sVAP-1 and Adropin Levels in Male Patients With Obstructive Sleep Apnea: Likely Predictions of Endothelial Dysfunction and Severity of Disease

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Research Article

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Abstract

Background: The main purpose of this study was to determine sVAP-1 levels in patients with moderate and severe obstructive sleep apnea (OSA) compared with healthy controls, and further determine the relationship between sVAP-1 concentration and biomarkers of vascular endothelial dysfunction (ED), including adropin and inflammatory factors.

Methods: In this study, we included 50 male patients with OSA (25 moderate and 25 severe) and 20 age- and sex-matched control subjects. The OSA patients underwent polysomnography and all subjects underwent fasting sampling of peripheral blood for laboratory analyses.

Results: Serum sVAP-1 levels and inflammatory biomarkers (IL-6, TNF-α, hsCRP) were significantly higher in patients with severe OSA in comparison with the moderate OSA and control groups, whereas plasma adropin levels presented a completely reverse trend. Moreover, sVAP-1 levels were in significant positive correlation with levels of AHI, ODI, TNF-α, IL-6 and hsCRP. However, it was significantly negative correlated with adropin levels. Receiver Operating Characteristic (ROC) analysis showed that AUC for sVAP-1levels in predicting OSA was 0.876 (P <.001,95% CI 0.784–0.968). Serum sVAP-1 cutoff value more than 445.5ng/mL provided 88% sensitivity and 80% specificity for the detection of OSA status. A multivariate regression analysis showed that sVAP-1 remained as a significant positive predictor of severe OSA status.

Conclusions: Serum sVAP-1 concentration significantly correlates with indices of OSA severity and biomarkers of ED, suggesting that sVAP-1 plays a vital role in the pathophysiology of ED-related diseases.

Introduction

Obstructive sleep apnea (OSA) is characterized by partial or complete obstruction of the upper airway during sleep, leading to abnormal ventilation, hypoxemia, and sleep fragmentation [1]. In recent years, more and more evidence supports a causative link between OSA and cardiovascular diseases (CVD) [2–3]. The pathogenesis of CVD caused by OSA remains largely unknown. One mechanism refers to the vascular endothelial damage which might be the earliest vascular pathological changes in OSA. Vascular endothelial dysfunction (ED) has attracted increasing attention in the field of OSA-related cardiovascular complications [4, 5].

Vascular adhesion protein-1(VAP-1) is a membrane-bound adhesion molecule, which is inactive due to sequestration in endosomes under normal physiological conditions. However, it can rapidly translocate to the cell surface in response to the local inflammation, consequently promoting lymphocyte adhesion and transmigration through the endothelium into the inflamed tissue [6]. Unlike other adhesion molecules, VAP-1 can be cleaved by matrix-metalloproteases, generating a soluble form of VAP-1 (sVAP-1). sVAP-1 possesses enzymatic ability as it can catalyze the oxidative deamination of primary amines into aldehydes, releasing hydrogen peroxide and ammonium, thus causing damages to the vascular endothelium and amplifying the inflammatory reaction [7]. Elevation of sVAP-1 is observed in many

diseases such as atherosclerosis, diabetes mellitus, obesity and CVD, and it has been widely proposed as an important biomarker of endothelial activity [8–10]. Since chronic low-grade inflammation, oxidative stress and ED are main pathophysiologic mechanisms in OSA [4, 5], sVAP-1 might increase in the development of OSA, and it might become a useful biomarker for evaluating the severity of OSA. To the best of our knowledge, there is no literature regarding the relationship between serum sVAP-1 production and OSA.

Adropin is a novel peptide hormone that is supposed to play a protective role on endothelial function through increased endothelial nitricoxide (NO) bioavailability by upregulating the endothelial NO synthase (eNOS) expression [11]. Several studies have reported a significant association between adropin and endothelial function in various diseases, including CVD, diabetes mellitus and OSA, thus its ability to regulate endothelial function has been widely proposed [12–15]. One recent study showed that there was a significant negative correlation of plasma adropin levels with systemic inflammatory factors in OSA patients [16]. Therefore, we suggest that a close connection might exist between adropin and sVAP-1.

Therefore, the main goals of the present study are to determine serum sVAP-1 and adropin levels in an adult male population of patients with moderate and severe OSA in comparison with the controls,and to assess the relationship between sVAP-1 and adropin along with parameters of sleep and systemic inflammatory biomarkers.

