Original Article

Relationship between monocyte to HDL cholesterol ratio and concomitant cardiovascular disease in Chinese Han patients with obstructive sleep apnea

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Background: Obstructive sleep apnea (OSA) is an independent risk factor for cardiovascular disease (CVD), which is attributed to chronic intermittent hypoxia (CIH) induced inflammation. As a new inflammatory biomarker of CVD, monocyte to high-density lipoprotein cholesterol ratio (MHR) has received little attention in OSA studies to date. Therefore, we aimed to investigate the correlation between MHR and concomitant CVD in Chinese Han patients with OSA.

Methods: A total of 657 Chinese Han subjects (169 controls, 145 mild, 94 moderate, and 249 severe OSA) of both genders were enrolled in this cross-sectional study, with an average BMI of 32.35±6.56 kg/m^2. The relationship between MHR and concomitant CVD in OSA patients was analyzed.

Results: The level of MHR was correlated positively with apnea-hypopnea index (AHI), while negatively with lowest SpO_2 (P<0.01). Moreover, the MHR values were higher in OSA patients with CVD than those without CVD (17.64±7.16 *vs.* 12.73±5.06, P<0.001). Logistic regression analysis demonstrated that MHR is an independent predictor of CVD (OR =1.190, P<0.001). The ROC analysis indicated that the best cut-off value of MHR for predicting CVD in OSA patients was 15.364 (sensitivity 65.0%, specificity 74.4%), while its cutoff value for identifying CVD in severe OSA patients was 15.362 (sensitivity 67.3%, specificity 80.1%).

Conclusions: MHR is strongly correlated with the severity of OSA and the occurrence of CVD in OSA patients. As an easy and available test, MHR is expected to be a promising biomarker candidate in predicting CVD in Chinese Han patients with OSA.

Keywords: Obstructive sleep apnea (OSA); cardiovascular disease (CVD); monocyte to high-density lipoprotein cholesterol ratio (MHR); biomarker

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Introduction

Obstructive sleep apnea (OSA) is a common condition characterized by recurrent partial or total obstructions of the upper airway, resulting in hypopnea or apnea (1,2). Several studies have revealed that OSA is an independent risk factor for cardiovascular diseases (CVD) (3-5). Chronic airway collapse leads to repeated hypoxia, which further contributes to increased sympathetic activation, oxidative stress, systemic

inflammation, and endothelial dysfunction (2,6). Systemic inflammation with subsequent vascular damage has been implicated as the potential mechanism leading to the development of CVD morbidity in OSA (2,7,8).

During the past decade, blood cell count and its subsets have been reported to be consistently associated with the risk of CVD (9,10). It has been proved that monocytes and differentiated macrophages could modulate inflammatory cytokines and vessel remodeling in the process of CVD (11). High-density lipoprotein cholesterol (HDL-C) could suppress the monocyte activation, inhibit the proliferation and differentiation of monocyte progenitor cells, and mediate cholesterol efflux from macrophages (12,13). The monocyte to HDL-C ratio (MHR) has been addressed as a novel predictor and prognostic biomarker for CVD (11,12,14). Recent study found significant increase of total monocyte in bone marrow and peripheral blood upon OSA related chronic intermittent hypoxia (CIH) exposure (15), and OSA severity was independently associated with low HDL-C values as well (16). Atan *et al.* (17) reported MHR increased as OSA severity increased, which can be used as a new predictor for OSA. However, the association between MHR and CVD occurrence in patients with OSA still lacks clinical evidence and has not been well understood, especially in Chinese Han population. Thus, we conducted the present study to assess the correlation between MHR values and CVD occurrence in Chinese Han patients with OSA, and to further investigate the relevance of MHR as a marker to predict CVD occurrence in OSA patients.

