

Outcomes and predictors of success of noninvasive ventilation in acute exacerbation of chronic obstructive pulmonary disease

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Background Noninvasive ventilation is appropriately used as a first-line treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in many emergency departments. It has been evaluated in a large number of trials, often with clinically important benefits, but the use of noninvasive positive pressure ventilation remains highly variable across institutions and geographical regions. The aim of the study was first to emphasize the superiority of noninvasive ventilation (NIV) in acute hypercapnic respiratory failure in patients with an AECOPD in comparison with conventional therapy alone and second was to identify the predictors of NIV failure in such patients.

Patients and methods A total of 50 patients were randomly allocated into two equal groups: 25 patients subjected to medical and oxygen therapy (group I) and 25 to medical and NIV (group II). All patients were followed until death or discharge.

Results Group II had a success rate (for weaning and discharge) of 76%, whereas in group I, it was 20% (odds ratio=0.0789, 95% confidence interval=0.021–0.302 and $P<0.001$). Hospital stay was significantly longer in group I. Complications were significantly higher in group I. Mortality was significantly higher in group I. Improvement of arterial blood gases, respiratory rate, dyspnea scores and hypercarbic encephalopathy was significantly better in non-invasive positive pressure ventilation (NIPPV) group.

Introduction

Noninvasive ventilation (NIV) is most beneficial for patients presenting with hypercapnic acute respiratory failure (ARF) caused by an exacerbation of COPD [1]. It has been introduced since the 1980s, and since then, its use in the ICUs in patients with acute respiratory acidosis has been increasing and has doubled over a period of 7 years [2,3].

Nevertheless, the failure of NIV failure may be potentially associated with prolonged invasive mechanical ventilation [4] and increased mortality rate, which can reach up to 45% in nonselected patient populations [2].

The benefits of NIV [in patients with COPD presenting with acute respiratory acidosis (ARF)] has been highly evidence based and is now documented in the scientific literature, with also a high degree of recommendation in different clinical guidelines [5–13].

The benefits of NIV for patients with acute exacerbation of COPD have been proven in many studies, and

Conclusion The addition of NIPPV to standard therapy confers more benefits in patients with AECOPD, with significant reduction of in-hospital mortality, rate of endotracheal intubation, incidence of complications and length of hospital stay compared with standard therapy alone. On the contrary, failure can be predicted by the presence of more comorbidities, signs of severe exacerbation, high BMI, high baseline blood sugar, rapid respiratory rate at admission, abnormal baseline renal functions, high baseline C-reactive protein, high baseline acute physiology and chronic health evaluation II and BAP 65: B=BUN; A=Altered mental status; P=Pulse rate; 65-age years (BAP 65) scores, severe acidosis before NIV treatment and persistent severe acidosis after 1 h of treatment.

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whether these benefits apply to all patients groups and in all settings deserves more assessment.

Aim

The objectives of the present study was first to emphasize the superiority of NIV in acute hypercapnic respiratory failure in patients with an acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in comparison with conventional therapy alone. The second purpose was to identify early predictors of NIV failure in same patients and parameters of shifting to invasive ventilation.

Patients and methods

Patients

After approval of the local Ethical Committee, the present study was carried out on 50 adult patients

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presenting with acute exacerbation of COPD to Gamal Abdelnasser insurance hospital.

Patients were randomly subdivided into two equal groups:

- (1) Group I: 25 patients allocated to receive controlled oxygen therapy in addition to medical treatment.
- (2) Group II: 25 patients allocated to receive noninvasive positive pressure ventilation (NPPV) plus medical treatment.

Methods

A written consent was taken from all participants before the beginning of the study according to the hospital's protocol. All patients in the present study were admitted to ICU and subjected to arterial blood gases (ABG) assessment [by GEM premier 3000 analyzer; Instrumental Laboratory, Bedford (UK), Massachusetts (USA)], routine laboratory testing, ECG and chest radiography. All patients were subjected to standard medical treatment: nebulized salbutamol 2.5–5 mg, nebulized ipratropium 500 µg, systemic glucocorticosteroids (40 mg prednisolone) and antibiotics if indicated. The first group was offered controlled oxygen therapy with a target saturation of 88–92% using venturi masks. The provided FiO₂ ranged from 24 to 40%. However, in the second group, NIV was provided within the first 60 min of their arrival. The participants were included according to the inclusion criteria, and others who met the exclusion criteria were excluded. Table 1 shows the NIPPV settings. All patients were started on an inspiratory positive airway pressure (IPAP) of 10 and expiratory positive airway pressure (EPAP) of 5 cm H₂O using oronasal mask. The pressures were gradually adjusted by physicians as tolerated based on continuous pulseoximetry, follow-up ABG, alleviation of patients' dyspnea, decrease in respiratory rate and good patient – ventilator synchrony. Duration of NIV per day was variable from patient to patient according to initial condition and severity of respiratory acidosis and patient response and tolerance. The least duration for those who tolerated and succeeded was 18 h and longest duration was 20 h/day. Least duration for those who could not tolerate and failed was 1 h.

Table 1 BiPAP settings in group II (n=25)

	Minimum–maximum	Mean±SD	Median
PEEP	5–10	6.8±2.1	7
IPAP	10–20	14.2±3.9	15
Duration NIV (h/day)	1–20	15.3±7.4	19
FiO ₂	21–100	33.8±25	24

NIV, noninvasive ventilation. PEEP, positive end-expiratory pressure

Regarding the definitions of treatment success or failure, success was defined as the achievement of a clinical and functional condition stable enough to allow patient discharge to the ward in both groups, whereas failure was defined as a sudden or progressive worsening of arterial blood gas tensions, dyspnea, and/or sensory deterioration leading to shift to NIV, intubation or death in group I and intubation or death in group II.