Methods

The Ethics Committee of Shanghai University of Traditional Chinese Medicine approved the study, and all patients signed the informed consent.

Subjects

This study included male subjects with newly diagnosed OSA who were enrolled at the ENT department of Putuo Hospital, Shanghai University of Traditional Chinese Medicine, between June 2019 and December 2020. Diagnosis of OSA is based on the results of Polysomnography (PSG). The apnea-hypopnea index (AHI) is defined as the number of apnea and hypopnea events that occur per one hour of sleep [17]. Therefore, according to the severity of OSA, our participants were classified into two groups: moderate OSA group (AHI 15–30 events/h, 25 patients) and severe OSA group (AHI > 30 events/h, 25patients). Exclusion criteria were:(1) patients with central sleep apnea syndrome; a known history of severe chronic pulmonary, renal, liver, thyroid, and cardiovascular dysfunction and rheumatic and hematologic disorders; (2) a diagnosed history of OSA and those who received medications before the study enrollment; (3) female patients.

Non-OSA individuals were enrolled from health examination center in Putuo Hospital as control. The control group was made up of 20 healthy male volunteers who were matched with the enrolled OSA patients according to age and body mass index (BMI). The Snoring, Tiredness, observed apnea and high blood pressure (STOP) questionnaire were adopted as a screening tool for identification of subjects with

a high risk of OSA development, and subjects whose scores ≥ 2 points regarding this questionnaire were excluded from the study [18]. PSG assessment was not performed for the control subjects. The control group underwent the same exclusion standard and assessment procedure as moderate and severe OSA patient groups.

Anthropometric measurements

After a detailed medical interview and physical examination, anthropometric measurements were performed for all the subjects included in the study. All subjects were lightly clothed when their weight and height were recorded. BMI was calculated as body weight (kg) divided by height squared (m^2). Neck circumference was measured at the position of the laryngeal prominence and waist circumference in the middle between the 12th rib and the iliac crest by a tape measure. Blood pressure of all subjects were taken on the right arm in a sitting position at least twice between8:00 and 9:00 am.

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Polysomnography

All subjects underwent polysomnography (Polysomnography system, Monet 24, Rembrandt Embla, Reykjavik, Iceland) between 22:00 and 07:00. The monitoring results were automatically recorded by the Alice software and then analysed by an expert. Apnea was defined as the absence of airflow ≥ 90% from baseline for ≥ 10s. Hypopnea was defined as a 30% or greater reduction in airflow lasting ≥ 10 s combined with a 4% or greater decrease in oxyhemoglobin saturation. AHI was calculated as the total number of apneas and hypopneas per hour of the sleep time. The OSA classifications are: under 5 times per hour, non-OSA; between 5 to 15 times per hour, mild OSAHS; between 15 to 30 times per hour, moderate OSA; and more than 30 times per hour, severe OSA.

Blood Sampling and Laboratory Analysis

Fasting blood samples were collected, centrifuged immediately and stored at − 80°C until analysis from all subjects. All blood samples were analyzed in the same biochemical laboratory and by the same specialist in medical biochemistry, following standard laboratory procedures. Quantitative determination of biomarkers analyzed in our study was measured with commercially available kits using enzyme linked immunosorbent assay (ELISA) methods (Human sVAP-1 ELISA kit, Biovendor; hsCRP/IL-6/TNF-α ELISA kit, abcam; Human adropin ELISA kit, Novus.)

Statistical analysis

All data analyses were performed using SPSS 20.0 Statistics system. Data were expressed by mean ± SD. Normality of data distribution was measured with the Kolmogorov-Smirnov test. Significant differences between groups were analyzed using either unpaired Student *t* tests or ANOVA with *post hoc* Tukey Honestly Significant Difference test for continuous variables. Pearson's correlation analyses were performed to assess association between sVAP-1 levels and anthropometric measurements, polysomnographic variables, adropin and inflammatory biomarkers (hsCRP, IL-6, TNF-α). A multivariate

regression analysis was used to determine the independent predictors among the selected variables (serum levels of sVAP-1 and other biomarkers). The regression model was adjusted for age and BMI and inspected for goodness of fit by the Hosmer-Leme show test. In addition, receiver operator curves (ROC) were calculated for prediction of OSA status based on sVAP-1 levels. The statistical significance reported at all instances in provided data was 2-tailed, set at $P < .05$ level.

