Plasma APRIL as a Potential Biomarker in the Diagnosis of Obstructive Sleep Apnea

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Research

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Abstract

Background: Obstructive sleep apnea (OSA) is the most common type of sleep breathing disorder and is characterized by chronic intermittent hypoxia, which could cause inflammation and NF-KB-dependent inflammatory pathways activation. Circulating APRIL might play an important role in promoting inflammation and NF-KB-dependent inflammatory pathways activation. We explored the role of APRIL as a potential mechanism of inflammation in OSA patients. Methods: After detailed sleep evaluated, venous blood and demographic data were collected from 155 subjects with varying severity of OSA and 52 control subjects. Plasma levels of APRIL were measured by human Magnetic Luminex assay. Results: Plasma APRIL levels were significantly higher in OSA subjects compared with control subjects. Categorization of the OSA subjects into mild, moderate, and severe OSA subgroups showed that plasma levels of APRIL increased with severity. After adjusting confounding factors, found that increased plasma APRIL levels were conferred a higher odds ratio (OR) of OSA. Moreover, plasma APRIL levels were positively associated with the apnea-hypopnea index. Furthermore, plasma APRIL showed higher discriminatory accuracy in predicting the presence of OSA. Conclusions:Plasma APRIL levels were significantly associated with the occurrence of OSA and its severity. APRIL could be a plasma biomarker with a positive diagnostic value for inflammation and NF-KB–dependent inflammatory pathways activation in subjects with OSA.

Backgroud

Obstructive sleep apnea (OSA) is a prevalent sleep breathing disorder and is characterized by recurrent collapse of the upper airway during sleep resulting in markedly reduced or absent airflow, sleep disruption, nightly chronic intermittent hypoxia (CIH), and surges of the sympathetic nervous system [1–3]. These physiological perturbations often cause endothelial dysfunction, inflammation and nuclear factor kappa B (NF-kB)-dependent inflammatory pathways activation, which was the potential pathogenesis of hypertension, diabetes mellitus and cardiovascular disorders [4–6]. A large body of evidence has shown that unrecognized and untreated OSA substantially increases cardiovascular risks in the general population [7, 8]. Given its association with cardiovascular disease, OSA has been proposed as an early intervention target for improving the quality of life and reducing morbidity and mortality rates. The AASM clinical practice guidelines suggest that screening questionnaires and facility-based polysomnography (PSG) can be used to screen and diagnose OSA in adult patients with suspected OSA [9]. However, screening questionnaires are limited by lower specificity and accuracy, PSG was expensive, labor-intensive, and time-consuming tests and impractical for the clinical evaluation of large at-risk populations [10]. Therefore, comprehensive dissection of the molecular indexes under OSA conditions is so paramount as that will help to precisely detect and diagnose this sleep disorder in clinical practice.

A proliferation-inducing ligand (APRIL, also named TNFSF13), a member of the tumor necrosis factor family, which was significantly higher in autoimmune diseases [11–14]. Current evidence suggests that APRIL could induce inflammatory activation by the activation of NF-KB signaling pathway [15, 16], and conversely, NF-KB-dependent signaling pathways, in turn, can influence APRIL secretion [17, 18]. The

activation of NF-KB–dependent inflammatory pathways by intermittent hypoxia and reoxygenation in OSA may be an important molecular mechanism of cardiovascular complication [4, 19, 20]. In addition, several studies showed that monocyte chemotactic protein-1 (MCP-1) and L-selectin as inflammation mediators can be regulated via the activation of NF-KB signaling pathways, and they were significantly elevated in patients with OSA [21–24].

The purpose of this study in patients with OSA was to evaluate whether levels of APRIL, MCP-1, and L-selectin by plasma are elevated; to identify whether the plasma APRIL levels were associated with the presence and severity of OSA and whether plasma APRIL could predict inflammation and NF-KB–dependent inflammatory pathways activation in OSA patients.

Methods

Study design and participants

We conducted an observational cross-sectional study in Beijing An-Zhen hospital. The study protocol was approved by the Medicine Ethics Committee of Beijing An-Zhen Hospital and adhered to the principles laid out in the Declaration of Helsinki. The project was approved by the Chinese Clinical Trial Registry (No. ChiCTRROC-17011027). In total, 240 participants were recruited and underwent overnight full PSG in Sleep Laboratory between March 2017 and November 2017. The study flow chart is shown in Additional file 1: Figure S1. Participants with central sleep apnea syndrome, chronic obstructive pulmonary disease, cancer, hepatic dysfunction, interstitial lung disease, acute infectious diseases, or abnormal renal function were excluded [25]. Participants refused to sign the consent form, or with incomplete information were also excluded. Finally, we selected a total of 207 eligible participants. Data on participants' baseline demographics were extracted from self-administered questionnaires. Weight (kilograms), height (meters), blood pressure and left ventricular ejection fraction were measured or calculated using standardized and reproducible study protocols. Body mass index (BMI) (kg/m^2) was calculated by the formula of weight divided by height squared. Current smokers were defined as participants who were smoking or stopping smoking for less than one year before enrollment in this study. Drinkers were subjects who consumed alcohol more than three days a week. The definitions of coronary heart disease (CHD), diabetes mellitus, hypercholesterolemia, and hypertension were based on subject medical histories. Serum lipid, high-sensitivity C-reactive protein, and other routine biochemical parameters were measured in a biochemical analyzer (Hitachi-7600, Tokyo, Japan) using blinded quality control specimens in the Department of the Biochemical Laboratory at Beijing An-Zhen Hospital.

Sleep Data

All participants(n = 207) included in this study underwent detailed sleep evaluated. Neck circumference (cm) was measured between the mid-cervical spine and mid-anterior neck, by using a flexible tape, with the participants in the standing position, head held erect [26]. The Epworth Sleepiness Scale (ESS), which

was signed to assess the risk of daytime sleepiness, were recorded for each study participant [27]. All participants underwent overnight PSG (SOMNO screen; SOMNO medics GmbH, Randersacker, Germany) approved by the US Food and Drug Administration. Alcohol or sleeping medicines were strictly prohibited before the PSG examination. The SOMNO screen device continuously monitored and recorded abdominal and ribcage motion, respiratory effort airflow, arterial oxygen saturation, electroencephalogram, and electrocardiogram by a computerized polysomnogram. Sleep stage and cardiopulmonary events were manually classified and evaluated by certified technicians according to the 2012 American Academy of Sleep Medicine criteria [9]. Hypopnea was defined as ≥ 3% oxygen desaturation sustaining for ≥ 10 s. Apnea was defined as a complete cessation of airflow or airflow decrease ≥ 90% relative to the baseline amplitude and persisting for ≥ 10 s. The apnea-hypopnea index (AHI) was calculated as the total number of hypopneas and apneas per hour of sleep. The AHI was used to categorize OSA as none (0-4.9 events/h), mild (5-14.9 events/h), moderate (15-29.9 events/h), and severe (AHI ≥ 30 events/h).