Methods

Study population

We observed consecutive subjects who recorded polysomnography (PSG) at the Sleep Disorders Center of Ruijin Hospital affiliated to Shanghai JiaoTong University from September 2009 to January 2017. All subjects were adults of Chinese Han nationality. Demographic characteristics, smoking status, and previous history of chronic diseases were recorded. Body mass index (BMI) was calculated. Established CVD was defined as a history of coronary artery disease (i.e., previous myocardial infarction ≥90 days prior; stable or unstable angina with a diagnostic coronary angiography or positive exercise stress test; multivessel percutaneous angioplasty and/or stent ≥90 days prior; and/or multivessel coronary artery bypass graft ≥1 year prior) or a history of cerebrovascular disease (i.e., previous stroke ≥90 days prior or neurologist-diagnosed transient ischemic attack (TIA) of the brain or retina 30 days to 1 year prior). Exclusive criteria included patients with neural-muscular disease, sleep disorders other than OSA (e.g., central sleep apnea syndrome, restless leg syndrome, narcolepsy), previous treatment for OSA [e.g., continuous positive airway pressure (CPAP), surgery, and oral device, etc.], hypoxemic lung disease, stroke due to subarachnoid haemorrhage, hematologic disease, liver or kidney disease, chronic alcoholism, malignancy, pregnancy, acute and/or chronic infection, autoimmune disease, and anti-inflammatory medication use (such as corticosteroids, non-steroid anti-inflammatory drugs and immunosuppressive agents, etc.). In total, 657 subjects aged ≥18 years were included. The study was approved by the local ethics committee of Ruijin Hospital, and all the participants were provided with written informed consent.

Polysomnographic evaluation

All of the study participants performed polysomnography (PSG) (Alice 5, Philips Respironics, USA) in our sleep laboratory. PSG channels included four electroencephalogram (EEG) channels, submental electromyogram (EMG), two electrooculogram (EOG; right and left) channels, two electrocardiography (ECG) channels, pulse oxygen saturation, oral and nasal airflow, nasal air pressure, thoracic-abdominal respiratory movement, snoring microphone, and body position. According to the apnea-hypopnea index (AHI), subjects were categorized into four groups, including the control group (AHI <5), mild (AHI: 5–14.9), moderate (AHI: 15–29.9), and severe OSA (AHI ≥30) group (18). Hypopnea was defined as the peak signal excursions drop by ≥30% of pre-event baseline using nasal pressure for at least 10 seconds with a ≥4% oxygen desaturation from pre-event baseline. The percentage of sleep duration with SpO_2 <90% (TS90), lowest pulse oxygen saturation ($LSpO_2$), and mean oxygen saturation (mean SpO_2) were also included.

Laboratory measurements

Fasting blood samples were taken in the morning after PSG monitoring. Blood samples were analyzed for complete blood count (CBC) using an automated hematology analysis device (CELL-DYN Ruby, Abbott Laboratories, USA). Serum fasting glucose and serum lipid profiles included total cholesterol (TC), triglycerides (TG), HDL-C and low-

density lipoprotein cholesterol (LDL-C) were determined with AU5811 automatic biochemical analyzer (Beckman Coulter, USA). MHR = the monocyte count (10^3/μL)/HDL level (mg/dL) (11,12,19).

Statistical analysis

Data analysis was performed using statistical software (IBM SPSS Statistics for Windows, Version 22.0, USA). Continuous variables were reported as means ± standard deviations (SD), or median with inter-quartile range if variables were not normally distributed. Categorical variables were reported as constituent ratio. The significance of the mean differences between groups was assessed by Student *t*-test and one-way analysis of variance (ANOVA). For measurement data that were heteroscedastic or not normally distributed, Mann-Whitney U test and Kruskall-Wallis H test were performed for the comparison among groups. Constituent ratio among groups was compared by a chi square test. The relationships were determined using Pearson's rank correlation. The effect of various variables on CVD was analyzed with logistic regression analysis. Receiver-operating characteristic (ROC) curve was used to estimate the predictive validity, and to determine the optimal MHR cut-off value (20). P value<0.05 was considered statistically significant.

