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Procalcitonin, C-reactive protein, PaCO₂, and noninvasive mechanical ventilation failure in chronic obstructive pulmonary disease exacerbation

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Abstract

It is unclear whether procalcitonin (PCT) is correlated with noninvasive ventilation (NIV) failure. This retrospective case–control study aimed to compare PCT levels, C-reactive protein (CRP) levels, and PaCO₂ in patients (05/2014–03/2015 at the Harrison International Peace Hospital, China) with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and NIV failure/success.

This was a retrospective case–control study of patients with AECOPD who required NIV between May 2014 and March 2015. All consecutive patients with AECOPD admitted at the Department of Critical Care Medicine and transferred from the general ward were included in the study. Hemogram, PCT, erythrocyte sedimentation rate (ESR), arterial blood gas (ABG), and CRP levels were measured ≤1 hour before NIV was used. NIV was considered to have failed if at least one of the following criteria was met: cardiac arrest or severe hemodynamic instability; respiratory arrest or gasping; mask intolerance; difficulty in clearing bronchial secretions; or worsening of ABGs or sensorium level during NIV. The factors associated with NIV failure were determined.

A total of 376 patients were included: 286 with successful NIV and 90 wither NIV failure. The multivariate analysis showed that PCT (OR = 2.0, 95%CI: 1.2–3.2, P = .006), CRP (OR = 1.2, 95%CI: 1.1–1.3, P < .001), and PaCO₂ (OR = 1.1, 95%CI: 1.1–1.2, P < .001) ≤1 hour before NIV were independently associated with NIV failure. The optimal cutoff were 0.31 ng/mL for PCT (sensitivity, 83.3%; specificity, 83.7%), 15.0 mg/mL for CRP (sensitivity, 75.6%; specificity, 93.0%), and 73.5 mm Hg for PaCO₂ (sensitivity, 71.1%; specificity, 100%). The area under the curve (AUC) was 0.854 for PCT, 0.849 for CRP, and 0.828 for PaCO₂. PCT, CRP, and PaCO₂ were used to obtain a combined prediction factor, which achieved an AUC of 0.978 (95%CI: 0.961–0.995).

High serum PCT, CRP, and PaCO₂ levels predict NIV failure for patients with AECOPD. The combination of these three parameters might enable even more accurate prediction.

Abbreviations: ABG = arterial blood gas, AECOPD = acute exacerbation of chronic obstructive pulmonary disease, ARF = acute respiratory failure, AUC = area under the curve, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, ETI = endotracheal intubation, ICU = intensive care unit, NIV = noninvasive ventilation, PCT = procalcitonin.

Keywords: arterial blood gas, chronic obstructive pulmonary disease, C-reactive protein, noninvasive ventilation, partial pressure of carbon dioxide, procalcitonin

1. Introduction

The use of noninvasive ventilation (NIV) during acute respiratory failure (ARF) has increased over the past 2 decades for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). NIV failure has been defined as the need for endotracheal intubation (ETI) or death.[1] Unsuccessful NIV was found to be independently associated with death, especially in patients with de novo ARF.[2]

Several previous studies tried to evaluate the best predictive risk factors for NIV failure and reviewed and analyzed the risk factors for NIV failure in patients with early hypercapnic respiratory failure.[3–5] The risk factors could include baseline abnormal blood gas and inability to correct the gas exchange disorder, disease severity increased, increased respiratory rate (>35 breaths/min), and disease severity score at baseline. Other factors could include malnutrition, increased heart rate, higher baseline CRP level, and white blood cell count level.[6] Nevertheless, to the best of our knowledge, despite the rather extensive literature in the NIV field, there is only one paper, published 11 years ago, summarizing the risk factors for NIV failure[7] and there is no study about the markers of NIV.

Procalcitonin (PCT) is the prohormone of the hormone calcitonin secreted by the thyroid C cells.[8] PCT levels increase rapidly during infection and are correlated with severity of illness, making PCT an ideal biomarker for bacterial infection. [9]AECOPD is an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. Various triggers for AECOPD have been identified; however, up to 75% of all exacerbations are associated with the detection of bacterial and/or viral respiratory pathogens.[10] A recent approach that holds considerable promise is serum PCT measurement.[11] PCT is liberated into circulation of patients in response to severe systemic inflammation, in particular by bacterial infection.[9] CRP levels were also examined for this purpose, but found to lack sensitivity and specificity.[12] Some studies showed that serum PCT could effectively discriminate bacterial infection from viral or other inflammatory pulmonary conditions.[13,14]

Some studies have demonstrated that mean PCT levels are increased in patients with severe AECOPD and receiving NIV,[15] and that PCT levels were associated with a higher rate of admission to the ICU.[16] There were significant differences in mean PCT levels according to the type and severity of AECOPD. Elevated PCT levels have been independently associated with an increased risk of intensive care unit (ICU) mortality in patients who required intubation and mechanical ventilation.[17] PCT levels have been associated with severity of respiratory failure and were higher in hospitalized patients receiving NIV compared with those treated without NIV.[15] Nevertheless, whether PCT can predict the risk of NIV failure in patients with AECOPD has not been reported.

We hypothesized that PCT levels are related to the severity of patients with NIV. Therefore, the aim of the present study was to compare PCT levels, CRP levels, and $PaCO_2$ in patients with AECOPD with NIV failure or success. The correlations between PCT levels and arterial blood gas (ABG) analysis, erythrocyte sedimentation rate, CRP, white blood cells, and neutrophils were also analyzed.

2. Materials and methods

2.1. Study design

This was a retrospective case–control study of patients with AECOPD who required NIV between May 2014 and March 2015 at the Department of Critical Care Medicine of the Harrison International Peace Hospital (Hengshui, Hebei, China). The study protocol was approved by the ethics committee at the hospital, and informed written consent was obtained from the patients or their legal representatives.

For sample size estimation, α was set at 0.05 and power (1−β) was set at 0.8. According to the literature about AECOPD patients, the PCT levels were estimated at 0.19 and 0.05 ng/mL in the NIV and control groups, respectively.[15] Hence, the estimated sample size was 20 patients.[18]

2.2. Patients

All consecutive patients with AECOPD admitted at the Department of Critical Care Medicine and transferred from the general ward were included in the study. All critically ill patients had to meet at least one of the following indications for NIV: respiratory acidosis (arterial pH ≤7.35 and/or $PaCO_2$ ≥6.0 kPa, 45 mm Hg); or severe dyspnea with clinical signs suggestive

of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.[19]

The exclusion criteria were: patients without any symptoms of an acute exacerbation for at least 4 weeks were considered cases with stable COPD; <18 years of age; abnormality of airway anatomy; cardiovascular or cerebrovascular diseases; pregnant women; patients with pulmonary diseases other than COPD (asthma, bronchiectasia, pneumonia, or tuberculosis); patients with sepsis or any cancer; unable to tolerate NIV[20]; fever (>38.5°C) before antibiotic treatment for >24 hours, extensive treatment with systemic corticosteroids (>30 mg of prednisolone or equivalent dose for >4 days), or radiographic signs of pneumonia[21]; or any missing data.

The diagnosis of an exacerbation of symptoms was based exclusively on the clinical presentation of the patients who complained of an acute change in dyspnea, cough, and/or sputum production that was beyond normal day-to-day variations.[20] The assessment of exacerbated symptoms was based on the patients' medical history, clinical signs of severity, and laboratory tests.[20]

NIV was considered to have failed if at least one of the following criteria was met within 48 hours after beginning NIV and ETI was promptly given: cardiac arrest or severe hemodynamic instability; respiratory arrest or gasping; difficulty in clearing bronchial secretions; or worsening of ABGs or sensorium level during NIV.[22] Invasive mechanical ventilation (IMV) was provided if NIV failed. Since 65% of the NIV failures occur during the first 48 hours of NIV, 48 hours was selected as the study cut off.[6]

2.3. Data collection

Hemogram, erythrocyte sedimentation rate, ABG (ABL90 FLEX, Aakandevej 21, DK-2700 Bronshoj, Denmark), serum CRP, and PCT tests were performed from blood samples taken ≤1 hour before NIV. A quantitative assessment of PCT levels was performed using the mini VIDAS system (Biomerieux Diagnostic, Marcy l'Etoile, France) and the enzyme-linked fluorescent assay (ELFA) method. The results were evaluated on the same day. In healthy individuals, the reference value was determined to be <0.05 ng/mL, varying only slightly depending on the analytical method used.

2.4. Statistical analysis

The Kolmogorov–Smirnov test was used to assess the normal distribution of the continuous data. Normally distributed data were presented as means ± standard deviation and analyzed using the Student t test. Non-normally distributed data were presented as medians (interquartile range) and analyzed using the Mann–Whitney U test. Categorical data were presented as frequencies and analyzed using the chi-square test.[23] Correlations among data with measurable outcomes were analyzed using the Spearman test. SPSS 18.0 (SPSS, Inc. Chicago, IL) was used for all statistical analyses. Two-tailed P-values <.05 were considered statistically significant.

To extract factors affecting NIV failure, a binary logistic regression analysis was performed. At first, univariate analyses were conducted, and factors that showed significant differences between groups were included in the logistic regression analysis[24]; the results were presented as odds ratios (OR) and 95% confidence interval (95%CI). The OR indicates that one

unit increase in continuous variables leads to an "OR"-fold increase in the odds of the event. The analysis was also adjusted for factors that were deemed clinically significant (e.g., age and gender). To test the value of risk factors in predicting NIV failure, a receiver operating characteristic (ROC) analysis was performed, and the area under curve (AUC) was calculated.

To avoid measurement errors and misclassification, the entire medical charts of all patients were reviewed to cross-reference all the important data in the present study in order to rule out, as much as possible, information bias. In addition, all important parameters (i.e., those that were included in the multivariable analysis) were examined prior to inclusion to rule out the possibility of uneven distribution and the possibility of the Simpson's paradox.[25]

3. Results

3.1. Patients

Figure 1 presents the patient flowchart: 402 patients with AECOPD were screened and 376 patients were included. Among them, 286 were treated successfully with NIV, and 90 had to receive endotracheal intubation and mechanical ventilation due to NIV failure. Seven patients were excluded because of missing data, 15 for concomitant diseases, and 4 because they were unable to tolerate NIV from the start.

3.2. Characteristics of the patients

The clinical characteristics are presented in Table 1. $PaCO_2$, serum PCT, and CRP levels were higher, and pH was lower in the NIV failure group compared with the NIV success group (all $P < .05$).

3.3. Correlations between PCT, ABG, and inflammation markers

No significant correlations were found between PCT level and variables of ABG and inflammation markers, except a weak positive correlation between PCT and CRP levels ($r = 0.176$, $P = .019$) (Table 2).

3.4. Multivariate analysis

To determine the factors associated with NIV failure, binary logistic regression analysis was carried out using the following
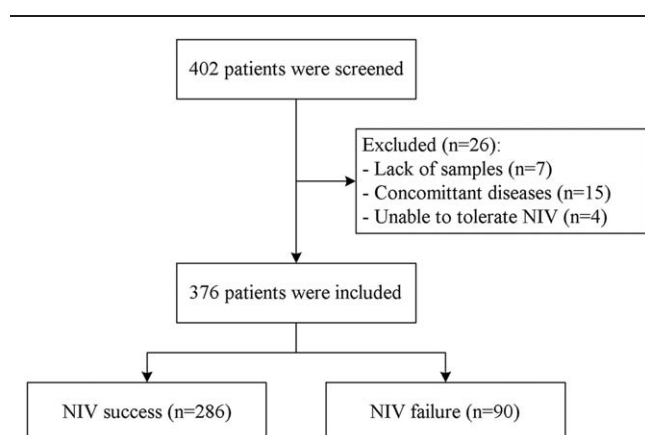
independent variables: age, gender, PCT levels, CRP levels, pH, and $PaCO_2$ at admission. The results showed that PCT levels (OR = 2.0, 95%CI: 1.2–3.2, $P = .006$), CRP levels (OR = 1.2, 95%CI: 1.1–1.3, $P < .001$), and $PaCO_2$ (OR = 1.1, 95%CI: 1.1–1.2, $P < .001$) were independently associated with NIV failure (Table 3).

3.5. ROC curve analysis

We performed a ROC analysis to determine the predictive levels of serum PCT, CRP, and $PaCO_2$ for assessing the need of IMV therapy (Table 4 and Fig. 2). The cut off values to achieve the highest Youden index were 0.31 ng/mL for PCT (sensitivity, 83.3%; specificity, 83.7%), 15.0 mg/mL for CRP (sensitivity, 75.6%; specificity, 93.0%), and 73.5 mm Hg for $PaCO_2$ (sensitivity, 71.1%; specificity, 100%). The area under the curve (AUC) was 0.854 (95%CI: 0.793–0.914) for PCT, 0.849 (95% CI: 0.787–0.911) for CRP, and 0.828 (95%CI: 0.761–0.896) for $PaCO_2$. The AUC for the combination of PCT, CRP, and $PaCO_2$ was 0.978 (95%CI: 0.961–0.995).

Table 1

Characteristics of the patients with AECOPD according to NIV success.

Characteristics	NIV success (n = 286)	NIV failure (n = 90)	P
Gender (male), n (%)	198 (69.2)	64 (71.1)	.74
Age, years	63 ± 6	64 ± 6	.17
FEV_1/FVC (%)	48.58 ± 8.08	50.00 ± 8.98	.16
GOLD stage, n (%)	—	—	.40
Mild	90 (31.5)	30 (33.3)	—
Moderate	85 (29.7)	30 (33.3)	—
Severe	65 (22.7)	22 (24.4)	—
Very severe	46 (16.1)	8 (8.9)	—
Smoking history (pack-year)	44 ± 15	42 ± 11	.24
Body mass index, kg/m^2	25.2 ± 2.7	25.1 ± 2.7	.90
Procalcitonin, ng/mL	0.65 ± 0.21	2.10 ± 0.44	<.001
Erythrocyte sedimentation rate, mm/h	26.3 ± 6.7	27.2 ± 7.4	.27
Neutrophil (%)	79.8 ± 11.6	77.6 ± 11.1	.12
C-reactive protein, mg/mL	7.85 ± 6.23	39.48 ± 16.77	<.001
White blood cells (×10^9/L)	9.90 ± 4.83	8.97 ± 3.90	.10
pH	7.18 ± 0.06	7.12 ± 0.08	<.001
$PaCO_2$, mm Hg	52.4 ± 10.1	79.4 ± 24.3	<.001

AECOPD = acute exacerbation of chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, NIV = noninvasive ventilation, $PaCO_2$ = partial pressure of carbon dioxide.

402 patients were screened	
	Excluded (n=26): - Lack of samples (n=7) - Concomittant diseases (n=15) - Unable to tolerate NIV (n=4)
376 patients were included	
NIV success (n=286)	NIV failure (n=90)

Figure 1. Patient flowchart.

Table 2

Correlations between PCT and variables of ABG and inflammation markers.

	r (Spearman's)	P
PCT × WBC	0.029	.70
PCT × CRP	0.176	.02
PCT × ESR	0.055	.47
PCT × NET	0.091	.23
PCT × pH	−0.115	.13
PCT × $PaCO_2$	0.104	.17

CRP = serum C-reactive protein, ESR = erythrocyte sedimentation rate, NET = serum neutrophil, PCT = procalcitonin, WBC = serum white blood cell.

Logistic regression analysis to predict noninvasive mechanical ventilation failure.

Variables	P	OR	95%CI
PCT	.006	2.0	1.2–3.2
PaCO$_2$	<.001	1.1	1.1–1.2
CRP	<.001	1.2	1.1–1.3
Gender	.32	2.1	0.6–3.2
Age	.07	1.4	0.7–1.9
pH	.21	1.1	0.3–12.1

CI = confidence interval, CRP = serum C-reactive protein, OR = odds ratio, PaCO$_2$ = partial pressure of carbon dioxide, PCT = procalcitonin.

4. Discussion

PCT levels are high in patients with severe AECOPD under NIV,[15] but it is unclear whether PCT is associated with NIV failure. Therefore, this study aimed to compare PCT levels, CRP levels, and PaCO$_2$ in patients with AECOPD with NIV failure or success. The results first showed that high serum PCT, CRP, and PaCO$_2$ levels predict NIV failure and their combination might enable accurate prediction for patients with AECOPD.

PCT and CRP are the most often studied biomarkers in patients with AECOPD. CRP alone is neither sufficiently sensitive nor specific to be a useful biomarker in the absence of symptom assessment and plasma CRP levels in the presence of a major exacerbated symptom is useful in confirming COPD exacerbation but not helpful in predicting exacerbation severity.[26–28] Previous studies have shown varying degrees of positive correlation between the CRP and PCT levels.[15,21,29,30] In the present study, only a weak positive correlation was found between PCT and CRP levels. A variety of reasons can be responsible for these discrepancies. PCT was positively correlated with disease severity, while CRP could not reflect disease severity. In the present study, the patients had more severe disease degree than the patients in the other studies and had higher PCT levels.[15,31]

Rammaert et al[17] showed high mortality rates in patients whose PCT levels were >0.24 ng/mL. In another study, PCT levels >0.25 μg/L in patients with COPD treated at the ICU were found to be related with mortality.[32] PCT cut-off value for NIV indication has been determined to be 0.10 ng/mL.[15] Unlike these studies, Hurst et al[26] reported that systemic biomarkers were not helpful in predicting the severity of AECOPD. In the present study, serum PCT levels, CRP levels, and PaCO$_2$ accurately predicted NIV failure and the need of IMV treatment. Each parameter itself had accurate diagnostic ability, but combining the three measurements increased the AUC to 0.978 (95% CI, 0.961–0.995), which is a very significant value. These parameters can be appropriate for identifying patients with high-risk NIV failure and therefore avoid emergency intubation. Different
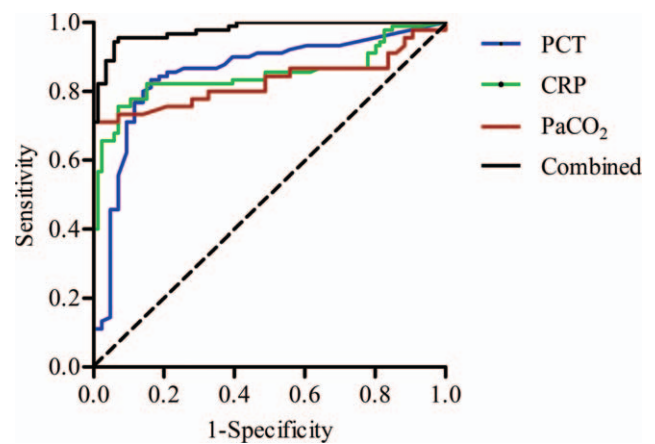

Figure 2. Receiver operating characteristic analysis of factors associated with NIV failure. The area under the curve (AUC) was 0.854 for PCT, 0.849 for CRP, and 0.828 for PaCO$_2$. AUC = area under the curve, CRP = serum C-reactive protein, NIV = noninvasive ventilation, PCT = procalcitonin.

factors have been associated with NIV failure. Fan et al[33] showed that a semiquantitative cough strength score, APACHEII, and total protein levels had an AUC of 0.86. Additional studies are necessary to determine the best combination of markers and factors for the prediction of NIV failure.

A large body of evidence clearly indicates that a lower baseline pH is a risk factor for NIV failure in COPD patients. NIV was unsuccessful in 50%–60% of patients with a baseline pH of <7.25.[3,34,35] Recently, NIV has been offered as an effective treatment option for patients with severe acidosis due to COPD.[36] In this previous study, NIV improved pH and PaCO$_2$ to the same extent in mild and severe acidosis (pH <7.25), and the overall survival rate was comparable.[36] In addition to baseline levels, pH values 1 hour after the application of NIV were shown to be strong predictors of the success of NIV.[37] In a study of more than 1000 COPD patients, Confalonieri et al[38] pointed out that a pH <7.25 after 1 hour of NIV use was associated with an increased risk of failure and that the risk of failure was even greater than when the pH levels were <7.25 at admission. In the present study, blood pH <1 hour before NIV was lower in the NIV failure group than in the NIV success group, but this factor was not independently associated with NIV failure and was not included in the ROC analysis. In our opinion, severe COPD patients always suffer from excessive volume depletion and require large volume fluid therapy early in the course of the disease. Hypovolemia induces metabolic acidosis and progressively influences pH.

Our study had some limitations. First, it was a single-center observational study and the physicians were not blinded to the

Predictive risk factors for NIV failure.

Risk factors	Cut off	Sensitivity (%)	Specificity (%)	AUC (95%CI)	Positive predictive value (%) (95%CI)	Negative predictive value (%) (95%CI)
PCT	0.31 ng/mL	83.3	83.7	0.854 (0.793–0.914)	61.61 (52.34–70.31)	94.10 (90.46–96.66)
CRP	15.0 mg/mL	75.6	93.0	0.849 (0.787–0.911)	77.23 (66.99–85.54)	92.39 (88.69–95.17)
PaCO$_2$	73.5 mm Hg	71.1	100	0.828 (0.761–0.896)	100.00 (94.31–100.00)	91.68 (88.04–94.49)
Combination	—	—	—	0.978 (0.961–0.995)	—	—

AUC = area under curve, CI = confidence interval, CRP = serum C-reactive protein, PaCO$_2$ = partial pressure of carbon dioxide, PCT = procalcitonin.

blood tests and patients' condition; furthermore, as per routine practice, the patients and their families could be informed of the test results if so desired. In addition, because of the selection criteria, selection bias may occur and the conclusions should be limited to the type of patient studied. Secondly, the decision to perform NIV was based on the routine clinical indications and physicians' experience. In addition, the data could be analyzed were limited to those available in the medical charts. An endotracheal aspirate culture was not performed because 25%–50% of patients with COPD are colonized with potential respiratory pathogens,[39] and PCT levels are not related to the presence of bacteria in the sputum.[21] Thirdly, especially in patients who were intubated and diagnosed by supine chest radiography, pneumonia could not have been excluded because of the low sensitivity of routine chest radiography. This might have resulted in high PCT levels in patients without IMV. Finally, and not the least, the present study was a derivative study and the findings have to be validated in an independent cohort.

5. Conclusions

The NIV failure group presented higher serum PCT, $PaCO_2$, and CRP levels, and lower pH compared with patients with NIV success. Serum PCT, CRP, and $PaCO_2$ were independently associated with NIV failure. High serum PCT levels (≥ 0.31 ng/mL), CRP levels (≥ 15.0 mg/mL), and $PaCO_2$ (≥ 73.5 mm Hg) predicted NIV failure in patients with AECOPD, and the combination of these three parameters might enable even more accurate prediction.

Acknowledgments

Author contributions

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Formal analysis: Huimian Shang, Xiaoya Yang.
Writing – original draft: Jinrong Wang, Shufen Guo, Zhaobo Cui.

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