Optimized Combination of Circulating Biomarkers as Predictors of Prognosis in AECOPD Patients Complicated with Heart Failure

Can Yao  
Shenzhen People's Hospital

Lingwei Wang  
Shenzhen People's Hospital

Fei Shi (shi.fei@szhospital.com)  
Shenzhen People's Hospital  https://orcid.org/0000-0002-9082-9140

Rongchang Chen  
Shenzhen People's Hospital

Binbin Li  
Shenzhen People's Hospital

Wenwen Liu  
Shenzhen People's Hospital

Mengjie Feng  
Shenzhen People's Hospital

Sinian Li  
Shenzhen People's Hospital

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Abstract

Background

Systematic inflammation, nutritional status, and cardiovascular function have been associated with the outcomes of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients with heart failure (HF). However, the value of their relevant biomarkers in predicting mortality has not been well defined yet. We aimed to investigate the prognostic value of circulating biomarkers including C-reaction protein (CRP) /albumin (ALB), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and N-terminal pro-brain natriuretic peptide (NT-proBNP) for AECOPD patients with HF.

Methods

A total of 146 cases of AECOPD complicated with HF were enrolled and classified into survivor group (n=94) and non-survivor group (n=52). The baseline characteristics and blood-based biomarkers were collected. The predictors for prognosis were analyzed by multivariate logistic regression, and the ability to predict 28-day mortality was evaluated by receiver operating characteristics curve (ROC) and the area under the curve (AUC).

Results

The patients in non-survivors had significantly higher levels of CRP, CRP/ALB, NLR, PCT and NT-proBNP, but lower ALB levels compared to the survivors [145.8±110.1 VS. 66.6±70.2mg/L, 5.9±4.9 VS. 2.3±2.6, 22.2 (11.1, 40.1) VS. 12.0 (6.2, 24.8), 2.6 (0.2, 10.3) VS. 0.08 (0.1, 0.5)ng/ml, 17912.5 (9344.0, 34344.5) VS. 9809.0 (4415.9, 16387.2)ng/ml, 26.8±6.4 VS. 31.0±4.6g/L; \( P < 0.001, <0.001, 0.001, <0.001, <0.001, <0.001, \) and < 0.001, respectively]. No significant difference in PLR was found between the two groups (\( P=0.413 \)). The logistic analysis revealed that CRP/ALB (OR=1.303, 95%CI: 1.145-1.483, \( P<0.001 \)), NT-proBNP (OR=1.041, 95%CI: 1.010-1.073, \( P=0.009 \)) and NLR (OR=1.010, 95%CI: 0.999-1.022, \( P<0.001 \)) are independent risk factors for predicting the 28-day mortality. The AUC of the ROC curves were 0.768, 0.767, 0.757, 0.723, 0.716, and 0.668 for CRP/ALB, PCT, CRP, NT-proBNP, ALB, and NLR, respectively. The combination of CRP/ALB, NLR and NT-proBNP as biomarkers was shown to have better accuracy for predicting prognosis (AUC=0.830, 95%CI: 0.761-0.899, \( P<0.001 \)), with a higher specificity of 80.8% and specificity of 77.7% as compared with each single biomarkers.

Conclusions

High levels of NLR, CRP/ALB and NT-proBNP may be clinical usefully predictors for death in AECOPD patients with HF. Combination of NLR with CRP/ALB and NT-proBNP can provide a higher accuracy for predicting 28-day mortality in these patients.

Background
Chronic Obstructive Pulmonary Disease (COPD), a common and progressive lung disease, is characterized by persistent respiratory symptoms and airflow limitation. COPD is currently a major cause of mortality and morbidity worldwide, and is estimated to become the third leading cause of death by 2020.\textsuperscript{1} Acute exacerbation of COPD (AECOPD) is the most common cause of increasing hospitalization rate, and accounts for increasing death among patients with COPD.\textsuperscript{2,3} Meanwhile, heart failure (HF) is one of the most critical comorbidities in patients with AECOPD. It was reported that the prevalence of COPD patients with systolic or diastolic HF ranges from 20 to 70\%, which is associated with higher incidence of hospitalization and mortality compared to patients without HF.\textsuperscript{2,4} Therefore, early identification of patients with poor prognosis is very critical to the optimization of personalized therapies. Circulating biomarkers, which are easily accessible from peripheral blood, might provide important information for clinical decision, but their roles in predicting prognosis in AECOPD complicated with HF has not been well be defined yet.

It has been recognized that systematic inflammation, nutritional status, and cardiovascular function play essential roles in the development of AECOPD.\textsuperscript{5-7} N-terminal pro-brain natriuretic peptide (NT-proBNP) is a well-established biomarker in determining diagnosis and prognosis in HF \textsuperscript{6,7}, and has also been found to be increased in AECOPD with or without HF\textsuperscript{8,9}. In addition, several novel inflammatory markers, such as C-reactive protein (CRP) / albumin (ALB) ratio, neutrophil–lymphocyte ratio (NLR), and platelet–lymphocyte ratio (PLR) have also been recently used for monitoring of inflammatory conditions. CRP is one of the non-specific proteins that represent systemic inflammation, while a low ALB level may reflect a temporary condition that requires medical intervention. It has been shown that CRP/ALB ratio can be used as a long-term marker of prognosis in septic patients, and provides more stable information than CRP or ALB alone.\textsuperscript{10} Moreover, both NLR and PLR are proved to play an important role in outcome prediction and prognosis of COPD patients and HF patients respectively.\textsuperscript{3,6-9} However, the prognostic value of these indicators in AECOPD patients with HF are still uncertain. This study aimed to demonstrate the utility of circulating biomarkers including CRP/ALB ratio, NLR, PLR, and NT-proBNP in predicting prognosis in AECOPD patients with HF.

**Methods**

**Patients and study design**

A total of 146 patients hospitalized for AECOPD complicated with HF was consecutively collected from January 1, 2013 to January 31, 2019. Demographic and medical data were retrospectively obtained from electronic patient records and paper notes of Shenzhen Institute of Respiratory Diseases, the Second Clinical College of Jinan University in Shenzhen, China. The study protocol (LL-KY-201932) was approved by the Ethics Committee of the Second Clinical College of Jinan University. Requirement for patient consent was waived.

Patients with COPD were identified by International Classification of Diseases, Tenth Revision (ICD-10) principal diagnosis codes J44.900; exacerbations were defined as cases’ hospitalized with the
code J44.100 and J44.101 as a main reason for admission; HF was identified by the codes I50.000, I50.001, I50.002, I50.100, I50.101, I50.102, I50.103, I50.907, and I50.900. We obtained data regarding baseline demographics, staging of COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD), laboratory parameters, chest radiographs, and echocardiograms at the time of admission.

The inclusion criteria was as follows: 1) diagnosis of AECOPD, defined as an acute worsening of respiratory symptoms that lead to need additional therapy; 2) HF occurred during the hospitalization and the diagnosis of HF was in accordance with the 2016 ESC Guidelines. We excluded patients with any of the following characteristics: asthma, pneumonia, pulmonary thromboembolism (PTE), tuberculosis, acute respiratory distress syndrome, rheumatic diseases, cancer, valvular heart disease, and acute myocardial infarction. We also excluded patients who died in the emergency room because the measurements were not available for these patients. More details were shown in the Figure 1.

**Data collection**

We collected clinical data and laboratory indexes of all subjects including age, sex, smoking status, comorbidities, left ventricular ejection fraction (LVEF), history of exacerbation, GOLD grade, COPD assessment test (CAT) score, length of stay (LOS) in hospital, LOS in ICU, probability of endotracheal intubation, the initial value of ALB and the New York Heart Association (NYHA) functional classification. Serum CRP levels, PCT levels, NT-proBNP levels and routine blood test results including neutrophils, lymphocytes and platelets were obtained within 2 hours of admission to the hospital.

**Outcomes**

Our primary outcome is 28-day mortality. It was assessed both from the medical records and phone calls. All the adverse events were adjudicated by clinicians. All the patients were divided into survivors group (n=94) and non-survivors group (n=52) according to their survival conditions.

