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Hypoxia and inflammation indicate significant differences in the severity of obstructive sleep apnea within similar apnea-hypopnea index groups

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Abstract
Purpose We determined whether hypoxia parameters are associated with C-reactive protein (CRP), mean platelet volume (MPV), white matter hyperintensity (WMH), and the severity of obstructive sleep apnea (OSA), and also evaluated whether hypoxia parameters, CRP, MPV, and WMH differ in patients with similar apnea-hypopnea index (AHI) scores.
Methods A total of 297 patients, who were evaluated using polysomnography, were assessed retrospectively. The measured hypoxia parameters included total sleep time with oxygen saturation <90% (ST_{90}), percentage of cumulative time with oxygen saturation <90% (CT_{90}), and lowest oxygen saturation (min SaO_2). The patients were divided into subgroups according to their CT_{90} values, and patients with different AHI severities were divided into subgroups according to their ST_{90} and min SaO_2 levels.
Results Hypoxia parameters are associated with CRP, MPV, WMH, and the severity of OSA ($P < 0.05$). The hypoxia parameters differed in all subgroup analyses of similar AHI groups ($P < 0.001$), and CRP differed only in severe OSA ($P < 0.008$, $P < 0.001$). In subgroup analyses of similar AHI groups, MPV and WMH were not significantly different ($P > 0.05$). Above the hypoxia threshold ($CT_{90} \geq 10\%$) of CRP, MPV increased significantly and the presence of WMH increased twofold.
Conclusions These data suggest that increased hypoxia severity may mediate increased inflammation and activation of platelets and contribute to the pathogenesis of WMH in patients with OSA. In addition, patients with severe OSA may show significant variability in inflammation and vascular risk. Further prospective data are needed.

Keywords C-reactive protein · Hypoxia · Inflammation · Platelets · Sleep disordered breathing · White matter hyperintensity

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of upper airway partial or complete collapse during sleep, resulting in hypopnea or apnea. The severity of OSA is traditionally stratified using the apnea-hypopnea index (AHI), regardless of the duration or morphology of apnea or hypopnea episodes [1]. Thus, AHI does not completely reflect the severity of hypoxia [2, 3]. In addition, patients who have similar AHI may have different clinical symptoms and outcomes. Deeper and longer oxygen desaturation events presumably contribute more to physiological stress and harmful health consequences than shallower and shorter events. In addition, patients with severe hypoxia, despite having a similar AHI, may have more severe physiological stress and cardiovascular consequences and could even die [3]. On the other hand, the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events classifies the severity of OSA according to the AHI, and it is recommended that nocturnal hypoxia be classified using the lowest oxygen saturation (min SaO_2) value [1]. Due to the lack of a more

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precise definition, there is no universally accepted quantitative clinical test to measure the intensity and/or severity of chronic intermittent hypoxia [4].

An association among OSA, cardiovascular disease, and coagulation abnormalities has been suspected for many years, although the mechanisms that mediate this association are still not completely understood. However, episodic collapse of the upper airway leads to chronic intermittent hypoxia, triggering oxidative stress and chronic inflammation and giving rise to detrimental effects on cardiovascular, neurocognitive, and metabolic functions [5]. The inflammatory processes leading to endothelial dysfunction also induce atherosclerosis in OSA [5, 6]. C-reactive protein (CRP) is a prototypic marker of inflammation and has an active role in atherogenesis by promoting expression of adhesion molecules. CRP levels may be an independent predictor of future cardiovascular events in apparently healthy subjects and patients who are diagnosed with cardiovascular disease [7]. Hypoxemia and increased oxidative stress are important mechanisms related to increased systemic inflammation in OSA [6]. An association between OSA and systemic inflammatory markers has been reported in several studies [2, 8].

Chronic intermittent hypoxia inducing sympathetic hyperactivity as well as high blood pressure and hemodynamic changes, including hypercoagulability and platelet activation, have been demonstrated in OSA. The cause of increased platelet activation remains unclear, but the severity of OSA seems to influence platelet aggregation as a function of nocturnal hypoxia [9]. Platelets play an important role in thrombosis, inflammation, and atherogenesis and activated platelets function in cardiovascular disease and complications [10]. Platelet volume is a recent marker of platelet activation and function, and mean platelet volume (MPV) is an indicator of platelet activation [11]. Increased MPV is associated with cardiovascular disease and vascular risk factors [10]. Furthermore, previous studies have demonstrated that high MPV is associated with OSA [12, 13].

