RESEARCH ARTICLE

Risk factors of coronary artery stenosis in patients with obstructive sleep apnoea: a prospective study

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Abstract

Objective: To investigate the prevalence of coronary artery disease and characteristics of coronary artery in patients with obstructive sleep apnoea.

Methods: The prospective study was conducted at the Affiliated Huai'an Hospital of Xuzhou Medical University, Huai'an, China, from January, 2012, to June, 2015, and comprised consecutive patients with diagnosed obstructive sleep apnoea. High-resolution 320-slice coronary computed tomography was performed in all the patients. Data was evaluated for the presence of coronary lumen narrowing. Demographic, clinical, laboratory, and echocardiographic characteristics were carefully recorded. Logistic regression was used for multivariate analysis of independent risk factors. SPSS 16 was used for data analysis.

Results: Of the 277 patients, 186(67.14%) were males. The overall mean age was 55.1±14.3 years. Coronary artery disease was found in 41(14.8%) patients. Prospective Cardiovascular Münster score, uric acid, triglyceride, C-reactive protein, apnoea hypopnoea index, Epworth sleepiness scale values were significantly higher in patients with the disease ($p<0.05$ each). Higher Prospective Cardiovascular Münster score, C-reactive protein, apnoea hyponoea index levels had a significant ability to reflect the occurrence of coronary artery disease ($p<0.05$ each).

Conclusions: Coronary heart disease occurrence in obstructive sleep apnoea patients was found to be strongly related to Prospective Cardiovascular Münster score, apnoea hyponoea index and C-reactive protein level.

Keywords: Obstructive sleep apnoea, Coronary artery disease, Coronary CT angiography, Risk factors.
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Introduction

Obstructive sleep apnoea (OSA) is a common and serious condition, affecting approximately 5-15% of adult population in developed countries.[1] Beyond poor quality of sleep and its directly related symptoms, OSA is associated with a more adverse cardiovascular risk factor profile and increased risk of coronary artery disease (CAD).[2,3] Although OSA patients have increased cardiovascular morbidity and mortality,[4] how much of it is due to OSA rather than to other risk factors, such as body mass index (BMI), insulin resistance (IR), age, serum lipid level and cigarette smoking, is yet unknown. To better understand the relation between OSA and CAD, examining the association between OSA and subclinical coronary artery changes may be valuable.[5] The severity of coronary artery stenosis assessed by contrast-enhanced multislice coronary computered tomography angiography (CTA) is a well-established surrogate marker that has been confirmed in numerous studies to be predictive of future coronary events.[6,7] However, the risk factors of coronary artery stenosis, such as Prospective Cardiovascular Münster (PROCAM) score[8] which provide a truer picture of a person's overall CAD risk, laboratory examinations, such as uric acid and C-reactive protein (CRP), Apnoea Hypopnoea Index (AHI) which aeesees OSA severity, have never been systematically evaluated. The current study was planned to investigate CAD prevalence and characteristics of coronary artery in OSA patient.

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Patients and Methods

The prospective study was conducted at departments of Ear, Nose and Thraot (ENT), Cardiology and Respirology, Affiliated Huai'an Hospital, Xuzhou Medical University, Huai'an, China, from January, 2012, to June, 2015, and comprised consecutive OSA patients who were recruited after approval was obtained from the institutional ethics committee.

After informed consent was taken from all the subjects, individual information was carefully identified at baseline. Those excluded were subjects with previous adverse reaction to iodinated contrast media, renal dysfunction, thyroid dysfunction, including subclinical hyperthyroidism, history of CAD, valvular heart disease, congestive heart failure (CHF), previous cardiac surgery, myocardial infarction (MI), hypertrophic and dilated cardiomyopathy and history of a disabling cerebral infarction or transient ischaemic attack (TIA), recent infection, autoimmune or inflammatory diseases, respiratory diseases and those consuming alcoholic beverages (Figure 1).

Clinical and demographic profile, including age, gender, smoking status, family history of CAD, medical history, history of drug therapy were recorded. Findings of laboratory examination, including uric acid, serum lipid level, CRP and white blood cell (WBC) count were recorded, and the PROCAM score of the patients was calculated and recorded. Echocardiogram variables and PSG test were carefully recorded.

