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High-pressure NIV for acute hypercapnic respiratory failure in COPD: improved survival in a retrospective cohort study

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ABSTRACT

Introduction Updated treatment guidelines for acute hypercapnic respiratory failure (AHRF) in chronic obstructive pulmonary disease (COPD) with non-invasive ventilation (NIV) in 2016 recommended a rapid increase in inspiratory positive airway pressure (IPAP) to 20 cm H_2O with possible further increase for patients not responding. Previous guidelines from 2006 suggested a more conservative algorithm and maximum IPAP of 20 cm H_2O.

Aim To determine whether updated guidelines recommending higher IPAP during NIV were related with improved outcome in patients with COPD admitted with AHRF, compared with NIV with lower IPAP.

Methods A retrospective cohort study comparing patients with COPD admitted with AHRF requiring NIV in 2012–2013 and 2017–2018.

Results 101 patients were included in the 2012–2013 cohort with low IPAP regime and 80 patients in the 2017–2018 cohort with high IPAP regime. Baseline characteristics, including age, forced expiratory volume in 1 s (FEV_1), pH and $PaCO_2$ at initiation of NIV, were comparable. Median IPAP in the 2012–2013 cohort was 12 cm H_2O (IQR 10–14) and 20 cm H_2O (IQR 18-24) in the 2017–2018 cohort (p<0.001). In-hospital mortality was 40.5% in the 2012–2013 cohort and 13.8% in the 2017–2018 cohort (p<0.001). The 30-days and 1-year mortality were significantly lower in the 2017–2018 cohort. With a Cox model 1 year survival analysis, adjusted for age, sex, FEV_1 and pH at NIV initiation, the HR was 0.45 (95% CI 0.27 to 0.74, p=0.002).

Conclusion Short-term and long-term survival rates were substantially higher in the cohort treated with higher IPAP. Our data support the current strategy of rapid increase and higher pressure.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Treatment of acute hypercapnic respiratory failure (AHRF) due to acute exacerbation of chronic obstructive pulmonary disease (COPD) with non-invasive ventilation (NIV) is well documented and widely implemented. With further attention to efficiency of treatment, updated Danish national NIV guidelines in 2016 recommended a paradigm shift with a new algorithm of initial rapid rise in pressure and use of higher pressures.

WHAT THIS STUDY ADDS

⇒ We performed a retrospective cohort study comparing patients with COPD with AHRF requiring NIV in 2012–2013, before introduction of updated guidelines, and in 2017–2018. Short-term and long-term survival rates were higher in patients undergoing NIV in 2017–2018 compared to those in 2012–2013.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ It seems plausible that improved survival is an effect of treatment with higher pressures and our data support the current strategy.

INTRODUCTION

For patients with chronic obstructive pulmonary disease (COPD), acute hypercapnic respiratory failure (AHRF) secondary to acute exacerbation of COPD (AECOPD) is associated with substantial mortality and risk of intubation. Treatment of AHRF with non-invasive ventilation (NIV) has improved these outcomes since the treatment was introduced in 1990.[1 2] Even though early studies showed more efficient resolution of respiratory acidaemia when using a inspiratory positive airway pressure (IPAP) of 20 cm H_2O than 12 cm H_2O,[1] early NIV treatment guidelines recommended quite conservative pressure settings. The Danish Society of Respiratory Medicine suggested initial IPAP of 12 cm H_2O, to be increased to a maximum 20 cm H_2O[3] but in a Danish retrospective study of 286 patients undergoing in-hospital NIV treatment in 2012–2013 median maximum IPAP was only 12 cm H_2O (IQR 12–14), that is, suggesting that the recommended use of higher IPAP was not implemented fully.[4] With evidence from randomised controlled trials (RCTs)

