Original Article

Prognostic efficacy of non-invasive ventilation in patients with overlap syndrome: chronic obstructive pulmonary disease and obstructive sleep apnea

Yang Gao[1]#, Zhengyang Fan[2]#, Hehe Zhang[1], Yuanni Jiao[1], Naima Covassin[3], Fei Li[1], Jiang Xie[1,4]

[1]Department of Pulmonary and Critical Care Medicine, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [2]Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China; [3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, USA; [4]Centre for Sleep Medicine and Science, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

Contributions: (I) Conception and design: Y Gao, Z Fan, N Covassin, J Xie; (II) Administrative support: J Xie; (III) Provision of study materials or patients: Y Gao, Z Fan, H Zhang, Y Jiao, F Li, J Xie; (IV) Collection and assembly of data: Y Gao, Z Fan, Y Jiao, J Xie; (V) Data analysis and interpretation: Y Gao, Z Fan, H Zhang, J Xie; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

#These authors contributed equally to this work as co-first authors.

Correspondence to: Jiang Xie, MD, PhD. Department of Pulmonary and Critical Care Medicine, Beijing Anzhen Hospital, Capital Medical University, 2# Anzhen Road, Beijing 100029, China; Centre for Sleep Medicine and Science, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. Email: frank782008@aliyun.com.

Background: Limited evidence exists regarding the effects of non-invasive ventilation (NIV) on the prognosis of patients with concomitant chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), also known as overlap syndrome (OS). This study aimed to assess whether NIV alongside standard care could improve the prognosis of this cohort.

Methods: We retrospectively collected data from 229 patients with severe OS treated in Beijing Anzhen Hospital between January 1, 2016 and January 1, 2020, with follow-up until December 1, 2023. All patients were recommended usual care and NIV and were subsequently divided into non-NIV (usual care only) and NIV groups (usual care plus NIV) per their willingness and adherence to NIV. Endpoints included all-cause and acute exacerbation of COPD (AECOPD)-associated death and re-hospitalization. Multivariate analyses were used to determine the relationship of NIV with prognosis.

Results: The follow-up lasted for a median of 760 days (interquartile range, 245–1,374 days). Patients in the NIV group showed lower rates of all-cause (37.5% *vs.* 65.1%, P<0.001) and AECOPD-associated (31.7% *vs.* 58.7%, P<0.001) death compared with patients in the non-NIV group. Compared with usual care only, NIV treatment was associated with significant reduction in all-cause death [relative risks (RR) =0.459, 95% confidence interval (CI): 0.315–0.668, P<0.001], AECOPD-associated mortality (RR =0.424, 95% CI: 0.283–0.635, P<0.001), and re-hospitalization for all causes (RR =0.455, 95% CI: 0.342–0.605, P<0.001) and for AECOPD (RR =0.421, 95% CI: 0.308–0.575, P<0.001) in Cox hazards models, with significance persisting after multivariable adjustment.

Conclusions: NIV may improve outcomes and survival in patients with severe OS of comorbid COPD and OSA. Confirmatory studies are needed to prove benefits.

Keywords: Chronic obstructive pulmonary disease (COPD); non-invasive ventilation (NIV); obstructive sleep apnea (OSA); overlap syndrome (OS); mortality; rehospitalization

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by progressive bronchial obstruction, is one of the leading causes of death worldwide (1), with acute exacerbation of COPD (AECOPD) and respiratory failure being the main determinants of adverse outcomes (2,3). Obstructive sleep apnea (OSA) is a prevalent respiratory disorder characterized by repeated upper airway obstructions resulting in severe intermittent hypoxia, sleep disruption, and respiratory muscle fatigue. OSA contributes to the worsening of underlying diseases and negative prognosis (4,5). Importantly, OSA is highly prevalent (65.9%) in patients with moderate to severe COPD (6). Patients with overlap syndrome (OS) exhibit ventilatory defects in both lower and upper airway and experience more adverse outcomes, including higher mortality rates than those with COPD or OSA alone (7,8).

Non-invasive ventilation (NIV) application, mostly in the form of bi-level positive airway pressure, has reportedly improved quality of life and survival in patients with COPD (9). Meanwhile, Marin and colleagues discovered that, when treated with continuous positive airway pressure (CPAP), mortality risk of patients with OS appeared to be comparable to that of patients with isolated COPD (10), implying that CPAP might mitigate the excess risk caused by OSA in that population. However, to the best of our knowledge, whether NIV can improve outcomes in patients with OS has not been reported. Considering that NIV might correct the ventilatory defect and further suppress

abnormal sleep breathing events, we hypothesized that NIV treatment would improve the prognosis of patients with OS of severe comorbid COPD and OSA. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-390/rc).