**Statistical analysis**

Statistical Package for Social Sciences (SPSS), version 13.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Measurement data from normal distribution was expressed as the mean ± standard deviation and independent-samples t test was used to assess significant differences. Non-normally distributed continuous data was expressed as the median (interquartile range, IQR), and two-sample Wilcoxon Rank Sum test was used to analyze. Chi-square test or Fisher’s exact test was for categorical variables. Multivariate logistic regression analysis was used to check the independent correlation factors. Receiver operating characteristic (ROC) curves were generated to evaluate the biomarkers for predicting the mortality hazard. The Youden index was used to determine the optimal cutoffs of variables including CRP/ALB, NLR, and NT-proBNP. The combination tests based on logistic models were performed to assess the prognostic performance of biomarker combinations. A P value of less than 0.05 (P<0.05) was considered as a statistically significant difference.
Results

Baseline characteristics

A total of 146 AECOPD patients complicated with HF were included in this analysis. The number of all patients with NYHA class II, III or IV were 29, 71 and 46, and GOLD grade 2, 3, or 4 were 41, 85 and 20, respectively. The baseline characteristics of the survivors and non-survivors are shown in Table 1. The mean age of the study patients was 79.17±9.56 years, 75% were male. However, there was no significant difference in age, gender, smoking status, complications, GOLD grade, baseline CAT score, LVEF and median hospital LOS, between the two groups. Among the 52 non-survivors, 38 (73%) needed for endotracheal intubation. Non-survivors were more likely to be in NYHA III – IV (Non-survivors VS. Survivors: 96.2% VS. 71.3%, \( P < 0.001 \)), have a longer median ICU LOS (Non-survivors VS. Survivors: 5 VS. 1 day, \( P < 0.001 \)), and have a higher probability of endotracheal intubation (Non-survivors VS. Survivors: 73% VS. 18%, \( P < 0.001 \)).

Biomarker Levels and outcomes

The comparison of laboratory indexes between the two groups was shown in table 2. The patients who survived in hospital had lower levels of serum CRP (survivors VS. non-survivors: 66.6±70.2 VS. 145.8±110.1mg/L, \( P < 0.001 \)), CRP/ALB (survivors VS. non-survivors: 2.3±2.6 VS. 5.9±4.9, \( P < 0.001 \)), NLR [survivors VS. non-survivors: 12.0 (6.2, 24.8) VS. 22.2 (11.1, 40.1), \( P = 0.001 \)], serum PCT [survivors VS. non-survivors: 0.08 (0.1, 0.5) VS. 2.6 (0.2, 10.3) ng/ml, \( P < 0.001 \)], and serum NT-proBNP [survivors VS. non-survivors: 9809.0 (4415.9, 16387.2) VS. 17912.5 (9344.0, 34344.5) ng/ml, \( P < 0.001 \)]. There were no differences in PLR between survivors and non-survivors (survivors VS. non-survivors: 311.9±253.1 VS. 346.8±326.4, \( P = 0.474 \)). We also noted that the patients who survived had higher ALB levels than the patients who died (31.0±4.6 VS. 26.8±6.4g/L, \( P < 0.001 \)). The multivariate logistic analysis suggested that CRP/ALB (OR = 1.303; 95% CI: 1.145-1.483; \( P = 0.001 \)), NT-proBNP (OR = 1.041; 95% CI: 1.010-1.073; \( P = 0.009 \)) and NLR (OR = 1.010; 95% CI: 0.999-1.022; \( P = 0.001 \)) can be independent risk factors for predicting the mortality of included subjects. More details in both groups were shown in table 2 and 3.

Predictive ability of biomarkers

To investigate the predictive abilities of biomarkers, ROC curve analysis was constructed (Table 4 and Figure 2). The AUC of CRP/ALB (AUC 0.768, 95% CI 0.684-0.850, \( P < 0.001 \)) was much greater than other single biomarkers. The optimal cutoff value for CRP/ALB was 2.48, with sensitivity of 73.1%, and specificity of 64.9%; 16.83 for NLR with 69.2% sensitivity and 64.9% specificity (AUC 0.668, 95% CI 0.577-0.759, \( P = 0.001 \)); 0.59 for PCT with 67.3% sensitivity and 80.9% specificity (AUC 0.767, 95% CI 0.684-0.850, \( P < 0.001 \)); and 14265.25 for NT-proBNP with 63.5% sensitivity and 72.3% specificity (AUC 0.723, 95% CI 0.637-0.809, \( P < 0.001 \)). We further investigated the prognostic value of different biomarker combinations: combining CRP/ALB with NT-proBNP increased predictive sensitivity (75.0%) and specificity (83.0%), with AUC of 0.821 (95% CI 0.751-0.892, \( P < 0.001 \)). The predictive value of any two biomarker combinations was accurate with a sensitivity less than 80%. Notably, ROC curve analysis
revealed, that the prediction of 28-day mortality was improved markedly by the combination of CRP/ALB, NLR, and NT-proBNP (sensitivity 80.8%, specificity 77.7%), with the best AUC of 0.830 obtained (95% CI 0.761-0.899, $P < 0.001$). The predictive accuracy of other single marker or a marker combination is listed in Table 4.

Discussion

In this study, we showed the better performance of combined circulating biomarkers in predicting mortality in AECOPD patients with HF. To our knowledge and by searching Pubmed, this study is the first report on using multiple blood-based biomarkers related to systematic inflammation, nutritional status, and cardiovascular function to predict mortality in AECOPD patients with HF. Our results revealed that AECOPD patients with HF who died had significantly higher levels of CRP/ALB, NLR, NT-proBNP, and higher NYHA functional classification compared with patients who survived. Furthermore, the combination of CRP/ALB, NLR, and NT-proBNP could potentially be used to predict 28-day mortality in AECOPD patients with HF.

Previous studies have shown that CRP could be used as an independent influencing factor to evaluate the control level of COPD chronic inflammation in patients,\textsuperscript{12-14} while ALB is a prognostic marker of infection-related disease.\textsuperscript{15} Our study observed that high CRP and PCT levels as well as low ALB level were associated with death in AECOPD patients with HF. This data confirmed that non-survivors have more severe systematic inflammatory response and lower nutrient intake than survivors. Although CRP and ALB have good prognostic significance for AECOPD patients, the early inflammatory response and nutritional status of the body may not change in equal proportion. Therefore, CRP/ALB ratio has been recently identified as a valuable predictor of prognosis in patients with various diseases such as tumor and sepsis,\textsuperscript{10,15,16} whereas its prognostic role remains unclear in AECOPD patients with HF. In our study, we showed that CRP/ALB ratio was significantly higher in non-survivors than in survivors ($P < 0.001$). The sensitivity and specificity of CRP/ALB ratio were 73.1% and 64.9% in predicting 28-day mortality when its cut-off value was 2.48. It showed that low-grade systemic inflammation and poor nutrition may play an essential role in leading to aggravation of disease. Furthermore, CRP/ALB ratio was proved as an independent risk predictor for the prognosis of AECOPD patients with HF in this study.

NT-proBNP is an important biomarker in the diagnosis of HF, and represents a novel indicator that identifies the risks of COPD exacerbation. In our study, we observed NT-proBNP level and NYHA functional classification were significantly higher in the non-survivors. Though, LVEF was similar between the two groups. Our finding also suggested that NT-proBNP is an independent death risk factor in AECOPD patients with HF. This result may be in favor of the results of previous studies.\textsuperscript{17,18} Moreover, our study demonstrated that NT-proBNP level is significantly associated with 28-day mortality, but its relevance to mortality is inferior to that of CRP/ALB. It suggested that dynamic detection of NT-proBNP levels may be helpful in predicting the prognosis of AECOPD patients with HF, while the cardiovascular functions cannot better assess patients’ mortality as compared with other factors such as systematic inflammation and nutrition.
We found that elevated NLR is also a strong predictor of poor outcomes in AECOPD patients with HF. In consistent with our findings, the range of NLR levels have been determined in COPD patients with different conditions (eg. acute respiratory failure, chronic respiratory failure, and existence of pneumonia) in previous studies. Furthermore, our study suggest higher NLR is related to 28-day mortality in AECOPD patients with HF. It is worth noting that the cut-off value of 16.83 for NLR was nearly two times higher in the AECOPD subjects with HF than in the COPD subjects in Yao et al's study.\(^3\) NLR is valuable in assessing the severity of COPD attack and heart function, and this may help to indicate the outcomes of AECOPD complicated with HF. Even though the predictive ability of NLR and the AUC (AUC = 0.668, 95% CI 0.577-0.759, \(P = 0.001\)) was less than the other inflammatory biomarkers including CRP/ALB and PCT, the combination of NLR and CRP/ALB with NT-proBNP increased prognostic accuracy for 28-day mortality in AECOPD patients with HF (AUC = 0.830, 95% CI 0.761-0.899, \(P< 0.001\)). It was suggested that NLR level should be explained with other inflammatory biomarker such as CRP/ALB and heart failure indicator to improve the ability of predicting mortality risk.

PLR is another indicator for systemic inflammatory disorders.\(^{19}\) El-Gazzar et al\(^{17}\) found that elevated PLR together with NLR were significantly associated with smoking index, COPD stage and dyspnea severity in stable COPD patients. However, conflicting with these findings, our study did not find the statistically significant difference in PLR between the survivors and non-survivors. The role of PLR in AECOPD complicated with HF and the reason why no difference of PLR ratios was found between the two groups is not clear. It may suggest that the predictive accuracy of PLR on the prognosis of AECOPD patients with HF need to be further investigated.

However, there were some limitations in our study. The small sample size and the limited number of events were major limitations, and the selection of patients was based only on the ICD codes which was related to selection bias. Further studies will be needed with larger patient series to evaluate the prognostic accuracy of combined circulating biomarkers in AECOPD patients with HF. Moreover, we only collected the circulating biomarkers once at baseline, which cannot represent the underlying changes of systematic inflammation, nutritional status, and cardiac function in patients. Because this is a retrospective study, some relevant information such as exercise tolerance, modified Medical Research Council dyspnea scale (mMRC), and pulmonary function test were not available. Nevertheless, the strength of our study is that we assessed the predictive value of multiple mortality-associated biomarkers, taking inflammation, nutrition and cardiovascular function into account, some of which were left out of the previous studies.

**Conclusion**

In summary, we suggest that the levels of NLR, CRP/ALB, and NT-proBNP may be used to be prognostic markers for assessing the severity of disease and predicting 28-day mortality in AECOPD patients with HF. The combination of NLR, CRP/ALB, and NT-proBNP may significantly increase the mortality prediction, and provide prognostic information for future studies of different population of AECOPD
patients. The findings indicate further work into the role of circulating biomarkers related to inflammation, nutrition and cardiac function in the comprehensive management of AECOPD patients with HF.

**Abbreviations**

COPD: Chronic Obstructive Pulmonary Disease; AECOPD: Acute exacerbation of COPD; HF: heart failure; NT-proBNP: N-terminal pro-brain natriuretic peptide; CRP: C-reaction protein; ALB: albumin; NLR: neutrophil–lymphocyte ratio; PLR: platelet–lymphocyte ratio; ICD-10: International Classification of Diseases, Tenth Revision; GOLD: Global Initiative for Chronic Obstructive Lung Disease; PTE: pulmonary thromboembolism; LVEF: left ventricular ejection fraction; CAT: COPD assessment test; LOS: length of stay; NYHA: New York Heart Association; SPSS: Statistical Package for Social Sciences; IQR: interquartile range; ROC: Receiver operating characteristic; mMRC: modified Medical Research Council dyspnea scale.

**Declarations**

**Ethics approval and consent to participate**

The study was approved by the Ethics Committee of the Second Clinical College of Jinan University. Since the study was a retrospective cohort and the data analyzed were anonymized, the Ethics Committee waived the requirement for written consent from the patients. We confirm that the patient data were maintained with confidentiality, in compliance with the Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Availability of data and materials**

Some or all data, or code generated or used during the study are available from the corresponding author by request.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**
Conceptualization: CY, LW, FS; Methodology: CY, LW, FS, RC; Formal analysis: CY; Writing - Original Draft: CY; Writing - Review & Editing: LW, FS, RC; Visualization: FS, BL; Supervision: FS, RC; Visualization: BL; Investigation: WL, MF, SL; Data Curation: BL, WL, MF and SL. All authors read and approved the final version of the manuscript.

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References

[1]. The Global Strategy for Diagnosis, Management and Prevention of COPD (updated 2019). 2018.11.07. www.goldcopd.org.

[2]. Claus F Vogelmeier, Criner Gerard J, Martinez Fernando J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med, 2017. 195(5): 557-582.

[3]. CaoYuan Yao, Liu XiaoLi, Tang Ze. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. Int J Chron Obstruct Pulmon Dis 2017. 12: 2285-2290.

[4]. S. P. Bhatt, Dransfield M. T. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res, 2013. 162(4): 237-251.

[5]. J. de Miguel Diez, Chancafe Morgan J., Jimenez Garcia R. The association between COPD and heart failure risk: a review. Int J Chron Obstruct Pulmon Dis, 2013. 8: 305-312.

[6]. W. Xiong, Xu M., Zhao Y., et al. Can we predict the prognosis of COPD with a routine blood test? Int J Chron Obstruct Pulmon Dis, 2017. 12: 615-625.

[7]. E. Durmus, Kivrak T., Gerin F., et al. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol, 2015. 105(6): 606-613.

[8]. X. Wang, Fan X., Ji S., et al. Prognostic value of neutrophil to lymphocyte ratio in heart failure patients. Clin Chim Acta, 2018. 485: 44-49.

[9]. Y. Pascual-Gonzalez, Lopez-Sanchez M., Dorca J., et al. Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review. Int J Chron Obstruct Pulmon Dis, 2018. 13: 3651-3662.

[10]. Ranzani Otavio T, Godinho Zampieri Fernando, Neves Forte Daniel, et al. C-Reactive Protein/Albumin Ratio Predicts 90-Day Mortality of Septic Patients. PLoS One, 2013: e59321.
[11]. P. Ponikowski, Voors A. A., Anker S. D., et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail, 2016. 18(8): 891-975.

[12]. H. K. Kang, Kim K., Lee H., et al. Y. COPD assessment test score and serum C-reactive protein levels in stable COPD patients. Int J Chron Obstruct Pulmon Dis, 2016. 11: 3137-3143.

[13]. Y. R. Chen, Chen V., Hollander Z., et al. C-reactive protein and N-terminal prohormone brain natriuretic peptide as biomarkers in acute exacerbations of COPD leading to hospitalizations. PLoS One, 2017. 12(3): e0174063.

[14]. A. Mendy, Forno E., Niyonsenga T., et al. Blood biomarkers as predictors of long-term mortality in COPD. Clin Respir J, 2018. 12(5): 1891-1899.

[15]. M. H. Kim, Ahn J. Y., Song J. E., et al. The C-Reactive Protein/Albumin Ratio as an Independent Predictor of Mortality in Patients with Severe Sepsis or Septic Shock Treated with Early Goal-Directed Therapy. PLoS One, 2015. 10(7): e0132109.

[16]. P. Sun, Chen C., Xia Y., et al. The Ratio of C-Reactive Protein/Albumin is a Novel Inflammatory Predictor of Overall Survival in Cisplatin-Based Treated Patients with Metastatic Nasopharyngeal Carcinoma. Dis Markers, 2017. 2017: 6570808.

[17]. Rita Pavasini, Tavazzi Guido, Biscaglia Simone, et al. Amino terminal pro brain natriuretic peptide predicts all-cause mortality in patients with chronic obstructive pulmonary disease: Systematic review and meta-analysis. Chronic Respiratory Disease, 2016. 14(2): 117-126.

[18]. W. W. Labaki, Xia M., Murray S., et al. NT-proBNP in stable COPD and future exacerbation risk: Analysis of the SPIROMICS cohort. Respir Med, 2018. 140: 87-93.

[19]. W. Yang, Wang X., Zhang W., et al. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are 2 new inflammatory markers associated with pulmonary involvement and disease activity in patients with dermatomyositis. Clin Chim Acta, 2017. 465: 11-16.

Tables

Table 1. Clinical summary of the AECOPD patients with HF
| Clinical characteristic                      | Overall (n=146) | Non-survivors (n=52) | Survivors (n=94) | $\chi^2$ / $t$ / $Z$ | $P$-value |
|---------------------------------------------|----------------|----------------------|------------------|---------------------|-----------|
| Age, year, mean±SD                          | 79.17±9.56     | 80.94±11.56          | 78.19±8.15       | 1.680               | 0.096     |
| Gender, n (%)                               |                |                      |                  |                     |           |
| Male                                        | 109 (75)       | 42 (81)              | 67 (73)          | 1.595               | 0.207     |
| Female                                      | 37 (25)        | 10 (19)              | 27 (27)          |                     |           |
| Smoking status, n (%)                       |                |                      |                  |                     |           |
| Current/ever                                | 81 (56)        | 27 (52)              | 54 (57)          | 0.414               | 0.520     |
| Never                                       | 65 (44)        | 25 (46)              | 40 (43)          |                     |           |
| With hypertension or diabetes, n (%)        |                |                      |                  |                     |           |
| Yes                                         | 107 (73)       | 39 (75)              | 68 (72)          | 0.121               | 0.728     |
| Not                                         | 39 (27)        | 13 (25)              | 26 (28)          |                     |           |
| Baseline CAT score, mean±SD                 | 23.38±4.71     | 24.29±5.12           | 22.87±4.42       | 1.752               | 0.082     |
| GOLD grade, 2 / 3 / 4, n (%) / n (%) / n (%)| 41 (28.1) / 85 (58.2) / 20 (13.7) | 13 (25.0) / 33 (63.5) / 6 (11.5) | 28 (29.8) / 52 (55.3) / 14 (14.9) | 0.930 | 0.628 |
| NYHA classification, II / III / IV, n (%) / n (%) / n (%) | 29 (19.9) / 71 (48.6) / 46 (31.5) | 2 (3.8) / 25 (48.1) / 25 (48.1) | 27 (28.7) / 46 (48.9) / 21 (22.3) | 4.090 | 0.000 |
| HF classification, n (%)                    |                |                      |                  |                     |           |
| Systolic heart failure                      | 88 (60.3)      | 35 (67.3)            | 53 (56.4)        | 2.637               | 0.268     |
| Diastolic heart failure                     | 28 (19.2)      | 10 (19.2)            | 18 (19.1)        |                     |           |
| Both                                        | 30 (20.5)      | 7 (13.5)             | 23 (24.5)        |                     |           |
| LVEF (%), mean±SD                           | 49.64±11.90    | 48.65±11.68          | 51.79±12.34      | 1.070               | 0.288     |
| Hospital LOS, day, median (IQR)             | 11 (6, 21.25)  | 16 (5, 23)           | 10.5 (7, 19)     | 0.254               | 0.800     |
| ICU LOS, day, median (IQR)                  | 2 (2, 9)       | 5 (1, 16.5)          | 1 (0, 5)         | 4.062               | 0.000     |
| Endotracheal intubation, n (%)              |                |                      |                  |                     |           |
| Yes                                         | 55 (38)        | 38 (73)              | 17 (18)          | 43.120              | 0.000     |
| Not                                         | 91 (62)        | 14 (27)              | 77 (82)          |                     |           |
Note: Data presented as mean ± SD and median (interquartile range).

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; HF, heart failure; SD, Standard Deviation; NYHA classification, New York Heart Association classification; CAT, COPD assessment test; LVEF, left ventricular ejection fraction; LOS, length of stay; ICU, Intensive Care Unit; IQR, interquartile range.

Table 2. Comparison of Laboratory indexes between the study groups

| Laboratory indexes          | Overall (n=146)          | Non-survivors (n=52)   | Survivors (n=94)    | t/Z    | P-value |
|-----------------------------|--------------------------|------------------------|---------------------|--------|---------|
| CRP, mg/L, mean±SD          | 94.8±94.2                | 145.8±110.1            | 66.6±70.2           | 4.689  | 0.000   |
| ALB, g/L, mean±SD           | 29.5±5.6                 | 26.8±6.4               | 31.0±4.6            | 4.680  | 0.000   |
| CRP/ALB, mean±SD            | 3.6±3.9                  | 5.9±4.9                | 2.3±2.6             | 4.880  | 0.000   |
| NLR, median (IQR)           | 14.9 (7.0, 28.3)         | 22.2 (11.1, 40.1)      | 12.0 (6.2, 24.8)    | 3.349  | 0.001   |
| PCT, ng/ml, median (IQR)    | 0.23 (0.1, 2.6)          | 2.6 (0.2, 10.3)        | 0.08 (0.1, 0.5)     | 5.364  | 0.000   |
| NT-proBNP, ng/ml, median (IQR) | 11997.3 (6128.2, 22030.7) | 17912.5 (9344.0, 34344.5) | 9809.0 (4415.9, 16387.2) | 4.446  | 0.000   |
| PLR, mean±SD                | 324.3±280.8              | 346.8±326.4            | 311.9±253.1         | 0.718  | 0.474   |

Note: Data presented as mean ± SD and median (interquartile range).

Abbreviations: CRP, C-reaction protein; SD, Standard Deviation; ALB, Albumin; CRP/ALB, C-reaction protein/Albumin; NLR, Neutrophil–lymphocyte ratio; IQR, interquartile range; PCT, procalcitonin; NT-proBNP, N terminal pro B-type natriuretic peptide; PLR, Platelet–lymphocyte ratio.

Table 3. Multivariate logistic regression analysis of AECOPD patients with HF
| Indicator         | OR     | 95%CI          | P-value |
|------------------|--------|----------------|---------|
| CRP              | 1.003  | 0.989~1.017    | 0.697   |
| ALB              | 0.987  | 0.890~1.094    | 0.800   |
| CRP/ALB          | 1.303  | 1.145~1.483    | 0.000   |
| NLR              | 1.010  | 0.999~1.022    | 0.000   |
| PCT              | 0.998  | 0.965~1.033    | 0.928   |
| NT-proBNP        | 1.041  | 1.010~1.073    | 0.009   |
| Age              | 0.951  | 0.973~1.030    | 0.552   |
| CAT score        | 1.064  | 1.008~1.124    | 0.132   |
| NYHA classification | 1.006 | 0.964~1.049 | 0.081   |
| MV               | 1.166  | 0.541~2.512    | 0.696   |

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP/ALB, C-reaction protein/Albumin; NLR, Neutrophil–lymphocyte ratio; NT-proBNP, N terminal pro B-type natriuretic peptide; PCT, procalcitonin; CRP, C-reaction protein; ALB, Albumin; MV, mechanical ventilation; NYHA classification, New York Heart Association classification; CAT, COPD assessment test; OR, odds ratio; CI, Confidence interval.

**Table 4.** Prognostic value of the biomarkers
| Indicator | AUC   | 95% CI         | Cut-off | Sensitivity | Specificity | \( P \)-value |
|----------|-------|----------------|---------|-------------|-------------|----------------|
| CRP (mg/L) | 0.757 | 0.679~0.836    | 100.71  | 0.654       | 0.766       | 0.000          |
| ALB (g/L)   | 0.716 | 0.622~0.810    | 26.75   | 0.577       | 0.851       | 0.000          |
| CRP/ALB     | 0.768 | 0.684~0.850    | 2.48    | 0.731       | 0.649       | 0.000          |
| NLR         | 0.668 | 0.577~0.759    | 16.83   | 0.692       | 0.649       | 0.001          |
| PCT (ng/ml) | 0.767 | 0.684~0.850    | 0.59    | 0.673       | 0.809       | 0.000          |
| NT-proBNP (ng/ml) | 0.723 | 0.637~0.809   | 14265.25 | 0.635   | 0.723       | 0.000          |
| CRP/ALB+NT-proBNP | 0.821 | 0.751~0.892  | -       | 0.750       | 0.830       | 0.000          |
| CRP/ALB+NLR | 0.782 | 0.707~0.856   | -       | 0.500       | 0.915       | 0.000          |
| NLR+NT-proBNP | 0.741 | 0.658~0.825  | -       | 0.712       | 0.670       | 0.000          |
| CRP/ALB+NLR+NT-proBNP | 0.830 | 0.761~0.899  | -       | 0.808       | 0.777       | 0.000          |

Abbreviations: CRP, C-reaction protein; ALB, Albumin; CRP/ALB, C-reaction protein/Albumin; NLR, Neutrophil–lymphocyte ratio; PCT, procalcitonin; NT-proBNP, N terminal pro B-type natriuretic peptide; PLR, Platelet–lymphocyte ratio; AUC, area under the curve; CI, Confidence interval.

**Figures**
322 patients enrolled from January 1, 2013 to January 31, 2019

- 23 patients did not die of AECOPD with HF directly;
- 4 patients refused to further treatment;
- 11 patients died in the emergency department (as outpatients);
- 7 patients combined with PTE;
- 10 patients combined with tumor;
- 3 patients combined with interstitial pulmonary disease;
- 40 patients combined with acute myocardial infarction;
- 46 patients combined with pneumonia;
- 32 patients without acute heart failure.

146 patients were finally enrolled

Survivors (n=94)  Non-survivors (n=52)

Figure 1

Screening and enrollment of the study.
Figure 2

ROC curves of the circulating biomarkers for predicting 28-day mortality of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients with heart failure (HF). The receiver operating characteristic (ROC) curves for single biomarkers and their combinations had the following areas: C-reactive protein (CRP) / albumin (ALB) ratio, 0.768; neutrophil–lymphocyte ratio (NLR), 0.668; N-terminal
pro-brain natriuretic peptide (NT-proBNP), 0.723; and combination of CRP/ALB, NLR and NT-proBNP, 0.830.