Strong
Uygur, 2016	201209–201403	Turkey	WBC, NEU, LYM, NLR, HGB, RDW, PLT, PDW, MPV	OSAS w/wo diabetes, hypertension, CVD and hyperlipidemia	Strong
Koseoglu, 2015	NA	Turkey	PLT, LYM, PLR, MPV, PDW, RDW	OSAS w/wo diabetes, hypertension, CVD and smoking	Strong
Sokucu, 2014	201201–201207	Turkey	WBC, RBC, HGB, HCT, PLT, MPV, PDW	OSAS w/wo smoking and hypertension but wo CVD and diabetes	Strong
Kanbay, 2013	200501–201010	Turkey	MPV, HGB, WBC, PLT	OSAS w/wo CVD	Strong
Kurt, 2013	201103–201207	Turkey	WBC, RDW, HGB, MPV, PDW, PLT	OSAS w/wo diabetes, hypertension, CVD, hyperlipidemia and smoking	Strong
Ozsu, 2012	NA	Turkey	HGB	OSAS w/wo diabetes, hypertension, CVD and smoking	Strong
Varol, 2011	200809–200909	Turkey	HGB, WBC, PLT, MPV	OSAS w/wo diabetes, hypertension and smoking	Strong
Varol, 2010	NA	Turkey	HGB, WBC, PLT, MPV	OSAS w/wo diabetes, hypertension and smoking	Strong
OSAS subjects without CVD					
Altintas, 2015	201301–201404	Turkey	NLR	OSAS wo diabetes, hypertension, CVD and smoking	Strong
Korkmaz, 2015	201211–201312	Turkey	WBC, NEU, LYM, NLR, LYM	OSAS wo diabetes, hypertension, CVD and hyperlipidemia	Strong
Koseoglu, 2015	201005–201307	Turkey	PLR, NLR	OSAS wo CVD	Strong
Yenigun, 2015	NA	Turkey	NLR, NEU, LYM, WBC	OSAS wo CVD.	Strong
Karakas, 2013	200903–201010	Turkey	HGB, PLT, MPV	OSAS wo diabetes, hypertension, CVD, hyperlipidemia and smoking	Strong
Nena, 2012	NA	Greece	MPV, PDW	OSAS wo diabetes and smoking	Strong
Choi, 2006	NA	California	HGB, HCT, WBC	OSAS wo diabetes, hypertension, CVD and smoking	Strong

*, all studies were retrospective case series. WBC, white blood cell; LYM, lymphocyte; NEU, neutrophil; NLR, neutrophil-to-lymphocyte ratio; RBC, red blood cell; PLT, platelet; PLR, platelet-to-lymphocyte ratio; HGB, hemoglobin; HCT, hematocrit; RDW, red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; w/o, without; w/wo, with and without.

mild OSAS group, 319 to the moderate OSAS group, 728 to the severe OSAS group and 453 to the control group. The average volumes of mean platelet volumes were 8.256, 8.553, 8.851 and 9.196 fL in control, mild, moderate and severe OSAS groups (*Table S3*). Total pooled analysis result showed that OSAS was associated with a higher level of MPV (WMD: 0.63; 95% CI: 0.29 to 0.98; P=0.0004). And we could observe a gradual increasing trend with the

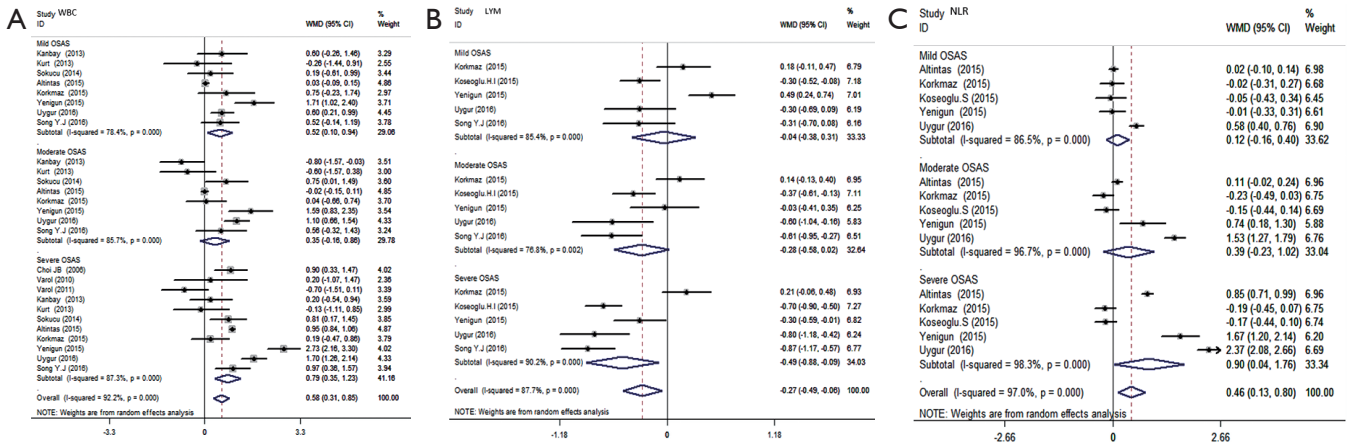

Figure 2 Forest plots of the relationship between inflammatory associated indices (WBC, LYM and NLR) and severity groups of OSAS versus control. OSAS, obstructive sleep apnea syndrome; WBC, white blood cell; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio.