Laboratory examinations, including complete blood count (CBC) and biochemical investigations, were performed in the fasting state. Levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were measured by enzymatic colorimetric methods. The WBC count was determined using a Coulter counter. The levels of serum CRP was assayed with the immunonephelometric method (Dade Behring Marburg, Marburg, Germany). The reference concentrations for CRP were 3mg/L. As a measure of renal function, the baseline estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) Equation:[9] Serum uric acid levels were measured by standard uricase enzymatic test (Normal range: 150-440 μmol/L for men; 90-380 μmol/L for women).

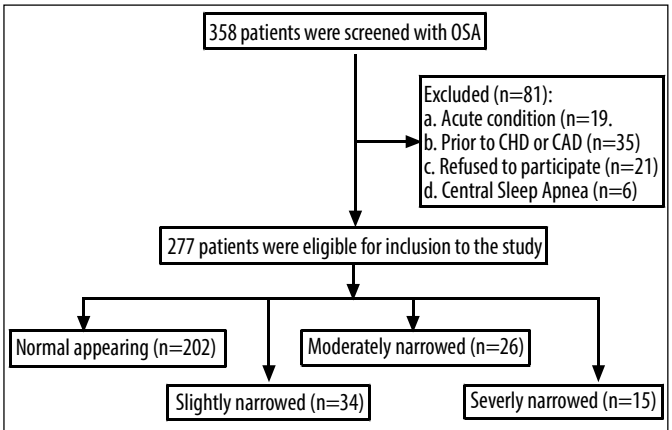

Figure-1: Flowchart showing the distribution of the patients eligible for inclusion in the study.

The subjects slept overnight with the use of Jaeger Sleeplab 1000 (Jaeger, Würzburg, Germany) PSG system. Signals noted included electroencephalogram (EEG), electroocculogram, submental electromyogram, and anterior tibialis electromyogram. Additionally, electrocardiography (ECG) and heart rate (HR) were recorded simultaneously. Snoring was recorded by a microphone placed at the jugular vein, and air flow was recorded by combined oronasal thermistors, while arterial oxyhaemoglobin saturation was recorded by a finger pulse oximeter. Thoracic cage and abdominal motion were recorded by inductive plethysmography. EEG recordings were manually scored according to the standard criteria[10]. The primary measure was the AHI, quantified as the total number of apnoeas and hypopnoeas per hour of sleep. Apnoea was defined as ≥90% decrease in airflow from the baseline value for ≥10 seconds. Apnoeas were further classified as obstructive or central based on the presence or absence of respiratory-related chest wall movement. Hypopnoea was defined as a 30-90% reduction in airflow from the baseline value ≥10 sec in conjunction with ≥4% oxygen desaturation. The respiratory event scoring was performed in accordance with the American Academy of Sleep Medicine's 2007 (alternative) guidelines.[11] The ESS was used to assess daytime sleepiness.[12] OSA diagnosis was made when AHI value exceeded 5, and over 10 points in the ESS.

Two-dimensional echocardiography with M-mode recording was obtained, according to American Society of Echocardiography guidelines[13] (iE33 xMATRIX Echocardiography System; Philips, the Netherlands). Data was interpreted by the same operator and recorded on videotape. Left ventricular end-diastolic dimension

(LVED), left atrial diameter (LAD) and left ventricular ejection fraction (LVED) were measured. The ejection fraction (EF) was calculated from area measurements using the area-length method[14] applied to the average apical area.

All patients were scanned using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems Corp.). CTA images were acquired with a collimation of 320 × 0.5 mm for the 320-slice scanner, a tube rotation time of 350 ms, and a tube current of 100 mA at 120 kV for patients with BMI <30kg/m^2. If a patient had a higher BMI, tube current was increased to 100 or 150mA at 135 kV. The acquisition of imaging was prospectively triggered at 75% of the R-R interval. Between 80 and 110 mL of nonionic contrast material (Iomeron 400H; Bracco Atlanta Pharma) was administered with a flow rate of 5 mL/s depending on the total scanning time. The timing of the scan was determined using automated detection of peak enhancement in the aortic root. CTA images were interpreted using transaxial image stacks and curved multiplanar reformatted images. Two reviewers independently evaluated the contrast-enhanced multi-slice CT (MSCT) scans by assessment of the axial slices, of multiplanar reformations and of three thin-slab maximum intensity projections. The reviewers were blinded to all clinical information as well as to the results of endothelial function and intima-media thickness (IMT) testing. Orientated along the heart axis, the thin-slab (5-mm thickness, 1-mm increment) maximum intensity projections were reconstructed perpendicular to each other. The coronary artery tree was segmented according to modified American Heart Association classification[15] and the segments were investigated for lumen narrowing. Segments were graded as small

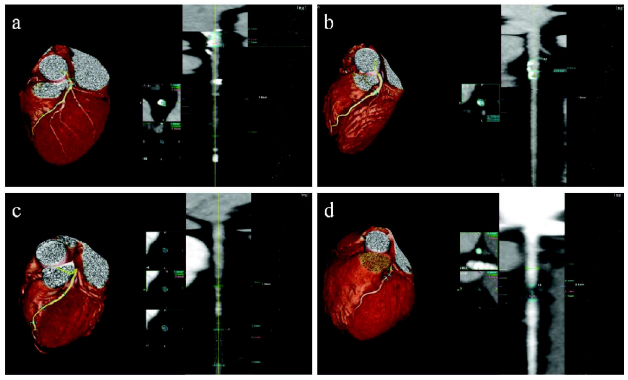

Figure-2: Grade of Coronary compyted tomography angiography (CTA) features. a.normal appearing, b.slightly narrowed, c.moderately narrowed, d.severely narrowed.

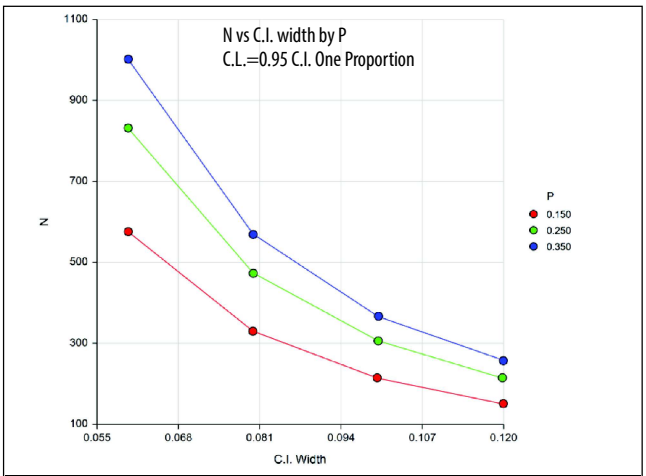

Figure-3: The sample size confirmed by PASS software.

(diameter < 1.5mm), normal appearing (stenosis grade 0-24%), slightly narrowed (stenosis grade 25-49%), moderately narrowed (stenosis grade 50-74%), and severely narrowed (stenosis grade 75%) (Figure 2). CAD was considered in segments of coronary artery lumen graded as moderately and severely narrowed.

Before the study started, a preliminary prevalence for OSA patients who had CAD was conducted. It was estimated that the prevalence of CAD in OSA patients was about 25%. The sample size was confirmed by PASS software.[16] Confidence Intervals (CIs) for One Proportion was adopted. A two-sided 95% exact CI was constructed for the population such that the width of the interval was no wider than 0.10. Instead of examining only the interval width of 0.10, widths of 0.08 and 0.12 were also considered. Though in the primary study, the prevalence of CAD in OSA patients was about 25%, a range of values, like 0.15 and 0.35, were included to determine the effect of the proportion estimate on necessary. Parameters above were set in the programme and the minimal sample size 215 was obtained when the proportion was 25% and the width was 0.12 (Figure 3). Continuous variables were presented as mean ± standard deviation. Univariate analysis to assess the predictive value of clinical variables on CAD in OSA patients was computed using the unpaired independent samples t-test for continuous variables and the chi-square test, if necessary, for categorical variables. To test the independence of the risk factors for CAD occurance in OSA patients, the significant variables ($p<0.05$) in the univariate analyses were entered into a multivariate logistic regression model with backward selection of independent variables. Risk

factors were checked for confounding and co-linearity. All statistical evaluations were made assuming a 2-sided test based on a 5% level of significance using SPSS 16.

Result

Of the 277 patients, 186(67.14%) were males. The overall mean age was 55.1±14.3 years. CAD was found in 41(14.8%) patients (Table 1).

