Original Article

Obstructive sleep apnea remains a risk factor for major adverse cardiovascular and cerebrovascular events even in hypertensive patients under treatment: the Urumqi Research on Sleep Apnea and Hypertension (UROSAH) data

Xiaoguang Yao[1,2,3,4,5#], Nanfang Li[1,2,3,4,5#], Mulalibieke Heizhati[1,2,3,4,5], Yingchun Wang[1,2,3,4,5], Yue Ma[1,2,3,4,5], Run Wang[1,2,3,4,5], Delian Zhang[1,2,3,4,5], Qin Luo[1,2,3,4,5], Junli Hu[1,2,3,4,5], Menghui Wang[1,2,3,4,5], Qing Zhu[1,2,3,4,5]

[1]Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China; [2]Key Laboratory of Xinjiang Uygur Autonomous Region "Hypertension Research Laboratory", Urumqi, China; [3]Xinjiang Hypertension Institute, Urumqi, China; [4]National Health Committee Key Laboratory of Hypertension Clinical Research, Urumqi, China; [5]Xinjiang Clinical Medical Research Center for Hypertension (Cardio-Cerebrovascular) Diseases, Urumqi, China

Contributions: (I) Conception and design: N Li, X Yao; (II) Administrative support: N Li, M Heizhati; (III) Provision of study materials or patients: D Zhang, Q Luo, J Hu, M Wang, Q Zhu; (IV) Collection and assembly of data: Y Wang, Y Ma, R Wang; (V) Data analysis and interpretation: X Yao, N Li, M Heizhati; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Nanfang Li, MD, PhD. Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China; Key Laboratory of Xinjiang Uygur Autonomous Region "Hypertension Research Laboratory", Urumqi, China; Xinjiang Hypertension Institute, Urumqi, China; National Health Committee Key Laboratory of Hypertension Clinical Research, Urumqi, China; Xinjiang Clinical Medical Research Center for Hypertension (Cardio-Cerebrovascular) Diseases, No. 91 Tianchi Road, Urumqi 830001, China. Email: lnanfang2016@sina.com.

Background: The impact of the co-occurrence of hypertension and obstructive sleep apnea (OSA) on the risk of long-term cardiovascular disease (CVD) outcomes has not been extensively studied in the Asian population, and the residual effect of OSA on CVD in patients under antihypertensive treatment is not clear. The study aimed to explore the impact of OSA on the risk of CVD outcomes in a large-scale Asian cohort under antihypertensive treatment using retrospective design.

Methods: Hypertensive patients who underwent polysomnography (PSG) test from January 2011 to December 2013 were recruited from the Urumqi Research on Sleep Apnea and Hypertension (UROSAH) cohort, which was conducted in Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region. OSA was defined as apnea hypopnea index (AHI) ≥5. Outcomes were extended major adverse cardiovascular and cerebrovascular events (MACCE), including the first occurrence of nonfatal myocardial infarction, nonfatal stroke, revascularization, rehospitalization due to unstable angina or heart failure and all-cause death. Cox regression analysis was performed to explore the effect of OSA and hypertension coexistence on MACCE.

Results: A total of 3,329 hypertension patients were enrolled, of whom 2,585 patients (about 77.7%) suffered from OSA. During a median follow-up period of 7.0 years, 415 patients developed extended MACCE. The incidence of extended MACCE was significantly greater in patients with OSA than those without OSA [hazard ratio (HR): 1.59; 95% confidence interval (CI): 1.27–1.99; P<0.001]. Overall, patients with OSA had an increased risk of cardiac events of 57% compared to those without OSA (HR: 1.57; 95% CI: 1.04–2.39, P=0.034) and the association did not change in further sensitivity analysis. Particularly in uncontrolled hypertension, OSA was found to have a 93% increased risk of cardiac events, compared with patients without OSA (P=0.036).

Conclusions: Untreated OSA seemed to be a factor affecting the prognosis of cardiac events in hypertensive patients, although the association between OSA and cardiac events would be attenuated by the pharmacological-induced blood pressure control, which highlights the need to treat OSA.

Keywords: Obstructive sleep apnea (OSA); hypertension; major adverse cardiovascular and cerebrovascular events (MACCE); antihypertensive treatment

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Introduction

Background

Obstructive sleep apnea (OSA) is one of the most common sleep disorders characterized by recurrent partial or complete cessation of breathing during sleep, affecting 1 billion adults aged 35–69 years globally (1). Numerous observational and prospective studies have proved the association between OSA and cardiovascular diseases (CVDs) [e.g., heart failure (HF), stroke, coronary heart disease, and atrial fibrillation] and all-cause mortality (2-5). Besides the health consequences, untreated OSA has also been associated with substantial financial burden on patients, the healthcare system, and society (6).