Results

Demographic characteristics

A total of 657 individuals (415 males, aged 37.97±15.02 years) were enrolled in the study, with average BMI 32.35±6.56 kg/m^2. All clinical variables collected were summarized in *Table 1*. The occurrence of CVD increased along with the severity of OSA (mild 5.52%, moderate 11.70%, and severe 39.36%, P<0.001; *Table 1*). Compared with the control group, the odds ratio (OR) of CVD was 4.53 (95% CI: 2.38–8.64; P<0.001) in the OSA group, and 9.32 in the severe OSA group (95% CI: 4.81–18.07; P<0.001).

Correlations between PSG parameters and MHR

As shown in *Table 1*, monocyte counts and MHR values were found elevated in parallel with the increase of OSA severity. Serum HDL-C levels in severe OSA group were the lowest among all 4 groups (P<0.05; *Table 1*). The MHR levels in severe OSA group were higher than those in the control group and mild group (P=0.002 and P=0.020, respectively). Moreover, MHR was positively correlated with AHI (r=0.167, P<0.001) and TS90 (r=0.110, P=0.005), while negatively with $LSpO_2$ (r=–0.123, P=0.002) and mean SpO_2 (r=–0.134, P=0.001).

The association between MHR and CVD in OSA subjects

In addition, the MHR values in OSA subjects were positively correlated with CVD occurrence (r=0.349, P<0.001). The levels of MHR were mostly higher in CVD patients with similar severity of AHI and $LSpO_2$ (*Figure 1*). We further compared the differences between OSA patients with (n=117) and without CVD (n=371) in *Table 2*. OSA patients with CVD were found to have higher AHI and lower $LSpO_2$, while the MHR values of OSA patients with CVD were significantly higher than those without CVD (17.64±7.16 *vs.* 12.73±5.06, P<0.001; *Table 2*). For the CVD patients, the levels of MHR in severe OSA group were found the highest among all OSA groups (mild 12.40±4.59, moderate 17.26±8.48, and severe 18.11±7.06, respectively).

In logistic regression analysis for the risk factors of CVD in OSA patients, MHR was determined as an independent predictor of CVD (OR =1.190, 95% CI: 1.128–1.256, P<0.001; *Table 3*). For the prediction of CVD in OSA patients, the ROC curve analysis performed the cut-off value of MHR (>15.364) with the greatest sum of sensitivity (0.65) and specificity (0.744), and area under the curve value (AUC) of 0.720 (95% CI: 0.664–0.775, P<0.001; *Figure 2A*). In addition, the AUC for MHR to identify CVD in severe OSA patients was 0.774 (95% CI: 0.712–0.835, P<0.001); the cut-off value was 15.362, with the greatest sum of sensitivity (0.673) and specificity (0.801) (*Figure 2B*).

Discussion

The present study mainly examined the relationship between MHR and CVD risk in Chinese Han patients with OSA. To the best of our knowledge, this is the first study to investigate this association among Chinese populations. The results showed that MHR increased along with the severity of OSA, and the MHR values were significantly higher in CVD patients with OSA, especially in those with severe OSA. Notably, we found that MHR act as an independent predictor of CVD in Chinese Han patients with OSA after adjusting for known important confounding variables including age, sex, BMI, smoking, hypertension, etc.

OSA is an independent risk factor for cardiovascular

Table 1 Baseline clinical, laboratory, and polysomnographic data of the study population