In brain magnetic resonance imaging (MRI), cerebral white matter hyperintensities (WMH) are hyperintense lesions in the periventricular or subcortical areas on T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences [14]. Although the pathological correlates of WMH are heterogeneous, the presence of focal myelinolysis, axonal loss, and gliosis associated with vessel wall hyalinosis suggests that chronic hypoperfusion may contribute to the development of WMH [15]. In addition, the association of vascular risk factors with WMH in OSA may explain why the pathogenesis of WMH is vascular in nature [16]. WMH are an important public health issue because they are associated with stroke, dementia, and death and may also be associated with OSA and CRP [16–18].

In this study, patients within the AHI severity categories were divided into subgroups based on total sleep time with oxygen saturation <90% (ST_{90}), percentage of cumulative time with oxygen saturation <90% (CT_{90}), and min SaO_2. Then, we determined whether hypoxia parameters are associated with CRP, MPV, WMH, and severity of OSA and also evaluated whether hypoxia parameters, CRP, MPV, and WMH differ in patients with varying OSA severity but similar AHI scores.

Materials and methods

Study design and patients

This study was performed at Baskent University Alanya Research and Medical Center (Alanya, Turkey). The medical charts of patients who underwent a complete polysomnography (PSG) test at our sleep disorder center (accredited by the Turkish Sleep Association) between October 2008 and October 2015 were evaluated. In total, 297 patients whose medical records contained CRP levels, complete blood counts, and MRI scans were included after application of exclusion criteria. Laboratory tests, CRP and MPV values, and the presence of WMH on MRI scans were collected retrospectively from the patients' medical records. Patients aged ≥18 years who had no anemia, no active infection, and CRP levels <10 mg/L were included in the study. Age, sex, body mass index (BMI), Epworth Sleep Scale (ESS), and hypoxia parameters, including min SaO_2, ST_{90}, CT_{90}, and sleep time, were calculated and recorded from the patients' PSG records. The presence of medical comorbidities including history of hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, cerebrovascular disease, and smoking status was recorded. Patients were excluded if they had central sleep apnea syndrome, narcolepsy, previous treatment for OSA (continuous positive airway pressure, surgery, and/or oral device), age <18 years, chronic obstructive pulmonary disease, bronchial asthma, dementia, renal failure, hepatic damage, malignancy, head trauma, or a brain tumor. Participants who had high CRP levels (≥10 mg/L) were excluded, because high CRP levels can result from non-specific inflammation and therefore might not provide a positive predictive value [7].

Thus, 223 OSA patients and 74 control subjects were included. Participants were divided into the following four groups based on their AHI: (1) normal/simple snoring, AHI < 5; (2) mild OSA, AHI 5 to <15; (3) moderate OSA, AHI 15 to <30; and (4) severe OSA, AHI ≥ 30. All of the participants were divided into the $CT_{90} < 10\%$ or $CT_{90} \geq 10\%$ hypoxia categories according to Zhang et al. [19]. In addition, the patients within the AHI severity categories were divided into subgroups according to the lowest and highest ST_{90} and lowest and highest min SaO_2.

This study was evaluated and determined to be exempt from the requirement for informed consent by the Baskent University Institutional Review Board due to its retrospective study design.

PSG

All of the study participants underwent PSG at a sleep laboratory using a computerized PSG device (E series, 44 channels; Compumedics, Victoria, Australia). During the PSG study (16 channels), the following parameters were documented: four-channel electroencephalogram, electrooculogram, submental and leg electromyogram, electrocardiogram, nasal airflow using a nasal pressure cannula, airflow at the nose and mouth (thermistors), chest and abdominal respiratory movements, oxygen saturation (pulse oximetry), snoring microphone, and body position. All of the studies were interpreted by a sleep specialist who was blinded to the participants' characteristics. Apnea was defined as cessation of airflow for ≥10 s with continued effort (obstructive) or lack of effort (central) to breathe. Hypopnea was defined as >50% decrease in a valid measure of airflow without a requirement for associated oxygen desaturation or arousal, and with less airflow reduction in association with oxygen desaturation >3% or an arousal of at least 10 s. The ST_{90} was recorded in minutes, and min SaO_2 and CT_{90} were recorded as percentages. The min SaO_2 value was the lowest oxygen saturation during sleep. Sleep staging was performed according to the American Academy of Sleep Medicine criteria [1].

