Mortality Prediction in Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea

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Research

Keywords: chronic obstructive pulmonary disease, obstructive sleep apnea, overlap syndrome, hypoxemia, mortality

Posted Date: April 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-404022/v1

Abstract

Background: Overlap syndrome of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) is associated with increased mortality. We aimed to assess all-cause mortality in patients with COPD, OSA, and the overlap syndrome and evaluate which polysomnographic indices—apnea-hypopnea index (AHI) or hypoxemic load measurements—better predict mortality within 10 years.

Methods: Adults who underwent polysomnography, spirometry, and bronchodilator response tests between 2000 and 2018 were included and divided into four groups according to the presence of COPD and moderate-to-severe OSA (AHI ³15/h). We estimated mortality using Cox model adjusted for demographic/anthropometric covariates and comorbidities; this was called the clinical model. To evaluate prognostic performance, we compared the concordance index (C-index) between the clinical model and extended models, which incorporated one of the polysomnographic indices—AHI, sleep time spent with SpO_2 < 90% (TS90), and mean and lowest SpO_2.

Results: Among 355 participants, patients with overlap syndrome of COPD and moderate-to-severe OSA had the highest risk of death (adjusted hazard ratio, 3.19; 95% confidence interval, 1.02 to 9.96). The C-indices of the extended models with TS90 (%) and mean SpO_2 were significantly higher than that of the clinical model (0.765 vs. 0.737 and 0.756 vs. 0.737, respectively; all P <0.05); however, the C-index of the extended model with AHI was not (0.739 vs. 0.737; P=0.15).

Conclusions: All-cause mortality was highest in patients with the overlap syndrome. The measurements of the hypoxemic load, not AHI, better predicted mortality in patients with COPD, OSA, and the overlap syndrome.

Background

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are common disorders with substantial impacts on global health [1]. In the general population of South Korea, OSA—defined as more than five apneas or hypopneas per hour of sleep—affects 45% of adults aged 40 years and older [2], and COPD affects 13% of them [3]. Approximately 5% of the Korean general population has both COPD and OSA [2], which is called the overlap syndrome [4].

Several studies have reported that mortality in patients with COPD–OSA overlap syndrome is higher than that in those with COPD alone or OSA alone [5–7], although one study reported an inconsistent result [8]. Both COPD and OSA have overlapping pathophysiological mechanisms, including hypoxia and airway and systemic inflammation [9, 10]. Patients with overlap syndrome have more prolonged and profound hypoxemia than those with either condition, which may produce a synergistic effect on oxidative stress and systemic inflammation, leading to increased cardiovascular disease and mortality [11–13].

The apnea-hypopnea index (AHI)—the frequency of apneas and hypopneas—has been used to diagnose OSA and assess its severity. However, it has been suggested that the AHI is limited to capturing various

physiological aspects of OSA, which makes it difficult to predict clinical outcomes, including cardiovascular mortality, among patients with OSA [14]. In addition, the use of the AHI in patients with chronic respiratory diseases, such as COPD is limited, as the current definition of hypopnea does not consider the degree and duration of hypoxemia [1]. Moreover, in patients with COPD, hypoxemia may occur without definite obstructive respiratory events, especially during rapid eye movement (REM) sleep [15]. Therefore, even with the same AHI, the degree or duration of hypoxemia may be different in patients with COPD, OSA, and overlap syndrome [16]. However, it is currently unknown which indices of polysomnography (PSG) better predict clinical outcomes in these patients.

Here, we aimed to assess all-cause mortality in patients with COPD, OSA, and the overlap syndrome and evaluate which PSG indices—the number of respiratory events or measurements of the hypoxemic load—better predict all-cause mortality in these patients.

Methods

Study Design and Population

Our retrospective cohort study included adults (≥19 years) who underwent overnight PSG, spirometry, and bronchodilator response tests at Seoul National University Hospital from January 2000 to June 2018. We excluded patients who were diagnosed with central sleep apnea (central AHI ≥5/h).

COPD was spirometrically diagnosed by the presence of a postbronchodilator FEV_1/FVC <0.70, according to the Global Initiative for Obstructive Lung Disease (GOLD) guidelines [17]. Patients with an AHI of ³15/h were diagnosed as having moderate- to-severe OSA. The cohort participants were divided into four groups: 1) patients with neither COPD nor moderate-to severe-OSA; 2) patients with moderate-to-severe OSA without COPD; 3) patients with COPD without moderate-to-severe OSA; and 4) patients with overlap syndrome of COPD and moderate-to-severe OSA.

This study was approved by the institutional review board of Seoul National University Hospital (H-2001-029-1092) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived.