Characteristics	Control (n=169)	Mild OSA (n=145)	Moderate OSA (n=94)	Severe OSA (n=249)	P value
Clinical parameters					
Age (years)	30.51±11.83	36.21±15.50*	38.65±16.25*	43.80±13.77*†§	<0.001
Male gender, n (%)	67 (39.64)	80 (55.17)*	57 (60.64)*	211 (84.74)*†§	<0.001
BMI (kg/m^2)	33.19±5.60	32.14±6.61	32.82±7.01	31.72±6.91*	0.125
Neck circumference (cm)	40.16±3.17	40.73±3.74	41.17±3.90*	42.39±4.25*†	<0.001
Cigarette smoking, n (%)	20 (11.83)	20 (13.79)	16 (17.02)	61 (24.50)*†	0.004
Hypertension, n (%)	44 (26.04)	61 (42.07)*	36 (38.30)*	149 (59.84)*†§	<0.001
Diabetes mellitus, n (%)	38 (22.49)	32 (22.07)	27 (28.72)	94 (37.75)*†	0.001
Dyslipidemia, n (%)	65 (38.46)	72 (49.66)*	56 (59.57)*	166 (66.67)*†	<0.001
CVD, n (%)	11 (6.51)	8 (5.52)	11 (11.70)	98 (39.36)*†§	<0.001
Laboratory parameters					
WBC count (10^3/μL)	7.46±1.75	7.46±1.72	7.45±1.98	7.49±2.11	0.997
Neutrophil count (10^3/μL)	4.28±1.61	4.25±1.27	4.33±1.75	4.32±1.81	0.967
Monocyte count (10^3/μL)	0.51±0.15	0.52±0.17	0.53±0.16	0.53±0.18	0.733
Triglyceride (mg/dL)	125.81 (92.14–171.00)	134.67 (103.22–209.10)*	160.37 (112.08–216.63)*	174.99 (129.36–253.17)*†	<0.001
Total cholesterol (mg/dL)	177.63±68.13	176.88±48.15	184.73±35.66	184.39±36.72	0.315
HDL cholesterol (mg/dL)	42.38±12.39	41.64±9.24	41.44±10.05	39.41±11.3*†	0.038
LDL cholesterol (mg/dL)	110.81±41.56	113.32±68.93	113.91±31.85	114.09±31.14	0.897
MHR	12.86±4.74	13.06±5.33	13.59±5.86	14.53±6.37*†	0.014
Polysomnographic parameters					
AHI (events/h)	1.94±1.40	9.46±2.84*	22.16±4.35*†	57.87±17.95*†§	<0.001
Mean SpO_2 (%)	96.22±1.46	95.56±2.14*	94.79±2.19*†	91.78±4.69*†§	<0.001
$LSpO_2$ (%)	90.0 (85.5–92.0)	85.0 (79.0–89.0)*	80.0 (72.0–86.0)*†	67.0 (55.5–77.0)*†§	<0.001
TS90 (%)	0.00 (0.00–0.20)	0.30 (0.00–1.60)*	1.37 (0.20–6.73)*†	18.30 (5.80–39.39)*†§	<0.001

Data are means ± standard deviation, numbers of subjects (%), or medians (range). OSA, obstructive sleep apnea; BMI, body mass index; CVD, cardiovascular disease; WBC, white blood cell; HDL, high density-lipoprotein; LDL, low density-lipoprotein; MHR, monocyte to high-density lipoprotein cholesterol ratio; AHI, apnea-hypopnea index; Mean SpO_2, mean oxygen saturation; $LSpO_2$, lowest pulse oxygen saturation; TS90, the percentage of sleep duration with SpO_2 <90%. *, severe OSA *vs.* Control, P<0.05; †, severe OSA *vs.* mild OSA, P<0.05; §, severe OSA *vs.* moderate OSA, P<0.05.

events (3-5). Chronic intermittent hypoxia (CIH) is a hallmark of OSA, which induces a state of low-grade circulation and systemic inflammation in OSA patients (2), leading to the cardiovascular damage (7,8,21-23). In our study, the risk of CVD in OSA patients increased more than four-fold compared with the control group. In addition, the risk of exhibiting CVD was 9.32-fold higher in severe OSA group, which may be related to the aggravated systemic inflammation resulted from OSA.