Laboratory measurements

Blood samples in phlebotomy tubes containing no anticoagulant were centrifuged at 3000 *g* for 10 min and subsequently analyzed. Serum CRP was measured using latex-enhanced immunoturbidimetry with monoclonal anti-CRP antibodies (Architect C 800, Abbott Diagnostic Systems, Abbott Park, IL, USA) (CRP reference level, ≤8 mg/L).

Blood samples in ethylenediaminetetraacetic acid (EDTA) tubes were analyzed using electrical impedance and optical fluorescence methods in an automated hematology analysis device (CELL-DYN Ruby, Diagnostic Systems, Abbott Park, IL, USA). The hematologic parameters measured included leukocyte count (reference range, 4.5 to 11 × 10^9/L), neutrophil count (2 to 6.9 × 10^9/L), lymphocyte count (0.6 to 3.4 × 10^9/L), hemoglobin (female, 12 to 16.5 mg/dL; male, 13.5 to 17.50 mg/dL), platelet count (140 to 440 × 10^9/L), MPV (0 to 99.9 femtoliters [fL]), and red cell distribution width (RDW) (11.6 to 17%).

The presence of WMH was evaluated by MRI of the whole brain. All of the MRI brain scans (1.0 Tesla, Siemens Magnetom Vision Plus, Siemens, Munich, Germany) were performed with the orbitomeatal line as a reference. The scans included ≥3 sequences as follows: sagittal T1-weighted, axial T2-weighted, and axial FLAIR images. The slice thickness was 5 mm, the gap was 1 mm, and no intravenous contrast was used. All of the MRI scans were reviewed and scored by a radiologist who was blinded to the clinical details. The scan results were reinvestigated for the presence of WMH.

Statistical analysis

Data analysis was performed using statistical software (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA). Continuous variables were reported as means ± standard deviations or medians (ranges). Categorical variables were reported as numbers (%). The normality of continuous variables was evaluated using Kolmogorov Smirnov tests. The similarities among groups were evaluated using variance Levene's tests. Differences in continuous variables between two groups were evaluated using independent samples *t* tests or Mann-Whitney tests. Comparisons between more than two groups were evaluated using one-way analysis of variance or Kruskal-Wallis tests. Pairwise comparisons were evaluated using Tukey's tests and Siegel Castellan's tests. Categorical variables were compared using Pearson's $\chi 2$ tests (chi-square tests). The relationships between continuous variables were determined using Spearman's rank correlation. Multiple stepwise linear regression analyses were used to determine the factors affecting ST_{90} and minSaO_2. The best MPV cutoff value for discriminating the hypoxia threshold ($CT_{90} \geq 10\%$) was determined using ROC curve analysis. The area under the curve (AUC), sensitivity, specificity, and negative and positive predictive values were calculated. Statistical significance was defined as $P \leq 0.05$.

Results

Comparisons of the demographic characteristics of the OSA and control groups are shown in Table 1. The odds ratio (OR) of WMH in the OSA group compared with the control group was 3.2 (95% confidence interval [CI] 1.84–5.71; $P < 0.001$). Univariate analyses revealed significant correlations between ST_{90} and age ($r = 0.370$), BMI ($r = 0.360$), AHI ($r = 0.808$), ESS ($r = 0.152$), CRP ($r = 0.433$), MPV ($r = 0.346$), and WMH (ESS, $P = 0.009$; all other parameters, $P < 0.001$). Univariate analyses also revealed significant inverse correlations between min SaO_2 and age ($r = -0.404$), BMI ($r = -0.385$), AHI ($r = -0.771$), ESS ($r = -0.149$), MPV ($r = -0.387$), and WMH (ESS, $P = 0.010$; all other parameters, $P < 0.001$). After adjusting for confounders, multiple linear regression revealed that ST_{90} was independently positively correlated with AHI ($r = 1.356$, $P < 0.001$), BMI ($r = 1.081$, $P = 0.038$), and CRP ($r = 2.772$, $P = 0.033$), and negatively correlated with min SaO_2 ($r = -2.926$, $P < 0.001$).