Collection And Storage Of Plasma Sample

Fasting whole blood sample was collected after the PSG examination. Procedures for plasma collection, processing, and storage have been previously described [28].

Luminex Assays

Magnetic Luminex® Assays was a magnetic bead-based antibody microarray founded upon the sandwich immunoassay principle, which can be used to facilitate the simultaneous quantitation of up to 100 soluble analytes in a single sample [29]. APRIL, MCP-1 and L-selectin concentrations were determined by the Luminex magnetic bead cytokines panel based on the competition principle (R&D Systems, Inc. Minneapolis, MN, USA). To ensure the accuracy and validity of the results, as previously described we evaluated the Luminex multiplex assay system by the standard curve and intra-assay variability. Firstly, the standard curve was critical for quantitation measurements. The assay sensitivity and detection range of cytokines were evaluated and the results were shown in Additional file 1: Table S1. Reading out of range of the standard curve were excluded from all subsequent analyses. Secondly, to determine the precision of the standards and cytokines levels values obtained by the Luminex platforms, we calculated intra-assay performance using the coefficient of variation (CV%) to determine the precision of results. Intra-assay CV < 10% being acceptable. In addition, all plasma samples were optimally diluted to ensure cytokine levels fell within the detection dynamic range of the assay. All standards and samples were run in duplicate according to the manufacturer's instructions [https://resources.rndsystems.com/pdfs/datasheets/lxsahm.pdf].

Statistical analysis

Continuous variables were tested for normality of distribution by the Kolmogorov–Smirnov test and were presented as means ± standard deviations (SD) (for normally distributed data) or presented as medians

(interquartile ranges) (for asymmetrically distributed data). Categorical variables were expressed as numerals (percentages). Analyses for comparisons demographic, sleep, biological, and cytokine values between OSA and control groups were performed using Student's t-tests for normally distributed data and using the Mann-Whitney U test for asymmetrically distributed data. Differences among mild OSA, moderate OSA and severe OSA were compared by analysis of variance (ANOVA) in normally distributed variables and the Kruskal–Wallis test in asymmetrically distributed variables. Categorical variables were compared by using the chi-square test followed by Fisher exact tests. Spearman correlation coefficient was used to analyze the correlations between cytokine levels and clinical parameters. Multiple logistic regression analyses (forced entry method) were performed to assess the association between OSA and plasma cytokines levels. Multiple linear regression analyses (forced entry method) were performed to assess the association between AHI and plasma cytokines levels. In addition, receiving operator curves (ROC) were calculated for the prediction of OSA based on cytokines levels and the area under curve (AUC), sensitivity, and specificity of the optimal cutoff cytokines were recorded. An AUC of 0.5 indicated no predictive power, whereas an AUC of 1 indicated perfect prediction. A p-value < 0.05 was considered as statistically significant. Analyses were performed using SPSS version 25 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics of the study population

The demographic and sleep data of the 207 individuals who participated in this study were shown in Table 1. Subjects with OSA had significantly higher BMIs, systolic blood pressure, diastolic blood pressure, neck circumference, ESS, AHI, the percentage of cumulative time with oxygen saturation below 90%, and arousal index than control subjects. The "Lowest SaO2" and "Mean SaO2" were lower in subjects with OSA. A greater proportion of subjects with OSA were male, had coronary heart disease or hypertension compared with the control group. There were no significant differences in age and left ventricular ejection fraction between the two groups. The prevalence of currents smokers, drinkers, diabetes mellitus, and hypercholesterolemia were also no differences between the two groups.

Table 1

Comparison of demographic and sleep data in the study population.

Parameters	Control (n = 52)	OSA (n = 155)	P-value
Age (years)	51.00(34.25–63.75)	54.00(42.00–60.00)	0.659
Male n(%)	33(63.46)	128(82.58)	0.004
BMI (kg/m^2)	23.01(20.74–27.01)	27.15(24.78–29.70)	< 0.001
SBP (mmHg)	120.00(112.25–132.00)	127.00(117.00-137.00)	0.044
DBP (mmHg)	75.29 ± 11.05	80.23 ± 11.64	0.008
LVEF (%)	63.50(60.00–68.00)	65.00(60.00–69.00)	0.226
Current smoker n(%)	16(30.77)	61(39.35)	0.268
Drinker n(%)	9(17.31)	39(25.16)	0.246
CHD n(%)	11(21.15)	74(47.74)	0.001
Diabetes mellitus n(%)	6(11.54)	23(14.84)	0.553
Hypercholesterolemia n(%)	7(13.46)	25(16.13)	0.645
Hypertension n(%)	19(36.54)	90(58.06)	0.007
Neck circumference (cm)	39.00(34.00–41.00)	42.00(38.00–44.00)	< 0.001
ESS	0.00(0.00–5.00)	9.00(4.00–12.00)	< 0.001
AHI (events/h)	3.10(2.03–3.88)	25.90(12.90–46.80)	< 0.001
Lowest SaO_2 (%)	92.00(91.00–93.00)	85.00(78.00–89.00)	< 0.001
Mean SaO_2 (%)	96.90(95.80–97.00)	94.80(93.00–96.00)	< 0.001
CT90 (%)	/	0.90(0.00-7.80)	< 0.001
Arousal index (events/h)	0.85(0.00-3.45)	11.55(5.40–27.90)	< 0.001
Data are presented as n, or median (interquartile range [IQR]), or n (%), or mean ± SD, unless otherwise stated.			
OSA, Obstructive sleep apnea; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; LVEF, Left ventricular ejection fraction; CHD, Coronary heart disease; ESS, Epworth Sleepiness Scale; AHI, Apnea-hypopnea index; CT90, Percentage of cumulative time with oxygen saturation below 90%.			

Subjects with OSA had significantly higher triglyceride, leukocyte, uric acid, ALT, GGT, creatinine, and glucose levels compared to patients in the control group (Table 2). Other biological parameters were not a significant difference between the two groups.

