Author’s response to reviews

Title: The Mortality Risk Factor of Community Acquired Pneumonia Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

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Author’s response to reviews:

Dear Prof. Fabiano Di Marco,

I am pleased to resubmit for publication the revised version of PULM-D-17-00388, "The Mortality Risk Factor of Community Acquired Pneumonia Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study". I appreciate the constructive criticisms of the reviewers. I have addressed each of their concerns as below.

Please find the attached point-by-point response to reviewer’s concerns. We sincerely hope you find our revised manuscript is acceptable for publication.

Sincerely,

Jin-Fu Xu, Ph.D., M.D.
Salvatore Battaglia (Reviewer 1):

1) METHODS: SEVERITY SCORES. "The severity scores were assessed using PSI, CURB-65 and APACHE- II scores by two doctors. The highest score within 72 hours of admission was chosen and recorded". The study is retrospective. Did the Authors calculated the severity scores retrospectively or instead the scores are those originally calculated by doctors who cured the patients?

Answer: We want to clarify that the severity scores, PSI, CURB-65 and APACHE- II, were collected and calculated by the authors retrospectively (by Dr. RD and Dr. QK). We modified the Methods in Line 13-16 on Page 7.

2) RESULTS: it is not clear whether COPD patients were in more severe conditions BEFORE hospital admission for CAP. Could the Authors provide some index of general performance status at admission? Did COPD patients suffer for chronic respiratory failure before admission? In this contest, the lack of lung function tests in non-COPD (see table 1) makes it impossible to state that nCOPD had normal lung function
Answer: We appreciate reviewer's suggestion. We examined general performance status at admission and recorded symptoms of the patients, which were highlighted in Table 1. We also did arterial blood gas analysis of COPD-CAP patients during stable stage, and the records were collected in Supplementary Materials Table 1. 24 (10.4%) COPD-CAP patients in stable stage had type 2 respiratory failure, less than on admission (52/22.6%). The procedure of data collecting is described in the Supplementary Materials Figure 5. As a retrospective study, patients who did not done lung function test were excluded. Only the patients with post-bronchodilator FEV1/FVC ≥ 70% were recruited in nCOPD-CAP group. Therefore, nCOPD-CAP patients in this study had normal lung function. We revised the highlighted sentences in the Patients characteristics on Page 9.

3) RESULTS AND TABLES 3 AND 4. The Authors only showed logistic analysis for mortality in COPD-CAP. Why they did not show data for nCOPD-CAP?

Answer: The logistic analysis for in-hospital mortality and 60-day mortality in nCOPD-CAP patients are showed in Supplementary Materials Table 2 and Table 3. Age≥70, coronary heart disease, cerebral infarction, need for NIMV, albumin<30g/dl, D-dimer>2.0μg/mL, PSI>130, CURB-65≥3, APACHE-II≥20 are recruited in multivariate analysis. PSI>130 (OR = 31.095, 95%CI = 1.443-670.154, P = 0.028), CURB-65≥3 (OR = 51.936, 95%CI = 3.130-861.725, P = 0.006) and APACHE-II≥20 (OR = 43.210, 95%CI = 2.705-690.249, P = 0.008) are the risk factors for in-hospital mortality. Cerebral infarction (OR = 20.659, 95%CI = 2.001-213.26, P = 0.011), PSI>130 (OR = 12.186, 95%CI = 1.744-85.153, P = 0.012) and CURB-65≥3 (OR =47.999, 95%CI = 2.619-879.551, P< 0.001) are the risk factors for 60-day mortality. We included this result in "Results"—"Mortality risk factors" on page 11-12.

4) RESULTS; MORTALITY RISK FACTORS: "Eleven covariates were recruited in the univariate analysis …". Given that COPD-CAP and nCOPD-CAP differed by comorbidities (see table 1: Coronary heart disease and Cerebral infarction) I would include these comorbidities in the multivariate analysis.