Table 1 Comparisons of the apnea-hypopnea index groups

Characteristic		Control	Mild OSA	Moderate OSA	Severe OSA	*P*
Apnea-hypopnea index (events/h)		<5	5 to <15	15 to <30	≥30	
No. of patients		74	69	55	99	
Age (years)		44 ± 13	53 ± 12	55 ± 12	57 ± 14	0.001[b]
Gender	Female	37 (50)	30 (44)	16 (29)	19 (19)	0.001
	Male	37 (50)	39 (57)	39 (71)	80 (81)	
Body mass index (kg/m^2)		28 ± 5	31 ± 6	32 ± 4	33 ± 5	0.001[c]
C-reactive protein (mg/L)		1.1 (0.1–5.8)	1.9 (0.2–9.7)	2.3 (0.8–9.3)	3.3 (0.60–9.9)	0.001[c]
Mean platelet volume (fL)		7.6 ± 1.2	8.1 ± 1.0	8.5 ± 1.3	9.1 ± 1.4	0.001[d]
ST_{90} (min)		0.2 (0–16.3)	0.9 (0–18.5)	6.9 (0–40.2)	42.9 (0.3–328)	0.001
CT_{90} (%)		0.04 (0–3.4)	0.2 (0–3.8)	1.8 (0–9.3)	10.9 (0.1–88.7)	0.001
Min SaO_2 (%)		90 ± 4	87 ± 4	81 ± 8	74 ± 10.0	0.001[e]
Total sleep time (min)		434 ± 40	435 ± 47	427 ± 60	420 ± 57	NS
White matter hyperintensities		22 (30)	39 (57)	28 (51)	62 (63)	0.001
Hypertension		23 (31)	35 (51)	35 (64)	61 (62)	0.001
Coronary heart disease		7 (9.2)	24 (31.6)	25 (37.3)	35 (30.7)	0.001
Hyperlipidemia		11 (15)	17 (25)	12 (22)	25 (25)	NS
Diabetes mellitus		7 (10)	14 (20)	14 (25)	43 (43)	0.001
Smoking		29 (26)	16 (23)	9 (16)	14 (14)	NS
Multinodular goiter		7 (10)	5 (7)	4 (7)	7 (7)	NS
Cerebrovascular disease		–	3 (4)	4 (7)	8 (8)	0.04

Data are means ± standard deviation, numbers of subjects (%), or medians (range)

CT_{90} percentage of cumulative sleep time with oxygen saturation <90%, *min O_2* lowest oxygen saturation, *OSA* obstructive sleep apnea, *ST_{90}* total sleep time with oxygen saturation <90%, *AHI* apnea-hypopnea index

[a] The AHI < 5 group was different from the mild, moderate, and severe OSA groups

[b] The <5 group was different from the mild, moderate, and severe OSA groups. The mild OSA group differed from the severe OSA group

[c] The <5 group was different from the mild, moderate, and severe OSA groups. The severe OSA group differed from the mild, moderate, and control groups

[d] All groups differed from each other

After adjusting for confounders, multiple linear regression analyses revealed that min SaO_2 was independently negatively correlated with AHI ($r = -0.197$, $P < 0.001$), BMI ($r = -0.224$, $P = 0.007$), age ($r = -0.087$, $P = 0.005$), CRP ($r = -0.430$, $P = 0.038$), MPV ($r = -1.226$, $P < 0.001$), and ST_{90} ($r = -1.054$, $P < 0.001$).

All participants were divided into the $CT_{90} < 10\%$ and $CT_{90} \geq 10\%$ hypoxia subgroups (Table 2). The CT_{90} values of approximately half of the patients with severe OSA (51; 52% of patients) were ≥10%. The OR of WMH in the $CT_{90} \geq 10\%$ group was 2.21 (95% CI, 1.17–4.16; $P = 0.0145$). According to receiver-operating characteristic (ROC) analysis, a MPV value >8.34 fL could predict a threshold $CT_{90} \geq 10\%$ with a sensitivity of 77% and a specificity of 57% (AUC, 0.714; 95% CI, 0.659–0.765; $P < 0.001$).