Statistical analysis

All statistical analyses were performed using PASW software (version 17; SPSS Inc., Chicago, Illinois, USA). All results were considered statistically significant at *P* less than 0.05. Quantitative variables were presented as mean±SD. Means for parametric variables were compared by Student *t*-test or analysis of variance according to situation. Nonparametric quantitative variables were compared by Mann–Whitney test and Kruskal–Wallis test according to situation. Qualitative variables were presented as frequencies, and comparisons were made by χ^2 -test.

Inclusion criteria

Patients who fulfilled the definition of ARF were included in the present study. An exacerbation of dyspnea lasting less than 2 weeks, signs of respiratory distress, a respiratory rate above 24 breaths/min, an arterial pH less than 7.35 and greater than 7.25 and PaCO₂ greater than 45 mmHg were the other inclusion criteria.

Exclusion criteria

Severe co-morbidity, severe respiratory acidosis pH less than 7.25, life-threatening hypoxemia, agitation/confusion/severe cognitive impairment [Glasgow coma scale (GCS)] less than or equal to 8, trauma/facial burns/recent upper airway or facial surgery, fixed upper airway obstruction, copious respiratory secretions, undrained pneumothorax, vomiting, upper gastrointestinal surgery, haemodynamically unstable requiring pressors/inotropes and bowel obstruction were the exclusion criteria.

Measurements

- (1) History parameters: it included age, sex, BMI (none of the overweighted patients who failed had obesity hypoventilation syndrome by history or previous pulmonology studies), pack-year index, duration of illness, number of non-ICU and ICU hospitalizations with COPD exacerbation, number of previous endotracheal intubation

(ETI), number of emergency department visits in last month and time since last hospitalization with AECOPD.

- (2) Clinical parameters: it included systemic blood pressure, mean arterial blood pressure heart rate, respiratory rate, temperature, visual analog score (VAS), clinical signs of exacerbation severity, acute physiology and chronic health evaluation II (APACHE II) prediction score, BAP 65 score, GCS, ABG, baseline renal function tests, baseline random blood sugar, C-reactive protein (CRP), and complete blood count values.
- (3) Follow-up parameters: respiratory rate, VAS, GCS, and ABG levels were followed at 1, 4, 12, 24, and 48 h after start of treatment. CRP and total leukocyte count were followed after 24 and 48 h.
- (4) Causes of ARF (or precipitating factors of exacerbation): (a) infections, including three subtypes (upper respiratory tract infections, acute bronchitis and pneumonia), (b) noncompliance on medications, (c) pulmonary embolism, (d) cardiac arrhythmias, (e) high-carbohydrate diet, (f) pneumothorax, (g) sedating drugs, and (h) recent exposure to smoke or dust.
- (5) Types and number of chronic comorbidities: (a) hypertension, (b) diabetes, (c) chronic kidney disease (CKD), (d) cardiac arrhythmias [atrial fibrillation (AF)], (e) ischemic heart disease (IHD), (f) congestive heart failure, (g) cerebrovascular disease (stroke), (h) hyperthyroidism, (i) hyperthyroidism, (j) atopy or allergic disorder, (k) rheumatological disease, and (l) other chest problems. Number of chronic comorbidities were categorized as follows: none, 1–2 and greater than or equal to 3 comorbidities.
- (6) Outcome measures: (a) treatment success or failure, (b) intolerance to NPPV, (c) endotracheal intubation, (d) dyspnea scores, (e) length of stay in hospital or ICU, (f) number and types of treatment complications, and (g) mortality.

Results

A total of 50 patients were randomly allocated into two equal groups: group I had 25 patients who were subjected to standard treatment (medical and oxygen therapy) and group II had 25 patients who received standard medical treatment plus NPPV. All patients were followed until death or discharge.

Table 2 demonstrates baseline clinical data of all cases included in the study. There were no statistically significant differences between the two groups regarding any of the following baseline clinical parameters.

With NIV, success rate of 76% was significantly higher than standard treatment group [odds ratio (OR)=0.0789, 95% confidence interval (95% CI)=0.021–0.302 and $P<0.001$]. Hospital stay was significantly shorter ($P<0.001$). Complications were significantly lower ($P<0.001$); (OR=5.41, 95% CI=1.017–28.792 and $P=0.047$). Mortality was significantly lower ($P=0.034$); (OR=5.411, 95% CI=1.017–28.79 and $P=0.047$). Tables 13–15 illustrate summary of the predictors of outcome and mortality in both studies groups.

Tables 3–5 show the associated precipitating factors of exacerbations and respiratory failure in all patients enrolled in the present study.

Tables 6 and 7 show the number of diseases other than AECOPD (associated comorbidities) in patients of both groups and their relation to outcomes.

Table 8 shows that baseline pH was significantly less acidotic in successful cases of group I, with P value 0.012. After 1 h of treatment, there was more significant improvement in acidosis in NIV group than medical group. Along the whole following intervals, there were more significant improvements in pH in group II than group I. PaCO₂ levels were significantly lower in group

Table 2 Distribution of baseline clinical data in studied groups (at admission)