Methods

Study design and patient enrollment

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Anzhen Hospital (No. ks2019020) and individual consent for this retrospective analysis was waived. All patients treated for COPD in Beijing Anzhen Hospital, Capital Medical University from January 1, 2016 to January 1, 2020 were retrospectively screened through chart review for eligibility. We enrolled severely ill patients whose medical providers indicated the need for long-term NIV therapy due to one or more of the following reasons: (I) refractory hypercapnia or repeated relapse of respiratory failure despite adequate pharmacotherapy (11); (II) intolerance to CPAP therapy; (III) high CPAP pressure exceeding 15 cm of water; (IV) development of hypercapnia after CPAP therapy. Although strongly recommended by clinicians, adoption of NIV was decided by the patients themselves based on their response and tolerance to initial attempts of NIV and financial considerations. Exclusion criteria were as follows: (I) low risk of OSA as determined by Berlin Questionnaire (12,13); (II) previous treatment with positive airway pressure for OSA or COPD; (III) neuromuscular or chest wall diseases; (IV) clinical indication for invasive mechanical ventilation; (V) end-stage chronic diseases such as, heart failure of New York Heart Association stage IV, advanced cancer and renal failure on dialysis; (VI) cognitive disorders or acute psychiatric episodes; (VII) unavailability of follow-up records (*Figure 1*).

Diagnosis of OS

The diagnoses of COPD and OSA were made by the attending physician, and two independent investigators extracted the relevant information manually. If patients were identified to have both COPD and OSA, OS was diagnosed retrospectively. Post-bronchodilator pulmonary

---

Highlight box

Key findings
- Non-invasive ventilation (NIV) reduces the incidence of re-hospitalization and mortality in patients with severe overlap syndrome (OS) of comorbid chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA).

What is known and what is new?
- Patients with OS experience more adverse outcomes, including higher mortality rates than those with COPD or OSA alone.
- Our study showed that, along with usual care, NIV treatment may be prognostically beneficial in patients with severe OS.

What is the implication, and what should change now?
- Well-designed, randomized studies are needed to confirm the prognostic improvement associated with NIV therapy for patients with OS.

```
                    ┌─────────────────────────────┐
                    │   NIV recommended (n=364)    │
                    └─────────────────────────────┘
                                  │
                                  │            ┌──────────────────────────────────────────┐
                                  ├───────────▶│ OSA excluded by BQ or sleep test (n=87)  │
                                  │            └──────────────────────────────────────────┘
                                  ▼
                    ┌─────────────────────────────┐
                    │   Patients with OS (n=277)   │
                    └─────────────────────────────┘
```

- Previous treatment of positive airway pressure (n=30)
- Neuromuscular or chest wall diseases (n=2)
- End stage of chronic diseases (n=4)
- Require invasive mechanical ventilation (n=3)
- Difficulties of follow-up (n=2)
- Unavailable records of follow-up (n=7)

```
                    ┌─────────────────────────────┐
                    │  Patients followed up (n=229)│
                    └─────────────────────────────┘
                           │               │
                           ▼               ▼
              ┌───────────────────┐  ┌───────────────────────┐
              │ NIV group (n=120) │  │ Non-NIV group (n=109) │
              └───────────────────┘  └───────────────────────┘
```
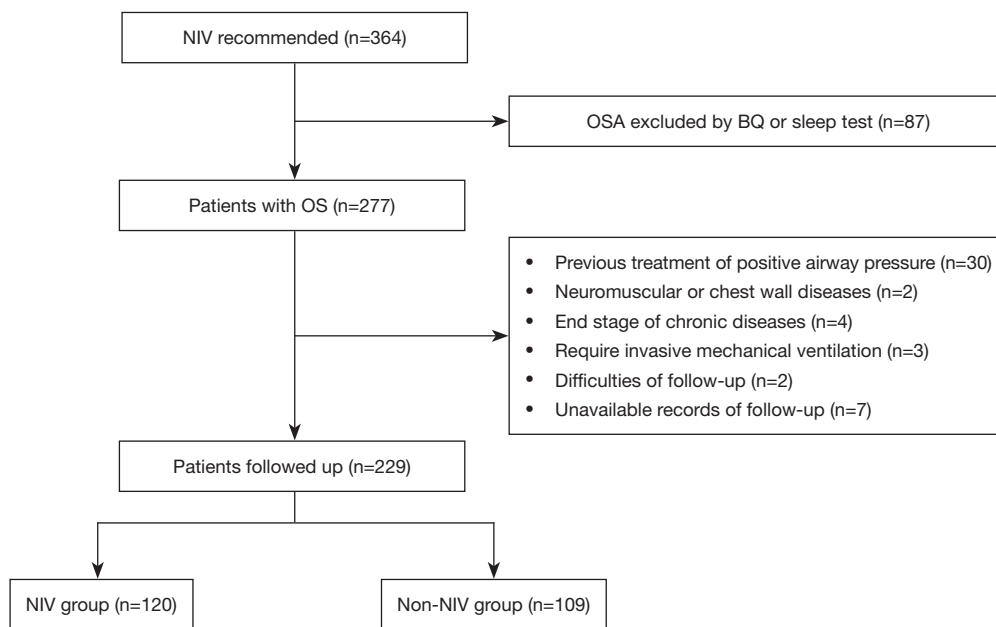
Figure 1 Flow chart of the enrollment of patients with severe OS (n=229). BQ, Berlin Questionnaire; NIV, non-invasive ventilation; OS, overlap syndrome; OSA, obstructive sleep apnea.

function was assessed by spirometry (Master Screen, Jaeger, Germany). Patients were instructed to breath normally for 30 s followed by forceful exhalation into the spirometer. Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and total lung capacity were measured. Predicted percentages (%) for FEV_1 were calculated, and COPD was diagnosed if FEV_1/FVC was lower than 70%. Previous diagnosis of COPD was ascertained by medical record review for 108 patients whose disease severity precluded spirometry during hospitalization.

