

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-24-831>

### Reviewer A

The authors investigated the prognostic factors associated with pulmonary aspergillosis. Given the poor prognosis for patients with this condition and its recent rise in attention, this type of study is essential. However, due to numerous flaws in the current study, I do not believe it should be accepted in its current form. I recommend that the following concerns be properly addressed.

#### Major concern #1

The study population includes both chronic pulmonary aspergillosis (CPA) and invasive pulmonary aspergillosis (IPA). Since the prognosis for IPA and that for CPA are totally different, these two conditions should be distinguished. Although the authors mentioned in the limitations section that they could not analyze CPA and IPA separately due to the small sample size, the results will not be meaningful unless the distinction is made.

Reply 1: Thank you very much for your constructive suggestions. According to your comments, we have made the following changes. We separated IPA and CPA, and only analyzed CPA. Because in CPA, we found smoking, simultaneous discovery with gram-negative bacteria, hypoalbuminemia, emphysema and lung cancer were associated with mortality of CPA. Among them emphysema and lung cancer were independent prognostic factors. We think that makes sense.

Changes in the text: see in Title, abstract, introduction, method, result, discussion, conclusion

#### Major concern #2

The descriptions in the Methods section are inadequate.

Reply 2: Thank you very much for your valuable comments, according to your comments, we added a detailed description of the methods section.

Changes in the text: see Page 8, line 156-159, Page 10, line 201-203

- It is unclear how the authors identified the study population. I imagine the authors collected data from patients' electronic health records and identified the study population via inclusion criteria. This should be mentioned early in the Methods section.

Reply: Thank you very much for your valuable comments. We described the study population in detail. "We searched the medical records system in the time period from November 2019 to August 2023, in the Respiratory Department of Anhui Chest Hospital, then collected medical records of patients who diagnosed with CPA. Those who met the inclusion criteria were included in our study."

Changes in the text: see Page 8, line 156-159

- I could not understand how patients were followed up. I imagine the start of the follow-up was the diagnosis date of pulmonary aspergillosis, and the end of the follow-up was the telephone contact date (or the date of death). The method of follow-up should be described more precisely, including at least the definitions of the start and end of the follow-up, the date of the telephone contact, and whether the date of death was identified in deceased cases.

Reply: Thank you very much for your valuable review comments. According to your suggestion, we made the following changes: "We collected medical records of these patients and then followed up by telephone, for patients who died, the end point of follow-up was defined as the date of death, for surviving patients, the end point of follow-up was defined as the date of the last telephone contact."

Changes in the text: see Page 10, line 201-203

- Univariate and multivariate Cox proportional hazard analyses were performed, but this was not mentioned in the Methods section. This should be explicitly stated. Furthermore, the criteria for selecting covariates included in the multivariate model should be clearly explained.

Reply: Thank you very much for your valuable review comments. According to your suggestion, We have added the description of this section. Univariate and multivariate Cox proportional hazards regression analyses were applied for identification of potential prognostic factors, the hazard ratio (HR) of a variable and 95% confidence intervals (95%CI) were calculated. We found five candidate variables (emphysema, smoking, hypoalbuminemia, lung cancer, gram-negative bacteria) in univariate Cox proportional hazard model, then we entered these into multivariate Cox proportional hazard model.

Changes in the text: see Page 11, line 213-218

### Major concern #3

The English in the manuscript is poor. Therefore, I recommend that the authors use an English proofreading service. Examples of poor English are as follows:

we have modified our text as advised as follows

- (Abstract > Introduction) “focus” should be “focusing”. See Page 4, line 62
- (Abstract > Methods) “analysis” should be “analyze”. See Page 4, line 65
- (Abstract > Results) “patients are male” should be “patients were male”. See Page 4, line 72
- (Abstract > Results) there are some expressions for Aspergillus. (“aspergillus”, “aspergillus”) These should be unified. The statement containing the word is deleted
- (Abstract > Conclusions) “we will pay” should be “we should pay”. See Page 5, line 95

(The followings are poor expression or sentences)

- (Introduction > L60) “when inhalation” See Page 6, line 107
- (Introduction > L64-66) “The occurrence of CPA is ~ and have a mild immune impairment” See Page 6, line 115
- (Introduction > L74) “using” See Page 6, line 124
- (Introduction > L97) “focus” See Page 8, line 152
- (Methods > L118-119) “Found evidence ~ were positive” See Page 9, line 189
- (Results > L158) “patients had” See Page 12, line 246
- (Discussions > L263) “improving” See Page 18, line 384

### Major concern #4

The authors should reference appropriate previous studies in the second paragraph of the Introduction section.

Reply 4: Thank you very much for your valuable review comments. According to your suggestions, in the second paragraph of the Introduction section, we have added the following relevant references.