Baseline clinical data	Group I (n=25)	Group II (n=25)	P
MABP	100.7±13.9	100.7±16.7	0.999
Heart rate	109.7±20.3	110.6±20.6	0.874
Temperature	37.8±1.2	37.5±0.5	0.202
VAS	100 (85–100)	100 (85–100)	0.486
Respiratory rate	38.2±7.4	37.6±6.6	0.764
GCS	14.1±1.0	13.7±1.7	0.167
APACHE II	13 (3–31)	12 (3–25)	0.698
BAP 65 score	1.9±1.2	1.7±1.3	0.501
TLC	12.8±6.9	10.6±3.1	0.151
CRP	30 (10–470)	37 (10–260)	0.892
RBS	140.2±24.1	137.8±21.5	0.859
Urea	81.1±47.0	59.1±48.3	0.097
Creatinine	1.2 (0.6–4.2)	1.1 (0.49–2.7)	0.228
pH	7.3±0.0	7.3±0.0	0.365
PaCO ₂	66.3±8.5	66.5±11.5	0.939
PaO ₂	79.4±14.2	76.7±13.1	0.485
HCO ₃	29.0±3.3	30.6±4.4	0.173
SaO ₂	93.2±2.9	93.4±3.9	0.845

Normally distributed quantitative data were expressed in mean±SD and were compared using Student's *t*-test, abnormally distributed data were expressed in median (minimum–maximum) and were compared using Mann–Whitney test. A, altered mental status; APACHE II, acute physiology and chronic health evaluation II; BAP 65, B=BUN greater than 24 mg/dl; CRP, C-reactive protein; GCS, Glasgow coma scale; MABP, mean arterial blood pressure; P, Pulse rate greater than 110/min; RBS, random blood sugar; TLC, total leukocyte count; VAS, visual analog score.

Table 3 Underlying precipitating factors in each group

Precipitating factors of exacerbations	Group I (n=25) [n (%)]	Group II (n=25) [n (%)]	χ^2	P
Infections	14 (46)	16 (64.0)	0.333	0.564
URTIs	4 (16.0)	7 (28.0)	1.049	0.306
Acute bronchitis	4 (16.0)	5 (20.0)	0.136	FE _P =1.000
Pneumonia	6 (24.0)	4 (16.0)	0.500	0.480
Noncompliance on medications	4 (16.0)	3 (12.0)	0.166	FE _P =1.000
Pneumothorax	2 (8.0)	1 (4.0)	0.355	FE _P =1.000
Arrhythmias	2 (8.0)	2 (8.0)	0.000	FE _P =1.000
High-carbohydrate diet	2 (8.0)	1 (4.0)	0.355	FE _P =1.000
Pulmonary embolism	0 (0.0)	1 (4.0)	1.020	FE _P =1.000
Recent exposure to smoke or dust	0 (0.0)	1 (4.0)	1.020	FE _P =1.000
Drugs	1 (4.0)	0 (0.0)	1.020	FE _P =1.000

χ^2 , P: χ^2 and P values for χ^2 -test for comparing between the two groups; FE, Fisher's exact; group I, standard medical treatment only; group II, noninvasive ventilation+standard medical treatment; URTIs, upper respiratory tract infections.

Table 5 Relation between precipitating factors of exacerbations and mortality in each group

Precipitating factors of exacerbations	Mortality [n (%)]		χ^2	FE _P
	Survived (n=17)	Nonsurvived (n=8)		
Group I				
Infections	9 (52.9)	5 (62.5)	0.202	1.000
URTIs	4 (23.5)	0 (0.0)	2.241	0.269
Acute bronchitis	4 (23.5)	0 (0.0)	2.241	0.269
Pneumonia	1 (5.9)	5 (62.5)	9.560*	0.006*
Noncompliance on medications	3 (17.6)	1 (12.5)	0.107	1.000
Pneumothorax	2 (11.8)	0 (0.0)	1.023	1.000
High-carbohydrate diet	2 (11.8)	0 (0.0)	1.023	1.000
Sedating drugs	1 (5.9)	0 (0.0)	0.490	1.000
Arrhythmias	0 (0.0)	2 (25.0)	4.620	0.093
	n=23	n=2		
Group II				
Infections	15 (65.2)	1 (50.0)	0.185	1.000
URTIs	7 (30.4)	0 (0.0)	0.845	1.000
Acute bronchitis	5 (21.7)	0 (0.0)	0.543	1.000
Pneumonia	3 (13.0)	1 (50.0)	1.870	0.300
Noncompliance on medications	4 (17.4)	1 (50.0)	1.223	0.367
Pneumothorax	1 (4.3)	0 (0.0)	0.091	1.000
Pulmonary embolism	0 (0.0)	1 (50.0)	11.979	0.080
High-carbohydrate diet	1 (4.3)	0 (0.0)	0.091	1.000
Recent exposure to smoke or dust	4 (17.4)	1 (50.0)	1.223	0.367
Arrhythmias	2 (8.7)	0 (0.0)	0.189	1.000

FE, Fisher's exact; group I, standard medical treatment only; group II, noninvasive ventilation+standard medical treatment; URTIs, upper respiratory tract infections. * $P \leq 0.05$, statistically significant.

Table 4 Relation between the precipitating factors and the outcome in both groups

Precipitating factors of exacerbations	Failed (n=20) [n (%)]	Success (n=5) [n (%)]	χ^2	FE _P
Group I				
Infections	12 (60.0)	2 (40.0)	0.649	0.623
Upper respiratory tract infection	3 (15.0)	1 (20.0)	0.074	1.000
Acute bronchitis	3 (15.0)	1 (20.0)	0.074	1.000
Pneumonia	6 (30.0)	0 (0.0)	1.974	0.289
Noncompliance on medications	1 (5.0)	3 (60.0)	9.003*	0.016*
	n=6	n=19		
Group II				
Infections	3 (50.0)	13 (68.4)	0.672	0.630
Upper respiratory tract infection	0 (0.0)	7 (36.8)	3.070	0.137
Acute bronchitis	1 (16.7)	4 (21.1)	0.055	1.000
Pneumonia	2 (33.3)	2 (10.5)	1.765	0.234
Noncompliance on medications	1 (16.7)	2 (10.5)	0.163	1.000
Arrhythmias	1 (16.7)	1 (5.3)	0.806	0.430

FE, Fisher's exact; group I, standard medical treatment only; group II, noninvasive ventilation+standard medical treatment.