Data Collection

The following data on the index date, i.e., the date of the PSG, were collected: age, sex, and body mass index (BMI); questionnaires, such as the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI); smoking history; and comorbidities. The Charlson comorbidity index (CCI) was calculated according to a previously described method [18]. Spirometric results and prescriptions for positive airway pressure (PAP) and bronchodilators for treatment were also recorded.

PSG Recordings and Variables

Patients underwent PSG at the Sleep Center of Seoul National University Hospital according to the American Academy of Sleep Medicine guidelines [19]. Apnea was defined as complete or almost complete (90% or more) cessation of airflow for more than 10 seconds. Hypopnea was defined as a reduction in the nasal pressure signal by ≥30% of the baseline that lasted ≥10 s, resulting in a ≥3 % decrease in oxygen saturation (SpO_2) from the baseline or arousal. Sleep time spent with SpO_2 less than 90% (TS90) and the mean and lowest SpO_2 were recorded to evaluate the duration and degree of hypoxemia. Nocturnal hypoxemia was defined as TS90 for at least 10 min.

Mortality Data

Data on the death of the patients were collected from Statistics of Korea, which occurred prior to December 31, 2018. We obtained the dates and causes of death, and the follow-up period was calculated from the date of PSG to the date of death or the end of December 2018, whichever occurred first.

Statistical Analysis

Clinical characteristics were compared between the four groups using the Kruskal–Wallis test followed by Bonferroni correction for continuous variables. Categorical variables were compared using either the $\chi 2$ test or Fisher's exact test.

We used Kaplan–Meier survival analysis to compare survival among the four groups. We estimated hazard ratios (HRs) for all-cause mortality by the presence of COPD and moderate-to-severe OSA using a Cox proportional hazard model adjusted for age, sex, BMI, and CCI. This model was called the clinical model. Next, we calculated the relative excess risk due to interaction (RERI) to examine the combined effect of COPD and moderate-to-severe OSA on all-cause mortality. A 95% confidence interval (CI) of RERI that crossed zero indicated insignificance of the interaction [20]. The same method was used to evaluate the combined effect of COPD and nocturnal hypoxemia on all-cause mortality.

To evaluate which PSG indices, i.e., index describing the number of respiratory events (AHI) or measurements of the hypoxemic load (TS90, mean and lowest SpO_2), predict death for up to 10 years, we defined five extended models. Each extended model included all covariates in the clinical model and one of the five logarithmically transformed PSG indices—AHI, TS90 (expressed in units of min and %), and the mean and lowest SpO_2. Before the logarithmic transformation, we added a constant value of 1 to AHI and TS90, as their values included zero. Then, we calculated the area under the incident/dynamic receiver operating characteristic (ROC) curve (AUC) and Harrell's concordance index (C-index) using the R package risksetROC to evaluate the prognostic performance of time-to-event models [21, 22]. We compared the C-index of each extended model with that of the clinical model. We also compared the C-index of the extended model including AHI with those of other extended models. Statistical comparisons and 95% CI of C-indices were estimated after 1,000 bootstrap replicates [23, 24]. The same steps for the comparisons between the clinical and extended models were performed in 1) the entire patient cohort; 2) patients with either COPD, moderate-to-severe OSA, or both; 3) all patients with OSA regardless of the presence of

COPD; 4) patients with moderate-to-severe OSA regardless of the presence of COPD; and 5) all patients with COPD regardless of the presence of OSA.

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using R 4.0.1 software (http://www.r-project.org) and Stata 13.1 software (StataCorp., College Station, Texas).

Results

Clinical Characteristics

Of the 366 study participants, 11 with central sleep apnea were excluded. Among the 355 participants (median age, 64 years; 58.6% men; median BMI, 24.2 kg/m^2), 146 (41.1%) had moderate-to-severe OSA, and 94 (26.5%) had COPD (Figure 1). Clinical characteristics of participants according to the presence of moderate-to-severe OSA and COPD are presented in Tables S1 and S2 in the Additional file 1, respectively.