Table 2
Biological parameters of the study population based on obstructive sleep apnea

Parameters	Control (n = 52)	OSA (n = 155)	P-value
Total cholesterol (mmol/L)	4.52(4.04–5.16)	4.75(3.81–5.59)	0.458
Triglyceride (mmol/L)	1.17(0.78–1.62)	1.50(1.08–1.99)	0.002
HDL-C (mmol/L)	1.20(1.04–1.44)	1.18(0.95–1.35)	0.187
LDL-C (mmol/L)	2.67 ± 0.91	2.88 ± 1.01	0.190
hsCRP (mg/L)	0.87(0.26–3.45)	1.36(0.58–3.02)	0.115
Platelet (G/L)	217.00(177.00-262.00)	218.00(193.00-252.50)	0.746
Leukocyte (G/L)	5.58(4.82–7.04)	6.42(5.53–7.43)	0.034
Uric acid (umol/L)	335.91 ± 79.58	389.14 ± 97.27	< 0.001
ALT (U/L)	22.00(13.00–30.00)	27.00(18.00–38.00)	0.005
GGT (U/L)	25.50(17.00-34.75)	33.50(22.00–54.00)	0.001
Homocysteine (umol/L)	10.10(8.78–15.30)	12.50(9.60–16.60)	0.177
Urea nitrogen (mmol/L)	4.50(4.10–5.90)	5.10(4.30–6.38)	0.100
Creatinine (umol/L)	61.45(56.10–74.10)	70.50(59.90–79.30)	0.008
ALP(U/L)	72.50(63.25-90.00)	74.00(61.75-90.00)	0.702
AST (U/L)	20.00(18.00–24.00)	22.00(18.00–29.00)	0.057
Creatine kinase (U/L)	87.50(66.00-110.50)	93.00(66.50-132.50)	0.516
Glucose (mmol/L)	5.13(4.83–5.42)	5.44(5.04–6.07)	0.001
APRIL (ng/mL)	2.97(1.51–3.99)	5.25(4.69–5.82)	< 0.001
MCP-1 (ng/mL)	0.25(0.13–0.31)	0.28(0.25–0.33)	0.003
L-selectin (ng/mL)	539.07(214.86-1041.19)	1090.31(1001.02-1311.15)	< 0.001
Data are presented as n, mean ± SD, or median (interquartile range [IQR]).			
OSA, Obstructive sleep apnea; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemoattractant protein-1.			

To determine whether OSA at different severity may differentially affect demographic, sleep and biological parameters, we compared the difference of several parameters among three different OSA status (Table 3). Compared to mild OSA, BMIs, diastolic blood pressure, neck circumference, ESS, AHI, the

percentage of cumulative time with oxygen saturation below 90%, arousal index, triglyceride, glucose were significantly increased in severe OSA groups. The “Lowest SaO2” and “Mean SaO2” decreased in a stepwise fashion from mild to severe OSA patients.

Table 3
Demographic and biological data of the obstructive sleep apnea population based on severity of obstructive sleep apnea

Parameters	Mild OSA (n = 44)	Moderate OSA (n = 44)	Severe OSA (n = 67)	P-value
Age (years)	57.50(46.50-62.75)	54.00(42.50–60.00)	50.00(42.00–59.00)	0.142
Male n(%)	30(68.18)	40(90.91)*	58(86.57)*	0.010
BMI (kg/m^2)	25.05(23.77-27.00)	26.95(25.11–29.70)*	28.38(26.70-31.55)*	< 0.001
SBP (mmHg)	123.00(110.25-135.25)	126.00(116.25–135.50)	129.00(120.00-138.00)	0.210
DBP (mmHg)	72.50(70.00-85.75)	77.50(72.25–89.75)	82.00(78.00–90.00)*	0.006
CHD n(%)	25(56.82)	21(47.73)	28(41.79)	0.301
Hypertension n(%)	21(47.73)	27(61.36)	42(62.69)	0.257
Neck circumference (cm)	37.00(34.00–42.00)	42.00(40.00–44.00)*	43.00(41.00–44.00)*	< 0.001
ESS	4.00(0.00-8.75)	8.00(5.25-12.00)*	11.00(8.00–15.00)*†	< 0.001
AHI (events/h)	10.25(7.15–11.98)	21.45(18.90-25.88)*	51.00(38.20–68.30)*†	< 0.001
Lowest SaO_2 (%)	90.00(86.00-91.75)	86.50(83.25-89.00)*	76.00(67.00–85.00)*†	< 0.001
Mean SaO_2 (%)	95.95(95.00–96.00)	95.00(94.00–96.00)	93.00(88.90–94.30)*†	< 0.001
CT90 (%)	0.00(0.00-0.33)	0.30(0.00-2.35)	9.60(1.80–26.00)*†	< 0.001
Arousal index (events/h)	4.55(0.63–11.13)	10.65(6.90-16.15)*	26.80(9.38–60.75)*†	< 0.001

Data are presented as median (interquartile range [IQR]), or n (%), or mean ± SD.

*P < 0.05 versus Mild OSA, †P < 0.05 versus Moderate OSA.

OSA, Obstructive sleep apnea; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CHD, Coronary heart disease; ESS, Epworth Sleepiness Scale; AHI, Apnea-hypopnea index; CT90, Percentage of cumulative time with oxygen saturation below 90%; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemoattractant protein-1.

Parameters	Mild OSA (n = 44)	Moderate OSA (n = 44)	Severe OSA (n = 67)	P-value
Triglyceride (mmol/L)	1.32(0.87–1.77)	1.44(0.96–1.75)	1.67(1.27–2.17)*	0.005
Leukocyte (G/L)	6.23(4.79–6.86)	6.45(5.50–7.49)	6.46(5.63–7.77)	0.256
Uric acid (umol/L)	368.75 ± 97.92	407.41 ± 85.20	391.38 ± 102.59	0.182
ALT (U/L)	23.50(15.75-37.00)	27.00(17.50–37.50)	29.00(19.25-42.00)	0.225
GGT (U/L)	33.00(20.00–43.00)	29.00(22.00-47.50)	43.00(25.75–69.25)	0.078
Creatinine (umol/L)	66.70(57.80-77.83)	73.00(62.40–79.60)	69.05(58.98–80.48)	0.194
AST (U/L)	21.00(18.75-28.00)	24.00(18.00–30.00)	22.00(18.25-28.00)	0.612
Glucose (mmol/L)	5.30(4.98–5.89)	5.36(4.81–5.98)	5.64(5.13–6.76)	0.047
APRIL (ng/mL)	4.77(4.32–5.35)	5.19(4.69–5.57)	5.64(5.02–6.30)*†	< 0.001
MCP-1 (ng/mL)	0.28(0.23–0.31)	0.27(0.24–0.33)	0.29(0.27–0.34)	0.036
L-selectin (ng/mL)	1069.02(985.35-1260.86)	1069.09(966.05-1267.15)	1140.94(1038.49-1390.79)	0.217
Data are presented as median (interquartile range [IQR]), or n (%), or mean ± SD.				
*P < 0.05 versus Mild OSA, †P < 0.05 versus Moderate OSA.				
OSA, Obstructive sleep apnea; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CHD, Coronary heart disease; ESS, Epworth Sleepiness Scale; AHI, Apnea-hypopnea index; CT90, Percentage of cumulative time with oxygen saturation below 90%; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemoattractant protein-1.				