[8] Feys S, Gonçalves SM, Khan M, et al. Lung epithelial and myeloid innate immunity in influenza-associated or COVID-19-associated pulmonary aspergillosis: an observational study. *The Lancet Respiratory Medicine* 2022;10:1147-59.

[9] Bongomin F, Harris C, Foden P, et al. Innate and Adaptive Immune Defects in Chronic Pulmonary Aspergillosis. *Journal of Fungi* 2017;3.

[10]. Barberan J, Sanz F, Hernandez J-L, et al. Clinical features of invasive pulmonary aspergillosis vs. colonization in COPD patients distributed by gold stage. *Journal of Infection* 2012;65:447-52.

Changes in the text: [See Page 6, line 119-132](#)

#### Major concern #5

Although the authors noted that the most significant and important "prognostic factor" is pulmonary TB, this is not true. I suspect the authors are misusing "prognostic factors" instead of "risk factors."

Reply 5: Thank you very much for your valuable review comments. Cox regression model also known as risk regression model Which takes binary outcome and survival time as dependent variables, and independent variables can be continuous variables or categorical variables. The most common use is to analyze survival data, such as studying the survival time of patients and the predictors that are related to survival time. It can also be used for prognostic assessment, that is, to determine the factors that affect a patient's prognosis. In our article we used Cox regression model to screen out the factors related to the prognosis of CPA. Linear regression, Logistica regression, and Cox proportional hazard regression are the three most common risk factor statistical schemes. Logistic regression model is a nonlinear regression analysis, which is a multiple regression analysis method to study the relationship between binomial or multinomial classification structure of dependent variables and some influencing factors, such as analyzing the quantitative relationship between the occurrence of diseases and various risk factors.

#### Major concern #6

In the Results section, the follow-up periods and 1-, 3-, and 5-year survival rates should be clearly specified.

Reply 6: Thank you very much for your valuable review comments. According to your suggestions, we added the data of The 1-, 3-year survival rates with emphysema were 75.2%, 64.9%,

respectively. While for those without emphysema were 92.6%, 85.9%, respectively.. Because the follow-up time of this study is not very long, so the 5-year survival was deficient.

Changes in the text: see Page 5, line 91-91; See Page 10, line 209-211, See Page 13, line 262-264

#### Major comment #7

Some prognostic factors independently associated with pulmonary aspergillosis were identified through multivariate Cox proportional analyses. Only these variables should be mentioned in the Abstract, Conclusions, and Key Findings sections. Variables that were significantly associated with poorer prognosis only in the log-rank tests and univariate Cox proportional analyses should not be included in these sections.

Reply 7: Thank you very much for your valuable review comments. According to your suggestions, In Abstract, Conclusions, and Key Findings sections, we only wrote the variables with statistical significance in multivariate Cox proportional hazard model.

Changes in the text: we have modified our text as advised (see Page 2, line 26; Page 5, line 93-93; Page 20, line 416-417)

#### Minor concern #1

I cannot understand the first diagnostic criteria for CPA.

Thank you very much for your valuable review comments. According to your suggestions, We deleted the first diagnostic criteria for CPA, and added as “(1) had clinical symptoms for more than 1 months, such as fever, cough, sputum, hemoptysis, dyspnea, etc,”

Changes in the text: we have modified our text as advised (see Page 9, line 174-176)

#### Minor concern #2

Results > L142 > “at the time of prognosis”

What does this mean? The authors likely mean "at the end of follow-up."

Reply 2: Thank you very much for your valuable review comments. It should be “at the time of diagnosis”

Changes in the text: we have modified our text as advised (see Page 11, line 224)

Minor comment #3

The expression “co-infected” should not be used for gram-positive and gram-negative bacteria, as they were likely merely colonized.

Reply 3: Thank you very much for your valuable review comments. According to your suggestions, we deleted “co-infected”, instead of “simultaneous discovered with gram-negative bacteria”

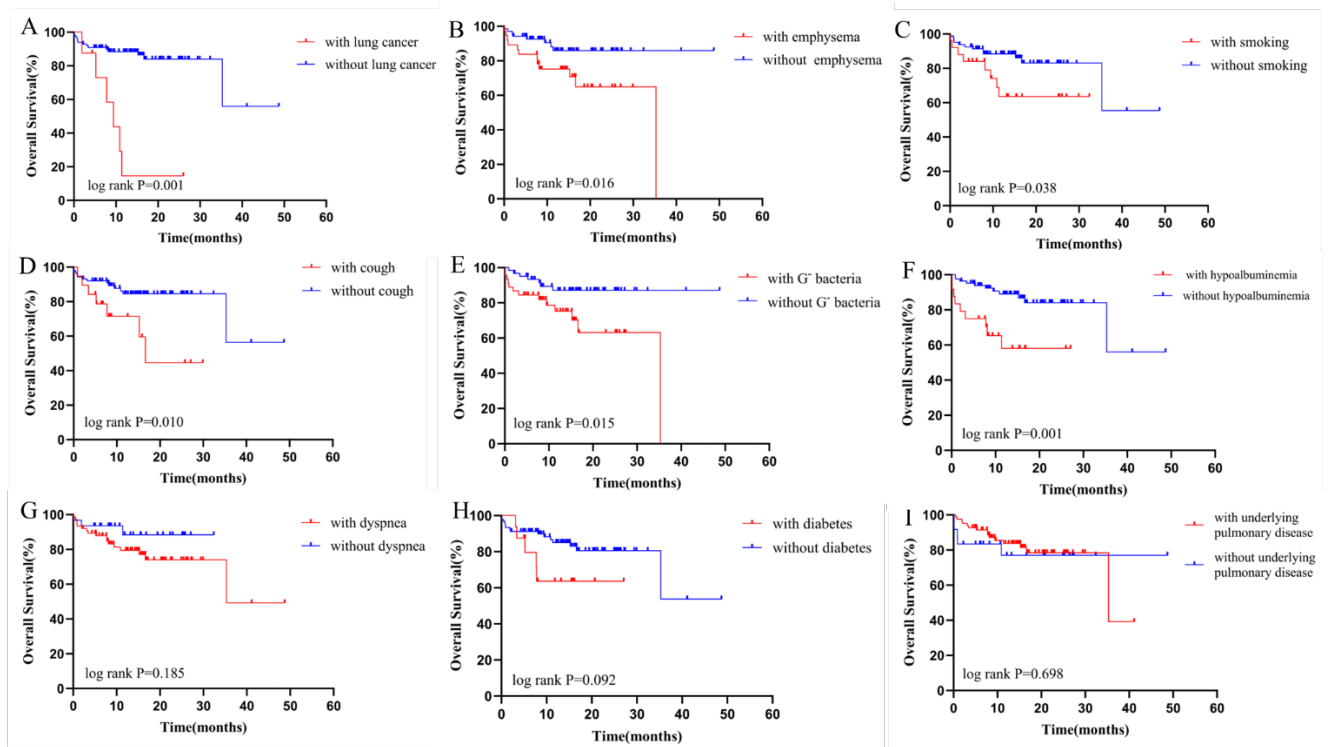
Changes in the text: we have modified our text as advised (see Page 12, line 254)

Minor comment #4

Figure 3 is too small. I recommend that the authors focus on specific variables to improve clarity. Additionally, the red line denotes "with" in some plots and "without" in others; this should be standardized for consistency.

Reply 4: Thank you very much for your valuable review comments. According to your suggestions, we unified red line as "with", blue line as "without". We attached a clear picture here for your convenience.

Changes in the text: we have modified our text as advised



## Reviewer B

1) The primary concern on this study is that the authors treat both invasive and chronic aspergillus infection confusingly. Basically, these infections are categorized into different diseases because these clinical courses differ significantly. As the authors mention in the Introduction section, IPA is an acute life-threatening infection with extremely high mortality, while CPA is a chronic infection which gradually destroys lung parenchyma. The authors showed that the existence of lung cancer or interstitial lung disease has significant relationships on patient mortality. In patients with CPA, it is easy to understand that the existence of both diseases poses considerable effect on patient mortality. However, can the authors say the same thing in patients with IPA through this study? I believe that the authors should evaluate both diseases separately. Otherwise, the effect or background of aspergillus infection can't be clarified through this study.

Reply 1: Thank you very much for your constructive suggestions. According to your comments, we have made the following changes. We separated IPA and CPA, and only analyzed CPA. Because in CPA, We found smoking, simultaneous discovery with gram-negative bacteria, hypoalbuminemia, emphysema and lung cancer were associated with mortality of CPA. Among them emphysema and lung cancer were independent prognostic factors. We will continue to study the prognosis of IPA later.

Changes in the text: see in Title, abstract, introduction, method, result, discussion, conclusion

2) In the Introduction, the number of mortality due to IPA is too many. The authors mention "2113 million", but the actual number should be "2.1 million". Please recheck the referenced article.

Reply 2: Thank you very much for your valuable review comments, we are sorry for our carelessness, since we deleted the IPA, we also deleted this sentence.

Changes in the text: The sentence was deleted

3) Introduction part seems to be a little lengthy. I recommend the authors to shorten this part.

Reply 3: Thank you very much for your constructive suggestions, according to your comments we shorten this part.

Changes in the text: see Page 6, line 120-123; Page 7, line 127-129,142-144

Anyway, the IPA and CPA should be evaluated separately. I strongly encourage the authors to submit their study once again after this re-evaluation.

Thank you very much for your constructive suggestions, we quite agree with you.