In this study, 152 (42.8%) participants had neither COPD nor moderate-to-severe OSA, 109 (30.7%) had moderate-to-severe OSA without COPD, 57 (16.1%) had COPD without moderate-to-severe OSA, and 37 (10.4%) had overlap syndrome of COPD and moderate-to severe-OSA (Figure 1). The clinical characteristics of the four groups are shown in Table 1. Patients with COPD with or without moderate-to-severe OSA were predominantly men and former or current smokers. Patients with overlap syndrome were more likely to have hypertension and coronary heart disease than those in the other groups, and their median CCI was 3 (interquartile range [IQR], 1–3). The median AHI of the groups with moderate-to-severe OSA only and overlap syndrome was 30.1/h and 33.1/h, respectively, which was not statistically different ($P > 0.99$ after Bonferroni correction). During PSG, the mean and lowest SpO_2 were lower in the groups with moderate-to-severe OSA only and overlap syndrome than in the groups with COPD without moderate-to-severe OSA and neither disease. The median TS90 of the groups with moderate-to-severe OSA only and overlap syndrome was 4 min and 7 min, respectively. Nocturnal hypoxemia was present in 4.0%, 41.3%, 7.0%, and 40.5% of the groups with neither COPD nor moderate-to-severe OSA, moderate-to-severe OSA without COPD, COPD without moderate-to-severe OSA, and overlap syndrome, respectively. More than 60% of patients with OSA were prescribed PAP, and approximately 50% of patients with COPD were prescribed bronchodilators.

All-Cause Mortality

During a median of 5.8 years (IQR, 2.9–10.3 years) of the follow-up period, there were 37 deaths: 11 patients (29.7%) died from malignant neoplasm, 10 (27.0%) from respiratory disease, and 4 (10.8%) from cardiovascular disease. Figure 2 shows the unadjusted Kaplan–Meier survival curves for the four groups. After adjusting for age, sex, BMI, and CCI, the highest HR of all-cause mortality was found in patients with overlap syndrome of COPD and moderate-to-severe OSA when compared with those who had neither disease. The adjusted HR of death for overlap syndrome was 3.19 (95% CI, 1.02 to 9.96), for moderate-to-severe OSA only was 1.37 (0.51 to 3.68), and that for COPD without moderate-to-severe OSA was 2.98 (95% CI, 1.14 to 7.80). There was no significant synergistic effect between COPD and moderate-to-severe

OSA (RERI, −0.16; 95% CI, −3.48 to 3.16; Additional file 1: Table S3). When considering the interaction between COPD and nocturnal hypoxemia on mortality, a synergistic effect was not observed (RERI, 2.97; 95% CI, −2.56 to 8.50; Additional file 1: Table S4).

Predictive Indices of Polysomnography for All-Cause Mortality

In the entire patient cohort, the C-index of the clinical model was 0.737 (95% CI, 0.648 to 0.827). The C-indices of the extended model with AHI, TS90 (expressed in units of min and %), and the mean and lowest SpO_2 were 0.739 (95% CI, 0.652 to 0.827), 0.763 (0.683 to 0.844), 0.765 (0.684 to 0.845), 0.756 (0.669 to 0.842), and 0.744 (0.658 to 0.830), respectively (Figure 3A). The C-index of the extended model with AHI was not different from that of the clinical model (P=0.15). However, the C-indices of the extended models with TS90 (expressed in units of min and %) and mean SpO_2 were significantly higher than those of the clinical model (all P <0.05). The same results were replicated in 203 patients with either COPD, moderate-to-severe OSA, or both (Figure 3B). The C-index of the extended model with AHI did not differ significantly from that of other extended models for the entire cohort (Figure 3A) and for patients with either COPD, moderate-to-severe OSA, or both (Figure 3B).

In all 262 patients with OSA (AHI ≥5/h), regardless of the presence of COPD, the C-indices of the extended models with TS90 (expressed in units of min and %) and mean SpO_2 were significantly higher than those of the clinical model (all P <0.05; Additional file 1: Figure S1A). When the same analysis was confined to 146 patients with moderate-to-severe OSA regardless of the presence of COPD, there were no significant differences in the C-indices of the clinical and extended models (Additional file 1: Figure S1B). In all 94 patients with COPD, regardless of the presence of OSA, the extended models with the lowest SpO_2 as well as those with TS90 (expressed in units of min and %) and mean SpO_2 had significantly better C-indices than the clinical model (P <0.05; Additional file 1: Figure S1C).

Discussion

In this cohort of adults suspected of having COPD, OSA, and the overlap syndrome, we showed that all-cause mortality was highest in patients with the overlap syndrome of COPD and moderate-to-severe OSA. We found that our models that incorporated the measurements of hypoxemic load and all covariates in the clinical model better predicted mortality within 10 years compared to the clinical model adjusted only for demographic/anthropometric covariates and comorbidities in patients with COPD, OSA, and the overlap syndrome.

In previous studies, the mortality of the overlap syndrome was higher than that of OSA or COPD alone [5–7]. In a cohort study of patients referred to an academic hospital in Spain, patients with overlap syndrome had higher all-cause mortality than those with COPD alone (relative risk of 2.23) [5]. Similarly, an analysis of the National Health and Nutrition Examination Survey (NHANES) data showed that all-cause mortality was 2.4 times higher in individuals with overlap syndrome than in those who did not have either disease [6]. In a clinical cohort in Canada, the highest hazard of the composite outcome—hospitalization due to

cardiovascular causes or death—was associated with patients having both severe OSA and COPD in untreated individuals (HR of 2.01). Here, we report consistent findings in Asian patients [7]. In our study, the adjusted HR for all-cause mortality in patients with overlap syndrome of COPD and moderate-to-severe OSA was 3.19 compared to those who did not have either disease. Although an inconsistent result has been reported from a cohort of veterans with hospitalizations, its results are difficult to generalize because of potential selection bias as acknowledged by the authors [8].

The mechanisms explaining increased mortality in patients with overlap syndrome are not clearly understood, but hypoxemia may play a major role. In OSA alone, recurrent intermittent hypoxemia occurs because of upper airway narrowing or obstruction at a relatively normal baseline oxygen saturation [13]. In COPD alone, prolonged and profound hypoxemia is presumed to be a consequence of hypoventilation, especially during REM sleep characterized by low tidal volume, and increased ventilation–perfusion mismatch during periods of reduced tidal volume [25]. Moreover, in patients with COPD and low baseline oxygen saturation while awake, a similar degree of hypoventilation is associated with greater desaturation because of the initial position being on the steep part of the oxyhemoglobin dissociation curve [13, 15, 25]. If COPD is accompanied by OSA, intermittent hypoxemia develops from a low baseline saturation, and the depth and duration of hypoxemia become more pronounced. This may promote increased oxidative stress, systemic inflammation, and sympathetic activation, thus contributing to cardiovascular and other comorbidities and mortality [26, 27].

Even in patients with OSA, the importance of hypoxemia has emerged as the AHI is considered to predict their outcomes poorly [14, 28]. The newly proposed PSG indices predicting outcomes of OSA include TS90 [29–32], nadir of hypoxemia [33], area under the oxygen desaturation curve [14], and respiratory event duration [28]. However, there have been few studies on PSG indices predicting mortality in patients with overlap syndrome that show more profound hypoxemia. Recently, a study reported that the greatest hazard of the composite cardiovascular outcome was found in patients with both COPD and nocturnal hypoxemia (TS90 $\geq$ 10 min), but not with AHI > 30 [7]. Our findings are consistent with those of previous studies. In our study, the extended models incorporating measurements of the hypoxemic load (TS90 and mean SpO_2) had higher C-indices than that of the clinical model, which was not adjusted for any indices of PSG. The C-index of the extended model with AHI did not show a significant difference from that of the clinical model. Moreover, our models incorporating measurements of the hypoxemic load consistently better predicted mortality within 10 years than the clinical model in the subcohorts of all 262 patients with OSA and all 94 patients with COPD.

In patients with COPD, the lowest SpO_2, TS90, and mean SpO_2 predicted mortality well. As discussed above, when OSA coexists with COPD, the degree of desaturation may be more pronounced because of the low starting baseline and sleep-related hypoventilation [13, 15, 25]. We speculate that the importance of the depth of hypoxemia in COPD is explained by its pathophysiology.

There was no statistically significant difference when comparing the C-index of our extended model with AHI and those of the extended models with other PSG measurements of the hypoxemic load. The C-index

of the extended model with AHI was not significantly higher than that of the clinical model (0.739 vs. 0.737). Our study might not be adequately powered to compare the predictive capacity of AHI and measurements of the hypoxemic load. Further large-scale longitudinal studies are needed to explore our findings.

Our study has notable strengths in the diagnosis of these diseases. In contrast to the previous studies [6–8], all study patients underwent spirometry and bronchodilator response tests, and COPD was spirometrically diagnosed according to the GOLD guidelines [17]. We divided study patients into two groups—those with moderate-to-severe (AHI ≥15 /h) OSA and those without—because long-term outcomes of mild (5 /h ≤ AHI < 15 /h) OSA are unclear [34, 35].

To appreciate the results of our study appropriately, its limitations must be recognized. First, this study was moderately sized and conducted in a single institution. Second, the oxygen desaturation index and the area under the oxygen desaturation curve were not available in our study. Further studies are required to evaluate the predictive power of these PSG metrics for mortality in patients with COPD and overlap syndrome. Third, because of the retrospective nature of the present study, data on patients' adherence to PAP and bronchodilators were not available, which could have modifying effects on the risks of adverse outcomes.

In conclusion, patients with the COPD–OSA overlap syndrome had increased all-cause mortality. The measurements of the hypoxemic load and not AHI better predicted mortality within 10 years than the clinical model that was not adjusted for any indices of PSG in patients with COPD, OSA, or the overlap syndrome.