on home long-term NIV (LT NIV) treatment of patients with COPD the use of higher IPAP to reduce $PaCO_2$ has become more common.[5] Updated Danish treatment guidelines for AHRF in 2016 recommend initial IPAP of 12–15 cm H_2O and a rapid increase to 20 cm H_2O within the first 30 min of treatment and possible further increase if the patient is not responding.[6] Recommendations were similar to the 2016 British Thoracic Society and Intensive Care Society 'Guideline for the ventilatory management of AHRF in adults'.[7] The efficacy and safety of using higher IPAP are mainly derived from data on out-of-hospital patients with COPD in LTNIV treatment and the high-intensity NIV concept.[8 9] Less is known of the short-term and long-term effects of increased IPAP in treatment of AHRF. Further RCT, comparing NIV with low and high IPAP settings, does not seem to be likely nor ethically justified.

The aim of this study was to determine whether NIV treatment according to updated guidelines, recommending rapid increase and higher IPAP, compared with earlier treatment regimens using lower IPAP, was associated with better outcome in patients with COPD admitted with AHRF.

MATERIALS AND METHODS
Study design
In this retrospective cohort study of patients admitted with AHRF due to AECOPD requiring acute NIV, we compared patients treated according to guidelines from 2006 recommending quite conservative settings and lower IPAP ('2012–2013 cohort'), with patients treated according to guidelines from 2016 recommending higher IPAP ('2017–2018 cohort'). We included all patients who received NIV due to AECOPD with AHRF at the Respiratory Unit, Department of Internal Medicine, Gentofte Hospital (Capital Region, Denmark) from 1 January 2012 to 31 December 2013, and from 1 January 2017 to 31 December 2018. Patients with AHRF due to other causes than AECOPD were not included.

Study population
All patients admitted due to AECOPD and/or respiratory failure were screened. Patients who underwent NIV treatment for AHRF in the respiratory ward were included. Patients who had NIV initiated at the intensive care unit (ICU) and were later transferred to the respiratory ward, still requiring NIV, were also included. The COPD diagnosis was defined in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition[10] and assessed by the treating physician based on clinical history, physical examination and spirometry. Initial examination including arterial blood gas analysis, blood samples and chest X-ray were performed at admission in the acute medical department. Acute medical treatment of AECOPD included bronchodilators, systemic corticosteroids, controlled oxygen therapy and, if indicated, antibiotics. Indication for NIV was pH <7.35 and $PaCO_2$ >6 kPa

after 1–2 hours of initial treatment, in accordance with GOLD.[10] Acute medical treatment of AECOPD, oxygen therapy recommendations and indication for NIV treatment were unchanged during the study period.

Data collection
Screening and data collection were performed according to a predefined protocol including baseline characteristics at index admission, data concerning index admission, and a 1-year follow-up of events, number of readmissions and death. Data on patients undergoing treatment in 2012–2013 cohort were already available, collected in 2014 and has previously been used in two publications.[4 11] Patients in the 2017–2018 cohort were screened for inclusion or exclusion in accordance with the protocol for the 2012–2013 cohort. All data, including data regarding mortality, were collected from electronic patient medical records, which correspond and are automatically updated through the Danish Cause of Death Registry.

NIV treatment
NIV treatment guidelines for AHRF from 2006 recommended an initial IPAP of 12 cm H_2O and with a maximum increase of IPAP to 20 cm H_2O. The 2016 NIV treatment guidelines for AHRF recommended a rapid increase in IPAP from initial IPAP of 12 to 15, to IPAP of 20 cm H_2O within the first 30 min after initiating NIV and that further increase could be considered if necessary, to acquire normalisation of pH and a decline in $PaCO_2$. In 2017–2018, these recommendations were the general clinical practice at the department. Treatment with NIV was performed in the respiratory ward with specially trained nursing staff, according to a standardised algorithm for collection of blood gas sample and adjustment of NIV setting. The ventilator settings used were pressure-targeted spontaneous/timed mode. NIV was delivered semicontinuous during the first 24 hours. As the patient's condition improved, and pH and $PaCO_2$ were normalised, a plan for NIV weaning was made. For successful withdrawal of treatment, the time with NIV was gradually reduced during the day while continuing overnight NIV. NIV failure was defined as patients not successfully responding to NIV, either requiring endotracheal intubation and ICU treatment or death for patients with NIV as ceiling of treatment. 'Do not intubate/Do not resuscitate' (DNI/DNR) orders were either classified as 'initial order', placed within 2 hours of the admission, or 'late order', placed later than 2 hours of admission during NIV treatment.

Statistical analysis
Primary outcome was in-hospital mortality. Secondary outcomes were 30-day and 1-year mortality and adherence to pressure setting according to treatment guidelines.

Categorical variables are presented as numbers and percentages and analysed using Pearson's χ^2 test. Continuous variables are presented as medians and IQRs and analysed using Mann-Whitney U test.

Survival analysis for in-hospital mortality, 30-day mortality and 1-year mortality was conducted. The cumulative probability of survival is presented as a Kaplan-Meier survival plot, compared using log-rank test. To control for potential confounders, logistic regression and a Cox proportional hazards regression analysis were performed, adjusted for age, sex, forced expiratory volume in first second (FEV_1) and pH at initiation of NIV, using a complete case analysis. Results are presented as odds ratio (OR) hazard ratio (HR) with a 95% confidence interval (95% CI). Furthermore, to assess robustness, calculation of E-values for estimation of the required strength of potential unmeasured confounders was performed.

Statistical analyses were performed in RStudio V.1.2.5001.

Patient and public involvement

Patients or public were not involved in the design of the study.

RESULTS

181 patients were included in the analyses: 101 patients in the 2012–2013 cohort with low IPAP regime and 80 patients in the 2017–2018 cohort with high IPAP regime (figure 1).

Baseline characteristics and data from index admission are presented in table 1. Overall, the two cohorts were similar on baseline chronic variables and admission data from the acute index admission. There was, however, a significant difference in pack-years; the 2012–2013 cohort had a history of a median of 40 pack-years (IQR 30–50) compared with 50 (IQR 40–60) in the 2017–2018 cohort. There was a trend towards higher body mass index in the 2017–2018 cohort, but not statistically significant. Respiratory rate on initiation of NIV was higher in the 2012–2013 cohort, 28 breaths per minute (IQR 24–32) compared with 24 breaths per minute (IQR 20–28) in the 2017–2018 cohort (p=0.001). Median IPAP in the 2012–2013 cohort was $12\,cm\,H_2O$ (IQR 10–14) compared with $20\,cm\,H_2O$ (IQR 18–24) in the 2017–2018 cohort (p<0.001). Spirometry measurements and FEV_1 were missing in 28 patients, as they had been diagnosed and received outpatient care at clinics outside the hospital.

In the 2012–2013 cohort 47 patients (46.5 %) had an initial DNI/DNR order, and 14 patients (13.9 %) had a late order. In the 2017–2018 cohort, 24 patients (30.8 %) had an initial DNI/DNR order and 9 patients (11.5 %) had a late order. NIV failure and the need for intubation and ICU treatment occurred in eight patients (8%) in the 2012–2013 cohort, and two patients (2.5%) required intubation (p=0.123).

Mortality and survival

Data on mortality are presented in table 2. In-hospital mortality was 40.5% in the 2012–2013 cohort to 13.8% in the 2017–2018 cohort (p<0.001). Furthermore, 30-day mortality and 1-year mortality were also significantly lower in the 2017–2018 cohort.

Unadjusted 1-year survival analysis with Kaplan-Meier plot is presented in figure 2. With the log rank test the cumulative estimate of survival was significantly higher in the 2017–2018 cohort (p=0.002). The adjusted regression model and Cox proportional hazards model are
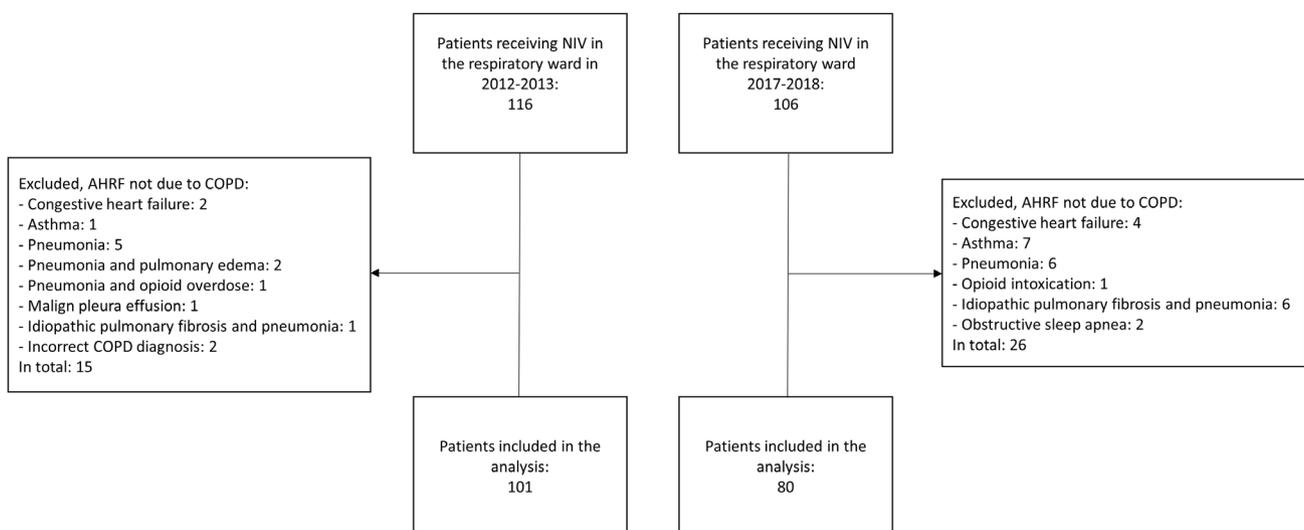

Figure 1 Flowcharts of the cohorts in the 2012–2013 and 2017–2018.
AHRF, acute hypercapnic respiratory failure; NIV, non-invasive ventilation, COPD, chronic obstructive pulmonary disease.

Table 1 Baseline characteristics and index admission data

	n	2012–13 cohort* n=101	2017–18 cohort† n=80	P value
Baseline characteristics				
Age (years)	181	78 (68–83)	78 (70–84)	0.472
Male, n (%)	181	27 (27)	25 (31)	0.573
BMI (kg/m^2)	133	23 (19–27)	25 (21–29)	0.055
FEV$_1$ % of predicted	153	33 (26–43)	38 (24–52)	0.246
MRC score	124	4 (3–5)	4 (3–5)	0.984
LTOT, n (%)	181	19 (18.8)	14 (17.5)	0.837
Smoker, n (%)	179			
Never		8 (7.9)	1 (1.2)	0.0460
Previous		50 (49.5)	51 (63.8)	0.198
Current		42 (41.6)	27 (33.8)	0.403
Pack-years	164	40 (30–50)	50 (40–60)	0.033
COPD admission prior to enrolment, n (%)	181			
Within 1 month		21 (20.8)	12 (15.0)	0.365
Within 1 year		40 (39.6)	27 (33.8)	0.520
Index admission data				
Duration of admission (days)	181	6 (3–9)	6 (4–8)	0.928
Fever (>38°C), n (%)	179	9 (8.9)	13 (16.2)	0.158
Maximum CRP	179	55 (19–135)	32 (14–117)	0.124
Antibiotics (oral or intravenous), n (%)	180	90 (90)	67 (84)	0.655
RR at NIV initiation	154	28 (24–32)	24 (20–28)	0.001
Arterial gasses at NIV initiation				
pH	181	7.28 (7.23–7.31)	7.29 (7.25–7.32)	0.552
PaCO$_2$ (kPa)	181	8.8 (7.7–11.0)	8.9 (7.8–9.9)	0.638
PaO$_2$ (kPa)	176	9.5 (7.9–11.0)	9.2 (8.3–10.4)	0.638
HCO$_3$– (mmol/L)	174	26.0 (23.0–31.0)	26.2 (23.2–28.8)	0.472
Base excess (mmol/L)	175	4.0 (–0.2 to 9.7)	4.0 (0.2–7.6)	0.596
Lactate (mmol/L)	170	1.1 (0.7–1.9)	1.2 (0.8–2.1)	0.395
Late-onset acidaemia (>12 hours after admission), n (%)	181	2 (2)	15 (18,8)	<0.001
Hyperoxia (Pa0$_2$ >16 kPa) on admission, n (%)	180	6 (6)	4 (4,9)	0.776
Max IPAP (cm H$_2$O)	180	12 (10–14)	20(18-24)	<0.001
Max EPAP (cm H$_2$O	180	5 (5–5)	5 (5–5)	0.119
Initially treated in ICU, n (%)	181	4 (4.0)	3 (3.8)	0.943
DNI/DNR-order, n (%)	179	61 (60)	33 (42)	0.098
Late, >2 hours of admission (% of all DNI/DNR orders)		14 (23)	9 (27)	
NIV failure, n (%)	181	8 (8.0)	2 (2.5)	0.123

Data is presented as median (IQR) unless stated otherwise. Comparison of groups using Mann-Whitney U test or χ^2 test.
*Low IPAP regime.
†High IPAP regime.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DNI/DNR, do not intubate/do not resuscitate; EPAP, expiratory positive airway pressure ; FEV$_1$, forced expiratory volume in 1 s; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen treatment; MRC, Medical Research Council Dyspnoea Scale; NIV, non-invasive ventilation; RF, respiratory frequency.

presented in table 3. The models are adjusted for age, sex, FEV$_1$ and pH at NIV initiation, and 153 patients were included in the complete case analysis. Patients in the 2017–2018 cohort had higher 1-year survival rates both with unadjusted (HR 0.50, 95% CI 0.32 to 0.77, p=0.002) and adjusted Cox proportional hazards model (HR 0.45,

Table 2 Mortality data

	2012–2013 cohort*	2017–2018 cohort†	P value
In-hospital mortality, n (%)	41 (40.5)	11 (13.8)	<0.001
30-day mortality, n (%)	47 (46.5)	19 (23.8)	0.002
1-year mortality, n (%)	61 (60.4)	32 (40.0)	0.006

*Low IPAP regime.
†High IPAP regime.
IPAP, inspiratory positive airway pressure.

95% CI 0.27 to 0.74, p=0.002). E values for the adjusted ORs and HRs are reported in table 3. All E values were 2.8 or larger, indicating that rather substantial unmeasured confounding, beyond the measured covariates, would be required to dismiss the effect estimate.

DISCUSSION

In this single-centre retrospective study, comparing two cohorts, treated for AHRF with NIV in 2012–2013 and 2017–2018, before and after introduction of a new treatment guideline in 2016 recommending a more rapid rise in pressure and use of higher IPAP, we found a significantly better short-time and long-time survival in the later cohort. To our knowledge, this is the first study to show a lower mortality when providing NIV with higher IPAP i for treatment of AHRF secondary to AECOPD. Additionally, data from the present study suggest that the risk of mortality following hospitalisation is highest immediately after discharge. For patients who survived the first 30 days post hospital discharge, the 1-year survival remained high (figure 2, Kaplan-Meier plot). This is in accordance with studies on survival after hospitalisation with AECOPD.[12]

Our data show that the new treatment guidelines were well implemented, with a median IPAP of 20 cm H_2O in 2017–2018 compared with 12 cm H_2O in 2012–2013. Apart from updated recommendations regarding the algorithm for pressure settings for NIV, standard

1-year survival

Log-Rank test: p= 0.002

Figure 2 Kaplan-Meier survival plot, survival 365 days after initiation of non-invasive ventilation for treatment of acute hypercapnic respiratory failure due to COPD.

treatment of AECOPD and the indication for NIV treatment were unchanged from 2012 to 2018.

Over the recent years, attention to improve suboptimal NIV treatment has risen. Insufficient pressure settings, especially inadequate IPAP, will not increase alveolar ventilation significantly. Focus on a more rapid improvement of pH within the first 4 hours after initiation of NIV is essential to reduce relative risk of NIV failure.[13] The improved survival in patients treated with higher IPAP in the present study, with otherwise comparable cohorts, suggests that using higher IPAP is more efficient to resolve AHRF and thus acute respiratory acidaemia. A rapid improvement of ventilation and patient's recovery may also increase patient acceptance of NIV treatment and reduce the risk of NIV failure. Furthermore, shortening length of treatment reduces risks of complications associated with hospitalisation and immobilisation; pulmonary embolism, hospital acquired pneumonia, and loss of physical mobility.

Other aspects in general COPD care changed from 2012 to 2018 and may have contributed to preventing admissions with AHRF and improving patient survival. Treatment with LT NIV has been shown to prevent hospitalisation in the subgroup of most severely ill patients with COPD.[5] LT NIV was introduced at the current department in the year 2000 and has become more frequent for the small subgroup of patients with COPD with chronic stable hypercapnia as well as for selected patients with recurrent exacerbations with AHRF.[14] Pharmaceutical treatment with long-term prophylactic azithromycin, as anti-inflammatory therapy, to reduce risk of exacerbations in patients with a history of recurrent exacerbations has also become more widespread.[15]

In research regarding treatment survival, mortality rates in observational studies are commonly higher compared with RCTs. Risk of in-hospital mortality was 99 per 1000 (95% CI 70 to 139) in the 2017 Cochrane meta-analysis analysing the results of 12 RCTs.[2] Published cohort studies on survival of AHRF show great variation in mortality. In a Danish nationwide register-based study of 12 847 patients admitted for AECOPD and treated with NIV in 2004 to 2011, median age 73.7 (IQR 66–80) years, in-hospital mortality was 24.4% (95% CI 24.3 to 24.5).[16] Among patients alive at discharge, 26.4% (95% CI 26.3 to 26.5) died within 1 year. In a smaller Dutch retrospective single-centre study of 78 patients admitted with AHRF
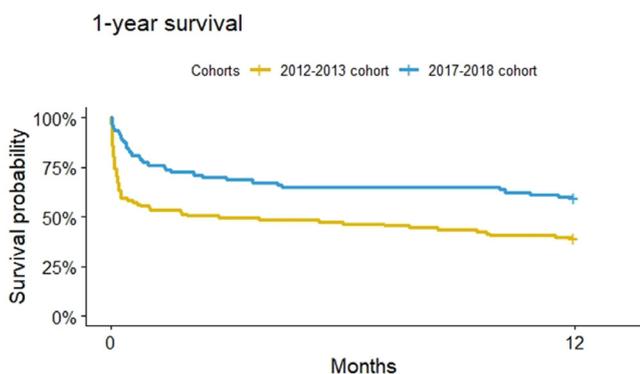
Table 3 Survival analysis

	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	E value (LL CI)
Logistic regression					
In-hospital mortality	0.22 (0.10 to 0.46)	<0.001	0.21 (0.079 to 0.51)	0.001	3.79 (2.15)
30-day mortality	0.36 (0.18 to 0.68	0.002	0.31 (0.14 to 0.67)	0.004	2.99 (1.74)
1-year mortality	0.44 (0.24 to 0.79)	0.007	0.38 (0.18 to 0.76)	0.007	2.63 (1.56)
Cox regression model					
1-year mortality	0.50 (0.32 to 0.77)	0.002	0.45 (0.27 to 0.74)	0.002	2.86 (1.77)

The adjusted models are adjusted for age, sex, FEV_1 and pH at NIV initiation.
FEV_1, forced expiratory volume in the first second; LL CI, lower limit of CI closest to the null; NIV, non-invasive ventilation.

requiring NIV in 2009 to 2011, in-hospital mortality was 14.1%, with 1-year mortality of 43.6%.[17] Mean age of the cohort was 71.0 (SD ±10.7) years, median FEV_1 39.0% (IQR 28.6–52.9) and median $PaCO_2$ before NIV 10.0 (IQR 8.5–11.2) kPa. Data from the national COPD audit in the UK in 2008 and 2014 showed a significantly improved in-hospital mortality of 24.9% and 16.8%, respectively.[18] Findings were explained due to better adherence to guideline recommendations of ventilatory settings, although data on pressure settings were not recorded, as well as improvements of general care such as controlled oxygen and early antibiotic treatment. Further retrospective data from the UK compared two cohorts, 2004–2010 and 2013–2017, of patients with COPD and first episode of ward-based NIV.[19] In-hospital mortality rates were 17.6% and 20.5% (p=0.378). Characteristics of the two cohorts were as follows, respectively: median age of 72.1 (IQR 64.2–78.8) and 69.9 (IQR 63.7–76.9) years, FEV_1 of 32 (IQR 24–39) and 35 (IQR 27–47)%, $PaCO_2$ before NIV of 9.36 (IQR 27–47) and 10.34 (IQR 8.89–11.8) kPa and maximum IPAP of 15 cm H_2O (IQR 12–18) and 18 (IQR 15–21).

Limitations of the present study are the limitations associated with a retrospective cohort study, the risk of selection and information bias with imprecise outcome registration and uneven collection of data. A potential selection bias is different selection of patients to whom physicians offered NIV treatment to in the two cohorts. As NIV was a newer, advanced technology in 2012–2013, physicians could have been more prone to select the most severely ill patients for NIV as rescue treatment, whereas in the later cohort, NIV could have been offered more broadly to patients with AHRF, despite the severity of acidaemia, comorbidities and performance status. However, baseline characteristics and blood gas levels of pH and $PaCO_2$ at initiation of NIV were comparable in the cohorts, which contradicts a selection bias. As a single-centre study with a small size cohort, there is the potential risk of overstating positive results and the lack of external validity required to support a more widespread generalisation of the results. The in-hospital mortality was notably high in both cohorts compared with the previously mentioned studies, reflecting the demographic composition of patients treated at the hospital, with median age of 78 in both cohorts. Other factors associated with death such as FEV_1 and pH and $PaCO_2$ before NIV are in accordance with data from previous studies. NIV was ceiling therapy for 60% of patients in the 2012–2013 cohort and 42% of patients in the 2017–2018 cohort. This is also reflected in the small percentage of patients transferred to the ICU due to NIV failure. Furthermore, about one out of four DNI/DNR orders were placed later than 2 hours of admission in both cohorts.

CONCLUSION

This observational study shows that patients with AHRF due to AECOPD treated with NIV using higher IPAP in 2017–2018, according to contemporary guidelines, had significantly better short-term and long-term survival compared with patients treated with lower IPAP in 2012–2013. It seems plausible that improved survival is an effect of higher IPAP; however, further research is needed, preferably multicentre studies including a larger number of patients.

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and the conduct of the study, had access to the data, and controlled the decision to publish. All authors contributed revision and final approval of manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by our local ethics committee (R-20067943) and data monitoring board (P-2020-881). The study is retrospective and in accordance with the approval from the ethics committee. Consent for participation was not required.

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