Monocytes and differentiated macrophages are essential components of innate immunity and can modulate the secretion of inflammatory cytokines and tissue remodeling, resulting in chronic inflammation and cardiovascular events (21,23,24). The effect of HDL-C on monocytes has also been proposed. HDL-C inhibits monocyte activation and extravagation by down-regulating the expression of CD11b (25), which counter acts the migration of macrophages and promotes efflux of oxidized cholesterol from these cells (11,23). HDL-C has

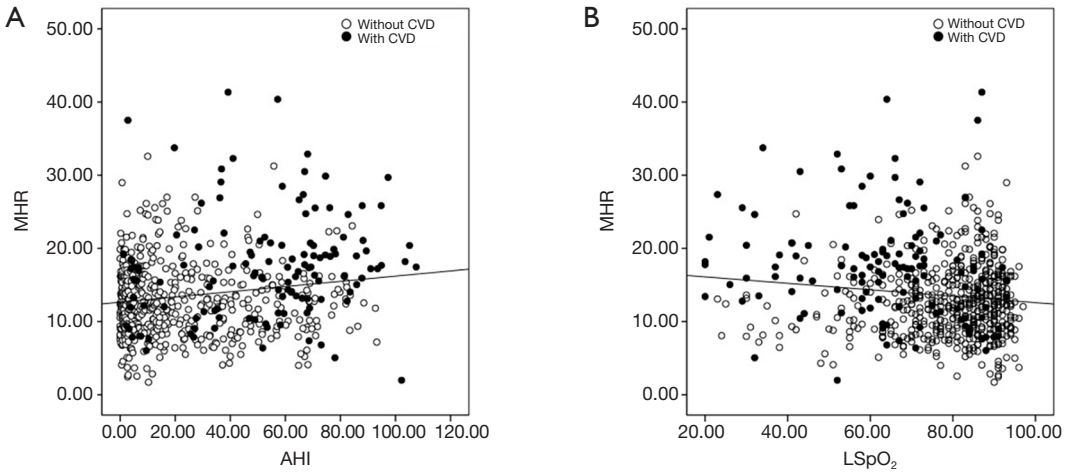

Figure 1 Relationships between MHR and PSG parameters. (A) The positive correlation of MHR and AHI (r=0.167, P<0.001). At the same level of AHI, patients with CVD (solid dot) showed higher levels of MHR; (B) the negative correlation of MHR and $LSpO_2$ (r=–0.123, P=0.002). At the same level of $LSpO_2$, patients with CVD (solid dot) showed higher levels of MHR. MHR, monocyte to high-density lipoprotein cholesterol ratio; AHI, apnea-hypopnea index; $LSpO_2$, lowest pulse oxygen saturation; CVD, cardiovascular disease.

Table 2 Comparison of clinical, laboratory and PSG data in OSA patients with or without CVD

Characteristics	OSA with CVD (n=117)	OSA without CVD (n=371)	P value
Age (years)	44.92±14.91	39.17±14.99	<0.001
Male gender, n (%)	102 (87.18)	246 (66.31)	<0.001
BMI (kg/m^2)	32.54±7.23	31.90±6.71	0.381
Neck circumference	43.00±4.17	41.26±4.00	<0.001
AHI (events/h)	57.36±24.43	30.06±22.44	<0.001
Mean SpO_2 (%)	90.60±5.15	94.45±3.10	<0.001
$LSpO_2$ (%)	63.00 (52.00–72.00)	79.00 (70.00–86.00)	<0.001
TS90 (%)	27.70 (10.90–44.40)	2.60 (0.20–10.60)	<0.001
White blood cell count ($10^3/\mu L$)	7.97±2.17	7.32±1.88	0.002
Neutrophil count ($10^3/\mu L$)	4.69±1.84	4.18±1.57	0.007
Monocyte count ($10^3/\mu L$)	0.60±0.19	0.50±0.16	<0.001
Triglyceride (mg/dL)	185.62 (134.01–301.68)	158.59 (111.41–216.41)	<0.001
Total cholesterol (mg/dL)	182.76±40.99	182.05±40.20	0.868
HDL cholesterol (mg/dL)	36.52±9.40	41.71±10.56	<0.001
LDL cholesterol (mg/dL)	111.86±34.85	114.45±48.75	0.596
MHR	17.64±7.16	12.73±5.06	<0.001