Increased plasma APRIL, MCP-1 and L-selectin levels in subjects with OSA

To determine the expression levels of APRIL, MCP-1, and L-selectin in subjects with OSA, we used human Magnetic Luminex assay to analyze plasma cytokines in subjects with confirmed OSA and controls. Plasma APRIL, MCP-1, and L-selectin concentrations were significantly higher in the OSA group than those in the control group (Fig. 1). Meanwhile, we explore the levels of APRIL, MCP-1, and L-selectin among three different OSA status. We found that the APRIL concentrations were the lowest in mild OSA subjects and increased as the AHI increased, with the highest concentrations in the severe OSA group. The plasma concentrations of MCP-1and L-selectin were no significant differences among mild OSA, moderate OSA and severe OSA groups (Fig. 2).

Association Between APRIL, MCP-1 And L-selectin Levels And OSA

To investigate whether the levels of APRIL, MCP-1, and L-selectin were correlated with OSA, we used Spearman's correlation to explore the associations. As shown by correlation analyses, AHI levels in all individuals were significantly positive correlated with APRIL ($r = 0.645$, $P < 0.001$), MCP-1 ($r = 0.261$, $P < 0.001$), and L-selectin ($r = 0.466$, $P < 0.001$). Moreover, the "Lowest SaO2" were significantly negatively correlated with APRIL ($r=-0.471$, $P < 0.001$), and L-selectin ($r=-0.405$, $P < 0.001$) (Fig. 3). In addition, plasma APRIL levels showed significantly positive correlation with plasma MCP-1 ($r = 0.329$, $P < 0.001$) and L-selectin ($r = 0.535$, $P < 0.001$) (Fig. 4).

Multiple logistic regression analyses were performed to examine whether circulating APRIL, MCP-1 and L-selectin were correlated with OSA. As shown in Table 4, demographics (age, sex, BMI, CHD, and hypertension), biological parameters (uric acid, ALT, GGT, creatinine, AST, and glucose) and APRIL levels as covariates, found that increased plasma APRIL levels conferred a higher odds ratio (OR) of OSA (OR: 5.808, 95% confidence interval (CI): 2.917 to 11.566; $P < 0.001$). After adjustment confounding factors, we also found that increased plasma MCP-1 levels (OR: 96979.076, 95%CI: 43.694 to 215247954.7; $P = 0.003$) and L-selectin levels conferred a higher risk for OSA (OR: 1.006, 95%CI: 1.003 to 1.008; $P < 0.001$) (Additional file 1: Table S2-S3).

Table 4

Association between OSA and APRIL in univariate and multiple logistic regression models

Variables	OSA(no vs.yes)					
	Univariate models			Multiple model (R^2 = 0.692, P < 0.001)		
	OR	95%CI	P value	OR	95%CI	P value
Age (years)	1.009	0.985 to 1.033	0.482	0.997	0.950 to 1.047	0.898
Sex (female vs.male)	0.366	0.182 to 0.738	0.005	1.105	0.244 to 5.006	0.897
BMI (kg/m^2)	1.296	1.172 to 1.432	< 0.001	1.221	1.031 to 1.446	0.021
CHD (no vs.yes)	3.448	1.650 to 7.203	0.001	1.581	0.407 to 6.134	0.508
Hypertension (no vs.yes)	2.405	1.258 to 4.599	0.008	1.412	0.415 to 4.799	0.581
Triglyceride (mmol/L)	1.192	0.871 to 1.631	0.272			
Leukocyte (G/L)	1.085	0.897 to 1.312	0.401			
Uric acid (umol/L)	1.006	1.003 to 1.010	0.001	1.002	0.995 to 1.010	0.567
ALT (U/L)	1.032	1.006 to 1.058	0.014	0.982	0.917 to 1.052	0.602
GGT (U/L)	1.023	1.007 to 1.040	0.006	0.998	0.981 to 1.016	0.838
Creatinine (umol/L)	1.035	1.009 to 1.060	0.007	1.045	0.987 to 1.107	0.128
AST (U/L)	1.039	0.999 to 1.081	0.059	1.054	0.919 to 1.210	0.453
Glucose (mmol/L)	1.749	1.185 to 2.581	0.005	1.323	0.692 to 2.530	0.397
APRIL (ng/mL)	6.255	3.520 to 11.113	< 0.001	5.808	2.917 to 11.566	< 0.001
Multiple logistic regression model includes age, sex, BMI and other variables with P < 0.100 in univariate model analysis						
R^2, adjusted R^2 of the multiple logistic regression model; OR odds ratio; CI, confidence intervals.						
OSA, Obstructive sleep apnea; BMI, Body mass index; CHD, Coronary heart disease; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand.						

Multiple linear regression analyses were performed to examine the association of the AHI and plasma APRIL, MCP-1 and L-selectin levels. After adjustment for demographics (age, sex, BMI, hypertension), biological parameters (triglyceride, leukocyte, uric acid, ALT, GGT, AST and glucose) and APRIL levels,

plasma APRIL levels were positively associated with the AHI (Beta:0.366, 95% CI: 4.089 to 8.299; P < 0.001) (Table 5), which represents the severity of OSA in this study. After adjustment confounding factors, we also found that plasma MCP-1 levels (Beta:0.163, 95% CI: 9.660 to 98.947; P = 0.017)and L-selectin levels (Beta:0.245, 95% CI: 0.008 to 0.025; P < 0.001) were positively associated with the AHI (Additional file 1: Table S4-S5).

Table 5

Association between levels of AHI and APRIL in univariate and multiple linear regression models

Variables	**AHI(events/h)**					
	Univariate models			Multiple model (R^2 = 0.456, P < 0.001)		
	Beta	95%CI	P value	Beta	95%CI	P value
Age (years)	-0.094	-0.418 to 0.077	0.176	-0.095	-0.396 to 0.047	0.122
Sex (female vs.male)	-0.173	-17.775 to -2.170	0.013	0.003	-6.614 to 6.937	0.963
BMI (kg/m^2)	0.537	2.269 to 3.522	< 0.001	0.292	0.930 to 2.372	< 0.001
CHD (no vs.yes)	0.002	-6.579 to 6.746	0.980			
Hypertension (no vs.yes)	0.190	2.618 to 15.571	0.006	0.057	-2.952 to 8.383	0.346
Triglyceride (mmol/L)	0.249	2.167 to 7.303	< 0.001	0.008	-2.135 to 2.424	0.901
Leukocyte (G/L)	0.162	0.252 to 3.735	0.025	0.041	-0.884 to 1.873	0.480
Uric acid (umol/L)	0.204	0.017 to 0.086	0.004	< 0.001	-0.030 to 0.029	0.998
ALT (U/L)	0.317	0.190 to 0.477	< 0.001	0.175	-0.017 to 0.398	0.072
GGT (U/L)	0.282	0.100 to 0.280	< 0.001	-0.009	-0.092 to 0.079	0.885
Creatinine (umol/L)	0.074	-0.078 to 0.256	0.296			
AST (U/L)	0.141	-0.004 to 0.585	0.053	-0.129	-0.700 to 0.120	0.165
Glucose (mmol/L)	0.366	4.142 to 8.662	< 0.001	0.219	1.845 to 6.042	< 0.001
Multiple linear regression model includes age, sex, BMI and other variables with P < 0.100 in univariate model analysis						
R^2, adjusted R^2 of the multiple linear regression model; Beta, standardized regression coefficients; CI, confidence intervals.						
AHI, Apnea-hypopnea index; BMI, Body mass index; CHD, Coronary heart disease ; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand.						

Variables	AHI(events/h)					
APRIL (ng/mL)	0.545	6.911 to 10.686	< 0.001	0.366	4.089 to 8.299	< 0.001
Multiple linear regression model includes age, sex, BMI and other variables with P < 0.100 in univariate model analysis						
R^2, adjusted R^2 of the multiple linear regression model; Beta, standardized regression coefficients; CI, confidence intervals.						
AHI, Apnea-hypopnea index; BMI, Body mass index; CHD, Coronary heart disease ; ALT, Alanine aminotransferase; GGT, γ-glutamyltransferase; AST, Aspartate aminotransferase; APRIL, A proliferation-inducing ligand.						

ROC curve analysis for OSA and APRIL, MCP-1, and L-selectin

We determined based on ROC curves analysis the optimal threshold value for the optimal meeting point between having the greatest sensitivity and specificity for predicting the occurrence of the OSA. The optimal cutoff value of plasma APRIL for the identification of OSA was 4.56 ng/mL with a corresponding sensitivity of 79.43% and specificity of 82.61%. The area under the curve of 0.856 with a P value < 0.001, indicating that APRIL concentration could be a predictor of OSA. The optimal cutoff value of plasma for MCP-1 the identification of OSA was 0.20 ng/ml (sensitivity:94.33%, specificity:47.83%) and the AUC was 0.673. The optimal cut-point for plasma L-selectin at OSA was 878.54 ng/ml (sensitivity:86.53%, specificity:43.48%) and the AUC was 0.692. Plasma APRIL showed higher discriminatory accuracy than plasma MCP-1 and L-selectin in predicting the presence of OSA (AUC, 0.856 vs 0.673, 0.692, respectively) (Fig. 5).

Discussion

In this study, we found that subjects with OSA have significantly elevated plasma APRIL, MCP-1 and L-selectin levels compared with controls. Plasma APRIL concentrations were the lowest in mild OSA subjects and increased as the AHI increased, with the highest concentrations in the severe OSA group. Plasma APRIL levels were significantly correlated with the AHI and the “Lowest SaO2”, and by multiple regression analyses, we found APRIL were positively and independently associated with the OSA and the AHI, respectively. Meanwhile, plasma APRIL showed higher discriminatory accuracy than plasma MCP-1 and L-selectin in predicting OSA.

Sleep deprivation, sympathetic activation, and CIH was the major pathophysiologic character of OSA, which lead to the release of proinflammatory mediators and the directional migration of leucocytes. These pathophysiological changes can stimulate the expression of acute-phase proteins and inflammatory mediators [2, 5]. Meanwhile, immune cells dominate early atherosclerotic lesions, their

effector molecules accelerate inflammation and NF-KB activity, which can elicit atherosclerotic lesions rupture and trigger the acute onset of arterial thrombosis [30, 31]. Several studies have shown that treating OSA with continuous positive airway pressure improves inflammation and reduces of NF-KB signaling [20, 32]. Even in patients with OSA who were free of overt cardiovascular disease, the physiological perturbations of inflammation and NF-KB-dependent inflammatory pathways activation often caused blood pressure and heart rate elevations, ventricular failure, myocardial infarction, and stroke [4, 33]. Given its association with cardiovascular disease, it was extremely essential to advance the research agenda to explore validated tools for diagnosing OSA in the early stage.

The AASM clinical practice guidelines suggest that OSA is diagnosed based on clinical measures, including the subjective assessment of somnolence and the overnight multi-channel PSG [9]. The former is limited by low specificity and accuracy for diagnosis of OSA, the latter is expensive, labor-intensive, time-consuming tests and impractical for the clinical evaluation of large at-risk populations [10]. Therefore, new technologies such as circulating biomarkers could provide important information on clinical significance for diagnosing OSA.