Patients without CAD significantly presented with lower cardiovascular risk profile, resulting in a lower 10-year risk for a cardiovascular event by the PROCAM score. Accordingly, less cardiovascular medications were taken by patients without CAD (p<0.05).

Table-1: Clincal characteristics of patients with Obstructive sleep apnoea (OSA).

Characteristics	With CAD (n=41)	Without CAD (n=236)	Univariate analysis p-value
Age (years)	54.6±15.5	55.2±14.1	0.81
Male/female	29/12	157/79	0.60
Body mass index	27.5±3.2	27.1±3.8	0.52
Diabetes	13(31.7%)	21(8.9%)	<0.001
Arterial hypertension	20(48.8%)	43(18.2%)	<0.001
Active smoke	15(36.6%)	52(22.0%)	0.045
Family history of CAD	13(31.7%)	76(32.2%)	0.95
10-yr risk for coronary event with PROCAM score	13.3±6.9	2.6±1.6	<0.001
Laboratory Examinations			
Uric acid (μmol/L)	7.04±2.1	5.79±1.77	<0.001
Triglyceride, mg/dL	3.5±1.6	1.8±2.1	<0.001
Total cholesterol, mg/dL	4.5±1.1	46±1.0	0.53
High density lipoprotein, mg/dL	1.3±0.3	1.4±0.3	0.36
Low density lipoprotein, mg/dL	2.5±0.8	2.5±0.7	0.797
eGFR (ml·min^{-1}·m^{-2})	113.4±79.9	103.8±34.0	0.17
White blood cell count (10*9/L)	6.5±3.0	7.1±2.3	0.13
C reactive protein (mg/L)	7.5±2.6	4.7±2.4	<0.001
Echocardiogram variables(mm)			
LAD	35.5±6.0	34.8±5.9	0.43
LVEDD	46.4±5.8	47.2±7.1	0.44
LVEF	63.7±9.3	64.8±9.8	0.55
Drug therapy			
Statins	3(7.3%)	11(7.3%)	0.47
Diuretics	4(9.8%)	14(5.9%)	0.36
ACEI/ARBs	10(24.4%)	21(8.9%)	0.004
Beta-blockers	6(14.6%)	14(5.9%)	0.047
CCBs	7(17.1%)	25(10.6%)	0.23
Polysomnography			
Apnea hypopnea index, events/h	48.3±12.8	18.9±10.2	<0.001
Lowest SaO2, %	80.6±6.6	70.2±9.8	<0.001
SaO2<90% (%TST)	34.4±11.1	12.6±10.5	<0.001
Epworth sleepiness scale	17.3±3.8	15.7±3.9	0.015

eGFR: estimated glomerular filtration rate; PROCAM: Prospective Cardiovascular Münster; LAVD: Left ventricular end-diastolic dimension; LAD: Left atrial diameter; LVEF left ventricular ejection fraction (LVEF); ACEI/ARB: Angiotensin converting enzyme inhibitor/ Angiotensin II receptor blockers. CCB: Calcium channel blocker.

Table-2: Independent risk factors for CAD in patients with Obstructive sleep apnoea (OSA).

Variables	Wald	OR (95% CI)	*p*-value
PROCAM score	18.119	1.593 (1.286-1.974)	<0.001
Uric acid μmol/L (per 1 unit increase)	1.522	1.004 (.998-1.011)	.217
Triglyceride mg/dL (per 1 unit increase)	2.192	1.173 (.950-1.449)	.139
Apnoea hypopnoea index (events/h)	7.813	1.091 (1.026-1.159)	.005
C reactive protein (mg/L) (per 1 unit increase)	5.369	1.332 (1.045-1.697)	.020
Diabetes	2.792	.231 (.042-1.288)	.095
Arterial hypertension	.849	.466 (.092-2.368)	.357

PROCAM: Prospective Cardiovascular Münster; OR: Odds ratio; CI: Cnfidence interval.

There were no significant differences between the two groups with respect to age, gender, BMI, TC, HDL, LDL, eGFR, WBC count, LAD, LVED and LVEF (p>0.05 each). The prevalences of diabetes and hypertension were significantly higher in OSA patients with CAD than those without CAD (p<0.05).

