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Long-term mortality in patients with chronic obstructive pulmonary disease requiring acute non-invasive ventilation with and without obstructive sleep apnoea

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ABSTRACT

Introduction Chronic obstructive pulmonary disease (COPD)/obstructive sleep apnoea (OSA) overlap syndrome (OVS) is associated with higher mortality compared with COPD alone in stable outpatients. However, the prognosis of patients hospitalised with acute hypercapnic respiratory failure (ARF) is unclear.

Methods In this retrospective cohort study, 124 patients with COPD and 44 patients with OVS were treated with positive airway pressure (PAP) for ARF and followed up for a median of 20.6 months (IQR 3.80–53.4). Patients treated in the emergency or intensive care units and did not continue PAP on the wards were excluded. We compared patient characteristics and overall survival.

Results Mean (SD) age of participants was 71 (9.7) years and 51% were males. Patients with OVS had a higher prevalence of hypertension (75% vs 50.0%, p=0.004) and type 2 diabetes mellitus (45.5% vs 19.4%, p<0.001). There was no difference in arterial pH or carbon dioxide levels at presentation. On univariate analysis, mortality was lower in OVS compared with patients with COPD alone (HR 0.57, 95% CI 0.37 to 0.87). Median survival was 51.0 (95% CI 38.1 to 93.7) months in OVS and 27.7 (95% CI 16.9 to 35.1) months in COPD alone. Median survival in OVS prescribed home PAP therapy was significantly higher (59.0 months) compared with OVS not discharged on therapy (36.1 months), and to patients with COPD, irrespective of home therapy prescription (p=0.022). After adjusting for multiple known confounders, patients with OVS still appeared to have lower mortality; however, this was no longer statistically significant (HR 0.75, 95% CI 0.45 to 1.24).

Discussion We found that patients with COPD and ARF requiring non-invasive ventilation may have higher mortality rates compared with patients with OVS. Patients with OVS treated with home PAP had lower mortality compared with patients not prescribed PAP on discharge. These findings suggest that patients with COPD who present with ARF may benefit from early diagnosis of OSA and initiation of long-term PAP therapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Overlap syndrome (OVS) is associated with higher mortality compared with chronic obstructive pulmonary disease (COPD) alone; however, the prognosis among patients with acute hypercapnic respiratory failure (ARF) is unclear.

WHAT THIS STUDY ADDS

⇒ Among patients with COPD and ARF, comorbid obstructive sleep apnoea appears to confer a better prognosis. Patients with OVS and ARF prescribed home positive airway pressure (PAP) therapy have a better prognosis compared with patients without PAP therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It may be a good opportunity to commence patients with OVS on long-term PAP therapy following hospitalisation with ARF.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disorder caused by inhalation of noxious stimuli, such as cigarette or biomass smoke, that results in airflow limitation, gas trapping and lung hyperinflation.[1] COPD is currently the third leading cause of death worldwide and COPD exacerbations represent a significant risk factor for mortality.[2 3] Obstructive sleep apnoea (OSA) is the most common sleep-related breathing disorder and is caused by repetitive upper airway collapse resulting in nocturnal hypoxia and sleep fragmentation. The co-occurrence of COPD and OSA, termed the 'overlap syndrome' (OVS), has been estimated to be as high as 50% in hospitalised patients with COPD, and

the long-term mortality of stable patients with OVS in the community with untreated OSA is reportedly higher compared with patients with COPD alone.[4–6] Treatment of OSA with continuous positive airway pressure (CPAP) has been associated with improved survival and reduced exacerbations in patients with OVS.[5–8] Despite increasing interest in OVS, there are still many unanswered issues such as the survival characteristics and clinical outcomes of patients with OVS who are admitted to hospital with acute hypercapnic respiratory failure (ARF).

Objectives

The primary aim of our study was to assess the impact of OSA on long-term mortality and hospital admissions among patients with COPD who are admitted to hospital with ARF requiring non-invasive ventilation (NIV). We also investigated the effects of domiciliary positive airway pressure (PAP) therapy on survival. Our secondary aims included comparison of acute NIV settings between patients with OVS and patients with COPD alone and differences in length of hospital stay, time to hospital readmission and the number of hospital readmissions.

METHODS

In accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement, we conducted a single-centre retrospective cohort study using data collected from the Royal Prince Alfred Hospital Respiratory Support Service (RSS) acute NIV database. Consecutive patients who were treated with acute NIV between 1 January 2010 and 31 December 2019 were enrolled (figure 1). Patients who were treated in the emergency department or intensive care unit who did not continue NIV on transfer to the wards or who died before coming to the wards were not included in the database. Each patient's electronic medical records (eMR) were accessed (BN) to retrieve additional medical data and clinical outcomes. Patients were followed up from their first admission with ARF requiring NIV during the study period until death or censored at the last point of contact with a health service as determined by the eMR or the online My Health Record (MHR). MHR is an Australian national online system containing patient health information including vital status, hospital discharge summaries, pathology results, diagnostic images, medication prescriptions and vaccination records.[9] Patients who had ARF due to any diagnosis other than COPD were excluded (online supplemental eTable 1). Furthermore, patients were excluded if their arterial blood gas (ABG) results prior to initiation of NIV were not consistent with ARF (ie, if pH≥7.35 or arterial partial pressure of carbon dioxide ($PaCO_2$)≤45 mm Hg). Patients were also excluded if they did not have spirometry or if spirometry demonstrated a forced expiratory volume in 1 s (FEV_1) to forced vital capacity ratio of greater than 0.7. Patients were deemed to have OVS if they had a physician diagnosis of OSA in their eMR or if they had a previous sleep study demonstrating an apnoea-hypopnoea index (AHI)≥10/hour. Sleep studies were not performing during the index admission for any of the patients. Medical comorbidities were obtained from the eMR, and 'cardiovascular disease' (CVD) for the purposes of multivariate analysis was defined as the presence of ischaemic heart disease, heart failure and/or stroke. NIV settings were titrated at the bedside during the patient's hospital stay. Detailed therapy data were obtained from the NIV devices. Inspiratory positive airway pressure (IPAP) was titrated according to the patient's tidal volumes, minute ventilation, ABG results and overnight oximetry. Expiratory positive airway pressure (EPAP) was titrated to overcome upper airway obstruction. Some patients also underwent formal PAP titration studies in the laboratory.

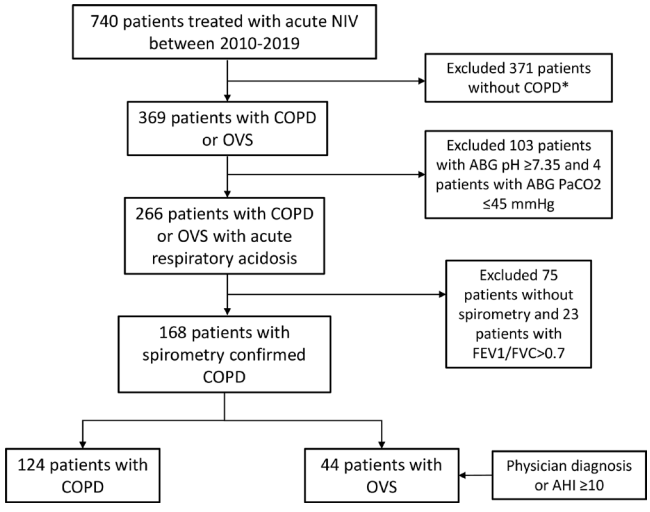

Figure 1 Study flow chart demonstrating cohort selection. ABG, arterial blood gas analysis; AHI, apnoea-hypopnoea index; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume in 1 s to forced vital capacity ratio; NIV, non-invasive ventilation; OVS, overlap syndrome; $PaCO_2$, partial pressure of carbon dioxide. *Patients excluded for diagnoses other than COPD included in online supplemental eTable 1.

Statistical analysis

Continuous data are presented as mean and SD if they had a normal distribution or median and IQR if they were not normally distributed. Categorical data are presented as frequency counts and percentages. Comparisons of continuous variables were performed using Student's t-test for parametric data or Mann-Whitney U test for non-parametric data. X^2 tests were used for categorical variables. Survival data were analysed using the Kaplan-Meier method and log-rank tests.[10] Patients were followed up from their first admission during the 2010–2019 period until their time of death or 16 March 2023, whichever came first. Survival time and readmission time were calculated from the date of their first hospital discharge. Patients who were lost to follow-up were censored from the last point of contact documented on the eMR or

MHR. Prognostic variables were analysed in univariate analysis and with a multivariate Cox proportional hazards model.[11] Prognostic factors used in the multivariate model were determined a priori and included age, gender, body mass index (BMI), FEV_1 %predicted and the presence of CVD. For all tests, the significance level was set at a two-tailed p value ≤0.05. Analyses were performed using Jamovi V.2.3.21.0 (https://www.jamovi.org) and R V.4.3.1 (https://www.r-project.org/).

Patient and public involvement

No patients were involved in the design or conduct of this study. Furthermore, there are no plans to disseminate these results directly to patients.

RESULTS

Between 2010 and 2019, seven hundred and forty patients were treated with acute NIV (figure 1). Patients who did not have a diagnosis of COPD confirmed by spirometry and those in whom the ABG result was not consisted with ARF were excluded, leaving 168 patients in the study. Of these, 44 patients had a concomitant diagnosis of OSA and were deemed to have OVS and 124 patients had COPD alone.

Baseline characteristics and physiology

Baseline characteristics were compared between patients with OVS and patients with COPD alone and showed no statistically significant differences in age, gender or smoking history although patients with COPD were more likely to be current smokers (40.3% vs 22.7%, p=0.036; table 1). Patients with OVS had a higher BMI (34.8 kg/m^2 vs 23.5 kg/m^2, p<0.001) and AHI (24.0/hour vs 3/hour, p<0.001) and were more likely to be on PAP therapy prior to hospital admission (38.6% vs 4.0%, p<0.001, online supplemental eTable 2). Patients with OVS also had a higher number of comorbidities compared with patients with COPD alone (2.0 vs 1.5, p=0.005), including hypertension (75% vs 50.0%, p=0.004) and type 2 diabetes mellitus (45.5% vs 19.4%, p<0.001). In contrast, patients with COPD had a significantly lower FEV_1 %predicted (36.7% vs 45.4%, p=0.005), and a higher proportion of patients with COPD GOLD stage IV (45.0% vs 19.0%, p=0.006). Both groups had a similar proportion of individuals prescribed long-term oxygen therapy (LTOT) prior to hospital admission. There were no differences in ABG pH, $PaCO_2$ or serum bicarbonate levels during the index admission with ARF. Prior to hospitalisation, 4.0% of patients with COPD were using NIV, 13.6% of patients with OVS were using CPAP and 25.0% of patients with OVS were using NIV.

NIV settings

Ventilator modes, pressure settings and use of supplemental oxygen are shown in table 2. All patients in this cohort used a full-face mask interface. There were no differences in modes of NIV between patients with OVS and patients with COPD alone. Patients with COPD were prescribed a lower IPAP (17.4 cmH_2O vs 18.7 cmH_2O, 95% CI −2.0 to 0.0) and EPAP (5 cmH_2O vs 10 cmH_2O, 95% CI −4.0 to −3.0), while higher levels of pressure support were used in patients with COPD alone (11.6 cmH_2O vs 9.2 cmH_2O, 95% CI 1.0 to 3.0). There were no differences in the backup rates or flow rate of supplemental oxygen between the groups.

Survival

Inpatient mortality was higher in patients with COPD alone compared with patients with OVS (9.7% vs 0%, p=0.032). Following hospital admission with ARF requiring NIV, patients were followed up over a median period of 20.6 (IQR 3.80–53.4) months, with an overall median survival for the entire cohort of 31.3 (95% CI 24.0 to 39.6) months. All-cause mortality was lower in patients with OVS compared with patients with COPD alone (HR 0.57, 95% CI 0.37 to 0.87; figure 2). Median survival was 27.7 (95% CI 16.9 to 35.1) months in patients with COPD alone compared with 51 (95% CI 38.1 to 93.7) months in patients with OVS. On multivariate analysis, patients with OVS demonstrated a trend towards lower mortality; however, this was no longer statistically significant after adjustment for age, gender, BMI, FEV_1 %predicted and presence of CVD (HR 0.75, 95% CI 0.45 to 1.24; table 3). When survival was analysed according to whether patients went home on PAP therapy or not, patients with OVS who were discharged home or continued PAP therapy demonstrated significantly lower mortality compared with patients with OVS who were not discharged home on PAP therapy (p=0.022; figure 3). Patients who were not prescribed PAP therapy had a greater smoking history (57.9 pack-year history vs 36 pack-year history, 95% CI 6.2 to 37.6; online supplemental eTable 3). However, there were no differences in rates of current smoking or lung function. In contrast, there were no differences in survival among patients with COPD regardless of whether or not they were on PAP therapy following hospital discharge. Analysis of the cohort without spirometry including an additional 14 patients with OVS and 61 patients with COPD alone did not impact the survival outcomes (online supplemental eTable 5).

Hospital length of stay and hospital readmissions

There were no differences in length of hospital stay between patients with OVS and patients with COPD alone, with a median length of stay of 10 (IQR 6–17) days and 9 (IQR 6–14.8) days, respectively (p=0.599; table 4). There were also no significant differences between groups in the time to hospital readmission with a median time to readmission of 2.23 (95% CI 1.28 to 7.06) months in patients with OVS

Table 1 Baseline characteristics of the study population

Patient characteristics	COPD (n=124)	OVS (n=44)	P value	95% CI
Age (years)	71.6 (9.9)	70.6 (9.4)	0.759	−3.0 to 4.0
Male (n, %)	61 (49.2)	24 (54.5)	0.542	
BMI (kg/m²)	23.5 (7.2)	34.8 (9.2)	<0.001	−13.8 to −8.4
AHI (/hour; median (IQR))*	3.0 (2.0–5.75)	24.0 (16.3–55.5)	<0.001†	−37.0 to −15.0
FEV_1 (L)	0.80 (0.4)	1.04 (0.4)	<0.001	−0.4 to −0.1
FEV_1 (%predicted)	36.7% (17.0)	45.4% (15.6)	0.005	−16.0 to −4.0
Severity of COPD				
FEV_1≥80% predicted (n, %)	0 (0)	0 (0)	0.006	
FEV_1 50–79% predicted (n, %)	25 (22.5)	18 (42.9)		
FEV_1 30–49% predicted (n, %)	36 (32.4)	16 (38.1)		
FEV_1<30% predicted (n, %)	50 (45.0)	8 (19.0)		
FVC (L)	1.9 (0.8)	2.0 (0.7)	0.373	−0.4 to 0.1
pH	7.26 (0.05)	7.26 (0.07)	0.492	−0.02 to 0.02
$PaCO_2$ (mm Hg)	73.5 (16.0)	76.1 (19.1)	0.395	−6.0 to 3.0
Bicarbonate (mmol/L)	31.7 (5.6)	31.8 (4.0)	0.858	−2.0 to 1.0
Current smoking (n, %)	50 (40.3)	10 (22.7)	0.036	
Smoking pack-years	56.7 (34.5)	48.2 (30.0)	0.175	−4.0 to 15.0
Home PAP therapy (n, %)	5 (4.0)	17 (38.6)	<0.001	
CPAP (n, %)	0 (0)	6 (13.6)		
NIV (n, %)	5 (4.0)	11 (25)		
Home oxygen (n, %)	28 (22.6)	11 (25)	0.744	
Number of comorbidities (median, IQR)	1.5 (1.0–3.0)	2.0 (1.75–3.0)	0.005†	−1 to 0.0
Ischaemic heart disease (n, %)	28 (22.6)	9 (20.5)	0.770	
Heart failure (n, %)	27 (21.8)	14 (31.8)	0.183	
Hypertension (n, %)	62 (50.0)	33 (75)	0.004	
Pulmonary hypertension (n, %)	9 (7.3)	4 (9.1)	0.696	
Type 2 diabetes mellitus (n, %)	24 (19.4)	20 (45.5)	<0.001	
Atrial fibrillation (n, %)	22 (17.7)	11 (25)	0.298	
Stroke (n, %)	7 (5.6)	4 (9.1)	0.427	
Chronic kidney disease (n, %)	10 (8.1)	3 (6.8)	0.790	
Psychiatric disorders (n, %)	37 (29.8)	10 (22.7)	0.367	

Results are expressed as mean (SD) unless otherwise stated.
Psychiatric disorders: schizophrenia, depression, bipolar disorder.
*n=52.
†Mann-Whitney U test.
AHI, apnoea-hypopnoea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NIV, non-invasive ventilation; OVS, overlap syndrome; $PaCO_2$, partial pressure of carbon dioxide; PAP, positive airway pressure.

and 3.42 months (95% CI 1.68 to 6.05) in patients with COPD alone (p=0.747). At 12 months of follow-up after hospital discharge, 79.8% of patients with COPD had represented to hospital compared with 84% of patients with OVS. There were also no differences in hospital readmission for any cause (p=0.072) or the number of readmissions requiring NIV (p=0.237; table 4). PAP therapy did not impact the time to hospital readmission (online supplemental eTable 4).

DISCUSSION

To our knowledge, this is the first study to examine long-term outcomes in patients with OVS following hospitalisation with ARF. Despite having more comorbidities, survival appeared to be higher in patients with OVS compared with patients with COPD alone. These results put to question the previously held belief that patients with OVS have a worse prognosis compared with patients with COPD alone. For example, Marin and colleagues

Table 2 Comparison of non-invasive ventilation set-up and settings

Ventilator settings	COPD (n=124)	OVS (n=44)	P value	95% CI
NIV mode				
S mode (n, %)	28 (22.6)	7 (15.9)	0.169	
ST mode (n, %)	96 (77.4)	36 (81.8)		
NIV settings				
IPAP (cmH_2O)	17.4 (3.1)	18.7 (2.9)	0.023	−2.0 to 0.0
EPAP (cmH_2O; median, IQR)	5.0 (5.0–6.25)	10.0 (8.0–10.0)	<0.001*	−4.0 to −3.0
PS (cmH_2O)	11.6 (3.1)	9.2 (2.7)	<0.001	1.0 to 3.0
Backup rate (breaths/min)	17.0 (1.7)	16.6 (1.8)	0.245	0.0 to 1.0
Supplemental oxygen (L/min; median, IQR)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	0.456*	−1.0 to 1.0

Results are expressed as mean (SD) unless otherwise stated.
*Mann-Whitney U test.
cmH_2O, centimetres of water; COPD, chronic obstructive pulmonary disease; EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, non-invasive ventilation; OVS, overlap syndrome; PS, pressure support; S, spontaneous; ST, spontaneous-timed.

examined survival among stable patients with OVS who were recruited in the ambulatory setting and found that patients with OVS had significantly higher mortality compared with patients with COPD alone (relative risk 2.23, 95% CI 1.59 to 3.14).[5] However, this mortality risk in patients with OVS was mitigated when sleep-disordered breathing was treated with CPAP, resulting in a similar survival rate as patients with COPD alone. It should be noted that the patients in the Marin study had less severe disease compared with our cohort.[5] The mean FEV_1 %predicted of patients with OVS and COPD alone in this earlier study was 57% and 56%, respectively, compared with 45.4% and 36.7% in OVS and COPD alone in our study. In addition, their patients were recruited in the outpatient setting and none required an LTOT prescription. In comparison, 25% of patients with OVS and 22.6% of patients with COPD in our study were prescribed LTOT. In addition, patients with OVS who were prescribed NIV were excluded from analysis in the Marin study, whereas our study exclusively assessed patients who required NIV at initial presentation.[5]

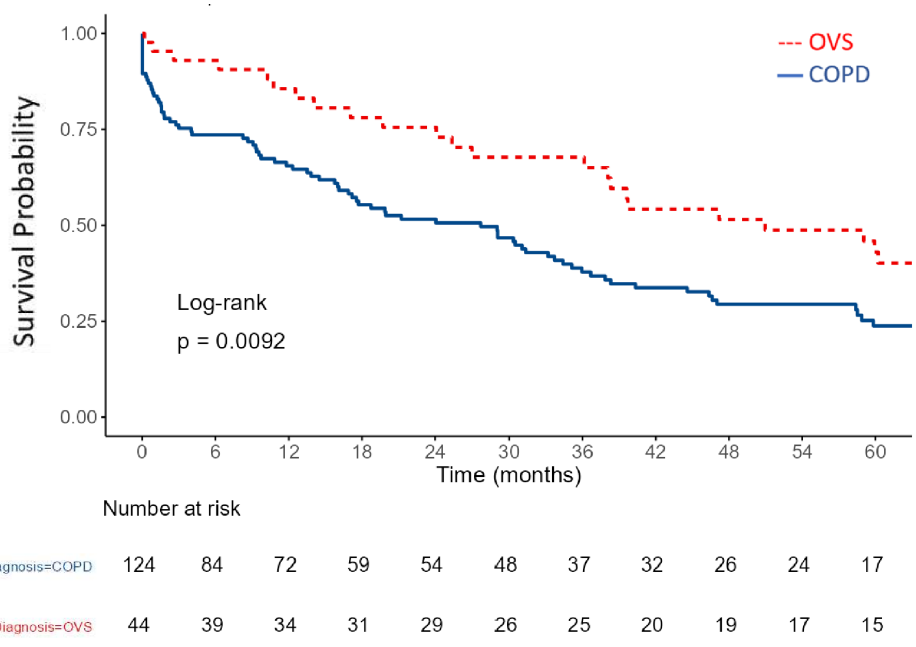

Figure 2 Kaplan-Meier curves demonstrating survival time from hospital discharge with index admission with acute hypercapnic respiratory failure until death between patients with OVS (dashed red) and patients with COPD alone (solid blue). Patients with OVS have lower mortality compared with patients with COPD alone; however, this was no longer statistically significant when analysed using multivariate Cox proportional hazards model. COPD, chronic obstructive pulmonary disease; OVS, overlap syndrome.

Table 3 Factors associated with mortality

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Diagnosis (reference: COPD alone)				
OVS	0.62 (0.40 to 0.96)	0.033	0.75 (0.45 to 1.24)	0.263
Age (per 10-year increase in age)	1.31 (1.06 to 1.60)	0.011	1.31 (1.04 to 1.66)	0.023
Gender (reference: Female)				
Male	1.21 (0.81 to 1.78)	0.350	1.08 (0.73 to 1.62)	0.689
BMI (per 1 kg/m^2 increase in BMI)	0.97 (0.95 to 0.99)	0.011	0.99 (0.96 to 1.01)	0.339
FEV_1 %predicted (per 10% increase in FEV_1 %predicted)	0.91 (0.81 to 1.04)	0.157	0.92 (0.79 to 1.07)	0.283
Presence of CVD (reference: No CVD)				
Yes	1.44 (0.97 to 2.13)	0.069	1.33 (0.88 to 2.01)	0.181

Adjusted and unadjusted associations of obstructive sleep apnoea and other prognostic factors and survival in patients with chronic obstructive pulmonary disease.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease (ischaemic heart disease, heart failure, stroke); FEV_1, forced expiratory volume in 1 s; OVS, overlap syndrome.

We explored potential predictors of mortality and found that advanced age and lower BMI were associated with lower survival. The patients with COPD in our cohort had a normal mean BMI of 23.5 kg/m^2. As expected, lung function severity represented by FEV_1 correlated with survival; however, this was not statistically significant (table 3). While FEV_1 is one method of classifying disease severity, it is clear that there are other factors that influence survival such as BMI and potentially other unmeasured variables including dyspnoea severity and exercise capacity.[12 13] After adjusting for multiple known clinical confounders, patients with OVS still appeared to have lower mortality compared with patients with COPD; however, the CI widened, rendering this outcome not statistically significant (HR 0.75, 95% CI 0.45 to 1.24; table 3).

Our results appear to be more consistent with long-term outcomes in patients with chronic respiratory failure on

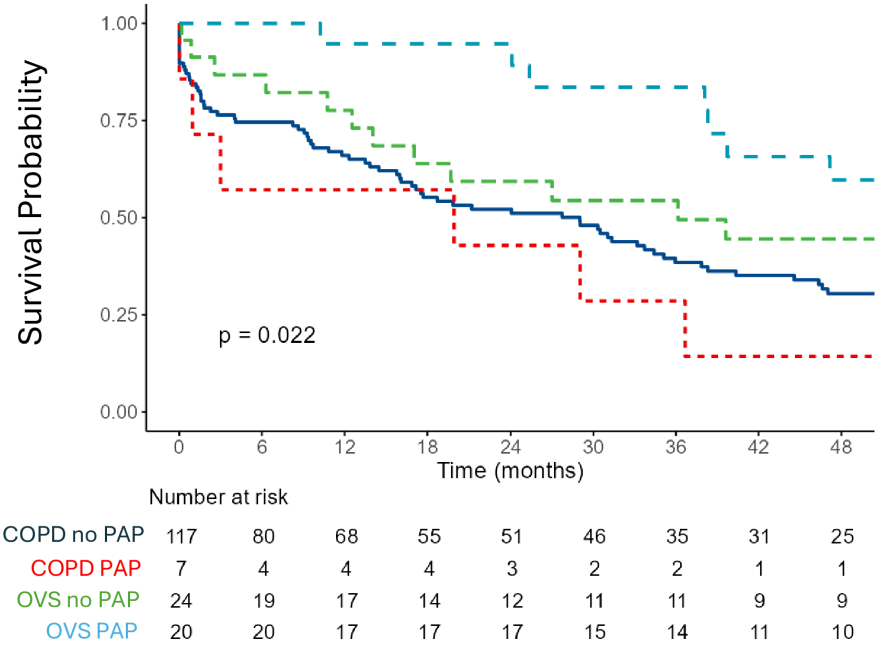

Figure 3 Kaplan-Meier curves demonstrating survival time from hospital discharge with index admission with acute hypercapnic respiratory failure until death between patients with COPD not treated with PAP therapy (solid dark blue), patients with COPD treated with PAP therapy (dashed red), patients with OVS not treated with PAP therapy (dashed green) and patients with OVS treated with PAP therapy (solid light blue). COPD, chronic obstructive pulmonary disease; OVS, overlap syndrome; PAP, positive airway pressure.

Table 4 Clinical outcomes in patients with COPD and OVS following hospital discharge with acute hypercapnic respiratory failure

Outcomes	COPD (n=124)	OVS (n=44)	P value*	95% CI
Inpatient days	10.0 (6–17)	9.5 (6–14.8)	0.599	−2.0 to 3.0
Inpatient mortality (n, %)	12 (9.7)	0 (0)	0.032	
Time to readmission (months, 95% CI)	3.42 (1.68 to 6.05)	2.23 (1.28 to 7.06)	0.747	1.06† (0.73 to 1.55)
Number of readmissions	3.0 (1.0–7.0)	5.0 (1.0–90)	0.072	−3.0 to 0.0
Number of readmissions requiring NIV	0 (0.0–2.0)	1.0 (0.0–1.0)	0.237	0.0
Time to readmission				
Within 1 month (n, %)	49 (39.5)	14 (31.8)	0.750	
Within 3 months (n, %)	72 (58)	25 (56.8)		
Within 6 months (n, %)	85 (68.5)	31 (70.4)		
Within 12 months (n, %)	99 (79.8)	37 (84)		

Results are expressed as median (IQR) unless otherwise stated.
*Mann-Whitney U test.
†HR.
COPD, chronic obstructive pulmonary disease; OVS, overlap syndrome; NIV, non-invasive ventilation.

home NIV.[14] Patout *et al* analysed data from 1746 patients using long-term NIV at two centres in Rouen, France and London, UK. Over a median follow-up period of 1.97 (0.78–3.78) years, they found that patients with hypercapnic COPD had significantly higher mortality compared with patients with OVS (HR 2.48, 95% CI 1.77 to 3.00). Our concordant results suggest that patients with OVS who are admitted with an episode of ARF may have more favourable outcomes compared with patients with COPD and respiratory failure.[5] One possible explanation is that patients with OVS develop hypercapnia at an earlier stage of their disease trajectory. While patients with COPD alone generally do not develop hypercapnia until they have reached an advanced stage of their disease, patients with OVS may develop hypercapnia with relatively preserved lung function,[15] as was the case in our cohort of patients (table 1). Similar findings were reported in an Italian study, where patients with hypercapnia with COPD alone had severely reduced FEV_1, whereas patients with OVS and hypercapnia had only moderately reduced FEV_1.[16] Thus, lower survival may be expected in patients with COPD who have reached a more advanced stage of their disease compared with patients with OVS who may have a tendency to develop hypercapnia at an earlier stage of their disease.

The other significant finding in our study was that patients with OVS, who were treated with PAP therapy on discharge from hospital, had significantly higher survival compared with patients who were not prescribed PAP therapy. Several observational studies have demonstrated significant clinical benefits in patients with OVS who are treated with PAP therapy in terms of associated reductions in mortality and hospitalisations.[5–8] Our study further confirms these observations and sheds light on the benefits of long-term PAP therapy in patients with OVS who are admitted to hospital with ARF. We found that patients with OVS, who were discharged home with a new PAP prescription or continued on PAP therapy following discharge, had significantly lower mortality compared with patients who were not discharged on PAP therapy (figure 3). There were only seven patients with COPD alone in our cohort who continued on PAP therapy following hospital discharge, and their mortality was not discernibly different from patients who were not prescribed NIV on discharge. There have been four randomised controlled trials (RCT) that assessed the impact of PAP therapy in patients with COPD following hospital admission with ARF, and the pooled data showed no differences in survival, exacerbations or hospital readmissions.[17–20] The two larger RCTs included in this analysis were the Respiratory Support in COPD after acute Exacerbation (RESCUE) study and the Home Oxygen Therapy and Home Mechanical Ventilation (HOT-HMV) study.[17 18] Both studies showed no differences in mortality between patients who were assigned to NIV or no NIV. However, unlike the RESCUE study, the HOT-HMV study assessed for the presence of persistent hypercapnia ($PaCO_2$>53 mm Hg) 2–4 weeks after hospital discharge prior to enrolment into the study and demonstrated that patients with persistent hypercapnia who were randomised to NIV had fewer exacerbations (3.8 exacerbations per year vs 5.1 exacerbations per year, respectively). The small sample size of our patients with COPD treated with NIV makes it impossible to comment on the clinical benefit of NIV in our cohort of patients with COPD alone. It should also be noted that our study spanned a 10-year period where practice guidelines for long-term NIV in patients following an admission for an acute COPD exacerbation continued to evolve over that time.[21 22]

The inpatient mortality rate was 9.7% for patients with COPD and 0% for patients with OVS (p=0.032), which is

similar to that reported in previous studies.[23 24] Interestingly, we did not demonstrate any differences in length of hospital stay or the number of hospital readmissions between patients with OVS and patients with COPD alone (table 4). Median time to readmission was 3.42 months in patients with COPD and 2.23 months in patients with OVS (HR 1.06, 95% CI 0.73 to 1.55) which is slightly longer than reported in previous studies. Chu and colleagues demonstrated the same 1-year readmission rate of 79.9% among their patients with COPD treated with NIV; however, the median time to first readmission was shorter at 57 days.[25] Another study demonstrated a median time to readmission ranging from 40 to 56 days.[26] These studies do have a number of important differences compared with our study. Patients in the study by Chu and colleagues had slightly worse lung function with mean FEV_1 of 33.3% compared with 36.7% in our study, and both studies excluded patients who required NIV on discharge, whereas this was not an exclusion criterion in our study. It should also be noted that all patients in our study had spirometry-confirmed COPD, whereas only 72% and 80% of patients had spirometry in other studies. Patients in our cohort with presumed COPD but no spirometric confirmation appeared to have worse prognosis (online supplemental eTable 5) compared with patients with documented spirometry. The reasons for this are not entirely clear as these patients had similar age, gender, acid–base abnormalities, use of PAP therapy prior to admission and length of hospital stay compared with patients with spirometry (online supplemental eTable 6). There are likely other unmeasured differences in these groups. As spirometry is often performed in the outpatient setting, patients without spirometry may represent a group of patients who are non-adherent to treatment or are less motivated or able to engage with the healthcare service.

Naranjo *et al* assessed hospital readmission rates following an exacerbation of COPD and found that patients with OVS had a threefold increased risk of 30-day and 6-month hospital readmissions compared with patients with COPD alone.[27] Notably, patients in this study did not have spirometry to confirm their COPD diagnosis or disease severity, and patients were excluded if they had high oxygen requirements, suggesting that patients in this study may have had milder disease severity compared with the patients in our study. Clinical outcomes in patients with OVS admitted to hospital were also assessed in a large retrospective cohort study involving 189 685 patients admitted across seven US states with an acute exacerbation of COPD.[28] They found that there was no difference in the rate of invasive mechanical ventilation between patients with OVS and patients with COPD alone after adjusting for confounders. Furthermore, patients with OVS were more likely to require PAP therapy (OR 2.78, 95% CI 2.63 to 2.95) compared with patients with COPD alone and were more likely to have a hospital length of stay of 4 days or greater (OR 1.19, 95% CI 1.15 to 1.23). Again, patients in this study did not have spirometry to confirm the diagnosis or the disease severity. Additionally, no distinction was made between CPAP and NIV use in patients who received PAP therapy on discharge.

Study limitations

Our study had several limitations including its retrospective design. However, we attempted to account for potential confounders by ensuring that all patients had lung function and ABG results and comorbidities accounted for. We also made efforts to ensure that the clinical data for each patient were accurate with a respiratory and sleep physician reviewing the medical records and clinic letters for each patient. We excluded 75 patients with a label of COPD but without a spirometry result. However, when these patients were added to the analysis, it did not change the survival outcomes (online supplemental eTable 5). Although we included all patients who were treated with acute NIV by the RSS team, this did not account for all patients who were treated with acute NIV but were not referred to the RSS. These patients included those who were treated in the emergency department and the intensive care unit who were either palliated or weaned off NIV before they came to the ward. However, the authors feel that the number of patients that bypassed the RSS was likely small given the well-established mobile acute NIV service that operates 24 hours/day, 7 days/week. Consequently, the majority of patients with ARF requiring NIV would be seen at some point by the Service, unless the patient had other life-threatening medical issues. Another limitation was the absence of PAP therapy adherence data. Although we found a significant survival benefit in patients with OVS who were prescribed PAP therapy, it is unclear how this relates to PAP therapy adherence. We also cannot exclude the possibility of selection bias that may have influenced the outcomes of patients who consented to using PAP therapy versus those who declined or were intolerant of treatment. Our multivariate model included six prognostic variables; however, our small sample was likely too small resulting in large SEs and widened CIs. However, we felt that it was important to include these known clinical confounders. Finally, our results may not be generalisable outside of the cohort of patients with OVS who are hospitalised with ARF. However, we felt that this was an important cohort to study given their high morbidity and mortality and cost to the healthcare system.

CONCLUSION

Our study demonstrated that patients with COPD and OSA who are admitted to hospital with ARF appear to have higher long-term survival compared with patients with COPD alone. This contrasts with previous studies that demonstrated worse prognosis among patients with OVS without ARF compared with patients with COPD alone. We suspect that this may be due to the propensity of patients with OVS to develop hypercapnia and

thus present in ARF at an earlier stage of their disease. Furthermore, we demonstrated that survival was improved when patients with OVS were treated with long-term PAP therapy. These results suggest that it may be a good opportunity to commence patients with OVS on long-term PAP therapy after they present to hospital with ARF. However, the use of PAP therapy did not alter the rate of rehospitalisation. While these results are interesting, they can only be hypothesis generating at best given the retrospective nature of the study. Prospective studies are warranted to confirm our findings and RCTs will be needed to elucidate the role of domiciliary/long-term PAP therapy in patients with OVS presenting with ARF, in particular the impact of PAP on exacerbations and hospitalisations.

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