

Predictors of Outcome in COPD Patients with Hypercapnic Respiratory Failure Requiring NIV

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Abstract

Background and Objectives:

Delay in identifying patients in whom NIV will be unsuccessful may postpone endotracheal intubation, increasing morbidity and mortality.

Aim of this study was to determine factors associated with NIV failure in patients with COPD exacerbations.

Methods:

We retrospectively evaluated COPD patients with acute respiratory failure due to an acute exacerbation, undergoing NIV for at least 12 hours.

Univariable analysis was performed on: age, gender, APACHE II, GCS, gas exchange at admission, during NIV and at discharge/death, length of stay.

A ROC curve for the variable pH START (arterial pH value at admission) was performed and sensitivity, specificity, likelihood ratios and confidence intervals, were calculated.

Results:

Among 201 enrolled individuals, NIV failed in 50 subjects, leading to invasive ventilation and/or death. NIV succeeded in patients with: lower APACHE II (20.02±4.81 in succeeding group vs 24.84±6.35 in failing group, $p<0.001$) and PaCO₂ at admission (93.10±15.08 vs 98.45±16.09, respectively, $p=0.029$) and after 2–4 hours of NIV (77.62±13.62 vs 82.12±15.24, respectively, $p=0.044$), and higher pH at admission (7.26±0.06 vs 7.23±0.08, respectively, $p=0.033$), and GCS (12.94±2.44 vs 11.24±3.32, respectively, $p=0.001$).

No variable was found to be able to predict NIV failure in patients with pH START >7.20 and ≤7.25, despite the high percentage of successes observed in this subset of individuals (81%).

Conclusion: Further multicentric studies are needed to better define NIV indications, with special reference to pH thresholds.

Keywords: Non invasive mechanical ventilation; COPD; Respiratory failure; Predictors

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Introduction

COPD is a progressive disease characterized by a persistent airflow limitation which is usually progressive, and associated with an abnormal inflammatory response of lung to noxious particles or gases. Exacerbations contribute to the overall severity in individual patients, and are defined as episodes of acute worsening of symptoms from the stable state which is beyond normal day to day variation [1].

While the impact of non invasive mechanical ventilation on stable COPD and on pulmonary fibrosis is under debate, NIV has significantly modified COPD exacerbation management and is usually indicated for the treatment of acute respiratory failure (ARF) in this subset of patients [2-8].

In the treatment of COPD exacerbations with respiratory acidosis both NIV and invasive mechanical ventilation (IMV) induce a significant improvement in gas exchange, associated with similar length of stay in Intensive Care Unit (ICU) and in-hospital mortality [9]. However NIV has multiple advantages over invasive ventilation, lowering risks of nosocomial infections, shortening ICUs or hospital lengths of stay diminishing weaning periods, and decreasing hospital admissions in the following 12 months [9-12].

Despite these observations, NIV guidelines recommend not to consider it as a substitute for IMV, in those cases in which respiratory conditions require endotracheal intubation [5,6]. Postponing the identification of patients who are likely to fail NIV may cause inappropriate delay in intubation, increasing morbidity and mortality [13]. Hence, it becomes important to identify early factors associated with NIV failure, recognizing subsets of patients who are likely not to respond to NIV. Previous reports have evaluated the presence of prognostic factors predicting NIV failure, considering different variables: Glasgow Coma Scale (GCS) score, age, ARF severity, response to NIV in the first hours of treatment, Acute Physiology and Chronic Health Evaluation (APACHE) II score, presence of comorbidities [14-22].

We aimed our study to analyze factors associated with an increased probability of NIV failure and in-hospital mortality rate in patients who underwent non-invasive mechanical ventilation for COPD acute exacerbation and hypercapnic failure.

Methods

Patients

We retrospectively reviewed the records of COPD patients who, between 2009 and 2011, underwent mechanical ventilation for at least 12 hours because of hypercapnic ARF due to an acute exacerbation. The COPD diagnosis was determined following guidelines [1].

Diagnostic criteria for respiratory failure were: hypoxemia ($\text{PaO}_2 < 50$ mmHg), $\text{pH} \leq 7.35$ and $\text{PaCO}_2 \geq 45$ mmHg, with dyspnoea, signs of increased respiratory work, respiratory rate > 30 breath/min [18,23,24].