Table 6 Distribution of number of comorbidities in studied groups

No. of comorbidities	Group I (n=25) [n (%)]	Group II (n=25) [n (%)]	χ^2	P
None	3 (12.0)	10 (40.0)	5.463	0.065
1-2	14 (56.0)	11 (44.0)		
≥ 3	8 (32.0)	4 (16.0)		

FE, Fisher's exact; group I, standard medical treatment only; group II, noninvasive ventilation+standard medical treatment

II at all intervals of follow-up. PaO₂ and SaO₂ values were unreliable, as some patients were on oxygen therapy before enrollment in the study.

Figure 1 shows a flow diagram illustrating the detailed outcome of all cases throughout the study.

Tables 9–12 show that the improvements of respiratory rate and dyspnea score (VAS) were more significant in NIPPV group vs. standard therapy group.

Discussion

The present study demonstrated that the use of NIPPV in addition to medical therapy in patients with COPD presenting with hypercapnic ARF significantly decreases the incidence of orotracheal intubation, the number of complications, hospital mortality, and hospital stay.

Regarding the ABG parameters in the present study, baseline pH seems to be the most important single

predictor of outcome. In medical group I, among patients with pH range from 7.25 to 7.30, 18 patients showed 100% failure, 77.8% total intubation, and 38.9% mortality; moreover; the

survived cases showed longer hospital stay and complications. On the contrary, among patients with pH range from 7.30 to 7.35, 28.6% showed failure, 14.2% total intubation and 14.2% mortality.

Table 7 Relation between the type of associated comorbidities and the outcome of cases in studied groups

Type of co-morbidity	Failure (n=20) [n (%)]	Success (n=5) [n (%)]	χ^2	^{FE} P
Group I				
Hypertension	13 (65.0)	0 (0.0)	6.771*	0.015*
Diabetes	9 (45.0)	1 (20.0)	1.042	0.615
CKD	7 (35.0)	0 (0.0)	2.431	0.274
IHD	7 (35.0)	0 (0.0)	2.431	0.274
CHF	2 (10.0)	0 (0.0)	0.543	1.000
AF	4 (20.0)	0 (0.0)	1.190	0.549
Stoke	3 (15.0)	0 (0.0)	0.852	1.000
Rheumatological	1 (5.0)	0 (0.0)	0.260	1.000
Atopy, allergic	3 (15.0)	1 (20.0)	0.074	1.000
Other chest problem	2 (10.0)	0 (0.0)	0.543	1.000
	n=6	n=19		
Group II				
Hypertension	5 (83.3)	5 (26.3)	6.177*	0.023*
Diabetes	4 (66.7)	1 (5.3)	10.746*	0.005*
CKD	4 (66.7)	0 (0.0)	15.079*	0.001*
IHD	4 (66.7)	1 (5.3)	10.746*	0.005*
AF	2 (33.3)	0 (0.0)	6.884	0.050
Hyperthyroidism	0 (0.0)	1 (5.3)	0.329	1.000
Stoke	1 (16.7)	1 (5.3)	0.806	0.430
Rheumatological	0 (0.0)	3 (15.8)	1.077	0.554
Atopy, allergic	0 (0.0)	1 (5.3)	0.329	1.000

AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; FE, Fisher's exact; IHD, ischemic heart disease; group I, standard medical treatment only; group II, noninvasive ventilation+standard medical treatment. *P<0.05, statistically significant.

In NIPPV group (II), patients with pH ranged from 7.25 to 7.30, (their no. was 12 out of 25 patients included in the group), 7 of these succeeded and 5 of these (41.7%) failed and intubated. As regards the survival, 2 of these didn't survive (16.7%) and 10 of them survived.

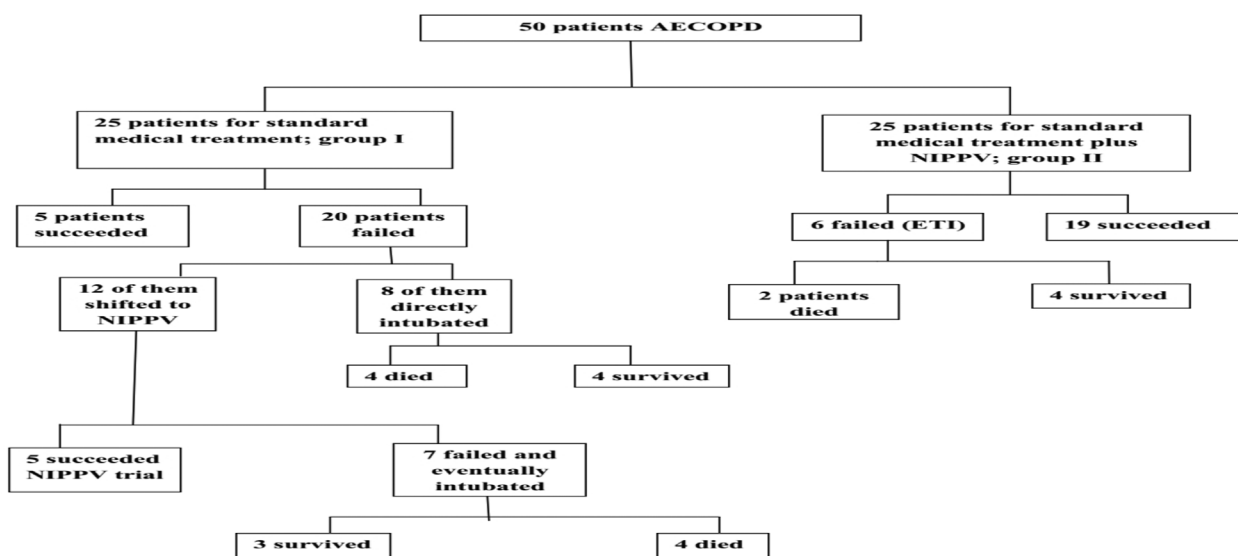
While patients with pH ranged from 7.30 to 7.35 in the same group, (13 patients out of 25), all of these succeeded 100%. As regards the survival, all 13 cases have been survived 100%, with one of them only complicated by chest infection.