Results

Patients'baseline characteristics

There were no significant differences among patients with OSA and control subjects in baseline anthropometric characteristics, except for neck circumference (37.72 ± 0.95 versus 39.01 ± 1.05 versus 40.54 ± 1.41cm, $P < .001$) and waist circumference (92.40 ± 5.06 versus 94.44 ± 5.42 versus 98.92 ± 7.15cm, $P = .002$) (**Table 1**). The analyses of PSG data are presented in **Table 2**. Patients with moderate OSA had significantly lower AHI (22.60 ± 4.11 versus 47.12 ± 9.39 events/h, $P < .001$) and ODI (23.25 ± 5.06 versus 48.11 ± 7.85 events/h, $P < .001$), and higher mean and minimum oxygen saturation (95.76 ± 1.56 versus 93.92 ± 1.78 events/h, $P < .001$and 84.60 ± 4.52 versus 75.56 ± 8.15 events/h, $P < .001$ respectively.)

Inflammatory biomarkers

Inflammatory biomarkers were significantly higher in patients with severe OSA in comparison with patients with moderate OSA and the control group: IL-6 (5.52 ± 1.38 versus 4.53 ± 1.30 versus 3.43 ± 1.34pg/mL, $P < .001$) and TNF-α (6.81 ± 1.36 versus 4.14 ± 1.42 versus 2.24 ± 1.67pg/mL, $P < .001$). Plasma levels of hsCRP were significantly higher in patients with severe OSA in comparison with controls (5.74 ± 1.63 versus 3.99 ± 1.34 mg/l, $P < .05$), however without significant differences between other groups (**Table 1**).

sVAP-1 and adropin levels in patients with OSA and control subjects

sVAP-1serum levels were significantly higher in patients with severe OSA in comparison with the moderate OSA and control groups (816.28 ± 178.58 versus559.96 ± 184.54 versus 344.45 ± 180.99ng/mL, $P < .001$) (**Fig. 1a**). Plasma adropin levels present a reverse trend, where patients with severe OSA presented significantly lower levels of adropin in comparison with the moderate OSA and control groups (3.81 ± 1.12 versus 5.97 ± 1.42 versus 8.27 ± 1.30ng/mL, $P < .001$) (**Fig. 1b**).

Pearson correlation analysis was conducted in the 50 patients with OSA to examine the relationship between sVAP-1 levels and OSA severity. Results showed that increasing AHI was independently associated with higher serum sVAP-1 levels (r = .693, $P < .001$) (**Fig. 2a**). Similar results were obtained when AHI was replaced by ODI (r = .493, $P < .001$) (**Table 3).** Regarding the inflammatory biomarkers, serum sVAP-1 levels were in significant positive correlation with plasma levels of TNF-α ($r = .753$, $P < .001$), IL-6($r = .730$, $P = .013$) and hsCRP ($r = .476$, $P < .001$) (**Table 3**), and in significant negative

correlation with adropin ($r = -.633$, $P < .001$) (**Fig. 2b**). As for adropin, it was in significant negative correlation with AHI ($r = -.721$, $P < .001$), ODI ($r = -.630$, $P < .001$), TNF-α ($r = -.759$, $P < .001$), IL-6($r = -.408$, $P = .002$), hsCRP ($r = -.335$, $P = .009$) (**Table 3**).

The ROC analysis (**Fig. 3**) showed that AUC for serum sVAP-1levels in excluding OSA status was 0.876 ($P < .001$, standard error 0.047, 95% CI 0.784 – 0.968). Serum sVAP-1 cutoff value more than 445.5ng/mL provided 88% sensitivity and80% specificity for the detection of positive OSA status.

A multivariate regression analysis showed that plasmasVAP-1 and TNF-α remained as significant positive predictors of severe OSA status when adjusted for age and BMI and computed along with other inflammatory biomarkers in the regression model (for sVAP-1: OR 1.014, 95% CI 1.002–1.025, $P = .006$ and for TNF-α: OR 4.368, 95% CI 1.189–16.047, $P = .026$) (**Table 4**). Nevertheless, adropin was a significant negative predictor of severe and moderate OSA status (for severe: OR 0.172, 95% CI 0.049–0.606, $P = .006$; and for moderate: OR 0.346, 95% CI 0.138–0.870, $P = .024$). Other biomarkers (IL-6 and hsCRP) were not found to be significant predictors in both regression models for either moderate or severe OSA (**Table 4**).