The probability of OSA was assessed for patients suspected of sleep disorders, either through administration of the Berlin Questionnaire (n=112) or sleep test (n=107). The Berlin Questionnaire comprises 11 questions investigating snoring, sleepiness, and cardiometabolic disorders (hypertension and obesity) (12). Questions were asked in Mandarin by physicians or investigators who assisted in filling out the questionnaires. Patients were considered to have OSA if at least two out of three categories were positive. Sleep tests were conducted using either the E-Series system for Sleep/EEG (Compumedics Ltd., Abbotsford, Victoria, Australia) or the Alice PDx portable sleep diagnostic system (Philips Respironics, Murrysville, PA, USA). Airflow was monitored using a nasal

pressure transducer and oronasal thermocouple. Surface electrodes were applied to record electroencephalogram, electrooculogram, and submental electromyogram. Breath-sensing plethysmography of thoraco-abdominal movement was adopted to measure respiratory effort. Experienced registered polysomnographic technologists, who were blinded to other clinical data, scored the sleep study digitally. Apnea was scored if thermal airway channel demonstrated a ≥90% airflow decrease lasting longer than 10 s, whereas hypopnea was scored if nasal pressure channel showed a ≥30% airflow decline lasting longer than 10 s with ≥3% oxygen desaturation associated with the aforementioned breathing events. Apnea-hypopnea index (AHI) is the number of apnea and hypopnea per hour, and patients with AHI ≥5/h were diagnosed with OSA.

Echocardiography

Transthoracic echocardiogram was completed by using Vivid7-BT06 color Doppler imaging (General Electric, Milwaukee, WI, USA). Tricuspid regurgitation peak velocity (TRV) and right atrium pressure were recorded at the end of expiration. Systolic pulmonary arterial pressure (SPAP) was calculated by using the following formula: SPAP

$= 4 \times TRV^2 +$ right atrium pressure.

NIV therapy and compliance

All participants accepted the usual care, such as bronchodilators and oxygen supplement as needed, and were divided into NIV (n=120) or non-NIV (n=109) groups according to their acceptance and adherence to NIV, although all patients were considered eligible for NIV. A fixed-pressure ventilatory mode, specifically the BiPAP ST mode, was selected for all patients. Manual titration was completed at the bedside without polysomnography monitoring. Expiratory positive airway pressure (EPAP) was set to reduce AHI to less than 15 events/h and inspiratory positive airway pressure (IPAP) was titrated to ensure reasonable tidal volume and arterial blood gas (ABG) analysis. In addition to nocturnal NIV treatment, patients were allowed to change the ventilatory settings temporarily if they decided to use NIV during the day. Ventilatory data were recommended to be evaluated routinely every 3 to 6 months after discharge, with settings adjusted if necessary. Adherence to NIV was deemed satisfactory when the system was used for more than 5 days a week and 4 hours per day. One patient from the NIV group crossed over into the non-NIV group because of low adherence (usage of NIV of less than 2 days/week).

Follow-up and outcomes

Patients were retrospectively contacted via telephone call or in-person interview to ascertain their vital status, NIV adherence and the incidence of clinical outcome variables following their discharge from the hospital. Additionally, to avoid the omission of re-hospitalization records, a thorough medical chart review was manually conducted at Beijing Anzhen Hospital. Primary outcomes were all-cause mortality and death due to AECOPD (including respiratory failure) (14), and secondary endpoints referred to all-cause and AECOPD-associated re-hospitalizations (14).

Statistical analysis

Continuous data were presented as medians with interquartile range (IQR), whereas categorical data were expressed as frequency and percentage. Differences between the groups were compared using Wilcoxon tests for continuous variables and chi-squared test for categorical variables. Kaplan-Meier cumulative-event curves were

constructed using NIV application as exposure to describe the probability of outcomes over time. Cox proportional hazard regression was used to determine whether NIV treatment was associated with improved long-term prognosis of OS patients. Confounding variables incorporated and adjusted for in the multivariable analysis included age, sex, and number of hospitalizations for AECOPD in the year prior to the enrollment, all widely recognized risk factors for adverse outcome of COPD (15). Relative risk (RR) and 95% confidence interval (CI) were calculated for the association between NIV application and clinical outcomes. Statistical analysis was performed using JMP software, Version 14.1 (SAS Institute, Cary, NC, USA), with a two-sided P<0.05 being considered as significant.

