Comparison of CRP, procalcitonin, neutrophil counts, sTREM-1,opn,clinical status and short-term outcomes between pneumonic and non-pneumonic exacerbations in COPD patients

SHAN MOU[1], Wei Zhang[1], Wei Zhang[1], ZhiJun Tang[1], and depeng jiang[1]

[1]Affiliation not available

October 16, 2020

Abstract

introduction:The patients with Community-Acquired Pneumonia(CAP) could have a higher risk of acute and severe respiratory illness than those without CAP in acute exacerbations of COPD(AECOPD).consequently,early identification of pneumonia in AECOPD is quite important. metholds:62 subjects with AECOPD+CAP and 107 subjects with AECOPD were enrolled from two clinical centers. Clinical parameters and the values of osteopontin (OPN),soluble triggering receptor expressed on myeloid cells-1 (sTrem-1), C-reactive protein (CRP),procalcitonin (PCT),and neutrophil counts (NEU) were measured and compared in AECOPD and AECOPD+CAP on the first day of admission. results:patients with AECOPD+CAP has increased presence of fever, sputum volume,sputum purulence,diabetes mellitus,lower blood pressure, and higher carbon dioxide partial pressure than AECOPD patients($p<0.05$).At day1,AECOPD+CAP patients had higher values of NEU,CRP,PCT and OPN,while serum sTREM-1 levels were similar in the two groups. CRP fares best at predicting acute exacerbation of COPD with pneumonia with an area under the curve (AUC) of 0.78, while OPN had similar accuracy with Neu and PCT.the AUC value of OPN,Neu and PCT was 0.61(95% CI 0.53-0.68) , 0.63(95% CI 0.55-0.70) and 0.68(95% CI 0.60-0.75) respectively($p<0.05$ for the test of difference). In multivariate analysis, plasma levels of CRP[?]15.8 mg/dL at day 1 and sputum purulence were promising predictors of pneumonia in AECOPD. Conclusions:Patients with CAP in AECOPD patients present more clinical parameters and increased biomarker levels but similar short-term outcomes. Combined with plasma CRP level and the clinical characteristic of purulent sputum can be used to predict COPD complicated with pneumonia.

Comparison of CRP, procalcitonin, neutrophil counts, sTREM-1,opn,clinical status and short-term outcomes between pneumonic and non-pneumonic exacerbations in COPD patients

Shan Mou[1], Wei Zhang[1], Wei Zhang[1], Yan Deng[1], Zhigang Tang[2] and Depeng Jiang[1]

[1]Department of Respiratory Medicine, the Second Clinical Hospital of Chongqing Medical University, Chongqing, China.[3]Nanchuan District People's Hospital of Chongqing, Chongqing, China.

Address all correspondence to: De Peng Jiang, Department of Respiratory Medicine, the Second Clinical Hospital of Chongqing Medical University,Chongqing, China,15334533987 Phone, depengjiang@163.com.

Comparison of CRP, procalcitonin, neutrophil counts, sTREM-1,opn,clinical status and short-term outcomes between pneumonic and non-pneumonic exacerbations in COPD patients

ABSTRACT

introduction: The patients with Community-Acquired Pneumonia(CAP) could have a higher risk of acute and severe respiratory illness than those without CAP in acute exacerbations of COPD(AECOPD).consequently,early identification of pneumonia in AECOPD is quite important.

methods: 62 subjects with AECOPD+CAP and 107 subjects with AECOPD were enrolled from two clinical centers. Clinical parameters and the values of osteopontin (OPN),soluble triggering receptor expressed on myeloid cells-1 (sTrem-1), C-reactive protein (CRP),procalcitonin (PCT),and neutrophil counts (NEU) were measured and compared in AECOPD and AECOPD+CAP on the first day of admission.

results: patients with AECOPD+CAP has increased presence of fever, sputum volume,sputum purulence,diabetes mellitus,lower blood pressure, and higher carbon dioxide partial pressure than AECOPD patients($p<0.05$).At day1,AECOPD+CAP patients had higher values of NEU,CRP,PCT and OPN,while serum sTREM-1 levels were similar in the two groups. CRP fares best at predicting acute exacerbation of COPD with pneumonia with an area under the curve (AUC) of 0.78, while OPN had similar accuracy with Neu and PCT.the AUC value of OPN,Neu and PCT was 0.61(95% CI 0.53-0.68) , 0.63(95% CI 0.55-0.70) and 0.68(95% CI 0.60-0.75) respectively($p<0.05$ for the test of difference). In multivariate analysis, plasma levels of CRP[?]15.8 mg/dL at day 1 and sputum purulence were promising predictors of pneumonia in AECOPD.

Conclusions: Patients with CAP in AECOPD patients present more clinical parameters and increased biomarker levels but similar short-term outcomes. Combined with plasma CRP level and the clinical characteristic of purulent sputum can be used to predict COPD complicated with pneumonia.

Keywords: COPD exacerbations, pneumonia ,Biomarkers, OPN, CRP, diagnostic accuracy

Clinical trial registration: ChiCTR-OOC-16009221.

introduction

Chronic obstructive pulmonary disease (copd) is characterized by persistent and progressive respiratory symptoms and airflow limitation due to inhalation of noxious gases most commonly from tobacco. Acute exacerbation of COPD (AECOPD) is a sudden and sustained worsening of respiratory symptoms in the natural course of COPD that requiring additional therapy. Many triggers have been shown to incite AECOPD, among which infectious origin including either viral, bacterial or both pathogens are the commonest inciting cause for AECOPD[1, 2]. these cases admitted with community-acquired pneumonia(CAP) were diagnosed with AECOPD+CAP. according to present studies, the patients who present with radiological pneumonia could have a more severe illness and a poorer prognosis than did those admitted without pneumonia in exacerbation of COPD[3-5]. consequently, early identification of patients with AECOPD and pneumonia is crucial for outcome. however, it is not easy to make an early diagnosis of pneumonia due to an blurred clinical picture or interpretation of the chest film. Hence, in order to initiate the proper treatments timely and improve their prognosis, clinicians need reliable surrogate biomarkers along with clinical signs and symptoms to predict pneumonia in patients with AECOPD.

OPN is expressed in plenty of immune cells including neutrophils, macrophages , dendritic Cells, Natural Killer cells, and T cells.it regulates both innate and adaptive immune responses by mediating Th1 inflammation, neutrophil chemotaxis and matrix remodeling[6].OPN has been found to be associated with lung inflammation in different pulmonary diseases, including stable COPD[7, 8],AECOPD[9], Klebsiella pneumoniae-induced pneumonia [10],and pneumococcal pneumonia[11].however, less is known about serum OPN levels in admitted AECOPD patients with pneumonia. OPN may also be a useful biomarker to discriminate pneumonia from AECOPD.

Triggering receptor expressed on myeloid cells (Trem-1),as a receptor, is expressed on neutrophils and monocytes. Its expression is up-regulated on phagocytic cells by bacterial or fungal products[12, 13].sTREM-1 is a soluble form of trem1.previous studies indicated that strem1 is a diagnostic marker of the presence of infectious disease including pneumonia[14] and sepsis[15, 16]. In addition, serum levels of strem1 is also increased in many non-infectious respiratory diseases such us asthma ,AECOPD[17, 18]. Hence, sTREM-1 may be useful for AECOPD and pneumonia. However, The value of serum sTREM-1 in distinguishing among pneumonic and non-pneumonic exacerbations in COPD patients has not been evaluated.

In summary, Elevated levels of the above-mentioned biomarkers seem to be implicated in the pathogenesis of pneumonia and AECOPD.Besides,Neutrophil counts(Neu),C-reactive protein (CRP) and procalcitonin (PCT) in peripheral blood are increased in AECOPD patients and more so in AECOPD complicated with pneumonia[5, 19, 20].Consequently,In this cross-sectional study, we compared the differences of CRP,PCT,OPN,STREM-1,Neu and clinical parameters in AECOPD patients with or without pneumonia in china. In addition, we compared with the diagnostic profiles of these biomarkers between pneumonic and non-pneumonic exacerbations in COPD patients.

Patients and methods

The prospective study followed the declaration of Helsinki and was conducted from September 2016 to February 2019 after receiving approval from the ethics Committee of the Second Clinical Hospital of Chongqing Medical University.All subjects signed informed consent before inclusion in this study. All patients who had a clinically identified AECOPD were recruited in this study once admitted to hospital.AECOPD is characterized by sudden worsening of respiratory symptoms including increased dyspnea, increased sputum volume and purulence.and requiring changes in treatment in patients with COPD. CAP was defined according to the following criteria:1. Clinical signs and symptoms of lung infection as well as a new radiographic pulmonary infiltrate at admission; 2. Compatible symptoms occur in the community rather than in the hospital.The CURB-65 pneumonia severity score was assessed and its interpretation is as follows:0-1: Probably suitable for home treatment; low risk of death,2: Consider hospital supervised treatment,3:Manage in hospital as severe pneumonia; high risk of death. Exclusion criteria were as follows: other significant respiratory diseases including asthma, tuberculosis, bronchiectasis and pulmonary fibrosis; Ischemic Heart Diseases such as a history of coronary heart disease, acute heart failure or acute attack of chronic heart failure and acute myocardial infarction; malignancy;autoimmune diseases;other inflammatory conditions or inflammatory processes that could be associated with abnormal sTREM-1 ,OPN ,PCT and CRP levels.In all subjects ,plasma CRP ,neu and plasma procalcitonin (PCT) were measured by routine automated tests. arterial blood gas analysis on admission. All patients underwent chest X-ray or CT examination in the outpatient or inpatient department.Lung function tests were implemented by professional technicians in all subjects.data on demographic variables were collected on admission. clinical manifestations of acute episodes were recorded and data on clinical status during hospitalization were collected.

Microbiological surveys

Sputum specimens were attempted to be obtained on admission for bacteria and fungi culture in all patients. Two blood cultures were performed when the AECOPD patients admitted to hospital with or without pneumonia had a fever. Besides, combined serological tests of immunoglobulin M antibodies to respiratory tract pathogens by pairing sera were performed at admission, which helped to diagnose the following microorganisms including Respiratory Syncytial Virus (RSV), Adenovirus, Legionella pneumophilia, Mycoplasma pneumonia, Chlamydophila pneumonia, rickettsia and parainfluenza virus.

Sample collection and measurement of OPN and sTREM-1.

Blood samples were drawn in coagulation promoting tubes and centrifuged at 3000 rpm for 10 min at room temperature within 120 minutes of collection. the supernatants were obtained and stored at -80degC until analysis the serum fraction was withdrawn and stored at -80degC for measurements of OPN, and Strem-1. The laboratory team who determined OPN, and Strem-1 was blinded to the clinical data.

Statistics

Normally distributed variables were presented as mean+-standard deviation (SD),and independent two-tailed test was used to analyze differences between the two groups. skewed variables were presented as median (interquartile ranges, IQR),and differences in the variables were analyzed using Mann-Whitney U-tests. Categorical variables are described as frequencies and proportions, their differences were evaluated by X2 test or Fisher's exact test when necessary. the above-mentioned statistical analyses were conducted by spss 23 software program (IBM Corporation, Armonk, NY,USA) ,and $p < 0.05$ was regarded as statistical significance.Variables with a P<0.15 in the univariate analysis were retained as covariates in the forward stepwise selection procedure of multivariate analysis, A Hosmer-Lemeshow goodness-of-fit test was also figured up.The Receiver operating characteristic (ROC) curves were calculated to compare the accuracy of blood biomarkers in diagnosis of pneumonia in patients with AECOPD using MedCalc software 15.8 (Mariakerke, Belgium).

Results

From November 2016 to February 2019,a total of 169 patients who met the inclusion criteria were enrolled, of which 107 patients had AECOPD and 62 patients were diagnosed with AECOPD and CAP. In this experiment, the combined serological tests of immunoglobulin M antibodies to nine respiratory tract pathogens were conducted in 50.3% of the patients, while blood culture examination and the sputum culture were implemented in 13% and 85.8% of patients respectively. CURB-65 score was 0-2 in all patients.there were no significant differences between the two groups in terms of age, BMI, sex, current smoking history, percentage of patients treated with inhaled glucocorticoids, systemic corticosteroids (SCS) or antibiotics,lung function and duration of copd exacerbation before Admission. (Table 1).

Compared with AECOPD group, more patients in AECOPD+CAP group had fever, increased sputum volume, increased sputum purulent components, diabetes mellitus, lower blood pressure, and higher carbon dioxide partial pressure. there was no significant difference in the proportion of patients requiring mechanical ventilation, emergency treatment, admission to the intensive care unit, invasive/noninvasive mechanical ventilation. In addition , no significant differences were found for respiratory failure(Table 2).confirmed infective pathogens were found in 24 patients with AECOPD(22.4%) and 11 patients with AECOPD+CAP(17.7%;not significant [NS]).(Table 3).Mixed infection was confirmed in 1 patient with AECOPD (4.2%%) and in 3 patients with AECOPD+CAP (27.3%; [NS]). By comparing the infection microorganisms, we found that AECOPD+CAP patients were prone to be infected with respiratory virus,and there were no difference in other microbial etiologies between groups.

On the first day after admission, we examined the levels of blood markers in 107 patients with AECOPD and 62 patients with AECOPD and CAP. The levels of CRP, PCT, Neu, and OPN in AECOPD+CAP patients were significantly higher than those in AECOPD patients. However, there were no significant differences in serum levels of sTREM-1 between the two groups(Table 2,Figure 2)

By using MedCalc software 15.8, we found that CRP showed the best diagnostic performance while PCT,NEU,OPN presented similar diagnostic discrimination property.the area under the ROC curve (AUC) was 0.78(95% CI 0.71-0.86) for CRP,0.68(95% CI 0.59-0.77) for PCT, 0.63(95%CI 0.54-0.72) for Neu, 0.61(95%CI 0.52-0.70) for OPN((Table4,Figure 1).

To characterize early clinical predictors of pneumonia in AECOPD patients, the logistic regression analysis (table 5) was performed. Variables including fever,sputum purulence, increased in sputum volume, diabetes mellitus ,PCT[?]0.07ng/mL,Neu[?]6.41x10^9/L, CRP[?]15.8 mg/dL and OPN [?]14.28ng/mL were retained as covariates in the forward stepwise selection procedure of multivariate analysis. we found that plasma level of CRP[?]15.8 mg/dL and sputum purulence are independent factors of pneumonia in AECOPD(Table 5).

Discussion

This study found that: 1) the levels of CRP, PCT, Neu, OPN were higher in patients with AECOPD and pneumonia than in AECOPD patients without pneumonia, while serum sTREM-1 were similar in the two groups. 2) We found that CRP showed the best diagnostic accuracy for identifying pneumonia in AECOPD patients,while OPN had poor and similar accuracy with Neu and PCT.3) Our logistic model found that combined with plasma CRP level and the clinical characteristic of purulent sputum can be used to predict COPD complicated with pneumonia.4)In the demographic variable comparison,patients admitted with pneumonia in AECOPD had increased presence of fever, sputum volume,sputum purulence,diabetes mellitus,lower blood pressure, and higher carbon dioxide partial pressure than AECOPD patients. 5) patients with radiological pneumonia had similar short-term outcomes with those admitted without pneumonia in exacerbation of COPD including hospital stays,use of ventilatory assistance, need for emergency treatment and admission to ICU.

Patients with COPD are prone to CAP than those without COPD[21, 22]. early identifying patients with AECOPD and CAP aids clinical treatment decisions, thus improving their prognosis. In clinical work, it is not easy to make an early diagnosis of pneumonia because sometimes chest radiography is not sensitive enough for identifying pulmonary exudation and consolidation[23-25]. consequently based on these, more and more scholars are trying to find reliable blood biomarkers to predict pneumonia in AECOPD in recent years, thus helping guide clinicians to make correct treatment decisions in these patients.

the present study demonstrated that CRP on day1 was significantly better than PCT,OPN,and NEU for discrimination of pneumonic and non-pneumonic exacerabtions in AECOPD patients. logistic regression model showed that CRP and increased sputum purulent components are independent predictors of pneumonia in AECOPD.similarly, A study in 2013 comparing the diagnostic performance of CRP, PCT, TNF-alpha and IL-6 demonstrated that only CRP on day 1 could independently predict AECOPD with pneumonia[26].However, two recent studies have shown that the AUC value of CRP was higher than PCT,and the test of difference was not statistically significant[19, 27].possible explanations for the gap may be due to the differences in copd severity[27] and pneumonia severity [19].In addition, previous studies suggested that PCT could be a promising biomarker for diagnosing bacterial infection during exacerbations of COPD,eapecially in severe COPD Exacerbations requiring Mechanical Ventilation [28, 29],while CRP was found to be correlated with mixed viral/bacterial infections of AECOPD[30].Recent studies have shown that CRP and PCT might be of interest as biomarkers in guiding the use of antibiotics in patients with AECOPD,without evidence of harm[30, 31].Herein, we take it that plasma CRP on day 1 is a promising biomarker to identify pneumonia in AECPD patients especially in some cases where infiltrates on chest x-ray or CT are doubtful or the property of the consolidation on LDCT in elderly patients is uncertain such us pneumonia, metastasis, lung cancer, and diffuse parenchymal lung diseases,etc. preclinical studies have shown that OPN seems to be involved in the pathogenesis of COPD and pneumonia.In our study,Increased serum level of OPN have been observed in patients with AECOPD and pneumonia,compared with patients with AECOPD. Future studies will have to explore the role of OPN in the pathogenesis of AECOPD and pneumonia and find its effective clinical applications such as a possible treatment target.The diagnostic accuracy of OPN was similar to that of PCT and Neu, but significantly lower than that of CRP.Serum OPN had a sensitivity of 65% and a specificity of 57% for diagnosing pneumonia in addition to COPD.accordingly,serum OPN as a single biomarker was not so reliable for diagnosing AECOPD with pneumonia. strem1 was found to be as a promising diagnostic marker of the presence of pneumonia[14], sepsis[32] and AECOPD[18]. to the best of our knowledge, no studies have compared strem1 levels in patients with AECOPD with or without CAP. We first discovered that strem1,an established biomarker of systemic inflammation, showed no predictive value for differentiating pneumonic and non-pneumonic exacerabtions in COPD patients.Moreover,in the study by Rohde et al,the value of serum Strem-1 in determination of AECOPD etiology were evaluated.the results showed that sTREM-1 could not be used to identify bacterial exacerbation of COPD[17].

our study found that patients with AECOPD+CAP present more severe clinical parameters. The patients showed increased presence of fever, sputum volume, sputum purulence, diabetes mellitus,lower blood pressure

and higher carbon dioxide partial pressure compare with AECOPD patients. In agreement with these findings, studies comparing clinical features between pneumonic and non-pneumonic exacerbations in COPD patients confirmed patients with pneumonia in addition to AECOPD tend to show presence of abnormal clinical symptoms and signs[5,25,26].as for infection microorganisms, we found that AECOPD+CAP patients were prone to be infected with respiratory virus,compared with patiens with AECOPD.However, the results should be interpreted with caution because of the small sample size.

In our study, none of patients with AECOPD with/without pneumonia died, so we could not provide data on short-term mortality outcome for AECOPD + CAP VS AECOPD. there was no significant difference in the risk of respiratory failure, need for intensive care unit, invasive/noninvasive mechanical ventilation and emergency treatment and in length of hospital stays between the two groups. The results indicated that short-term clinical outcomes during hospitalization were similar between groups.

The strength of our study is that our study compare the clinical parameters and diagnostic accuracy of serum OPN,STREM1, CRP, PCT, and NEU in a real-world environment. consequently, these findings can be transferred to the hospital's outpatient clinics and emergency department.

There are some limitations in our study. One limitation is that we didn,t follow up the patients after discharge. Another limitation is that we didn,t know the levels of the biomarkers during stale COPD, and many inflammatory markers' levels in peripheral blood had been found to be increased during the stable phase of COPD. In addition, according to CRUB-65 score, pneumonia is not severe in patients included in our article, and some marker levels and clinical parameters can be different in severe and non severe pneumonia patients. Therefore, our research results can only explain the relative difference between AECOPD patients with non-severe pneumonia and those without pneumonia.

In summary, we find that AECOPD patients with pneumonia have severe clinical features, similar short-term outcomes and higher levels of inflammatory biomarkers including CRP,PCT, OPN and Neu, compared to those with pneumonia.In addition,CRP had the best ability to diagnose AECOPD with CAP,compared with PCT, OPN and Neu. OPN,Neu,PCT and sTREM-1 blood levels have poor abilities to identify patients with AECOPD and pneumonia, indicating that CRP maintains the major role at this regard. combination with CRP and sputum purulence is useful to predict pneumonia in AECOPD patients.

Abbreviations

COPD:Chronic obstructive pulmonary disease;AECOPD:acute exacerbations of Chronic obstructive pulmonary disease;AUC: Area Under the Curve; IQR:Interquartile range;CI:Confidence interval; ROC: Receiver operating characteristic; SD: Standard deviation; BMI: Body mass index;SCS: Systemic corticosteroids;ICS: Inhaled corticosteroids;FEV1/FVC: The ratio of the forced expiratory volume in the first 1s to the forced vital capacity of the lungs; FEV1, % predicted:Baseline forced expiratory volume in the first 1s, % of expected;GOLD: Global Initiative for Obstructive Lung Disease;ICU:intensive care unit;CURB-65: confusion, uremia, respiratory rate, blood pressure, age [?] 65 years;CRP: C-reactive protein;PCT: procalcitonin;NEU:neutrophil;sTREM-1: soluble triggering receptor expressed on myeloid cells-1;OPN: osteopontin;CAP: Community-Acquired Pneumonia;CT: computed tomography;RSV:respiratory syncytial virus

Acknowledgements

The authors would like to express our appreciation for the assistance of the staff at the respiratory department, geriatric department at the Second Clinical Hospital of Chongqing Medical University and the support of the stuff at Nanchuan District People's Hospital of Chongqing.

Disclosure of interest

The authors report no conflict of interest.

Funding

This work was supported by the National Natural Science Foundation of China [grant number 81650003] and the Health and Family Planning Commission of Chongqing City [grant numbers 2016HBRC004].

Conflict of Interest

The authors declare that they have no competing interests.

References

1. Global Initiative for Chronic Obstructive Lung Disease [internet].America(DC): Signalfire;[cited 2020 May 18].Available from: https://goldcopd.org/gold-reports/.
2. Miravitlles M,Anzueto A.Role of infection in exacerbations of chronic obstructive pulmonary disease. Curr Opin Pulm Med.2015;21(3):278-83.
3. Finney LJ,Padmanaban V,Todd S,et al.Validity of the diagnosis of pneumonia in hospitalised patients with COPD. ERJ Open Res.2019;5:00031-02019.
4. Saleh A,Lopez-Campos JL, Hartl S et al.The Effect of Incidental Consolidation on Management and Outcomes in COPD Exacerbations:Data from the European COPD Audit. PLoS One. 2015;10:e0134004.
5. Lieberman D,Lieberman D,Gelfer Y,et al.Pneumonic vs Nonpneumonic Acute Exacerbations of COPD.Chest.2002; 122(4):1264-70.
6. Castello LM,Raineri D,Salmi L et al.Osteopontin at the Crossroads of Inflammation and Tumor Progression. Mediators of Inflammation.2017;2017:4049098.
7. Papaporfyriou A, Loukides S, Kostikas K,et al.Increased levels of osteopontin in sputum supernatant in patients with COPD. Chest.2014;146(4):951-8.
8. Schneider DJ,Lindsay JC,Zhou Y,et al.Adenosine and Osteopontin Contribute to the Development of Chronic Obstructive Pulmonary Disease. FASEB J.2010;24(1):70-80.
9. Shi L,Zhu BJ,Xu ML,et al.Selection of AECOPD-specific Immunomodulatory Biomarkers by Integrating Genomics and Proteomics With Clinical Informatics.Cell Biol Toxicol.2018;34(2):109-123.
10. Windt GJWVD, Hoogendijk AJ,Schouten M,et al.Osteopontin promotes host defense during Klebsiella pneumoniae-induced pneumonia. Eur Respir J.2010;36(6):1337-45.
11. Windt GJWVD, Hoogendijk AJ,Schouten M,et al.Osteopontin Impairs Host Defense During Pneumococcal Pneumonia. J Infect Dis.2011;203(12):1850-58.
12. Quenot JP,Luyt CE,Roche N,et al.Role of biomarkers in the management of antibiotic therapy:an expert panel review II:clinical use of biomarkers for initiation or discontinuation of antibiotic therapy. Annals of Intensive Care.2013;3:21.
13. Arts RJW,Ioosten LAB,Meer JWMVD,et al.TREM-1: intracellular signaling pathways and interaction with pattern recognition receptors. Journal of Leukocyte Biology.2013(2);93:209-15.
14. YE W,Hu YJ,Zhang RF,et al.Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in lower respiratory tract infections:A meta-analysis.Respirology.2014;2014(4):501-17.
15. Gibot S, Kolopp-Sarda MN,PharmSci MC,et al.Plasma Level of a Triggering Receptor Expressed on Myeloid Cells-1:Its Diagnostic accuracy in patients with suspected sepsis. Ann Intern Med .2004;141(1):9-15.
16. El-Madbouly AA,Sehemawy AAEI,Eldesoky NA,et al.Utility of presepsin, soluble triggering receptor expressed on myeloid cells-1, and neutrophil CD64 for early detection of neonatal sepsis. Infect Drug Resist.2019;12:311-9.
17. Rohde G,Radsak MP,Borg I,et al.Levels of Soluble Triggering Receptor Expressed on Myeloid Cells 1 in Infectious Exacerbations of Chronic Obstructive Pulmonary Disease. Respiration.2012;83(2):133-9.
18. Phua J,Koay ESC,Zhang D,et al.Soluble triggering receptor expressed on myeloid cells-1 in acute respiratory infections. Eur Respir J. 2006;28(4):695-702.
19. Halici A,Hur I,Kerim A,et al.The role of presepsin in the diagnosis of chronic obstructive pulmonary disease acute exacerbation with pneumonia. Biomark Med.2020;14(1):31-41.
20. Pascoe SJ,Papi A,Midwinter D,et al.Circulating neutrophils levels are a predictor of pneumonia risk in chronic obstructive pulmonary disease. Respiratory Research.2019;23;20(1):195.

21. Bordon J, Slomka M,Gupta R,et al.Hospitalization due to community-acquired pneumonia in patients with chronic obstructive pulmonary disease: incidence, epidemiology and outcomes.Clin Microbiol Infect.2020;26(2):220-6.
22. Janson C, Johansson G, Stallberg B,et al.Identifying the Associated Risks of Pneumonia in COPD Patients:ARCTIC an Observational Study. Respiratory Research.2018;19(1):172.
23. Claessens YE,Debray MP,Tubach F,et al.Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia.Am J Respir Crit Care Med.2015;192(8):974-982.
24. Upchurch CP,Grijalva CG,Wunderink RG,et al.Community-Acquired Pneumonia Visualized on CT Scans but Not Chest Radiographs: Pathogens, Severity, and Clinical Outcomes. Chest.2018;153(3):601-10..
25. Garin N,Marti C,Scheffler M,et al.Computed tomography scan contribution to the diagnosis of community-acquired pneumonia.Curr Opin Pulm Med .2019;25(3):242-8.
26. Huerta A,Crisafulli E,Menendez R,et al. Pneumonic and nonpneumonic exacerbations of COPD: inflammatory response and clinical characteristics.chest.2013;144(4):1134-42.
27. Titova E,Christensen A,Henriksen AH,et al. Comparison of procalcitonin, C-reactive protein, white blood cell count and clinical status in diagnosing pneumonia in patients hospitalized with acute exacerbations of COPD: A prospective observational study. Chron Respir Dis.2019;16:1479972318769762.
28. Ergan B,Şahin A A,Topeli A,et al.Serum Procalcitonin as a Biomarker for the Prediction of Bacterial Exacerbation and Mortality in Severe COPD Exacerbations Requiring Mechanical Ventilation.Respiration.2016;91(4):316-24..
29. Tanrıverdi H,Örnek T,Erboy F,et al.Comparison of diagnostic values of procalcitonin,C-reactive protein and blood neutrophil/lymphocyte ratio levels in predicting bacterial infection in hospitalized patients with acute exacerbations of COPD. Wien Klin Wochenschr.2015;127(19-20):756-63.
30. Butler CC, Gillespie D,White P,et al.C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. N Engl J Med.2019;381(2):111-20.
31. Mathioudakis AG,Chatzimavridou-Grigoriadou V,Corlateanu A,et al.:Procalcitonin to guide antibiotic administration in COPD exacerbations:a meta-analysis.Eur Respir Rev,2017;31;26(143):160073.
32. Gibot S,Béné MC,Noel R,et al.Combination Biomarkers to Diagnose Sepsis in the Critically Ill Patient. Am J Respir Crit Care Med.2012;186(1):65-71.

Hosted file

`tables.pdf` available at https://authorea.com/users/367858/articles/487129-comparison-of-crp-procalcitonin-neutrophil-counts-strem-1-opn-clinical-status-and-short-term-outcomes-between-pneumonic-and-non-pneumonic-exacerbations-in-copd-patients

Hosted file

`figures.pdf` available at https://authorea.com/users/367858/articles/487129-comparison-of-crp-procalcitonin-neutrophil-counts-strem-1-opn-clinical-status-and-short-term-outcomes-between-pneumonic-and-non-pneumonic-exacerbations-in-copd-patients