Discussion

In recent years, multiple studies have found the association between OSA and adverse cardiovascular diseases such as hypertension, ischemic heart disease and stroke [2–3]. These chronic diseases are characterized by several pathophysiologic mechanisms, among which endothelial dysfunction (ED) and inflammation caused by hypoxia must be the most likely ones. Previous researches have shown that intermittent hypoxia in OSA can cause ED [19] and there is a statistically significant correlation between arterial function and the severity of hypoxia [20]. Compared with healthy controls, patients with OSA had increased plasma levels of endothelin-1which was closely related with vascular activity [21]. Some other researchers have found an improvement in endothelial function after successful treatment of OSA [22]. Therefore, it is possible that many factors are involved in the interrelation between ED and OSA, such as inflammation, oxidative stress or cellular apoptosis, which are activated during sleep apnea.

The relationship between sVAP-1 and severity of disease in OSA patients is of particular interest in this study. In our study we showed that sVAP-1 was the highest in patients with severe OSA, followed by the patients with moderate OSA. According to the PSG parameters, serum sVAP-1 levels were significantly correlated with AHI, which means that severity of OSA affects expression of sVAP-1. sVAP-1 can be secreted by vascular smooth muscle cells, adipocytes, and endothelial cells and increasing expression of sVAP-1 has been observed in many inflammatory diseases, including psoriasis, chronic kidney and liver disease, multiple sclerosis, and et al [2–3, 23]. Li et al [24–25] demonstrated that serum sVAP-1 levels increased in patients diagnosed with diabetes mellitus and it could predict mortality and severity of end-stage renal disease. In addition, sVAP-1 was reported to participate in proliferative diabetic nephropathy and macrovascular complications such as increased thickness of carotid endothelium [24, 26]. Salmi et al [27] have demonstrated that sVAP-1 plays an important role in coronary artery disease via its direct

adhesive effect or by its enzymatic activity. To conclude, sVAP-1 was proved to be a vascular function dependent molecule which allows us to assume that it might be a predictive marker of OSA in which ED and inflammation are the main features.

It is well established that intermittent hypoxia, a remarkable feature of OSA, is responsible for upregulation of inflammatory reaction in patients with OSA. Increased sVAP1 can mediate migration of neutrophil and other adhesive cells to the inflammatory area, after which endothelial cells would induce expression of ICAM-1, VCAM-1, IL8 and et al. Kushimoto et al [28] discovered that blocking the expression of sVAP1 can significantly inhibit inflammatory angiogenesis, suggesting that VAP1 can accelerate the occurrence and development of inflammation. In line with this, our results showed that plasma levels of inflammatory biomarkers as hsCRP, IL-6, and TNF-α were significantly increased in patients with moderate and severe OSA in comparison with the control group, and there was a positive correlation between serums sVAP-1 levels and these inflammatory molecules. Therefore, it could be reasonably hypothesized that increased sVAP-1 levels are most likely contributing to increased systemic inflammation burden.

Data obtained from ROC analysis demonstrated that sVAP-1 showed a significant value (AUC = 0.876, $P < .001$) in terms of OSA status detection, and data from multivariate regression analysis showed that plasma sVAP-1 was an independent predictor of severe OSA. These results suggest that the increasing trend of sVAP-1 levels is consistent with the progression of OSA severity and it might be used as a valuable biomarker of OSA prediction. Importantly, our model was adjusted for age and BMI, because some authors considered that obesity might be a main confounder leading to misinterpretation of the results [29]. The Regression analysis also showed that TNF-α was a significant positive predictor of severe OSA which was in agreement with the findings reported by Li and Zheng who showed that circulating TNF-α levels were significantly higher in patients with OSA [30].

In our study, plasma adropin was proved to be an independent negative predictor of severe and modera OSA according to the regression analysis. Adropin is a novel peptide that may play a protective role in endothelial homeostasis as demonstrated by Lovrenet al, and it was proved to reduce systemic inflammation through regulating eNOS activity via VEGFR2-extracellular signal-regulated kinase pathway, leading to increased proliferation, migration, and capillary-like tube formation as well as decreased permeability and apoptosis of endothelial cells [11]. Moreover, some studies showed that adropin can reduce messenger RNA expression levels of TNF-α and IL-6, establishing suppressive effects on systemic inflammation [31]. As in OSA, one recent study showed that there was a significant negative correlation of plasma adropin levels with mediators of systemic inflammation in OSA patients [16]. Circulating adropin concentrations are highly regulated by energy intake as well as being involved in cardiovascular function, particularly in endothelial function [11, 13, 15, 32]. Theoretically, adropin and sVAP-1 may have contrary effects on the process of ED, our study showed that there was a significant negative correlation of plasma adropin levels with sVAP-1, reinforcing the concept that sleep disorders impose a significant ED burden on the affected individuals.

