

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

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| TITLE (PROVISIONAL) | Fibrosis-4 Index as a Predictor for Mortality in Hospitalized Patients with COVID-19: a retrospective multicenter cohort study |
| AUTHORS | Park, Jung Gil; Kang, Min Kyu; Lee, Yu Rim; Song, Jeong Eun; Kim, Na Young; Kweon, Young Oh; Tak, Won Young; Jang, Se Young; Lee, Changhyeong; Kim, Byung Seok; Hwang, Jae Seok; Jang, Byoung Kuk; Bae, Jinmok; Lee, Ji Yeon; Suh, Jeong Ill; Park, Soo Young; Chung, Woo Jin |

VERSION 1 – REVIEW

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| REVIEWER | Emanuele Valeriani Internal Medicine Department, Campus Bio-Medico University of Rome, Italy |
| REVIEW RETURNED | 06-Aug-2020 |

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| GENERAL COMMENTS | <p>In this manuscript the authors tried to identify variables that may predict the risk of mortality in hospitalized patients with COVID-19 receiving respiratory support. The authors presented interesting data on a clinically relevant topic. They may consider clarifying some aspects of the methods to improve the overall quality of the manuscript. Discussion may be shortened to increase readability. The text contains some errors that require editing.</p> <p>Major comments</p> <p>ABSTRACT</p> <ol style="list-style-type: none">1. Authors should include the aim of the study2. More information on Methods should be provided (patients included, enrollement times, primary outcome)3. Authors should avoid reporting just the p values without related measures of effect. <p>INTRODUCTION</p> <ol style="list-style-type: none">1. Authors should shorten the part of the Introduction in which they discuss about general information on COVID-19. Furthermore, they should introduce Fibrosis-4 index putting it within context (it is mentioned first within the statistical analysis paragraph). Why did they choose this index of liver fibrosis? Readers may be unaware of the relation between Fibrosis-4 index and COVID-19. |
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| | <p>METHODS</p> <p>1. Inappropriate follow-up period: As specified within the methods, authors include in survival analysis also patients with one day of follow-up. Did the authors consider these patients as censored observation (no information on censored patients has been provided within the text nor within the Kaplan-Meier curves). Furthermore, they should report within the text the number of patients who were still hospitalized at the end of follow-up and adding this among limitations.</p> <p>2. Scant information on statistical analysis: Author should better clarify statistical methods used for the analysis. In particular, they should better describe the covariates for the construction of the Cox proportional hazard model and whether they had been chosen a priori. Furthermore, they should better describe any other planned analysis (some of data appeared directly on the Results without any information within the Methods). Finally, they should include the R packages name used to perform the statistical analysis.</p> <p>3. Authors should describe what “respiratory support” means. The type of respiratory support has been specified just in the Results. Furthermore, they consider within the analysis any kind of respiratory support, possibly biasing the analysis. Patients receiving invasive ventilation presented, indeed, a higher disease severity and mortality risk than patients receiving low flow nasal cannula (Figure 1). Authors should consider performing an additional survival analysis on patients with non-invasive or invasive ventilation and high or low fibrosis-4 index.</p> <p>4. Authors should define the Fibrosis-4 index within methods</p> <p>5. Sepsis definition is not provided within the text</p> <p>6. Please better describe the secondary objective and differences than the primary objective</p> <p>RESULTS</p> <p>1. Authors should be aware that the number of tested covariates was quite high for the number of events. They should acknowledge this within Limitations.</p> <p>2. Authors should consider reducing the list of variables in Table 1. They could include some of these variables within a supplementary Table. Furthermore, they should shorten the Results deleting some of the information that has been twice reported within the text and Table 1.</p> <p>DISCUSSION</p> <p>1. Authors should consider to shorten the Discussion and revise some sentences that appeared difficult to read.</p> <p>Minor comments</p> <p>Authors should begin the Discussion reporting the main results of the study.</p> |
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| | <p>Please amend the sentence:</p> <ul style="list-style-type: none"> - “The treatment patients received included...” page 7, line 41. - “primary objective of this study was to identify clinical and laboratory risk factors predictive of in-hospital mortality for any reason within 56 days...”. Page8, line 26-31. This sentence appears misleading for readers who may consider “56” as the length of follow-up. <p>Please check the correctness of the percentage of patients with ARDS (Page 10, line 29)</p> |
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| REVIEWER | Giada Sebastiani McGill University Health Centre, Canada |
| REVIEW RETURNED | 19-Aug-2020 |

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| GENERAL COMMENTS | <p>The study by Park et al reports the results of a retrospective, multicenter cohort study to identify risk factors for in-hospital mortality in COVID-19 confirmed adult patients in South Korea. Out of 1,005 patients, 289 received respiratory support, while 70 patients died. The researchers found that, on multivariable analysis, high FIB-4 index, low lymphocyte count and systemic inflammatory syndrome were independent risk factor for mortality in patients receiving respiratory support, with good accuracy.</p> <p>There is a clear need for biomarkers of severity and prognosis in COVID-19 infection. The study is interesting and well written.</p> <p>Comments</p> <ul style="list-style-type: none"> - authors should quote and comment the following paper, on similar topic: "Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19", published in Journal of Infectious Diseases (Luis Ibáñez-Samaniego, Federico Bighelli, Clara Usón, Celia Caravaca, Carlos Fernández Carrillo, Miriam Romero, Mónica Barreales, Christie Perelló, Antonio Madejón, Aránzazu Caballero Marcos, Agustín Albillos, Inmaculada Fernández, Javier García-Samaniego, José Luis Calleja, Rafael Bañares). - please replace the word "controlled" with "characterized" in the abstract (line 9); this wording is confusing for the study design. - in the result section of the abstract, please better explain lines 37-44, these results are not presented in a clear way. The authors should report the hazard ratio for the first sentence rather than the p value ("Regardless of respiratory support..."). For the second sentence, should be detailed as now it is too specific (remove the p-value and list the risk factors with HR; "A number of risk factors...") - strengths and limitations section: ", it is a most single reliable predictor of mortality in patients with COVID-19 regardless of respiratory support." Please rephrase, unclear meaning. - in the statistical analysis section, the researchers should provide details on how the multivariable models were built, how the exposures were chosen. Also, why the SOFA score was not included in this study? And, why sex was not included in the multivariable model? - more details on how patients were selected for antiviral therapy should be provided. - chronic liver diseases diagnosis should be better defined. How was that assessed? The prevalence at 5% seems quite low, |
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| | probably not including NAFLD. Which other aetiologies were included? |
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Emanuele Valeriani

Institution and Country

Internal Medicine Department, Campus Bio-Medico University of Rome, Italy

Please state any competing interests or state 'None declared': None declared

In this manuscript the authors tried to identify variables that may predict the risk of mortality in hospitalized patients with COVID-19 receiving respiratory support. The authors presented interesting data on a clinically relevant topic. They may consider clarifying some aspects of the methods to improve the overall quality of the manuscript. Discussion may be shortened to increase readability. The text contains some errors that require editing.

Major comments

ABSTRACT

Authors should include the aim of the study

As your comment, we revised our abstract with preferred format of this journal.

More information on Methods should be provided (patients included, enrollment times, primary outcome)

As your comment, we revised our abstract with preferred format of this journal.

Authors should avoid reporting just the p values without related measures of effect.

As your comment, we added effect size of survival analysis.

INTRODUCTION

Authors should shorten the part of the Introduction in which they discuss about general information on COVID-19. Furthermore, they should introduce Fibrosis-4 index putting it within context (it is mentioned first within the statistical analysis paragraph). Why did they choose this index of liver fibrosis? Readers may be unaware of the relation between Fibrosis-4 index and COVID-19. While we are submitting our manuscript, one article regarding relationship of FIB-4 and COVID-19 was published in Journal of Infectious disease (J Infect Dis 2020;222(5):726-33), which was mentioned from second reviewer. Though the design of published study is similar with our study, the interpretation of result is quite different. We think the patients with high FIB-4 is independently associated with mortality, because age, AST, and platelet count are associated with mortality in patient with COVID-19. It is not because of advanced fibrosis estimated by FIB-4. We did not mention