In the subgroup analysis of ST_{90} and min SaO_2 within the AHI severity categories, hypoxia parameters (ST_{90}, CT_{90}, and min SaO_2) were significantly different in all OSA severity categories, and CRP values were significantly different only in the severe OSA group. MPV and WMH were not different in the subgroup analysis of hypoxia parameters in similar AHI groups (Tables 3 and 4).

Discussion

The main goal of this study was to evaluate the associations between hypoxia parameters (ST_{90}, CT_{90}, and min SaO_2) and CRP, MPV, and WMH on brain MRI with regard to OSA severity. This study revealed that ST_{90} and min SaO_2 were significantly correlated not only with CRP and MPV ($P < 0.001$) but also with WMH on brain MRI. In addition, a CT_{90} value ≥10% was reported to have clinical relevance [19, 27]. Above this threshold, CRP and MPV were significantly elevated and WMH was increased twofold in patients with OSA (Table 2). MPV can be used as a moderate quality

Table 2 Distribution of the parameters according to CT_{90} below and above 10%

Parameter		CT_{90} < 10 (*n* = 246)		CT_{90} ≥ 10%(*n* = 51)		*P*
Age (years)		51 ± 13		59 ± 14		0.001
Body mass index (kg/m^2)		31 ± 5		35 ± 5		0.001
Mean platelet volume (fL)		8.2 ± 1.3		9.2 ± 1.4		0.001
Total sleep time		430 ± 51		424 ± 53		NS
Apnea-hypopnea index (events/h)		11.1 (0–99)		58 (33–106)		0.001
Epworth sleepiness scale		9 (0–24)		12 (0–24)		0.004
C-reactive protein (mg/L)		2 (0.1–9.8)		4 (0.94–9.9)		0.001
ST_{90} (min)		1.63 (0–41)		109 (41–328)		0.001
Min SaO_2 (%)		86 (48–98)		68 (44–87)		0.001
		Number of patients	(%)	Number of patients	(%)	
Gender	Female	91	37	11	22	NS
	Male	155	63	40	78	NS
White matter hyperintensity		117	48	34	67	0.02
Hypertension		120	49	34	67	0.03
Coronary heart disease		63	26	16	31	NS
Hyperlipidemia		50	20	15	29	NS
Diabetes mellitus		53	22	25	49	0.001
Cerebrovascular disease		11	5	4	8	NS

Data are means ± standard deviation, numbers of subjects (%), or medians (range)

CT_{90} percentage of cumulative sleep time with oxygen saturation <90%, *min SaO_2* lowest oxygen saturation, *ST_{90}* total sleep time with oxygen saturation <90%

indicator of hypoxia threshold (CT_{90} ≥ 10%) at the optimal cutoff value 8.34 fL, with a sensitivity of 77% and a specificity of 57%. Furthermore, in subgroup analyses of the ST_{90} and min SaO_2 values in the different OSA severity categories, hypoxia parameters were different in all similar AHI groups and CRP levels significantly differed only in the severe OSA group (Tables 3 and 4). These data suggest that increased severity hypoxia may mediate increased inflammation and platelet activation and contribute to the pathogenesis of WMH in patients with OSA. In addition, patients with severe OSA may show significant variability in inflammation and vascular risk.

Previous studies have also reported an association between hypoxia parameters and CRP levels in patients with OSA [2, 8]. In one study, hypoxia was measured by pulse oximetry during sleep in the homes of middle-aged community residents [8]. In another study, ST_{90} was only evaluated in patients with severe OSA [2]. In this study, ST_{90} and min SaO_2 were independently correlated with CRP ($P < 0.033$ and $P < 0.038$, respectively). In addition, in a subgroup analysis of the hypoxia parameters in different OSA severities, CRP levels only significantly differed in the severe OSA group (Tables 3 and 4). CRP is an important inflammatory marker and predicts the vascular risk [7]. These findings suggest that despite similar AHI values, patients with severe hypoxia had a greater level of inflammation and increased vascular risk. However, variable results have been reported in previous studies [20, 21]. Guilleminault et al. reported that BMI was associated with CRP in OSA patients; however, the patients in that study were fewer and older than those in our study [20]. The Wisconsin Sleep Cohort Study reported that CRP levels were associated with BMI but not with OSA severity. The authors suggested that obesity might be the primary reason for the relationship between OSA and CRP levels [21]. The discrepancy with our results may be due to differences in subject characteristics and the methods used to assess OSA. This study included a greater percentage of males (66%) than the Wisconsin Sleep Cohort Study (55%), which may have affected the results, as obesity is associated with elevated levels of CRP and the association is stronger in women [22].

