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COPD

# Survival Benefit of CPAP Favors Hypercapnic Patients with the Overlap Syndrome

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**Abstract**
*Background* Patients with the combination of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), known as the "overlap syndrome," have a substantially greater risk of morbidity and mortality compared to those with either COPD or OSA alone. The study's objective was to report on the long-term outcome of hypercapnic ($PaCO_2 \geq 45$ mmHg) and normocapnic patients with the overlap syndrome treated with continuous positive airway pressure (CPAP).
*Methods* A nonconcurrent cohort of consecutive patients with the overlap syndrome was followed for a median duration of 71 months (range 1–100) at a VA sleep center. All patients were managed according to the prevailing recommendations of both diseases. The end point of the study was all-cause mortality.
*Results* Of the 271 patients identified, 104 were hypercapnic ($PaCO_2 = 51.6 \pm 4.3$ mmHg). Both normocapnic and hypercapnic patients had comparable apnea–hypopnea indexes (AHI) ($29.2 \pm 23.8$ and $35.2 \pm 29.2$/h, respectively; $p = 0.07$) and similar adherence rates to CPAP (43 and 42 %, respectively, $p = 0.9$). Survival analysis revealed that hypercapnic patients who were adherent to CPAP had reduced mortality compared to nonadherent hypercapnic patients ($p = 0.04$). In contrast, the cumulative mortality rate for normocapnic patients was not significantly different between the adherent and the nonadherent group ($p = 0.42$). In multivariate analysis, the comorbidity index was the only independent predictor of mortality in normocapnic patients with the overlap syndrome [hazard ratio (HR) 1.68; $p < 0.001$] while CPAP adherence was associated with improved survival (HR 0.65; $p = 0.04$).
*Conclusions* CPAP mitigates the excess risk of mortality in hypercapnic patients but not in normocapnic patients with the overlap syndrome.

**Keywords** Overlap syndrome · Continuous positive airway pressure · Hypercapnia · Mortality

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## Introduction

The "overlap syndrome" is characterized by the occurrence of repetitive episodes of apnea and hypopnea caused by obstruction of the upper respiratory tract in a patient with chronic obstructive pulmonary disease (COPD). The term overlap syndrome was first described by Flenley in 1985 [1]. Flenley was among the first to envision that the overlapping of COPD and OSA would have greater deleterious effects on the patient than either condition alone.

One prominent feature of this syndrome is the greater degree of nocturnal hypoxemia than with COPD or OSA alone, particularly during REM sleep [2, 3]. Alveolar hypoventilation has been considered the prime culprit for most of the oxygen desaturation. Other causes include decreased ventilation–perfusion matching, respiratory muscle dysfunction, and decreased end expiratory lung volume [4, 5]. The cumulative effects of these physiologic disturbances often result in pulmonary hypertension and cor pulmonale [6].

Despite the high prevalence of overlap syndrome, only limited data are available on its clinical consequences. Recent epidemiological studies have pointed out that patients with overlap syndrome have a worse prognosis than patients with only one of these diseases. Three studies have recently published outcomes data on patients with overlap syndrome and patients with COPD, both with and without continuous positive airway pressure (CPAP) treatment [7–9]. After adjusting for anthropomorphic parameters and COPD severity, untreated OSA was associated with increased risk of death. CPAP mitigated recurrent hospitalizations and excess mortality for those who were adherent to treatment. A similar trend of reduced frequency of COPD exacerbations and improved survival was also shown in stable hypercapnic patients with COPD without OSA who received nocturnal positive pressure ventilation [10, 11]. Whether the attributed mortality benefit in the overlap syndrome patients from CPAP is related to hypercapnia per se remains unclear as none of the existing studies have included a stratification analysis based on $PaCO_2$.

To clarify whether treatment of overlap syndrome is associated with a better prognosis in patients with documented hypercapnia, we performed a retrospective analysis of the Veterans Affairs Computerized Patient Record System (CPRS) at the Western New York facility. The current study was designed to test the hypothesis that in hypercapnic patients with the overlap syndrome, those treated for OSA would have improved outcomes compared with those not treated for OSA.

