

Department of Internal Medicine, Faculty of Medicine, Sleep Medicine and Research Center, Sleep Medicine Research Group, King Abdulaziz University, Jeddah, Saudi Arabia, ¹Department of Nursing, College of Applied Medical Sciences, Majmaah University, Al Majmaah, Saudi Arabia, ²Department of Medicine, Wythenshawe Hospital, Manchester University NHS Trust, Manchester, UK, ³Department of Clinical Laboratory Medicine, Immunology Lab, King Abdulaziz University Hospital, Jeddah, Saudi Arabia, ⁴Department of Medicine, King Abdulaziz University – Rabigh Branch, Rabigh, Saudi Arabia, ⁵Department of Child Health, Child Health Research Institute, The University of Missouri School of Medicine, Columbia, MO, USA

Address for correspondence:

Prof. Siraj Omar Wali,
College of Medicine, King Abdulaziz University,
Jeddah 80215,
Saudi Arabia.
Sleep Medicine and Research Center, King Abdulaziz University Hospital, PO Box: 21589,
Jeddah 80215,
Saudi Arabia.
E-mail: sowali@kau.edu.sa

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Putative associations between inflammatory biomarkers, obesity, and obstructive sleep apnea

Siraj Omar Wali, Md. Dilshad Manzar¹, Mohammed M. Abdelaziz², Ranya Alshomrani, Faris Alhejaili, Jamil Al-Mughales³, Wail Alamoudi⁴, David Gozal⁵

Abstract:

BACKGROUND: Previous studies have reported increased levels of inflammatory mediators in patients with obstructive sleep apnea (OSA), but their relation with the severity of OSA is controversial.

OBJECTIVE: To address potential relationships between OSA-related inflammatory markers, namely, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and fibrinogen, with different oxygenation parameters and with BMI.

METHODS: All eligible patients with suspected OSA newly referred to the Sleep Medicine Research Center at King Abdulaziz University Hospital, Jeddah, were evaluated demographically and anthropometrically, and underwent overnight polysomnography. Fasting morning blood samples were collected to measure serum levels of CRP, fibrinogen, TNF- α , and IL-6. Potential correlations between these inflammatory mediators and severity measures of OSA and body mass index (BMI) were explored.

RESULTS: Sixty-four patients completed the study (40 with OSA and 24 without OSA). Significantly increased levels of CRP, fibrinogen, IL-6, and TNF- α emerged in patients with OSA compared to non-OSA. Significant associations between log CRP and log fibrinogen levels emerged with increasing BMI. However, there was no significant association between any of the inflammatory markers and the severity of OSA based on the apnea/hypopnea index or oxyhemoglobin saturation-derived parameters.

CONCLUSIONS: OSA patients exhibit increased levels of inflammatory mediators that do not appear to be associated with polysomnographic measures, but exhibit positive correlation with the degree of adiposity.

Keywords:

C-reactive protein, fibrinogen, inflammation, interleukin-6, obstructive sleep apnea, SpO₂, tumor necrosis factor-alpha

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disease associated with significant cardiovascular and cerebrovascular morbidity, as well as organ-specific and overall mortality.^[1-3] There is evolving evidence that inflammatory processes resulting in endothelial dysfunction play a critically important role in OSA-associated morbidities.^[4] Fleming

et al.^[5] reported that several biomarkers are more likely affected by the presence of OSA, and that these biomarker signatures of the disorder may assist in the initial screening of patients with suspected OSA, as well as in their follow-up responses to therapy.

Prototypic biomarkers serving as indicators of systemic inflammation include erythrocyte sedimentation rate, C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and

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fibrinogen.^[6-12] CRP has been widely studied in OSA, and is frequently reported to be increased, particularly among those patients with concurrent obesity, dyslipidemia, diabetes, and cardiovascular diseases.^[13-16] TNF- α , on the other hand, is a key modulator of systemic inflammation,^[17-19] and TNF inhibition has been shown to ameliorate the progression of OSA^[20] or ameliorate some of its important manifestations, such as excessive daytime sleepiness.^[21,22] Moreover, Li and Zheng^[23] found that TNF- α was significantly higher in patients with OSA than in controls, and this difference was more prominent with the severity of OSA, indicating again that TNF- α might be a circulating biomarker favorable for the development of OSA. Similarly, significant elevations in serum levels of interleukin 1 β and IL-6 have been observed in patients with OSA.^[22,24] In a recent open-label controlled trial, we reported the presence of an augmented inflammatory state among patients recently diagnosed with OSA, as reflected by significant increases in the levels of circulating TNF- α and IL-6.^[25]

There are conflicting data in the literature regarding the link between the levels of inflammatory markers and the severity of OSA based on the apnea/hypopnea index (AHI). Some studies support such an association; however, other studies showed no evidence of a significant relationship.^[26-28] For example, the Icelandic Sleep Apnea Cohort study revealed that OSA severity was an independent predictor of IL-6 and CRP levels; however, this relationship was found only in obese patients.^[28] Furthermore, only a scarcity of studies looked at such an association when examining other polysomnographic severity parameters. Arnardottir *et al.*^[28] reported that CRP levels correlate significantly with minimum oxygen saturation (SaO₂) only but not with other sleep measures. In addition, Kim *et al.*^[29] reported that hsCRP levels were associated with the AHI and the SaO₂ nadir, even after adjustment for potential confounding factors. Hence, it is still not clear whether these inflammatory markers are affected by the heterogeneity of OSA syndrome, including the differences in severity and oxygenation parameters among these patients.^[30] Therefore, the aim of this study was to investigate possible relationships between OSA-related biomarkers of inflammation, namely, CRP, fibrinogen, IL-6, and TNF- α , with the severity of OSA based on AHI as well as oxygenation parameters in a population of consecutively enrolled, newly diagnosed and otherwise healthy OSA patients.

Methods

Design and setting

This prospective, cross-sectional study was conducted at the Sleep Medicine Research Center (SMRC) of King Abdulaziz University Hospital (KAUH), Jeddah,

Saudi Arabia. The study was ethically approved by the Institutional Review Board of KAUH (Reference Number 178-18).

Population

This study targeted all consecutive patients newly referred to the SMRC with the suspected diagnosis of sleep apnea for assessment that required diagnostic polysomnography (PSG). Known cases of OSA were excluded. Other exclusion criteria are presented in Table 1.

Procedures

Initial assessment

A standard medical history taking and physical examination were performed for all patients referred for sleep studies. Demographic and anthropometric data including age, sex, body mass index (BMI), and neck circumference were recorded. Sleepiness was evaluated using the Epworth Sleepiness Scale.^[31] Patients were assessed for eligibility according to the exclusion criteria. Eligible patients were then invited to participate by signing a consent form explaining the objectives and procedure of the study.

Polysomnography

All participants underwent overnight full PSG using a commercially available digital system (Somnomedics™; SOMNOmedics plus; SOMNOmedics, Randersacker, Germany). A standard diagnostic montage as per the recommendation of the American Academy of Sleep Medicine (AASM) was used.^[32] Respiratory events and sleep states were scored according to the AASM guidelines.^[32] The diagnosis of OSA was based on the

Table 1: List of exclusion criteria

| |
|---|
| Previous diagnosis of OSA |
| Previous OSA treatment |
| Mild OSA |
| Neuromuscular disorders |
| Infectious diseases |
| Rheumatic diseases |
| Immunological diseases |
| Tumors/malignancies |
| Peripheral vascular disease |
| Coagulation disorders |
| Hepatic/renal disease |
| Diabetes mellitus |
| Psychogenic disorders |
| Smoking within past 6 months |
| History of injury/surgery in past 3 months |
| Chronic anoxia, e.g., chronic obstructive pulmonary disease, obesity hypoventilation syndrome, interstitial lung disease, or congestive heart failure |
| Recent (<3 months) use of antibiotics, immunosuppressants, cytotoxins, free-radical scavengers |