Results

Baseline characteristics of patients enrolled

In total, 229 severely ill patients who met the screening criteria (149 males, 65.1%) were selected. Of these, 109 (47.6%) patients were verified to accept usual care only (non-NIV group), whereas 120 (52.4%) patients adhered to NIV treatment alongside usual care (NIV group). Patients' characteristics at baseline are shown in *Table 1*. Compared to patients in the non-NIV group, patients who accepted the NIV treatment were significantly more obese and had higher values of SPAP and TRV on echocardiographic findings as well as partial pressure of carbon dioxide (PCO_2) on ABG tests. No significant differences were noted between the two groups regarding most of the other clinical data, including age, sex, prevalence of hypertension, diabetes, coronary heart diseases, cerebrovascular diseases, and use of inhaled bronchodilators and corticosteroids. Regarding the severity of COPD, NIV and non-NIV groups presented with similar post-bronchodilator spirometric data, i.e., FEV_1/FVC and $FEV_1\%$ predicted, and number of hospitalizations for AECOPD in the year prior to enrollment.

NIV treatment

Three-to-twelve months post discharge from the hospital, the changes of $FEV_1\%$ predicted and FEV_1/FVC were not significantly different between patients with and without NIV treatment (2.9% *vs.* 1.3%, P=0.12, and 1.43% *vs.* 0.35%, P=0.29). However, NIV treatment significantly reduced SPAP and TRV, with changes in both variables

Table 1 Characteristics of patients with severe OS grouped by NIV application

Characteristics	Total (N=229)	NIV (n=120)	Non-NIV (n=109)	P
Age, years	69 [64–77.8]	69 [64–77]	70 [64–78.5]	0.59
Sex, male	149 [65.1]	74 [61.7]	75 [68.8]	0.26
BMI, kg/m^2	27.1 [23.3–31.6]	27.5 [24.5–32.8]	24.3 [21.7–28.9]	0.001
AHI	22.5 [12.2–41.2]	26.3 [13.8–44.1]	20.1 [8.2–31.7]	0.07
Epworth Sleepiness Scale	10 [5–12]	10 [5–13.5]	10 [5–12]	0.98
FEV$_1$/FVC, %	63.3 [48.2–73.2]	61.3 [50.2–75.6]	64.3 [46.7–72.1]	0.59
FEV$_1$, % predicted	43.6 [30.7–68.9]	42.3 [29.5–71.4]	44.7 [31.9–66.5]	0.67
FEV$_1$, L	1.05 [0.79–1.55]	1.03 [0.67–1.52]	1.06 [0.9–1.64]	0.44
FVC, L	1.79 [1.38–2.36]	1.79 [1.22–2.34]	1.83 [1.46–2.40]	0.47
No. of hospitalizations for AECOPD in the year prior to enrollment	2 [1–3]	2 [1–3]	2 [1–3]	0.62
CAT	21 [19–25]	22 [18–25.8]	21 [19–23.5]	0.26
PH in ABG	7.37 [7.32–7.41]	7.37 [7.33–7.4]	7.38 [7.3–7.43]	0.43
PCO$_2$ in ABG, mmHg	54.6 [45.5–64]	58 [51.3–68.4]	51.9 [41.4–59.9]	<0.001
Echocardiography				
Systolic pulmonary arterial pressure, mmHg	43 [31–60]	47 [34.8–64]	40 [28–52]	0.007
Tricuspid regurgitation peak velocity, s/m	286 [233–353.5]	317 [262–379.3]	262 [208.8–311.8]	<0.001
Comorbidities				
Hypertension	141 [62]	73 [61]	68 [62]	0.81
Diabetes	63 [28]	34 [28]	29 [27]	0.77
Coronary artery diseases	72 [32]	41 [34]	31 [29]	0.40
Cerebrovascular disease	40 [17]	21 [18]	19 [17]	0.99
Medication in follow-up				
Inhaled corticosteroids	188 [82]	99 [83]	89 [82]	0.87
Inhaled bronchodilators	222 [97]	116 [97]	106 [97]	0.80

Data are presented as median [IQR] or n [%]. ABG, arterial blood gas analysis; AECOPD, acute exacerbation of COPD; AHI, apnea-hypopnea index; BMI, body mass index; CAT, COPD Assessment Test; FEV$_1$, forced expiratory volume in the first second; FVC, forced vital capacity; IQR, Interquartile range; NIV, non-invasive ventilation; OS, overlap syndrome; PH, potential of hydrogen; PCO$_2$, partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease.

differing significantly between NIV and non-NIV groups (–8 *vs.* 6 mmHg, P=0.01, and –48 *vs.* 61 m/s, P<0.001).

NIV and risk of mortality

After a median 25 months of follow-up, 45 (37.5%) and 71 (65.1%) patients in the NIV group and non-NIV group died, respectively. The causes of mortality were AECOPD (including respiratory failure) [102 (87.9%)], cardiovascular events [7 (6.0%)], cancer [4 (3.5%)], acute abdominalgia [1 (0.9%)], and accidents [2 (1.7%)].