In this study, we found that OSA severity, ST_{90}, and min SaO_2 significantly correlated with MPV ($P < 0.001$). In a subgroup analysis of hypoxia parameters in similar AHI groups, MPV did not differ significantly (Tables 3 and 4). In addition, a higher MPV was an independent predictor of hypoxia. MPV can be used as a moderate quality indicator of hypoxia threshold (CT_{90} ≥ 10%) at the best cutoff value, 8.34 fL, with a sensitivity of 77% and a specificity of 57%. These findings suggest that a hypoxia above this threshold indicates an increased MPV turnover. Larger MPVs are enzymatically more active and associated with platelet reactivity and platelet activity, which increase in vascular diseases [10, 11]. Previous results showed that MPV is associated with the desaturation index, and another study reported that MPV is

Table 3 Relationships between measured variables of obstructive sleep apnea for patients with the lowest and highest ST_{90} in similar apnea-hypopnea groups

	AHI < 5		AHI 5–15		AHI 15–30		AHI ≥30	
	Lowest ST_{90}	Highest ST_{90}	Lowest ST_{90}	Highest ST_{90}	Lowest ST_{90}	Highest ST_{90}	Lowest ST_{90}	Highest ST_{90}
No. of patients	37	37	34	35	27	28	49	50
Age (years)	40 (22–78)	45 (28–76)	50 (20–77)	55 (37–76)	51 (36–75)	60 (28–83)	55 (23–82)	58 (35–84)
p	NS		0.017		0.008		NS	
Apnea-hypopnea index (events/h)	1.5 (0–4.9)	2.4 (0–4.8)	6.9 (5–14.4)	10.5 (5.1–18.5)	20.5 (15.2–29.3)	24.5 (15.1–29.6)	47.3 (30–98.5)	57.6 (33–105.9)
p	NS		0.002		NS		0.001	
Epworth sleepiness scale	8 (0–18)	8 (0–21)	10 (0–21)	10 (0–21)	10 (0–17)	12 (0–24)	9 (0–24)	12 (0–24)
p	NS		NS		NS		0.022	
ST_{90} (min)	0 (0–18)	0.6 (0.2–16.3)	0.23 (0–0.98)	2.22 (0.57–18.45)	1.65 (0–6.87)	16.5 (4.1–40.2)	13.9 (0.28–41.18)	110.7 (43.0–328.3)
p	<0.001		<0.001		<0.001		<0.001	
CT90 (%)	0 (0–0.4)	0.12 (0.04–3.38)	0.05 (0–0.23)	0.58 (0.15–3.81)	0.43 (0–2.01)	3.83 (0.94–9.24)	3.17 (0.06–13.72)	30.65 (10.11–88.72)
p	<0.001		<0.001		<0.001		<0.001	
Min SaO_2 (%)	92 (88–98)	89 (74–97)	89 (84–93)	84 (76–90)	86 (80–90)	78 (48–84)	82 (67–88)	68 (44–87)
p	<0.001		<0.001		<0.001		<0.001	
Body mass index (kg/m^2)	27.9 (18.2–45.5)	26.7 (19.7–37.3)	29.4 (22.8–50.1)	31.0 (23.1–49.1)	31.1 (26–40.8)	30.1 (24.8–41.9)	31.2 (25.2–38.7)	34 (25.1–48.3)
p	NS		0.048		NS		0.021	
C-reactive protein (mg/dL)	1.2 (0.2–5.8)	1.1 (0.1–3.9)	2.3 (0.5–9.7)	1.9 (0.2–8.9)	2.3 (0.8–9.3)	2.2 (0.8–9.0)	3 (0.6–9.8)	4.2 (0.9–9.9)
p	NS		NS		NS		0.008	
Mean platelet volume (fL)	7.1 (5.7–11.8)	7.8 (5.7–10.2)	7.8 (5.5–11.6)	8.3 (6.4–9.8)	8.4 (6.5–12.6)	8.4 (6.2–12.5)	8.6 (7.0–12.9)	9 (7.3–13.8)
p	0.027		NS		NS		NS	
WMH	16.2%	43.2%	55.9%	57.1%	48.1%	53.6%	57.1%	68%
p	0.022		NS		NS		NS	