By human Magnetic Luminex assay, we evaluated plasma APRIL, MCP-1, and L-selectin levels in subjects with confirmed OSA and controls. Intriguingly, we found that plasma APRIL, MCP-1, and L-selectin levels were significantly higher in the OSA group compared with the control group. In addition, plasma APRIL levels were statistically higher in subjects with severe OSA than subjects with mild OSA. APRIL(also named TNFSF13), a member of the tumor necrosis factor family, which is secreted as a soluble factor at low levels in immunological tissues especially by antigen-presenting cells, inactive B cells, T cells, monocytes, neutrophils, macrophages, and dendritic cells, as well as by epithelial cells, osteoclasts, and megakaryocytes [34–36]. Increased levels of APRIL have been found in several autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and immunodeficiency [11–14]. Several studies have indicated that the relationship of APRIL and NF-KB signaling pathway activation is one of a complex interactive, APRIL could induce inflammatory activation by the activation of NF-KB signaling pathway [15, 16], and conversely, NF-KB-dependent pathways can influence APRIL secretion [17, 18]. A large body of evidence, including experimental and clinical studies, have demonstrated that the activation of NF-KB–dependent inflammatory pathways by intermittent hypoxia and reoxygenation in OSA may be an important molecular mechanism of cardiovascular complication [4, 19, 20]. Moreover, both RNA and protein expression of APRIL have been shown in human plaque lymphocytes and macrophages and plasma [37, 38]. Recently, Bernelot Moens et al found that APRIL transgenic mice do show potential plaque stabilizing features in advanced atherosclerotic lesions [39]. However, to the best of our knowledge, no previous studies have investigated the relationship between the circulating APRIL and the presence of OSA. The present study showed that a progressive increase in the concentrations of APRIL with the severity of OSA, increase plasma APRIL levels were significantly associated with the occurrence of OSA and its severity.

MCP-1 is one of the best-studied CC chemokines that is expressed by inflammatory cells and stromal cells, and its chemotactic activity could be upregulated after proinflammatory stimuli [40, 41]. Evidence

from animal models and in vitro experiments suggested that IH induced the synthesis and expression of MCP-1 via the activation of NF-KB signaling pathway [21, 42]. Furthermore, early studies suggested that OSA-induced hypoxia would increase circulating MCP-1 levels and effective therapy for OSA could reduce the expression of MCP-1 [43, 44]. Our results suggested that the plasma MCP-1 level was significantly higher in subjects with OSA compared with subjects without OSA, but there were no statistical differences in MCP-1 levels among the mild OSA, moderate OSA, and severe OSA.

L-selectin is a cell membrane-surface receptor on leukocytes, which mediated the rolling and tethering of leukocytes into the injured tissues independently of other adhesion molecules [24]. Early studies found that the monocyte/leukocyte induced effects on expression of the L-selectin through the NF-KB signaling pathway [23]. Meanwhile, some evidence demonstrated that circulating L-selectin levels were significant and independent indicators of accentuated atherogenesis in patients with OSA [24, 45]. However, some studies showing the correlation between circulating L-selectin and OSA were not detected, probably due to the defining criteria of the OSA were inconsistent [46, 47]. In the present study, we found that the circulating L-selectin levels were significantly increased in the OSA group, and it was independently associated with the occurrence of the OSA and its severity. Of note, no significant differences in L-selectin levels were observed among the mild OSA, moderate OSA, and severe OSA.

And intriguingly, we also found that plasma APRIL levels were significantly correlated with plasma MCP-1 and L-selectin levels. Of note, in terms of AUC, the discriminatory accuracy of plasma APRIL significantly exceeded those of plasma MCP-1and L-selectin. These interesting findings implied that plasma APRIL levels might be related to inflammation and NF-KB–dependent inflammatory pathways activation induced by OSA.

Care was taken to avoid bias in this study, the Luminex experiment was performed according to the manufacturer’s instructions by a trained experimenter who was unaware of patients' clinical data. Moreover, in the statistical analysis, adjustments were made for the confounding effects of risk factors for plasma APRIL levels and OSA/AHI. However, our study had several certain limitations. First, we included only newly diagnosed, and untreated OSA. Second, our results didn't elucidate the specific mechanisms of APRIL in OSA.

Conclusions

In conclusion, we found that plasma APRIL levels were significantly elevated in patients with OSA and were associated with the occurrence of OSA and its severity. Plasma APRIL levels provided higher discriminatory accuracy levels for patients with OSA. APRIL could be a biomarker with a positive diagnostic value for inflammation and NF-KB–dependent inflammatory pathways activation in patients with OSA. Future studies are needed to highlight underlying mechanisms and the predictive value of APRIL for outcome in OSA patients.

Abbreviations

OSA, Obstructive sleep apnea; CIH, Chronic intermittent hypoxia; NF-kB, Nuclear factor kappa B; PSG, Polysomnography; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1; BMI, Body mass index; CHD, coronary heart disease; ESS, Epworth sleepiness scale; AHI, Apnea-hypopnea index; CV, Coefficient of variation; ROC, Receiving operator curves; AUC, Area under curve; OR, odds ratio; CI, confidence interval.

Declarations

Acknowledgments

We thank all the participants in this study.

Authors' contributions

Ming Zhang and Yong-Xiang Wei have substantial contributions to the design the research; Yun-Xiao Yang, Yi-Fan Jia, and Meng-Ling Huang have substantial contributions to the acquisition, analysis, and interpretation of data for the research. Wan-Wan Wen and Hai-Li Sun have substantial contributions to draft this paper. Yun-Hui Du, Yan-Wen Qin, and Fang Fang have substantial contributions to revise this paper.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The project was approved by the Chinese Clinical Trial Registry (No. ChiCTRROC-17,011,027). The study protocol was approved by the Medicine Ethics Committee of Beijing Anzhen Hospital and adhered to the Declaration of Helsinki. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

All authors declare no conflict of interest.

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Additional File

Additional file 1: Table S1: Evaluation of Luminex assay standard curves and intra-assay variability for APRIL, MCP-1, and L-selectin levels determined using the Luminex. Table S2: Association between OSA and MCP-1 levels in univariate and multiple logistic regression models. Table S3: Association between OSA and L-selectin levels in univariate and multiple logistic regression models. Table S4: Association between levels of AHI and MCP-1 levels in univariate and multiple linear regression models. Table S5: Association between levels of AHI and L-selectin levels in univariate and multiple linear regression models. Figure S1: Flow diagram of participants recruitment in this study.