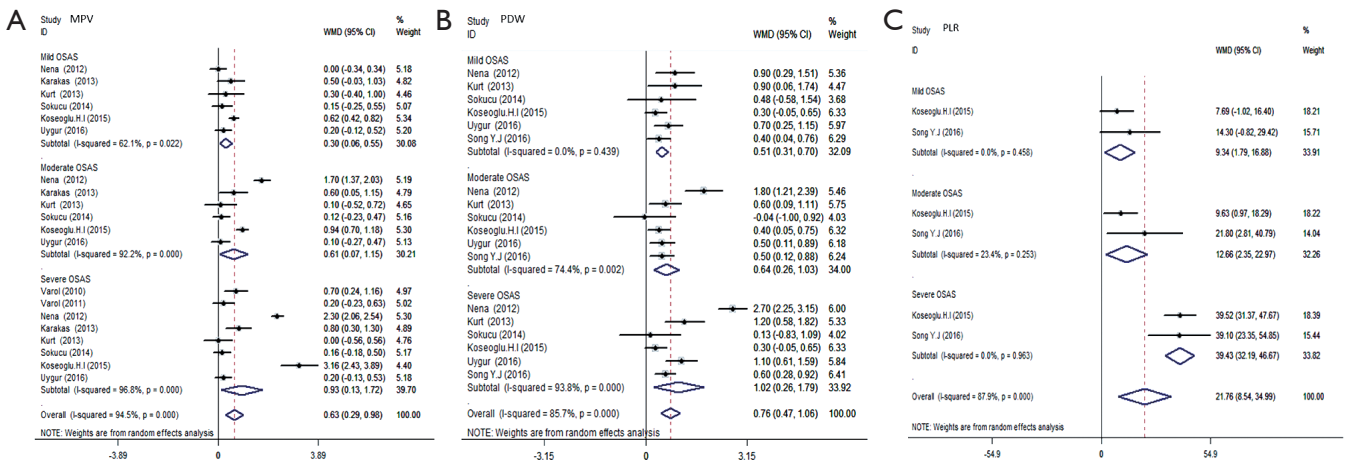

Figure 3 Forest plots of the relationship between platelet associated indices (MPV, PDW and PLR) and severity groups of OSAS versus control. OSAS, obstructive sleep apnea syndrome; MPV, mean platelet volume; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio.

development of OSAS severity. The severe OSAS group (WMD =0.93, 95% CI: 0.13 to 1.72, P=0.02) increased more than mild OSAS (WMD =0.30, 95% CI: 0.06 to 0.55, P=0.02) and moderate OSAS groups (WMD =0.61, 95% CI: 0.07 to 1.15, P=0.03). However, the moderate (I^2=92.2%, P=0.000) and severe OSAS groups (I^2=96.8%, P=0.000) had remarkable heterogeneity while mild OSAS group had moderate heterogeneity (I^2=62.1%, P=0.022) (*Figure 3A*).

PDW

A total of 1,911 subjects were enrolled from 6 studies (19,30-32,40,41), of which 391 were allocated to the mild OSAS group, 348 to the moderate OSAS group, 738 to the severe OSAS group and 434 to the control group. Mean platelet distribution widths were 14.818%, 15.431%, 15.445% and 15.823% in control, mild, moderate and severe OSAS groups (*Table S3*). Total pooled analysis result showed that OSAS was associated with a higher level of PDW (WMD: 0.76; 95% CI: 0.47 to 1.06; P<0.00001). And the evaluated PDW of severe OSAS (WMD =1.02, 95% CI: 0.26 to 1.79, P=0.008) was much higher than the moderate OSAS (WMD =0.64, 95% CI: 0.26 to 1.03, P=0.001) and mild OSAS group (WMD =0.51, 95% CI:

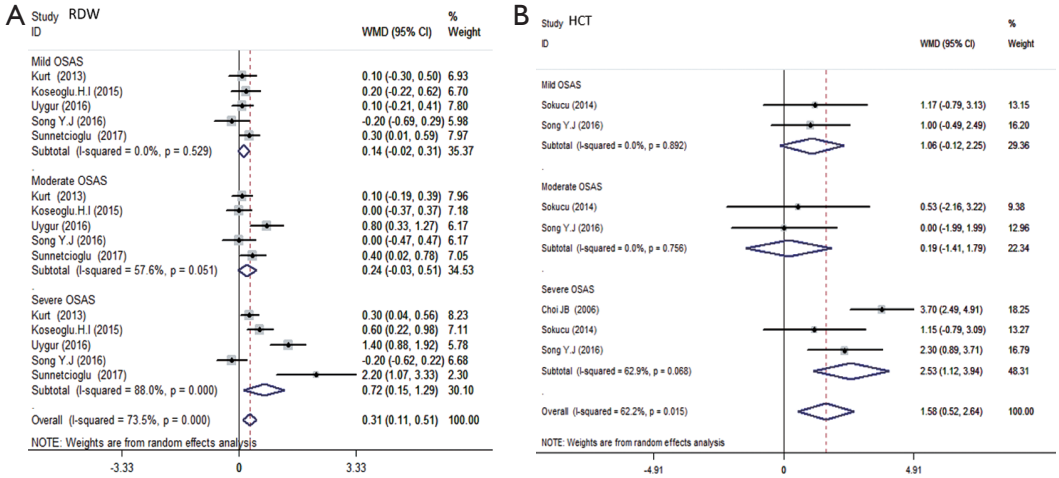

Figure 4 Forest plots of the relationship between erythrocyte associated indices (RDW and HCT) and severity groups of OSAS versus control. OSAS, obstructive sleep apnea syndrome; RDW, red cell distribution width; HCT, hematocrit.

0.31 to 0.70, P<0.00001). However, the moderate (I^2=74.4%, P=0.002) and severe OSAS groups (I^2=93.8%, P=0.000) had remarkable heterogeneity while mild OSAS group didn't have heterogeneity (I^2=0%, P=0.439) (*Figure 3B*).