At admission, the following parameters were recorded: demographics (age, gender), comorbidities, respiratory rate (RR), pH and arterial blood partial pressure of oxygen (PaO_2) and carbon dioxide (PaCO_2) measured by blood gas analyzer (Radiometer®, Copenhagen, Denmark), GCS [25] and APACHE II score [26].

Patients affected by severe renal failure, severe heart failure, neoplastic disease and acute cerebrovascular event were excluded from further evaluation.

The decision of starting mechanical ventilation (MV) was based on the lack of gas exchanges improvement, despite a 1 hour maximum medical treatment on controlled oxygen therapy.

In presence of an alteration of consciousness, patients underwent invasive mechanical ventilation (IMV), unless previous willingness not to be resuscitated was declared, and were excluded from evaluation.

Mechanical Ventilation Settings and Assessment of Patients during NIV

The following criteria allowed to begin NIV: mental status (i.e. ability to follow simple commands and to clear secretions) and a cardiovascular stable condition [27]. After NIV beginning, the following conditions were criteria for switch to IMV: cardiac or respiratory arrest; non-respiratory organ failure; facial surgery or trauma; upper-airway obstruction; inability to protect the airway and inability to clear secretions [13].

Mechanical ventilation was performed by Puritan Bennett 7200 A ventilator® (Nellcor Puritan Bennett Inc. 4280, Pleasanton, CA, USA) in CPAP mode (with Pressure Support, PS, ventilation), via face mask (Respironics®) or full face mask (Ultramirage™ Full Face Mask NV, Harol, S. Donato Milanese, Italia), when needed.

PS was the maximum inspiration pressure value tolerated by patients, able to ensure an exhaled tidal volume equal to a body weight (Kg) x 8 ml; to minimize inspiratory effort during NIV a Positive End Expiratory Pressure (PEEP) between 4 and 6 cm H_2O was applied [28].

Adjustments of ventilator settings were made on the basis of the blood gas data obtained within 2 - 4 hours following initiation of MV, and on the RR and SpO_2 (percutaneous oxygen saturation) on-line recorded by a finger probe.

The inspired oxygen fraction (FiO_2) was set in order to achieve a SpO_2 between 88% and 92% [5,6].

Blood gas balance was measured on admission (PaO_2 , PaCO_2 , pH START), 1 h after modifying the ventilator's settings, and within 2 - 4 hours following initiation (PaO_2 , PaCO_2 , pH NIV) and after NIV cessation (at discharge/death/ETI; PaO_2 , PaCO_2 , pH END).

Standard medical therapy (bronchodilators, corticosteroids, antibiotics, and controlled oxygen) was maintained all along during in-hospital stay.

Length of stay, need for ETI, success (and failure) rate, number of deaths, discharges, transfers to other wards or ICUs were also recorded.

Statistical Analysis

A retrospective analysis was conducted on all patients to select characteristics at the time of admission, or during the in-hospital stay, that could predict a poor outcome from an episode of acute respiratory failure requiring NIV.

The outcome variable was defined as failure of NIV leading to invasive ventilation or death.

Results are presented as number (percentage) or mean; median (standard deviation) unless otherwise stated.

Continuous variables were analyzed using a Student's *t* test (for normal distributed data) or Mann-Whitney *U*-test (for non-normal distributed data); categorical values were analyzed using the χ^2 test or the Fisher's exact test. Statistical significance was assumed at a *p* value less than 0.05.