List Of Abbreviations

AHI: apnea-hypopnea index; BDI: Beck Depression Inventory; BDR: bronchodilator response; BMI: body mass index; CCI: Charlson comorbidity index; CI: confidence interval; C-index: concordance index; COPD: chronic obstructive pulmonary disease; ESS: Epworth Sleepiness Scale; HR: hazard ratio; OSA: obstructive sleep apnea; PAP: positive airway pressure; PFT: pulmonary function test; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; REM: rapid eye movement; RERI: relative excess risk due to interaction; SpO_2: oxygen saturation; TS90: Sleep time spent with SpO_2 less than 90%

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

J.C. 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. E.B. and J.C. contributed to the study concept and design, analysis and interpretation of data, and writing and revision of the manuscript. N.K., S.M.C., J.L., Y.S.P., C.H.L., S.M.L., and C.G.Y. contributed to patient enrollment and data acquisition. All authors have read and approved the final manuscript.

Acknowledgements

Clinical data of this study were derived from the clinical data warehouse of Seoul National University Hospital (SNUH), SUPREME®. We are grateful to the Medical Research Collaborating Center at SNUH for the statistical consultation.

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Tables

Table 1. Clinical Characteristics of the Study Patients

Variables	Neither COPD nor moderate-to-severe OSA (n=152)	Moderate-to-severe OSA only (n=109)	COPD without moderate-to-severe OSA (n=57)	COPD with moderate-to-severe OSA (n=37)	*P* Value
Demographics					
Male	65 (42.8)	64 (58.7)	48 (84.2)	31 (83.8)	<0.001
Age, years	61 (55–67)	65 (56–70)	69 (62–75)	65 (59–73)	<0.001
BMI, kg/m^2	23.7 (21.6–26.0)	25.4 (23.1–28.0)	23.7 (21.7–25.7)	25.7 (22.9–28.4)	<0.001
Smoking status					
Never	104 (68.4)	67 (61.5)	16 (28.1)	8 (21.6)	<0.001
Former or current smoker	40 (26.3)	41 (37.6)	39 (68.4)	29 (78.4)	
Unknown	8 (5.3)	1 (0.9)	2 (3.5)	0 (0)	
Pack-year (n=321)	0 (0–1)	0 (0–18)	20 (0–40)	30 (8–50)	<0.001
Comorbidities					
Hypertension	45 (29.6)	58 (53.2)	23 (40.4)	24 (64.9)	<0.001
Diabetes mellitus	24 (15.8)	27 (24.8)	11 (19.3)	8 (21.6)	0.34
Coronary heart disease	9 (5.9)	17 (15.6)	9 (15.8)	8 (21.6)	0.01
Congestive heart failure	1 (0.7)	3 (2.8)	0 (0)	1 (2.7)	0.29
Stroke	5 (3.3)	6 (5.5)	4 (7.0)	2 (5.4)	0.60
Depression	15 (9.9)	12 (11.0)	3 (5.3)	3 (8.1)	0.66
CCI	2 (1–3)	2 (1–4)	2 (1–3)	3 (1–3)	0.002
Questionnaire					
ESS (n=177)	7 (4–11)	7 (4–12)	10 (3–12)	6 (5–8)	0.92
PSQI (n=147)	13 (9–15)	11 (8–13)	11 (5–13)	10 (6–14)	0.045

BDI (n=174)	15 (8–22)	17 (11–21)	13 (9–21)	9 (5–15)	0.14
PSG variables					
Total sleep time, min	396 (347–433)	386 (308–428)	386 (318–433)	390 (341–432)	0.56
Sleep efficiency, %	80.9 (72.0–89.4)	79.0 (66.0–88.3)	79.0 (68.0–86.0)	78.4 (72.0–88.0)	0.15
Total slow wave sleep, % (n=314)	2.3 (0.1–7.5)	0.8 (0–7.9)	0.7 (0–2.6)	0.5 (0–4.5)	0.051
Sleep latency, min	11 (4–25)	10 (5–23)	14 (7–26)	10 (5–19)	0.23
REM latency, min (n=353)	96 (70–145)	104 (68–176)	96 (75–154)	95 (76–164)	0.97
AHI, /h	5.2 (1.8–9.0)	30.1 (23.0–45.1)	6.1 (3.1–9.6)	33.1 (25.8–44.8)	<0.001
REM AHI, /h (n=254)	7.7 (2.8–17.8)	35.8 (23.2–50.3)	9.0 (3.3–18.1)	34.3 (15.9–55.4)	<0.001
NREM AHI, /h (n=254)	3.3 (1.6–6.9)	28.5 (20.0–46.0)	4.8 (2.2–8.0)	30.6 (19.9–40.9)	<0.001
Supine AHI, /h (n=252)	7.7 (3.1–13.8)	37.8 (27.0–61.5)	10.4 (5.4–16.6)	49.5 (36.0–66.6)	<0.001
Nonsupine AHI, /h (n=252)	1.0 (0–4.8)	9.8 (0.6–22.6)	2.7 (0.9–5.3)	11.6 (1.2–26.6)	<0.001
TS90, min	0 (0–1)	4 (1–39)	0 (0–1)	7 (2–85)	<0.001
TS90, %	0 (0–0.1)	1.1 (0.1–7.6)	0 (0–0.1)	1.5 (0.3–17.9)	<0.001
Nocturnal hypoxemia	6 (4.0)	45 (41.3)	4 (7.0)	15 (40.5)	<0.001
Mean SpO_2, %	96 (95–97)	94 (92–96)	96 (94–97)	93 (90–95)	<0.001
Lowest SpO_2, %	90 (86–93)	83 (78–87)	89 (87–91)	80 (66–86)	<0.001
Spirometry					
Post-BDR FEV_1/FVC	81 (75–85)	79 (74–83)	61 (53–66)	65 (53–68)	<0.001
Post-BDR FEV_1, %	104 (94–117)	105 (92–116)	81 (71–94)	87 (71–97)	<0.001
Post-BDR FVC, %	98 (86–105)	94 (83–105)	93 (83–101)	97 (89–106)	0.71
Treatment prescription					
PAP	9 (5.9)	70 (64.2)	0 (0)	23 (62.2)	<0.001
Bronchodilator	8 (5.3)	12 (11.0)	26 (45.6)	20 (54.1)	<0.001

Definition of abbreviations: AHI = apnea-hypopnea index; BDI = Beck Depression Inventory; BDR = bronchodilator response; BMI = body mass index; CCI = Charlson

comorbidity index; COPD = chronic obstructive pulmonary disease; ESS = Epworth Sleepiness Scale; NREM = non-rapid eye movement; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement; SpO_2 = oxygen saturation; TS90 = sleep time spent with oxygen saturation less than 90%.
Data are presented as n (%) or median (interquartile range), unless otherwise noted.

Table 2. Multivariable Analysis of All-Cause Mortality

	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Neither COPD nor moderate-to-severe OSA	1	1
Moderate-to-severe OSA only	2.01 (0.79 to 5.10)	1.37 (0.51 to 3.68)
COPD without moderate-to-severe OSA	4.14 (1.71 to 9.98)	2.98 (1.14 to 7.80)
COPD with moderate-to-severe OSA	4.55 (1.57 to 13.18)	3.19 (1.02 to 9.96)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OSA = obstructive sleep apnea.

*Adjusted for age, sex, body mass index, Charlson comorbidity index.