PLR

A total of 998 subjects were selected from 3 studies (28,30,31), of which 227 were recruited in the mild OSAS group, 204 to the moderate OSAS group, 401 to the severe OSAS group and 166 to the control group. In this subgroup, we first enrolled all eligible studies into meta-analysis but the results showed a significant heterogeneity, but when we excluded Koseoglu (28), there were no heterogeneity among mild and severe OSAS group and low heterogeneity among moderate OSAS group (details in *Table S3*). The mean platelet-to-lymphocyte ratios of final included studies were 103.61, 107.09, 110.63 and 123.63 in control, mild, moderate and severe OSAS groups (*Table S3*). The final total pooled analysis result showed that OSAS was associated with a higher level of PLR (WMD: 21.76; 95% CI: 8.54 to 34.99; P=0.001). And there was a gradual rising trend from mild OSAS (WMD =9.34, 95% CI: 1.79 to 16.88, P=0.02), moderate OSAS (WMD =12.66, 95% CI: 2.35 to 22.97, P=0.02) to severe OSAS (WMD =39.43, 95% CI: 32.19 to 46.67, P<0.00001). And moderate OSAS group (I^2=23.4%, P=0.253) had low heterogeneity while mild and moderate OSAS group didn't have heterogeneity (I^2=0.0%) (*Figure 3C*).

RDW

A total of 1,701 subjects were enrolled from 5 studies (29-32,40), of which 381 were allocated to the mild OSAS group, 320 to the moderate OSAS group, 547 to the severe OSAS group and 453 to the control group. Mean RDWs were 14.46%, 14.56%, 14.72% and 15.32% in control, mild, moderate and severe OSAS groups (*Table S3*). The total pooled analysis result showed that OSAS was associated with a higher level of RDW (WMD: 0.31; 95% CI: 0.11 to 0.51; P=0.002). And there was a gradual rising trend from mild OSAS (WMD =0.14, 95% CI: –0.02 to 0.31, P=0.08) to severe OSAS which ultimately significant increased (WMD =0.72, 95% CI: 0.15 to 1.29, P=0.01) but was with considerable heterogeneity (I^2=88.0%, P=0.000) (*Figure 4A*).

HCT

A total of 662 subjects were included from 3 studies (22,30,35), of whom 105 were assigned to the mild OSAS group, 102 to the moderate OSAS group, 303 to the severe OSAS group and 152 to the control group. Mean hematocrits were 41.25%, 43.07%, 42.25% and 43.64% in control, mild, moderate and severe OSAS groups (*Table S3*). The total pooled analysis result showed that OSAS was associated with a higher level of HCT (WMD: 1.58; 95% CI: 0.52 to 2.64; P=0.003). And the values of HCT evaluated and reached a statistical significant increase

until it was severe in OSAS group (WMD =2.53, 95% CI: 1.12 to 3.94, P=0.0004). Nevertheless, we could observe a moderate heterogeneity in severe OSAS group (I^2=62.9%, P=0.068) (*Figure 4B*).

Other subgroups

When we took the comorbidities of CVD into consideration, we divided the OSAS patients into two subgroups: OSAS subjects without CVD or with/without CVD, according to the inclusion criteria of each eligible study (details in the *Table 1*). Hematological parameters (WBC, MPV and PDW) still revealed a developed trend in OSAS subjects without CVD and indices (LYM, NLR, MPV, PDW) in OSAS subjects with/without CVD. It was noteworthy that the overall pooled analyses of neutrophil and PLR subgroups showed no significant increase or decrease just because they exhibited an opposite trend in OSAS subjects without CVD or with/without CVD. Subgroup of RDW and HCT only available in OSAS subjects with/without CVD (details in *Table S4*).

Sensitivity analysis

Although all the subgroups showed a moderate or significant heterogeneity, the sensitivity analyses couldn't found out the source of heterogeneity excepted the PLR subgroup.

Publication bias

We summarized the P values of Egger's test and Begg's test of each subgroup into a publication bias table (*Table S5*). And all the results suggested that there were no evidence of publication bias (P>0.05).

Discussion

OSAS is characterized by recurrent obstruction of partial or total upper airway during sleep, causing more than ten seconds of breathing (apnea) cessation, despite ongoing respiratory effort. Our results showed that there was a positive correlation between the levels of hematological indices and the severity of OSAS including WBC, LYM, NLR, MPV, PDW, PLR, RDW and HCT. That meant the higher the AHI, the higher the levels. To the best of our knowledge, this is the first meta-analysis to analyze the association between hematological parameters and the OSAS severity.

Clinical implication

We proposed the hematological indices (WBC, LYM, NLR, MPV, PDW, PLR, RDW and HCT) could be alternative markers to evaluate the inflammation in OSAS patients, which was useful to assess the severity of OSAS. Moreover, the elevated hematological parameters could assist in timely identification of high-risk OSAS patients and alert clinicians to the potential increased risk of CVDs in them. As compare with the present biochemical markers used clinically, such as IL6 and C-reactive protein, hematological parameters were comparatively cheap, readily-measurable, easy and practical laboratory markers, especially in developing countries. Besides, blood routine examination is used more frequently than disease-specific biochemical markers in primary hospital.

Possible mechanisms

OSAS is a chronic disease which can lead to various comorbidities in subject with the degree of OSAS severity, including pulmonary disease, endocrine dysfunction, and cognitive impairment (42-44). And CVD occupies a large part among the comorbidities (4-6). Newman *et al.* (45), Lattanzi *et al.* (46,47) and Javaheri *et al.* (48) found that patients with OSAS had an increased risk of CVDs and suggested that OSAS was a major risk factor for CVDs. For example, the autonomic and neurohumoral abnormalities perpetuated beyond the offending obstructive events and persisted into the daytime, resulting in a disturbance of the overall circadian blood pressure rhythm and an increase in short- and long-term blood pressure variability (46,47,49). The high absolute blood pressure levels but even their fluctuations were related to development and progression of organ damage by promoting arterial remodelling, microvascular damage, hemodynamic instability, and vascular reactivity impairment (50-53).

The relationship between OSAS and accompanying changes of hematological parameters is complicated. Three main mechanisms may be implicated as follow.