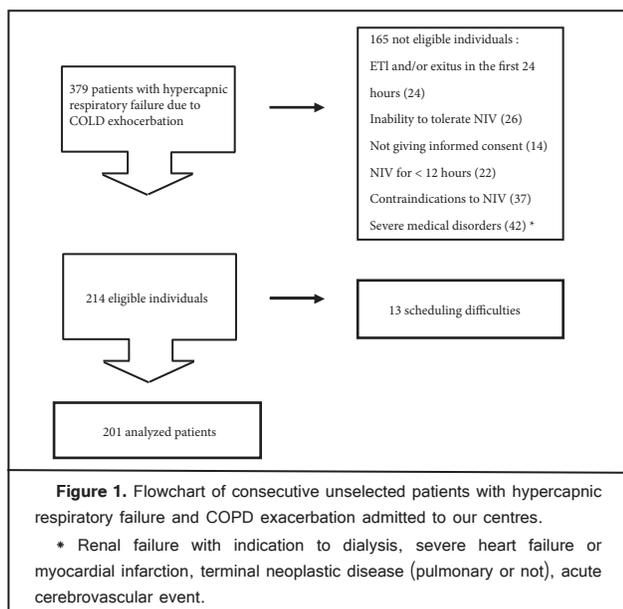
Then we selected the variable pH START (arterial pH value at admission, before starting mechanical ventilation), and we calculated sensitivity, specificity, likelihood ratios and confidence intervals, and we performed the receiving operating characteristics (ROC) curve, which was constructed by plotting sensitivity on the y-axis and 1 - specificity on the x-axis. Finally we choose two cut-off values (7.20 and 7.25) and then "dichotomized" the continuous variable pH START on the basis of these cut-offs.

We finally identified a subgroup of patients with pH START > 7.20 and ≤ 7.25, and repeated univariable analysis. Statistical analysis was performed using the statistical package SPSS (version 19; SPSS Inc; Chicago, IL, USA).

Results

Analysis of the Entire Cohort

Among a total of 379 patients admitted for the management of an episode of ARF due to COPD exacerbation, 201 individuals fulfilled the study entry criteria (Figure 1).



Demographic characteristics, baseline parameters at admission and evaluated outcomes are shown in **Table 1**.

NIV was successful in 151 patients (75.1 %), while NIV failure was observed in the remaining 50 individuals.

NUMBER OF INDIVIDUALS	201	
GENDER (M/F)	107/94	
AGE (years)	71.63; (8.69)	
COMORBIDITIES	Renal failure	33 (16.4%)
	Diabetes	29 (14.4%)
	Cardiovascular disease	88 (43.8%)
	Fibrothorax	14 (6.96%)
	Obesity	26 (12.9%)
	OSAS	10 (4.97%)
	Renal TB	1 (0.5%)
	Cancer	6 (3%)
	Cor pulmonale	89 (44.3%)
	Kyphoscoliosis	4 (2%)
	Hepatopathy	1 (0.5%)
	Encephalopathy	1 (0.5%)
	Hypertension	59 (29.3%)
Bipolar disorder	4 (2%)	
Neuromuscular disease	1 (0.5%)	
Cachexia	1 (0.5%)	
GCS	12.52; (2.78)	
APACHE II	21.22; (5.62)	
PaO ₂ START (mmHg)	57.01; (17.27)	
PaCO ₂ START (mmHg)	94.43; (15.47)	
pH START	7.26; (0.06)	
RR START breaths/min	24.93; (8.00)	
PaO ₂ NIV (mmHg)	67.87; (13.00)	
PaCO ₂ NIV (mmHg)	78.74 (14.14)	
pH NIV	7.34; (0.06)	
PaO ₂ END (mmHg)	67.07; (11.44)	
PaCO ₂ END (mmHg)	70.43; (21.13)	
pH END	7.37; (0.08)	
LENGTH OF STAY (days)	13.00; (11.34)	
SUCCESS/FAILURE	151/50	
ETIs (n)	23 (11.4%)	
TRACHEOSTOMIES (n)	9 (4.5%)	
DEATHS (n)	33 (16.4%)	
DISCHARGES/TRANSFERS TO OTHER UNITS (n)	157 (78.1%)	
TRANSFERS TO ICU	10 (4.97%)	

Table 1. Demographic characteristics, baseline parameters at admission and evaluated outcomes. Continuous variables are expressed as mean; (standard deviation). Categorical variables are expressed as absolute number and/or percentage of the total. OSAS: Obstructive Sleep Apnea Syndrome; TB: Tuberculosis; GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; PaO₂: partial pressure of arterial oxygen; PaCO₂: partial pressure of arterial carbon dioxide; RR: respiratory rate; NIV: Non invasive ventilation; ETI: Endotracheal intubation; ICU: Intensive Care Unit; PaO₂, PaCO₂, pH, RR START: values measured at admission; PaO₂, PaCO₂, pH NIV: values measured after 2 - 4 hours of NIV; PaO₂, PaCO₂, pH END: values measured at discharge/death/ETI.

Table 2 illustrates the variables which may be associated with a successful outcome.

