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 with 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/L 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.[1–5] 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. PCT levels increase rapidly during infection and are correlated with severity of illness, making PCT an ideal biomarker for bacterial infection. 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. A recent approach that holds considerate promise is serum PCT measurement. PCT is liberated into circulation of patients in response to severe systemic inflammation, in particular by bacterial infection. Sedimentation rate, CRP, white blood cells, and neutrophils were also analyzed. PCT levels and arterial blood gas (ABG) analysis, erythrocyte sedimentation rate, CRP, white blood cells, and neutrophils were also examined for this purpose, but found to lack sensitivity and specificity. Some studies showed that serum PCT could effectively discriminate bacterial infection from viral or other inflammatory pulmonary conditions.

Some studies have demonstrated that mean PCT levels are increased in patients with severe AECOPD and receiving NIV, and that PCT levels were associated with a higher rate of admission to the ICU. 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. PCT levels have been associated with severity of respiratory failure and were higher in hospitalized patients receiving NIV compared with those treated without NIV. 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 PaCO₂ 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. Hence, the estimated sample size was 20 patients.

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 PaCO₂ ≥ 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.

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, bronchiectasis, pneumonia, or tuberculosis); patients with sepsis or any cancer; unable to tolerate NIV; 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; 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. The assessment of exacerbated symptoms was based on the patients’ medical history, clinical signs of severity, and laboratory tests.

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. Invasive mechanical ventilation (IMV) was provided if NIV failed. Since 6.5% of the NIV failures occur during the first 48 hours of NIV, 48 hours was selected as the study cut off.

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. 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; the results were presented as odds ratios (OR) and 95% confidence interval (95% CI). The OR indicates that one
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. PaCO2, 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, and PaCO2 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 PaCO2 (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 PaCO2 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 PaCO2 (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 PaCO2. The AUC for the combination of PCT, CRP, and PaCO2 was 0.978 (95% CI: 0.961 – 0.995).

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Table 1

| 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 |
| FEV1/FVC (%) | 48.58 ± 8.08 | 50.00 ± 8.98 | .16 |
| GOLD stage, n (%) | — | — | .40 |
| Mild | 90 (31.9) | 30 (33.3) | — |
| Moderate | 85 (29.7) | 30 (33.3) | — |
| Very severe | 46 (16.1) | 8 (8.9) | — |
| Smoking history (pack-year) | 44 ± 15 | 42 ± 11 | .24 |
| Body mass index, kg/m² | 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 | 30.48 ± 16.77 | < .001 |
| White blood cells (>10³/μL) | 9.90 ± 4.83 | 8.97 ± 3.90 | .10 |
| pH | 7.18 ± 0.06 | 7.12 ± 0.08 | < .001 |
| PaCO2, 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, PaCO2 = partial pressure of carbon dioxide.

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Table 2

| 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 × PaCO2 | 0.104 | .17 |

CRP = serum C-reactive protein, ESR = erythrocyte sedimentation rate, NET = serum neutrophil, PCT = procalcitonin, WBC = serum white blood cell.
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 PaCO2 in patients with AECOPD with NIV failure or success. The results first showed that high serum PCT, CRP, and PaCO2 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[33] reported that systemic biomarkers were not helpful in predicting the severity of AECOPD. In the present study, serum PCT levels, CRP levels, and PaCO2 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, 0.963–0.995), 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 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 PaCO2 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

| Table 3 | Logistic regression analysis to predict noninvasive mechanical ventilation failure. |
|---------|----------------------------------|
| Variables | P | OR | 95%CI |
| PCT     | .006 | 2.0 | 1.2–5.2 |
| PaCO2   | <.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, PaCO2 = partial pressure of carbon dioxide, PCT = procalcitonin.

| Table 4 | 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 (90.46–90.66) |
| 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) |
| PaCO2   | 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, PaCO2 = 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, and PCT levels are not related to the presence of bacteria in the sputum. 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, PaCO₂, and CRP levels, and lower pH compared with patients with NIV success. Serum PCT, CRP, and PaCO₂ were independently associated with NIV failure. High serum PCT levels (≥0.31 ng/mL), CRP levels (≥15.0 mg/L), and PaCO₂ (≥73.5 mm Hg) predicted NIV failure in patients with AECOPD, and the combination of these three parameters might enable even more accurate prediction.

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References
[1] Moretti M, Caliote C, Tampieri A, et al. Incidence and causes of noninvasive mechanical ventilation failure after initial success. Thorax 2000;55:819–25.
[2] Demoule A, Girou E, Richard JC, et al. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med 2006;32:1756–65.
[3] Conti G, Antonelli M, Navalese P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. Intensive Care Med 2002;28:1701–7.
[4] Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. Respir Care 2003;50:610–6.
[5] Celikel T, Sungur M, Ceyhan B, et al. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. Chest 1998;114:1636–42.
[6] Ozyilmaz E, Ugurlu AO, Nava S. Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med 2014;14:119.
[7] Nava S, Ceriana P. Causes of failure of noninvasive mechanical ventilation. Respir Care 2004;49:295–303.
[8] Rennhert K, Messmer M. Biomarkers in the critically ill patient: procalcitonin. Crit Care Clin 2011;27:253–63.
[9] Vijayan AL, Vaninayama R, Ravindran S, et al. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. J Intensive Care 2017;5:51.
[10] Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008;359:2355–65.
[11] Lacoma A, Prat C, Andreu F, et al. Value of procalcitonin, C-reactive protein, and neopterin in exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011;6:157–69.
[12] Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol 2018;9:754.
[13] van der Meer V, Neven AK, van den Broek PJ, et al. Diagnostic value of C-reactive protein in infections of the lower respiratory tract: systematic review. BMJ 2005;331:26.
[14] Fowler CL. Procalcitonin for triage of patients with respiratory tract symptoms: a case study in the trial design process for approval of a new diagnostic test for lower respiratory tract infections. Clin Infect Dis 2011;52 Suppl 4:S351–56.
[15] Pazarli AC, Koseoglu HI, Doruk S, et al. Procalcitonin: Is it a predictor of noninvasive positive pressure ventilation necessity in acute chronic obstructive pulmonary disease exacerbation? J Respir Med 2012;17:1047–51.
[16] Stolz D, Christ-Crain M, Morgenhalter NG, et al. Copeptin, C-reactive protein, and procalcitonin as prognostic biomarkers in acute exacerbation of COPD. CHEST 2007;131:1038–47.
[17] Rammaert B, Verduer N, Cavestri B, et al. Procalcitonin as a prognostic factor in severe acute exacerbation of chronic obstructive pulmonary disease. Respirology 2009;14:969–74.
[18] Noordzij M, Dekker FW, Zoccali C, et al. Sample size calculations. Nephrol Clin Pract 2011;118:319–323.
[19] Vensio J, Hard SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347–63.
[20] Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;163:3.
[21] Daniels JM, Schoof M, Snijders D, et al. Procalcitonin vs C-reactive protein as predictive markers of response to antibiotic therapy in acute exacerbations of COPD. CHEST 2010;138:1108–15.
[22] Scala R, Naldi M, Maccari U. Early fiberoptic bronchoscopy during noninvasive ventilation in patients with decompensated chronic obstructive pulmonary disease due to community-acquired pneumonia. Crit Care 2010;14:R80.
[23] Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. Ann Transl Med 2016;4:91.
[24] Zhang Z. Model building strategy for logistic regression: purposeful selection. Ann Transl Med 2016;4:1111.
[25] Hammer GP, du Pre LJB, Blatter M. Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. Dtsch Arztebl Int 2009;106:664–8.
[26] Hurst JR, Donaldson GC, Ferera WR, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006;174:867–74.
[27] Gallego M, Pomares X, Capilla S, et al. C-reactive protein in outpatients with acute exacerbation of COPD: its relationship with microbial etiology and severity. Int J Chron Obstruct Pulmon Dis 2016;11:2633–40.
[28] Bircan A, Gokirmak M, Kilic O, et al. C-reactive protein levels in patients with chronic obstructive pulmonary disease: role of infection. Med Princ Pract 2008;17:202–8.
[29] Tarnawski D, Blum B, Auer M, et al. Procalcitonin and C-reactive protein levels in predicting bacterial infection in hospitalized patients with acute exacerbations of COPD. Wien Klin Wochenschr 2013;125:71–8.
[30] Rafaeldel M, Clark TW, Reid C, et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. CHEST 2011;139:1410–8.
[31] Polzin A, Petz M, Erbes R, et al. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. Eur Respir J 2003;21:939–43.
[32] Daubin C, Parienti J-J, Vabret A, et al. Procalcitonin levels in acute exacerbation of COPD admitted in ICU: a prospective cohort study. BMC Infect Dis 2008;8:145.

[33] Fan L, Zhao Q, Liu Y, et al. Semiquantitative cough strength score and associated outcomes in noninvasive positive pressure ventilation patients with acute exacerbation of chronic obstructive pulmonary disease. Respir Med 2014;108:1801-7.

[34] Carlucci A, Richard JC, Wysocki M, et al. Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. Am J Respir Crit Care Med 2001;163:874-80.

[35] Miller D, Fraser K, Murray I, et al. Predicting survival following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease. Int J Clin Pract 2012;66:434-7.

[36] Crummy F, Buchan C, Miller B, et al. The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. Respir Med 2007;101:53-61.

[37] Ambrosino N, Foglio K, Rubini F, et al. Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 1995;50:755-7.

[38] Confalonieri M, Garuti G, Cattaruzza MS, et al. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur Respir J 2005;25:348-55.

[39] Sapey E, Stockley R. COPD exacerbations 2: aetiology. Thorax 2006;61:250-8.