First, acute and chronic hypoxia may be associated with the changes of MPV, PDW, HCT. Nena *et al.* (19) found that MPV and PDW were negative related to average SpO_2 and minimum SpO_2 and implied that hypoxia could activate platelet function. And Rahangdale *et al.* (54) demonstrated that high level of oxygen desaturation was

linked with higher platelet surface adhesion molecules, activated glycoprotein receptor expression, platelet-monocyte aggregation and platelet-neutrophil aggregation. Moreover, a fundamental research demonstrated chronic intermittent hypoxia increases platelet reactivity directly in rats (55). As to the parameters of red blood cell, Hematocrit is more closely tied to hypoxia. It is well known that hypoxemic state is interrelated with high hematocrit levels, as oxyhemoglobin desaturation can stimulate erythropoiesis, leading to increased hematocrit. Svatikova *et al.* (56) reported that ANP (atrial natriuretic peptide) was increased overnight in those untreated OSAS patients, and ANP levels decreased with CPAP treatment. It indicated that hemoconcentration might lead to increased hematocrit.

Second mechanism appears to be sympathetic overactivity. It results in many pathophysiological changes such as episodic hypoxemia, recurrent arousals and increased inspiratory effort. OSAS patients exhibited high levels of sympathetic nerve activity even when they were fully awake, which contributed to platelet activation and CVDs (57). Larsson *et al.* (58) suggested that platelet aggregability was increased by high levels of circulating catecholamine *in vivo*. Therefore, hematological indices associated with platelet activation (MPV, PDW, PLR) might change in OSAS patients caused by catecholamine discharge. On the other hand, the continuous high level of catecholamine contributes to hypertension, endothelial dysfunction and organ damage. And CVDs have a close relation with hematological parameters. For example, RDW has been found to be negative associated with the outcomes of heart failure, pulmonary hypertension and many other CVDs. Also, previous studies showed that there was a significant correlation between the RDW values and the AHI (23,35).

The third mechanism is chronic inflammation. The importance of inflammatory processes in the pathogenesis of OSAS has been strongly supported by a great number of studies (12). Moreover, Yokoe *et al.* (59) demonstrated that elevated inflammatory markers in OSAS patients significantly decreased after CPAP treatment (17). Some fundamental researches declared that Nuclear factor kappa B (NF-κB), a master transcription factor regulated the downstream inflammatory gene expression, was found to be selective activated by hypoxia and reoxygenation (60). NF-κB activity also resulted in an increased number of circulating neutrophils and monocytes. And the apoptosis of neutrophils was dysregulated in the process of OSAS (61). Both lead to the elevated level of neutrophil in peripheral blood of OSAS patients. As for lymphocyte, OSAS patients combined with CVDs were found to have a lower lymphocyte levels compared to those without CVDs, which could be due to the uncontrolled inflammatory pathway (62). Moreover, some researchers demonstrated that lower lymphocyte counts were related to activation of the hypothalamus-hypophysis-adrenal (THA) axis, increase production of systemic cortisol levels and altered sleeping habits (63). The NLR, a novel marker of systemic inflammation, was associated with many chronic diseases, also could be an indicator used to predict CVDs in OSAS patients (32). On the other hand, many pro-inflammatory cytokines, such as IL6, could significantly promote the production and activation of platelet, which contributed to the changes of those hematological parameters including PLR, MPV and PDW (64).

In summary, derangements including acute/chronic hypoxia, sympathetic overactivity, chronic systematic inflammation and even neurohumoral abnormalities interacted with each other synergistically rather than independently in the development of severity and complication of OSAS.

Limitation

Several limitations of our meta-analysis might be outlined as follows. First, all the eligible studies were retrospective studies and used observational data, which made it difficult to identify the causal relationship between hematological parameters and OSAS severity for possible residual confounding from unmeasured variables might exist. Second, although all the blood samples from different patients during data-gathering process were detected timely, it couldn't be guaranteed that the process was performed with identical methods at different times. And some minute differences still existed in several studies. For example, Sökücü *et al.* (35) used automatic analyzers instead of manual microscopic counting used by Nena *et al.* (19). Third, all hematological indices were performed with just one single measurement. Therefore, it was unsure whether the positive correlation was continuous or temporal. Fourth, although some hematological indices were considered as inflammatory markers, such as NLR and PLR, it was supposed to use classical established inflammatory markers like IL6 as a reference for comparison during detection process (12,13,21). Fifth, the

exclusion criteria in the subgroup of OSAS subjects without CVD was mainly dependent on the past medical history and physical examination, which making possible coexistence of asymptomatic cardiovascular diseases. And only some studies excluded the influence of recent medication history of antiplatelet drugs (such as aspirin) when detecting MPV, PDW and PLR. Sixth, all eligible studies were preliminary researches without further fundamental mechanism research. And the cut-off point of hematological indices values determining an individual's OSAS severity risk was unclear which needed further detailed study. Seventh, another two studies (ineligible studies) already declared the HCT and NLR were decreased after CPAP therapy in OSAS patients (65,66). But since the small sample size, further prospective study with adequate large sample size was desirable. At last, Heterogeneity in our meta-analysis was comparatively significant. But the sensitivity analyses couldn't found out the source of heterogeneity except the PLR subgroup. And although we changed median (Q25–Q75) into mean ± SD following the Cochrane handbook, it still might cause bias.

Suggestions for future

However, because all eligible studies were preliminary researches, the result of our meta-analysis was considered as a proposal. Further prospective studies are warranted to implement the finding to evaluate the prognostic outcomes of OSAS patients with elevated hematological indices, the practical utility in improving cardiovascular outcomes and monitoring the effects of continuous positive airway pressure (CPAP) therapy.