OSA=Obstructive sleep apnea

AHI as per the AASM diagnostic criteria.^[33] The AHI was calculated by dividing the total number of apneas and hypopneas by the sleep time. The severity of OSA was determined according to the AASM recommendation using the AHI: 5–14/hrTST, mild; 15–29/hrTST, moderate; and ≥ 30 /hrTST, severe.^[33]

Group allocation

Based on the PSG findings, patients were categorized into two groups. The first group included those with confirmed OSA of moderate–severe degree according to the AASM definitions^[33] (OSA Group). The second group included those without OSA (control group). In the day after the diagnostic PSG (day 0), fasting blood samples were collected between 8 and 9 am from all patients to measure serum levels of proinflammatory markers. These markers, including CRP, fibrinogen, TNF- α , and IL-6, were measured and compared between the groups. The detailed description of the technical steps involved in measuring the inflammatory markers was reported previously.^[25] We then assessed the correlation between these inflammatory markers and the followings measures:

1. Severity of sleep apnea based on the AHI
2. Oxygen desaturation index (ODI): Number of oxygen desaturations per hour of sleep
3. Oxygen saturation (SpO₂) nadir: An indication of the minimum pulse oximetry SpO₂ value during the total sleep time (TST)
4. Average SpO₂: Average value of the complete SpO₂ curve
5. Sum of all desaturations: Duration of all desaturations as a percentage of TST
6. Desaturation below 90%: Percentage of TST spent with SpO₂ below 90%
7. Total arousal index: Number of all arousals per hour of TST
8. Respiratory arousal index: Number of arousals per hour of TST that correlates with respiratory events.

Statistical analysis

SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform data analysis in the study. Participants' characteristics, inflammatory marker levels, and polysomnographic parameters were presented using the mean with standard deviation and frequency with percentage. An independent samples *t*-test, the Chi-square test, the Mann–Whitney test, Pearson's/Spearman's correlation test, and multiple linear regression tests were used. Pearson's/Spearman's correlation test was used to identify independent variables ($P < 0.25$) among the participants' sociodemographic and polysomnographic characteristics to perform a multiple linear regression test to identify factors associated with the four inflammatory markers. Serum levels of TNF α , IL-6, CRP, and fibrinogen were converted to logarithmic

values to perform regression analysis to satisfy normality assumptions.

Results

Participants' characteristics

Sixty-four patients completed the study, 40 in the OSA group and 24 in the non-OSA group. Table 2 summarizes the demographic features and characteristics of the two groups. The serum log TNF- α , log IL-6, log CRP, and log fibrinogen levels were 0.64 ± 0.36 pg/ml, 0.41 ± 0.40 pg/ml, 2.49 ± 0.12 mg/dl, and 0.70 ± 0.33 mg/dl, respectively. Those subjects with OSA had significantly higher serum log fibrinogen ($t [57] = -2.00, P = 0.05$), log CRP ($t [52.37] = -2.46, P = 0.02$), log TNF- α ($t [62] = -2.08, P = 0.04$), and log IL-6 ($t [62] = -1.81, P = 0.05$) levels compared to controls [Table 2].

Polysomnographic parameters

The polysomnographic parameters for both groups are summarized in Table 3.

Multiple linear regression: Factors associated with fibrinogen levels

Multiple linear regression analysis was used to assess the association of log fibrinogen levels with sociodemographic and polysomnographic characteristics. Increasing levels of fibrinogen were predicted by increasing age ($\beta = 0.416, P = 0.025$) and BMI ($\beta = 0.704, P = 0.001$) (model adjusted $R^2 = 0.286, P = 0.021$) [Table 4].

Multiple linear regression: Factors associated with C-reactive protein levels

Increasing levels of log CRP level were predicted by an increasing BMI ($\beta = 0.497, P = .006$) (model adjusted $R^2 = 0.238, P = 0.044$) [Table 5].

Multiple linear regression: Factors associated with tumor necrosis factor-alpha and interleukin-6 levels

No significant model emerged for the prediction of TNF- α levels in the study population (model adjusted $R^2 = 0.035, P = 0.305$). Similarly, no significant model was identified for the prediction of IL-6 levels (model adjusted $R^2 = 0.023, P = 0.336$).