Our correlation analysis also showed that plasma adropin levels have a significant inverse relationship with AHI, used as an index of OSA severity, based on the PSG results. The pathogenesis of ED in OSA remains largely unknown. One mechanism might be the malfunction of endothelial nitric oxide synthase (eNOS) which causes a decrease of NO synthesis [33]. Nitric oxide (NO) production and availability in the vascular endothelium is an essential determinant of vascular endothelial function and activity [34]. Mechanistically, adropin's protective role can be achieved through interactions of adropin with eNOS, leading to an increased output of NO. Reduction of adropin' level in OSA generally reflects the degree of hypoxic burden which can elicit harmful effects on eNOS, consequently sustaining and further aggravating ED.

Our study has some limitations because it was a prospective analysis based on a relatively limited number of patients. Furthermore, our analyzed sample did not contain female patients. Therefore, our results cannot be applied to a whole population. Finally, a full-night PSG was not performed among control group and for this reason it cannot be fully excluded that some of the healthy volunteers might have had OSA that was not detected. However, the control individuals with a low score (< 2) obtained on the STOP questionnaire has a high negative predictive value for OSA status, especially for patients with moderate and severe OSA, as demonstrated in large number of validation cohorts and relevant systematic researches [35–36]. Moreover, we performed additional analysis using the full STOP-BANG questionnaire instead of the STOP questionnaire in order to increase sensitivity for moderate and severe OSA. Our analysis showed that none of the 20 subjects had a high risk for OSA. Therefore, we can reasonably conclude that our volunteer subjects (control group) were highly unlikely to have clinically significant OSA, despite not being tested with full night PSG.

Conclusion

In conclusion, this is the first study performed in patients with OSA that showed a significant association of sVAP-1 serum levels with PSG sleep parameters, plasma adropin and circulating markers of inflammation in order to demonstrate the relationship between the factors that affect the vascular endothelial function. However, future clinical studies with larger patient enrollment are necessary to fully elucidate the role of these parameters in terms of mechanisms of the disease.

Declarations

Funding None

Conflicts of interest The authors declare that they have no conflict of interest

Ethical approval All procedures performed in studies involving human participants were in accordance with the Ethics Committee of Shanghai University of Traditional Chinese Medicine

Consent to participate Informed consent was obtained from all individual participants included in the study

Consent for publication All the authors approved the publication of this article

Availability of data and material All the data and material are transparency in this article

Code availability SPSS 20.0 Statistics system

Authors' contributions Yuehong Liu and Zhongyu Kong made the same contribution to this study

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Tables

Due to technical limitations, table 1 to 4 is only available as a download in the Supplemental Files section.

