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Original Research

Association of Obstructive Sleep Apnea With Cardiovascular Events in Acute Coronary Syndrome Patients With or Without Excessive Daytime Sleepiness: A Prospective Cohort Study

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Abstract

Background: Excessive daytime sleepiness (EDS) is a commonly observed symptom in people with obstructive sleep apnea (OSA). However, the impact of EDS on the outcome of patients with acute coronary syndrome (ACS) and OSA is not known. Therefore, this study aimed to investigate the association between OSA and cardiovascular events in ACS patients with or without EDS. **Methods**: This cohort study prospectively enrolled eligible ACS patients who underwent cardiorespiratory polygraphy during hospitalization between June 2015 and January 2020. We defined OSA as an apnea–hypopnea index (AHI) $\geq$15 events per h. EDS was described as having an Epworth Sleepiness Scale score $\geq$10. Major adverse cerebrovascular and cardiovascular events (MACCEs) were the primary outcome and included cardiovascular death, stroke, myocardial infarction, ischemia-driven revascularization, or hospitalization for heart failure or unstable angina. **Results**: The final study cohort comprised 1154 participants, of whom 398 (34.5%) had EDS, and 607 (52.6%) had OSA. During the median follow-up period of 2.9 years (interquartile range 1.5, 3.6), OSA was associated with a significantly increased risk of MACCEs in patients without EDS (adjusted hazard ratio (HR) = 1.42, 95% CI: 1.01–2.02, $p = 0.046$), but not in patients with EDS (adjusted hazard ratio HR = 1.05, 95% CI: 0.67–1.66, $p = 0.84$). **Conclusions**: OSA was associated with an elevated risk of MACCEs In ACS patients without EDS but not those with EDS. Therefore, screening for OSA should be performed in ACS patients without EDS, and future trials should prioritize such high-risk patients. **Clinical Trial Registration**: NCT03362385, https://clinicaltrials.gov/study/NCT03362385.

Keywords: obstructive sleep apnea; acute coronary syndrome; excessive daytime sleepiness; cardiovascular events

1. Introduction

Obstructive sleep apnea (OSA) is a prevalent sleep disorder that is characterized by repeat occurrences of partial or complete obstruction of the upper airway during sleep. Recent studies have highlighted the substantial public health cost associated with OSA, with the global prevalence in 30–69 year old adults estimated to be 940 million [1]. The incidence of OSA in patients with acute coronary syndrome (ACS) was found to be 36–63% in different races [2]. Several different studies have reported that OSA has prognostic significance in ACS patients [3,4]. However, there may be specific subsets (e.g., with different symptoms or comorbidities) that are more likely to be affected by OSA [5–7] and have yet to be identified.

Patients with OSA are commonly accompanied by sleep disruption, which frequently results in excessive daytime sleepiness (EDS). EDS may adversely impact daily performance, emotional states, and various facets of overall well-being [8–10]. Neuroimaging also reveals changes in the white matter and gray matter within the cerebral structure of individuals presenting with both OSA and EDS. A higher mean diffusivity and significant gray matter concentration deficits were detected in the EDS group by whole-brain analysis [11,12]. Recent work has also proposed an association between EDS and major adverse cerebrovascular and cardiovascular events (MACCEs) after myocardial infarction (MI) [13]. Currently, therapy with continuous positive airway pressure (CPAP) or pharmacological treatments are usually offered to OSA patients with EDS. However, it is still unclear if the effect of OSA on cardiovascular outcome differs according to the EDS status. In the present study we therefore investigated whether OSA was associated with cardiovascular events in ACS patients who did or did not have EDS. To achieve this, we conducted post-hoc analyses of an earlier OSA-ACS study.

2. Materials and Methods

2.1 Study Design and Participants

The OSA-ACS project (NCT03362385) was a large, prospective cohort study that that has been reported previously [5]. The study enrolled eligible ACS patients aged 18 to 85 years at the Beijing Anzhen Hospital, Capital Medical University with the aim of investigating possible associations between OSA and cardiovascular outcomes. Data collection occurred between June 2015 to January 2020, with the participants followed until December 2020. The exclusion criteria were: individuals with cardiogenic shock, cardiac arrest, cancer, patients with unsuccessful sleep monitoring due to unsatisfactory or inadequate signal recording, and patients who received regular CPAP treatment. Also excluded were patients who had predominantly central sleep apnea ($\geq$50% central events and a central apnea-hypopnea index (AHI) $\geq$10 events per hour), as well as patients lost to follow-up following hospital discharge.

MI diagnosis followed the universal definition of myocardial infarction, requiring both clinical evidence of acute myocardial ischemia and cardiac biomarker changes [14, 15]. Unstable angina (UA) diagnosis was based on the guideline, primarily emphasizing ischemic symptoms without mandatory biomarker elevation [16].

This investigation followed the principles of the Declaration of Helsinki, and was approved by the Ethics Committee, Beijing Anzhen Hospital, Capital Medical University (2013025). Written informed consent was obtained from all participants.

2.2 Sleep Study and Procedures

Following clinical stabilization in the hospital, all eligible participants underwent an overnight sleep study with a Type III portable cardiorespiratory polygraphy instrument (ApneaLink Air; ResMed, San Diego, California, USA). The mean time interval from admission to sleep study was 2 ± 1 days. This was independently applied at bedtime by trained research personnel. Data output from this device was collected by researchers who were blinded to patient information. Recorded parameters included nasal airflow, snoring episodes, heart rate, thoraco-abdominal movement, and nocturnal oxygen saturation (SaO2). Apnea was defined as airflow cessation lasting $>$10 seconds (obstructive in the presence of thoraco-abdominal movement, and central in the absence of thoraco-abdominal movement). Hypopnea was defined as a $>$30% decrease in airflow for $>$10 seconds, with a $>$4% reduction in arterial SaO2. We defined AHI as the number of apnea and hypopnea events per hour recorded over the total period. As per previous guidelines, we classified OSA as an AHI $\geq$15 events/h. Conversely, individuals that had an AHI $<$15 events/h were classified non-OSA [3,17–19]. Standard treatment was given to participants during hospitalization for the ACS event, as per current guidelines [20,21].

2.3 Epworth Sleepiness Scale

Sleepiness was self-reported using the Epworth Sleepiness Scale (ESS). Patients subjectively assessed their daytime sleepiness by completing the ESS questionnaire [22]. This scale includes eight questions, each relating to the risk of falling asleep in different situations over the past month. A categorization of EDS was assigned to patients who scored at least 10 out of a possible total of 24.

2.4 Follow-up and Endpoints

All eligible patients were monitored until December 2020. Follow-up assessments were performed 1, 3 and 6 months post-discharge, then subsequently each year. Adverse clinical events were registered through clinic visits, review of medical records, and phone interviews by researchers who were blinded to sleep data for each patient. The primary endpoint (MACCEs) included cardiovascular death, stroke, ischemia-driven revascularization, MI, and hospitalization due to UA or heart failure (HF). As detailed previously [23], secondary endpoints were single components of the primary endpoint, all-cause death, all repeat revascularization, and an amalgam of all events. Endpoints were established using definitions outlined by the Standardized Data Collection for Cardiovascular Trials Initiative [24]. Only the first occurrence from baseline was counted when the patient experienced multiple events. Events and source documents were assessed independently by researchers who were blind to the sleep study results.

2.5 Statistical Analyses

Quantitative data was presented as mean $\pm$ SD, or median (Q1, Q3), and evaluated by Student's *t*-test or Mann-Whitney U test. Qualitative data was presented as a percentage and analyzed by Chi-square test or Fisher's exact test. Kaplan-Meier analysis was performed to compare outcomes for OSA and non-OSA patient groups and according to EDS status.

Cox proportional hazards regression analysis was used to assess whether OSA was an independent prognostic factor for the observed events, with stratification for EDS status. Adjustments were made in the multivariable models for confounders that were clinically related to the outcomes, or showed an association with these endpoints in univariate analysis. The first model was constructed without any adjustments, while age and sex were covariates in the second model. The third model included variables from the second model, as well as body mass index (BMI), history of hypertension, hyperlipidemia, diabetes, current smoking, prior stroke, prior MI, and the clinical presentation including acute MI versus UA. All analyses were conducted by using SPSS, version 26.0 (IBM SPSS, Armonk, New York, NY, USA).

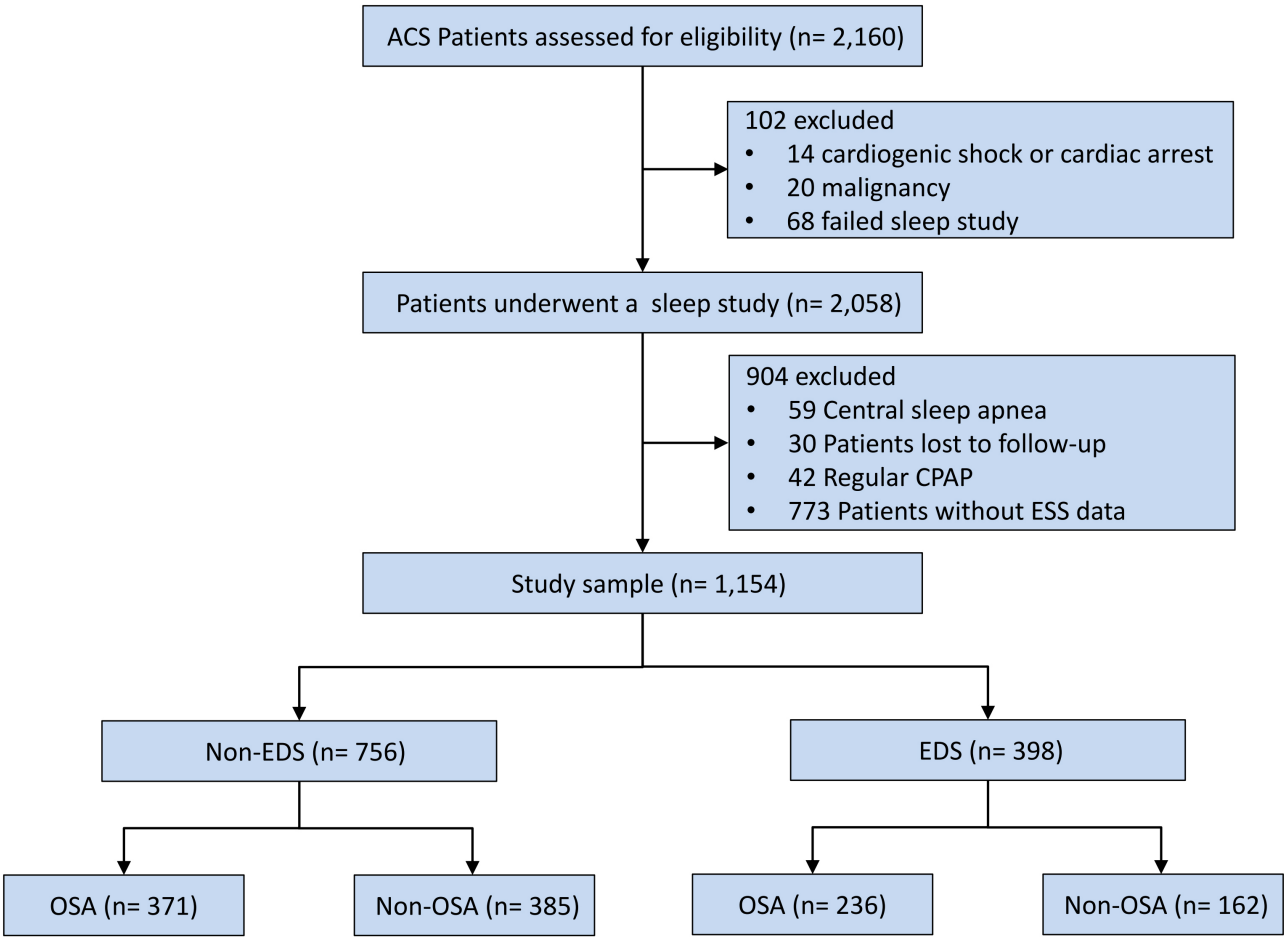

Fig. 1. Study flowchart. Abbreviations: ACS, acute coronary syndrome; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, epworth sleepiness scale; OSA, obstructive sleep apnea.

3. Results

3.1 Baseline and Clinical Characteristics

The final analysis included 1154 patients (Fig. 1), of which 398 subjects (34.5%) had EDS and 756 (65.5%) did not have EDS. The EDS group had a greater percentage of males compared to the non-EDS group. EDS patients exhibited higher measures of obesity (BMI, waist and hip circumferences, ratio of waist/hip, neck circumference) and OSA (AHI, oxygen desaturation index [ODI], time with SaO2 <90%, ESS), along with elevated levels of triglycerides (**Supplementary Table 1**). A total of 607 (52.6%) patients had OSA. OSA was more common in the EDS group than in the non-EDS group (59.3% vs. 49.1%).

The measures of obesity and high-sensitivity C-reactive protein (hs-CRP) levels were elevated in the OSA group, both for EDS and non-EDS patient groups. No other differences were found in EDS patients. In non-EDS patients, those with OSA had a greater prevalence of hypertension, prior percutaneous coronary intervention (PCI), current drinking, a higher level of triglyceride, higher proportion of PCI, and larger number of stents placed compared to those without OSA (Table 1). Additionally, there is no difference in the primary baseline data and outcomes (Log rank $p = 0.200$) between excluded patients (n = 773) and included patients (n = 1154) (**Supplementary Table 4**, **Supplementary Fig. 2**).

3.2 Outcomes for EDS and non-EDS Groups

MACCEs occurred in 223 patients during the median follow-up period of 2.9 years (interquartile range: 1.5–3.6), accounting for 19.3% of the total cohort. The incidence of MACCEs was not significantly different between patients who did or did not have EDS (adjusted hazard ratio (HR) = 1.16, 95% CI: 0.89–1.52, $p = 0.28$) (**Supplementary Fig. 1**). For the secondary endpoints, cardiovascular death was observed in 22 patients (1.9%), MI in 31 patients (2.7%), stroke in 24 patients (2.1%), ischemia-driven revascularization in 133 patients (11.5%), hospitalization for UA in 156 patients (13.5%), and hospitalization for HF in 7 patients (0.6%). For the other individual cardiovascular events, no significant differences were observed between EDS and non-EDS patients (**Supplementary Table 3**).

Table 1. Demographic and clinical characteristics in OSA versus non-OSA stratified by ESS categories.

Variables	ESS ≥10 (n = 398)			ESS <10 (n = 756)		
	OSA (n = 236)	Non-OSA (n = 162)	*p*-value	OSA (n = 371)	Non-OSA (n = 385)	*p*-value
Demographics						
Age, years	55.25 ± 10.60	56.1 ± 9.49	0.565	56.89 ± 11.14	56.66 ± 10.30	0.766
Male	210 (89)	141 (87)	0.555	316 (85.2)	302 (78.4)	0.017
BMI, kg/m^2	28.52 ± 3.35	26.15 ± 3.54	<0.001	27.72 ± 3.68	25.74 ± 3.40	<0.001
Waist circumference, cm	103.7 ± 10.22	96.77 ± 9.13	<0.001	101.81 ± 8.66	95.52 ± 8.7	<0.001
Neck circumference, cm	42.05 ± 3.50	40.31 ± 2.97	<0.001	41.04 ± 3.21	39.27 ± 3.40	<0.001
Hip circumference, cm	103.6 ± 7.39	99.81 ± 7.15	<0.001	102.35 ± 7.10	99.21 ± 6.57	<0.001
Waist/hip ratio	1.00 (0.96–1.03)	0.97 (0.94–1.01)	0.001	0.99 (0.95–1.02)	0.97 (0.93–1.00)	<0.001
Medical history						
Hypertension	158 (66.9)	103 (63.6)	0.487	252 (67.9)	224 (58.2)	0.006
Hyperlipidemia	73 (30.9)	60 (37)	0.205	120 (32.3)	114 (29.6)	0.416
Diabetes	76 (32.2)	55 (34)	0.716	107 (28.8)	107 (27.8)	0.949
Prior PCI	44 (18.6)	36 (23.5)	0.244	95 (25.6)	63 (16.4)	0.002
Prior stroke	31 (13.1)	18 (11.1)	0.546	40 (10.8)	38 (9.9)	0.680
Prior MI	32 (13.6)	31 (19.1)	0.134	72 (19.4)	60 (15.6)	0.166
Current smoking	119 (50.4)	78 (48.1)	0.656	176 (47.4)	157 (40.8)	0.065
Current drinking	84 (35.6)	55 (34)	0.736	130 (35)	108 (28.1)	0.039
Laboratory data						
Creatinine, μmol/L	74.7 (65.8–84.0)	73.3 (64.0–81.5)	0.222	73.7 (65.4–83.0)	70.8 (61.3–81.3)	0.019
Hs-CRP, mg/L	2.64 (1.16–8.14)	1.50 (0.51–5.56)	0.001	2.44 (0.87–6.79)	1.41 (0.62–4.13)	<0.001
LVEF, %	61 (56–65)	62 (56–66)	0.416	60 (55–65)	62 (58–65)	0.085
LDL-C, mmol/L	2.55 (2.01–3.09)	2.36 (1.81–3.24)	0.358	2.4 (1.88–3.01)	2.43 (1.85–3.12)	0.644
HDL-C, mmol/L	0.97 (0.86–1.11)	0.96 (0.85–1.16)	0.797	0.98 (0.84–1.14)	1.03 (0.88–1.22)	0.005
TC, mmol/L	4.26 (3.62–4.88)	4.01 (3.35–5.19)	0.422	4.05 (3.45–4.81)	4.13 (3.42–4.98)	0.246
TG, mmol/L	1.76 (1.26–2.40)	1.50 (1.15–2.32)	0.066	1.52 (1.12–2.14)	1.40 (1.04–2.02)	0.031
HbA1c, %	6.2 (5.6–7.4)	5.9 (5.5–6.9)	0.089	6.1 (5.6–7.0)	6.0 (5.6–6.8)	0.113
Systolic BP, mmHg	126 (119–138)	124 (112–135)	0.071	126 (117–139)	127 (118–139)	0.876
Diastolic BP, mmHg	76 (70–86)	75 (67–80)	0.045	77 (70–85)	75 (69–83)	0.079
Sleep information						
AHI, events per hr	33.45 (22.35–48.97)	7.95 (4.1–11.2)	<0.001	28.2 (20.1–41.6)	7.6 (4.2–10.3)	<0.001
ODI, events per hr	30.6 (21.7–46.9)	8.8 (5.0–12.0)	<0.001	26.5 (19–38.5)	8.25 (4.92–11.60)	<0.001
Minimum SaO2, %	82 (75–86)	87 (85–89)	<0.001	83 (77–86)	88 (85–90)	<0.001
Mean SaO2, %	94 (93–95)	93 (92–94)	<0.001	93 (92–94)	94.3 (93–95)	<0.001
Percentage of time with SaO2 <90%, %	8.0 (2.0–21.0)	1.0 (0.15–3.0)	<0.001	12.91 (2.0–17)	5.42 (0.10–3.15)	<0.001
Epworth Sleepiness Scale	13.43 ± 2.9	12.88 ± 2.6	0.06	5.09 ± 2.9	4.42 ± 2.8	0.002
Diagnosis			0.448			0.273
STEMI	60 (25.4)	38 (23.5)		85 (22.9)	70 (18.2)	
NSTEMI	52 (22)	29 (17.9)		67 (18.1)	73 (19.0)	
Unstable angina	124 (52.5)	95 (58.6)		219 (59.0)	242 (62.9)	
Non-obstructive CAD						
MINOCA	6/112 (5.4)	3/67 (4.5)	0.781	5/152 (3.3)	11/143 (7.7)	0.092
INOCA	12/124 (9.7)	9/95 (9.5)	0.963	19/219 (8.7)	19/242 (7.9)	0.775
Procedures						
Coronary angiography	228 (96.6)	157 (96.9)	0.867	366 (98.7)	375 (97.4)	0.218
PCI	137 (58.1)	83 (51.2)		211 (56.9)	187 (48.6)	
PTCA	21 (8.9)	13 (8.0)	0.449	31 (8.4)	35 (9.1)	0.164
CABG	12 (5.1)	15 (9.3)		23 (6.2)	36 (9.4)	
Multivessel disease	153 (64.8)	107 (66)	0.968	242 (65.2)	221 (57.4)	0.082
Number of stents	1 (0–1)	1 (0–1)	0.227	1 (0–2)	0 (0–1)	0.009

Table 1. Continued.

Variables	ESS ≥10 (n = 398)			ESS <10 (n = 756)		
	OSA (n = 236)	Non-OSA (n = 162)	*p*-value	OSA (n = 371)	Non-OSA (n = 385)	*p*-value
Medications on discharge						
Aspirin	229 (97.0)	154 (95.1)	0.310	361 (97.3)	377 (97.9)	0.578
$P2Y_{12}$ inhibitor	219 (92.8)	149 (92.0)	0.760	342 (92.2)	347 (90.1)	0.321
ACEI or ARB	153 (64.8)	95 (58.6)	0.211	236 (63.6)	216 (56.1)	0.035
CCB	56 (23.7)	30 (18.5)	0.215	80 (21.6)	67 (17.4)	0.148
β-blockers	185 (78.4)	124 (76.5)	0.664	298 (80.3)	286 (74.3)	0.048
Statins	234 (99.2)	157 (96.9)	0.095	363 (97.8)	381 (99.0)	0.219

Abbreviations: ACEI, angiotensin-converting enzymes inhibitor; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blockers; ESS, epworth sleepiness scale; HDL-C, high-density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; INOCA, ischemia with non-obstructive coronary artery disease [defined as angina with non-obstructive CAD (<50% diameter stenosis)]; LVEF, left ventricular ejection fractions; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary artery disease [defined as MI with non-obstructive CAD (<50% diameter stenosis)]; NSTEMI, non-ST-segment elevation myocardial infarction; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SaO2, arterial oxygen saturation; STEMI, ST-segment-elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; Data are presented as mean ± standard deviation, median (first quartile, third quartile), n (%).

3.3 Outcomes for OSA and Non-OSA Groups Stratified According to EDS Status

We next categorized EDS patients into those with or without OSA, and non-EDS patients into those with or without OSA. For EDS patients, no significant difference in MACCEs was found between OSA and non-OSA groups (HR = 1.12, 95% CI: 0.72–1.72, $p = 0.63$). Moreover, the outcomes did not change after adjusting for clinical confounders (adjusted HR = 1.05, 95% CI: 0.67–1.66, $p = 0.84$). Similarly, in patients with EDS, no significant differences were found between OSA and non-OSA groups for any secondary endpoint. For patients without EDS, a significantly higher risk of MACCEs was observed in OSA patients compared to non-OSA patients (HR = 1.57, 95% CI: 1.12–2.20, $p = 0.008$). Following adjustment for clinical confounders, multivariable analysis revealed OSA was an independent predictor for MACCEs in patients without EDS (adjusted HR = 1.42, 95% CI: 1.01–2.02, $p = 0.046$). No significant interactions between EDS and OSA were observed for MACCEs (interaction $p = 0.23$). Notably, in patients without EDS, a difference in hospitalization for unstable angina was observed in model 1 (HR = 1.32, 95% CI: 0.99–2.22, $p = 0.05$). However, this difference was not significant in model 2 and model 3. No differences were observed in other secondary endpoints (Table 2, Fig. 2).

Finally, we performed sensitivity analysis to assess stability of the effect on the primary endpoint in patients without EDS. The observed association between OSA and MACCE showed no influence from confounding factors (Table 3).

4. Discussion

For ACS patients without EDS, OSA was found to be associated with subsequent adverse cardiovascular events. However, this association was not observed for patients with EDS. Additionally, subgroup analyses revealed no differences in the non-EDS OSA group, indicating that OSA was a key predictor of MACCEs in patients with no EDS. These results advance our understanding in this field, as previous research suggested that EDS was associated with poor prognosis. Furthermore, our findings suggest that more attention should be given to OSA patients without EDS, as they may have an elevated risk of adverse events that has been overlooked in the past.

An earlier study indicated that EDS was associated with a higher incidence of MACE during a 4-year follow-up period in post-MI patients with moderate to severe OSA [13]. This relationship has been consistently observed in a wider cohort, including non-MI patients [25–27]. It suggests there may be an underlying pathophysiological mechanism that connects sleep disorder with cardiovascular risks, such as intermittent hypoxia, systemic inflammation, and other metabolic disorders [28]. However, some studies have reported different findings. Longitudinal analysis of participants in the Nurses' Health Study II found that daytime sleepiness was not independently associated with the risk of cardiovascular disease [29]. Another recent study based on the UK Biobank database revealed that EDS was not a significant risk factor for incident MI or stroke, regardless of sleep duration [30]. The focus of our study was patients with established ACS. An increased risk of subsequent MACCEs was observed in OSA patients with no

Table 2. Cox regression analysis for clinical outcomes in OSA versus non-OSA stratified by ESS.

Variables	ESS ≥10 (n = 398)		ESS <10 (n = 756)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MACCE				
Model 1	1.12 (0.72–1.72)	0.63	1.57 (1.12–2.20)	0.008
Model 2	1.13 (0.73–1.75)	0.60	1.52 (1.09–2.14)	0.015
Model 3	1.05 (0.67–1.66)	0.84	1.42 (1.01–2.02)	0.046
Cardiovascular death				
Model 1	0.87 (0.23–3.24)	0.84	1.72 (0.56–5.24)	0.34
Model 2	0.90 (0.24–3.35)	0.87	1.62 (0.53–4.97)	0.40
Model 3	0.71 (0.19–2.70)	0.62	1.68 (0.53–5.31)	0.38
Myocardial infarction				
Model 1	0.89 (0.27–2.91)	0.85	2.08 (0.84–5.15)	0.12
Model 2	0.89 (0.27–2.93)	0.85	1.87 (0.75–4.67)	0.18
Model 3	0.91 (0.26–3.20)	0.89	1.43 (0.56–3.67)	0.45
Stroke				
Model 1	0.86 (0.26–2.83)	0.81	0.92 (0.31–2.73)	0.88
Model 2	0.88 (0.27–2.88)	0.83	0.90 (0.30–2.69)	0.85
Model 3	0.94 (0.27–3.25)	0.93	0.84 (0.27–2.58)	0.76
Ischemia-driven revascularization				
Model 1	1.30 (0.64–2.65)	0.47	1.32 (0.79–2.22)	0.29
Model 2	1.32 (0.65–2.70)	0.44	1.26 (0.75–2.11)	0.39
Model 3	1.20 (0.57–2.52)	0.64	1.13 (0.66–1.93)	0.66
Hospitalization for unstable angina				
Model 1	1.22 (0.71–2.09)	0.48	1.47 (0.99–2.18)	0.05
Model 2	1.23 (0.72–2.11)	0.45	1.43 (0.96–2.13)	0.08
Model 3	1.13 (0.64–1.99)	0.67	1.37 (0.91–2.06)	0.14
Hospitalization for heart failure				
Model 1	0.75 (0.05–12.1)	0.84	1.58 (0.27–9.48)	0.61
Model 2	0.68 (0.04–11.3)	0.79	1.38 (0.23–8.25)	0.73
Model 3	0.23 (0.01–5.67)	0.37	1.18 (0.19–7.51)	0.86

Abbreviations: CI, confidence interval; ESS, epworth sleepiness scale; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event. Model 1: Unadjusted model; Model 2: Adjusted for age, sex; Model 3: Adjusted for age, sex, body mass index, current smoking, history of hypertension, diabetes, dyslipidemia, prior myocardial infarction, prior stroke, and clinical presentation (acute myocardial infarction vs unstable angina).

EDS, but not in those with EDS. However, the small size of each group and low frequency of events reduced the statistical power of the study. Hence, caution is required in interpreting the results, and additional trials with large cohorts are needed to validate our results.

To minimize the potential bias, patients with regular CPAP were excluded from this analysis. However, from an ethical perspective, OSA patients with severe daytime sleepiness should be treated with CPAP. Notably, previous randomized controlled trials on patients with cardiovascular disease did not demonstrate a benefit from CPAP on the incidence of cardiovascular events [31,32]. Post hoc analysis indicated that patients who adhered to CPAP therapy (≥4 h per night) had better outcomes than those who did not receive CPAP, or who used it for <4 h per night [33]. Our findings highlight that OSA patients have an increased cardiovascular risk, even without EDS. Therefore, intervention for OSA should not be completely neglected with this phenotype. It may not be appropriate to completely reject any intervention for OSA patients without EDS. Nevertheless, the challenge of maintaining CPAP adherence and the potential impact of patient characteristics on treatment outcomes should not be ignored. Indeed, CPAP is not the only intervention option for OSA. Given the emphasis on the heterogeneity of OSA and baseline characteristics, improving the 'personalization' of OSA therapy and identifying high-risk indications for potential benefit may be the best option. Weight loss regimen in concert with CPAP therapy reduced

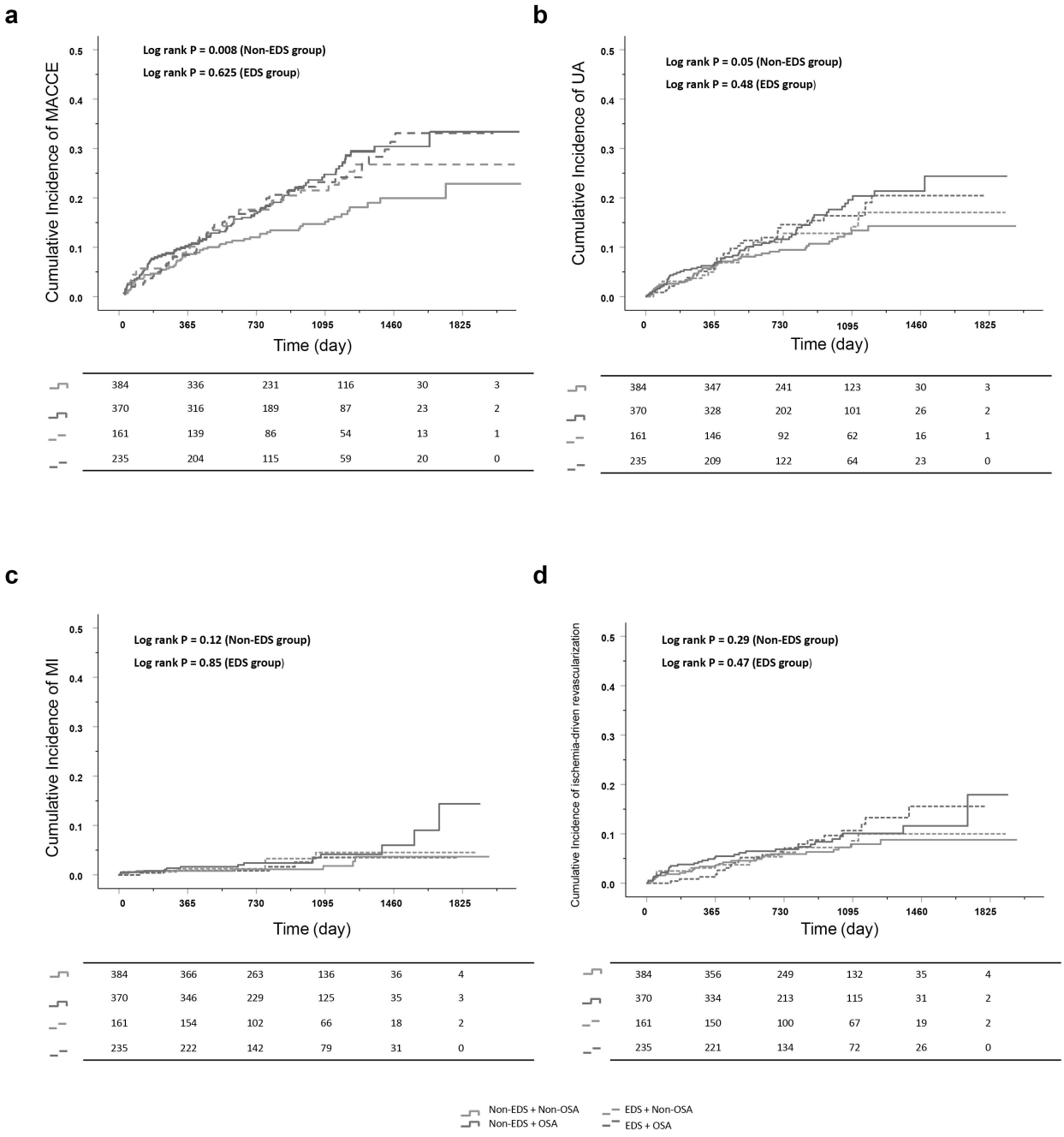

Fig. 2. Kaplan-Meier curves in OSA vs non-OSA groups stratified by EDS categories. (a) MACCE, (b) hospitalization for unstable angina, (c) myocardial infarction, and (d) ischemia-driven revascularization. Abbreviations: MACCE, major adverse cardiovascular and cerebrovascular event; EDS, Excessive daytime sleepiness; MI, myocardial infarction; OSA, obstructive sleep apnea; UA, unstable angina.

cardiovascular risk factor compared with either intervention alone [34]. Beneficial effects on blood pressure have also been shown with the use of devices for mandibular advancement [35].

Potential associations between OSA and clinical outcomes in patients without EDS may be better understood by analyzing the unique characteristics of OSA symptoms, pathophysiological mechanisms, and their consequences. Exploring endocrine dysfunction, inflammation, sympathetic hyperactivity, and oxidative stress in sleep-deprived individuals may clarify the mechanisms linking non-EDS and cardiovascular outcomes in ACS patients. EDS is closely associated with established factors for cardiovascular risk, including obesity, uncontrolled hypertension, diabetes, and a sedentary lifestyle [36,37]. Notably, while our findings indicated that OSA had a more pronounced impact

Table 3. Sensitivity analysis of MACCE in OSA vs. Non-OSA in patients without EDS.

Subgroups	HR (95% CI)	*p*-value	*p*-value for interaction
Old age			0.257
Yes	2.199 (1.108–4.363)	0.024	
No	1.389 (0.939–2.055)	0.100	
Sex			0.897
Male	1.522 (1.053–2.201)	0.026	
Female	1.675 (0.709–3.956)	0.239	
Obesity			0.448
Yes	1.931 (0.982–3.797)	0.057	
No	1.408 (0.936–2.12)	0.101	
Diabetes			0.120
Yes	2.297 (1.282–4.116)	0.005	
No	1.287 (0.846–1.957)	0.239	
Dyslipidemia			0.306
Yes	2.123 (1.116–4.036)	0.022	
No	1.393 (0.934–2.079)	0.104	
Hypertension			0.714
Yes	1.621 (1.069–2.459)	0.023	
No	1.402 (0.781–2.516)	0.257	
Diagnosis			0.743
STEMI	1.568 (0.793–3.098)	0.196	
NSTEMI	1.145 (0.566–2.320)	0.706	
UA	1.765 (1.102–2.828)	0.018	

Abbreviations: HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina. Data are presented as median (first quartile, third quartile).

on the prognosis of non-sleepy patients compared to those of sleepy patients, EDS per se still had an adverse trend (although not statistically significant) on the prognosis. This observation aligns with the study focused on the symptom subtypes, which reported that patients with the excessively sleepy subtype were at increased risk of cardiovascular disease compared to patients with minimally or moderately sleepy [27].

OSA correlates with a higher prevalence of hypertension, HF, diabetes, and atrial fibrillation. Even in patients without EDS, those with OSA tend to have a poor prognosis. The obstructive respiratory episodes characteristic of OSA may induce circadian dysregulation, primarily mediated by sleep disorder and intermittent hypoxia. This disruption triggers inflammatory responses and disturbs neural and hormonal balance, ultimately leading to dysregulation of the molecular circadian clock and associated biological pathways [38]. Prolonged exposure to hypoxia is implicated in the development of disorders commonly associated with circadian rhythm disturbances, including cardiovascular and respiratory diseases, dementia, cancer, and metabolic disorders [39,40]. Several studies have also demonstrated that OSA patients exhibit significantly higher sympathetic nerve activity in postganglionic muscles during wakefulness and normal breathing patterns [41,42]. Additionally, patients with OSA have increased basal sympathetic tone during wakefulness, and experience acute cyclical sympathetic excitation during sleep [43]. We hypothesize that sympathetic excitation in OSA patients without EDS may further contribute to poor prognosis. Additional research is needed to investigate such mechanisms.

The present study has a number of limitations. Firstly, Type III portable polygraphy was used to diagnose OSA. This could underestimate the severity of OSA, as the total sleep time cannot be calculated accurately. Nevertheless, portable polygraphy is a viable alternative to polysomnography for diagnosing OSA [44]. Second, OSA severity in the acute setting of ACS may have been overestimated [45]. To minimize this potential bias, clinical stabilization was achieved prior to conducting the sleep study during hospitalization. Third, because of its subjectivity the assessment of daytime sleepiness was limited to a one-time questionnaire. Daytime sleepiness is variable and may not be accurately captured by a single measurement. Fourth, about 40% of patients were excluded due to unavailable ESS, which may lead to selection bias. But there was no difference in the primary baseline data and outcomes between excluded patients and included patients, which may allay some of the concerns of selection bias. Fifth, our study was that the majority of participants were of Asian population. This demographic characteristic may limit the generalizability of our findings to other ethnic populations. Sixth, this cohort showed a high proportion of UA and a low proportion of revascularization, suggesting that enrolled ACS patients were relatively at lower risk. This may introduce a potential bias and the results need to be further validated in high-risk populations.

5. Conclusions

A higher risk of MACCEs was observed in ACS patients with OSA but with no EDS. This finding highlights the necessity for comprehensive OSA screening of all ACS patients, regardless of their EDS status. Moreover, this study also underlines the importance of intervention in OSA patients without EDS.

Abbreviations

ACEI, angiotensin-converting enzymes inhibitor; ACS, acute coronary syndrome; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blockers; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HR, hazard ratio; Hs-CRP, high-sensitivity C-reactive protein; INOCA, ischemia with non-obstructive coronary artery

disease [defined as angina with non-obstructive CAD (<50% diameter stenosis)]; LVEF, left ventricular ejection fractions; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary artery disease [defined as MI with non-obstructive CAD (<50% diameter stenosis)]; NSTEMI, non-ST-segment elevation myocardial infarction; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SaO2, oxygen saturation; STEMI, ST-segment-elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; UA, unstable angina.

Availability of Data and Materials

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

Author Contributions

Study concept and design: XW, SPN, YYQ and ZXL. Acquisition, analysis, or interpretation of data: WH, XCL, QG, YYG, BQ, WG, WZ. Drafting of the manuscript: YYQ and WH. Critical revision of the manuscript for important intellectual content: All authors. Obtained funding: XW, SPN, WH. Administrative, technical, or material support: BQ, WG, WZ,LX. XW, SPN, YYQ, ZXL, WH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The research protocol was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (Ethic Approval Number: 2013025). All of the participants provided signed informed consent.

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Conflict of Interest

Dr. Shaoping Nie: research grants to the institution from Boston Scientific, Abbott, Jiangsu Hengrui Pharmaceuticals, China Resources Sanjiu Medical & Pharmaceuticals, East China Pharmaceuticals. The rest of the authors have no relevant relationships to disclose.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM33439.

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