Discussion

In this cross-sectional study, we examined putative associations between OSA-related inflammatory markers, namely, CRP, IL-6, TNF- α , and fibrinogen, and different well-established polysomnographic parameters. Although these inflammatory markers were found to be significantly increased in patients with OSA, no significant associations emerged between the

Table 2: Participants' characteristics

| Characteristics | No OSA (n=24) | OSA (n=40) | P |
|-------------------------------------|---------------|------------|--------|
| Sex, n (%) | | | |
| Female | 13 (20.31) | 15 (23.44) | 0.193 |
| Male | 11 (17.19) | 25 (39.06) | |
| Age (years), Mean ± SD | 31.7±11.7 | 47.5±13.18 | <0.001 |
| BMI (kg/m ²), Mean ± SD | 30.0±8.6 | 37.5±11.4 | 0.004 |
| Neck circumference (cm), Mean ± SD | 34.3±5.9 | 39.3±4.0 | <0.001 |
| Mallampati score, Mean ± SD | 2.2±1.0 | 2.9±1.1 | 0.01 |
| Blood pressure (mmHg) | | | |
| Systolic, Mean ± SD | 132.0±16.1 | 138.3±21.9 | 0.235 |
| Diastolic, Mean ± SD | 72.5±7.5 | 82.4±23.9 | 0.05 |
| ESS, Mean ± SD | 13.2±5.9 | 11.5±6.2 | 0.266 |
| Comorbidity | | | |
| Yes, n (%) | 9 (14.06) | 23 (35.94) | 0.121 |
| No, n (%) | 15 (23.44) | 17 (26.56) | |
| Log fibrinogen*, Mean ± SD | 2.45±0.12 | 2.51±0.12 | 0.05 |
| Log CRP*, Mean ± SD | 0.61±0.24 | 0.80±0.35 | 0.02 |
| Log TNF-α, Mean ± SD | 0.52±0.35 | 0.71±0.36 | 0.04 |
| Log IL-6, Mean ± SD | 0.30±0.30 | 0.48±0.43 | 0.05 |

*For these two parameters, data were available comprised of no OSA (n=20) and OSA (n=39). BMI=Body mass index, ESS=Epworth sleepiness scale, OSA=Obstructive sleep apnea, CRP=C-reactive protein, TNF-α=Tumor necrosis factor-alpha, IL-6=Interleukin-6

Table 3: Polysomnographic parameters among participants

| Characteristics | No OSA (n=24) Mean ± SD | OSA (n=40) Mean ± SD | t statistics/U statistics | P |
|---------------------------------------|----------------------------|-------------------------|---------------------------|--------|
| AHI | 2.9±2.0 | 36.74±23.60 | U=9.0, Z=-6.53 | <0.001 |
| Hypopnea average duration | 22.8±8.4 | 20.17±5.79 | t (62)=1.468 | 0.147 |
| Desaturation index | 6.1±7.3 | 26.73±36.67 | U=73.50, Z=5.64 | <0.001 |
| Minimum SpO ₂ | 86.0±12.8 | 81.38±10.74 | t (62)=1.539 | 0.129 |
| Average SpO ₂ (%) | 96.2±1.6 | 94.4±1.85 | t (62)=3.899 | <0.001 |
| Sum of all desaturations | 5.6±7.1 | 26.84±18.01 | U=87.00, Z=-5.45 | <0.001 |
| Total arousal index | 15.6±6.5 | 33.43±19.37 | U=153.00, Z=-4.53 | <0.001 |
| Average apnea duration | 6.6±7.7 | 14.24±7.77 | U=165.00, Z=-3.27 | 0.001 |
| SpO ₂ time below 90% (min) | 1.1±1.4 | 5.64±9.26 | U=223.50, Z=-2.90 | 0.004 |
| SpO ₂ time below 90% | 0.8±1.1 | 16.80±36.63 | U=313.00, Z=-2.41 | 0.016 |
| Respiratory arousal index | 1.3±0.9 | 17.06±15.39 | U=15.50, Z=-6.25 | <0.001 |
| REM duration (min) | 54.7±41.7 | 43.37±43.35 | U=356.50, Z=-1.44 | <0.001 |
| Number of apneas during REM | 0.6±1.5 | 11.37±15.54 | U=110.00, Z=-3.61 | <0.001 |
| Number of apneas during NREM | 1.1±2.4 | 42.32±94.52 | U=116.00, Z=-3.78 | <0.001 |
| Number of hypopneas during REM | 6.7±7.0 | 18.08±18.65 | U=258.50, Z=-2.42 | 0.015 |
| Number of hypopneas during NREM | 6.3±5.4 | 76.03±68.94 | U=36.50, Z=-6.15 | <0.001 |
| AHI REM | 8.7±10.6 | 47.98±29.98 | U=105.00, Z=-5.07 | <0.001 |
| AHI NREM | 2.0±1.8 | 34.42±25.22 | U=11.00, Z=6.50 | <0.001 |

AHI=Apnea-hypopnea index, REM=Rapid eye movement sleep, NREM=Non-REM, SpO₂=Oxygen saturation, OSA=Obstructive sleep apnea

circulating concentrations of inflammatory markers and the severity of OSA based on AHI or based on any of several oxygenation-related indicators. Nevertheless, increasing CRP and fibrinogen levels were significantly associated with BMI.

Our findings of increased levels of inflammatory markers among OSA patients compared to matched controls conform with the results of the majority of the previous studies on this topic.^[27,34] However, although no significant correlation between increased levels

of inflammatory mediators and the severity of OSA was found in this study, there are conflicting data in the literature regarding the association between these markers and OSA severity. A possible explanation could be that the presence of OSA is sufficient to induce the activation and propagation of inflammatory processes as an "all or none" phenomenon, such that the degree of severity of OSA would not be associated with these inflammatory markers and yet as shown herein OSA patients would still exhibit increased levels of these markers.

Table 4: Factors associated with log fibrinogen level

| Independent variable | Beta coefficient | SE | t-values | P | Model unadjusted R ² ; adjusted R ² ; P |
|--------------------------------------|------------------|-------|----------|-------|---|
| Age | 0.416 | 0.002 | 2.348 | 0.025 | 0.510; 0.286; 0.021 |
| Sex | -0.013 | 0.044 | -0.077 | 0.939 | |
| BMI | 0.704 | 0.002 | 3.696 | 0.001 | |
| Neck circumference | -0.158 | 0.004 | -1.006 | 0.321 | |
| Systolic blood pressure | 0.129 | 0.001 | 0.991 | 0.329 | |
| Average duration of hypopnea | 0.106 | 0.003 | 0.731 | 0.470 | |
| Minimum SpO ₂ | -0.088 | 0.002 | -0.579 | 0.567 | |
| Average SpO ₂ | 0.360 | 0.017 | 1.369 | 0.180 | |
| Sqrt desaturation index | -0.786 | 0.028 | -1.417 | 0.165 | |
| Sqrt AHI | -0.400 | 0.054 | -0.385 | 0.703 | |
| Sqrt sum of all desaturation | 0.646 | 0.034 | 1.215 | 0.233 | |
| SpO ₂ below 90% | 0.278 | 0.013 | 1.078 | 0.288 | |
| Sqrt respiratory arousal index | -0.399 | 0.035 | -0.737 | 0.466 | |
| Sqrt number of hypopneas during NREM | -0.152 | 0.007 | -0.689 | 0.495 | |
| Sqrt AHI during REM | -0.101 | 0.009 | -0.490 | 0.627 | |
| Sqrt AHI during NREM | 0.979 | 0.058 | 0.838 | 0.408 | |
| Intercept | -0.033* | 1.707 | -0.019 | 0.985 | |

*Unstandardized beta coefficient for intercept; for all other independent variables, standardized beta coefficients are shown. BMI=Body mass index, AHI=Apnea-hypopnea index, REM=Rapid eye movement sleep, NREM=Non-REM, SpO₂=Oxygen saturation, SE=Standard error, Sqrt= Square root

Table 5: Factors associated with log C-reactive protein level

| Independent variable | Beta coefficient | SE | t-values | P | Model unadjusted R ² ; adjusted R ² ; P |
|--------------------------------------|------------------|-------|----------|-------|---|
| Age | 0.251 | 0.004 | 1.485 | 0.147 | 0.471; 0.238; 0.044 |
| BMI | 0.497 | 0.005 | 2.925 | 0.006 | |
| Neck circumference | -0.197 | 0.010 | -1.162 | 0.253 | |
| Systolic blood pressure | 0.144 | 0.002 | 0.998 | 0.326 | |
| Average duration of hypopnea | 0.091 | 0.007 | 0.603 | 0.551 | |
| Minimum SpO ₂ | 0.062 | 0.004 | 0.432 | 0.668 | |
| Average SpO ₂ | 0.445 | 0.042 | 1.680 | 0.102 | |
| AHI | -0.882 | 0.131 | -0.880 | 0.385 | |
| Sqrt sum of all desaturations | 0.274 | 0.057 | 0.765 | 0.449 | |
| Sqrt total arousal index | -0.131 | 0.076 | -0.346 | 0.731 | |
| Sqrt SpO ₂ time below 90% | 0.324 | 0.049 | 1.371 | 0.179 | |
| Sqrt respiratory arousal index | -0.587 | 0.126 | -0.760 | 0.452 | |
| Sqrt number of hypopneas during NREM | -0.374 | 0.018 | -1.622 | 0.114 | |
| Sqrt AHI during REM | 0.197 | 0.023 | 0.873 | 0.389 | |
| Sqrt AHI during NREM | 1.641 | 0.143 | 1.445 | 0.158 | |
| Intercept | -6.870* | 4.212 | -1.631 | 0.112 | |

*Unstandardized beta coefficient for intercept; for all other independent variables, standardized beta coefficients are shown. BMI=Body mass index, AHI=Apnea-hypopnea index, REM=Rapid eye movement sleep, NREM=Non-REM, SpO₂=Oxygen saturation, SE=Standard error, Sqrt= Square root

Several studies have shown correlations between high levels of CRP and AHI and other oxygen parameters. Indeed, Yokoe *et al.*^[35] have shown that reduced blood oxygenation is a strong predictor of increased CRP in patients with OSA. Moreover, Li *et al.*^[26] reported that CRP levels in 156 OSA patients, compared with those in 110 healthy subjects, were positively linked with the severity of OSA (odds ratio: 1.481, 95% confidence interval: 1.261--1.741; $P < 0.001$) after simple logistic regression analysis. The levels of serum CRP ($P < 0.001$) were significantly higher in patients with severe OSA than in those with moderate OSA. In keeping with these findings, a recent meta-analysis

again confirmed that CRP was higher in OSA patients than in controls, and furthermore, with subgroup analysis, serum CRP levels were found to be higher in more severe OSA based on AHI.^[34] In another study, this independent association of AHI and CRP levels was highlighted again after adjusting for BMI and visceral fat.^[36] In multiple regression analysis, Guven *et al.*^[6] reported that hs-CRP levels were associated with AHI ($F = 3.293$, $P = 0.033$), independent of BMI. This finding concurs with that of a large trial where CRP levels were significantly increased in patients with OSA without comorbidities and correlated with OSA severity.^[37]

Moreover, Drummond *et al.*^[38] reported that CRP levels correlated significantly not only with AHI but also with ODI and SaO₂ nadir. In addition, in another large population-based study, Kim *et al.*^[29] reported that hsCRP levels increased dose dependently with the severity of OSA and that hsCRP levels were negatively associated with the SaO₂ nadir, even after adjustment for potential confounding factors.

In contrast to the previously mentioned studies, our study demonstrated no correlation between the levels of CRP and AHI or any of the other oxygenation parameters, but a significant correlation with BMI emerged ($P = 0.006$). In agreement with our results, a large study ($n = 907$) by Taheri *et al.*^[15] showed no independent associations of AHI with CRP levels after adjustment for confounders. In another study, serum CRP levels were higher in severe OSA patients; however, this link was lost after adjustment for confounding factors, and only BMI remained significantly associated.^[39] In addition, although Arnardottir *et al.*^[28] initially reported an independent association of OSA severity with CRP levels for minimum SaO₂ only and not for AHI, the statistical significance of this association was subsequently lost in nonobese individuals. More recently, Wu *et al.*^[40] showed again that obesity was independently associated with serum CRP levels with no association with OSA severity or sex.

Similarly, in our study, IL-6 and TNF- α failed to show a significant correlation with all oxygenation parameters and AHI. In the previously quoted study by Arnardottir *et al.*,^[28] this clearly supports the independent role of OSA in IL-6 levels, but also revealed that the association between IL-6 levels and severity measures of OSA is only found in obese individuals. These severity parameters included ODI, desaturation below 90%, and SaO₂ nadir, but not AHI.^[28] Moreover, Drummond *et al.*^[38] demonstrated that IL-6 levels at baseline correlated significantly and negatively with nocturnal SaO₂ nadir. On the other hand, many studies like ours support the increase in TNF- α in OSA patients;^[27] however, few also support the association of TNF levels with AHI severity and nocturnal hypoxemia measures as surrogate markers for sleep apnea.^[41,42] Fornadi *et al.*^[43] did not observe such a correlation in keeping with our findings. More recently, Wu *et al.*^[40] reported that OSA severity based on AHI, sex, or obesity had no effect on TNF- α levels individually and interactively.

Fewer studies have examined the link between fibrinogen levels in OSA patients and severity parameters. Our study, however, found increasing levels of fibrinogen with increasing age ($\beta = 0.416$, $P = 0.025$) and increasing BMI ($\beta = 0.704$, $P = 0.001$) but no correlation with AHI or other oxygenation parameters. Shamsuzzaman *et al.*^[44] reported that fibrinogen levels were directly associated

with the AHI and arousal index and inversely associated with the mean and SpO₂ nadir during sleep even after correction for confounders. In a recent cross-sectional study that recruited 2983 patients with OSA, fibrinogen levels were found to correlate with the severity of OSA.^[37] Nevertheless, in agreement with our findings, another study in children with OSA failed to show any significant association between the severity of OSA and circulatory fibrinogen levels.^[45]

This discrepancy regarding the correlation between the increased level of inflammatory markers and severity of OSA and oxygenation parameters in the different studies in the literature, including ours, could be explained partly by different methodologies and numbers of patients or cohorts of patients enrolled in the different studies. Moreover, it is unclear how to best define OSA severity. The current guidelines categorize OSA severity according to the AHI, as mentioned above.^[33] This currently used classification of OSA severity as per the AASM recommendations is not evidence based and needs further clinical validation. In a recent study, however, we reported a direct correlation between OSA severity based on the AHI and SpO₂ parameters, thus supporting the clinical reliability of using this widely accepted severity classification.^[46] Notwithstanding, the above-mentioned possibility of an all or none determinant of inflammation (OSA severity level) could lead to the heterogeneity of the findings across the studies.

The present study has some limitations that may hinder the generalizability of its findings. One of the limitations involves the relatively small sample size, which may result in type II errors. Second, failure to conduct adjusted analysis regarding obesity and age made it difficult to assess the confounding role of these risk factors. In addition, we believe that in future studies, the heterogeneity of OSA and its subgroups should be considered and taken into account.

Conclusion

Our study supports the likelihood that an increase in the levels of inflammatory markers is present among OSA patients. However, there was no significant correlation between increasing levels of these mediators and the severity of OSA based on the AHI. Furthermore, this study failed to show any correlation between OSA severity based on oxygenation parameters and the other inflammatory markers, IL-6, TNF- α , CRP, and fibrinogen. More randomized controlled trials with a larger study population and participants with variable severity of OSA are warranted.

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Conflicts of interest

There are no conflicts of interest.

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