FIB-4 in introduction section because relationship between FIB-4 and COVID-19 was revealed during analysis of risk factors. However, as your comments, we think that introduction of FIB-4 is needed to be better to understanding our study for readers. Thus, we added explanation of FIB-4 in Method (definition) section. In addition, we quoted and commented regarding "Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19", published in Journal of Infectious Diseases in discussion section. (page 15, line 21- page 16 line 6)

METHODS

Inappropriate follow-up period: As specified within the methods, authors include in survival analysis also patients with one day of follow-up. Did the authors consider these patients as censored observation (no information on censored patients has been provided within the text nor within the Kaplan-Meier curve). Furthermore, they should report within the text the number of patients who were still hospitalized at the end of follow-up and adding this among limitations.

Thank you for good comments. Due to all cohort of COVID-19 patients was strictly monitored by Korean Government and law, it was impossible to be censored. All outcomes of the patients with COVID-19 were daily updated at website. As your comments, it is possible to be still hospitalized. We limited 56 days for follow-up period but there was no mortality thereafter. I think that is strength of our study.

Scant information on statistical analysis: Author should better clarify statistical methods used for the analysis. In particular, they should better describe the covariates for the construction of the Cox proportional hazard model and whether they had been chosen a priori. Furthermore, they should better describe any other planned analysis (some of data appeared directly on the Results without any information within the Methods). Finally, they should include the R packages name used to perform the statistical analysis.

As your comments, add revised 'Statistical analysis' section regarding Cox regression, its valuables, and the version of R package.

Authors should describe what "respiratory support" means. The type of respiratory support has been specified just in the Results. Furthermore, they consider within the analysis any kind of respiratory support, possibly biasing the analysis. Patients receiving invasive ventilation presented, indeed, a higher disease severity and mortality risk than patients receiving low flow nasal cannula (Figure 1). Authors should consider performing an additional survival analysis on patients with non-invasive or invasive ventilation and high or low fibrosis-4 index.

As your comments, we performed additional survival analysis in patients receiving high-dose oxygen. We added these results in last part of 'Result' section.

Authors should define the Fibrosis-4 index within methods

We added those as mentioned above

Sepsis definition is not provided within the text

I think that was misterm. We changed sepsis to persistent hypotension with designated definition in 'Method (Definition)' section.

Please better describe the secondary objective and differences than the primary objective

As your comments, we revised primary and secondary objective in Method (Study outcomes).

RESULTS

Authors should be aware that the number of tested covariates was quite high for the number of events. They should acknowledge this within Limitations.

As your comments, we performed multivariate analysis with quite high covariates. However, one in ten rules would be too conservative in some study. Instead of acknowledge of limitation, we added stepwise multivariate analysis with less covariates at the end of the paragraph to avoid risk of overfitting (Table S2).

Authors should consider reducing the list of variables in Table 1. They could include some of these variables within a supplementary Table. Furthermore, they should shorten the Results deleting some of the information that has been twice reported within the text and Table 1.

As your comment, we deleted explanation of Table 1. to make authors easy to read.

DISCUSSION

Authors should consider to shorten the Discussion and revise some sentences that appeared difficult to read.

We deleted some sentence regarding cohort to make authors easy to read (at first part of 'Discussion' section).

Minor comments

Authors should begin the Discussion reporting the main results of the study.

We added main results of our study in the beginning of the 'Discussion' section.

Please amend the sentence:

- "The treatment patients received included..." page 7, line 41.

We amended the sentence that you commented.

- "primary objective of this study was to identify clinical and laboratory risk factors predictive of in-hospital mortality for any reason within 56 days...". Page8, line 26-31. This sentence appears misleading for readers who may consider "56" as the length of follow-up.

As you read, it is both endpoint and follow-up period of this study. It is not misleading. In addition, the maximal follow-up of the survival was 52 days, thus all of patients died or discharged with a recovery within 56 days in this study.

Please check the correctness of the percentage of patients with ARDS (Page 10, line 29)

We corrected the percentage of patients with ARDS of 11.2% to 39.1%. That was typo.

Reviewer: 2

Reviewer Name

Giada Sebastiani

Institution and Country

McGill University Health Centre, Canada

Please state any competing interests or state 'None declared':

None

Please leave your comments for the authors below

The study by Park et al reports the results of a retrospective, multicenter cohort study to identify risk factors for in-hospital mortality in COVID-19 confirmed adult patients in South Korea. Out of 1,005 patients, 289 received respiratory support, while 70 patients died. The researchers found that, on multivariable analysis, high FIB-4 index, low lymphocyte count and systemic inflammatory syndrome were independent risk factor for mortality in patients receiving respiratory support, with good accuracy.

There is a clear need for biomarkers of severity and prognosis in COVID-19 infection. The study is interesting and well written.

Comments

- authors should quote and comment the following paper, on similar topic: "Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19", published in Journal of Infectious Diseases (Luis Ibáñez-Samaniego, Federico Bighelli, Clara Usón, Celia Caravaca, Carlos Fernández Carrillo, Miriam Romero, Mónica Barreales, Christie Perelló, Antonio Madejón, Aránzazu Caballero Marcos, Agustín Albillos, Inmaculada Fernández, Javier García-Samaniego, José Luis Calleja, Rafael Bañares).

As your comments, we quoted and commented regarding the article which was recently published while we submitted this study (page 15, line 21- page 16 line 6).

Though the design of published study was similar with our study, the interpretation of result was quite different. Please see additional discussion.

- please replace the word "controlled" with "characterized" in the abstract (line 9); this wording is confusing for the study design.

As your comments, we amended that.

- in the result section of the abstract, please better explain lines 37-44, these results are not presented in a clear way. The authors should report the hazard ratio for the first sentence rather than the p value ("Regardless of respiratory support..."). For the second sentence, should be detailed as now it is too specific (remove the p-value and list the risk factors with HR; "A number of risk factors...")

As your comments, we revised results of abstract with more clear and less specific.

- strengths and limitations section: ", it is a most single reliable predictor of mortality in patients with COVID-19 regardless of respiratory support." Please rephrase, unclear meaning.

We rephrased all with several words instead of sentence to avoid unclear meaning.

- in the statistical analysis section, the researchers should provide details on how the multivariable models were built, how the exposures were chosen. Also, why the SOFA score was not included in this study? And, why sex was not included in the multivariable model?

In clinical practice, not ICU, it is hard to use SOFA score. While we investigate the risk factors of COVID-19, we found that variables in FIB-4 including ratio of AST/ALT, platelet count, and age, which is widely used in clinical practice, is closely related with severity of FIB-4. Instead of SOFA, we used SIRS as a variable regarding serious inflammatory condition (Page 12, line 6-11).

We revised 'Statistical analysis' section with additional details on multivariate models. In addition, we added stepwise multivariate analysis with less variables to avoid a concern regarding the one in ten rule (table S2). It would provide robustness of multivariate analysis in this study.

- more details on how patients were selected for antiviral therapy should be provided.

As you know, this study is retrospective study and there was no guideline regarding antiviral therapy for COVID-19. The use of antiviral therapy depended on doctor's clinical decision.

- chronic liver diseases diagnosis should be better defined. How was that assessed? The prevalence at 5% seems quite low, probably not including NAFLD. Which other aetiologies were included?

As your comments it is too low if NAFLD is included on etiologies of chronic liver disease. But we defined chronic liver disease as chronic hepatitis B and C infection and cirrhosis, and HCC. We added these definitions on end of the Method (Definition) section.

I think impacts of NAFLD on COVID-19 is still need to be investigated.

VERSION 2 – REVIEW

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| REVIEWER | Giada Sebastiani McGill University Health Centre, Canada |
| REVIEW RETURNED | 20-Sep-2020 |
| GENERAL COMMENTS | The manuscript has significantly improved in this revised version. However, there are still some typos or sentences requiring proofreading. For example, see the opening sentence in the abstract below: Please check carefully for typos: beginning of the abstract: "The reliable risk factors... has not evaluated in well..." should read "Reliable risk factors... have not been evaluated in well..." |