Therefore, we make four suggestions for further research. First, more research data in this field from different countries are needed for the present studies are mainly from Turkey. Second, it is supposed to use classical established inflammatory markers like IL6 as a reference for comparison during detection process. Third, the cut-off point of hematological indices values determining an individual's OSAS severity risk need further detailed study. Researchers may use receiver operating characteristic (ROC) curve analysis to determine the cut-off value of hematological indices when used to predict the severity or complication of OSAS, because ROC analysis could provide sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for all tests respectively. Fourth, further prospective studies with adequate large sample size are warrant, which might focus on the change of hematological parameters in OSAS patients before and after medical or surgical treatment.

Conclusions

Hematological indices are comparatively simple, inexpensive and practical severity markers of obstructive sleep apnea syndrome including WBC, LYM, NLR, MPV, PDW, PLR, RDW and HCT. But further prospective studies are warranted to substantiate our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Demographic data of eligible studies

Author	Year	Total size	Group*	AHI	Size	Age	BMI (kg/m^2)	Male (%)
Sunnetcioglu	2018	600	Control	2.6±1.4	197	40±11.5	28.3±4.7	152 (77.1)
			Mild OSAS	9.2±3.1	149	44.5±11.3	30.1±5.2	113 (75.8)
			Moderate OSAS	21.5±4	98	48.7±10.5	32±6.8	69 (70.4)
			Severe OSAS	57.6±24.1	156	48.5±12	33±7.1	122 (78.2)
Song	2016	290	Control	NA	61	44±15.4	24.2±4.43	33 (54.1)
			Mild OSAS	NA	67	48.2±13.4	24.7±3.2	39 (58.2)
			Moderate OSAS	NA	61	49.1±11.8	26.4±3.58	41 (67.2)
			Severe OSAS	NA	101	51.4±12.5	26.9±3.41	80 (79.2)
Uygur	2016	289	Control	2.2±1.3	118	50.3±11.7	29.4±7.8	61 (57.0)
			Mild OSAS	11.3±2.2	57	53.7±10.8	30.8±5.7	36 (21.0)
			Moderate OSAS	23.7±3.6	53	51.8±12.1	31.6±8.1	30 (23.0)
			Severe OSAS	56.1±18.7	61	54.5±12.7	32.1±7.1	39 (22.0)
Altintas	2015	561	Control	NA	80	47.3±10.8	32.5±7.8	56 (70.0)
			Mild OSAS	9.83±2.66	163	48.9±12.8	32.4±7.3	90 (73.0)
			Moderate OSAS	21.44±4.46	158	48.3±10.8	32.6±8.4	111 (70.0)
			Severe OSAS	62.8±25.01	160	48.9±10.5	34.3±7.5	110 (69.0)
Korkmaz	2015	146	Control	NA	40	43.4±11.14	29.27	14 (35.0)
			Mild OSAS	NA	27	44.96±9.25	29.15	18 (67.0)
			Moderate OSAS	NA	37	47.24±9.12	31.97	21 (57.0)
			Severe OSAS	NA	42	49.35±9.79	32.6	26 (62.0)
Koseoglu	2015	424	Control	2.6±2.1	57	43.5±11.2	29±4.8	23 (40.0)
			Mild OSAS	10.6±7.2	93	51.1±8.6	30.2±4.8	58 (62.0)
			Moderate OSAS	21.8±3.8	82	51.1±10.9	32.4±6.4	62 (76.0)
			Severe OSAS	58.5±24.1	192	51.6±10.6	35.3±7.2	139 (72.0)
Koseoglu	2015	284	Control	NA	48	43.08±8.88	27.0±3.76	29 (60.4)
			Mild OSAS	NA	67	47.2±10.14	30.67±4.6	167 (70.7)
			Moderate OSAS	NA	61			
			Severe OSAS	NA	108			
Yenigun	2015	136	Control	NA	38	48.08±8.82	30.5±6.16	20 (52.0)
			Mild OSAS	NA	34	46.75±8.06	33.9±6.79	24 (70.0)
			Moderate OSAS	NA	30	53.64±12.6	33.5±6.66	14 (46.0)
			Severe OSAS	NA	34	52.9±12.21	36.1±6.63	18 (53.0)
Sokucu	2014	200	Control	2.84±1.41	30	38.4±12.29	26.9±4.61	15 (50.0)
			Mild OSAS	9.58±2.91	38	43.5±12.15	29.1±4.51	30 (78.9)
			Moderate OSAS	21.12±3.88	41	47.2±10.95	30.0±4.52	33 (80.5)
			Severe OSAS	54.1±18.81	91	45.6±10.15	31.7±4.53	76 (83.5)
Kanbay	2013	205	Control	NA	35	51.2±12.6	29.2±8.4	22 (63.0)
			Mild OSAS	NA	20	55.6±11.6	31.4±5.2	13 (65.0)
			Moderate OSAS	NA	42	52.9±13.3	31.7±7.5	20 (47.0)
			Severe OSAS	NA	108	55.5±11.9	32.4±6.1	74 (68.0)
Karakas	2013	124	Control	NA	31	46.7±8.4	28.9±2.9	NA
			Mild OSAS	10.3±3	30	46.1±8.2	28.4±3.1	NA
			Moderate OSAS	21.5±3.5	32	48.3±7.6	28.7±2.7	NA
			Severe OSAS	59.4±15.9	31	47.3±7.7	29.2±2.9	NA
Kurt	2013	98	Control	NA	20	46.3±13.1	29.4±4.9	11 (55.0)
			Mild OSAS	NA	15	51.7±8.9	28.4±3.3	11 (73.0)
			Moderate OSAS	NA	26	53.9±12.4	31.7±4.8	15 (58.0)
			Severe OSAS	NA	37	58.1±10.9	33.2±5.7	25 (68.0)
Nena	2012	610	Control	NA	148	53.4±12.5	35±7.2	NA
			Mild OSAS		121			
			Moderate OSAS		85			
			Severe OSAS		256			
Ozsu	2012	137	Control	2.5±1.4	25	50 [23–67]	30 [25–41]	7 (28.0)
			Mild OSAS	10.5±3.4	15	51 [21–77]	32.4 [24–69]	9 (60.0)
			Moderate OSAS	21.7±3.7	26	49 [21–76]	27 [22–52]	18(69.0)
			Severe OSAS	60.2±22	71	53 [30–73]	32 [21–62]	51 (72.0)
Varol	2011	56	Control	2.8±1.6	25	49.6±8.5	30.9±2.9	14 (56.0)
			Severe OSAS	55.8±15.1	31	53.8±9.2	32.5±3.3	21 (67.0)
Varol	2010	95	Control	2.6±1.4	24	45.6±13.9	28.2±5	14 (58.0)
			Mild-moderate OSAS	15.6±7.5	42	50.1±9.3	29±4.1	22 (52.0)
			Severe OSAS	56.5±22.4	29	49.6±10.2	31.5±4	21 (72.0)
Choi	2006	263	Control	2.8±1.3	61	37.6±8.4	24.9±3.8	29 (37.7)
			Mild-moderate OSAS	15.7±7.3	91	44.1±8.9	28.5±5	62 (68.1)
			Severe OSAS	67.2±25.8	111	47.3±9.3	32±5.5	98 (88.3)