Patients with CAD were characterised by significantly higher TG levels as well as a trend of having more active smoking (p<0.05). CRP was markedly increased in patients with CAD (p<0.05). Compared to those with non-CAD, OSA patients with CAD were significantly more likely to have higher serum uric acid (p<0.05). Compared with OSA patients with the non-CAD, those with CAD had longer duration of oxygen saturation (SaO_2)<90%, higher AHI, ESS scores and values of lowest nocturnal SaO_2.

Factors independently associated with CAD in OSA patients included PROCAM score, CRP and AHI (Table 2).

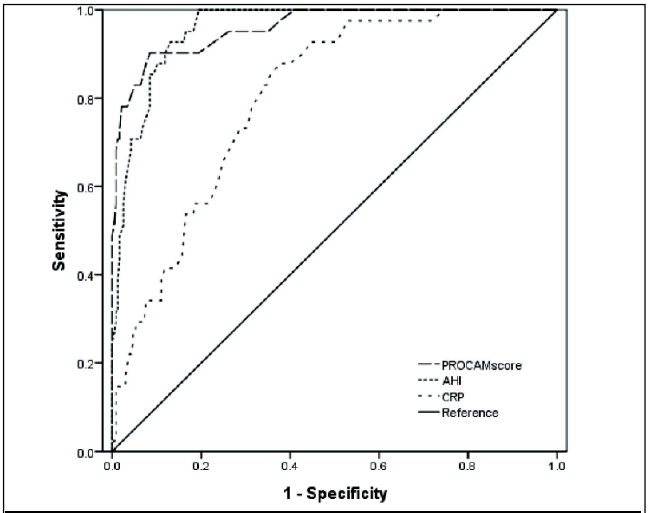

Figure-4: Comparison of the Receover operating characteristics (ROC) plots of different parameters with respect to their ability to reflect significant differences in the area under curve (AUC) for coronary artery disease (CAD). PROCAM: Prospective Cardiovascular Münster; AHI: Apnoea hypopnoea index; CRP: C-reactive protein.

Table-3: Comparison of the ROC plots of different parameters with respect to their ability to reflect significant differences in the AUCs for CAD in OSA patients.

Test Result Variable(s)	Area	SE	95%CI	Cut-off	Sensitivity (%)	Specificity (%)
PROCAM score	.960	.015	.930-.990	4.5	90.2	91.5
AHI	.957	.011	.935-.980	33.5	87.8	89.9
CRP	.802	.031	.741-.863	5.95	72.5	70.7

PROCAM: Prospective Cardiovascular Münster; AHI: Apnoea hypopnoea index; CRP: C-reactive protein; CAD: Coronary artery disease; OSA: Obstructive sleep apnoea; ROC: Receover operating characteristics; AUC: Area under curve.

Area under curve (AUC) in ROC curve showed significant differences between CAD andf nn-CAD OSA patients in terms of PROCAM score, AHI and CRP level (Table 3; Figure 4).

Discussion

Intermittent hypoxia, the primary characteristics of OSA have been associated with an increased vulnerability for sudden coronary stenosis, leading to acute ischaemic coronary syndromes. The ability to detect the coronary stenosis at early stages by a noninvasive methodology would probably improve risk stratification of these patients. The current prospective study indicates that such coronary stenosis can be detected in a high proportion of patients investigated by 320-slice CTA for suspected CAD in OSA patients. These patients were characterised by higher PROCAM score, AHI, TG, uric acid and CRP levels and by a trend of having diabetes mellitus. Furthermore, the study demonstrates that PROCAM score, AHI and CRP were the best independent risk factors for CAD development in OSA patients in multivariate regression analysis.

There is increasing evidence, based on large cohorts, that OSA may increase the incidence of CAD.[17-19] The identification of OSA patients at increased risk for an potentially life-threatening cardiovascular condition is a very difficult task in sleep medicine. Despite extensive research and testing, traditional cardiovascular risk factors fail to predict development of CAD in a large group of patients.[20] With the development of radiological technology and the application of multi-slice CT, coronary CTA has been introduced as noninvasive technique for the reliable detection of coronary stenosis and its micro-structure of coronay artery lesion.[21,22] Compared with invasive coronary angiography (ICA), clinical guideline for detecting CAD, noninvasive anatomic assessment by CTA is being increasingly used as an accurate tool for detecting or excluding CAD.[23] The current study assessed the prevalence of coronary artery stenosis in a population of consecutive OSA patients with 320-slice CTA. This population is believed to benefit from noninvasive coronary CTA. The coronary CTA investigations allowed for a separation of the population into two groups: 1) CAD was ruled out in approximately three-fourth of studied patients; 2) CAD with coronary stenosis was present in another one-fourth of investigated patients. There is increasing recognition that noncalcified plaques, defined as clearly discernible lesion with radiodensity greater than the surrounding soft tissue and lower than the luminal contrast, resulted in luminal stenosis of the contrast-enhanced lumen.