## Materials and Methods

### Study Population

A nonconcurrent cohort study was performed of all consecutive patients with COPD who had a diagnosis of OSA established by overnight polysomnography (SomnoStar Pro, Viasys Healthcare) at the Veterans Affairs Western New York Healthcare System Sleep Center in Buffalo from January 2004 to June 2012. The inclusion criteria included patients with OSA and COPD in whom $FEV_1$, FVC, and arterial blood gas values were determined before starting CPAP therapy. Patients who had an inconclusive sleep study (<2 h of sleep), diagnosed with mixed sleep apnea, or who were already on positive pressure therapy were excluded from further analyses. Patients with bronchogenic carcinoma or concomitant interstitial lung disease were also not included. The institutional review board approved the research protocol and granted a waiver of informed consent.

### Study Variables

Baseline biometric parameters of age, height, weight, BMI, and gender were extracted from the CPRS. Collected data included demographic, anthropometric, and clinical characteristics; smoking status [current (more than 10 cigarettes per day) or past/never smoker]; diabetes mellitus; hypertension (defined according to international guidelines or through the use of antihypertensive drugs); hypercholesterolemia (defined as >250 mg/dl in blood serum or current use of lipid-lowering agents); and medication use, including antihypertensive drugs, lipid-lowering agents, antiplatelet therapy, and anticoagulants. Forced spirometry was performed according to the guidelines of the American Thoracic Society [12].

### Sleep Study and CPAP Treatment

The definitions and criteria used in the sleep laboratory during the period of review were based on the American Academy of Sleep Medicine practice parameters current at the time of the study [13]. Apnea was defined as a complete cessation of airflow lasting for >10 s. Hypopnea was defined as reduction in the respiratory airflow of ≥30 % or thoracoabdominal excursion lasting >10 s, and accompanied by a decrease of ≥4 % in oxygen saturation and/or an arousal. The AHI was defined as the number of apneas and hypopneas per hour of sleep. Severity of OSA was judged from AHI data and graded as mild ($5 \geq AHI < 15$/h), moderate ($15 \geq AHI \leq 30$/h), or severe (AHI > 30/h).

Once the diagnosis of OSA was established, nasal CPAP was prescribed to all patients following a CPAP titration study according to standard sleep laboratory protocols. Supplemental $O_2$ was added during the CPAP titration when, prior to the CPAP titration, the patient's awake supine $SpO_2$ while breathing room air was ≤88 %. Otherwise, supplemental oxygen was provided during the CPAP titration when $SpO_2$ is ≤88 % for ≥5 min in the absence of obstructive respiratory events. In both instances, supplemental $O_2$ was introduced at 1 l/min and titrated upward to achieve a target $SpO_2$ between 88 and 94 %. A respiratory therapist provided education about the basic

operation and care of the CPAP device and the mask. An educational brochure on OSA and CPAP treatment was given to each patient during the education session. The respiratory therapist would then select and fit a comfortable CPAP mask from a wide range of choices.

Adherence to CPAP was always objectively assessed by reading the time counter of the device from the start of treatment to the end of follow-up (death or censorship). Patients were classified as being adequately treated with CPAP if treatment had been started and the average cumulative adherence was at least 4 h/night, and as untreated if CPAP was not prescribed or if the patient declined to use, could not tolerate the device, or was persistently noncompliant (average use <4 h/night).

### Follow-up

All patients were managed according to the prevailing international recommendations for these diseases. Patients were seen at 3-month intervals during the first year and every 6 months thereafter in the outpatient sleep clinic. Date and death and underlying contributory causes of death were obtained from medical records and the New York Vital Statistics. Vital status was further checked against the US Social Security Death Index and the National Death Index.

### Statistical Analysis

Continuous variables were analyzed with the Student's $t$ test or Mann–Whitney $U$ test when the distribution departed from normality and were described as mean (standard deviation) or median (range of values), respectively. Discrete variables are summarized as frequency (group percentage). Proportions were compared using the $\chi^2$ test with Yates correction or Fisher's exact test when necessary. The primary end point in our study was all-cause mortality. Nonadjusted survival was calculated by the Kaplan–Meier method, with data censored at the time of the end of follow-up. The log rank test was used to compare differences among groups. Multivariate Cox proportional hazard regression models were used to determine whether hypercapnia increases the risk of all-cause mortality among patients with overlap syndrome not adherent to CPAP treatment. Hazard ratios (HR) and 95 % confidence intervals were calculated to assess the unadjusted and adjusted relationships between independent variables and the primary end point. In the univariate analysis, we considered the following variables as potential prognostic factors: age, BMI, Charlson Index, use of lipid-lowering and antiplatelet agents, $FEV_1$, and CPAP adherence. Variables with a significant unadjusted association with outcome ($p \leq 0.1$) were entered into a forward stepwise Cox model. All tests are 2-tailed with a 0.05 significance level. Analyses were completed using STATA 12 software (StataCorp LP, College Station, TX).

## Results

### Patient Characteristics

A total of 271 patients with overlap syndrome were identified during the study period. One hundred four had daytime hypercapnia with a mean $PaCO_2$ of 51.6 ± 4.3 mmHg. The baseline patient characteristics for the hypercapnic and normocapnic groups of patients with OSA are given in Table 1. The two groups were similar in age, gender, BMI, smoking, medications, and underlying comorbidities; however, hypercapnic patients had worse pulmonary function and were more likely receiving supplemental oxygen therapy compared to nonhypercapnic patients. There were no

**Table 1** Characteristics of the study population

| | Nonhypercapnic ($n = 167$) | Hypercapnic ($n = 104$) | $p$ |
|---|---|---|---|
| Age (years) | 67.9 ± 10.7 | 68.2 ± 9.7 | 0.83 |
| Gender (M/F) | 165/2 | 102/2 | 0.64 |
| BMI (kg/m$^2$) | 34.7 ± 6.8 | 36.4 ± 8.7 | 0.07 |
| Hypertension [$n$ (%)] | 131 (78) | 84 (81) | 0.65 |
| Diabetes [$n$ (%)] | 72 (43) | 52 (50) | 0.27 |
| Hyperlipidemia [$n$ (%)] | 75 (45) | 50 (48) | 0.70 |
| Current smoking [$n$ (%)] | 60 (36) | 32 (31) | 0.46 |
| Lipid-lowering therapy [$n$ (%)] | 18 (11) | 10 (10) | 0.92 |
| Antiplatelet therapy [$n$ (%)] | 65 (39) | 44 (42) | 0.67 |
| Supplemental oxygen [$n$ (%)] | 67 (40) | 80 (77) | <0.001 |
| Charlson comorbidity index (range) | 6 (4–7) | 6 (4.5–7) | 0.62 |
| $FEV_1$ (L) | 2.1 ± 0.56 | 1.7 ± 0.5 | <0.001 |
| FVC (L) | 3.2 ± 0.79 | 2.8 ± 1.1 | <0.001 |
| $FEV_1$/FVC (%) | 62.1 ± 7.2 | 58.2 ± 9.9 | <0.001 |
| $PaCO_2$ (mmHg) | 37.0 ± 2.7 | 51.6 ± 4.3 | <0.001 |
| Epworth sleepiness scale | 12 (8–14) | 11 (9–14) | 0.32 |
| AHI (h$^{-1}$) | 29.2 ± 23.8 | 35.2 ± 29.2 | 0.07 |
| Severity of OSA [$n$ (%)] | | | 0.20 |
| Mild | 70 (42) | 34 (33) | |
| Moderate | 43 (26) | 26 (25) | |
| Severe | 54 (32) | 44 (42) | |

significant differences in daytime sleepiness, total sleep time, sleep efficiency, or sleep architecture between the two groups. However, hypercapnic patients were more likely to spend time sleeping with $SpO_2 < 90$ % than normocapnic patients (32.7 ± 31.9 vs. 24.2 ± 27.9; $p = 0.03$). Although the severity of sleep apnea was higher in the hypercapnic group (AHI 35.2 ± 29.2 events/h) compared to the nonhypercapnic group (AHI 29.2 ± 23.8 events/h), the difference was not statistically significant ($p = 0.07$).

## CPAP Treatment

The mean CPAP pressure following the titration study was 9.1 ± 2.6 cm $H_2O$ for the nonhypercapnic group and 10.9 ± 3.7 cm $H_2O$ for the hypercapnic group ($p = 0.24$). CPAP treatment did not affect sleep efficiency or total sleep time in either group; however, it significantly improved the sleep architecture in both groups by decreasing the proportion of stage 1 sleep and increasing slow-wave sleep as well as REM stage sleep (Table 2). CPAP treatment also significantly increased the minimal $SaO_2$ and the time spent with $SpO_2 < 90$ % in both groups. The rate of CPAP adherence was 43 and 42 % for the normocapnic group and the hypercapnic group ($p = 0.9$) with a median of 5.4 and 5.1 h/night, respectively (Table 3).

## Mortality

During a median follow-up of 71 months, 64 deaths (24 % mortality rate) were reported. The mortality rate was significantly higher in the hypercapnic group than in the normocapnic group [36 deaths (35 % mortality rate) vs. 28 deaths (17 % mortality rate); $p = 0.001$]. Cardiovascular disease was the most common cause of death (9.6 %), followed by respiratory failure (6.6 %) and malignancies (4.1 %). Causes of death for the hypercapnic and the normocapnic group were respiratory failure (12.5 vs. 2.9 %), cardiovascular disease (11.5 vs. 8.4 %), cancer (5.8 vs. 3.0 %), and other (4.8 vs. 2.4%) (Table 4). A higher survival rate was observed for CPAP-treated patients compared to untreated patients with the overlap syndrome ($p = 0.048$) (Fig. 1). Kaplan–Meier analysis showed that hypercapnic patients who were adherent with CPAP had reduced mortality compared to nonadherent hypercapnic patients ($p = 0.04$) (Fig. 2). In contrast, the cumulative mortality rate for normocapnic patients was not significantly different between the adherent and nonadherent groups ($p = 0.42$) (Fig. 2).

**Table 2** Polysomnographic characteristics before and after CPAP titration

| | Nonhypercapnic ($n = 167$) | | Hypercapnic ($n = 104$) | |
|---|---|---|---|---|
| | Baseline | CPAP | Baseline | CPAP |
| TST (min) | 204.6 ± 54.3 | 199.7 ± 47.1 | 191.4 ± 61.1 | 194.3 ± 42.3 |
| Sleep efficiency (%) | 63.1 ± 20.2 | 64.3 ± 18.7 | 62.6 ± 18.7 | 61.3 ± 20.5 |
| N1 (%) | 21.1 ± 16.4 | 15.3 ± 8.9* | 20.9 ± 15.6 | 16.5 ± 8.5* |
| N2 (%) | 39.7 ± 13.5 | 41.2 ± 14.7 | 42.8 ± 14.9 | 39.1 ± 12.6 |
| N3 (%) | 7.1 ± 1.2 | 8.6 ± 2.3 | 4.3 ± 1.9 | 7.7 ± 2.4* |
| REM (%) | 6.7 ± 4.8 | 11.3 ± 5.6* | 3.9 ± 5.4 | 7.3 ± 4.9* |
| AHI ($h^{-1}$) | 29.2 ± 23.8 | 3.1 ± 2.1* | 35.2 ± 29.2 | 4.2 ± 2.5* |
| CT90 (%) | 24.2 ± 27.9 | 5.4 ± 7.8* | 32.7 ± 31.9 | 11.7 ± 14.3* |
| $O_2$ nadir (%) | 80.1 ± 6.3 | 89.3 ± 2.9* | 77.4 ± 8.5 | 87.9 ± 2.3* |

*TST* total sleep time

* $p < 0.05$ compared to baseline

**Table 3** Demographic and baseline sleep characteristics stratified by CPAP adherence

| CPAP | Nonhypercapnic | | Hypercapnic | |
|---|---|---|---|---|
| | Adherent ($n = 72$) | Nonadherent ($n = 95$) | Adherent ($n = 44$) | Nonadherent ($n = 60$) |
| Age (years) | 69.8 ± 10.1 | 66.7 ± 11.2 | 67.8 ± 10.6 | 68.6 ± 9.0 |
| BMI ($kg/m^2$) | 33.7 ± 5.6 | 35.2 ± 7.7 | 37.1 ± 10.7 | 36.1 ± 7.3 |
| Charlson index | 6 (5–7) | 5 (4–7) | 6 (5–7) | 6 (4–6) |
| ESS | 11.5 (8–13) | 12 (9.5–15) | 10.5 (9–14) | 11 (10–13) |
| AHI ($h^{-1}$) | 32.1 ± 24.4 | 27.0 ± 23.1 | 38.8 ± 31.9 | 32.2 ± 24.6 |

*ESS* epworth sleepiness scale

**Table 4** All-cause mortality in the study cohort

| Causes of death | Nonhypercapnic | | Hypercapnic | |
|---|---|---|---|---|
| | Adherent ($n = 72$) | Nonadherent ($n = 95$) | Adherent ($n = 44$) | Nonadherent ($n = 60$) |
| Cardiovascular [$n$ (%)] | 4 (6) | 10 (11) | 3 (7) | 9 (15) |
| Respiratory failure [$n$ (%)] | 1 (1) | 4 (4) | 5 (11) | 8 (13) |
| Cancer [$n$ (%)] | 2 (3) | 3 (3) | 1 (2) | 5 (8) |
| Other [$n$ (%)] | 3 (4) | 1 (1) | 2 (5) | 3 (5) |

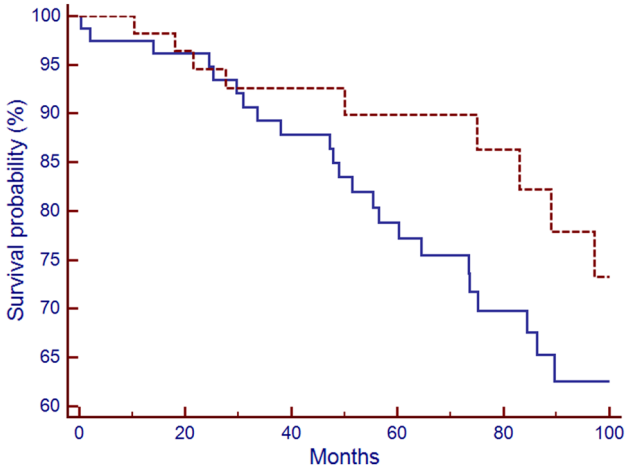


**Fig. 1** Kaplan–Meier survival curves comparing continuous positive airway pressure (CPAP)-treated (*dotted line*) versus nontreated patients (*continuous line*) in the cohort group of overlap syndrome. Log rank test 3.88; $p = 0.048$ for the comparison between CPAP-treated and nontreated groups

The results of the univariate Cox proportional hazards models for predictors of mortality in the normocapnic and the hypercapnic group are presented in Table 5. Age and Charlson Index were related to increased risk of death from any cause in the nonhypercapnic group, while CPAP adherence was associated with improved survival in the hypercapnic patients. In multivariate analysis, CPAP adherence was the only factor independently responsible for attenuation of the mortality risk in hypercapnic patients with the overlap syndrome (HR 0.65; $p = 0.04$) (Table 6). In normocapnic patients, the Charlson Index remained a significant risk of all-cause mortality after adjustment for age and AHI (HR 1.68; $p < 0.001$). CPAP adherence in this group was not shown to confer decreased risk of death ($p = 0.21$).

## Discussion

The current study suggests that hypercapnic patients with the overlap syndrome are at increased risk of mortality, particularly from cardiovascular diseases, independent of age, gender, or BMI in comparison to normocapnic patients with the overlap syndrome. CPAP treatment reduced the excess risk of death in hypercapnic but not in normocapnic patients despite similar adherence rate in both groups.

Our findings concur with those of prior investigations that pointed to a reduced risk of mortality from CPAP treatment in patients with the overlap syndrome. However, our results suggest that the benefit is restricted to the hypercapnic group only. This unexpected observation raises two questions: was the reduction in mortality related to the CPAP-improved physiologic derangements of severe COPD per se, or was the lack of benefit in the nonhypercapnic group the byproduct of statistical sampling?