Figures

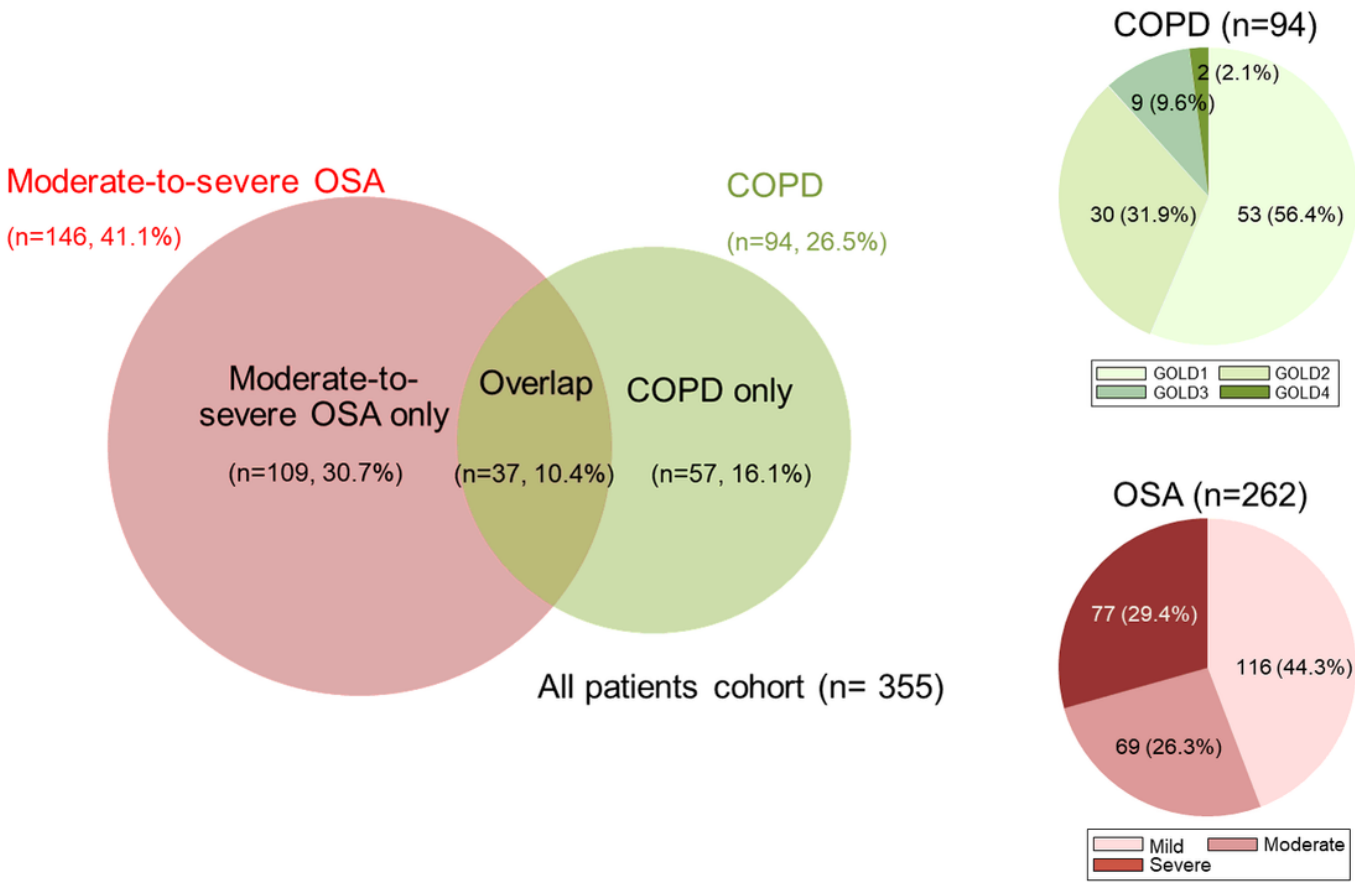
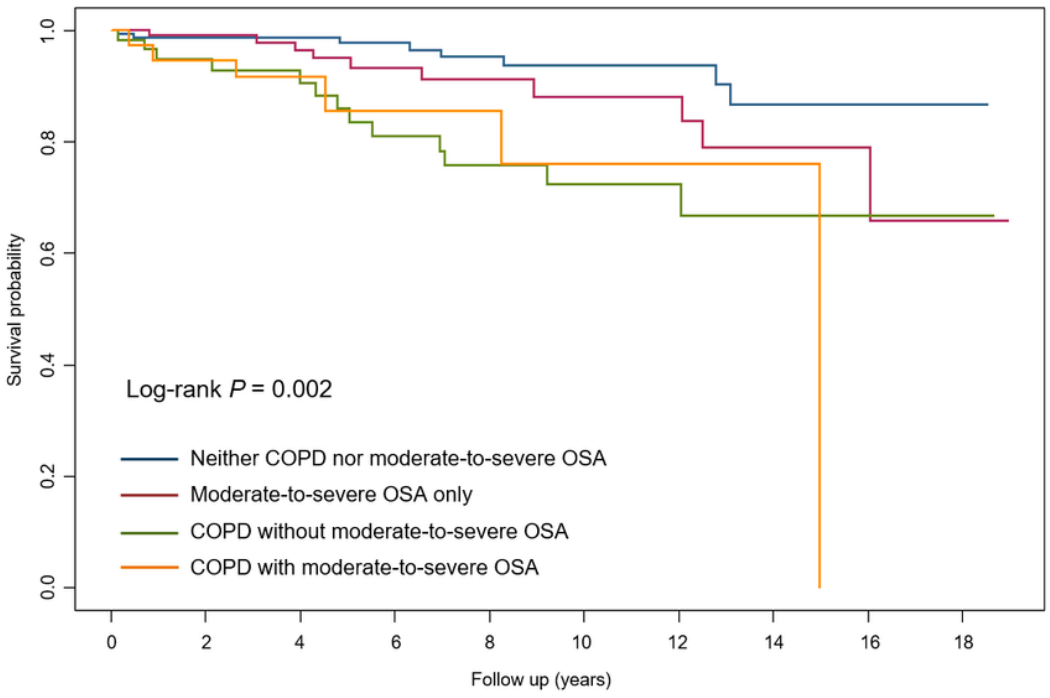