The analysis of the response to NIV, evaluated as variations of pH, PaO₂, and PaCO₂ after 2-4 hours of treatment (Δ pH, Δ PaO₂ e Δ PaCO₂), failed to show a significant association with the outcome (Table 2).

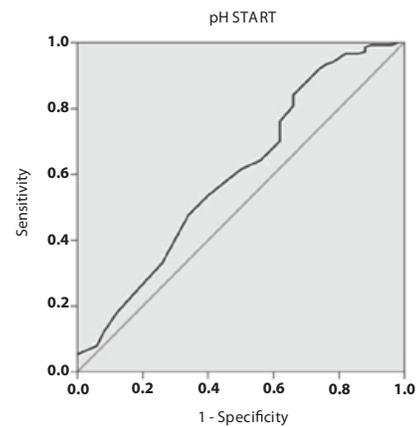
CONTINUOUS VARIABLES		SUCCESS (N=151)	FAILURE (N=50)	p		
		Mean; (SD)	Mean; (SD)			
AGE (years)		70.99; (8.74)	73.56; (8.35)	0.058°		
PaO ₂ START (mmHg)		57.48; (17.26)	55.62; (17.38)	0.392°		
PaCO ₂ START (mmHg)		93.10; (15.08)	98.45; (16.09)	0.029°		
pH START		7.26; (0.06)	7.23; (0.08)	0.033°		
RR START (breaths/min)		24.76; (7.55)	25.42; (9.28)	0.237°		
GCS		12.94; (2.44)	11.24; (3.32)	0.001°°		
APACHE II		20.02; (4.81)	24.84; (6.35)	< 0.001°		
PaO ₂ NIV (mmHg)		66.96; (12.03)	70.62; (15.31)	0.235°		
PaCO ₂ NIV (mmHg)		77.62; (13.62)	82.12; (15.24)	0.044°		
pH NIV		7.34; (0.06)	7.32; (0.08)	0.060°		
LENGHT OF STAY (days)		12.14; (7.67)	15.60; (18.30)	0.528°		
PaO ₂ END (mmHg)		67.21; (9.48)	66.66; (16.08)	0.187°		
PaCO ₂ END (mmHg)		62.40; (8.33)	94.68; (28.50)	< 0.001°		
pH END		7.39; (0.04)	7.28; (0.10)	< 0.001°		
Δ pH (NIV-START)		0.08; (0.05)	0.09; (0.07)	0.266°°°		
Δ PaO ₂ (NIV-START) (mmHg)		9.48; (17.26)	15; (22.32)	0.071°°		
Δ PaCO ₂ (START-NIV) (mmHg)		15.48; (12.09)	16.33; (14.27)	0.682°°		
CATEGORICAL VARIABLES		SUCCESS	FAILURE	p*	OR	95% CI
GENDER	M (107)	77 (51%)	30 (60%)	0.269	1	0.36-1.33
	F (94)	74 (49%)	20 (40%)		0.69	
DICHOTOMIZED pH START	≤ 7.25 (83)	58 (38%)	25 (50%)	0.149	1.60	0.84-3.05
	> 7.25 (118)	93 (61.6%)	25 (50%)		1	
DICHOTOMIZED pH START	≤ 7.20 (41)	24 (15.9%)	17 (34%)	0.006	1	0.18-0.76
	> 7.20 (160)	127 (84.1%)	33 (66%)		0.37	

Table 2. Analysis of the association of the evaluated variables with the outcome: univariable analysis (entire cohort, n= 201). PaO₂: partial pressure of arterial oxygen; PaCO₂: partial pressure of arterial carbon dioxide; RR: respiratory rate; GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; NIV: Non invasive ventilation; PaO₂, PaCO₂, pH, RR START: values measured at admission; PaO₂, PaCO₂, pH NIV: values measured after 2 - 4 hours of NIV; PaO₂, PaCO₂, pH END: values measured at discharge/death/ETI; Δ pH, Δ PaO₂, Δ PaCO₂: variations of pH, PaO₂, and PaCO₂ after 2-4 hours of treatment. SD: Standard Deviation; ° Mann-Whitney test; °° t-test; °°° Unequal variance t-test; * Chi-square test; OR: Odds ratio; 95% CI: 95% confidence interval.