Survival was longer in the NIV group than in the non-NIV group (844 *vs.* 599 days, P=0.007). Compared with the NIV group, a higher proportion of patients in the non-
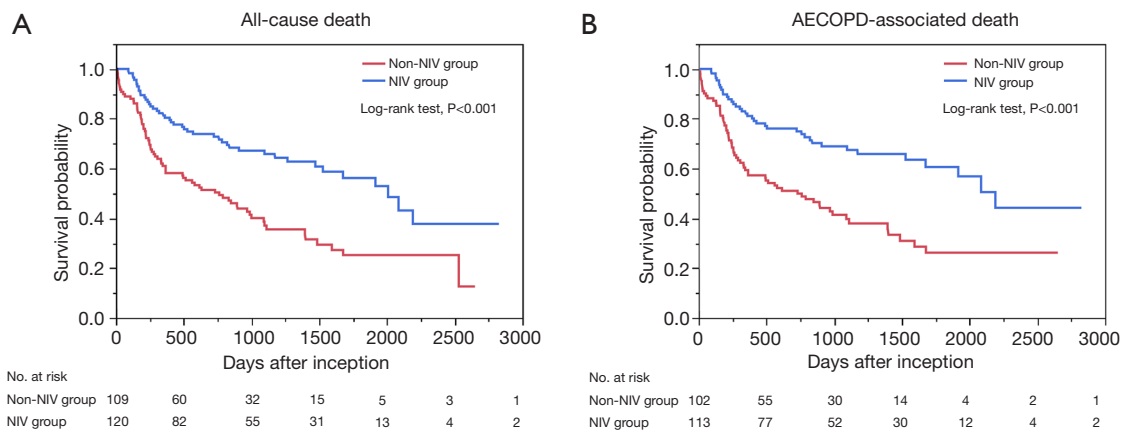
Figure 2 Kaplan-Meier curves for all-cause mortality (A) and AECOPD-associated mortality (B) in NIV and non-NIV groups. The median follow-up for patients in NIV group (n=120) was 844 days (IQR, 345–1,516 days) and for those in non-NIV group (n=109) was 599 days (IQR, 209–1,085 days). AECOPD, acute exacerbation of COPD; NIV, non-invasive ventilation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

Table 2 Univariate and multivariate Cox proportional hazard models for the association between NIV and mortality

Variables	Univariate model		Multivariate model[†]	
	RR (95% CI)	P	RR (95% CI)	P
All-cause mortality				
Treatment, NIV vs. non-NIV	0.459 (0.315–0.668)	<0.001	0.473 (0.324–0.690)	<0.001
Sex, male vs. female	0.974 (0.668–1.420)	0.89	1.033 (0.700–1.525)	0.87
Age, per 1-year increase	1.022 (1.005–1.041)	0.01	1.020 (1.002–1.039)	0.03
Number of hospitalizations for AECOPD in the year prior to enrollment, each unit increase	1.006 (0.863–1.171)	0.93	1.028 (0.879–1.198)	0.73
AECOPD-associated mortality				
Treatment, NIV vs. non-NIV	0.424 (0.283–0.635)	<0.001	0.442 (0.294–0.663)	<0.001
Sex, male vs. female	0.975 (0.652–1.457)	0.90	1.043 (0.691–1.574)	0.84
Age, per 1-year increase	1.021 (1.003–1.041)	0.02	1.017 (0.999–1.037)	0.07
Number of hospitalizations for AECOPD in the year prior to enrollment, each unit increase	1.032 (0.876–1.214)	0.70	1.045 (0.886–1.232)	0.60

[†], treatment, sex, age, and number of hospitalizations for AECOPD in the year prior to enrollment were analyzed in multivariate model. AECOPD, acute exacerbation of COPD; CI, confidence interval; NIV, non-invasive ventilation; RR, relative risks.

NIV group died of all causes (65.1% vs. 37.5%, P<0.001) and AECOPD (58.7% vs. 31.7%, P<0.001) (Figure 2A,2B). Compared to patients in the non-NIV group, patients in the NIV group had reduced risk of all-cause death (RR =0.459, 95% CI: 0.315–0.668, P<0.001) and AECOPD-associated mortality (RR =0.424, 95% CI: 0.283–0.635, P<0.001) in Cox analyses (Table 2), with the significance persisting after adjusting for multiple covariates (RR =0.473,

95% CI: 0.324–0.690, P<0.001, and RR =0.442, 95% CI: 0.294–0.663, P<0.001).