Table 8 Comparison between baseline and follow-up pH and PaCO₂ of successful cases in both groups at different studied periods (n=24)

	Group I (n=25)	Group II (n=25)	P
pH			
On admission	7.33±0.01	7.31±0.03	0.012*
After 1 h	7.34±0.01	7.36±0.03	0.014*
After 4 h	7.34±0.02	7.39±0.03	0.002*
After 12 h	7.35±0.02	7.39±0.02	<0.001*
After 24 h	7.36±0.01	7.40±0.03	0.006*
After 48 h	7.37±0.02	7.41±0.03	0.003*
PaCO₂			
On admission	64.6±1.1	61.4±7.4	0.085
After 1 h	61±3.6	50.9±6.3	0.002*
After 4 h	58.4±3.8	45.9±4.5	<0.001*
After 12 h	55.8±4.5	45.3±3.4	<0.001*
After 24 h	51.8±4.2	42.8±4.8	0.001*
After 48 h	51.4±7.1	41.1±3.1	0.030*

*Statistically significant at P<0.05.

Figure 1



Flow diagram illustrating the detailed outcome of all cases throughout the study

Table 9 Improvement of respiratory rate in successful cases of group I (n=5) at different studied periods

	Admission	After				
		1 h	4 h	12 h	24 h	48 h
Respiratory rate	32.6±3.9	32.8±6.4	31.6±5.2	30±3.1	27.8±4.2	29.4±5.9
P		0.880	0.230	0.049*	0.005*	0.083

p₁: P-value for Post Hoc Test (LSD) for ANOVA with repeated measures for comparison between pre admission with each other period.

*Statistically significant at P≤0.05.

Table 10 Improvement of respiratory rate in successful cases of group II (n=19) at different studied periods

	Admission	After				
		1 h	4 h	12 h	24 h	48 h
Respiratory rate	35.3±5.6	31.7±5.2	29.2±5.2	27.5±4.5	26.3±5	25.2±4.2
P		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

p₁: P-value for Post Hoc Test (LSD) for ANOVA with repeated measures for comparison between pre admission with each other period.

*Statistically significant at P≤0.05.

Table 11 Improvement of visual analog score in successful cases of group I (n=19) at different studied periods

	Admission	After				
		1 h	4 h	12 h	24 h	48 h
VAS	90 (85–95)	90 (80–90)	80 (80–85)	77 (70–85)	70 (70–75)	85 (60–90)
P		0.083	0.038*	0.042*	0.038*	0.068

p₁: P-value for Wilcoxon signed ranks test for comparing between pre admission with each other period. VAS, visual analog score.

*Statistically significant at P≤0.05.

Table 12 Improvement of visual analog score in successful cases of group II (n=19) at different studied periods

	Admission	After				
		1 h	4 h	12 h	24 h	48 h
VAS	100 (85–100)	80 (60–90)	60 (40–85)	50 (20–75)	40 (15–70)	20 (5–55)
P		<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

p₁: P-value for Wilcoxon signed ranks test for comparing between pre admission with each other period. *Statistically significant at P≤0.05.

The conclusion is that the successful cases among NIV group showed statistically significant higher mean pH (7.31±0.03) than that of failed cases (7.25±0.01); with P value of <0.001. The lower the pH on admission, the higher the failures and mortality.

There was a significant increase in intubation rates with lower pH values in both groups (P<0.001). These findings were supported by previous randomised studies [13–15]. A low pH at presentation has shown an association with increased mortality [15,16] and the need for intubation [17] in patients presenting with COPD exacerbations. These results emphasize the importance of baseline severity of acidosis and its important correlation with the prognosis and survival from respiratory failure in patients with COPD. Therefore, early correction of acidosis is a crucial objective in managing those patients [15].

Plant *et al.* [18] also demonstrated that there is a 22-fold higher risk for meeting criteria for intubation in patients with a pH of 7.35 and a PaCO₂ of 6 kPa than those with a pH of 7.25 and a PaCO₂ of 12 kPa.

Additionally, the baseline pH had a reliable predictive effect among several variables [19]. In addition to baseline levels, pH values after 1 h of NIV has proved to be a powerful predictor of outcome of NIV as well [20]. In the present study, after 1 h of NIPPV; the successful cases of group II showed statistically significant higher mean pH (7.36±0.03) and lower PaCO₂ level (50.87±6.29) than the failed cases. This means that the severity of acidemia and the degree of hypercapnea after 1 h of treatment may be predictive factors for the success of NIPPV in COPD cases, and this was in agreement with other studies such Agarwal *et al.* [21] and Antón *et al.* [12] who also suggested that if NIPPV does not improve pH and RR within the first 2 h, intubation should be considered.