Answer: We appreciate your constructive advice. We have done logistics analysis on coronary heart disease and cerebral infarction. The results are added in Result -Table 3 and Table 4. According to the results, comorbid with coronary heart disease is the risk factor for 60-day mortality in CAP-COPD patients. We revised the manuscript by including the analysis of coronary heart disease and cerebral infarction (the first paragraph on Page 11).
5) RESULTS; ROC CURVES: in the method sections the Authors indicated that: "The optimal cut-off values were determined by the Youden index". However, in the result section the optimal cutoff point is not reported for PSI, CURB-65 and APACHE-II. AUC, Se and Sp were only reported. It is not clear whether the Authors use the worst score for each index as cutoff point (i.e. CURB >3; PSI> 130, and APACHE-II >20).

Answer: We appreciate reviewer's comments. We want to clarify that the cut-off values were determined by the maximum Youden index (Youden index = Se + Sp – 100%), which means the optimal Sensitivity and Specificity of ROC curve. The data and computing processes (Medcalc Version 15.2.2 software (Mariakerke, Belgium)) of ROC curves are showed in Supplementary Materials Figure 2, and the optimal Sensitivity and Specificity of each ROC curve are highlighted. The classification of severity scoring systems was based on related references and determined by Dr. RD and Dr. QK [1, 2].

6) TABLE 1 AND METHODS: need for NIMV. One of the criteria of "Need for non-invasive mechanical ventilation (NIMV) was respiratory acidosis (pH<7.35). However the pH range is 7.35-7.45. As consequence the statistical difference in NIMV for COPD-CAP was not related to respiratory acidosis. Since respiratory acidosis is expected to be the most frequent cause of need for NIMV in COPD patient, the Authors should show the cause that lead to NIMV.

Answer: The need for NIMV was determined according to 2002 BTS Guideline [3]. “Need for non-invasive mechanical ventilation (NIMV) was applied to situations when a patient met one of these criteria, diagnosed COPD with a respiratory acidosis pH 7.25–7.35 (H+ 45–56nmol/l), hypercapnic respiratory failure secondary to chest wall deformity (scoliosis, thoracoplasty) or neuromuscular diseases, cardiogenic pulmonary edema unresponsive to continuous positive airway pressure (CPAP), weaning from tracheal intubation”. COPD patients, combined with carbon dioxide retention, were easier to present type 2 respiratory failure when they had bacteria infection. Confalonieri M. et al indicated that using NIMV could improve survival of severe CAP patients comorbid with COPD [4]. Following these criteria, we compared the number of patients in need for NIMV. The number of COPD-CAP patients, who were in need for NIMV, were much greater than that in nCOPD-CAP patients. Therefore, there was significant difference between COPD-CAP patients and nCOPD-CAP patients in need for NIMV.

7) DISCUSSION: the authors should report the main finding(s) of the study in the first paragraph of the discussion. In addition the discussion is not easy-to-follow. Main findings, novelty, comparison with literature, mechanisms and limitations should be addressed in a clearer manner.

Answer: We appreciate reviewer's suggestion. We revised Discussion in highlighted sentences as your suggestions and hope it will make the discussion part clearer and more comprehensive.
8) CONCLUSIONS: it seems that COPD-CAP has identical mortality rate in spite of worst initial conditions. This is not expected and deserve discussion.

Answer: Thanks for your suggestion. We revised Discussion and Conclusion in highlighted sentences. We hope it will make the two parts more profound.

Silvia Terraneo, MD (Reviewer 2)

Major:

I suggest better clarifying the aim of the study and consequently structuring the text. The title of this work refers to "mortality risk factor of CAP in COPD" but at the end of the introduction you wrote about the comparison of the predictive values among the scores on different clinical outcomes.

First: what do you mean with "different" outcomes? I guess mortality (in-hos and 60-days) but it would be better to clarify it. In methods you categorized mortality as primary outcomes and the need for NIMV and ICU admission as secondary but I could not find analysis about this last in Results section. Why? And then, the first part of results is about COPD characteristics and outcomes compared to non-COPD and the comparison between scores is on the contrary reported at the end of the "Results" section. The same suggestions apply to the abstract as well.

Answer: We appreciate reviewer's comments and suggestion. We revised the Introduction and we clarify there the aim of this study is to study mortality risk factors of CAP in COPD. In terms of "different outcomes", we categorized in-hospital mortality and 60-day mortality as primary outcomes, and need for ICU admission and need for NIMV as secondary outcomes in our study. Therefore, the “different” outcomes here mean the primary and secondary outcomes in the manuscript. We revised the manuscript. (Line 15-17, Page 4; Line 16, Page 10) We did ROC analysis of both primary and secondary outcomes. ROC analysis of primary outcomes is shown in the Result part. In the Supplementary Material Figure 3, we analyzed secondary outcomes among PSI, CURB-65 and APACHE-II scores using ROC curves. In predicting need for ICU admission, there was a trend toward significance between PSI and APACHE-II (Z statistic = 1.840, P = 0.0658), and there was no significance between PSI and CURB-65 (Z statistic = 1.355, P = 0.175), and between CURB-65 and APACHE-II (Z statistic = 0.0622, P =0.9504). Moreover, there was a significance between PSI and CURB-65 (Z statistic = 3.411, P = 0.0006), and between CURB-65 and APACHE-II (Z statistic = 4.110, P <0.0001) in predicting need for NIMV. There was no significance between PSI and APACHE-II (Z statistic = 0.679, P =
We revised the manuscript as you suggested by including the analysis of secondary outcomes on Page 13.

We want to clarify that in the first part of Result we compared the characteristics between COPD-CAP patients and nCOPD-CAP patients. In the logistic regression analysis and ROC analysis, we selected COPD-CAP patients as study population. We revised the abstract in the manuscript (Line 19-20, Page 2) as your suggestions and hope it will make Abstract part clearer.

Methods

I suggest to better explaining: how did you select CAP patients? Do you have a prospectic database? Did you collect the data from medical records? Please explain how were the patients diagnosed with CAP (please explain ref 3). Please explain what do you mean with life threatening diseases over 1 year (second exclusion criteria) and why did you choose it as exclusion criteria. Data collection: please better explain how did you collect data: two independent physician but how? Did both physicians collect all data? How did you choose which data to analyze? How did you assess mortality?

Answer: Dr. RXD and Dr. QHK recruited CAP patients from the database of Shanghai Pulmonary Hospital and Shanghai Dahua Hospital. All the data were collected from medical records in Electronic Medical Record Management System.

CAP patients were diagnosed in accordance with 2009 BTS Guidelines [5]. The main criterions are as following. We revised the Methods in Line 3-8 on Page 5.

→ Symptoms of an acute lower respiratory tract illness (cough and at least one other lower respiratory tract symptom);

→ New focal chest signs on examination;

→ At least one systemic feature (either a symptom complex of sweating, fevers, shivers, aches and pains and/or temperature of 38°C or more);

→ No other explanation for the illness, which is treated as CAP with antibiotics.

As for the second exclusion criteria, it means excluding the patients who had been diagnosed with life-threatening disease within the past year. The life threatening diseases included advanced malignant tumor, severe cardiopulmonary dysfunction, renal or liver dysfunction, etc. which was expected to limit patients' life to less than 12 months. We chose these as exclusion criteria to rule out the factors that could contribute to the all-cause mortality, in order to ensure the all-cause
mortality was only caused by CAP. This exclusion criteria is also used in the study by Steer J. et al [6]. We revised the Methods in first paragraph in Line 11-13 on Page 5.

All data were independently collected by Dr. RXD and Dr. QHK according to the inclusion criteria (1) age ≥18 years; 2) diagnosed with CAP on admission) with unified Excel table. The unified Excel table was designed by Dr. RXD and Dr. QHK, it included the information which should be collected. The unified Excel table is showed in Supplementary Material Figure 4. Then the Excel tables were compared for discrepancies. Differences were resolved after discussion, and extreme values were examined by rechecking the data collection forms. We revised the Method in the second paragraph on Page 7.

The in-hospital mortalities were assessed by medical records and 60-day mortalities were assessed by telephone survey.

Abstract line 13: I suggest inserting the percentage of COPD

Methods, statistical analysis line 17: I suggest inserting "Receiver-operating characteristic"

Results patient's characteristics line 2 page 2: I suggest to remove "The COPD-CAP patients were predominant in GLOD 2 and GLOD 3 (34.8%, 38.3%)", this information is clear from table 1

Answer: Thanks for your suggestion. We revised the manuscript according to your advices. (Line 10, Page 2; Line 19, Page 8; Line 7-8; Page 10)

Reference