NIV and risk of re-hospitalization

A total of 102 (93.6%) and 89 (74.2%) patients in the non-NIV and NIV groups were re-hospitalized during the follow-up, respectively (P<0.001) (Figure 3A). NIV
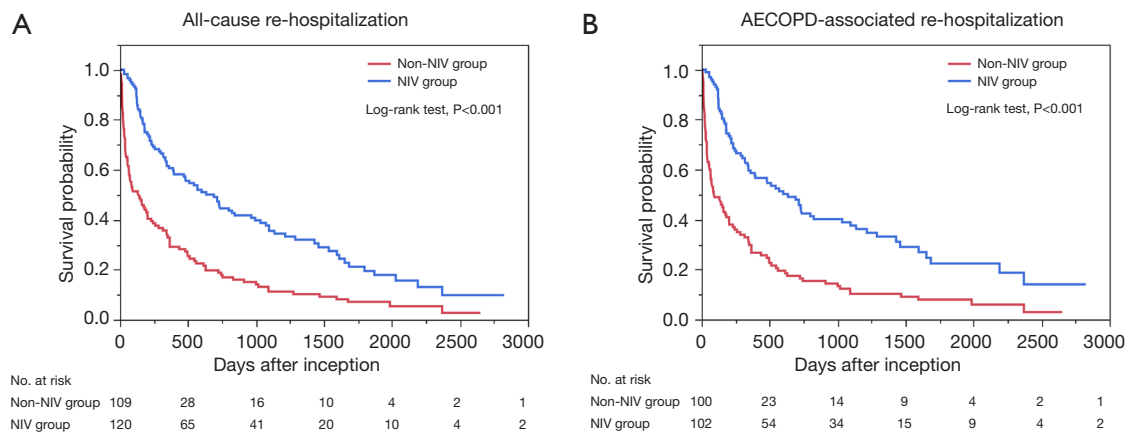
Figure 3 Kaplan-Meier curves for all-cause re-hospitalization (A) and re-hospitalization due to AECOPD (B) in NIV and non-NIV groups. AECOPD, acute exacerbation of COPD; NIV, non-invasive ventilation; COPD, chronic obstructive pulmonary disease.

Table 3 Univariate and multivariate Cox proportional hazard models for the association between NIV and re-hospitalization

Variables	Univariate model		Multivariate model[†]	
	RR (95% CI)	P	RR (95% CI)	P
All-cause re-hospitalization				
Treatment, NIV *vs.* non-NIV	0.455 (0.342–0.605)	<0.001	0.391 (0.290–0.528)	<0.001
Sex, male *vs.* female	1.151 (0.855–1.551)	0.35	1.214 (0.890–1.656)	0.22
Age, per 1-year increase	1.012 (0.998–1.026)	0.08	1.011 (0.998–1.025)	0.11
Number of hospitalizations for AECOPD in the year prior to enrollment, each unit increase	1.188 (1.059–1.332)	0.004	1.303 (1.158–1.464)	<0.001
Re-hospitalization for AECOPD				
Treatment, NIV *vs.* non-NIV	0.421 (0.308–0.575)	<0.001	0.381 (0.276–0.524)	<0.001
Sex, male *vs.* female	1.152 (0.830–1.600)	0.39	1.305 (0.928–1.835)	0.12
Age, per 1-year increase	1.013 (0.999–1.029)	0.07	1.011 (0.996–1.026)	0.15
No. of hospitalizations for AECOPD in the year prior to enrollment, each unit increase	1.231 (1.086–1.394)	0.001	1.317 (1.158–1.495)	<0.001

[†], treatment, sex, age, and number of hospitalizations for AECOPD in the year prior to enrollment were analyzed in multivariate model. AECOPD, acute exacerbation of COPD; CI, confidence interval; NIV, non-invasive ventilation; RR, relative risks.

treatment was associated with reduced risk of all-cause re-hospitalization in univariate (RR =0.455, 95% CI: 0.342–0.605, P<0.001) and multivariate Cox (RR =0.391, 95% CI: 0.290–0.528, P<0.001) analyses (*Table 3*). AECOPD was the most common reason for readmission (164 out of all 191 re-hospitalized patients, 85.9%). AECOPD-free days were longer in the NIV group than in the non-NIV group (549 *vs.* 139 days, P<0.001). Patients treated by NIV

manifested a lower incidence of hospitalized AECOPD than those in the non-NIV group (59.2% *vs.* 85.3%, P<0.001) (*Figure 3B*). Compared to patients in the non-NIV group, those in the NIV group had a lower risk of re-hospitalization for AECOPD (RR =0.421, 95% CI: 0.308–0.575, P<0.001), with the association remaining significant after adjusting for multiple covariates (RR =0.381, 95% CI: 0.276–0.524, P<0.001) (*Table 3*).

Discussion

Despite the proposed comprehensive approaches, the prognosis of patients with severe COPD, particularly those with comorbidities, remains largely unfavorable. The key finding of this study is the evidence of the beneficial effect of NIV on the prognosis of patients diagnosed with severe OS. Both all-cause and AECOPD-associated death and re-hospitalization episodes were significantly reduced by effective NIV therapy. To the best of our knowledge, this is the first study to show the survival benefits of NIV usage in patients with OS, although CPAP and NIV have been reported to improve the outcomes of patients with OSA (16) and COPD (14) alone, respectively. Our findings provide evidence to support the application of NIV on patients with severe OS.

Although COPD and OSA occur independently, their pathological interaction with each other causes severe impairment compared with isolated disorders (17). COPD-associated hypercapnia aggregates respiratory muscles fatigue and blunts respiratory response to hypoxia, resulting in a prolonged breathing cessation (18). In contrast, negative thoracic pressure exaggeration during the respiratory effort of sleep apnea worsens muscular fatigue and subsequently decreases the ventilatory volume of patients with COPD. Previous studies from our group and from others showed that patients with OS suffer from lower hypoxemia than individuals with OSA alone and have greater reductions in ventilatory volume than isolated COPD cases (7,19,20). Mostly because of the mechanisms mentioned above, in line with previous studies (21,22), the majority of our patients with OS were found to have high pulmonary arterial pressure, frequent AECOPD relapse, and alarming mortality rates.

COPD management is generally achieved by using bronchodilators with or without corticosteroids (23). NIV is recommended in COPD patients with hypercapnia because of the evidence of improved lung function, life qualify, ABG, and even hard endpoints (9,14). Notably, Sigurd and colleagues' study revealed that residual nocturnal breathing events manifested frequently in COPD patients treated with long-term NIV for chronic hypercapnic respiratory failure (24), indicating prevalent OSA after conventional NIV and providing rationale for further intervention. For COPD patients with OSA, pressure titration is mainly required to determine the ventilatory settings of EPAP and pressure support to simultaneously mitigate nocturnal airway obstruction and ensure adequate pulmonary ventilation. Furthermore, based on Murphy and colleagues'

trial on the clinical safety and efficacy of auto-titrating NIV device (25), fixed-level NIV could potentially be replaced by auto-ventilation with respiratory back-up rate for patients with OS without complex apnea (e.g., central sleep apnea).

Our results regarding risk reduction by NIV are in line with those from trials endorsing the application of CPAP (16) and NIV (14) in patients with OSA and COPD, respectively. To the best of our knowledge, there is a dearth of direct evidence supporting NIV treatment in OS. In Borel and colleagues' study on patients with obesity hypoventilation syndrome (26), a subgroup analysis showed that NIV was associated with favorable clinical outcomes in COPD patients with obesity (the strongest predictor of OSA). Nevertheless, considering the high prevalence of OSA in patients with COPD (6), COPD treatment via low-EPAP NIV may result in residual apnea events among several patients, which could contribute to adverse prognosis. High-EPAP application in the settings of NIV mode, which would be equivalent to CPAP, could abolish OSA. However, our study included only patients with severe OS who experienced multiple episodes of hypercapnic respiratory failure prior to the enrollment; therefore, it is unclear if our results can be extrapolated to patients with mild OS. Considering the high prevalence of OS (6), additional research in this area is essential. Lastly, a long duration of nocturnal NIV usage is suggested for the OS patients, since prior trials revealed that patients seemed to benefit from positive airway pressure therapy only if >4 h ventilator usage was achieved (16,27).

As shown in our baseline data, the patients treated with NIV were generally obese with high AHI, implying that some of them might have benefited directly from CPAP therapy. Indeed, there are available studies in the literature that support the survival efficacy of CPAP for patients with OS (10,28). Interestingly, NIV was selected in our study due to concerns about hypercapnia and respiratory failure, demonstrating the effectiveness of NIV for hypercapnic OS, or as a rescue strategy for OS patients after failing CPAP therapy or developing carbon dioxide retention. This concept is in line with the suggestion of using NIV for hypercapnic COPD in previous literature (11).

Our retrospective-designed study had a few limitations. Firstly, selective bias was likely present because this was not a randomized trial and group assignment was based on patients' preference and adherence to NIV. Notably, the majority of patients in both NIV and non-NIV groups showed similar demographic and clinical baseline features, which may have attenuated the bias. Secondly, some patients

with severe COPD were diagnosed based on their medical history because they could not undergo spirometry during hospitalization. Furthermore, as a retrospective study, follow-up data such as residual AHI or ABG values, which are commonly used when monitoring NIV treatment, could not be obtained. As a result, based on the data available to us, we cannot unequivocally confirm the efficacy of NIV. Additionally, instead of initiating CPAP therapy, as it is conventionally done for patients with OS, the patients in our study were prescribed NIV for their specific condition. Therefore, the conclusions drawn from this patient cohort cannot be extrapolated to the general OSA population, who may still start with CPAP therapy with monitoring of ABG and ventilatory function. Finally, OSA was partly assessed based on the Berlin Questionnaire instead of an objective sleep test, although Berlin Questionnaire has been found to perform satisfactorily as a screening tool for OSA in patients with COPD (27).

Conclusions

In conclusion, our study demonstrated that NIV treatment, in addition to usual care, improved overall survival and reduced the incidence of AECOPD-associated re-hospitalization and mortality in patients with severe OS. Given the high fatality rate exhibited in this patient population, future clinical trials confirming the benefits of long-term domiciliary NIV are warranted.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-390/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-390/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-390/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-390/coif). J.X. has received a speaker honorarium from ResMed and Philips Respironics. Y.G. was supported by the Open Project of the State Key Laboratory of Respiratory Disease (SKLRD-OP-201909). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Beijing Anzhen Hospital (No. ks2019020) and individual consent for this retrospective analysis was waived.