Total was based on means and standard deviations, except that Ozsu was based on medians and ranges. *, according to the AHI, all eligible studies subjects were categorized into four groups: control subjects (AHI <5 events/hour), mild subjects (5 events/hour ≤ AHI ≤15 events/hour, moderate subjects (15 events/hour ≤ AHI ≤30 events/hour) and severe subjects (AHI e30 events/hour). AHI, apnea-hypopnea index; BMI, body mass index.

Table S2 Quality assessment of included studies using the EPHPP tool*

Author/year	Overall quality assessment	Quality assessment for study components			
		Selection bias	Study design	Data collection methods	Confounders
Sunnetcioglu 2018	Strong	Strong	Moderate	Strong	Moderate
Song 2016	Strong	Strong	Moderate	Strong	Moderate
Uygur 2016	Strong	Strong	Moderate	Strong	Moderate
Altintas 2015	Strong	Strong	Moderate	Moderate[1]	Strong
Korkmaz 2015	Strong	Strong	Moderate	Strong	Strong
Koseoglu 2015	Strong	Strong	Moderate	Strong	Moderate
Koseoglu 2015	Strong	Strong	Moderate	Strong	Strong
Yenigun 2015	Strong	Strong	Moderate	Strong	Strong
Sökücü 2014	Strong	Strong	Moderate	Strong	Moderate
Kanbay 2013	Strong	Strong	Moderate	Strong	Moderate
Karakas 2013	Strong	Strong	Moderate	Strong	Strong
Kurt 2013	Strong	Strong	Moderate	Strong	Moderate
Nena 2012	Strong	Strong	Moderate	Strong	Strong
Ozsu 2012	Strong	Strong	Moderate	Strong	Moderate
Varol2011	Strong	Strong	Moderate	Strong	Moderate
Varol2010	Strong	Strong	Moderate	Strong	Moderate
Choi 2006	Strong	Strong	Moderate	Strong	Strong

*, EPHPP: Effective Public Health Practice Project tool (Hamilton, Ontario, Canada); [1], original data was based on median (Q25–Q75), and we changed it into mean ± SD, according to the Cochrane handbook.