Data are means ± standard deviation, numbers of subjects (%), or medians (range)

AHI apnea-hypopnea index, *CT_{90}* percentage of cumulative sleep time with oxygen saturation <90%, *min SaO_2* lowest oxygen saturation, *ST_{90}* total sleep time with oxygen saturation <90%, *WMH* white matter hyperintensity

Table 4 Relationships between measured variables of obstructive sleep apnea for patients with the lowest and highest min SaO_2 in similar apnea-hypopnea index groups

	AHI < 5		AHI 5–15		AHI 15–30		AHI ≥ 30	
	Lowest min SaO_2	Highest min SaO_2	Lowest min SaO_2	Highest min SaO_2	Lowest min SaO_2	Highest min SaO_2	Lowest min SaO_2	Highest min SaO_2
No. of patients	37	37	34	35	27	28	49	50
Age (years)	42 (26–78)	41 (22–68)	57 (38–76)	50 (20–77)	60 (28–83)	53 (36–75)	56 (35–84)	56 (23–84)
p	NS		0.005		NS		NS	
Apnea-hypopnea index (events/h)	2.7 (0–4.9)	1 (0–4.13)	8.9 (5–18.5)	9.5 (5.3–15.6)	23.2 (15.1–29.3)	22.5 (15.2–29.6)	57 (30.6–105.9)	45.9 (30–98.5)
p	<0.001		NS		NS		0.008	
Epworth sleepiness scale	7 (0–21)	9 (0–18)	10 (0–21)	9 (0–21)	12 (0–24)	9 (0–15)	12 (0–24)	10 (0–21)
p	NS		NS		NS		NS	
ST_{90} (min)	0.3 (0–14.3)	0.03 (0.2–16.3)	2.0 (0.1–18.45)	0.47 (0–7.32)	16.33 (0.88–40.2)	1.86 (0–33.23)	100.2 (13.4–328.3)	14.4 (0.28–289.9)
p	0.004		<0.001		<0.001		<0.001	
CT_{90} (%)	0.07 (0–3.38)	0 (0–3.38)	0.45 (0.02–3.81)	0.1 (0–2.4)	3.45 (0.21–9.24)	0.57 (0–7.10)	22.4 (2.99–88.72)	3.41 (0.06–63.15)
p	0.004		<0.001		<0.001		<0.001	
Min SaO_2	89 (74–91)	93 (91–98)	84 (76–87)	89 (87–93)	78 (48–83)	86 (83–90)	67 (44–75)	82 (76–88)
p	<0.001		<0.001		<0.001		<0.001	
Body mass index (kg/m^2)	27.9 (20.7–45.5)	26.6 (18.2–38.8)	30.9 (22.8–45.3)	29.4 (23.7–50.1)	30.5 (25.6–41.9)	32.1 (24.8–40.8)	33.7 (25.1–48.3)	31.4 (25.2–38.7)
p	NS		NS		NS		0.013	
C-reactive protein (mg/dL)	1.03 (0.2–4.1)	1.3 (0.1–5.8)	1.7 (0.2–8.9)	2.3 (0.5–9.7)	2.2 (0.9–9.0)	2.4 (0.8–9.3)	4.5 (1.0–9.9)	2.7 (0.6–8.4)
p	NS		NS		NS		<0.001	
Mean platelet volume (fL)	7.7 (5.7–10.2)	7.2 (5.7–11.8)	8.3 (6.2–11.6)	7.9 (5.5–10.1)	8.4 (6.2–12.6)	8.2 (6.5–11.2)	8.9 (7.3–13.8)	8.6 (7.0–12.7)
p	NS		NS		NS		NS	
WMH	35.1%	24.3%	64.7%	48.6%	51.9%	50%	67.3%	58%
p	NS		NS		NS		NS	

Data are means ± standard deviation, numbers of subjects (%), or medians (range)

AHI apnea-hypopnea index, *CT_{90}* percentage of cumulative sleep time with oxygen saturation <90%, *min SaO_2* lowest oxygen saturation, *ST_{90}* total sleep time with oxygen saturation <90%, *WMH* white matter hyperintensity

associated with ST_{90} and min SaO_2 only in patients with severe OSA [12, 13]. However, another study reported an inverse correlation between MPV and min SaO_2, but no correlation between MPV and OSA severity [23]; the sample size of that study was smaller ($n = 98$) than that in our study.

In this study, patients with OSA had a threefold increased risk of exhibiting WMH compared with the control group. In addition, the risk of exhibiting WMH was 2.2-fold higher in the $CT_{90} \geq 10\%$ group than the $CT_{90} < 10\%$ group. Hypoxia above the threshold ($CT_{90} \geq 10\%$) may be important in the pathogenesis of WMH in patients with OSA. Nevertheless, WMH was not different in the subgroup analysis of hypoxia parameters according to the different severity of OSA in similar AHI groups (Tables 3 and 4). Earlier studies have reported that moderate to severe OSA resulted in a twofold increased risk of exhibiting WMH [17, 18]. However, some previous studies did not demonstrate a relationship between OSA and WMH. One study was limited by its small sample size and another by the older age of its subjects [24, 25]. The pathogenesis of WMH suggests that it represents ischemic tissue developing from inflammation, atherosclerosis, and repeated episodes of cerebrovascular shearing stress [15]. Microglial activation may occur during chronic cerebral hypoperfusion and could contribute to further tissue damage. Oligodendrocytes and neurons may be more susceptible to hypoperfusion under chronic low-grade inflammation, and lesions may progress at a more rapid rate [26].

Previous studies observed that a $CT_{90} \geq 10\%$ and $ST_{90} > 36$ min is an important threshold for predicting surgical outcome [19, 27]. These parameters could reflect the severity of intermittent hypoxia during sleep, which may be associated with destabilized respiratory control, decreased respiration chemoreceptor sensitivity, and impaired pharyngeal dilator muscle function. Nocturnal intermittent hypoxia above this threshold may disrupt the normal structured autonomic and hemodynamic responses to sleep [28–30]. In the current study, OSA patients above this threshold have more hypoxia, inflammation, vascular risk factors, and WMH, as compared to those with an OSA under this threshold ($CT_{90} < 10\%$) (Table 2). It could be hypothesized that neurophysiologic compensation mechanisms are irreversibly damaged in these patients. Together, these data suggest that approximately half of the severe OSA patients are in the irreversible stage, and any treatment modality (CPAP and/or surgery) may avoid further damage but have only symptomatic utility and not reverse abnormalities in the neurologic structures.

The strength of this study lies in the subgroup analyses of CRP, MPV, WMH, and hypoxia parameters among patients with similar AHI values. In addition, participants were divided into $CT_{90} < 10\%$ or $CT_{90} \geq 10\%$ hypoxia categories. The limitations of this study include its retrospective design, inherent problems of selection bias, and that it was a single-institutional analysis, which could lead to referral bias. In addition, vascular factors, such as coronary heart disease, hypertension, hyperlipidemia, diabetes mellitus, smoking, and obesity, were not strictly excluded. The lack of measurements of other platelet-activating factors, such as thromboxane A2 and β-thromboglobulin, and thrombotic or endothelial dysfunction factors, such as tissue plasminogen activator, the von Willebrand factor, and homocysteine, is also a limitation. Comparing our results with levels of other thrombotic and endothelial dysfunction markers may improve the understanding of OSA pathophysiology. Furthermore, MRI scans and blood tests were not performed immediately after PSG, and we did not evaluate the localization or number of WMH.

In conclusion, these data suggest that increased hypoxia severity may mediate increased inflammation and platelet activation and contribute to the pathogenesis of WMH in patients with OSA. In addition, patients with severe OSA may show significant variability in inflammation and vascular risk. On the other hand, inflammation, platelet activation, and WMH increase on brain MRI in patients with hypoxia above a certain threshold ($CT_{90} \geq 10\%$); therefore, vascular risk factors increase even more in these hypoxic patients. Based on the present and previous studies, AHI combined with hypoxia parameters may enable better identification of prognostic information and selection of individualized treatment options in patients with OSA. Further prospective data are needed.

Authors' contributions A. Yilmaz Avci and S. Avci designed the study. A. Yilmaz Avci and H. Lakadamyali acquired and interpreted the data. A. Yilmaz Avci, S. Avci, and U. Can revised the manuscript for important intellectual content.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Because this was a retrospective study, no ethical committee approval was taken. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Oral informed consent was taken from all the participants.

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