Figures

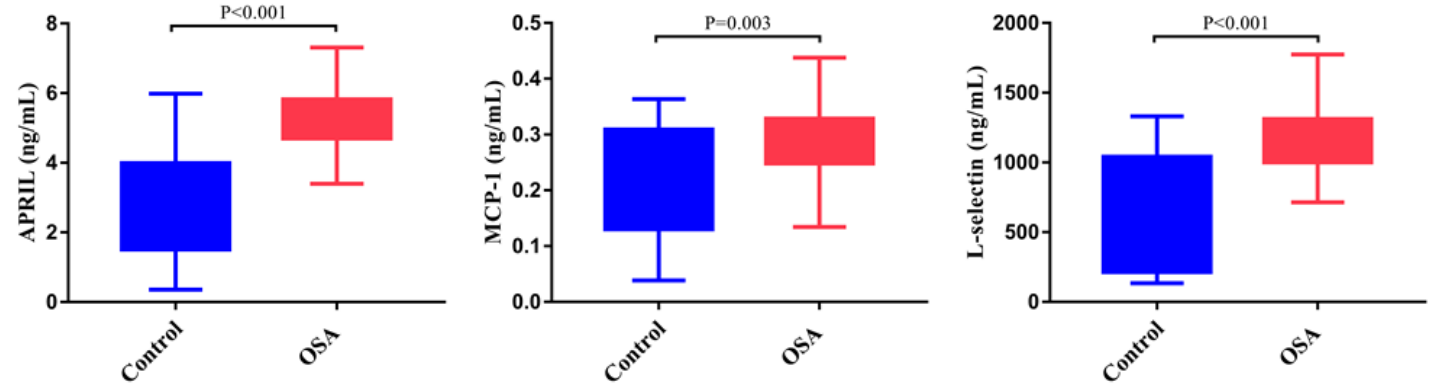

Figure 1

Plasma APRIL, MCP-1, and L-selectin levels in Control and OSA groups. Data are median (interquartile range). APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1; OSA, Obstructive sleep apnea.

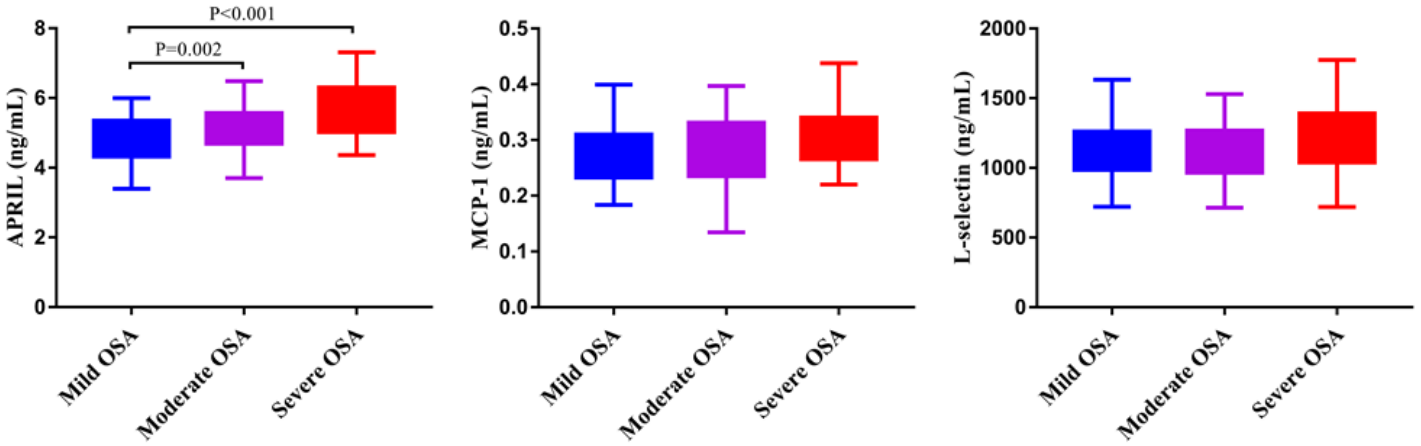

Figure 2

Plasma APRIL, MCP-1, and L-selectin levels in mild, moderate, and severe OSA groups. Data are median (interquartile range). APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1; OSA, Obstructive sleep apnea.

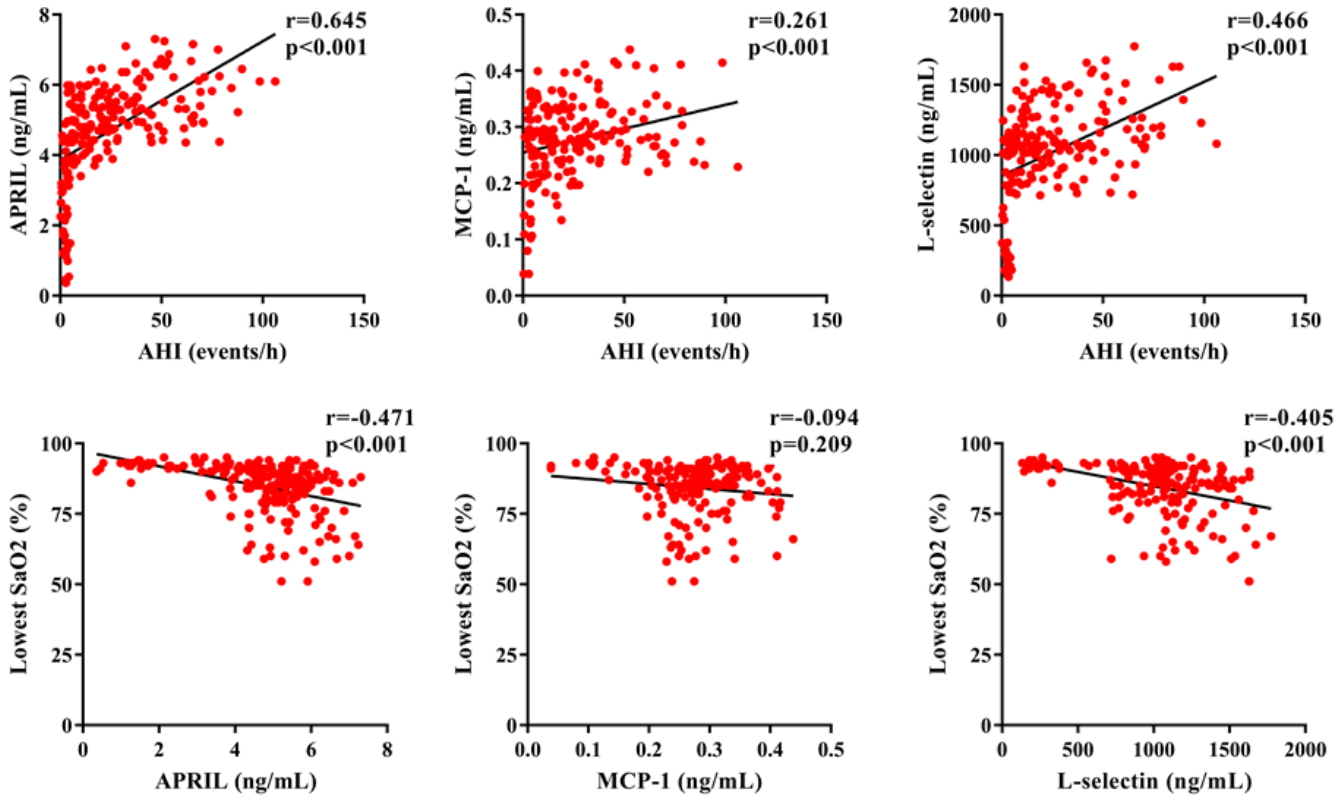

Figure 3

Scatterplots of APRIL, MCP-1, and L-selectin plasma levels vs AHI/Lowest SaO2. r: Spearman correlation coefficients; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1; AHI, Apnea-hypopnea index.

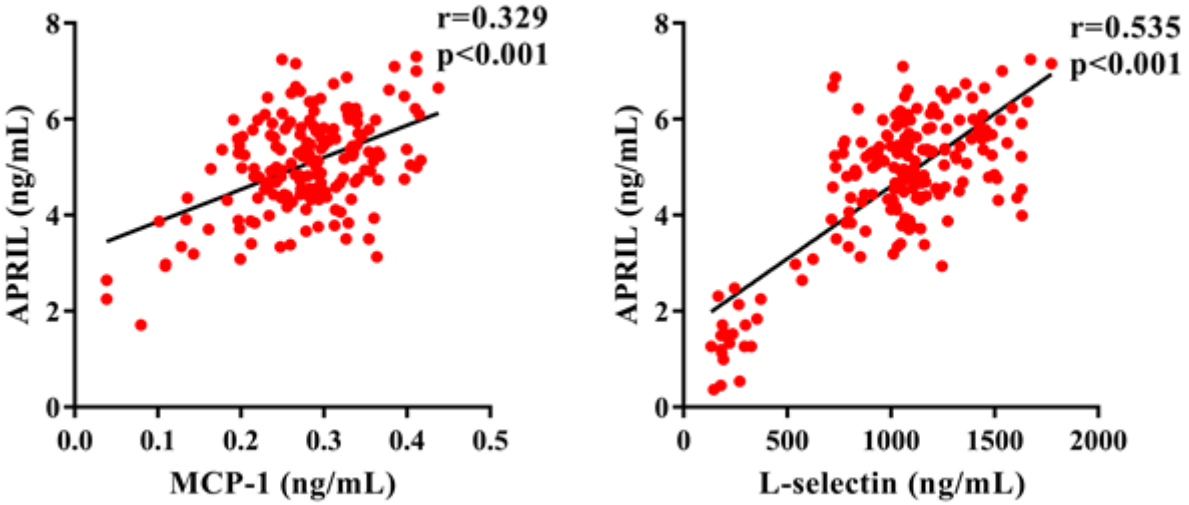

Figure 4

Scatterplots of MCP-1 and L-selectin plasma levels vs APRIL plasma levels. r: Spearman correlation coefficients; APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1.

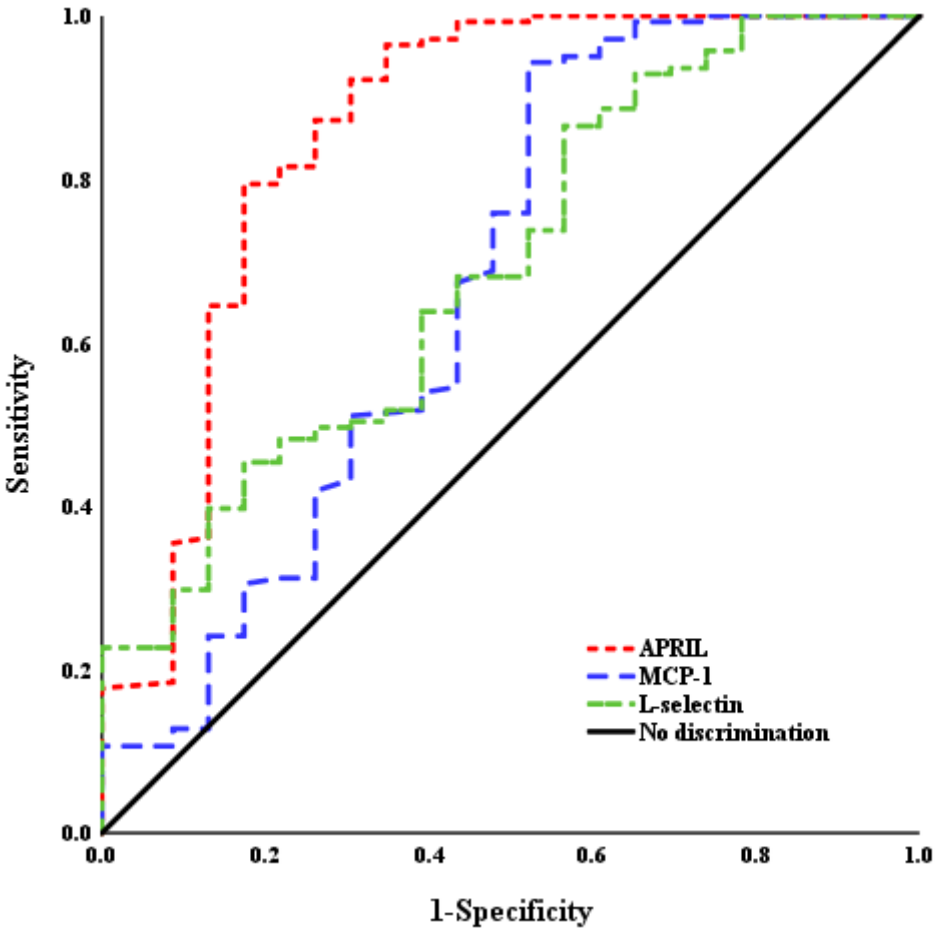

Figure 5

Receiving operator curves using plasma APRIL, MCP-1, and L-selectin levels for prediction of OSA. The AUC for the plasma APRIL levels (0.856) was higher than plasma MCP-1 (0.673), and L-selectin (0.692). APRIL, A proliferation-inducing ligand; MCP-1, Monocyte chemotactic protein-1; OSA, Obstructive sleep apnea; AUC, Area under curve.

Supplementary Files

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