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The predictive value of serum procalcitonin for non-invasive positive pressure ventilation in the patients with acute exacerbation of chronic obstructive pulmonary disease

Linlin Liu, PhD[a], Ying Luan, PhD[b], Ling Xiao, PhD[a], Ning Wang, PhD[a], Jing Wang, PhD[a], Zhaobo Cui, PhD[a,*]

Abstract

This study aimed to estimate the value of serum procalcitonin (PCT) for non-invasive positive pressure ventilation (NIPPV) prediction in the patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

A total of 220 AECOPD patients were divided into NIPPV group (n = 121) and control group (routine treatment, n = 99) based on the routine standards and physicians' experience. Logistic regression analysis was performed to identify the independent factors for NIPPV treatment. Additionally, the predictive values of the factors were measured through receiver operation characteristic (ROC) curve.

NIPPV group and control group showed significant differences in respiratory rate (RR), PaO_2, $PaCO_2$, pH, oxygenation index, erythrocyte sedimentation rate (ESR), neutrophil, CRP (C-reaction protein), and PCT ($P < .05$ for all). PCT, CRP, $PaCO_2$, RR, and neutrophil were independently correlated with NIPPV treatment in AECOPD. ROC curve showed that PCT had superior predictive value, with AUC of 0.899, the sensitivity of 86%, and the specificity of 91.9%. The cut-off value of serum PCT for NIPPV prediction was 88.50 ng/l.

AECOPD patients who require NIPPV treatment frequently have high levels of PCT, CRP, $PaCO_2$, RR and neutrophil. Serum PCT may be employed as an indicator for NIPPV treatment in AECOPD patients.

Abbreviations: AECOPD = Acute exacerbation of COPD, AUC = Area under the curve, CHD = Coronary heart disease, CLIA = Chemiluminescence immunoassay, COPD = Chronic obstructive pulmonary disease, CRP = C-reaction protein, ESR = Erythrocyte sedimentation rate, FEV1 = Forced expiratory volume in the first second, FVC = Forced vital capacity, GSC = Glasgow Coma scale, ICU = Intensive care unit, NIPPV = Non-invasive positive pressure ventilation, PCO_2 = Partial Pressure of Carbon Dioxide, PCT = Procalcitonin, ROC = Receiver operation characteristic, RR = Respiratory rate, SD = Standard deviation, WBC = White blood cell.

Keywords: AECOPD, chronic obstructive pulmonary disease, non-invasive positive pressure, procalcitonin

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease which is characterized by long-term airflow obstruction.[1] The morbidity of COPD is high globally, leading to high death and disability rates.[2] In China, the occurrence rate of COPD varied between 1.20% and 8.87% across different cities.[3] COPD is regulated by the interaction of genetic and environmental factors, and exposures to tobacco and pollutants are considered as the pivotal risk environmental factors.[4,5] With the aggravation of air pollution, the morbidity of COPD shows increasing tendency, which is predicted as the third reason of deaths around the world by 2020.[2] COPD may gradually impair the immune lung defense system that makes the cases are more susceptible to infection, and bacterial infections represent a leading reason for acute exacerbation of COPD (AECOPD).[6] AECOPD is a key event for disease progression, intensive care unit (ICU) admission, medical costs and death among COPD patients.[7] Moreover, AECOPD may result in acute respiratory failure, leading to high disability and death rates. Ventilation is accepted as the first-line treatment for the patients with acute respiratory failure. Non-invasive positive pressure ventilation (NIPPV) has been proved to be a safe approach for treatment of respiratory failure among the COPD patients, and it can avoid trauma and infections.[8] However, the application standards for NIPPV in COPD are broad, and the abuse of NIPPV may result in some complications, including pneumothorax, hypotension, aspiration pneumonia and so on. Therefore, it is necessary to explore novel indicators for NIPPV treatment in COPD.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Respiratory and Critical Care Medicine, [b] Department of Specialist Care, Harrison International Peace Hospital, Hengshui, Hebei, China.

[*] Correspondence: Zhaobo Cui, Department of Respiratory and Critical Care Medicine, Harrison International Peace Hospital, Hengshui, Hebei, China (e-mail: pbjvwx@yeah.net).

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Bacterial infection has been reported to be responsible for about 50% of AECOPD.[9] Procalcitonin (PCT) is a glycoprotein composed by 116 amino acids, and secreted by the medullary C-glands of the thyroid.[10] Under normal physiological condition, serum PCT is nearly undetectable, but its circulating level is obviously increased with the presence of bacterial infections, moreover, its expression levels show mild changes under viral infection.[11,12] Therefore, serum PCT is considered as a promising biomarker for bacterial infection.[13] It has been reported that serum PCT was closely correlated with bacterial respiratory infection, which could guide antibiotic administration in AECOPD patients.[14] However, the predictive value of serum PCT for NIPPV treatment among AECOPD patients still remains unclear.

In this study, the predictive performance of serum PCT for NIPPV treatment in AECOPD was measured. The receiver operation characteristic (ROC) curve was plotted to obtain the cut-off value of serum PCT, which may further improve the NIPPV management among AECOPD patients.

2. Materials and methods

2.1. Study subjects

A total of 220 AECOPD cases who admitted the Respiratory general ward of our hospital between January 2017 and December 2017 were prospectively included in our study. All the patients signed the written informed consents. The study was approved by the Ethic committee of Harrison International Peace Hospital.

The inclusion criteria of the AECOPD cases were as follows:

1. The cases were diagnosed with COPD according to the gold guidelines,[15] with a ration of forced expiratory volume in the first second (FEV_1) to forced vital capacity less than 70% in post-bronchodilator spirometry, and with the presence of worse respiratory symptoms that beyond normal day-to-day changes, the cases were confirmed as AECOPD.
2. The patients were older than 40 years.

In addition, with the presence of the following conditions, the patients would be excluded:

1. pregnancy;
2. other lung disease, such as asthma, bronchiectasis, pneumonia, tuberculosis, etc;
3. other diseases that might influence serum PCT levels, such as septicemia, lung and extrapulmonary malignancies;
4. antibiotic treatment history before admission;
5. combined with other organ failures;
6. critical conditions that needed to be admitted to intensive ICU for endotracheal intubation;
7. poor therapy compliance.

2.2. Grouping

All the patients met the criteria of admission to the general respiratory ward in the acute exacerbation period of COPD. The patients were divided into NIPPV and control groups according to the routine standards and. The indications for NIPPV treatment were as follows:

1. moderate to severe dyspnea clinical characterized by respiratory distress, with respiratory rate (RR) > 24 times/min;
2. using the accessory respiratory muscles or paradoxical respiration;
3. abnormal blood gas [$pH < 7.35$, PCO_2 (partial pressure of carbon dioxide) >45mmHg, or oxygenation index<200 mmHg].

The two groups were matched in age and gender.

The baseline characteristics of the participants were collected from their medical records, regarding demographic characteristics, laboratory testing data, as well as the clinical characteristics, and complications.

2.3. Treatments

All the patients received routine treatments, including anti-infection treatments, anti-tussive and expectorant treatments, anti-asthmatic treatments and so on. In addition, NIPPV treatment was performed by BiPAP through nose mask. The breathing mode was S/T mode, and the minimum inspiratory pressure was set as 8mmHg, and the maximum was 20mmHg. The minimum inspiratory pressure was 4mmHg, and the maximum value was 12mmHg. The oxygen flow rate was 5 to 8 l/min, and the range of inhaled oxygen concentration was 35% to 60%. The ventilator was timely adjusted according to the vital signs, and the oxygen saturation was kept above 90%. The detection indicators were measured before and on the first, third and fifth day after treatment.

2.4. Laboratory tests

The lung function of the patients was measured by Master-Screen pulmonary function meter. Blood routine examinations were performed using automatic biochemical analyzer. Serum PCT detection was performed by chemiluminescence method, and the normal range of serum PCT was 0–1.5 ng/ml. Serum PCT >2.5 ng/ml indicated the positive bacterial infection. In brief, 2 ml fasting blood sample was collected from every patient, and centrifuged to isolate serum specimens. Then the detection was performed on the fully-auto chemiluminescence immunoassay (CLIA) analyzer Maglumi 1000 from Snibe Diagnostics following the operational introduction.

C-reaction protein (CRP) was measured by nephelometry assay, and the procedures were carried out following the recommendations of the manufacturer. The normal range of CRP was 0–3 mg/l, and the value more than 8 mg/l indicated the acute infection.

Blood gas analysis was achieved using ABL80FLEX CO-OX Analyzer (Radiometer medical Aps, USA).

2.5. Statistical analysis

The data analysis was performed using SPSS 18.0 software. The continuous data were expressed as mean ± standard deviation (SD), and their distributions were measured by Kolmogorov – Smirnov Z test. The comparisons of continuous data between two groups were performed by student's *t* test (normal distribution) or Mann – Whitney u test (non-normal distribution). The categorical variables were recorded as case number with percentages, and their comparisons were carried out by chi-square test. Logistic regression model was adopted to explore the risk factors for NIPPV treatment among AECOPE patients. The predictive values of serum PCT for NIPPV treatment in AECOPE patients were estimated through ROC curve. All the tests were two-tailed, and *P* values less than.05 indicated the statistical significance.

3. Results

3.1. Baseline characteristics of the study population

A total of 220 AECOPD cases were included in our study, including 115 males (52.27%) and 105 (47.73%) females, and their average age was 66.14 ± 9.92 years. The mean BMI value of the participants was 24.2 ± 1.94 kg/m^2. The COPD curse of the patients was 5.93 ± 1.53 years, and their mean AECOPD duration was 3.15 ± 2.01 days. The smoking index was 317.85 ± 167.31, and Glasgow Coma scale (GSC) score was 8.81 ± 3.33. 88 (40%) cases were diagnosed with hypertension, 89 (40.45%) cases were diabetes mellitus, and 90 (40.91%) cases were combined with coronary heart disease (CHD). The mean FEV_1/FVC was 48.2 ± 5.16, RR was 32.47 ± 4.91 beats/min, PaO_2 was 40.33 ± 6.25mmHg, $PaCO_2$ was 58.77 ± 12.79, oxygenation index was 186.44 ± 54.75 mmHg, and pH value was 7.25 ± 0.18. Laboratory tests suggested that the mean erythrocyte sedimentation rate (ESR) was 28.79 ± 3.07 mm/h, neutrophil was 77.6 ± 6.45%, white blood cell (WBC) was 10.14 ± 1.30 × 10^9/l, CRP value was 15.71 ± 7.45 mg/L, and PCT value was 165.14 ± 102.88ng/l. The baseline characteristics of the study subjects were summarized in Table 1.

3.2. The comparison between NIPPV and control groups

According to the therapeutic strategies, the patients were divided into NIPPV group (n = 121) and control group (n = 99). Statistical analyses demonstrated that NIPPV group and control group showed significant differences in RR (34.62 ± 3.20 vs. 29.85 ± 5.35, $P < .001$), PaO_2 (42.13 ± 6.22 vs. 38.13 ± 5.56, $P < .001$), $PaCO_2$ (64.60 ± 11.23 vs. 51.66 ± 10.87, $P < .001$), pH (7.20 ± 0.23 vs. 7.32 ± 0.06, $P < .001$), oxygenation index (162.16 ± 39.44 vs. 216.12 ± 56.35, $P < .001$), ESR (29.16 ± 2.85 vs. 28.33 ± 3.28, $P = .044$), neutrophil (79.58 ± 5.85 vs. 75.17 ± 6.34, $P < .001$), CRP (19.47 ± 7.43 vs. 11.11 ± 4.21, $P < .001$), and PCT (233.58 ± 85.78 vs. 81.48 ± 42.37, $P < .001$) (Fig. 1). Meanwhile, the two groups did not show obvious differences in gender ($P = .734$), age ($P = .270$), BMI ($P = .467$), COPD course ($P = .682$), AECOPD duration ($P = .121$), smoking index ($P = .155$), GSC score ($P = .060$), FEV_1/FVC (forced vital capacity) ($P = .166$), the occurrences of hypertension, diabetes mellitus, or CHD ($P > .05$ for all) (Table 1).