Data are means ± standard deviation, numbers of subjects (%), or medians (range). PSG, polysomnography; OSA, obstructive sleep apnea; CVD, cardiovascular disease; BMI, body mass index; AHI, apnea-hypopnea index; Mean SpO_2, mean oxygen saturation; $LSpO_2$, lowest pulse oxygen saturation; TS90, the percentage of sleep duration with SpO_2 <90%; HDL, high density-lipoprotein; LDL, low density-lipoprotein; MHR, monocyte to high-density lipoprotein cholesterol ratio.

Table 3 Risk factors for CVD in patients with obstructive sleep apnea

Independent variables	All the subjects			Obstructive sleep apnea		
	Odd ratio	95% CI	P value	Odd ratio	95% CI	P value
Age (years)	1.048	1.025–1.071	<0.001*	1.048	1.023–1.074	<0.001*
Male gender	1.468	0.730–2.951	0.281	1.358	0.619–2.979	0.446
BMI (kg/m^2)	1.005	0.960–1.053	0.818	1.005	0.957–1.056	0.835
AHI (events/h)	1.021	1.008–1.034	0.002*	1.026	1.011–1.041	<0.001*
Mean SpO_2 (%)	0.923	0.798–1.067	0.278	0.936	0.804–1.089	0.390
$LSpO_2$ (%)	0.991	0.967–1.016	0.483	0.989	0.963–1.015	0.411
TS90 (%)	1.014	0.987–1.041	0.327	1.015	0.987–1.044	0.304
MHR	1.187	1.130–1.246	<0.001*	1.190	1.128–1.256	<0.001*
Cigarette smoking	1.145	0.600–2.185	0.680	1.151	0.578–2.292	0.689
Hypertension	0.559	0.312–1.003	0.051	0.502	0.265–0.953	0.035*
Diabetes mellitus	0.759	0.434–1.328	0.334	0.867	0.474–1.585	0.643
Dyslipidemia	1.101	0.623–1.947	0.740	1.056	0.567–1.968	0.863

CVD, cardiovascular disease; BMI, body mass index; AHI, apnea-hypopnea index; Mean SpO_2, mean oxygen saturation; $LSpO_2$, lowest pulse oxygen saturation; TS90, the percentage of sleep duration with SpO_2 <90%; MHR, monocyte to high-density lipoprotein cholesterol ratio. *P<0.05: statistical significance.

