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Safety and Efficacy of Noninvasive Ventilation in Patients With Acute Exacerbations of Chronic Obstructive Pulmonary Disease and Decreased Level of Consciousness: A Retrospective Study

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ABSTRACT

Background: Noninvasive ventilation (NIV) is the treatment of choice in cases of acute exacerbations of chronic obstructive pulmonary disease (AECOPD). However, depressed mental status, frequently caused by AECOPD, represents a relative contraindication to NIV. This study evaluates the efficacy of NIV in patients with AECOPD with moderate to severe impairment of consciousness.

Methods: In this monocentric, retrospective study, we included patients admitted to the emergency department (ED) from January 2018 to December 2022 for AECOPD, altered mental status (GCS ≤ 13 and/or KMS ≥ 2) and treated with NIV.

Results: Out of 919 patients admitted with acute respiratory failure, 228 (24.8%) met the inclusion criteria for AECOPD. Of these, 205 (90%) underwent NIV during the ED admissions without adverse events. In 48 patients (21.1%), NIV was withdrawn due to clinical improvement. Only 23 (10.1%) experienced NIV failure with worsening of hypoxemia and occurrence of hypotension, of whom 16 (7% of the total population) died in the ED. Severe neurological impairment (low GCS) was an independent predictor of mortality. Systolic and diastolic blood pressure, SpO_2, pH value and lactate levels were predictive of early mortality. COVID-19 status did not significantly affect mortality rates.

Conclusion: NIV was feasible and associated with successful outcomes in a majority of patients with AECOPD and moderate to severe neurological impairment. Specific parameters, including initial GCS, blood pressure, SpO_2, and blood gas profiles, can help predict outcomes and treatment efficacy.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ED, emergency department; GCS, Glasgow Coma Scale; NIV, noninvasive ventilation; P/F, PaO_2/FiO_2 ratio; SpO_2, saturation of peripheral oxygen.

1 | Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive disease of the airways and lungs, characterised by bronchial obstruction that is not fully reversible with bronchodilators. The natural history of COPD includes exacerbation episodes, defined as an acute worsening of respiratory function lasting at least 48 h and necessitating treatment intensification. These exacerbations lead to an accelerated decline in lung function, poor quality of life, increased mortality and high healthcare costs. Acute exacerbations of COPD (AECOPD) are a significant cause of emergency department (ED) admissions, accounting for more than 1.5 million visits and 700 000 hospitalisations in the United States in 2010 [1]. Patients with COPD flare-ups often present with acute respiratory failure, characterised by hypoxemia and hypercapnia due to air trapping and respiratory distress. Hypercapnia, indicative of respiratory fatigue, results from decreased alveolar ventilation [2]. COPD-related acute respiratory crisis can cause altered consciousness up to coma, and ultimately death due to global respiratory failure [3]. The severity of altered mental status is assessed using two standardised rating scales: the Glasgow Coma Scale (GCS) and the Kelly–Matthay Scale (KMS) [4, 5].

Noninvasive ventilation (NIV) is the primary therapeutic strategy for respiratory failure in COPD [6]. NIV alleviates breathing difficulty by increasing alveolar ventilation and reducing hypercapnia. The proper use of NIV in critically ill patients can significantly improve long-term prognosis and reduce the need for endotracheal intubation [7–9]. However, inappropriate patient selection and incorrect NIV use can increase the risk of endotracheal intubation and prolonged admission to the Intensive Care Unit (ICU). Severe encephalopathy, defined as a GCS < 10, is a contraindication for NIV [10–13]. In patients with acute global respiratory failure and altered mental status, data on the use of NIV are conflicting due to limited patient compliance and increased risk of aspiration from reduced airway protective reflexes [14, 15]. The real-world application of NIV diverges from guideline recommendations, particularly in terms of patient selection and the timing of initiation [16].

The lack of precise data prompted the present study, which is aimed at investigating the efficacy of NIV in patients with AECOPD and moderate to severe impairment of consciousness.

2 | Materials and Methods

This monocentric retrospective study was conducted between January 2018 and December 2022 in the ED of St. Anna University Hospital in Ferrara, Italy. Serving as a third-level referral centre for time-sensitive emergencies, this hospital provides medical care to over 80 000 patients annually. The inclusion criteria for the study were (i) admission to the ED with a life-threatening AECOPD (patients with a state of respiratory acidosis (pH < 7.35 and pCO2 > 45) and severe respiratory activation) [17]; (ii) altered mental status assessed by a GCS ≤ 13 and/or a KMS ≥ 2; (iii) application of a NIV strategy using pressure support ventilation (PSV) or bi-level mode. Exclusion criteria included (i) preserved state of consciousness (GCS > 13 and/or KMS < 2); (ii) incomplete data. The objective of the study is to evaluate the effectiveness of NIV in patients with acute respiratory failure and altered mental status. Additionally, given the global impact of the coronavirus disease 2019 (COVID-19) pandemic during the study period, we evaluated the potential influence of SARS-CoV-2 infection on clinical outcomes. COVID-19 status was recorded for all eligible patients to assess whether the presence of infection significantly affected the efficacy of NIV and the overall in-hospital mortality in this specific population. Data on mental status, vital signs, noninvasive ventilator settings, and blood gas analysis were collected at both admission and discharge. Clinical improvement was reported in case of improvement in any of the serum pH, mental status or lactate levels. NIV failure was defined as the absence of clinical or blood gas improvement compared with baseline ($pO_2 < 60$ mmHg, $pCO_2 > 45$ mmHg, pH < 7.35), need for orotracheal intubation or death in the ED.

The study was approved by the Ethics Committee of the Area Vasta Emilia Centro (NIV2023, protocol number: 447/2021/Disp/AOUFe).

3 | Statistical Analysis

Normally distributed data were described as mean ± standard deviation (SD); categorical data were expressed as absolute numbers and percentages. All appropriate statistical analyses were performed using SPSS v. 25 (Apache Software Foundation, Chicago, Illinois, United States) and MedCalc version 17.6 (MedCalc Software BVBA).

4 | Results

During the study period, 919 patients with acute respiratory failure were admitted to the hospital from the ED. A total of 691 patients did not meet the inclusion criteria and were therefore excluded from the study. Thus, 228 patients (121 females, 107 males) were included in the study. In 205 patients (90%), NIV was beneficial, with 48 patients (21% of the included sample) who withdrawal NIV for early improvement; in 23 patients, we assisted a failure of NIV and 16 of them (69.5%, 7% of the included sample) died in the ED (see Figure 1 for the CONSORT flow diagram). The main characteristics of the included patients are summarised in Tables 1, 2 and 3.

The predictors of mortality in the ED were as follows: average lower SpO_2 (81% vs. 90%, $p = 0.002$), systolic (102 mmHg vs. 131 mmHg, $p = 0.003$), diastolic blood pressure (60 mmHg vs. 74 mmHg, $p = 0.011$) and GCS at both admission (4 vs. 7, $p = 0.020$) and discharge (3 vs. 12, $p < 0.001$) Moreover, patients who died in the ED had lower pH levels (7.1 vs. 7.2, $p < 0.001$) at both admission and after 6 h of NIV (7.1 vs. 7.3 in survivors, $p < 0.012$), higher lactate (7.9 vs. 2.4, $p < 0.001$) and higher serum creatinine levels (3.05 vs. 1.61, $p < 0.001$). Ventilatory parameters did not differ significantly in terms of mortality (Table 1). Patients who died in the ED were more likely to require intensive care (18% vs. 12.3%, $p = 0.453$) and tracheal intubation (TI) due to clinical deterioration (6.7% vs. 0%, $p < 0.001$). No cases of inhalation were reported. Additionally, none of the patients who died in the ED had a COVID-19 infection (Table 2).

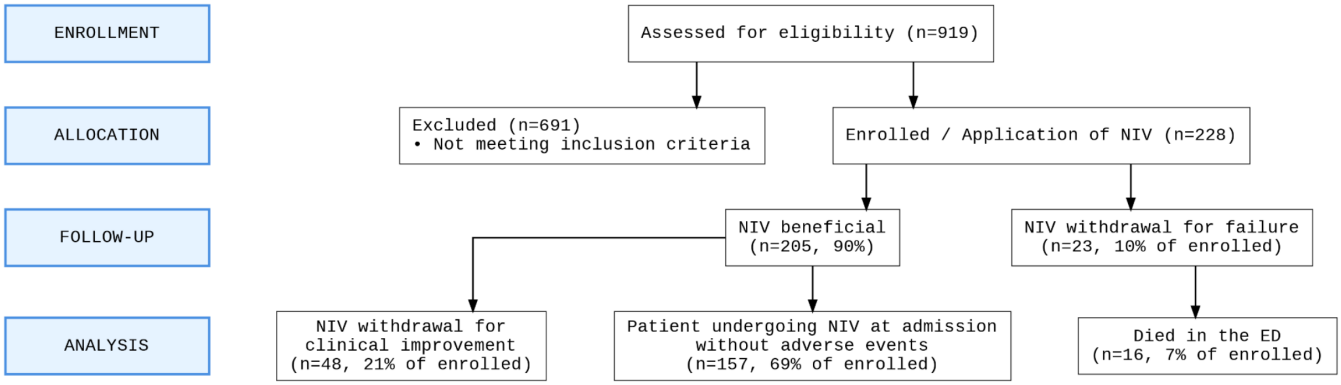

FIGURE 1 | Consort Flow diagram.

TABLE 1 | Clinical factors affecting outcome in patients who underwent NIV. Severe neurological impairment is closely related to in-hospital mortality. The NIV parameters do not influence clinical improvement.

	Survived $N=212$ (93%)	Deceased $N=16$ (7%)	p
SpO_2, %	90 (8)	81 (14)	0.002
SBP, mmHg	131 (31)	102 (29)	0.003
DBP, mmHg	74(17)	60 (19)	0.011
Admission GCS	7 (3)	4 (2)	0.020
pH	7.292 (0.122)	7.136 (0.125)	0.001
Lactate, mmol/L	2.4 (2.5)	7.9 (17)	<0.001
Urea, mg/dL	85 (66)	165 (164)	0.004
Creatinine, mg/dL	1.61 (1.29)	3.05 (3.06)	<0.001
PS, cmH_2O	10 (3)	9 (4)	0.85
PEEP, cmH_2O	6 (2)	6 (3)	0.78
Rise time, msec	121 (45)	100 (40)	0.69
Discharge GCS	12 (5)	3 (0)	<0.001
Clinical deterioration	79 (37.3)	16 (100)	<0.001
COVID-19	30 (14.2)	0 (0)	0.13
OTI for deterioration	0 (0)	1 (6.7)	<0.001
Intensive care	26 (12.3)	3 (18.7)	0.453
Inhalation	0 (0)	0 (0)	—

Note: All data are reported as mean (SD) or number (%).
Abbreviations: COVID-19, coronavirus disease 19; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; OTI, orotracheal intubation; PEEP, positive end-expiratory pressure; PS, pressure support; SpO_2, peripheral oxygen saturation; SBP, systolic blood pressure.

TABLE 2 | The improvement of respiratory acidosis is related to clinical amelioration. The NIV parameters do not influence clinical improvement.

	Survived patients = 212 NIV withdrawal for clinical improvement		
	No $N=179$ (78.8%)	Yes $N=48$ (21.1%)	p
Admission pH	7.277 (0.123)	7.324 (0.127)	0.027
Admission pCO_2, mmHg	63.6 (27.3)	54.4 (23.8)	0.042
Admission GCS	7 (3)	7 (4)	0.45
PS, cmH_2O	10 (3)	9 (3)	0.38
PEEP, cmH2O	6 (2)	6 (2)	0.78
Rise time, ms	121 (45)	100 (35)	0.96
Discharge pH	7.321 (0.102)	7.361 (0.088)	0.034
Discharge pCO_2, mmHg	58.3 (20.8)	49.9 (16.2)	0.026
Discharge GCS	9 (6)	14 (2)	0.004

Note: All data are reported as mean (SD) or number (%).
Abbreviations: DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; PEEP, positive end-expiratory pressure; PS, pressure support; SBP, systolic blood pressure.

In 22% of patients, NIV was discontinued due to clinical improvement. As for the predictors of success, there were significant improvements in GCS score (14 vs. 7, $p=0.004$), pCO_2 levels (49.9 mmHg vs. 54.4 mmHg, $p=0.026$), and respiratory acidosis (pH 7.361 vs. 7.324, $p=0.034$). Improvement in mental status was associated with increased survival (29.7% of patients vs. 6.2% of those who died, $p=0.044$). NIV parameters did not significantly influence clinical improvement (Table 2).

NIV treatment was discontinued due to failure in 10.1% of cases. Compared with patients who continued NIV, patients in whom NIV was stopped had lower mean SpO_2 (54.8% vs. 83.9%, $p=0.033$) and lower diastolic blood pressure (64 mmHg vs.

TABLE 3 | Hypoxia and hypotension are predictive of ventilatory therapy failure. The NIV parameters do not influence clinical improvement.

	NIV withdrawal for failure		
	No *N* = 205 (90%)	**Yes *N* = 23 (10%)**	***p***
Admission GCS	7 (3)	6 (3)	0.54
DBP, mmHg	74 (17)	64 (20)	0.011
SpO_2, %	83.9 (57.4)	54.8 (13.1)	0.033
$d(A\text{-}a)O_2$	239.8 (187.4)	141.3 (118.1)	0.049
PS, cmH_2O	10 (3)	9 (4)	0.48
PEEP, cmH_2O	6 (2)	7 (2)	0.38
Rise time, ms	121 (45)	100 (40)	—
Leukocytes, / mmol	13 482 (6637)	10 099 (3884)	0.020
Discharge KMS	2 (1)	4 (2)	0.020
OTI	0 (0)	1 (4.3)	
Death in the ED	0 (0)	16 (70)	
Exclusive palliative care	0 (0)	7 (30)	

Note: All data are reported as mean (SD) or number (%).
Abbreviations: d(A-a)O2, alveolar-arterial oxygen gradient; DBP, diastolic blood pressure; ED, emergency department; GCS, Glasgow Coma Scale; KMS: Kelly mental status; OTI, orotracheal intubation; PEEP, positive end-expiratory pressure; PS, pressure support; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation.

74 mmHg, $p = 0.011$). However, there were no significant differences in NIV parameter settings (Table 3).

In the remaining 54 patients (38.3%), NIV did not determine significant changes in clinical evolution.

5 | Discussion

NIV represents the primary therapeutic strategy in acute global respiratory failure [18]. Nevertheless, according to the classical international guidelines, NIV is contraindicated in hypercapnic encephalopathy syndrome due to poor compliance secondary to confused/agitated patients and the risk of aspiration pneumonia because of compromised airway protective reflexes [10]. Current literature validates NIV as a strictly monitored trial for hypercapnic encephalopathy [7, 10, 12, 14, 16, 17, 19–21], a strategy recently bolstered by findings linking use of NIV instead of TI to reduced mortality and hospital stay in comatose patients [19]. Beyond AECOPD management, NIV plays a dual role in patients with respiratory distress and end-stage disease: When invasive care is disproportionate, it may represent the sole viable therapeutic option and an essential palliative tool [22–26]. Consequently, this approach was considered ethically acceptable, balancing the potential for recovery with the need to minimise invasiveness in this fragile population.

According to the results of the present study, 90% of patients admitted to the ED for acute COPD exacerbation with respiratory distress and altered mental status underwent NIV for the entire duration of their stay in the ED without complications, allowing noninvasive therapy to be stopped in 21.1% of cases for early improvement. In 2019, Lemyze et al. tested the efficacy of NIV treatment in acute hypercapnic respiratory failure, even in cases with extreme respiratory acidosis and hypercapnic coma at admission. The use of NIV in these severely hypercapnic patients resulted in increased survival rates at hospital discharge [3]. Our data (as indicated in Table 2) support the use of NIV treatment in AECOPD patients, resulting in improved clinical and blood gas profiles, with discontinuation of mechanical ventilation in 22% of cases. The comprehensive data collected in this study enabled us to identify potential parameters associated with successful NIV outcomes in these patients. Ventilatory settings had no impact on clinical improvement. However, blood gas profiles with pH values at admission demonstrated a strong correlation with successful NIV therapy outcomes as indicated by an OR of 21 (95% CI of 1.38–418). Additionally, pH improvement during ventilation proved to be a reliable predictor of treatment success, making it a valuable index for patient monitoring until NIV was discontinued. Similarly, pCO_2 predicted NIV efficacy (OR = 0.98; 95% CI, 0.97–0.99, $p = 0.044$) due to the effect of pCO_2 on alertness and the ability to achieve adequate ventilation [12]. Furthermore, higher oxygen saturation levels at the time of admission strongly correlated with successful treatment outcomes. This finding is in keeping with the evidence that better initial oxygenation facilitates faster recovery from respiratory failure, as the intervention was initiated in patients with less severe clinical states. These parameters help outline a precise profile of the patient who benefits from the NIV approach [11]. Conversely, hypotension was confirmed as a relevant factor in NIV failure [17], a finding that can be explained by the increased thoracic pressure on the patient's haemodynamic balance, such as a reduction in cardiac output and, consequently, mean arterial pressure [27]. Therefore, a cautionary approach is necessary when using NIV in hypotensive patients, as it may worsen an already weak cardiocirculatory compensation [12]. We also considered COVID-19 infection, but this condition did not prove statistically significant in terms of mortality.

Classical international guidelines traditionally contraindicate the use of NIV in patients with hypercapnic encephalopathy syndrome. However, recent studies suggest that the risks associated with pulmonary aspiration and the perceived inefficacy of noninvasive positive pressure ventilation are likely overstated. This evidence supports a cautious trial of NIV or intermittent lung ventilation in carefully selected patients with AECOPD presenting with hypercapnic encephalopathy syndrome [10, 20, 21]. According to the most recent Chest guideline, severe encephalopathy (GCS < 10) is only a relative contraindication to NIV, especially in settings with high clinical and instrumental monitoring capacity [17]. Severe neurological impairment, indicated by a low GCS at admission, is strongly associated with in-hospital mortality [17]. The analysis of the three components of the GCS (i.e., eye, verbal, and motor responses) revealed that only the eye-opening holds significance as a prognostic marker in patients with AECOPD

undergoing NIV. Notably, patients with lower initial GCS-eye scores, such as 1, experienced higher mortality rates in the ED compared with those with higher scores. Also, a low GCS-eye parameter was associated with an increased risk of in-hospital mortality (OR = 0.42; 95% CI 0.18–0.94, $p = 0.036$), suggesting that a diminished ocular performance can be an indicator of the patient's neurological state. A possible explanation is that eye opening reflects arousal and brainstem function more directly than motor response, which may be preserved despite CO_2 narcosis. Reduced eye responsiveness may therefore be an earlier indicator of hypercapnia-related depression of consciousness. GCS-eye may be used as a valuable criterion to identify candidates suitable for NIV treatment. This insight represents a novel contribution to existing literature. It highlights that the existence of a pronounced neurological dysfunction likely reflects a more severe respiratory crisis and overall increased patient frailty. In this line, our analysis is in line with the retrospective study by Innocenti et al., who showed a high mortality in patients with acute respiratory failure undergoing NIV who had a low GCS score [11, 17]. Despite a very low GCS on admission, survivors had a GCS > 12 at discharge, demonstrating the significant efficacy of NIV in these patients. A NIV approach was practical in patients admitted to the ED with a GCS of 7 ± 3 ($p = 0.020$). Although a lower GCS correlates with more mortality, the use of NIV seems to improve the outcome of some of these patients, supporting the present study's objective. Although the data of this study confirmed that a particularly compromised GCS on admission is an independent predictor of mortality, this does not contradict our findings. In these high-risk patients, NIV should be viewed as a carefully monitored therapeutic trial rather than a definitively 'effective' treatment, especially considering that immediate intubation also carries substantial risks.

The NIV effectively reduces intubation rates (from 10% to 6%) and in-hospital mortality (from 20% to 10%) [17]. Despite the high risk of NIV failure due to reduced level of consciousness, the high mean age and the low pH level of patients in our study (all well-recognised predictors of NIV failure) [17], the in-hospital mortality occurred only in 7%, with only one patient who underwent TI and three patients referred to the ICU.

This study has several strengths. First, the population examined was obtained from an ED, and the sample size was substantial and evenly distributed across gender and age groups. Second, existing research on the efficacy of NIV in comatose patients in emergency settings (regardless of the underlying cause of respiratory failure) is notably sparse.

Several limitations should be noted. First, the study's retrospective approach relied exclusively on the final ED report. The results of this study allow us to define NIV as a treatment associated with success in the majority of selected patients, but not to define NIV as an effective treatment, as there is no control group. Second, it included patients from a single ED, meaning the frequency of observed pathologies was representative only of the local epidemiology. Third, there was no post-discharge follow-up to evaluate patient outcomes. Lastly, the use of NIV in emergency settings varies considerably and is primarily influenced by the expertise of individual healthcare providers.

6 | Conclusion

NIV has become the treatment of choice for managing COPD. Our study supports this approach, supporting the feasibility and potential benefit of NIV with acute global respiratory failure and moderate to severe impairment of consciousness. Our data indicate that NIV can significantly improve clinical outcomes even in those presenting with AECOPD and compromised neurological status. This highlights the importance of considering NIV as a viable option in cases of acute respiratory failure, particularly when traditional methods are ineffective. The successful application of NIV in such critically ill patients highlights its role in reducing the need for invasive procedures, improving patient prognosis, and potentially decreasing healthcare costs associated with prolonged hospital stays and ICU admissions. Further prospective, multicentric studies on larger series are eagerly awaited to confirm the usefulness of NIV in patients with AECOPD and compromised neurological status.

Author Contributions

Conceptualisation: M.G.; data analysis: M.D.S., M.G.; methodology: A.V., M.D.S., B.P. and R.D.G.; project administration: M.D.S, B.P., C.P. and R.D.G.; supervision: M.D.S., C.P., A.P., R.D.G. and M.G.; writing original draft: I.S.F., T.P., Y.D., A.P. and A.V.; writing/review and editing: I.S.F., T.P., Y.D., A.P., A.V., F.L., B.P., C.P., A.P., M.D.S., R.D.G. and M.G. All authors have read and agreed to the published version of the manuscript.

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Ethics Statement

The study was evaluated by the Ethics Committee of the Area Vasta Emilia Centro (CE-AVEC) and approved on NIV2023 (Protocol n. 447/2021/Disp/AOUFe). The entire study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Informed Consent Statement

As a retrospective study not directly involving patients, a signed consent to participate in the study was deemed unnecessary.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated are not publicly available but are obtainable from the corresponding author on reasonable request.

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