3.3. The related factors for NIPPV treatment among AECOPD patients

Logistic regression model was adopted to identify the independently related factors for NIPPV treatment among AECOPD patients. The results suggested that PCT (OR = 1.035, 95%CI: 1.017–1.053, $P < .001$), CRP (OR = 1.170, 95%CI: 1.013–1.351, $P = .033$), $PaCO_2$ (OR = 1.170, 95%CI: 1.054–1.300, $P = .003$), RR (OR = 1.396, 95%CI: 1.074–1.814, $P = .013$), and neutrophil (OR = 1.154, 95%CI: 1.004–1.327, $P = .043$) were independently correlated with NIPPV treatment in the patients diagnosed with AECOPD (Table 2).

3.4. The predictive value of the indicators for NIPPV treatment in AECOPD patients

In order to estimate the values of the independent factors for NIPPV prediction in AECOPD cases, ROC analyses were performed. As displayed in Figure 2, all the independent factors could be used for prediction of NIPPV treatment. The area under the curve (AUC) value, sensitivity, specificity and cut-off values of

Table 1

Baseline characteristics of the study subjects.

Characteristics	Total	NIPPV group	Control group	P
Case number	220	121	99	
Gender				.734
Male	115 (52.27%)	62 (51.24%)	53 (53.54%)	
Female	105 (47.73%)	59 (48.76%)	46 (46.46%)	
Age (year)	66.14 ± 9.92	66.81 ± 9.86	65.32 ± 9.98	.270
BMI (kg/m^2)	24.2 ± 1.94	24.11 ± 1.97	24.3 ± 1.90	.467
COPD course (year)	5.93 ± 1.53	5.89 ± 1.63	5.98 ± 1.40	.682
AECOPD duration (day)	3.15 ± 2.01	3.34 ± 2.22	2.92 ± 1.71	.121
Smoking index	317.85 ± 167.31	303.33 ± 164.41	335.60 ± 169.94	.155
GSC score	8.81 ± 3.33	9.19 ± 3.48	8.34 ± 3.08	.060
Hypertension	88 (40%)	43 (35.54%)	45 (45.45%)	.135
Diabetes mellitus	89 (40.45%)	45 (37.19%)	44 (44.44%)	.275
CHD	90 (40.91%)	53 (43.8%)	37 (37.37%)	.335
FEV_1/FVC (%)	48.20 ± 5.16	48.64 ± 5.10	47.67 ± 5.20	.166
RR (beats/min)	32.47 ± 4.91	34.62 ± 3.20	29.85 ± 5.35	<.001
PaO_2 (mmHg)	40.33 ± 6.25	42.13 ± 6.22	38.13 ± 5.56	<.001
$PaCO_2$ (mm Hg)	58.77 ± 12.79	64.60 ± 11.23	51.66 ± 10.87	<.001
pH	7.25 ± 0.18	7.20 ± 0.23	7.32 ± 0.06	<.001
Oxygenation index (mmHg)	186.44 ± 54.75	162.16 ± 39.44	216.12 ± 56.35	<.001
ESR (mm/h)	28.79 ± 3.07	29.16 ± 2.85	28.33 ± 3.28	.044
Neutrophil (%)	77.6 ± 6.45	79.58 ± 5.85	75.17 ± 6.34	<.001
WBC (×10^9/L)	10.14 ± 1.30	10.02 ± 1.32	10.27 ± 1.27	.160
CRP (mg/L)	15.71 ± 7.45	19.47 ± 7.43	11.11 ± 4.21	<.001
PCT (ng/l)	165.14 ± 102.88	233.58 ± 85.75	81.48 ± 42.37	<.001

Notes: AECOPD = acute exacerbation of chronic obstructive pulmonary disease, BMI = body mass index, CHD = Coronary heart disease, COPD = chronic obstructive pulmonary disease, CRP = c-reaction protein, ESR = erythrocyte sedimentation rate, GCS = Glasgow Coma scale, PCT = procalcitonin, RR = Respiratory rate.

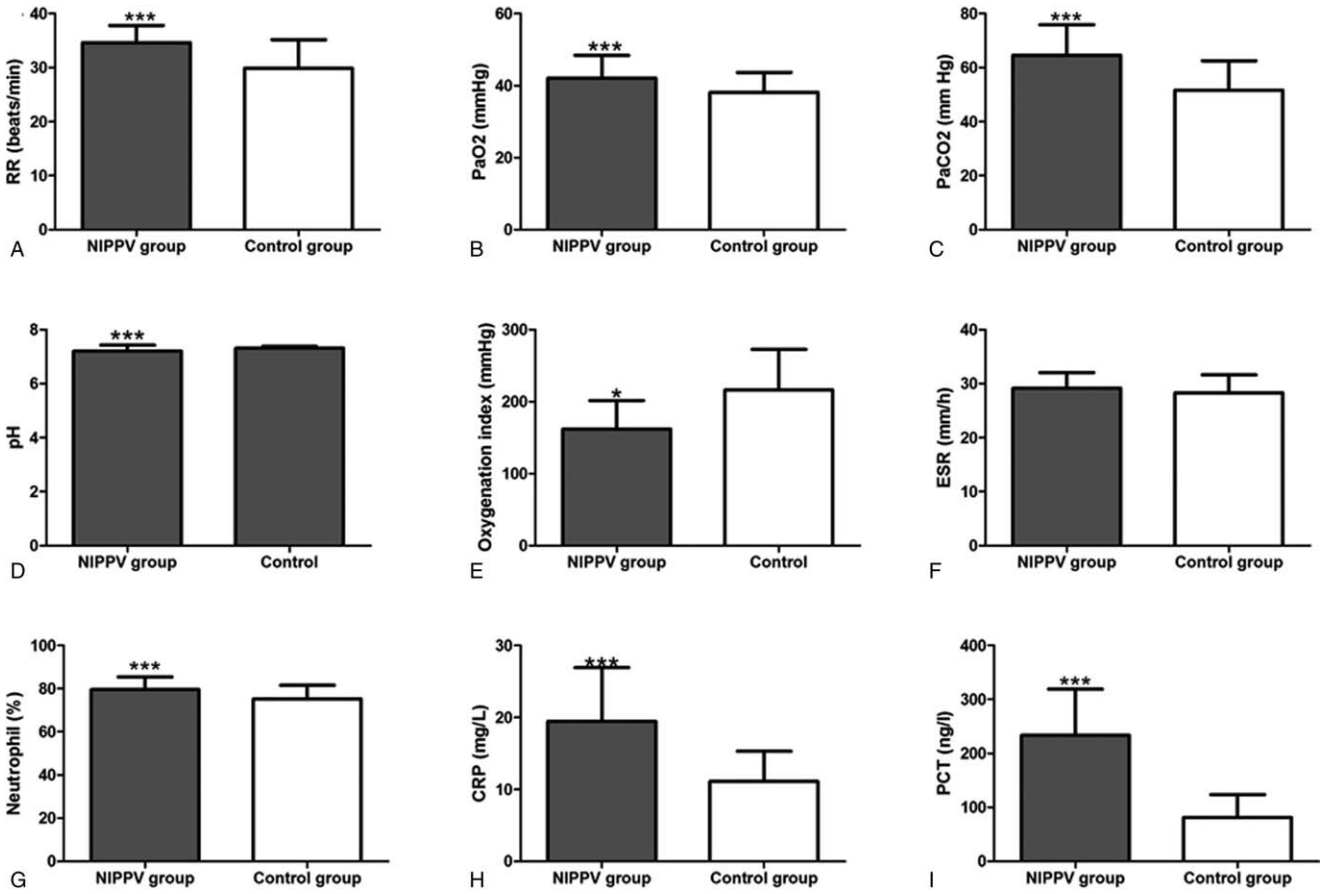

Figure 1. The comparisons of RR, $PaCO_2$, pH, oxygenation index, ESR, neutrophil, CRP, and PCT between NIPPV and control groups.

the factors were shown in Table 3. Compared to other factors, PCT showed superior predictive value, with the AUC value of 0.899, the sensitivity of 86%, and the specificity of 91.9%. The cut-off value of serum PCT for NIPPV prediction was 88.50 ng/l.

4. Discussion

COPD is a frequently diagnosed chronic disease, with high mortality and morbidity. AECOPD refers the acute situation of COPD featured by the worsening of the patient's respiratory symptoms.[16] Bacterial infection is a leading reason for AECOPD, and antibiotic treatment is necessary for the patients. In addition to antibacterial treatment, the appropriate NIPPV treatment could shorten the hospitalization time, improve the pain, and reduce the need of endotracheal intubation.[17]

Table 2

The independent related factors for NIPPV treatment among AECOPD patients.

Variables	OR	95%CI	*P*
PCT	1.035	1.017–1.053	<.001
CRP	1.170	1.013–1.351	.033
$PaCO_2$	1.170	1.054–1.300	.003
RR	1.396	1.074–1.814	.013
Neutrophil	1.154	1.004–1.327	.043

However, there are no credible indicators for application of NIPPV among AECOPD patients. In this study, we estimated the predictive value of serum PCT for NIPPV treatment in AECOPD patients. The results suggested that serum PCT levels were significantly different between the cases in NIPPV group and control group. Serum PCT was independently correlated with NIPPV treatment, which might be employed as an indicator for NIPPV treatment in AECOPD patients. The results were consistent with this study conducted by Pazarli et al In their study, PCT level was also confirmed as a predictor to determine the necessary of NIPPV treatment in AECOPD patients.[18]

For COPD patients, the long-term airflow obstruction could impair their immune lung defense systems, which make the patients are more easily to be infected by bacteria, leading to AECOPD.[19] Bacterial infection and inflammation play important roles in progression of AECOPD. Circulating PCT level is considered to be a specific indicator for bacterial infection, and its levels are closely correlated with infection severity.[20] In the present study, 220 AECOPD patients were divided into NIPPV group and control group according to the routine standards and physicians' experience. The comparison analysis suggested that compared to those in control group, the individuals in NIPPV group were more likely to show high RR, PaO_2, $PaCO_2$, ESR, neutrophil, CRP and PCT levels, as well as low pH and oxygenation index. All the results demonstrated the aggressive inflammation, severe infection, and poor pulmonary function of NIPPV cases. Logistic regression analysis suggested that PCT,

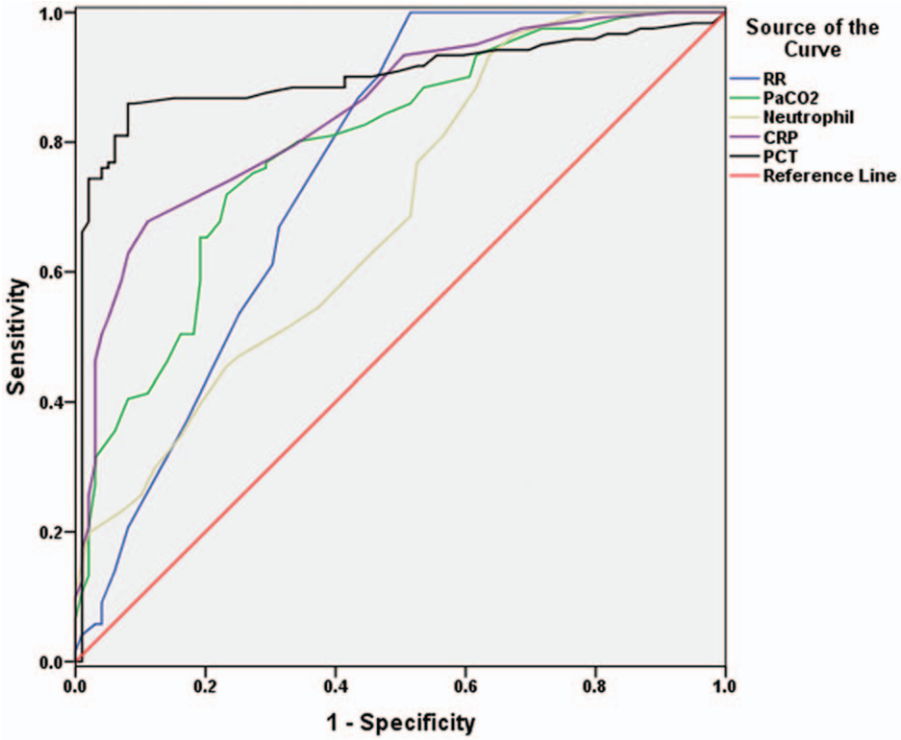

Figure 2. ROC curves were plotted to estimate the predictive values of PCT, RR, $PaCO_2$, CRP and neutrophil for NIPPV treatment among the patients with AECOPD.

CRP, $PaCO_2$, RR, and neutrophil were independently correlated with NIPPV treatment in AECOPD. The study carried out by Sarika et al suggested that PCT level was significantly elevated in AECOPD patients, compared to stable COPD patients.[21] Hamid Borsi et al reported that serum PCT might be employed as a biomarker for the differentiation of AECOPD patients from stable COPD patients.[22] All the data revealed the close relationship between serum PCT and COPD progression.

The appropriate application of NIPPV treatment could help improve the clinical prognosis of AECOPD patients, but the abuse of NIPPV may lead to some serious complications, such as pneumothorax, hypotension, aspiration pneumonia, and so on.[23,24] Therefore, the specific indicators are necessary to guide NIPPV treatment in AECOPD patients. In our study, ROC curve demonstrated that PCT, CRP, $PaCO_2$, RR, and neutrophil could distinguish between NIPPV group and control group. Moreover, compared to other indicators, PCT showed superior values, with better AUC, sensitivity and specificity. Serum PCT might be adopted as an indicator to guide NIPPV treatment among AECOPD patients. Serum PCT had been confirmed as an indicator for antibiotic treatment of AECOPD. A meta-analysis carried out by Li et al demonstrated that the antibiotic treatment guided by PCT showed similar efficacy and safety with standard antibiotic treatment, and has fewer antibiotic prescriptions.[25] Moreover, the AECOPD patients with high serum PCT levels were more likely to undergo NIPPV failure.[26] The present study might be the first study to explore the predictive value of serum PCT for NIPPV treatment in COPD patients.

Several limitations in present study should be stated. Firstly, the sample size was relatively small that might reduce the statistical power of our analysis. Secondly, due to the selection criteria, the selection bias might be introduced, and the conclusion was limited by the studied subjects. Thirdly, NIPPV treatment was performed based on routine standards and the physicians' experience that might influence the analysis results. Therefore, the well-designed prospective studies with large sample size are required to improve our analysis.

In conclusion, AECOPD patients who require NIPPV treatment frequently have high levels of PCT, CRP, $PaCO_2$, RR and neutrophil. Serum PCT may be employed as an indicator for NIPPV treatment in AECOPD patients, and the cut-off value was 88.50 ng/l.

Table 3

ROC analysis for the identified factors of NIPPV treatment.

Variables	AUC	Sensitivity	Specificity	Cut-off value
RR (beats/min)	0.759	100%	48.5%	29.50
$PaCO_2$ (mm Hg)	0.793	71.9%	76.8%	57.50
Neutrophil (%)	0.687	93.4%	36.4%	71.50
CRP (mg/L)	0.847	67.8%	88.9%	14.50
Serum PCT (ng/l)	0.899	86%	91.9%	88.50

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Author contributions

Conceptualization: Linlin Liu.
Data curation: Linlin Liu.

Formal analysis: Ying Luan.
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Methodology: Ling Xiao.
Project administration: Ning Wang.
Resources: Ning Wang.
Software: Jing Wang.
Supervision: Jing Wang.
Validation: Zhaobo Cui.
Visualization: Zhaobo Cui.
Writing – original draft: Zhaobo Cui.

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