Table S3 Detailed primary data of each hematological parameters

Group	Author/year	Control group			Mild OSAS group			Moderate OSAS group			Severe OSAS group		
		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
WBC (10^9/L)	Altintas 2015	80	3.34	0.45	163	3.37	0.49	158	3.32	0.526	160	4.29	0.319
	Uygur 2016	118	6.1	1.3	57	6.7	1.2	53	7.2	1.4	61	7.8	1.5
	Kanbay 2013	35	8.6	1.8	20	9.2	1.4	42	7.8	1.6	108	8.8	2.3
	Korkmaz 2015	40	6.999	1.566	27	7.751	2.27	37	7.039	1.55	42	7.194	1.491
	Kurt 2013	20	7.636	1.872	15	7.375	1.66	26	7.04	1.355	37	7.506	1.656
	Sökücü 2014	30	7.08	1.37	38	7.27	1.97	41	7.83	1.79	91	7.89	1.99
	Yenigun 2015	38	6.61	1.13	34	8.32	1.76	30	8.2	1.87	34	9.34	1.33
	Song 2016	61	6.759	1.806	67	7.283	2.031	61	7.314	2.976	101	7.724	2.051
	Choi 2006	61	5.7	1.8	–	–	–	–	–	–	111	6.6	1.9
	Varol 2010	24	8.6	2.2	–	–	–	–	–	–	29	8.8	2.5
	Varol 2011	25	8.2	1.5	–	–	–	–	–	–	31	7.5	1.6
	Total or average	532	6.874	–	421	7.159	—	448	6.968	–	805	7.586	–
LYM (10^9/L)	Uygur 2016	118	2.3	1.3	57	2	1.2	53	1.7	1.4	61	1.5	1.2
	Korkmaz 2015	40	2.309	0.6	27	2.488	0.598	37	2.448	0.587	42	2.52	0.641
	Koseoglu 2015	57	2.98	0.68	93	2.68	0.65	82	2.61	0.72	192	2.28	0.68
	Yenigun 2015	38	2.37	0.56	34	2.86	0.54	30	2.34	0.94	34	2.07	0.67
	Song 2016	61	3.61	0.987	67	3.3	1.28	61	3	0.922	101	2.74	0.835
	Total or average	314	2.714	–	278	2.666	–	263	2.419	–	430	2.222	–
NLR	Altintas 2015	80	1.52	0.46	163	1.54	0.44	158	1.63	0.56	160	2.37	0.63
	Uygur 2016	118	1.81	0.5	57	2.39	0.6	53	3.34	0.9	61	4.18	1.1
	Korkmaz 2015	40	1.8	0.64	27	1.78	0.57	37	1.57	0.54	42	1.61	0.56
	Koseoglu 2015	48	2.017	0.85	67	1.97	1.25	61	1.87	0.66	108	1.85	0.64
	Yenigun 2015	38	1.7	0.71	34	1.69	0.69	30	2.44	1.44	34	3.37	1.21
	Total or average	324	1.769	–	348	1.874	–	339	2.17	–	405	2.676	–
MPVfL	Uygur 2016	118	7.9	1.2	57	8.1	0.9	53	8	1.1	61	8.1	1
	Karakas 2013	31	7.8	0.9	30	8.3	1.2	32	8.4	1.3	31	8.6	1.1
	Kurt 2013	20	8.2	1.1	15	8.5	1	26	8.3	1	37	8.2	0.9
	Koseoglu 2015	57	6.64	0.54	93	7.26	0.7	82	7.58	0.9	192	9.8	5.04
	Nena 2012	148	9.8	1.1	121	9.8	1.6	85	11.5	1.3	256	12.1	1.3
	Sökücü 2014	30	9.21	0.75	38	9.36	0.94	41	9.33	0.72	91	9.37	1.02
	Varol 2010	24	8.2	0.7	–	–	–	–	–	–	29	8.9	1
	Varol 2011	25	8.3	0.96	–	–	–	–	–	–	31	8.5	0.59
	Total or average	453	8.256	–	354	8.553	–	319	8.851	–	728	9.196	–
PDW (%)	Uygur2016	118	13.4	0.6	57	14.1	1.7	53	13.9	1.4	61	14.5	1.9
	Kurt 2013	20	13.2	0.5	15	14.1	1.6	26	13.8	1.2	37	14.4	1.8
	Koseoglu 2015	57	17.5	1.03	93	17.8	1.1	82	17.9	1.04	192	17.8	1.57
	Nena 2012	148	13.2	2.2	121	14.1	2.8	85	15	2.2	256	15.9	2.2
	Sokucu2014	30	15.71	2.12	38	16.19	2.34	41	15.67	1.91	91	15.84	2.88
	Song 2016	61	15.9	1.12	67	16.3	0.95	61	16.4	0.99	101	16.5	0.82
	Total or average	434	14.818	–	391	15.431	–	348	15.445	–	738	15.823	–
PLR	Koseoglu 2015	57	87.38	22.9	93	95.07	31.3	82	97.01	29.1	192	126.9	39.4
	Koseoglu 2015	48	123.97	35.34	67	112.4	38.35	61	113.59	35.16	108	105.4	32.98
	Song 2016	61	99.5	42.1	67	113.8	45.2	61	121.3	62.9	101	138.6	59.9
	Total or average	166	103.61	–	227	107.09	–	204	110.63	–	401	123.63	–
RDW (%)	Uygur 2016	118	13.1	1.1	57	13.2	0.9	53	13.9	1.6	61	14.5	1.9
	Kurt 2013	20	16.5	0.4	15	16.6	0.7	26	16.6	0.6	37	16.8	0.6
	Koseoglu 2015	57	15.7	1.07	93	15.9	1.54	82	15.7	1.13	192	16.3	1.8
	Sunnetcioglu 2017	197	13.5	1.3	149	13.8	1.4	98	13.9	1.7	156	15.7	7.1
	Song 2016	61	13.5	1.57	67	13.3	1.25	61	13.5	1.05	101	13.3	0.76
	Total or average	453	14.46	–	381	14.56	–	320	14.72	–	547	15.32	–
HCT (%)	Sökücü 2014	30	43.76	4.24	38	44.93	3.89	41	44.29	7.27	91	44.91	5.87
	Song 2016	61	40.2	4.4	67	41.2	4.2	61	40.2	6.6	101	42.5	4.5
	Choi 2006	61	39.8	4	–	–	–	–	–	–	111	43.5	3.6
	Total or average	152	41.25	–	105	43.07	–	102	42.25	–	303	43.64	–

WBC, white blood cell; LYM, lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; HCT, hematocrit; RDW, red cell distribution width; MPV, mean platelet volume; PDW, platelet distribution width.

Table S4 Random-effects pooled WMD for association between Hematological Parameters and severity of OSAS