Previous studies addressing predictors of survival in COPD patients have established, although not consistently, that chronic hypercapnia in COPD was linked to a higher mortality rate [14]. Knowing that respiratory muscle weakness and hypercapnic ventilatory response are mediators of hypercapnia, institution of positive airway pressure has been implicated in decreasing muscle load, promoting inspiratory muscle strength and endurance, and improving ventilation/perfusion ratio [15, 16]. De Miguel et al. [17] evaluated the effects of CPAP therapy on lung function in patients with overlap syndrome over two consecutive years. After 6 months of CPAP therapy, there were statistically significant increases in $PaO_2$, $FEV_1$, and forced vital capacity. The amelioration was most notable in the hypercapnic group of patients with overlap syndrome. Mansfield and Naughton [18] reported similar improvement in gas exchange after 3 months of CPAP therapy. More importantly, two recent studies have suggested survival benefit from positive airway pressure in hypercapnic COPD patients [10, 19]. The premise for the reduction in mortality has not been completely elucidated, although it should be stated that none of these studies has investigated the possibility of coexisting sleep-disordered breathing in these patients.

Surprisingly, we did not find evidence for an association between severity of airway obstruction and risk of mortality in the hypercapnic and normocapnic groups. This was reported previously in a study by Oswald-Mammosser et al. [20] among 84 COPD patients receiving long-term oxygen therapy. Survival analysis of their study revealed

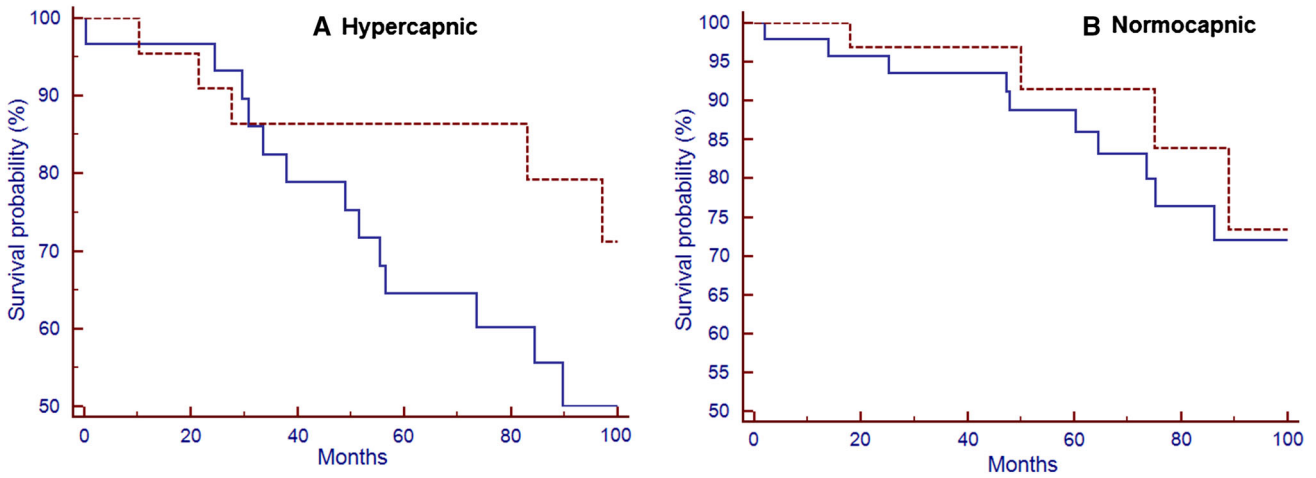


**Fig. 2** Kaplan–Meier survival curves comparing continuous positive airway pressure (CPAP)-treated (*dotted line*) versus nontreated patients (*continuous line*) in the cohort group of hypercapnic patients with the overlap syndrome (*left*) and normocapnic patients with the overlap syndrome (*right*). Log rank test 4.16; $p = 0.04$ for the comparison between CPAP-treated and nontreated hypercapnic patients. Log rank test 0.63; $p = 0.42$ for the comparison between CPAP-treated and untreated normocapnic patients

**Table 5** Univariate cox proportional hazard ratios for the risk of death in patients with hypercapnia and nonhypercapnia

| | Nonhypercapnic | | Hypercapnic | |
|---|---|---|---|---|
| | HR (95 % CI) | *p* | HR (95 % CI) | *p* |
| Age (years) | 1.04 (1.01–1.07) | 0.01 | 1.00 (0.96–1.03) | 0.87 |
| BMI (kg/m$^2$) | 0.98 (0.96–1.02) | 0.22 | 1.02 (0.99–1.05) | 0.16 |
| Charlson index | 1.69 (1.31–2.19) | <0.001 | 1.2 (0.97–1.49) | 0.08 |
| FEV1 (L) | 0.61 (0.32–1.18) | 0.14 | 0.79 (0.38–1.87) | 0.23 |
| ESS | 1.01 (0.93–1.10) | 0.71 | 1.12 (0.97–1.36) | 0.11 |
| AHI (h$^{-1)}$ | 1.09 (0.96–1.11) | 0.08 | 1.00 (0.99–1.02) | 0.21 |
| CPAP adherence | 0.72 (0.32–1.63) | 0.43 | 0.47 (0.23–0.89) | 0.006 |

**Table 6** Multivariate cox proportional hazard ratios for the risk of death in patients with hypercapnia and nonhypercapnia

| | HR (95 % CI) | *p* |
|---|---|---|
| Nonhypercapnic | | |
| Age (years) | 0.99 (0.95–1.03) | 0.85 |
| Charlson index | 1.68 (1.27–2.23) | 0.0003 |
| AHI (h$^{-1}$) | 1.01 (1.00–1.03) | 0.24 |
| Hypercapnic | | |
| Charlson index | 1.14 (0.89–1.35) | 0.18 |
| CPAP adherence | 0.65 (0.31–0.92) | 0.04 |

that the level of pulmonary artery pressure and not $FEV_1$ predicted survival. Stanchina et al. [9] had similar findings. We attribute our observation to the relatively homogeneity of the participants in each study group. In addition, our sample size may have been too small to achieve adequate power to test this hypothesis.

Although cardiovascular disease was the predominant cause of death in our study cohort, mortality in the hypercapnic group was attributed predominantly to hypercapnic respiratory failure. Hypoxemia, which is more pronounced in hypercapnic patients than in normocapnic patients with overlap syndrome, may contribute to skeletal muscle dysfunction through the activation of inflammatory pathways. Clinical studies in COPD patients have found that circulating levels of TNF-α and soluble TNF receptors increase as arterial oxygen saturation decreases [21]. These levels and the levels of other circulating inflammatory cytokines such as interleukin-8 have been shown to correlate with the degree of muscle dysfunction in COPD [22]. By unloading the respiratory muscles, CPAP treatment delays pump failure but the level of inspiratory pressure may have not been adequate to achieve maximum benefit [23].

Limitations to our study include its retrospective nature. CPAP treatment was not randomly allocated in both the hypercapnic and normocapnic groups. It is possible that some patients may have been mistakenly classified as treated due to difficulty in assessing long-term CPAP compliance. Also, patients who were classified as untreated may have started CPAP treatment at a later date. A randomized prospective trial to test our hypothesis would have been ideal but not possible, since withholding CPAP therapy from patients with OSA would have been challenged on ethical grounds because of the long-term follow-up and the presence of symptomatic patients in whom CPAP could not be withheld. Second, the study participants were all enrolled after referral to the sleep clinic, which could have resulted in selection bias. Although this

limitation is unavoidable in a clinical cohort, we included all COPD patients who were referred to our sleep clinic over the 8-year period. Third, the present study could be implicated in selection bias when comparing patients who tolerate CPAP therapy with those who do not insofar as intolerant patients could have a distinct profile for adherence to other treatments. This potential incongruity in health profiles may have explained the increase in cardiovascular risk, which could have led to excessive mortality rates. Although this could be the case, we used a multivariate statistical analysis to take into account all the confounding parameters (full model) that we considered important for explaining the differences in mortality. Fourth, pulmonary hypertension has been shown to be more prevalent in patients with overlap syndrome than in those patients with COPD alone [24]. Whether the increased mortality in overlap syndrome patients can be linked to pulmonary hypertension is difficult to ascertain from this study as estimates of pulmonary artery pressure were not documented consistently.

In conclusion, our results suggest that OSA in hypercapnic patients but not in normocapnic patients with the overlap syndrome has an unfavorable effect on long-term mortality. CPAP treatment is associated with a reduction in this excess risk. Future studies should be targeted in improving CPAP compliance in hypercapnic patients with the overlap syndrome.

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**Conflict of interest** The authors have no conflicts of interest or financial ties to disclose.

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