Figure 1

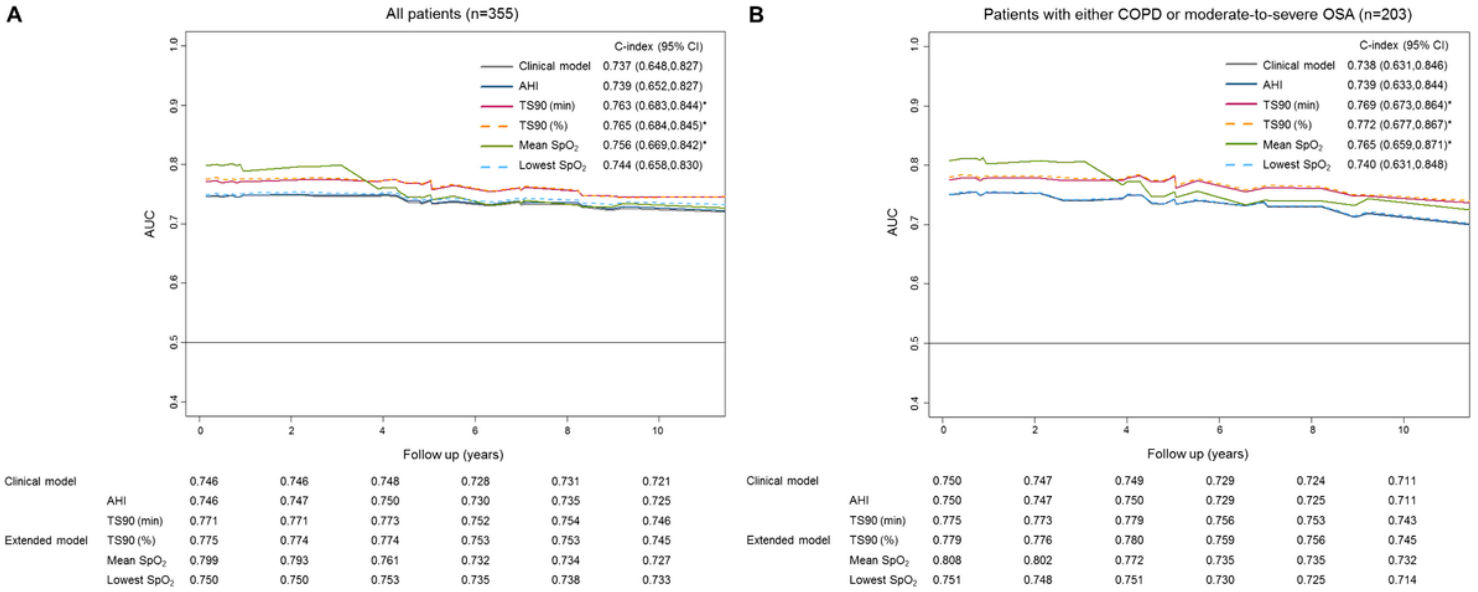
Venn diagram showing the proportion of patients with chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), and the overlap syndrome.



Neither COPD nor moderate-to-severe OSA	152	128	105	84	69	41	33	18	7	1
Moderate-to-severe OSA only	109	88	69	48	32	23	20	8	6	2
COPD without moderate-to-severe OSA	57	48	42	31	26	19	13	7	3	2
COPD with moderate-to-severe OSA	37	32	17	12	9	7	6	1	0	0

Figure 2

Unadjusted Kaplan–Meier survival curves for all-cause mortality by the presence of COPD and moderate-to-severe OSA.



Clinical model		0.746	0.746	0.748	0.728	0.731	0.721
Extended model	AHI	0.746	0.747	0.750	0.730	0.735	0.725
	TS90 (min)	0.771	0.771	0.773	0.752	0.754	0.746
	TS90 (%)	0.775	0.774	0.774	0.753	0.753	0.745
	Mean SpO_2	0.799	0.793	0.761	0.732	0.734	0.727
	Lowest SpO_2	0.750	0.750	0.753	0.735	0.738	0.733

Clinical model		0.750	0.747	0.749	0.729	0.724	0.711
Extended model	AHI	0.750	0.747	0.750	0.729	0.725	0.711
	TS90 (min)	0.775	0.773	0.779	0.756	0.753	0.743
	TS90 (%)	0.779	0.776	0.780	0.759	0.756	0.745
	Mean SpO_2	0.808	0.802	0.772	0.735	0.735	0.732
	Lowest SpO_2	0.751	0.748	0.751	0.730	0.725	0.714

Figure 3

Area under incident/dynamic receiver operating characteristic curve to predict mortality (A) in all patients (n=355), and (B) in patients with either COPD or moderate-to-severe OSA (n=203). *P <0.05 compared to the C-index of the clinical model.

Supplementary Files

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- Additionalfile1.docx