Subgroup	Severity	OSAS subjects without CVD	OSAS subjects with/without CVD	All OSAS subjects
WBC	Mild OSAS	0.80 [–0.36, 1.96] (P=0.18); I^2=92% (P<0.00001)	0.48 [0.20, 0.77] (P =0.0008); I^2=0% (P=0.65)	0.52 [0.10, 0.94] (P=0.01); I^2=78% (P<0.0001)
	Moderate OSAS	0.49 [–0.40, 1.37] (P=0.28); I^2=88% (P=0.0002)	0.24 [–0.54, 1.03] (P=0.54); I^2=83% (P=0.0001)	0.35 [–0.16, 0.86] (P=0.18); I^2=86% (P<0.00001)
	Severe OSAS	1.29 [0.12, 2.47] (P=0.03); I^2=95% (P<0.00001)	0.56 [0.00, 1.12] (P=0.05); I^2=81% (P<0.00001)	0.79 [0.35, 1.23] (P=0.0005); I^2=87% (P<0.00001)
Neutrophil	Mild OSAS	0.04 [–0.07, 0.15] (P=0.50); I^2=0% (P=0.35)	0.78 [0.52, 1.03] (P<0.00001); I^2=0% (P=0.50)	0.54 [0.09, 1.00] (P=0.02); I^2=87% (P<0.00001)
	Moderate OSAS	–0.10 [–0.21, 0.01] (P=0.09); I^2=0% (P=0.57)	1.00 [–0.02, 2.01] (P=0.05); I^2=94% (P<0.00001)	0.53 [–0.30, 1.35] (P=0.21); I^2=97% (P<0.00001)
	Severe OSAS	–0.30 [–0.40, –0.20]; (P<0.00001) I^2=0% (P=0.44)	1.93 [0.43, 3.42] (P=0.01); I^2=95% (P<0.00001)	1.03 [–0.04, 2.11] (P=0.06); I^2=98% (P<0.00001)
Lymphocyte	Mild OSAS	0.34 [0.04, 0.65] (P=0.03); I^2=60% (P=0.12)	–0.30 [–0.47, –0.13] (P=0.0006); I^2=0% (P=1.00)	–0.04 [–0.38, 0.31] (P=0.84); I^2=85% (P<0.0001)
	Moderate OSAS	0.08 [–0.13, 0.30] (P=0.45); I^2=0% (P=0.48)	–0.47 [–0.65, –0.30] (P<0.00001); I^2=0% (P=0.43)	–0.28 [–0.58, 0.02] (P=0.06) I^2=77% (P=0.002)
	Severe OSAS	–0.04 [–0.54, 0.46] (P=0.87) I^2=85% (P=0.01)	–0.76 [–0.91, –0.61] (P<0.00001) I^2=0% (P=0.63)	–0.49 [–0.88, –0.09] (P=0.02); I^2=90% (P<0.00001)
NLR	Mild OSAS	0.01 [–0.10, 0.12] (P=0.87); I^2=0% (P=0.93)	0.30 [–0.28, 0.88] (P=0.31); I^2=90% (P=0.002)	0.12 [–0.16, 0.40] (P=0.40); I^2=86% (P<0.00001)
	Moderate OSAS	–0.06 [–0.30, 0.17] (P=0.59); I^2=69% (P=0.04)	1.18 [0.41, 1.95] (P=0.003); I^2=84% (P=0.01)	0.39 [–0.23, 1.02] (P=0.22); I^2=97% (P<0.00001)
	Severe OSAS	0.17 [–0.60, 0.94] (P=0.66); I^2=97% (P<0.00001)	2.04 [1.36, 2.73] (P<0.00001); I^2=84% (P=0.01)	0.90 [0.04, 1.76] (P=0.04); I^2=98% (P<0.00001)
MPV	Mild OSAS	0.21 [–0.28, 0.69] (P=0.40); I^2=59% (P=0.12)	0.35 [0.07, 0.63] (P=0.01); I^2=60% (P =0.06)	0.30 [0.06, 0.55] (P=0.02); I^2=62% (P=0.02)
	Moderate OSAS	1.17 [0.10, 2.25] (P=0.03); I^2=91% (P=0.0008)	0.34 [–0.17, 0.85] (P=0.19); I^2=83% (P<0.0001)	0.61 [0.07, 1.15] (P=0.03); I^2=92% (P<0.00001)
	Severe OSAS	1.57 [0.10, 3.04] (P=0.04); I^2=96% (P<0.00001)	0.69 [0.05, 1.33] (P=0.04); I^2=92% (P<0.00001)	0.93 [0.13, 1.72] (P=0.02); I^2=97% (P<0.00001)
PDW	Mild OSAS	0.90 [0.29, 1.51] (P=0.004)	0.46 [0.25, 0.67] (P<0.0001); I^2=0% (P=0.55)	0.51[0.31, 0.70] (P<0.00001); I^2=0% (P=0.44)
	Moderate OSAS	1.80 [1.21, 2.39] (P<0.00001)	0.46 [0.27, 0.66] (P<0.00001); I^2=0% (P=0.82)	0.64 [0.26, 1.03] (P=0.001); I^2=74% (P =0.02)
	Severe OSAS	2.70 [2.25, 3.15] (P<0.00001)	0.68 [0.32, 1.05] (P=0.0002); I^2=65% (P=0.02)	1.02 [0.26, 1.79] (P=0.008); I^2=94% (P<0.00001)
PLR	Mild OSAS	–11.57 [–25.14, 2.00] (P=0.09)	9.34 [1.79, 16.88] (P=0.02); I^2=0% (P=0.46)	3.53 [–10.25, 17.31] (P=0.62); I^2=73% (P=0.02)
	Moderate OSAS	–10.38 [–23.71, 2.95] (P=0.13)	12.66 [2.35, 22.97] (P=0.02); I^2=23% (P=0.25)	6.21 [–10.08, 22.49] (P=0.46); I^2=78% (P=0.01)
	Severe OSAS	–18.57 [–30.34, –6.80] (P=0.002)	39.43 [32.19, 46.67] (P<0.00001); I^2=0% (P=0.96)	19.97 [–18.77, 58.71] (P=0.31); I^2=97% (P<0.00001)
RDW	Mild OSAS	–	0.14 [–0.02, 0.31] (P=0.08); I^2=0 (P=0.53)	–
	Moderate OSAS	–	0.24 [–0.03, 0.51] (P=0.08); I^2=58 (P=0.05)	–
	Severe OSAS	–	0.72 [0.15, 1.29] (P=0.01); I^2=88% (P<0.00001)	–
HCT	Mild OSAS	–	1.06 [–0.12, 2.25] (P=0.08); I^2=0% (P=0.89)	–
	Moderate OSAS	–	0.19 [–1.41, 1.79] (P=0.82); I^2=0% (P=0.76)	–
	Severe OSAS	–	2.53 [1.12, 3.94] (P=0.0004); I^2=63% (P=0.07)	–

OSAS, obstructive sleep apnea syndrome; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; HCT, hematocrit.

Table S5 Publication bias of each subgroup using Stata SE12.0

Subgroup	Included studies	Begg's test	Egger's test
WBC	11	0.081	0.082
Lymphocyte	5	0.480	0.589
NLR	5	0.322	0.883
MPV	8	0.651	0.121
PDW	6	0.129	0.079
PLR	3	1.000	0.820
RDW	5	0.480	0.592
HCT	3	0.296	0.217

All studies were without publication bias (P>0.05). WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; MPV, mean platelet volume; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; HCT, hematocrit.