Rationale and knowledge gap

Both OSA and hypertension are well-known CVDs risk factors, with a strong bidirectional association between OSA and hypertension (7). Furthermore, OSA has been independently associated with target-organ damage (e.g., arterial stiffness, heart remodeling and left ventricular hypertrophy) in patients with hypertension (8,9), suggesting a potential role of OSA in hypertension prognosis. Hence, the co-occurrence of OSA and hypertension is thought to significantly increase the risk of CVDs (10). However, to date, the impact of the co-occurrence of OSA and hypertension on the risk of long-term CVD outcomes has not been extensively studied, especially in the Asian population.

As one of the effective methods to treat OSA, continuous positive airway pressure (CPAP) is recommended for patients with OSA and hypertension besides antihypertensive drugs in clinical practice. However, many early randomized controlled trials (RCTs) have shown a mild reduction in blood pressure (BP) (mean 2–4 mmHg) with treatment by CPAP in OSA patients (11-14). Recent large-scale studies have failed to observe the benefit of CPAP therapy in reducing the incidence of cardiovascular events in patients with OSA and CVDs, which questions the prognostic value of OSA in patients with cardiovascular risk factors (15-17). In an 8-week randomized control study, antihypertensive medication induced a 4-fold higher decrease in mean 24-hour BP compared to CPAP in untreated hypertensive patients with OSA (18). That study suggested that antihypertensive drugs might have more potent cardiovascular protection than CPAP therapy in patients with hypertension and OSA. However, the residual effect of OSA on long-term CVDs in patients under antihypertensive treatment has been rarely explored. Hence, the potential relevance of OSA in the hypertension scenario should be exercised.

Objective

This study aimed to evaluate the impact of the coexistence of OSA and hypertension on the incidence of cardiovascular events in hypertensive patients receiving antihypertensive treatment. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-284/rc).

Highlight box

Key findings

- Untreated obstructive sleep apnea (OSA) seemed to be a factor affecting the prognosis of cardiac events in hypertensive patients, but the association would be attenuated by the antihypertensive-drug induced controlled blood pressure.

What is known and what is new?

- There is huge number of patients with hypertension and OSA, and it is often recommended to treat hypertension with continuous positive airway pressure (CPAP). However, the CPAP treatment has a mild effect on blood pressure reduction.
- Controlled blood pressure would partially reduce the risk of cardiac events in patients with hypertension and OSA despite of the lack of OSA-specific treatment.

What is the implication, and what should change now?

- Our results highlighted the need to identify and treat OSA in patients with hypertension besides of antihypertensive drugs.

Methods

This study was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (No. 2019030662) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived because all data were retrospectively collected and individual information was not disclosed.

Study design and subjects

Urumqi Research on Sleep Apnea and Hypertension (UROSAH) was a single-center retrospective cohort study assessing the association between OSA and long-term CVDs in patients with hypertension, which was conducted in Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous Region, a provincial tertiary hospital. The specialty center provides individualized hypertension treatment and identification of secondary hypertension (19). A total of 3,605 consecutive hypertensive patients with suspected OSA aged ≥18 years admitted to the center between January 2011 and December 2013 were recruited. The inclusion criteria were: (I) patients with hypertension who pursue for the causes of secondary hypertension; (II) patients who were clinically suspicious of OSA and were referred for sleep monitoring for the first time, experiencing snoring with or without apnea at night, witnessed apnea and arousal frequently during sleep, unexplained daytime sleepiness, unexplained morning headache, unexplained lip and/or tongue dryness, unexplained cyanosis of lip and/or nail bed and resistant hypertension. Exclusion criteria for UROSAH were described in our previous study (20): patients with acute severe cardiovascular and cerebrovascular diseases in recent 3 months; patients who were using steroids, bronchodilators, and antihistamines; secondary hypertension such as renal and renal vascular hypertension, pheochromocytoma, aldosterone adenoma, Cushing's syndrome, and other common secondary hypertension patients; patients with malignant tumor, acute infection, and autoimmune diseases; patients with acute asthma, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary tuberculosis, and other respiratory diseases; patients who failed to complete the sleep study (patients without adequate and satisfactory signal recording). All inpatients were assessed for office BP measurement, target organ damage and complications (e.g., heart, brain, kidney, vascular and retinal damage), and screening of secondary hypertension based on their medical history, physical examination, biochemical test, chest X-ray, ultrasonography, in-laboratory full-night polysomnography (PSG) examination, etc. Then, all patients were given individualized treatment, including lifestyle modification suggestions, medication regimens, and/or OSA-specific therapy (i.e., oral appliance and CPAP treatment if necessary). In the present study, participants who were lost to follow-up were not included (n=276). Finally, 3,329 patients were enrolled for the final analysis.