Figures

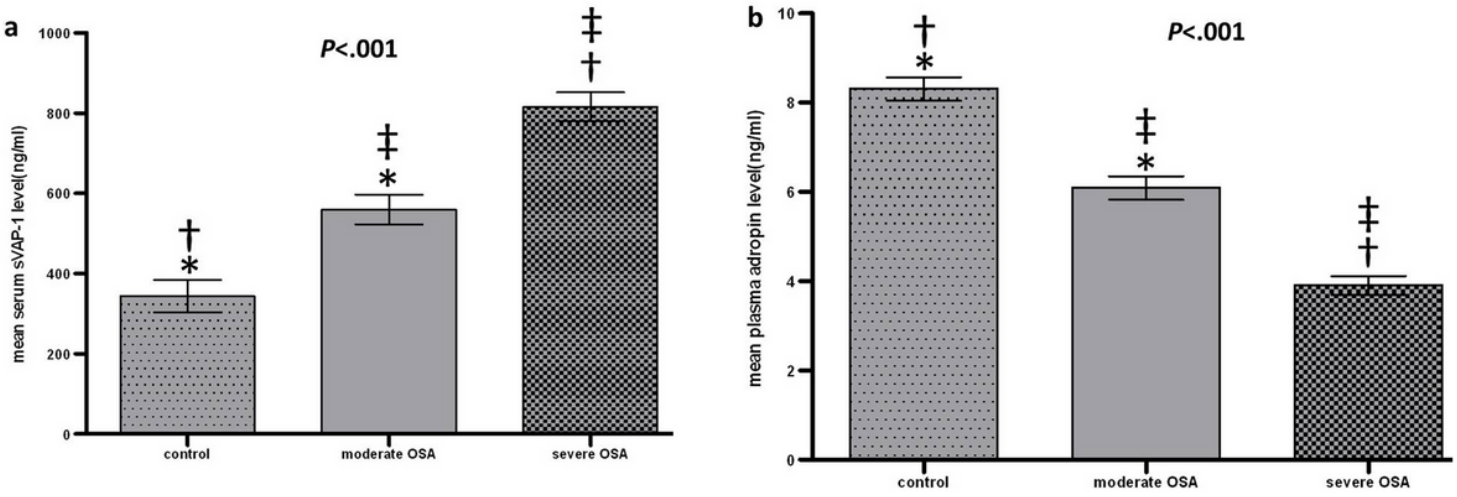

Figure 1

Averaged biomarkers' levels between OSA groups and controls(n=50) (A)sVAP-1, (B) adropin. Data are tested with ANOVA with post hoc Tukey Honestly Significant Difference test and presented as mean ± standard deviation. * = P<.05 between patients with moderate OSA and controls. † = P < .05 between patients with severe OSA and controls. ‡ = P < .05 between patients with moderate and severe OSA

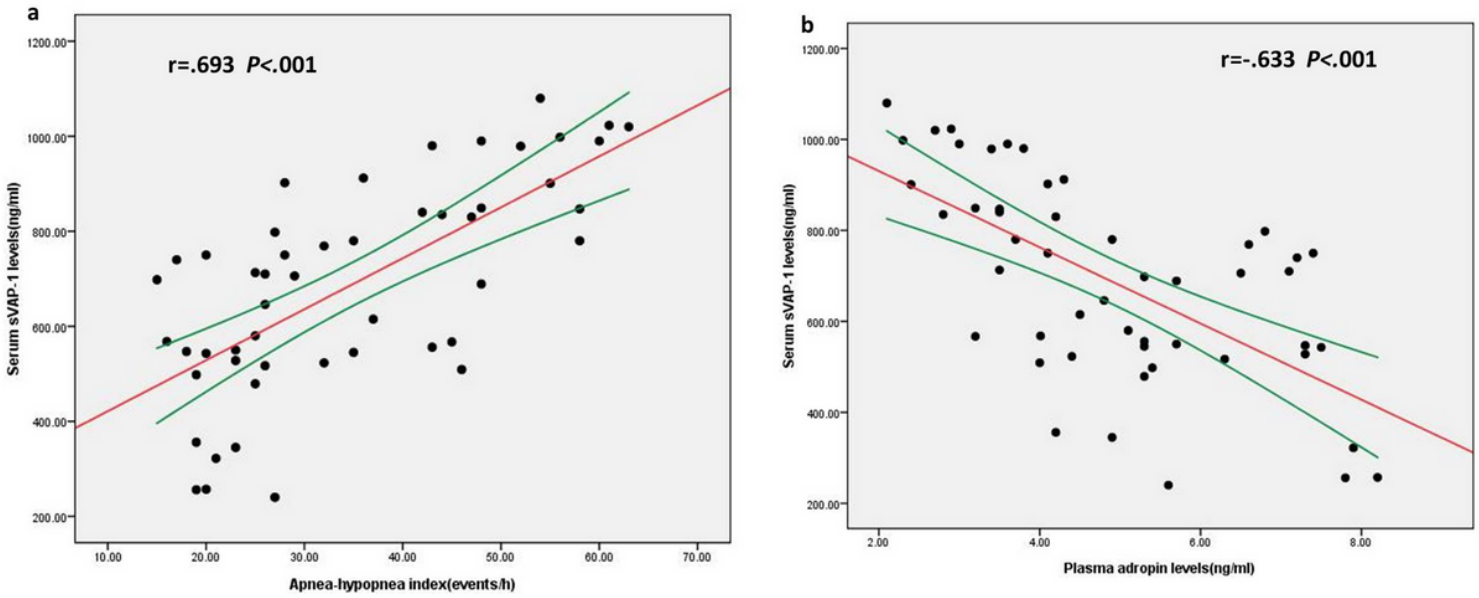

Figure 2

Correlations in composite of moderate and severe OSA patient groups (n=50) Correlations between serum sVAP-1 levels and (A) apnea-hypopnea index, (B) adropin in composite of moderate and severe OSA

patient groups. Red lines represent Pearson correlation coefficient and green lines represent respective 95% confidence intervals.