References

1. WHO. The Top 10 Causes of Death. World Health Organisation. 2020. Available online: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
2. Hillas G, Perlikos F, Tzanakis N. Acute exacerbation of COPD: is it the "stroke of the lungs"? Int J Chron Obstruct Pulmon Dis 2016;11:1579-86.
3. Prediletto I, Giancotti G, Nava S. COPD Exacerbation: Why It Is Important to Avoid ICU Admission. J Clin Med 2023;12:3369.
4. Xie J, Sert Kuniyoshi FH, Covassin N, et al. Nocturnal Hypoxemia Due to Obstructive Sleep Apnea Is an Independent Predictor of Poor Prognosis After Myocardial Infarction. J Am Heart Assoc 2016;5:e003162.
5. McNicholas WT. Does Obstructive Sleep Apnea Lead to Progression of Chronic Obstructive Pulmonary Disease. Sleep Med Clin 2024;19:253-60.
6. Soler X, Gaio E, Powell FL, et al. High Prevalence of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc 2015;12:1219-25.

7. Adler D, Bailly S, Benmerad M, et al. Clinical presentation and comorbidities of obstructive sleep apnea-COPD overlap syndrome. PLoS One 2020;15:e0235331.

8. Du W, Liu J, Zhou J, et al. Obstructive sleep apnea, COPD, the overlap syndrome, and mortality: results from the 2005-2008 National Health and Nutrition Examination Survey. Int J Chron Obstruct Pulmon Dis 2018;13:665-74.

9. White DP, Criner GJ, Dreher M, et al. The role of noninvasive ventilation in the management and mitigation of exacerbations and hospital admissions/readmissions for the patient with moderate to severe COPD (multimedia activity). Chest 2015;147:1704-5.

10. Marin JM, Soriano JB, Carrizo SJ, et al. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med 2010;182:325-31.

11. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2014;2:698-705.

12. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999;131:485-91.

13. Tan A, Yin JD, Tan LW, et al. Using the Berlin Questionnaire to Predict Obstructive Sleep Apnea in the General Population. J Clin Sleep Med 2017;13:427-32.

14. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA 2017;317:2177-86.

15. Müllerová H, Shukla A, Hawkins A, et al. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. BMJ Open 2014;4:e006171.

16. Yu J, Zhou Z, McEvoy RD, et al. Association of Positive Airway Pressure With Cardiovascular Events and Death in Adults With Sleep Apnea: A Systematic Review and Meta-analysis. JAMA 2017;318:156-66.

17. McNicholas WT, Hansson D, Schiza S, et al. Sleep in chronic respiratory disease: COPD and hypoventilation disorders. Eur Respir Rev 2019;28:190064.

18. Radwan L, Maszczyk Z, Koziorowski A, et al. Control of breathing in obstructive sleep apnoea and in patients with the overlap syndrome. Eur Respir J 1995;8:542-5.

19. Schreiber A, Cemmi F, Ambrosino N, et al. Prevalence and Predictors of Obstructive Sleep Apnea in Patients with Chronic Obstructive Pulmonary Disease Undergoing Inpatient Pulmonary Rehabilitation. COPD 2018;15:265-70.

20. Xie J, Li F, Wu X, et al. Prevalence of pulmonary embolism in patients with obstructive sleep apnea and chronic obstructive pulmonary disease: The overlap syndrome. Heart Lung 2019;48:261-5.

21. McNicholas WT. COPD-OSA Overlap Syndrome: Evolving Evidence Regarding Epidemiology, Clinical Consequences, and Management. Chest 2017;152:1318-26.

22. Naranjo M, Willes L, Prillaman BA, et al. Undiagnosed OSA May Significantly Affect Outcomes in Adults Admitted for COPD in an Inner-City Hospital. Chest 2020;158:1198-207.

23. Halpin DMG, Criner GJ, Papi A, et al. Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2021;203:24-36.

24. Aarrestad S, Qvarfort M, Kleiven AL, et al. Sleep related respiratory events during non-invasive ventilation of patients with chronic hypoventilation. Respir Med 2017;132:210-6.

25. Murphy PB, Arbane G, Ramsay M, et al. Safety and efficacy of auto-titrating noninvasive ventilation in COPD and obstructive sleep apnoea overlap syndrome. Eur Respir J 2015;46:548-51.

26. Borel JC, Pepin JL, Pison C, et al. Long-term adherence with non-invasive ventilation improves prognosis in obese COPD patients. Respirology 2014;19:857-65.

27. Khan SU, Duran CA, Rahman H, et al. A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. Eur Heart J 2018;39:2291-7.

28. Sterling KL, Pépin JL, Linde-Zwirble W, et al. Impact of Positive Airway Pressure Therapy Adherence on Outcomes in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2022;206:197-205.