Baseline information recording

Baseline information collection was conducted between 2011 and 2013, including demographics, anthropometric measurements, medication history, laboratory test results, and echocardiographic evaluation results. The details of information collection have been described in our previous study (20). Data for height and weight were taken by trained nurses following a protocol standardized to an accuracy of 0.1 kg and 0.1 cm, respectively, then body mass index (BMI) was calculated as weight (kg)/height (m^2). Baseline seated BP was measured using a mercury sphygmomanometer after the patient rested quietly for at least 10 minutes, and the average of three measurements was taken as the systolic BP and diastolic BP values.

Diagnosis of hypertension

Hypertension was defined as the resting BP of at least 140/90 mmHg or the current use of antihypertensive drugs (21). In the present study, controlled hypertension was defined as systolic BP (SBP) of <140 mmHg and diastolic BP (DBP) of <90 mmHg after antihypertensive treatment. Uncontrolled hypertension was defined as SBP of ≥140 mmHg and/or DBP of ≥90 mmHg under antihypertensive treatment.

Overnight sleep study and diagnosis of OSA

All patients underwent in-laboratory overnight PSG (Compumedics E series, Australia) examination. Detailed information on PSG and the diagnosis of OSA was described in our previous studies (22). OSA was defined as an apnea hypopnea index (AHI) of ≥5 events per hour. Then, OSA severity was defined by AHI as follows: non-OSA (AHI <5), mild OSA (5≤ AHI <15), moderate OSA (15≤ AHI <30), and severe OSA (AHI ≥30).

Follow-up and outcomes

All patients were followed up by the trained nurses and physicians of the hypertension center, and all clinical outcomes were collected via inpatient medical records, outpatient visits, or telephone calls. Additionally, data on the latest BP level and treatment of OSA (i.e., oral appliance, CPAP, surgery) after the initial diagnosis were collected, including treatment modality (CPAP, oral appliance, and surgery), frequency and duration of treatment, etc. Regular CPAP treatment was defined as average treatment ≥4 hours/night for >70% of the entire follow-up period, or on average of ≥4 hours per night (CPAP devices only provide cumulative hours of use) (23). For each patient, follow-up time was calculated from the baseline date and accrued until a CVD incident. The deadline for follow-up was January 2021. The primary outcomes in the study were extended major adverse cardiovascular and cerebrovascular events (MACCE), which included a newly diagnosed MACCE and all-cause death during the study period. MACCE included death from heart and cerebrovascular disease, non-fatal myocardial infarction (MI), non-fatal stroke [including transient ischemic attack (TIA)], revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)], and rehospitalization because of unstable angina or HF. Further, cardiac events included death from heart diseases, non-fatal MI, revascularization (PCI, CABG), and rehospitalization because of unstable angina or HF. All endpoints were defined according to the proposed definitions by the Standardized Data Collection for Cardiovascular Trials Initiative (24). If MACCE was not diagnosed in our hospital, the patients were asked to provide diagnosis and treatment data. For a sudden death case, the cause of death was asked from bereaved relatives and verified by the hospital death certificate, local police system, or hospitalization data. The International Classification of Diseases (ICD-10) classification code was used to classify 75 cases of the causes of death. All clinical events were confirmed by medical documentation and identified by the clinical event committee of our hospital. Finally, 3,329 patients were enrolled for the data analysis (Figure S1).

Statistical analysis

Categorical variables were presented as observed numbers and percentages and compared using Pearson Chi-square test among the groups. Skewness-kurtosis method was used to perform test of normality. Continuous variables were reported as mean ± standard deviation (SD) if normally distributed and as the median and interquartile range (IQR) if not normally distributed.

Differences between two groups for normally distributed continuous variables were compared using the independent samples *t*-test, and Mann-Whitney *U* test was used for non-normally distributed continuous variables. A total of 276 individuals who were lost to follow-up were not included in the analysis. The cumulative incidence of primary outcomes was estimated by Kaplan-Meier survival curves, and Log-rank test was used to estimate the difference between patients with and without OSA. Multivariable Cox proportional hazard models were performed to identify independent predictors for extended MACCE and its components adjusted for factors known to influence MACCE in the whole population and subgroups stratified by BP control. The multiplicative interaction between presence of OSA and BP control status (controlled or uncontrolled) was also tested in a Cox model. Sensitivity analysis was performed in patients without OSA-specific treatment (i.e., CPAP, oral appliance, and surgery) to exclude the potential benefit of OSA treatment. The impact of hypertension and OSA on the incidence of extended MACCE and cardiac events was assessed and adjusted for confounders as well. Data were analyzed using SPSS statistical software (version 25.0, SPSS Inc., Chicago, IL, USA), and all analyses were two-tailed. A P value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the subjects

Of all participants, 77.7% (2,585/3,329) were diagnosed with OSA, and the proportion of severity of mild, moderate, and severe OSA was 37.9% (981/2,585), 32.1% (829/2,585), and 30.0% (775/2,585), respectively. The overall mean age was 48.6 years, and 80.9% of patients were aged 30–60 years. The mean age, BMI, baseline office SBP, serum estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-c), and AHI of patients with OSA were significantly higher than in those without OSA, while the mean oxygen saturation (SaO_2) and nadir SaO_2 in the OSA group were much lower than that of patients without OSA. The constituent ratio of males, type 2 diabetes, coronary heart disease, and smokers in the OSA group was significantly higher than that in patients without

OSA. Additionally, the proportion of ≥3 antihypertensive drugs, lipid-modifying agents, and antiplatelet drugs was greater in the OSA group. During follow-up (median: 7.0 years), crude incidence of extended MACCE was 18.8 per 1,000 person-years in total population, 20.6 per 1,000 person-years in the OSA group, and 13.2 per 1,000 person-years in patients without OSA (*Table 1*).

MACCE incidence

In total, 415 individuals experienced extended MACCE at a median follow-up of 7.0 years. The incidence of extended MACCE was significantly greater in the OSA group compared with the non-OSA group [hazard ratio (HR): 1.59; 95% confidence interval (CI): 1.27–1.99; P<0.001] (*Figure 1A*). However, the incidence of all-cause death (*Figure 1B*) and stroke (*Figure 1C*) between the OSA and non-OSA groups was not significant. While the incidence of cardiac events was significantly greater in the OSA group compared with the non-OSA group (HR: 2.44; 95% CI: 1.80–3.29; P<0.001) (*Figure 1D*).

OSA and extended MACCE and cardiac events

Table 2 presents the association between OSA and extended MACCE, as well as cardiac events, in the total population. In the crude model, OSA was shown as a risk factor for extended MACCE and cardiac events. Adjusted for confounders, no significant association between OSA and extended MACCE was observed. Still, patients with OSA had an increased risk of cardiac events of 57%, compared to those without OSA (HR: 1.57; 95% CI: 1.04–2.39; P=0.034) and the association did not change in further sensitivity analysis. However, no association between OSA and stroke and all-cause death in the total population was observed (Table S1).

OSA and BP status

The interaction between OSA status and BP level (≥140/90 or <140/90 mmHg) was not significant for extended MACCE (HR: 1.12; 95% CI: 0.91–1.36; P=0.287) or cardiac events (HR: 1.15; 95% CI: 0.88–1.50; P=0.321) (Table S2). In the uncontrolled hypertension population, OSA was found to have a 93% increased risk of cardiac events compared with patients without OSA (P=0.036) after adjustment for confounders. Further sensitivity analysis also showed OSA as a significant risk factor for cardiac events, regardless of OSA-specific treatment. In contrast, in the controlled hypertension, OSA showed a 1.23-fold higher risk of cardiac events in the OSA group than in those without OSA, and as adjusted for confounding factors, the P value did not reach statistical significance (P=0.489). However, no significant association between OSA and extended MACCE, stroke, and all-cause death was observed neither in the controlled hypertension nor in the uncontrolled hypertension group (*Table 3*, Table S3).

Discussion

Our study was conducted in Asian hypertensive population with high OSA prevalence, showing that OSA remained a risk factor for cardiac events rather than extended MACCE, although all patients received antihypertensive treatment. Although the association between OSA and cardiac events might be attenuated by pharmacological BP control, untreated OSA seemed to be a factor affecting the prognosis of cardiac events in hypertensive patients coexistent with OSA.

One strength of our study was that all patients were evaluated with full-night PSG. There are many methods to diagnose or screen OSA in clinical work, such as PSG, home sleep apnea testing (HSAT), signs and symptoms, scoring scales (such as the Berlin questionnaire, Epworth score, and STOP-Bang questionnaire), and clinical prediction models (e.g., the morphological prediction model), but the gold standard for diagnosis is PSG (25). Nevertheless, the questionnaires and/or HSAT are generally used to define the status of OSA in many large-scale epidemic studies. Furthermore, even well-designed questionnaires have shown low specificity and can be susceptible to bias in determining OSA (26). Our study provided a more accurate diagnosis of OSA than questionnaires or home monitoring devices and added methodological rigor.

Some limitations should be discussed. A substantial proportion of patients were suspected of having OSA, and the detection rate of OSA was very high. However, more than half of the patients were referred from different districts and regions of Xinjiang, which might have attenuated the population selection bias. In addition, our results come from a highly selected population which is at high risk of CVDs, thus, the conclusions should be cautiously generalized to the community. Further, the results should not be extrapolated to other zones of the world since this is an exclusively Asian study. Although all patients with severe OSA were initially recommended the