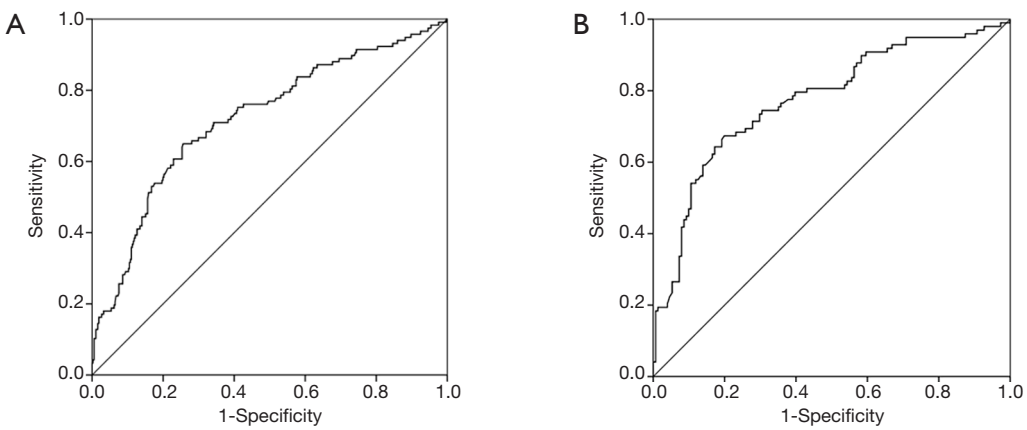

Figure 2 The ROC curve analysis for MHR in predicting CVD. (A) In OSA patients, the cut-off value of MHR was 15.364, with a sensitivity of 0.65 and a specificity of 0.744, AUC: 0.720 (95% CI: 0.664–0.775, P<0.001); (B) in severe OSA patients, the cut-off value of MHR was 15.362, with the greatest sum of sensitivity (0.673) and specificity (0.801), AUC: 0.774 (95% CI: 0.712–0.835, P<0.001). ROC, receiver operating characteristic; MHR, monocyte to high-density lipoprotein cholesterol ratio; CVD, cardiovascular disease; OSA, obstructive sleep apnea; AUC, area under the curve.

been proven to have anti-inflammatory, antioxidant, and antithrombotic effects (26). Therefore, MHR may represent the balance between inflammatory and anti-inflammatory factors (25). Several studies suggested that MHR is related to cardiovascular outcomes, and is an independent predictor of stent thrombosis in acute ST-segment elevation myocardial infarction (STEMI) patients (27). Increased MHR is also in accordance with the higher recurrence of atrial fibrillation (28), existence of slow coronary flow (29), thrombolysis in myocardial infarction (TIMI) score (23),

and in-hospital major adverse cardiovascular events (MACEs) in patients with STEMI (30).

Recently, Alvarez-Martins *et al.* found an increase in the CD11b+ myeloid cells, the majority of which are monocytes, in CIH exposed rats (15). The European Sleep Apnea Database (ESADA) cohort, included 8592 patients, identified a strong association between lower HDL-C and OSA severity (16). We attempted to determine the role of MHR in CVD occurrence of patients with OSA. In our study, significantly higher MHR values were observed in patients with OSA when compared with the control group. The MHR values had a linear correlation with AHI, and the severity of hypoxemia defined by mean SpO_2, $LSpO_2$ and TS90, which was consistent with previous studies (17,19). Furthermore, the levels of MHR were significantly higher in OSA patients with CVD, especially in severe OSA group. Logistic regression analysis demonstrated that MHR was independently associated with the incidence of CVD, which indicated that an increased MHR might be a predictor for the development and progression of cardiovascular events in OSA patients. The finding was consistent with Kanbay's report, which reckoned MHR as an independent predictor of major cardiovascular injuries in chronic kidney disease patients (31). As for the cut-off value of MHR in predicting CVDs, different values varying from 14.73 to 21.3 have been reported (19,24). Geovanini *et al.* pointed out the pathways linking OSA to CVD are complex and the associations between them vary across population groups (32). We herein found that MHR of 15.36 could predict CVD occurrence in Chinese Han patients with OSA, with the greatest sum of sensitivity (0.65) and specificity (0.744). Moreover, with the increasing severity of OSA, the cutoff value of MHR for detecting CVD in severe OSA patients with a sensitivity of 0.673 and a specificity of 0.801, which suggested that the predictive value of MHR may be more remarkable in CVD with severe OSA patients.

Several limitations should be mentioned. First, given the cross-sectional nature of this single center study, inferences on the cause-and-effect sequence between OSA and CVD are not possible. Second, we did not study MHR changes before and after CPAP treatment. Thus, further well-designed, multi-center, prospective interventional clinical trials with CPAP treatment are needed in the future.

Conclusions

In summary, the results of our study implied the importance of MHR in the prediction of CVD among Chinese Han patients with OSA from a relatively large population. It is suggested that MHR, which is an easy and available test, might be an available biomarker to evaluate CVD risk in OSA patients, especially in severe OSA patients.

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Footnote

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

Ethical Statement: All the authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has been approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai JiaoTong University School of Medicine ([2018] No.107). All the subjects gave their informed consent prior to their inclusion in the study.

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