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Long-term mortality risk in obstructive sleep apnea: the critical role of oxygen desaturation index

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Abstract

Background Mortality predictors in obstructive sleep apnea (OSA) patients yet to be comprehensively understood, especially within large cohorts undergoing long-term follow-up. We aimed to determine the independent predictors of mortality in OSA patients.

Methods In our retrospective cohort study, 3,541 patients were included and survival data was obtained from electronic medical records. Demographic characteristics, anthropometric measurements, comorbidities, laboratory tests, and polysomnography parameters were analyzed for the survived and deceased patient groups. Univariate and multivariate Cox regression analyses were performed to determine independent predictors of all-cause mortality in patients followed for at least 5 years.

Results Among all patients, 2,551 (72%) patients were male, with a mean age of 49.7 years. 231 (6.5%) patients had died. Deceased patients were significantly older and had higher waist-to-hip ratio and Epworth Sleepiness Scale ($p < 0.001$, $p < 0.001$, $p = 0.003$). OSA (nonpositional and not-rapid eye movement-related), periodic limb movements in sleep and Comorbidities of Sleep Apnea Score ≥ 1 were found to be associated with increased mortality ($p < 0.001$). Systemic immune-inflammation index was also significantly higher in the deceased group ($p < 0.001$). Higher oxygen desaturation index (ODI) and apnea-hypopnea index (AHI) were associated with increased mortality ($p < 0.001$). Due to the high correlation between ODI and AHI, two separate multivariate Cox regression models were created. While AHI lost its significance in the multivariate analysis, ODI remained significantly higher in the deceased patient group (HR = 1.007, 1.001–1.013, $p = 0.01$).

Conclusion ODI, as the only polysomnography parameter, emerged as an independent predictor of mortality in OSA patients.

Keywords Obstructive sleep apnea · Mortality predictors · ODI · AHI

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Introduction

Obstructive Sleep Apnea (OSA) is characterized as a disorder marked by recurrent apnea or hypopnea episodes, often accompanied by reduced blood oxygen saturation, despite ongoing respiratory efforts during sleep [1]. Epidemiological studies indicate that the prevalence of OSA varies between 2% and 26%, influenced by factors such as gender, diagnostic criteria, and the demographic characteristics of the study population [2]. OSA is associated with numerous severe health complications including atherosclerosis, coronary artery disease, cardiac arrhythmias, acute coronary syndromes which may result in nocturnal sudden death, heart failure, systemic and pulmonary hypertension, cerebrovascular disease, type 2 diabetes mellitus, and end-stage renal disease [3]. Although methodological limitations exist in researches exploring the mortality impact of OSA, the evidence tends to support an elevated risk of mortality. Age [4, 5], body mass index (BMI) [5], and comorbidities [6] are particularly noteworthy as potential predictors of mortality.

The apnea-hypopnea index (AHI) has traditionally served as a key measure for assessing the severity of OSA. However, chronic intermittent hypoxia plays a crucial role in promoting the adverse outcomes associated with OSA, thereby indicating the insufficiency of AHI in fully capturing the extent of hypoxia. This understanding has resulted in a greater focus on using desaturation parameters to better evaluate chronic intermittent hypoxia. It has been documented that desaturation episodes cause systemic inflammation and play a significant role in the onset of cardiovascular and metabolic dysfunctions. Parameters such as minimum peripheral oxygen saturation (SpO_2), mean SpO_2, time spent with oxygen saturation below 90% (T90), and the oxygen desaturation index (ODI) have been critically examined in the literature as effective measures of desaturation [7–9]. However, these studies encountered several limitations. These include categorizing desaturation parameters, incomplete analysis of all desaturation parameters, variations in sleep scoring and recording systems across multiple centers, and insufficient representation of different OSA severity groups, genders, and age groups. These limitations highlight the need for broader analyses, including AHI, desaturation, and other mortality-linked factors in polisomnography (PSG) parameters.

In this study, we aimed to determine the independent predictors of mortality over a long follow-up period with a large cohort, considering all potential predictors as much as possible in addition to AHI and desaturation parameters to evaluate their role in predicting mortality in OSA patients.

Materials and methods

Study design and setting

This retrospective cohort study was conducted at our institution, a prominent referral center for the diagnosis and follow-up of sleep disorders. Our sleep center is part of a training and research hospital with national accreditation. The scoring of sleep studies was conducted by two physicians who are nationally board-certified in sleep medicine, demonstrating high interobserver reliability. We assessed the data of patients who underwent PSG from January 2012 to January 2018.

Our study was conducted in line with the Declaration of Helsinki. The local institutional ethics committee approved the study protocol (Ethics approval number: 2022 – 243) and the requirement for written informed consent was waived by our ethics committee.

Study population

Patients who underwent Type 1 PSG from January 2012 to January 2018 were included in the study, ensuring a minimum 5-year follow-up. Exclusions were made for those with central sleep apnea on the diagnostic study ($n = 14$), sleep-related hypoventilation ($n = 104$), simple snoring ($n = 350$), and missing PSG data ($n = 23$) (Fig. 1).

Data collection

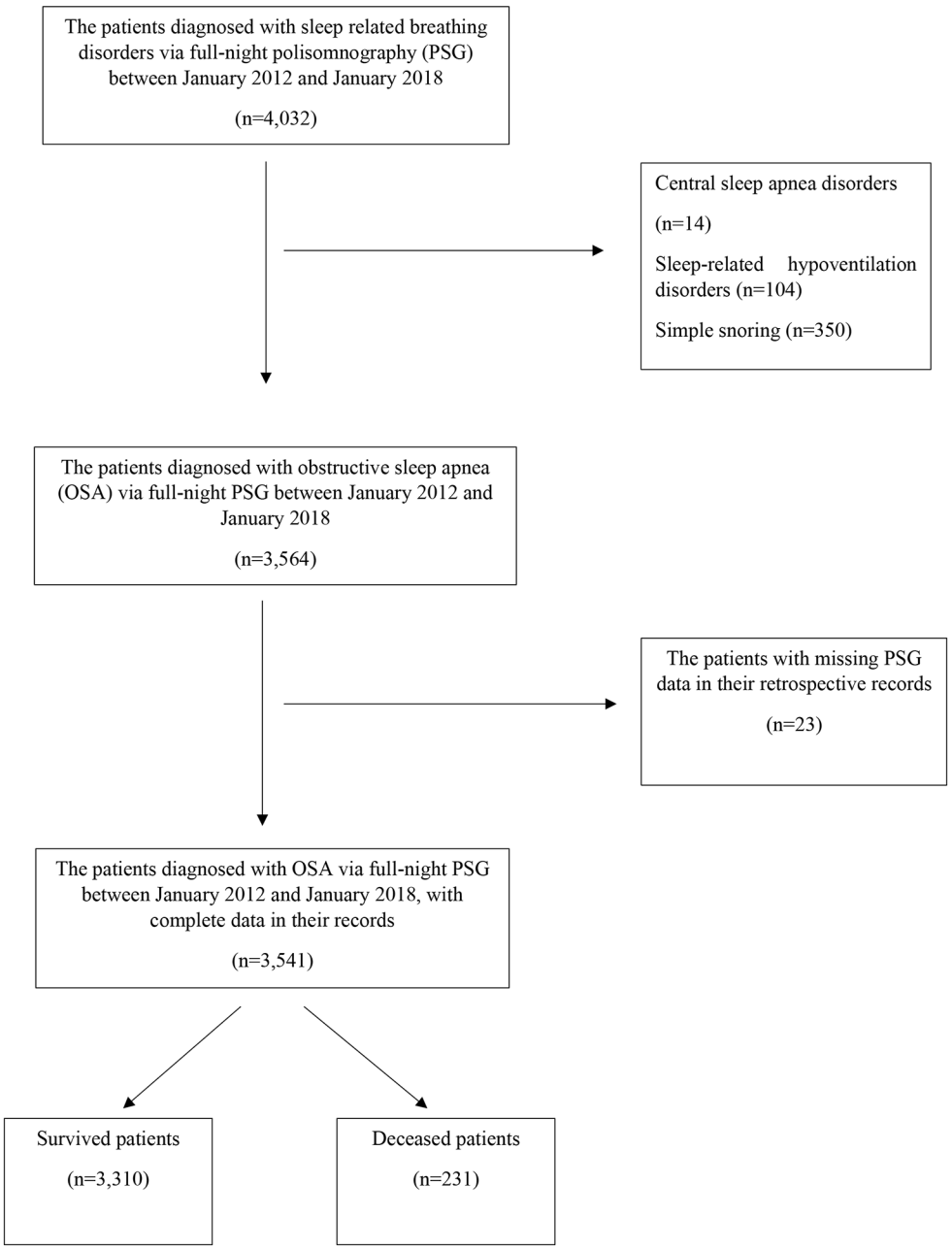
The study recorded demographic characteristics, comorbidities and anthropometric measurements. The Epworth Sleepiness Scale (ESS) was assessed and documented before PSG. On the morning following the diagnostic PSG, as part of a routine procedure, laboratory tests including hemogram, biochemistry profile, thyroid function tests, hemoglobin a1c (Hba1c), cholesterol, triglycerides, and high-density lipoprotein (HDL) levels, which were derived from venous blood samples were conducted. Monocyte/HDL ratio, Neutrophil/Lymphocyte ratio, and Systemic Immune-Inflammatory Index (SII) were calculated. The SII was calculated as follows: SII = Platelet count × (Neutrophil count/Lymphocyte count). Survival data for patients were gathered from the National Death Notification System.

The primary outcome was all-cause mortality, defined as any documented death occurring during the follow-up period.

Measurements

OSA was defined as an AHI ≥ 5. Based on the detailed analysis of patients' PSG reports, the subtypes of OSA

Fig. 1 Flow chart



were categorized according to AASM rules [1]. Positional obstructive sleep apnoea (POSA) was defined as a supine AHI twice or more compared to the AHI in other positions, with the AHI in those positions being < 5 per hour. Rapid eye movement (REM)-related OSA was defined as REM-AHI being twice or more the nonREM AHI, with the AHI in the nonREM stage being < 5 per hour. Patients who met the criteria for both REM and positional OSA were categorized as having REM-related and positional OSA. When the AHI in any particular position or sleep stage did not exceed twice that of the others, it was defined as OSA (nonpositional and not-REM-related). Sleep movement disorders encompassed periodic limb movements in sleep (PLMS) and restless legs syndrome. PLMS were defined if a series of at least four movements with amplitude ≥ 8 uV occurs in a row, lasting 0.5–10 s in duration and recurs every 5–90 s. The Periodic Limb Movement Index (PLMI), which assesses the frequency of PLMS, is the number of PLMSs per hour of total sleep time. PLMS is diagnosed when the frequency of limb movements over than 15/h. The diagnosis of Restless Legs Syndrome was based on the International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria [10].

Polysomnography

Prior to arriving at the sleep laboratory, patients were advised to refrain from daytime sleeping and to avoid consuming caffeinated food and beverages, alcohol, and medications (such as hypnotics and antihistamines) that could affect sleep patterns. Patients were admitted to the sleep laboratory at 09:00 pm to allow time to acclimatize to the environment and their rooms, to receive information about the procedure, and to undergo pre-sleep questioning. The polysomnographic examinations were conducted by trained and experienced sleep technicians. Full-night PSG was conducted using the Embla A-10 system (Embla, Medcare Flaga, Reykjavik, Iceland) for data acquisition and analysis. Physiological parameters were recorded through electroencephalography, electrooculography, electromyography, respiratory inductive plethysmography, piezoelectric sensors, nasal pressure cannula (Medcare Flaga), pulse oximetry, and electrocardiography (lead II). Two experienced pulmonologists scored the sleep stages, arousals, and respiratory events using the Somnologica Studio software (Medcare Flaga), adhering to the guidelines of the American Academy of Sleep Medicine scoring manual [11], demonstrating high interobserver reliability. Apnea was defined by a reduction in airflow of at least 90% from baseline for a duration of 10 s or more, while hypopneas were defined as a reduction in airflow of 30% or more for at least 10 s, accompanied by either an arousal or a 3% or greater drop in oxygen saturation. AHI was calculated by dividing the total number of apneas and hypopneas by the total hours of sleep. Similarly, ODI was calculated by dividing the number of oxygen desaturations ($\geq 3\%$) by the total sleep hours.

Treatment

Patients with an AHI ≥ 5 on diagnostic PSG overnight reports and with symptoms of excessive daytime sleepiness, snoring or diagnosed apnea, or with cardiovascular or metabolic comorbidities, or with an AHI ≥ 15 even if they did not describe symptoms, were titrated with appropriate positive airway pressure (PAP) therapy under supervision of a sleep techinician in a second night of polysomnography.

Data analysis and statistical methods

The study data were analyzed using IBM SPSS Statistics 29.0. Patients were categorized into survived and deceased groups for comparison. Continuous data were presented as mean $\pm$ standard deviation (SD) and categorical data as number and percentage. Univariate Cox regression analysis identified factors affecting mortality. Multivariate Cox regression analysis included only one of highly correlated variables ($r > 0.7$) to avoid multicollinearity. Two models were constructed based on significant parameters: the AHI model and the ODI model, analyzed separately due to high correlation. Statistical significance was set at $p < 0.05$.

Results

The study included 3,541 patients with a mean age of 49.7 ± 10.7 years, of which 72% were male. 231 patients (6.5%) died during the study, with a higher mean age in deceased patients compared to survivors (58.9 vs. 49.0 years). Among participants, 61% were diagnosed with nonpositional and not-REM-related OSA, while 39% had other subtypes. Deceased patients showed a higher prevalence of OSA (80.1% vs. 59.7%). PLMS were observed in 11.6% of patients. 51.2% had comorbidities, with a higher rate in deceased patients (76.2% vs. 49.4%). The mean BMI was 32.6 ± 5.9 kg/m2, waist/hip raito (WHR) was 0.97 ± 0.07, and body adiposity index (BAI) was 31.5 ± 7.1 cm/m2. Other anthropometric measurements were higher in deceased patients. The mean ESS score was 9.4 ± 5.0, with a higher score in deceased patients (10 vs. 9). CoSA score was 1.5 ± 1.9 and higher in deceased patients (3 vs. 1) (Table 1).

The mean sleep efficiency was 81.7%, the mean AHI was 33 events per hour, the mean ODI was 30.5 events per hour, mean T90 was 45.9 min, and the mean number of PLMS was 46.3 per hour. All polysomnographic parameters are presented in Table 2.

Univariate Cox regression analysis identified predictors of mortality. Factors such as advanced age, increased neck, waist, hip circumference, BMI, WHR, and BAI were associated with higher mortality rates ($p < 0.001$). OSA (nonpositional and not-REM-related), sleep movement disorder, PLMS, CoSA ≥ 1, smoking pack-years increase, and elevated ESS score also correlated with increased mortality ($p < 0.001$ for each). Laboratory test results showed associations between higher creatinine, HbA1c, T4, neutrophil/lymphocyte ratio, SII, decreased hemoglobin, and increased mortality ($p < 0.001$ for each). Furthermore, an elevated monocyte/HDL ratio was linked to increased mortality ($p = 0.01$). PSG parameters including total AHI, supine AHI, nonsupine AHI, REM AHI, nonREM AHI, low mean SpO2, low minimum SpO2, prolonged T90 duration, and ODI were also indicators of increased mortality risk ($p < 0.001$ for each). Effect sizes and confidence intervals are presented in Table 3.

As a result of univariate Cox regression analysis, ODI was included in the multivariate models due to having the highest HR among the oxygenation parameters. Separate models were created for these two parameters because of the high correlation between AHI and ODI ($r = 0.9$, $p < 0.001$).

Table 1 Characteristics, anthropometric measurements, comorbidities and laboratory tests findings of all patients and patients who deceased/survived

Variable; mean ± SD, *n*/(%)	All patients (*n* = 3541)	Survived patients (*n* = 3310)	Deceased patients (*n* = 231)
Demographic Parameters			
Age (years)	49.7 ± 10.7	49.09 ± 10.53	58.9 ± 10.11
Male gender	2,551 (72.0)	2,377 (71.8)	174 (75.3)
Subtype of OSA			
OSA (Nonpositional and not-REM-related)	2,160 (61)	1,975 (59.7)	185 (80.1)
Positional OSA	989 (27.9)	959 (29)	30 (13)
REM-related OSA	375 (10.6)	359 (10.8)	16 (6.9)
REM + Positional OSA	17 (0.5)	17 (0.5)	0 (0)
Sleep Related Movement Disorders	560 (15.8)	496 (15)	64 (27.7)
PLMS	409 (11.6)	359 (10.8)	50 (21.6)
Restless Legs Syndrome	210 (5.9)	192 (5.8)	18 (7.8)
Anthropometric Measurements			
Height (cm)	1.68 ± 0.09	1.68 ± 0.09	1.67 ± 0.09
Weight (kg)	92.4 ± 16.6	92.03 ± 16.46	98.22 ± 18.08
Neck circumference (cm)	38.9 ± 4.0	38.81 ± 3.99	40.89 ± 4.34
Waist circumference (cm)	104.8 ± 12.4	104.35 ± 12.16	112.66 ± 13.6
Hip circumference (cm)	107.5 ± 10.6	107.33 ± 10.35	110.91 ± 13.51
BMI (kg/m^2)	32.6 ± 5.9	32.44 ± 5.82	35.39 ± 7.06
WHR	0.97 ± 0.07	0.97 ± 0.07	1.01 ± 0.08
BAI (cm/m^2)	31.5 ± 7.1	31.35 ± 6.99	33.82 ± 9.07
Comorbidity			
At least one comorbidity	1,812 (51.2)	1,636 (49.4)	176 (76.2)
Diabetes Mellitus	721 (20.4)	636 (19.2)	85 (36.8)
Hypertension	1200 (33.9)	1061 (32.1)	139 (60.2)
Heart failure	238 (6.7)	191 (5.8)	47 (20.3)
Ischemic heart disease	259 (7.3)	217 (6.6)	42 (18.2)
Hyperlipidemia	170 (4.8)	159 (4.8)	11 (4.8)
COPD	260 (7.3)	195 (5.9)	65 (28.1)
Hypothyroidism	157 (4.4)	147 (4.4)	10 (4.3)
Hyperthyroidism	19 (0.5)	18 (0.5)	1 (0.4)
Psychiatric illness	250 (7.1)	233 (7)	17 (7.4)
Cerebrovascular disease	40 (1.1)	32 (1)	8 (3.5)
Malignancy	187 (5.3)	171 (5.2)	16 (6.9)
Dementia	8 (0.2)	5 (0.2)	3 (1.3)
End-stage renal failure	31 (0.9)	24 (0.7)	7 (3)
ESS	9.4 ± 5.0	9.4 ± 5	10.43 ± 5.54
COSA score	1.50 ± 1.96	1.38 ± 1.86	3.21 ± 2.51
COSA classification			
0	1,791 (50.6)	1,745 (52.7)	46 (19.9)
1–3	1,320 (37.3)	1,217 (36.8)	103 (44.6)
4–6	349 (9.9)	293 (8.9)	56 (24.2)
>6	81 (2.3)	55 (1.7)	26 (11.3)
Smoking Status			
Smoking (pack-years)	12.5 ± 14.1	12.2 ± 13.6	18 ± 18.7
Active smoker	1,209 (34.1)	1,151 (34.8)	58 (25.1)
Non smoker	1,400 (39.5)	1,310 (39.6)	90 (39)
Quite smoking	932 (26.3)	849 (25.6)	83 (35.9)
Alcohol History			
Alcohol drinkers	273 (7.7)	248 (7.5)	25 (10.8)
Non-alcohol drinkers	3,228 (91.2)	3,025 (91.4)	203 (87.9)
Social drinker of alcohol	40 (1.1)	37 (1.1)	3 (1.3)

Table 1 (continued)

Variable; mean ± SD, *n*/(%)	All patients (*n* = 3541)	Survived patients (*n* = 3310)	Deceased patients (*n* = 231)
Laboratory Tests			
Creatinine (mg/dl)	0.85 ± 0.39	0.84 ± 0.32	1.02 ± 0.88
Total Cholesterol (mg/dl)	213.9 ± 44.3	214.3 ± 43.75	209.51 ± 52.06
Hba1c (%)	5.7 ± 0.98	5.66 ± 0.78	7.70 ± 2.47
Hemoglobin (g/dL)	14.6 ± 1.5	14.65 ± 1.48	14.09 ± 1.68
T4 (ng/dl)	0.83 ± 0.1	0.83 ± 0.14	0.87 ± 0.19
TSH (miu/L)	2.14 ± 4.1	2.16 ± 4.22	1.9 ± 1.73
Neutrophils/Lymphocytes	1.77 ± 0.89	1.74 ± 0.87	2.12 ± 1.12
Monosit/HDL Ratio	0.014 ± 0.006	0.014 ± 0.005	0.015 ± 0.006
SII	450.97 ± 243.20	445.10 ± 233.07	536.16 ± 349.33

*Continuous variables are presented as mean ± SD. Categorical data are presented as numbers (percentage). Abbreviations: OSA: Obstructive sleep apnea, REM: Rapid eye movements, PLMS: Periodic limb movements of sleep, BMI: Body mass index, WHR: Waist/hip ratio, BAI: Body adiposity index, COPD: Chronic obstructive pulmonary disease, ESS: Epworth Sleepiness Scale, CoSA: Comorbidities of Sleep Apnea, Hba1c: Hemoglobin a1c, TSH: Thyroid stimulating hormone, HDL: High-density lipoprotein, SII: Systemic immune-inflammation index

In the first model, AHI, OSA (nonpositional and not-REM-related), presence of chronic obstructive pulmonary disease (COPD), presence of PLMS, age, gender, WHR, ESS, CoSA ≥ 1, SII, monocyte/HDL ratio were included and multivariate Cox regression analysis was applied. In model 1; presence of PLMS (HR = 1.41; 1.01–1.97), presence of COPD (HR = 1.99; 1.43–2.76), advanced age (HR = 1.07; 1.05–1.09), higher WHR (HR = 1.25; 1.05–1.50), CoSA ≥ 1 (HR = 1.58; 1.06–2.3), and higher SII (HR = 1.05; 1.01–1.10) were independent predictors of mortality (Table 4).

In the second model, the following parameters were included: OSA (nonpositional and not-REM-related), presence of COPD, presence of PLMS, age, gender, WHR, ESS, CoSA ≥ 1, SII, and monocyte/HDL ratio. Multivariate Cox regression analysis was then applied. In model 2, presence of COPD (HR = 1.96;1.41–2.73), presence of PLMS (HR = 1.39;1.00-1.93), advanced age (HR = 1.07;1.06–1.09), higher WHR (HR = 1.24;1.04–1.47), CoSA ≥ 1 (HR = 1.55;1.04–2.31), higher SII (HR = 1.05;1.01–1.10), and higher ODI (HR = 1.007;1.01–1.01) were found to be independent predictors of mortality (Table 5).

Discussion

In our study evaluating demographic data, anthropometric measurements, laboratory tests, and PSG parameters in OSA patients, ODI emerged as an independent predictor of mortality, whereas AHI did not. Other independent mortality predictors included age, WHR, CoSA score, presence of COPD, presence of PLMS, and SII.

In a large cohort, age emerged as an independent predictor of mortality [5]. In this study, there is a potential for sampling bias as patients with more severe sleep apnea might be directed to formal sleep laboratories rather than home testing. Over a 10-year follow-up period with more than 25,000 OSA patients, mortality increased with age [12]. However, important confounding factors such as anthropometric measurements, PSG parameters, and cardiovascular comorbidities were not analyzed.

Obesity is a well-known risk factor for OSA, affecting 60 to 90% of adult patients [13]. However, in a cohort with an average BMI of 35, obesity was paradoxically associated with reduced mortality [14]. This "obesity paradox" is observed in various chronic diseases, indicating that BMI alone may not fully capture obesity's impact on health outcomes. Mechanisms linking obesity to OSA development include fat tissue accumulation in the pharyngeal region, narrowing the upper airway [15], and abdominal fat reducing lung volume, increasing upper airway collapsibility [16]. While BMI was not associated with OSA in a cohort with an average BMI of 31.9, trunkal obesity, defined as WHR ≥ 1 in men and ≥ 0.85 in women, was linked to OSA [17]. Our cohort, with a high average BMI (32 in survivors, 35 in deceased patients), found WHR to be a stronger predictor of mortality (HR = 1.24) than BMI, suggesting its superiority in predicting mortality in OSA patients, reflecting a more specific pathophysiology for OSA than BMI alone.

Cardiovascular diseases [4, 13], hypertension [6], COPD [13, 18], renal failure [13], and malignancy [13] have been identified as predictors of mortality in OSA patients. Charlson Comorbidity Score was found to predict mortality in a study involving a substantial number of individuals diagnosed with OSA [12]. However, this study lacked inclusion of BMI, PSG parameters, and cardiovascular comorbidities, limiting its findings. Chiang et al. explored the impact of comorbidities on mortality in OSA patients using the CoSA score [19]. Analyzing data from 9,000 sleep apnea patients, they found higher mortality risk in those with comorbidities, particularly hypertension and COPD. Similarly, COPD

Table 2 Polysomnographic parameters of all patients and patients who deceased/survived

Parameter, mean ± SD	All patients ($n=3541$)	Survived patients ($n=3310$)	Deceased patients ($n=231$)
Total sleep time (min)	371.7 ± 69.4	373.83 ± 68.8	341.95 ± 71.24
Sleep efficiency %	81.7 ± 11.6	82.17 ± 11.47	75.83 ± 12.43
AHI (number/hour)	33.1 ± 25.3	32.56 ± 25.2	42.24 ± 25.81
Supine AHI (number/hour)	48.7 ± 30.5	48.32 ± 30.64	55.39 ± 28.75
Nonsupine AHI (number/hour)	23.3 ± 26.7	22.5 ± 26.42	34.94 ± 28.71
REM AHI (number/hour)	37 ± 24.7	36.67 ± 24.71	42.96 ± 23.91
Non-REM AHI (number/hour)	31.7 ± 27.1	31.1 ± 27	41.24 ± 27.26
REM duration (min)	65.2 ± 30.6	66.16 ± 30.58	52.39 ± 28.09
NonREM duration (min)	306.1 ± 54.1	307.31 ± 53.73	289.45 ± 57.51
Supine time (min)	161.9 ± 99.1	164 ± 98.73	131.69 ± 100.85
Nonsupine time (min)	209.3 ± 97.6	209.33 ± 97.53	209.17 ± 99.68
Mean SpO2, %	91.8 ± 4.1	92 ± 4	89.54 ± 4.98
Minimum SpO2, %	80 ± 9.9	80.34 ± 9.71	75.42 ± 11.43
T90 (minutes)	45.9 ± 74.7	42.79 ± 71.2	91.72 ± 104
ODI (number/hour)	30.5 ± 24.6	29.78 ± 24.33	41.81 ± 25.77
Number of limb movements	93.1 ± 96.3	91.16 ± 93.99	113.65 ± 117.38
Limb movement index, %	16.4 ± 16.8	16.18 ± 16.7	19.81 ± 18.13
PLMS number	46.3 ± 86	43.87 ± 81.48	82.39 ± 130.36
PLMS index, %	8 ± 16	7.53 ± 15.16	15.34 ± 25.38
Time to fall asleep (min)	18.9 ± 21.8	18.87 ± 21.84	19.3 ± 21.31
REM duration, %	16.9 ± 6.7	17.14 ± 6.71	14.74 ± 6.83
NonREM 1 duration (min)	36.8 ± 22	36.19 ± 21.18	46.41 ± 30
NonREM 1, %	10.5 ± 8.6	10.3 ± 8.47	14.25 ± 9.7
NonREM 2 duration (min)	192.3 ± 46.2	193.23 ± 46	179.59 ± 48.56
NonREM 2, %	52 ± 11.7	52 ± 11.84	52.66 ± 10.21
NonREM 3 duration (min)	77.5 ± 40.1	78.55 ± 39.67	63.7 ± 43.7
NonREM 3, %	20.7 ± 11.7	20.84 ± 11	18.87 ± 19.2
Supine apnea + hypopnea count	117.8 ± 100	118.18 ± 100	111.72 ± 100.35
Prone time (min)	8 ± 25.5	8.12 ± 25.85	6.83 ± 19.87
Prone apnea + hypopnea count	3 ± 15.7	2.92 ± 15.46	4.78 ± 18.76
Left side duration (min)	81.6 ± 74.9	81.26 ± 74.29	86.47 ± 83.91
Left-sided apnea + hypopnea count	32.3 ± 57.2	31 ± 54.78	50.56 ± 83
Right side duration (min)	119.6 ± 85.3	119.94 ± 84.76	115.86 ± 93.96
Numberof right-sided apnea + hypopnea	43.1 ± 69.5	41.47 ± 68.17	67.43 ± 84
Nonsupine apnea + hypopnea count	79.7 ± 104.1	76.84 ± 102.37	121.4 ± 119.89
REM apnea count	27.6 ± 28.8	27.84 ± 29.13	24.49 ± 24.33
NonREM apnea count	118.9 ± 135.6	117 ± 135.18	145.97 ± 139.82
Total number of sleep apneas	146.4 ± 149.1	144.74 ± 148.8	170.46 ± 152
REM hypopnea count	11.4 ± 12.1	11.44 ± 12.13	11.44 ± 12.77
NonREM hypopnea count	40.4 ± 37.5	39.62 ± 36.28	52.9 ± 50.83
Total number of sleep hypopneas	51.9 ± 41.2	51 ± 40	64.35 ± 54.92
REM apnea + hypopnea count	38.9 ± 31.1	39.17 ± 31.44	35.9 ± 26.75
nonREM apnea + hypopnea count	159.2 ± 141.7	156.52 ± 141.35	198.67 ± 142.41
Total number of sleep apnea + hypopnea	198.2 ± 152.4	195.69 ± 152.25	234.58 ± 151
REM apnea duration (min)	13.5 ± 15.5	13.54 ± 15.58	13.75 ± 14.66
NonREM apnea duration (min)	48.8 ± 62	47.93 ± 61.47	63.15 ± 69.38
Duration of all sleep apnea (min)	62.4 ± 71.8	61.49 ± 71.26	76.93 ± 78.22
REM hypopnea time (min)	5.2 ± 5.5	5.23 ± 5.52	5.39 ± 5.98
NonREM hypopnea time (min)	15.4 ± 13.8	15.19 ± 13.46	19.86 ± 18.78
Total sleep hypopnea time (min)	20.7 ± 15.6	20.41 ± 15.25	25.25 ± 20.82
REM apnea + hypopnea duration (min)	18.7 ± 15.8	18.75 ± 15.93	19.3 ± 14.8

Table 2 (continued)

Parameter, mean ± SD	All patients ($n=3541$)	Survived patients ($n=3310$)	Deceased patients ($n=231$)
NonREM apnea + hypopnea duration (min)	64.3 ± 62.9	63.±62.35	83.82 ± 68
Duration of all sleep apnea + hypopnea (min)	83.1 ± 71.2	81.77 ± 70.75	103.12 ± 74.94

*Continuous variables are presented as mean ± SD. Abbreviations: AHI: apnea-hypopnea index, REM: Rapid eye movements, SpO_2: peripheral oxygen saturation, ODI: Oxygen desaturation index, PLMS: periodic limb movements of sleep, T90: Time spent with oxygen saturation below 90%, min: minutes

emerged as an independent predictor of mortality in our study. Additionally, they identified other predictors such as diabetes mellitus, ischemic stroke, malignancy, heart failure, dementia, atrial fibrillation, end-stage renal failure, and aortic aneurysm. CoSA score was developed based on these comorbidities along with age ≥ 65 years. However, PSG parameters were lacking in their study. Our analysis identified the impact of CoSA score ≥ 1 on mortality after adjusting for demographic, anthropometric measurements, laboratory tests, and PSG parameters.

Noteworthy for its large sample size and extended follow-up, one study demonstrated PLMS's association with mortality, excluding OSA, narcolepsy, and restless legs syndrome patients [20]. Another investigation in males found PLMI > 30 associated with coronary artery and peripheral artery diseases [21]. However, limited by home sleep test diagnoses, this study may overestimate PLMS. Because home tests include PLMs related to respiratory events in the scoring. Nevertheless, only 35% of the cohort had OSA. In our analysis, carried out with a cohort entirely comprising OSA patients, PLMS has been established as an independent predictor of mortality in this population.

For years, AHI has been a cornerstone parameter in OSA assessment, with an emphasis on its predictive value for mortality risk stratification. A comprehensive meta-analysis of 22 observational studies revealed an elevated mortality risk associated with OSA severity [22]. However, recent studies indicate limitations in using AHI alone to reflect OSA outcomes. In an anlysis considering various confounding factors, AHI did not independently predict mortality [18]. Another investigation, predominantly involving men, identified severe OSA as a predictor of cardiovascular mortality and morbidity, which did not apply to mild to moderate OSA.

AHI might not fully capture the chronic intermittent hypoxia underlies morbidity and mortality in OSA. In severe OSA-diagnosed male patients, T90 emerged as the strongest predictor for elevated hsCRP levels, a systemic inflammation marker in OSA [23]. Thus, combining AHI with hypoxia parameters is suggested for stratifying severity of OSA. An additional investigation underscored the significance of desaturation parameters, indicating that while AHI was not linked to.

all-cause mortality after adjusting for age, the desaturation index (< 94% SpO2) predicted mortality in the 31–50 age group [5]. However, these studies commonly included patients diagnosed with home sleep tests, potentially biasing results toward less severe cases. Furthermore, other research found T90, not AHI, associated with mortality [24].

The ESADA Sleep Cohort, analyzing multicenter data from 24 sleep centers, highlighted the importance of ODI in assessing the relationship between OSA and hypertension [9]. Despite the emphasis on desaturation parameters in predicting hypertension, treating AHI and ODI as categorical variables resulted in loss of information and precision. Moreover, the cross-sectional nature of the study hindered establishing causality between intermittent hypoxemia and arterial hypertension. Additionally, being a multinational study might have introduced heterogeneity in sleep apnea severity indices due to differences in scoring and recording systems among sleep laboratories. The limitations of AHI include its low correlation with symptoms [25] and comorbidities [26], and high night-to-night variability. Research findings indicated misdiagnosis rates for OSA ranging from 30 to 50% in single-night recordings [27]. Another investigation revealed misclassifying ODI (ODI ≤ 15 or > 15) for assessing severity of OSA with a single-night recording occurred in 14.4% of cases [28]. In Punjabi et al.'s review, the debate over AHI as an index derived from total sleep time is discussed [29]. This debate highlights how events concentrated in a short period versus spread throughout the night may yield the same AHI but different physiological outcomes, a limitation also applicable to ODI. Additionally, variations in the frequency of desaturations, apneas, and hypopneas during sleep may depend on position or sleep stage. Our study included various OSA subtypes in regression models, finding ODI to be an independent predictor while AHI lost significance. However, parameters focusing solely on frequency may not fully address temporal distribution issues.

Within our investigation, ODI shows a stronger association with mortality than AHI, reflecting the chronic intermittent hypoxia in OSA pathophysiology and its link to cardiovascular outcomes. However, ODI has limitations, such as lacking depth and duration information of desaturations, and the inability to differentiate OSA-related

Table 3 Univariate Cox regression analysis of demographic data, anthropometric measurements, laboratory tests and PSG parameters

Variable	P value	HR	CI 95%
Age (years)	**<0.001**	1.094	1.080–1.108
Male gender	0.30	1.169	0.867–1.576
Height (cm)	**0.01**	0.173	0.046–0.656
Weight (kg)	**<0.001**	1.020	1.013–1.027
Neck circumference (cm)	**<0.001**	1.131	1.096–1.167
Waist circumference (cm)	**<0.001**	1.047	1.037–1.057
Hip circumference (cm)	**<0.001**	1.026	1.016–1.036
BMI (kg/m)^2	**<0.001**	1.072	1.053–1.092
WHR	**<0.001**	1.075	1.058–1.092
BAI (cm/m)^2	**<0.001**	1.041	1.025–1.057
OSA (Nonpositional and not-REM-related)	**<0.001**	2.526	1.829–3.490
Sleep movement disorder	**<0.001**	2.218	1.662–2.959
PLMS	**<0.001**	2.278	1.666–3.116
Restless Legs Syndrome	0.14	1.436	0.888–2.324
CoSA ≥ 1	**<0.001**	4.288	3.105–5.922
CoSA Score	**<0.001**	1.358	1.300-1.418
ESS	**0.003**	1.038	1.013–1.063
Smoking (pack-years)	**<0.001**	1.025	1.017–1.032
Smoking history	0.83	1.028	0.789–1.339
Alcohol use	0.14	1.366	0.902–2.070
Creatinine (mg/dl)	**<0.001**	1.613	1.422–1.828
Total Cholesterol (mg/dl)	0.11	0.998	0.995–1.001
Hba1c	**<0.001**	2.656	1.521–4.638
Hemoglobin (g/dL)	**<0.001**	0.788	0.725–0.856
T4 (ng/ml)	**<0.001**	2.922	1.690–5.050
TSH (miu/L)	0.42	0.977	0.922–1.035
Neutrophils/Lymphocytes	**<0.001**	1.196	1.128–1.269
Monosit/HDL ratio	**0.01**	1.300	1.064–1.588
SII	**<0.001**	1.085	1.054–1.117
AHI (number/hour)	**<0.001**	1.012	1.008–1.017
Supine AHI (number/hour)	**<0.001**	1.008	1.004–1.012
Nonsupine AHI (number/hour)	**<0.001**	1.013	1.009–1.017
REM AHI (number/hour)	**<0.001**	1.009	1.004–1.014
NonREMAHI (number/hour)	**<0.001**	1.011	1.007–1.015
Mean SpO2%	**< 0.001**	0.921	0.905–0.938
Minimum SpO2%	**< 0.001**	0.966	0.957–0.975
T90 (minutes)	**< 0.001**	1.006	1.005–1.007
ODİ (number/hour)	**<0.001**	1.015	1.011–1.020

*Categorical data are presented as number (percentage). Abbreviations: BMI: Body mass index, WHR: Waist/hip ratio, BAI: Body adiposity index, OSA: Obstructive sleep apnea, PLMS: Periodic limb movements of sleep, CoSA: Comorbidity of Sleep Apnea Score, ESS: Epworth sleepiness scale, Hba1c: Hemoglobin a1c, TSH: Thyroid stimulating hormone, HDL: High density lipoprotein, SII: Systemic immune-inflammation index, AHI: Apnea-hypopnea index, REM: Rapid eye movements, SpO_2: Peripheral oxygen saturation, T90: Time spent with oxygen saturation below 90%, ODI: Oxygen desaturation index

desaturations from those of other cardiopulmonary diseases or obesity-hypoventilation. Our findings underscore the importance of desaturation measurements in developing comprehensive prognostic models for OSA.