Table 1 Baseline characteristics of the subjects

Variables	Total subjects (n=3,329)	OSA (n=2,585)	without OSA (n=744)	P value
Age (year)	48.6±11.0	49.7±10.8	44.8±10.8	<0.001
Gender (male)	2,184 (65.6)	1,775 (68.7)	409 (55.0)	<0.001
BMI (kg/m^2)	27.6 (25.4–30.1)	28.1 (25.9–30.6)	26.2 (24.2–28.7)	<0.001
Baseline office SBP (mmHg)	139.6±19.5	140.0±19.8	138.4±18.5	0.046
Baseline office DBP (mmHg)	91.7±13.8	91.7±14.1	91.8±12.9	0.820
Baseline MAP (mmHg)	107.7±14.5	107.8±14.7	107.3±13.6	0.452
Smoker	1,099 (33.0)	906 (35.0)	193 (25.9)	<0.001
GGT (mmol/L)	28.4±22.3	28.6±20.4	27.5±27.9	0.217
GOT (mmol/L)	22.2±14.2	22.4±14.5	21.6±12.8	0.171
eGFR (mL/min/1.73 m^2)	96.8±21.9	100.2±21.8	95.9±21.9	<0.001
LDL-C (mmol/L)	2.61±0.79	2.63±0.80	2.54±0.78	0.006
Total sleep time (min)	390.2±51.7	389.8±50.8	391.4±54.7	0.510
Sleep efficiency (%)	73.5±9.6	73.6±9.6	73.0±9.5	0.169
AHI (event/h)	14.4 (5.6–26.9)	19.7 (10.7–32.2)	1.7 (0.7–3.1)	<0.001
Mean SaO_2 (%)	93.0 (91.0–94.0)	92.0 (91.0–94.0)	94.0 (93.0–95.0)	<0.001
Lowest SaO_2 (%)	82.0 (77.0–86.0)	80.0 (75.0–84.0)	88.0 (87.0–90.0)	<0.001
Moderate-to-severe OSA	1,604 (48.2)	1,604 (62.1)	0	–
Diabetes (%)	550 (16.5)	478 (18.5)	72 (9.7)	<0.001
CHD (%)	373 (11.2)	317 (12.3)	56 (7.5)	<0.001
Antihypertensive regimen				<0.001
0–1 drug	1,183 (35.5)	845 (32.7)	338 (45.4)	
2 drugs combination	1,660 (49.9)	1,327 (51.3)	333 (44.8)	
≥3 drugs combination	486 (14.6)	413 (16.0)	73 (9.8)	
Lipid-modifying agents	2,070 (62.2)	1,693 (65.5)	377 (50.7)	<0.001
Antiplatelet drugs	1,639 (49.2)	1,348 (52.1)	291 (39.1)	<0.001
Antidiabetic drugs use in patients with DM2	442 (80.4)	383 (80.1)	59 (81.9)	0.717
Regular CPAP treatment	0	114 (4.4)	0	
Follow-up years	7.0 (6.0–8.1)	6.9 (6.0–8.0)	7.3 (6.3–8.1)	
Person-years followed	22,016.15	16,932.46	5,083.69	–
Total primary endpoints	415	348	67	–
Outcome per 1,000 person-years	18.8	20.6	13.2	–

Data were presented as mean ± standard deviation, n (%) or median (interquartile range), unless otherwise indicated. OSA, obstructive sleep apnea; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; GGT, alanine transaminase; GOT, aspartate transaminase; eGFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; AHI, apnea hypopnea index; SaO_2, arterial oxygen saturation of blood oxygen; CHD, coronary heart diseases; DM2, diabetes type 2; CPAP, continuous positive airway pressure.

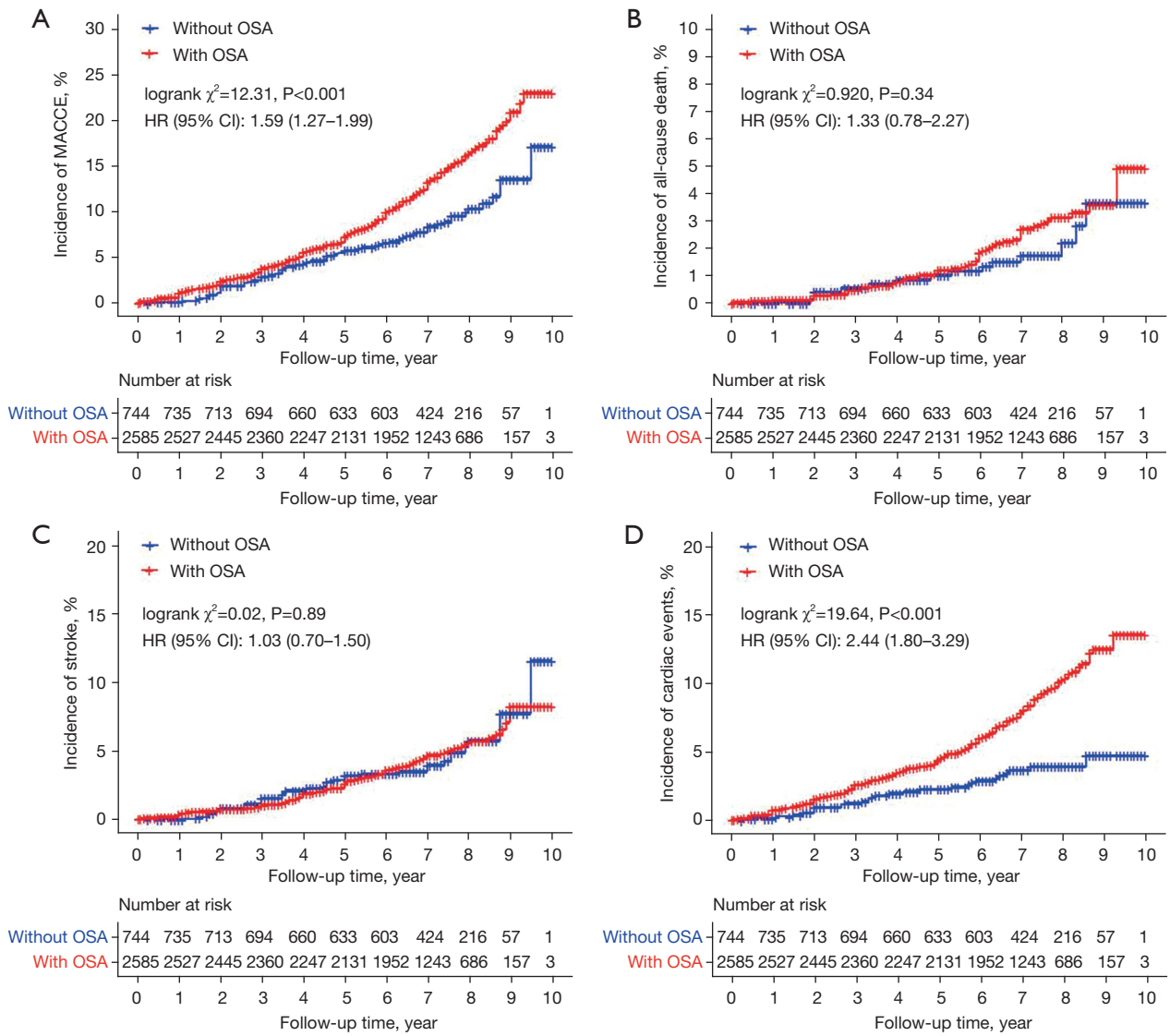

Figure 1 Kaplan-Meier curve of cardiovascular events. Proportion of patients with cardiovascular events for patients with OSA and without OSA. (A) Cumulative incidence of extended MACCE. (B) Cumulative incidence of all-cause death. (C) Cumulative incidence of stroke. (D) Cumulative incidence of cardiac events. OSA, obstructive sleep apnea; MACCE, major adverse cardiovascular and cerebrovascular events; HR, hazard ratio; CI, confidence interval.

treatment with CPAP as soon as they were diagnosed, a substantial proportion of patients refused the treatment, and the treatment effect of OSA on MACCE was not discussed further due to low utilization of CPAP. Nonetheless, these patients were followed up in our hypertension center and provided information on the natural history of untreated OSA. Finally, the lack of information about the class of hypertensive drugs used and the medication adherence, as well as the control of metabolic disorders, was not fully assessed and followed up. The positive association between OSA and cardiac events might have been contaminated by poorly controlled known CVDs risk factors, which need further prospective verification studies.

Numerous studies have shown the association between OSA and MACCE or its components. However, the impact of co-existent OSA and hypertension on the risk of CVDs has not been extensively studied. Recently, a prospective cohort study, Diastolic Chronic Heart Failure Study

Table 2 Association between OSA and extended MACCE and cardiac events in the total cohort (n=3,329)

Model	Extended MACCE		Cardiac events	
	HR (95% CI)	P value	HR (95% CI)	P value
Crude model	1.59 (1.23–2.07)	0.001	2.44 (1.63–3.68)	<0.001
Partially adjusted model	1.24 (0.95–1.61)	0.117	1.83 (1.21–2.76)	0.004
Fully adjusted model	1.11 (0.84–1.45)	0.461	1.57 (1.04–2.39)	0.034
Sensitivity analysis	1.07 (0.81–1.40)	0.645	1.53 (1.01–2.33)	0.046

Partially adjusted model: adjusted for age and sex. Fully adjusted model: adjusted for age, sex, body mass index, baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, eGFR, smoking, type 2 diabetes, history of coronary heart diseases, lipid-lowering drugs, antidiabetic drugs, and antiplatelet drugs. Sensitivity analysis was performed in 3,201 hypertensive patients without OSA-specific treatment, i.e., CPAP, oral appliance, surgery, etc. The confounders in the fully adjusted model were included. OSA, obstructive sleep apnea; MACCE, major adverse cardiovascular and cerebrovascular events; HR, hazard ratio; CI, confidence interval; eGFR, glomerular filtration rate; CPAP, continuous positive airway pressure.

Table 3 Association between OSA and extended MACCE and cardiac events in the subgroups stratified by blood pressure control (n=3,267)

Model	BP controlled <140/90 mmHg		BP controlled ≥140/90 mmHg	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Extended MACCE				
Crude model	1.60 (1.06–2.42)	0.027	1.56 (1.08–2.25)	0.017
Partially adjusted model	1.21 (0.79–1.84)	0.377	1.28 (0.88–1.86)	0.200
Fully adjusted model	1.01 (0.66–1.56)	0.957	1.22 (0.83–1.78)	0.310
Sensitivity analysis	0.96 (0.62–1.48)	0.853	1.17 (0.80–1.72)	0.411
Cardiac events				
Crude model	2.10 (1.19–3.69)	0.010	2.50 (1.38–4.54)	0.003
Partially adjusted model	1.52 (0.86–2.67)	0.151	1.96 (1.07–3.59)	0.029
Fully adjusted model	1.23 (0.69–2.19)	0.489	1.93 (1.04–3.57)	0.036
Sensitivity analysis	1.18 (0.66–2.11)	0.580	1.89 (1.02–3.49)	0.044

Partially adjusted model: adjusted for age and sex. Fully adjusted model: adjusted for age, sex, body mass index, baseline systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, eGFR, smoking, type 2 diabetes, history of coronary heart diseases, lipid-lowering drugs, antidiabetic drugs, and antiplatelet drugs. Sensitivity analysis was performed in 3,139 hypertensive patients without OSA-specific treatment, i.e., CPAP, oral appliance, and surgery. The confounders in the fully adjusted model were included. OSA, obstructive sleep apnea; MACCE, major adverse cardiovascular and cerebrovascular events; BP, blood pressure; HR, hazard ratio; CI, confidence interval; eGFR, glomerular filtration rate; CPAP, continuous positive airway pressure.

(DIAST-CHF), has assessed the adverse effects of OSA on cardiovascular morbidity and mortality in patients with cardiovascular risk factors (27), but did not find a significant association, in which the effective pharmacological interventions and a limited number of severe OSA patients might have been the possible reasons. Similarly, all subjects in our study were prescribed individualized antihypertensive regimens after systemic evaluation of hypertension, and lipid-lowering drugs, antidiabetic drugs, and antiplatelet drugs were given if necessary. Hence, the association between OSA and MACCE/cardiac events might be underestimated due to pharmacological interventions.

Additionally, OSA had a 93% increase in the risk of cardiac events in uncontrolled hypertension, which was much higher than that in controlled hypertension (*Table 3*), and the association did not change after the exclusion of patients receiving OSA-specific treatment, indicating an independent effect of untreated OSA on the incident cardiac

events. Our result was supported by a previous study which evaluated whether the impact of anti-hypertensive response on arterial stiffness and BP control was OSA dependent. The study did not observe the difference in 24-hour BP and arterial stiffness between hypertensive patients with and without OSA, with combined antihypertensive treatment aimed at controlling BP (28). Moreover, a very recent cohort study concluded that CPAP treatment might be protective in individuals with moderate/severe OSA in patients with resistant hypertension, but they did not find the presence/severity of OSA could worsen CVDs prognosis (29).

Our data did not observe the significant interaction between OSA and BP levels regarding extended MACCE. A previous study provided evidence that OSA and hypertension had an additive role regarding the increase in blood levels of inflammatory markers for atherosclerosis and progression of carotid atherosclerosis (30). Additionally, OSA leads to plaque instability, plaque vulnerability, and coronary artery calcification (31). In our study, the main population of this study was middle-aged individuals and all the individuals were diagnosed with hypertension, the cutoff point of BP level was 140/90 mmHg when performed for the interaction between OSA and BP levels. Besides, we have observed a relatively small number of MACCEs. So the main effect of OSA rather than the interaction of OSA and BP levels on extended MACCE were observed. Anyway, our study provided information to the efficacy of pharmacological treatments in patients with OSA and hypertension. Further large-scale prospective studies featuring antihypertensive drugs and CPAP treatment are needed to serve as a guide for future studies related to OSA and hypertension.

Conclusions

Untreated OSA seemed to be a factor affecting the prognosis of cardiac events in hypertensive patients coexistent with OSA, although the association between OSA and cardiac events would be attenuated by the pharmacological-induced BP control, which highlights the need to treat OSA itself besides of antihypertensive drugs.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-284/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-284/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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 was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (No. 2019030662) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived because all data were retrospectively collected and individual information was not disclosed.

References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019;7:687-98.
2. Coniglio AC, Mentz RJ. Sleep Breathing Disorders in Heart Failure. Heart Fail Clin 2020;16:45-51.
3. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation 2021;144:e56-67. Erratum in: Circulation 2022;145:e775.
4. Wang G, Miao H, Hao W, et al. Association of obstructive sleep apnoea with long-term cardiovascular events in patients with acute coronary syndrome with or without hypertension: insight from the OSA-ACS project. BMJ Open Respir Res 2023;10:e001662.
5. Peker Y, Thunström E, Glantz H, et al. Effect of Obstructive Sleep Apnea and CPAP Treatment on Cardiovascular Outcomes in Acute Coronary Syndrome in the RICCADSA Trial. J Clin Med 2020;9:4051.
6. Wickwire EM. Value-based sleep and breathing: health economic aspects of obstructive sleep apnea. Fac Rev 2021;10:40.
7. Redline S, Azarbarzin A, Peker Y. Obstructive sleep apnoea heterogeneity and cardiovascular disease. Nat Rev Cardiol 2023;20:560-73.
8. Saeed S, Romarheim A, Solheim E, et al. Cardiovascular remodeling in obstructive sleep apnea: focus on arterial stiffness, left ventricular geometry and atrial fibrillation. Expert Rev Cardiovasc Ther 2022;20:455-64.
9. Cabrini ML, Macedo TA, Castro E, et al. Obstructive sleep apnea and hypertension-mediated organ damage in nonresistant and resistant hypertension. Hypertens Res 2023;46:2033-43.
10. Salman LA, Shulman R, Cohen JB. Obstructive Sleep Apnea, Hypertension, and Cardiovascular Risk: Epidemiology, Pathophysiology, and Management. Curr Cardiol Rep 2020;22:6.
11. Dissanayake HU, Colpani JT, Sutherland K, et al. Obstructive sleep apnea therapy for cardiovascular risk reduction-Time for a rethink? Clin Cardiol 2021;44:1729-38.
12. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. J Am Coll Cardiol 2017;69:841-58.
13. Gagnadoux F, Priou P, Meslier N, et al. Effects of sleep apnoea therapy on blood pressure and metabolism: a CPAP sex gap? Eur Respir J 2017;50:1700987.
14. Chalegre ST, Lins-Filho OL, Lustosa TC, et al. Impact of CPAP on arterial stiffness in patients with obstructive sleep apnea: a meta-analysis of randomized trials. Sleep Breath 2021;25:1195-202.
15. McEvoy RD, Antic NA, Heeley E, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med 2016;375:919-31.
16. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012;307:2161-8.
17. Peker Y, Glantz H, Eulenburg C, et al. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med 2016;194:613-20.
18. Pépin JL, Tamisier R, Barone-Rochette G, et al. Comparison of continuous positive airway pressure and valsartan in hypertensive patients with sleep apnea. Am J Respir Crit Care Med 2010;182:954-60.
19. Wang L, Li N, Yao X, et al. Detection of Secondary Causes and Coexisting Diseases in Hypertensive Patients: OSA and PA Are the Common Causes Associated with Hypertension. Biomed Res Int 2017;2017:8295010.
20. Cai X, Li N, Hu J, et al. Nonlinear Relationship Between Chinese Visceral Adiposity Index and New-Onset Myocardial Infarction in Patients with Hypertension and Obstructive Sleep Apnoea: Insights from a Cohort Study. J Inflamm Res 2022;15:687-700.
21. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. J Hypertens 2020;38:982-1004.
22. Liang S, Li N, Heizhati M, et al. What do changes in concentrations of serum surfactant proteins A and D in OSA mean? Sleep Breath 2015;19:955-62.
23. Xu PH, Hui CKM, Lui MMS, et al. Incident Type 2 Diabetes in OSA and Effect of CPAP Treatment: A Retrospective Clinic Cohort Study. Chest 2019;156:743-53.
24. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol 2015;66:403-69.

25. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13:479-504.
26. Xu H, Zhao X, Shi Y, et al. Development and validation of a simple-to-use clinical nomogram for predicting obstructive sleep apnea. BMC Pulm Med 2019;19:18.
27. Haarmann H, Koch J, Bonsch N, et al. Morbidity and mortality in patients with cardiovascular risk factors and obstructive sleep apnoea: results from the DIAST-CHF cohort. Respir Med 2019;154:127-32.
28. Fatureto-Borges F, Jenner R, Costa-Hong V, et al. Does Obstructive Sleep Apnea Influence Blood Pressure and Arterial Stiffness in Response to Antihypertensive Treatment? Hypertension 2018;72:399-407.
29. Cardoso CRL, Salles GF. Prognostic importance of obstructive sleep apnea and CPAP treatment for cardiovascular and mortality outcomes in patients with resistant hypertension: a prospective cohort study. Hypertens Res 2023;46:1020-30.
30. Damiani MF, Zito A, Carratù P, et al. Obstructive Sleep Apnea, Hypertension, and Their Additive Effects on Atherosclerosis. Biochem Res Int 2015;2015:984193.
31. Jehan S, Zizi F, Pandi-Perumal SR, et al. Obstructive sleep apnea, hypertension, resistant hypertension and cardiovascular disease. Sleep Med Disord 2020;4:67-76.

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