Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-2024-2171

Review Comments

COPD's current mortality projection ranks third among all causes.

Response: Thank you for raising this important point regarding the global ranking of mortality due to COPD. We fully understand your question and have conducted an in-depth review of the literature.

The data on the ranking of COPD mortality cited in this study are derived from the latest "Related Global Health Estimates" report and the fact sheet on the official website of the World Health Organization (WHO). According to our verification prior to submission, WHO still lists it as the fourth leading cause of death globally. Relevant links:
https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))

We have also noted the point mentioned by the reviewer, which likely originates from another authoritative data source—the Global Burden of Disease Study (GBD). The GBD 2019 and subsequent analyses (e.g., PMID: 39548320, 40684784) often rank COPD as the third leading cause of death. This discrepancy arises from differences in data modeling, statistical methods, and data source integration among different institutions.

To address your comment and ensure clarity and accuracy in our statements, we have revised the introduction section (Page 2, lines 39-42) of the manuscript to explicitly state that our data source is WHO. We have also fine-tuned the relevant wording to avoid any potential misunderstandings due to differences in data sources.

Once again, we appreciate your rigorous and professional review, which is crucial for improving the quality of our paper.

Please, provide a definition of exacerbation as well as sepsis.

Response: Thank you for your careful review and emphasis on the precise definition of the terms. Below are the definitions of the two terms provided in accordance with widely accepted guidelines:

Sepsis: As used in our study and in line with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is identified by an acute change in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of ≥2 points following infection (PMID:26903338). This definition is strictly applied in our methodology for patient identification.

Exacerbation (COPD Acute Exacerbation): An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is typically defined as an acute event characterized by a worsening of the patient's respiratory symptoms (e.g., increased dyspnea, increased sputum purulence, and/or increased sputum volume) beyond normal day-to-day variations and leading to a change in medication regimen (Global Initiative for Chronic Obstructive Lung Disease, GOLD 2024 Report, https://goldcopd.org/2024-gold-report/).

We would like to kindly clarify that while the concept of COPD exacerbation is mentioned in the introduction as part of the broader clinical context of these patients, our study does not specifically investigate or use exacerbation as a variable in our predictive model. Our analysis is based on the 30-day mortality of patients with COPD complicated by sepsis as defined above.

We hope this clarification is helpful. Thank you again for your comments.

Which parameters were considered for sepsis diagnosis? was procalcitonin detected?
On line 32 please replace restriction with airflow limitation. Better clarify the clinical outcomes considered and the parameters for defining sepsis.
What about vaccination to prevent exacerbations?
Clarify which biological samples were being considered for microbiological analysis.
How was the diagnosis of COPD made in the ICUs?
Explain what the highest levels of severity are and what the main causes of death are.
Explain why the choice of the anion gap as the covariate

Response: Thank you for raising this important question. The diagnosis of sepsis in this study strictly follows the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [PMID: 26903338]. This criterion requires the fulfillment of the following two conditions:

1. Confirmed Infection: Confirmed by positive microbiological culture results from biological samples (such as blood, sputum, urine, or other body fluids).

2. Acute Organ Dysfunction: An increase in the Sequential Organ Failure Assessment

(SOFA) score of ≥2 points from the baseline. The SOFA score is calculated based on the worst values within the first 24 hours after the patient's admission to the ICU and includes the following parameters, all of which are extracted from the MIMIC-IV database: Respiratory system: PaO_2/FiO_2 ratio; Coagulation system: Platelet count; Liver: Bilirubin level; Cardiovascular system: Mean arterial pressure or the need for vasopressor use; Central nervous system: Glasgow Coma Score (GCS); Kidney: Creatinine level or urine output.

Regarding Procalcitonin (PCT), we acknowledge its significant value as a biomarker for bacterial infection and the severity of sepsis. However, in the patient cohort included in our study, the MIMIC-IV database did not routinely test for or provide data on PCT levels. Therefore, our diagnostic criteria are based on the internationally recognized Sepsis-3 definition to ensure the standardization and reproducibility of the methods in this retrospective study.

Response: Thank you for your careful review and valuable suggestions. We have made revisions to this part based on your advice. For detailed information on the modifications, please refer to the manuscript.

Response: Thank you for raising this important question. The diagnosis of sepsis in this study strictly adhered to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [PMID: 26903338]. This criterion requires simultaneous fulfillment of the following two conditions:

1. Confirmed infection: Confirmed by positive microbial culture results from biological samples (such as blood, sputum, urine, or other body fluids).

2. Acute organ dysfunction: An increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score from the baseline. The SOFA score is calculated based on the worst values within the first 24 hours after the patient's admission to the ICU and includes the following parameters, all of which were extracted from the MIMIC-IV database: Respiratory system: PaO_2/FiO_2 ratio; Coagulation system: Platelet count; Liver: Bilirubin level; Cardiovascular system: Mean arterial pressure or the need for vasopressor use; Central nervous system: Glasgow Coma Scale (GCS); Kidney: Creatinine level or urine output.

Regarding vaccination for the prevention of exacerbations, we acknowledge its significant value. However, in the patient cohort included in our study, the MIMIC-IV database did not routinely test for or provide data on vaccinations for the prevention of exacerbations. We would like to kindly clarify that, although the concept of COPD exacerbations was mentioned in the introduction as part of the broader clinical context of these patients, our study did not investigate exacerbations as a specific variable or

use them in our predictive model. Our analysis was based on the 30-day mortality of COPD patients with sepsis as defined above.

Response: Thank you for these questions regarding our methodological details. Please find our clarifications below:

Microbiological Analysis for Sepsis Diagnosis:
The diagnosis of infection, in accordance with the Sepsis-3 criteria, was confirmed by a positive microbial culture. The MIMIC-IV database contains records of cultures obtained from a wide range of biological samples pertinent to the ICU setting. This includes blood (most common for systemic sepsis), sputum (particularly relevant for respiratory infections in COPD patients), urine, cerebrospinal fluid, and wound swabs, among others.

Diagnosis of COPD in the ICU:
The identification of COPD patients was based on International Classification of Diseases (ICD) codes recorded in the MIMIC-IV database. Specifically, we utilized ICD-9 codes (491.20, 491.21, 491.22, 496) and ICD-10 codes (J44, J44.0, J44.1, J44.9), an approach consistent with previously published studies using the MIMIC-IV database [PMID: 37484842]. These ICD codes reflect clinical diagnoses made during hospitalization, which are typically established by treating clinicians based on a combination of patient history, pre-admission pulmonary function tests (where available), imaging findings (e.g., chest X-ray or CT demonstrating emphysema or hyperinflation), and compatible symptoms (e.g., chronic cough, dyspnea).

We hope these clarifications satisfactorily address your questions.

Response: Thank you for your careful review and valuable questions. Here are our clarifications regarding the issues you raised:

1. Highest Severity Level:

In this study, the highest severity level refers to the most severe value of each vital sign and biochemical indicator collected within the first 24 hours after ICU admission, which is selected as the representative data. For example, indicators such as glucose, creatinine, white blood cell count (WBC), PaO_2, and PCO_2 are all recorded with their most abnormal values (either the highest or lowest, depending on clinical significance). Specific details are shown in Table S1 (Page 5, line 128).

2. Primary Cause of Death:

This study focuses on the robust primary endpoint of 30-day all-cause mortality, and

the MIMIC-IV database does not allow us to determine a specific single cause of death for each patient. However, based on the clinical characteristics of our cohort (patients with both COPD and sepsis) and established medical literature, the most likely primary cause of death is due to progressive organ failure and complications of sepsis, such as cardiovascular failure caused by refractory septic shock and respiratory failure (PMID: 38745253, 40230845).

We hope that the above clarifications fully address your concerns.

Response: Thank you for your careful review and valuable questions. Here are our explanations regarding the issues you raised:

During the variable selection stage of our predictive model development, anion gap was considered as a candidate predictor because of its clear clinical significance as a marker of metabolic acidosis. Elevated AG is closely related to conditions such as tissue hypoperfusion and lactic acidosis, which are both common and crucial in patients with severe COPD [PMID: 38444550] and sepsis [PMID: 36660703]. Given that our study population suffers from both conditions, we hypothesized that AG might be a valuable variable for predicting mortality risk.

It is important to note that although AG was initially selected as a candidate predictor based on clinical reasoning and further shortlisted by the LASSO regression algorithm (as described in the manuscript), it was ultimately not retained in the multivariate Cox regression model. This indicates that, despite its clinical relevance, the predictive contribution of AG was not independent of other stronger predictors (such as age and APSIII), which ultimately constituted our nomogram.

Thank you for highlighting this point. We hope that the above clarifications fully address your concerns.

what functional parameters were considered, were complications assessed?

Response: Thank you for your careful review and valuable comments. Here are our responses to the questions you raised:

1. In our study, the term “functional parameters” mainly refers to vital signs and laboratory indicators that reflect the physiological functions of patients. These parameters are collected within the first 24 hours after ICU admission to assess the degree of organ function and failure. Specifically, they include:

- Respiratory function: Respiratory rate, SpO_2, PaO_2, PCO_2, and PaO_2/FiO_2 ratio (included in scores such as SOFA).
- Circulatory function: Heart rate, mean blood pressure (MBP), and the use of

vasopressors.
- Renal function: Urine output, serum creatinine, and blood urea nitrogen (BUN).
- Hepatic function: Bilirubin.
- Coagulation function: Platelet count, PT, PTT, and INR.
- Acid-base balance and metabolic function: pH, anion gap, and bicarbonate.
- Others: Body temperature, blood glucose, etc.

These parameters have been detailed in Table 1 of the paper. We have revised the manuscript to more clearly articulate the functional classification of these parameters in the Methods section (Section 2.3) (Pages 4-5, lines 104-129).

2. We have assessed comorbidities. A variety of important comorbidities were included in this study, with the data extracted from the MIMIC-IV database. Complications were assessed using components of the Charlson Comorbidity Index and ICD codes. The main comorbidities included congestive heart failure (46.7% vs 41.8%, $p = 0.107$), mild liver disease (17.9% vs 10.6%, $p < 0.001$), renal disease (28.5% vs 22.6%, $p = 0.024$), and malignancy (18.2% vs 11.2%, $p = 0.001$). Organ dysfunction was captured by the SOFA/APSIII score. These were included in the LASSO/Cox model.

Thank you for highlighting this point. We hope that the above clarifications fully address your concerns.

better explain in Table 1 which test was applied and in general which subgroups were compared.

Response: Thank you for your careful review and valuable comments. Here are our responses to the questions you raised:

Table 1 compares all baseline characteristics between the “30-day survival” and “30-day death” subgroups within the entire study population.

Statistical tests applied: For continuous variables (such as age, scores, laboratory indicators), we used the median (interquartile range) [Median (IQR)] for description. Since these data are usually non-normally distributed, we used the Wilcoxon-Mann-Whitney U test for between-group comparisons. For categorical variables (such as gender, race, treatment measures, comorbidities), we used frequency and percentage (n, %) for description and the chi-square test for between-group comparisons.

Based on your suggestion, we have revised the Methods section (Sections 2.2/2.4) to provide a more detailed explanation of the primary outcome variable of this study and the specific statistical methods used to ensure complete transparency (Page 4, lines 97-102; Page 5, lines 131-135).

Thank you for highlighting this point. We hope that the above clarifications fully

address your concerns.

Explain in the methods what is meant by train set

Response: Thank you for your careful review and valuable comments. Regarding the issues you raised, we have added the definitions of the training set and validation set in the Methods section (Section 2.2) (Page 4, lines 97-102). Please refer to the manuscript for the specific details of the revisions.

Once again, thank you for taking the time and effort to review our paper and provide these constructive suggestions. We hope that the above responses and corresponding revisions meet your requirements.

Factors influencing the onset and evolution of COPD should be discussed
I suggest to include the following reference, useful for the discussion
Int J Chron Obstruct Pulmon Dis. 2023 Dec 1; 18:2861-2865

Response: Thank you for your careful review and valuable comments. Based on your suggestions, we have enriched the discussion section of the article, providing a more comprehensive discussion on the general factors influencing the onset and progression of COPD. Meanwhile, we have also cited the literature you recommended, which offers valuable insights into this process. We have incorporated it into the revised manuscript to strengthen the background of our discussion. Please refer to the manuscript (Pages 8-9, lines 231-244) for the specific details of the revisions. We hope you will be satisfied with our modifications.