Interestingly, OSA patients with CAD had higher TG and CRP levels. The development of systemic inflammation, characterised by elevated levels of certain potent pro-inflammatory mediator, such as CRP, may have an important and direct role in the development of atherosclerotic lesions and in promoting cardiovascular disease. The significantly higher CRP values in OSA patients with coronary stenosis are of particular interest. In OSA patients, the effect of hypoxia and reoxygenation episodes can activate inflammatory cells,[24] and ongoing inflammatory responses may also play important roles in coronary atherosclerosis.[25] Although CRP is a nonspecific marker of inflammation, meta-analysis have shown that CRP is an independent predictor of risk of future coronary heart disease.[26] Furthermore, many studies have confirmed that CRP itself plays a direct role on the expression of inflammatory mediators by vascular endothelium, up-regulation of adhesion molecules and the release of monocyte chemoattractant protein-1 in human endothelial cells.[27,28] Therefore, CRP, as a risk factor and an active pathogenic agent, plays a vital role in coronary atherosclerosis. The current study shows that the elevated CRP value was closely related to the development and progression of coronary stenosis.

The evaluation of traditional cardiovascular risk factors for coronary stenosis cannot fully identify the OSA patient population with CAD. The PROCAM study in Europe,[29] implemented by statistical procedures such as stepwise logistic regression or the Cox proportional hazards model, may provide a truer picture of a person's overall risk of CAD than clinical classification but may prove comprehensive in clinical practice. This scoring scheme contained nearly all the information present within the

Cox function with continuous variables and performed very well in calculating the absolute risk of an acute coronary event. The current study suggests that OSA patients with CAD may have had higher TG values and higher prevalence of hypertension and diabetes mellitus, which are part coefficients of PROCAM scoring scheme. PROCAM score can evaluate person's overall risk of CAD. so all managements of CAD, including quitting smoking, high HDL, low LDL were applied to the OSA patients with CAD.

Data from clinic and community-based studies, although not all, generally suggest that CAD is more frequent in OSA cohorts[30] and vice versa that patients with CAD are more likely to have sleep disorders even allowing for the effect of obesity and other confounding factors.[31] For example, one such study prospectively followed more than 6,000 participants suffering from the burden of self-reported CAD in the Sleep Heart Health Study among these subjects, and reported the increased prevalence of AHI from 9% in the lowest to 19% in the highest, a relationship that survived adjustment for confounding factors.[32] It is unclear if the presence and severity of OSA can actually be used to predict the risk of developing CAD, however. While data from relatively small, but well-organised studies of inpatients suggest a strong dose-response relationship between the severity of OSA and CAD,[33] these results from a population-based study cannot be reproduced at the same degree. A community-based study of North American subjects for average follow-up of about 8 years have shown relatively modest relationship between OSA and CAD incidence.[29] Within this group of 4,422 (43.6% male) subjects, only severe OSA in men aged 70 or less can increase the risk of developing symptomatic CAD. Furthermore, death analysis has shown that severe OSA served as an independent predictor of mortality of this cohort, and particularly death related to CAD.[34] Similar findings were seen about this relationship across the population of the current study.

So far, very little research has addressed the epidemic of CAD by contrast-enhanced multislice coronary ATA in OSA population. The single-centre nature and the relatively small sample size are the main limitations of the current study. Reliability of data would be increased by multicentre study. With a large size, a model of joint AUC of the three variables mentioned would be set up for achieving higher sensitivity and specificity. However, the study may encourage clinicians to perform early detection and intervention to CAD in OSA patients with high risk. In addition, multivariate analysis was performed to identify independent factors of interest.

Conclusions

Coronary heart disease occurrence in OSA patients was found to be strongly related to PROCAM score, AHHI and CRP values. These results might be helpful for monitoring the occurrence of coronary heart disease in OSA patients.

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Conflict of Interest: None.
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