The ROC analysis results for the variable pH START (arterial pH value at admission), considering NIV failure as outcome, showed a cut off value of 7.255, with a sensitivity of 0.616 a specificity of 0.500 and a likelihood ratio of 1.23 (Figure 2). We also considered the pH START cut off value of 7.205, obtaining a sensitivity of 0.84, with a specificity of 0.340 and a likelihood ratio of 1.27. The variable pH START was then considered both as absolute value (continuous variable) and as dichotomized value (pH START \leq or $>$ 7.205 or 7.255; categorical variable).

Subgroup Analysis of a Cohort of Patients with pH START > 7.20 and \leq 7.25

Of the 42 individuals with a pH at admission $>$ 7.20 and \leq 7.25, NIV was successful in 34 patients (81%), while NIV failure was observed in the remaining 8 (19%). None of the examined variables were found to be significantly associated with the outcome at the univariable analysis (Table 3), except for a slight significance for the dichotomized variable Δ pH ($<$ 0.1/ \geq 0.1; $p = 0.054$).



CONTINUOUS VARIABLES	SUCCESS (N=34)	FAILURE (N=8)	p*			
	Mean; (SD)	Mean; (SD)				
AGE (years)	70.71; 70.50 (7.26)	72.75; 72.50 (6.65)	0.413			
PaO ₂ START (mmHg)	57.00; 54.50 (18.17)	61.13; 64.00 (10.01)	0.290			
PaCO ₂ START (mmHg)	93.29; 92.00 (14.13)	94.25; 97.50 (14.81)	0.724			
pH START	7.23; 7.23 (0.012)	7.24; 7.24 (0.012)	0.079			
RR START (breaths/min)	24.00; 25.00 (9.43)	23.38; 27.00 (8.88)	0.797			
GCS	12.76; 13.00 (2.13)	11.38; 12.50 (3.50)	0.362			
APACHE II	20.71; 20.00 (4.66)	22.50; 22.00 (5.78)	0.500			
PaO ₂ NIV (mmHg)	68.91; 65.50 (13.91)	67.25; 66.00 (6.02)	0.936			
PaCO ₂ NIV (mmHg)	78.91; 76.50 (14.16)	83.63; 85.50 (12.42)	0.344			
pH NIV	7.32; 7.32 (0.047)	7.29; 7.29 (0.053)	0.187			
LENGHT OF STAY (days)	12.50; 9.00 (8.28)	11.25; 8.00 (10.37)	0.395			
Δ pH (NIV-START)	0.09; 0.09 (0.05)	0.056; 0.06 (0.05)	0.107			
Δ PaO ₂ (NIV-START)	11.91; 12.00 (18.13)	6.12; 3.5 (13.92)	0.336			
Δ PaCO ₂ (START-NIV)	14.38; 14.00 (9.85)	10.62; 12.50 (11.20)	0.451			
CATEGORICAL VARIABLES		SUCCESS	FAILURE	p**	OR	95% CI
GENDER	M (21)	16 (47.1%)	5 (62.5%)	0.432	1	0.11-2.59
	F (21)	18 (52.9%)	3 (37.5%)		0.533	
DICHOTOMIZED Δ pH	< 0.1 (24)	17 (50%)	7 (87.5%)	0.054	0.143	0.016-1.290
	\geq 0.1 (18)	17 (50%)	1 (12.5%)		1	

Table 3. Analysis of the association of the evaluated variables with the outcome: univariable analysis (subgroup analysis of patients with pH START > 7.20 and \leq 7.25, n= 42).

PaO₂: partial pressure of arterial oxygen; PaCO₂: partial pressure of arterial carbon dioxide; RR: respiratory rate; GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II; NIV: Non invasive ventilation; PaO₂, PaCO₂, pH, RR START: values measured at admission; PaO₂, PaCO₂, pH NIV: values measured after 2 - 4 hours of NIV; Δ pH, Δ PaO₂, Δ PaCO₂: variations of pH, PaO₂, and PaCO₂ after 2-4 hours of treatment.

SD: Standard Deviation; *Mann-Whitney test; ** Chi-square test; OR: Odds ratio; 95% CI: 95% confidence interval.

Discussion

In our study we evaluated a group of consecutive unselected patients undergoing NIV because of hypercapnic acute respiratory failure due to COPD exacerbation and obtained a success rate and failure percentage in line with previous reports [8,13,14].

Importantly, while confirming pH meaning in identifying patients at risk of NIV failure, we observed that NIV was successfully performed in patients with severe hypercapnic acidosis and pH values lower than those recommended by guidelines.

Because inability to individuate patients who are going to fail NIV may determine an inappropriate deferral of intubation, we analyzed the role of several prognostic factors which may be used as reliable tools to help physicians in deciding therapeutic strategies during NIV trial. Consistently with other papers, we found that patients in whom NIV succeeded had higher initial GCS score and arterial pH, and lower PaCO₂ values (at admission and after 2-4 hours of NIV) and APACHE II score [14,15-18,24]. Accordingly to literature [14,17,24], we found that high GCS scores were higher in the subset of individual in whom NIV was successful, showing that the impairment of mental status could produce an increased risk for intubation. On the other hand ETI role in patients with severely altered level of consciousness is still matter of debate [9].

As observed in our report, in controlled and uncontrolled NIV trials, a high initial PaCO₂ level has been associated with a poor outcome [5,15], suggesting that the respiratory failure severity can be used to stratify patients according to the risk of meeting criteria for intubation. Similarly a fall in PaCO₂ during NIV has also been shown to be protective [15].

Accordingly with previous reports we also found that APACHE II score had a significant predictive effect in anticipating NIV success/failure.

APACHE II score is one of the most commonly used score to assess severity illness and has been evaluated by several authors as predicting factor in patients treated with NIV. Since the 90s, increased values of APACHE II have been reported among patients who failed to improve with NIV [15]. These findings were confirmed by Chakrabarti et al. [16], and Confalonieri et al. [14], who identified its power as prognostic index in the ability to incorporate a combination of variables which could together contribute to influence the outcome. Several studies designed to assess the best predictors of NIV outcomes agree with the observations that pH values, measured at baseline and/or after a trial of NIV, are the most powerful factors linked to success or failure [14,15].

Although in our study, patients in whom NIV was successful had higher initial arterial pH, we found that the response to NIV (evaluated as variations of pH, PaO₂, and PaCO₂ after 2-4 hours of treatment, and/or as absolute values) failed to show a significant association with the outcome. Our observation may be in line with Moretti et al. findings who, analyzing predictors of "late failure" in subjects initially responding to NIV, found that, among with other variables, lower pH at admission was a good predictor of late failure [18]. Importantly in our study a significant success rate was obtained in the subset of patients with pH ≤ 7.25 and > 7.20, considerably below the range of pH suggested in current guidelines for NIV indication [5,6].

Current guidelines highlight a number of key points that may indicate or contraindicate NIV in patients with acute respiratory failure [5,6], suggesting a pivotal role for arterial pH. However, everyday clinical practice may force physicians to face situations that could affect the recommended decision making process. Nowadays, in the 'real world', the suggested thresholds may be forcedly modified, because ICU beds are in such short supply that if COPD patients are to receive NIV it must be on a ordinary respiratory ward, or on RIICU (Respiratory Intermediate Intensive Care Units) [29].

IPrevious reports have identified [5,9] a 7.25 a priori pH cut-off level to discriminate "severe and mild hypercapnic acidosis", obtaining a mortality rate significantly different in the two subsets of individuals and pointing out a crucial role for pH in predicting NIV failure.

In the present study, ROC analysis allowed us to identify two pH threshold values (7.20 and 7.25), that define a "grey area" in which this variable loses its ability to clear predict NIV outcome. Recently a new research area is evaluating the role of systemic biomarkers in predicting NIV failure in COPD patients. Nowadays evidence is rather scarce and there are few reports on the field. Haja et al., using a multivariable statistical approach, found that a combination of performance status and anemia was able to identify patients who were likely to fail NIV [30]. We believe that this may be a new exciting field to be explored and further studies should be performed to discover analytes that could foresee, with acceptable specificity and sensitivity, the outcome of NIV in this subset of individuals.

Our data, together with the recent technological advancements and the improved physicians practice in the treatment of hypercapnic respiratory failure due to COPD exacerbation, point out the need for further multicentric studies aimed to better define NIV indication in this subset of patients, with special reference to pH thresholds.

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