Furthermore, it was notable that the percentage of pH improvement in successful cases of group II after 1 h of treatment was by 0.76±0.23, whereas in group I was only by 0.11±0.06. This came in agreement with a review by Ram *et al.* [22]. The pH significantly improved with NIPPV in comparison with usual medical care, which was significantly boosted by NIPPV. SooHoo *et al.* [23] also

Table 13 Predictors of primary outcome for patients of group I

	Successful	Failed	P
pH on admission	7.33±0.01	7.27±0.02	<0.001*
pH after 1 h	7.34±0.01	7.25±0.04	<0.001*
PaCO ₂ after 1 h	61±3.5	74.9±12.1	<0.001*
Baseline GCS	15±0	13.9±1.0	<0.001*
GCS after 1 h of treatment	15±0	12.5±1.6	<0.001*
Baseline heart rate	88±6.7	115.1±18.8	<0.001*
Baseline VAS	90 (85–95)	100 (90–100)	<0.001*
VAS after 1 h of treatment	90 (80–90)	100 (90–100)	<0.001*
BAP 65	0.2±0.5	2.4±0.9	<0.001*
APACHE II score	4.8±1.8	15.4±6	0.001*
Age	51.4±3.3	69.2±8.4	<0.001*
Number of comorbidities			
None	3 (60)	0 (0)	0.003*
1–2	2 (40)	12 (60)	
≥3	0 (0)	8 (40)	
Number of ICU hospitalizations dt AECOPD	0±0	1.1±0.8	0.007*
Abdominal paradox	0 (0)	13 (65)	0.015*
Pack-year index	18±27.6	48.1±18.7	0.025*
RBS	140.2±24.9	281±152.9	0.032*
Sex			
Male	2 (40)	18 (90)	0.038*
Female	3 (60)	2 (10)	

Qualitative data were described using number and percentage and compared using χ^2 -test or Fisher's exact test. Normally quantitative data were expressed in mean±SD and compared using Student's *t*-test, and abnormally distributed data were expressed in median (minimum–maximum) and compared using Mann–Whitney test. AECOPD, acute exacerbations of chronic obstructive pulmonary disease; APACHE II, acute physiology and chronic health evaluation II; GCS, Glasgow coma scale; RBS, random blood sugar; VAS, visual analog score. * $P\leq 0.05$, statistically significant.

demonstrated that lack of improvement in respiratory acidosis and respiratory rates during the first few hours of NIV carried a higher likelihood of NIV failure. Confalonieri *et al.* [24] who studied more than 1000 patients with COPD concluded that a pH less than 7.25 after 1 h of NIV use was associated with an increased risk of NIV failure, with even more failure risk when the pH levels were less than 7.25 on admission [24]. Hence, application of NIV in patients with a pH less than 7.25 outside well-equipped settings was not recommended [25].

Thus, pH seems to be a very important variable in predicting failure of medical or NPPV, however; there is much debate what is the correct cutoff value to choose. In the present study, cutoff point of baseline

Table 14 Predictors of primary outcome for patients of group II

	Successful	Failed	P
pH on admission	7.31±0.03	7.25±0.01	<0.001*
pH after 1 h	7.36±0.03	7.27±0.03	<0.001*
PaCO ₂ on admission	61.4±7.4	82.7±4.8	<0.001*
PaCO ₂ after 1 h	50.9±6.3	77±13.6	0.004*
Baseline GCS	14.4±0.7	10.8±0.8	<0.001*
GCS after 1 h of treatment	15±0	10.7±1.5	0.001*
Baseline VAS	100 (85–100)	100 (100–100)	<0.041*
Baseline respiratory rate	35.3±5.6	45±3.4	<0.001*
VAS after 1 h of treatment	80 (60–90)	100 (90–100)	<0.003**
BAP 65 score	1.2±0.9	3.3±0.8	<0.001*
Pedal edema	0 (0)	6 (100)	<0.001*
APACHE II score	9.5±4.2	21.5±2.4	0.024*
BMI	26.8±2.7	32.0±2.7	<0.001*
Number of comorbidities			
None	10 (52.6)	0 (0)	<0.001*
1–2	9 (47.4)	2 (33.3)	
≥3	0 (0)	4 (66.7)	
Type of comorbidities			
CKD	0 (0)	4 (66.7)	0.001*
Diabetes	1 (5.3)	4 (66.7)	0.005*
IHD	1 (5.3)	4 (66.7)	0.005*
Hypertension	5 (26.3)	5 (83.3)	0.023*
Number of ICU hospitalizations dt AECOPD	0.3±0.5	1.3±0.8	0.004*
Abdominal paradox	5 (26.3)	5 (83.8)	0.023*
Pack-year index	30.8±14.2	53.3±19.9	0.026*
RBS	137.4±21.5	456.8±82.5	<0.001*
Central cyanosis	0 (0)	3 (50)	0.009*
TLC	9.8±2.1	13±2.6	0.014*
CRP	55.6±69.9	126.2±67.6	0.014*

Qualitative data were described using number and percentage and was compared using χ^2 -test or Fisher's exact test. Normally quantitative data were expressed in mean±SD and was compared using Student's *t*-test, and abnormally distributed data were expressed in median (minimum–maximum) and were compared using Mann–Whitney test. AECOPD, acute exacerbations of chronic obstructive pulmonary disease; APACHE II, acute physiology and chronic health evaluation II; CKD, chronic kidney disease; CRP, C-reactive protein; GCS, Glasgow coma scale; IHD, ischemic heart disease; RBS, random blood sugar; TLC, total leukocyte count; VAS, visual analog score. * $P\leq 0.05$, statistically significant.

pH as a predictor of treatment failure in group I was found by ROC curve to be less than or equal to 7.30 (area under the curve: 0.980; 95% CI: 0.828–0.999, $P<0.001$). Cutoff point of baseline pH in group II was obtained as less than or equal to 7.26 (area under the curve: 0.9473; 95% CI: 0.778–0.997, $P<0.001$).

This came in line with the BTS guidelines 2008 [26] which stated that NIV should be considered in all patients with an AECOPD in whom a respiratory acidosis ($\text{pH}\geq 7.26<7.35$) resists maximum standard medical treatment on controlled oxygen therapy for no

Table 15 Predictors of mortality on univariate analysis of patients in both studied groups

	Survivors	Nonsurvivors	P
Group I			
GCS	14.7±0.6	13±0.8	<0.001*
APACHE II score	10.9±6.1	18.4±6.1	<0.001*
BAP 65	1.5±1.1	2.8±1	<0.001*
Heart rate	101.6±15.7	126.9±18.7	0.002*
Abdominal paradox	5 (29.4)	8 (100)	0.002*
RBS	181.9±75.4	403.5±155	0.004*
Pneumonia	1 (5.9)	5 (62.5)	0.006*
TLC	10.4±5.8	18±7.4	0.008*
Pedal edema	3 (17.6)	6 (75)	0.010*
Stroke	0 (0)	3 (37.5)	0.024*
VAS	100 (85–100)	100 (100–100)	0.038*
Group II			
BAP 65	1.5±1.1	4±0	<0.001*
GCS	13.9±1.4	10±0	<0.001*
Urea	48.2±31.4	184.5±6.4	<0.001*
pH	7.30±0.03	7.26±0.01	0.002*
RBS	189.4±119	498±144.3	0.002*
AF	0 (0)	2 (100)	0.003*
Central cyanosis	1 (4.3)	2 (100)	0.010*
PaCO ₂ (mmHg)	64.9±10.3	85.5±6.4	0.011*
CKD	2 (8.7)	2 (100)	0.020*
Comorbidities			
None	10 (43.5)	0 (0)	0.021*
1–2	11 (47.8)	0 (0)	
≥3	2 (8.7)	2 (100)	
APACHE II score	11.5±6	22±1.4	0.024*
Creatinine	1.1 (0.5–2.7)	2.4 (2.3–2.5)	0.045*
Pedal edema	4 (17.4)	2 (100)	0.050*

Qualitative data were described using number and percentage and was compared using χ^2 -test or Fisher's exact test. Normally quantitative data were expressed in mean±SD and were compared using Student's *t*-test, and abnormally distributed data were expressed in median (minimum–maximum) and were compared using Mann–Whitney test. AECOPD, acute exacerbations of chronic obstructive pulmonary disease; APACHE II, acute physiology and chronic health evaluation II; CKD, chronic kidney disease; CRP, C-reactive protein; GCS, Glasgow coma scale; IHD, ischemic heart disease; RBS, random blood sugar; TLC, total leukocyte count; VAS, visual analog score. *Statistically significant at $P \leq 0.05$.

more than 1 h. Although some RCTs show evidence for the efficacy of NIV in patients with COPD with a pH less than 7.26 [27]. However, NIV treatment failure and intubation are more common in these patients. Moreover they need more intensive monitoring and a lower threshold for intubation [25].

Regarding the comorbidities, it was notable that there was a direct relationship between the increase in comorbidities and the probability of treatment failure in both groups, with *P* value of 0.003 in group I and of less than 0.001 in group II. A large cross-sectional study performed in the USA has shown that, among other variables, more comorbid conditions were independent risk factors for in-hospital mortality [28].

In NIPPV group, 83.3% of failed cases had hypertension ($P=0.023$), 66.7% had diabetes ($P=0.005$), 66.7% had CKD ($P=0.001$), and 66.7% had evidence of IHD ($P=0.005$).

Systemic inflammation is part of COPD pathogenesis, which is also related to hypertension and is correlated with higher Medical Research Council dyspnea scores, declined ability for physical activity [29] and airflow obstruction [30].

Moreover in diabetes, there is peripheral airways affection and impaired compliance [31]. The outcomes of COPD are deteriorated by diabetes as it affects a number of parameters; such as shortening time to first hospitalization, increasing hospitalization time and risk of death during exacerbations, increasing Medical Research Council dyspnea scores, and reducing six-minute walking distance [29]. Diabetes negatively affects 5-year mortality in patients with COPD [32,36]. Uncontrolled hyperglycemia in most diabetic patients in the present study played a major role in the adverse outcomes. Random blood sugar was significantly higher in failed cases in both studied groups. Specific details about patients with hyperglycemia treated with NIV are scarce. However, a minute study suggested that 'late failure', defined by falling gas exchange that occurred repeatedly in patients, showed an increased blood sugar initially [37]. A larger but retrospective review of a mingled population of random patients with COPD noted prolonged hospital stays and high levels of death in patients presenting with random blood glucose of greater than 7 mmol/l. Pretherapy hyperglycemia is a freelance predictor of a worse outcome [29,38–42]. More recently, in a relatively small study, Chakrabarti *et al.* [43] discovered that hyperglycemia, even when detected at only one time point, linked to the eventual result irrespective of the diagnosis of diabetes, utilization of insulin or use of corticosteroid per mouth before. In general, the level of hyperglycemia noted was moderate, but it may still represent the considerable physiological stress connected to diminishing gas exchange and declining lung mechanics, often associated with pulmonary infection. Some patients had radiological clue of pneumonia, but this did not illustrate the existence of hyperglycemia in most patients nor did it foretell NIV failure [43,44]. Strict glycaemic dominance has its supporters [45,46], but precise prospective studies will be indispensable before this policy can be counseled in the management of patients with primary chest illnesses managed with NIV [43].

Regarding CKD, declined normal renal functional reserve was caused by the arterial rigidity and endothelial dysfunction was caused by COPD [47]. Detrioration of renal functional reserve in patients with COPD is associated with more severe airway obstruction and inflammation [47]. Patients with COPD have around double the incidence of acute renal failure, and triple the prevalence of diagnosed chronic renal failure than age-matched and sex-matched controls [47,48].

COPD and IHD share smoking as a common major risk factor. Chronic sustained inflammation and coagulopathy are the traits of both diseases. Elevated CRP level is the key mediator of this sustained inflammation in COPD, and it maintains bronchial constriction and increases the risk for coronary disease [36,49].

In group II, it was notable that all nonsurvived cases had CKD ($P=0.020$) and AF ($P=0.003$), which were the only comorbidities associated with significant relation to mortality in NIV group. AF and COPD are often coexist [50]. AF is itself a known risk factor for stroke and systemic embolism, which may be the causes of death in such cases. The Dyspnea, Eosinopenia, Consolidation, Acidemia and AF (DECAF) score was introduced by Steer *et al.* [51] as a predictor of mortality in hospitalized patients with COPD exacerbations [51,52]. The score comprises five predictors: dyspnea, eosinopenia, consolidation, acidemia, and AF. AF (on admission ECG) was scored as 1 point in DECAF score. Using the model, the higher the score the higher the mortality rate. High score of 3–6 points indicated in-hospital mortality of 34.6% [51].

Regarding the respiratory rate, it was significantly more on admission in the patients who failed NIPPV ($P<0.001$). This means that the baseline respiratory rate could possibly be used as a predictor of success or failure of NIV in cases of AECOPD [53,54]. An initial high respiratory rate and its decrease after 1 h of NIV have been shown to be correlated with successful NIV outcomes in patients with COPD. From the present study results, the cutoff point of baseline respiratory rate to predict the failure in group I was obtained as greater than 33 breaths/min, whereas in group II, it was greater than 41 breaths/min. Singh *et al.* [55] reported that a respiratory rate of 30–34 and ≥ 35 breaths/min at admission were demonstrated to lead to NIV failure, with an OR of 1.83 and 2.66, respectively, whereas the ratios increased to 2.67 and 4.95, respectively, for the same breathing frequency after 2 h of NIV.

Using the respiratory rate as a follow-up parameter for comparing the efficacy of each type of treatment, there was a significant decrease in respiratory rate at all studied periods ($P<0.001$) in group II, whereas in group I, a significant improvement appeared only after 12 and 24 h ($P=0.049$ and 0.005 , respectively).

As one of the effects of the NIV is decreasing the load on the respiratory muscles, the RR can fall, the associated pulmonary hyperinflation decreases along with the work of breathing and dyspnea improves [56]. Brochard *et al.* [57] illustrated reductions in respiratory rate and transdiaphragmatic activity with elevation in tidal volume and minute ventilation. Thus NPPV rapidly improves gas exchange and allows respiratory muscle rest, decreasing respiratory muscle activity in respiratory failure; hence, NPPV gives more time for respiratory muscle recovery and for other conventional treatments (bronchodilators, oxygen, corticosteroids, antibiotics, etc.) to act [57]. Regarding the breathlessness scores, VAS was used in the present study as a measurement of dyspnea in all patients. It was significantly higher in failed cases of both groups. After 1 h of starting treatment, failed cases had higher values as well. This suggests that VAS could be a predictor of success or failure before starting treatment and even after the first hour of therapy. On the contrary, by comparison between successful cases in both groups, statistically significant improvement of VAS at 4, 12, 24, and 48 h was noticed in favor of NIPPV group. This came in agreement with three studies that measured breathlessness scores using three variable methods (Borg score; [58] VAS; [59] and a verbal-rating scale [13]).

Regarding GCS, it was significantly lower in failed cases of group I either on admission or after 1 h of follow-up. In NIPPV group, GCS was significantly lower in failed cases at admission, 1 h and 4 h after follow-up. GCS was also significantly lower in nonsurvived cases in both groups ($P<0.001$). This came in agreement with most studies and guidelines which excluded patients with disturbed consciousness owing to theoretical concerns about the propability of aspiration and expected nontolerance to NIV [60–62].

Overall, NIV in the present study was associated with reducing the incidence of orotracheal intubation, which asserts the previous studies' results [5,10,13,59,60,63–65].

Complications were also significantly decreased in NIV group (OR=5.41, 95% CI: 1.017–28.792 and $P=0.047$), confirming previous reports [27,57,58].

Duration spent in ICU and hospital stay were significantly larger in medical group I than in NIPPV, with P less than 0.001, which came in line with previous studies [22,66]. NIV has been shown to be cost-effective in ICU setting, resulting in a better clinical outcome and decreased costs [67,68,69].

In-hospital mortality was considerably less in NIV group (OR=5.411, 95% CI: 1.017–28.79 and $P=0.047$), confirming previous reports [22,66].

NIV bilevel positive airway pressure (BiPAP), especially in the early course of the disease, appears to be an influential add-on therapy with the standard treatment for AECOPD. It appears to be a safe, readily applied modality of ventilatory assistance that reduces the need for intubation, the number of complications and in-hospital mortality. It also accelerates recovery, and shortens hospital stay. It ought to be considered for all the patients with AECOPD with respiratory acidosis unless there is a contraindication for its use, such as a severe respiratory acidosis pH less than 7.25, life-threatening hypoxemia, severe cognitive impairment (GCS) less than or equal to 8, failure to secure the airway, profuse respiratory secretions or haemodynamic instability. Risk factors related to its failure may be patient related or nonpatient related, and the emergency medicine clinicians ought to remain vigilant while using NIV. Continuous monitoring and re-evaluation remains the key to the successful use of this therapy. Further studies on large number of cases and meta-analysis studies are recommended to develop evidence-based recommendations for the predictors of outcome of NIPPV in patients with AECOPD.

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Conflicts of interest

There are no conflicts of interest.

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