While benefiting from a large cohort and an in-depth exploration of mortality-related risk factors, our study is limited by its retrospective nature. Despite a routine follow-up program, limitations include missing data on causes of death, Continuous Positive Airway Pressure (CPAP) adherence, and insufficient follow-up observations to monitor changes in patients' health status and treatment adherence over time.

Table 4 Multivariate Cox regression analysis: model 1

Variable	Category	Univariate Analysis				Multivariate Analysis		
		n	Hazard Ratio	Confidence Interval (%95)	*P*	Hazard Ratio	Confidence Interval (%95)	*P*
OSA subtype	NPOSA and not-REM-related OSA	2,160	2.526	1.829–3.490	**<0.001**	1.397	0.961–2.030	0.08
	Others	1,381	1	Ref				
COPD	(+)	260	5.559	4.172–7.406	**<0.001**	1.991	1.434–2.763	**<0.001**
	(-)	3,281	1	Ref				
PLMS	(+)	409	2.278	1.666–3.116	**<0.001**	1.416	1.018–1.970	**0.03**
	(-)	3,132	1	Ref				
Age (years)			1.094	1.080–1.108	**<0.001**	1.076	1.059–1.092	**<0.001**
Gender	Male	2,551	1.169	0.867–1.576	0.30	1.271	0.913–1.769	0.15
	Female	990	1	Ref				
WHR			1.075	1.058–1.092	**<0.001**	1.259	1.056-1.500	**0.01**
ESS			1.038	1.013–1.063	**0.003**	1.022	0.997–1.047	**0.08**
CoSA skoru ≥ 1	≥ 1	1,750	4.288	3.105–5.922	**<0.001**	1.588	1.069–2.358	**0.02**
	0	1,791	1	Ref				
Monosit/HDL			1.300	1.064–1.588	**0.01**	1.205	0.968–1.499	0.09
SII			1.085	1.054–1.117	**<0.001**	1.059	1.019–1.101	**0.004**
AHI (number/hour)			1.012	1.008–1.017	**<0.001**	1.003	0.997–1.009	**0.34**

Abbrevations: OSA: Obstructive sleep apnea, NPOSA: Nonpositional OSA, REM: Rapid eye movements, COPD: Chronic obstructive pulmonary disease, PLMS: Periodic limb movements in sleep, WHR: Waist/hip ratio, ESS: Epworth sleepiness scale, COSA: Comorbidities of Sleep Apnea, HDL: High-density lipoprotein, SII: Sytemic immune-inflammation index, AHI: Apnea-hypopnea index

Table 5 Multivariate Cox regression analysis: model 2

Variable	Category	Univariate Analysis				Multivariate Analysis		
		n	Hazard Ratio	Confidence Interval (%95)	*P*	Hazard Ratio	Confidence Interval (%95)	*P*
OSA subtype	NPOSA and not-REM-related OSA	2,160	2.526	1.829–3.490	**<0.001**	1.249	0.860–1.816	0.24
	Others	1,381	1	Ref				
COPD	(+)	260	5.559	4.172–7.406	**<0.001**	1.968	1.418–2.731	**<0.001**
	(-)	3,281	1	Ref				
PLMS	(+)	409	2.278	1.666–3.116	**<0.001**	1.392	1.000-1.939	**0.049**
	(-)	3,132	1	Ref				
Age (years)			1.094	1.080–1.108	**<0.001**	1.077	1.060–1.094	**<0.001**
Gender	Male	2,551	1.169	0.867–1.576	0.30	1.284	0.922–1.790	0.13
	Female	990	1	Ref				
WHR			1.075	1.058–1.092	**<0.001**	1.241	1.041–1.479	**0.01**
ESS			1.038	1.013–1.063	**0.003**	1.019	0.994–1.044	0.13
CoSA skoru ≥ 1	≥ 1	1,750	4.288	3.105–5.922	**<0.001**	1.554	1.046–2.310	**0.02**
	0	1,791	1	Ref				
Monosit/HDL			1.300	1.064–1.588	**0.01**	1.178	0.946–1.467	0.14
SII			1.085	1.054–1.117	**<0.001**	1.058	1.017-1.100	**0.005**
ODI (number/hour)			1.015	1.011–1.020	**<0.001**	1.007	1.001–1.013	**0.01**

Abbrevations: OSA: Obstructive sleep apnea, NPOSA: Nonpositional OSA, REM: Rapid eye movements, COPD: Chronic obstructive pulmonary disease, PLMS: Periodic limb movements in sleep, WHR: Waist/hip ratio, ESS: Epworth sleepiness scale, COSA: Comorbidities of Sleep Apnea, HDL: High-density lipoprotein, SII: Sytemic immune-inflammation index, ODI: Oksygen desaturation index

Conclusion

Our study provides a comprehensive examination of various parameters in a large OSA patient cohort, shedding light on mortality outcomes over a long follow-up period. Specifically, we found associations between mortality and factors such as advanced age, higher WHR, presence of COPD, CoSA ≥ 1, presence of PLMS, higher SII, and higher ODI. Our findings suggest that ODI may be a stronger predictor of mortality than other oxygenation parameters. Identifying high-risk patients allows for timely interventions and improved outcomes.

Author contributions Damla Azakli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Damla Azakli, Celal Satici, Sinem Nedime Sokucu, Senay Aydin, Furkan Atasever and Cengiz Ozdemir contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Data availability The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the University Of Health Sciences Yedikule Chest Disease and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethical Committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.
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