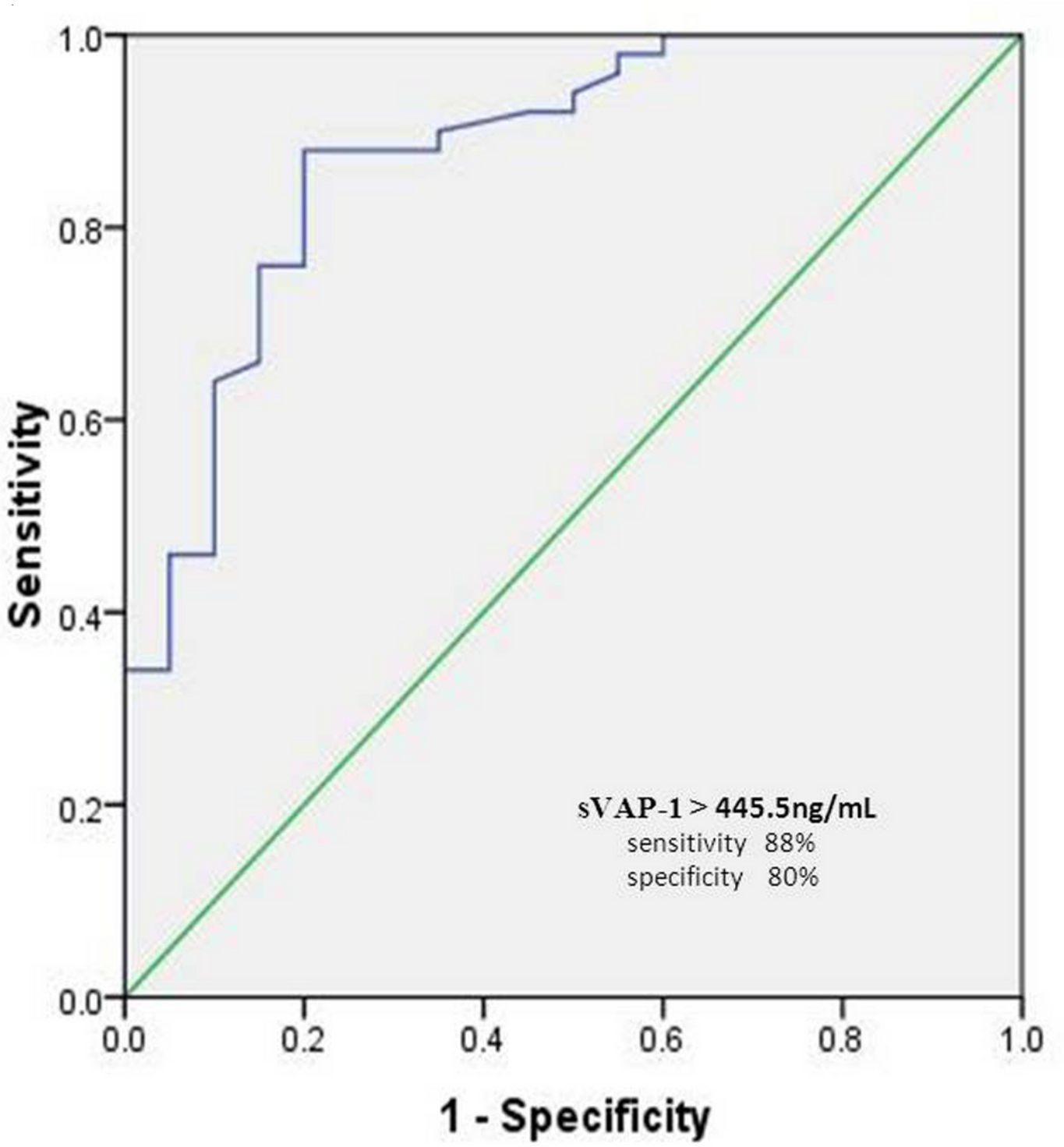

Figure 3

Receiver operating characteristic analysis of sVAP-1 cutoff value in detection of OSA status.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx