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Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis

Saniya Khan, Jaya Benjamin, Rakhi Maiwall, Harshita Tripathi, Puja Bhatia Kapoor, Varsha Shasthry, Vandana Saluja, Prashant Agrawal, Shalini Thapar, Guresh Kumar

Corresponding author
Jaya Benjamin
Department of Clinical Nutrition, Institute of Biliary Sciences, New Delhi, India

Handling editor:
Michal Heger
Department of Pharmaceutics, Utrecht University, the Netherlands
Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

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1st Editorial decision
22-Mar-2022

Ref.: Ms. No. JCTRes-D-22-00018
Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis
Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Apr 21, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: The authors present a well written assessment of the impact of sarcopenia on outcomes of critically ill cirrhotic patients. Their study was performed in a prospective manner which sets it apart from other similar evaluations. Furthermore the study uses the well validated system of CT analysis of muscle mass.

Questions/Concerns:

1) While I think I understand the presentation of the data, the manuscript could be more clear on the assessment of mortality. It is my impression you are primarily assessing outcomes in the ICU. In table for example, there is a statistical difference in mortality, does this reflect ICU mortality only? If so this should be clarified because based on the Kaplan Meier data, there is no difference in overall mortality at 28 days. It is not clear in the methods section if your intent was to follow patients through ICU admission, the hospital stay or to 28 days? Please clarify the assessment period of interest.

2) This is a minor concern: I assume you are using the APASL definition of ACLF? Given that 17% of your patients had ACLF and that there several methods for defining ACLF, clarifying may be of interest to some readers.

3) Minor consideration: Karvellas et al (Critical Care Medicine 46:1783) have published data that shows the CLIF-ACLF score is an excellent predictor of ICU outcomes in critically ill cirrhotics and performs better than CTP and APACHE II, was this score assessed in your study? I do not feel that this would be required for acceptance of your manuscript, simply curious given the fidelity of that model in multinational studies.

Authors' response

To, Date:
31.03.2022

Dr. Michal Heger

Editor-in-Chief

Journal of Clinical and Translational Research

Dear Dr. Heger,

Please find attached herewith the revised manuscript entitled **"Sarcopenia is the independent predictor of mortality in critically ill patients with cirrhosis"** along with the point- to- point reply to the reviewers' comments, for your kind consideration.

The suggested changes have been incorporated in the manuscript and highlighted in track change format.

Thank you very much for reconsidering this manuscript for publication in your esteemed journal.

Please do let us know in case anything else is required.

Thanking you

Best Regards

Dr. Jaya Benjamin**,** PhD

Associate Professor

Department of Clinical Nutrition

Institute of Liver & Biliary Sciences (ILBS)

New Delhi – 110070, India

Email: jayabenjaminilbs@gmail.com

Point to point reply to reviewer's comments

1) While I think I understand the presentation of the data, the manuscript could be more clear on the assessment of mortality. It is my impression you are primarily assessing outcomes in the ICU. In table for example, there is a statistical difference in mortality, does this reflect ICU mortality only? If so this should be clarified because based on the Kaplan Meier data, there is no difference in overall mortality at 28 days. It is not clear in the methods section if your intent was to follow patients through ICU admission, the hospital stay or to 28 days? Please clarify the assessment period of interest.

Reply 1: We thank the reviewer very much for the keen observations and insightful comments. As rightly suggested, the primary objective of this study was to assess the impact of sarcopenia on the overall ICU mortality in critically ill patients with cirrhosis.

In table 4, the mortality shown, reflects the overall ICU mortality only. 72.4% (55/76) of the sarcopenics and 40% (14/35) of the non-sarcopenics (p=0.001) died in the ICU. However, the Kaplan Meier curve (Fig. 3) takes into account the time to death (days) in the ICU, wherein there was no difference in the days to death between sarcopenics and non-sarcopenics (p=0.138); hence, the Kaplan Meier was found to be non-significant. Thus suggesting, there were significantly higher number of deaths in the ICU among sarcopenics as compared to non-sarcopenics, but there was no significant difference in the time to death (days) in the ICU between sarcopenic and non-sarcopenic critically ill patients with cirrhosis.

The patients were assessed at baseline at the time of ICU admission and then to study the impact of sarcopenia on the outcomes in the ICU, these patients were followed up every day till their stay in the ICU i.e. until their death or discharge from the ICU. None of the patients were followed up after their discharge from the ICU and the 28-days mortality reflected in the Kaplan Meier curve is the length of ICU stay (also shown in table 4, line 2). Hence, the period of assessment is only till the patient's stay in the ICU.

As suggested by the esteemed reviewer, the definition of mortality has been added in the methods section, under the definition of outcome variables and the word 'ICU mortality' has been replaced by mortality on page 5, line 22; page 7, line 31 and last line of table 4. All these changes have been highlighted in red text.

2) This is a minor concern: I assume you are using the APASL definition of ACLF? Given that 17% of your patients had ACLF and that there several methods for defining ACLF, clarifying may be of interest to some readers.

Reply 2: As rightly pointed out by the reviewer, we missed out on quoting the reference for the diagnosis of ACLF in the manuscript but as suggested, the same (reference 14) has been added in the manuscript (page 4, line 24) and in the references also.

3) Minor consideration: Karvellas et al (Critical Care Medicine 46:1783) have published data that shows the CLIF-ACLF score is an excellent predictor of ICU outcomes in critically ill cirrhotics and performs better than CTP and APACHE II, was this score assessed in your study? I do not feel that this would be required for acceptance of your manuscript, simply curious given the fidelity of that model in multinational studies.

Reply 3: The CLIF-C ACLF score was not assessed in this study, however, as suggested, the individual data points that were recorded for calculating other disease severity scores have now been used to calculate the CLIF-C ACLF score. The results of the CLIF-C ACLF score are as follows: The mean CLIF-C ACLF score of critically ill cirrhotics (n=111) was 49±12.6. CLIF-C ACLF score of the non-survivors (n=69) was 53.3±11.8, which was significantly higher than that of survivors (n=92) 43±10.3; p- value <0.001; OR (95% CI) :1.084 (1.04-1.128).

The results of a multivariate logistic regression analysis including the calculated CLIF-C ACLF score are given in the table below.

Independent factors associated with mortality in critically ill cirrhotics

Variables	**Univariate regression analysis**		**Multivariate regression analysis**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age (years)	1.02 (0.98-1.05)	0.264		
Gender (M:F)	0.58 (0.19-1.77)	0.582		
Dry_BMI (kg/m^2)	0.93 (0.84-1.02)	**0.124**		
Shock	8.16 (1.79-37.04)	**<0.001**		
Respiratory distress	3.02 (1.17-7.78)	**0.022**		

Variceal bleed	0.56 (0.18-1.74)	0.565		
Encephalopathy	0.75 (0.34-1.65)	0.488		
Sepsis	7.48 (3.0- 18.64)	**<0.001**	3.76 (1.34-10.51)	**0.012**
Mechanical Ventilation	0.145 (0.6-3.54)	**<0.001**		
Hemoglobin (g/dL)	0.81 (0.66-0.99)	**0.043**		
Total leucocyte count (cumm)	1.07 (1.0- 1.14)	**0.027**		
International normalized ratio	1.45 (0.97-2.14)	**0.064**		
Sodium (mmol/L)	1.04 (9.81-1.10)	**0.187**		
Calcium (mg/dL)	1.36 (0.88-2.09)	**0.163**		
Albumin (g/dL)	1.75 (0.86-3.56)	0.118		
Total Bilirubin (mg/dL)	1.03 (0.99-1.07)	**0.081**		
Lactate (mmol/L)	1.08 (0.93-1.27)	0.288		
Sarcopenia	3.92 (1.69-9.12)	**0.001**	4.01 (1.43-11.25)	**0.008**
SOFA score	1.22 (1.09-1.37)	**0.001**		
APACHE II score	1.12 (1.06-1.18)	**<0.001**	1.07 (1-1.14)	**0.044**
CTP	1.31 (1.05-1.65)	**0.015**		
MELD	1.05 (1.0- 1.11)	**0.038**		
CLIF-C ACLF	1.084 (1.04-1.13)	**<0.001**	1.06 (1.01-1.11)	**0.013**

BMI- Body Mass Index, TLC- Total Leucocyte count, INR- International normalized ratio, SOFA- Sequential Organ Failure Assessment, APACHE II- Acute Physiology, Age, Chronic Health Evaluation II, CTP- Child-Turcotte-Pugh, MELD- Model for End-Stage Liver Disease, CLIF-C ACLF- Chronic liver failure Consortium- Acute on Chronic Liver Failure

2nd Editorial decision
01-Apr-2022

Ref.: Ms. No. JCTRes-D-22-00018R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: