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Identifying critically ill patients with cirrhosis who benefit from nutrition therapy: the mNUTRIC score study

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1st Editorial decision
02-May-2022

Ref.: Ms. No. JCTRes-D-22-00038
Identifying the critically ill cirrhotics who benefit the most from nutrition therapy: The mNUTRIC score study
Journal of Clinical and Translational Research

Dear Dr. Benjamin,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jun 01, 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: Thank you for the opportunity to perform this peer review on your manuscript that describes your observational study using the Modified Nutrition Risk in Critically Ill patients with cirrhosis to identify those at highest risk for morbidity and mortality.
- Overall, I commend you for this contribution to the literature specific to the critically ill patient with cirrhosis; aside from the population, there does not appear to be anything novel or innovative in the use of the mNUTRIC as it performed exactly as intended by its creator, D. Heyland. The tool was "designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy." It would have been interesting to see patient response to a modified nutrition protocol to support the high risk score but it sounds as though nutritional management was standard of care. See my comment below.

- The health care community has the position that reference to patients should be 'people before condition'. So... critically ill patients with cirrhosis not "cirrhotics". Also, "bleeder" is not an appropriate reference (see Nutritional Management)...perhaps patient with GI bleed.

- Abstract is fairly comprehensive and clear except for the Conclusion. This needs to be re-written with 2 separate sentences. Graphical abstract is informative. The actual study design (observational) is never mentioned in the abstract or paper.

- Introduction Lines 13-17 suggest: Standardized therapies and interventions have improved the overall survival of these patients, yet this population very often faces...(ICU) admission.

- In Data collection paragraph the use of the word "like" is repetitive and a bit distracting; Line 36 try using decompensation status including ascites, jaundice, etc. And Line 46 hemodynamic parameters of heart rate, etc. And Line 48 biochemical parameters of complete blood count, etc.
Who performed the data collection, was this an author or an unbiased clinical staff member? Were these data extracted by an individual from an electronic health record?

- It is not clear what the actual benefit to survival was in the HNS group if mortality was 70%. What is the mortality in this population in general? Table 6 shows mean LOS 5 days and MV 5 days for the HNS...is this because most of this group died at 5 days? One way to clarify benefit to critically ill patients on mechanical ventilation is to describe ventilator-free days instead. Do you have hospital LOS data?

- The Discussion seems to focus on the value of using the mNUTRIC to identify patients at high nutritional risk in order to provide appropriate goal-directed nutrition therapy and

improve survival, but this study does not describe any manipulation of the nutritional therapy. Please explain what is meant by the goal-directed nutrition therapy in your study. Most ICU teams initiate a nutritional care plan based on energy and protein needs of the patient population so it is not clear what is unique about your approach; the paper states nutritional management was according to protocol. Nutritional adequacy was greater than reported in many studies but fell short of goal-directed targets. The low feeding intolerance rates and complications are impressive; generally the sicker the patient the more feeding intolerance.

- In Discussion pg 13 Line 56 the statement that only three studies have examined targeted nutrition therapy and NUTRIC score does not seem to be accurate; in addition to several papers in your reference list, a quick Pubmed search turns up several papers with just a few listed here:

- Acehan, S., Gulen, M., Isıkber, C., Unlu, N., Sumbul, H. E., Gulumsek, E., & Satar, S. (2021). mNUTRIC tool is capable to predict nutritional needs and mortality early in patients suffering from severe pneumonia. Clinical nutrition ESPEN, 45, 184-191. https://doi.org/10.1016/j.clnesp.2021.08.030.

- Wang, N., Wang, M. P., Jiang, L., Du, B., Zhu, B., & Xi, X. M. (2021). Association between the modified Nutrition Risk in Critically Ill (mNUTRIC) score and clinical outcomes in the intensive care unit: a secondary analysis of a large prospective observational study. BMC anesthesiology, 21(1), 220. https://doi.org/10.1186/s12871-021-01439-x.

- Ata Ur-Rehman, H. M., Ishtiaq, W., Yousaf, M., Bano, S., Mujahid, A. M., & Akhtar, A. (2018). Modified Nutrition Risk in Critically Ill (mNUTRIC) Score to Assess Nutritional Risk in Mechanically Ventilated Patients: A Prospective Observational Study from the Pakistani Population. Cureus, 10(12), e3786. https://doi.org/10.7759/cureus.3786.

- Alramly, M. K., Abdalrahim, M. S., & Khalil, A. (2020). Validation of the modified NUTRIC score on critically ill Jordanian patients: A retrospective study. Nutrition and health, 26(3), 225-229. https://doi.org/10.1177/0260106020923832.

- Sutrisnawati, I., Darmono, D., Murbawani, E., Puruhita, N., Probosari, E. 2021. Correlation between nutric score and adequacy of energy and protein intake with duration of mechanical ventilation in the intensive care unit Dr. Kariadi Hospital, Semarang-Indonesia. Bali Medical Journal 10(1): 392-396. DOI:10.15562/bmj.v10i1.2196

- In Discussion, pg 12, Line 48-51: Suggest revising the sentence to Similarly, other studies have reported a longer duration of ventilator days apart from longer duration of hospital stay. 6, 13, 14 Reference 27 is an ASPEN consensus guideline and would not provide sufficient evidence for "similar studies" - you would need to cite the one reference from these guidelines. Also, this guideline reference is older than #3 in your reference list and therefore you should only use #3 as it is more current. However, you still need a primary reference here and not a guideline document.

- Lastly, the paper should end with mentioning Limitations followed by a Conclusion paragraph. For help with formatting a research paper, checklists from the EQUATOR Network are particularly useful. In this case. the STROBE checklist would be used.

- The tables and figures are very helpful and easy to understand.

- References are relevant, appropriate, and sufficiently recent. There are now several published papers on mNUTRIC and mortality outcome since 2019.

Reviewer #2: The authors present an interesting study regarding use of the mNUTRIC score and its impact on survival in patients with cirrhosis admitted to the ICU.

Questions/concerns:

1) The manuscript would benefit from a review grammar.

2) The authors indicate that the number one reason for admission was altered mental status. This is an interesting finding. Can you comment on the use of lactulose in this population? What is the impact on nutritional status or the ability to administer nutrition to patients who are receiving lactulose?

3) I have concerns with the last paragraph on page 11, you state that "most of the time appropriate nutritional interventions are relegated to the background" though you have indicated that nutrition support/therapy is on of the top 3 most important considerations for managing a critically ill cirrhotic patient. Why in your facility is nutritional support being relegated to the background? This seems to be an institutional problem and should be more clearly described. I would argue that the majority of high functioning ICU do not "relegate nutritional support to the background"

Authors' response

Point to point reply to reviewers' comments

Reviewer #1: Thank you for the opportunity to perform this peer review on your manuscript that describes your observational study using the Modified Nutrition Risk in Critically Ill patients with cirrhosis to identify those at highest risk for morbidity and mortality.

- Overall, I commend you for this contribution to the literature specific to the critically ill patient with cirrhosis; aside from the population, there does not appear to be anything novel or innovative in the use of the mNUTRIC as it performed exactly as intended by its creator, D. Heyland. The tool was "designed to quantify the risk of critically ill patients developing adverse events that may be modified by aggressive nutrition therapy." It would have been interesting to see patient response to a modified nutrition protocol to support the high risk score but it sounds as though nutritional management was standard

of care. See my comment below.

- The health care community has the position that reference to patients should be 'people before condition'. So...critically ill patients with cirrhosis not "cirrhotics". Also, "bleeder" is not an appropriate reference (see Nutritional Management)...perhaps patient with GI bleed.

- As very rightly pointed out by the esteemed reviewer, the word "cirrhotics" has been changed to critically ill patients with cirrhosis and "bleeder" to patients with GI bleed.

- Abstract is fairly comprehensive and clear except for the Conclusion. This needs to be re-written with 2 separate sentences. Graphical abstract is informative. The actual study design (observational) is never mentioned in the abstract or paper.

- As suggested, the conclusion of the abstract has been revised as follows:-

Conclusion: mNUTRIC score is a useful tool in recognizing nutrition risk in critically ill patients with cirrhosis. Goal directed nutrition therapy especially in patients with high mNUTRIC score can significantly improve survival in this group of patients.

- The word ‘prospective observational study’ has been added on page no. 9 under the section study design.

- Introduction Lines 13-17 suggest: Standardized therapies and interventions have improved the overall survival of these patients, yet this population very often faces...(ICU) admission.

Sorry, we could not understand this statement/question, hence we but the question remains incomplete hence no reply has been given.

- In Data collection paragraph the use of the word "like" is repetitive and a bit distracting; Line 36 try using decompensation status including ascites, jaundice, etc. And Line 46 hemodynamic parameters of heart rate, etc. And Line 48 biochemical parameters of complete blood count, etc.

Who performed the data collection, was this an author or an unbiased clinical staff member? Were these data extracted by an individual from an electronic health record?

As suggested the data collection paragraph has been revised in the manuscript.

This observational study was the thesis research conducted for the partial fulfillment of the post graduate certificate course (PGCC) in Clinical Nutrition at our institute. The data was collected prospectively by the student from the daily bedside records of the patient. The student is the first author of the manuscript.

- It is not clear what the actual benefit to survival was in the HNS group if mortality was 70%. What is the mortality in this population in general? Table 6 shows mean LOS 5 days and MV 5 days for the HNS...is this because most of this group died at 5 days? One way to clarify benefit to critically ill patients on mechanical ventilation is to describe ventilator-free days instead. Do you have hospital LOS data?

- The overall mortality was 64%, of these, 70% patients had a high mNUTRIC score (HNS) at the time of ICU admission, who showed higher mortality than those with low mNUTRIC score (LNS). Hence patients with baseline HNS had higher risk of mortality in the ICU. But the probability of survival improved in this group (HNS) of patients with an increase in the nutritional adequacy unlike patients with LNS.

- The mean LOS and MV for the HNS was 5 days which suggests that most of the patients either died or got discharged from the ICU in ~ 5 days.

- As rightly suggested by the reviewer that ventilator free days is used in the studies on the critically ill patients. However, in our study the patients were of end stage liver disease with compromised organ function (high SOFA score), majority (65%) being on mechanical ventilation with an average length of ICU stay of just 5 days. Hence, the total number of mechanical free ventilator days as well as the percentage of patients off mechanical ventilation were very low, from which it is difficult to derive any meaningful conclusion. For this reason the mechanical ventilator free days was not described in our study.

- The patients were not followed up after the discharge from the ICU, hence the data on length of hospital stay is not available.

- The Discussion seems to focus on the value of using the mNUTRIC to identify patients at high nutritional risk in order to provide appropriate goal-directed nutrition therapy and improve survival, but this study does not describe any manipulation of the nutritional therapy. Please explain what is meant by the goal-directed nutrition therapy in your study. Most ICU teams initiate a nutritional care plan based on energy and protein needs of the patient population so it is not clear what is unique about your approach; the paper states nutritional management was according to protocol. Nutritional adequacy was greater than reported in many studies but fell short of goal-directed targets. The low feeding intolerance rates and complications are impressive; generally the sicker the patient the more feeding intolerance.

- As rightly suggested by the esteemed reviewer though the approach to nutritional management for patients in our ICU may not be unique as compared to the other ICUs but it was focused on meeting the daily protein and calorie targets as per the standard recommendations giving due attention to the protein requirements in the obese and those on renal replacement therapies also. Hence, an effort to comply with the daily energy and protein requirements was the "goal" therefore called as "goal directed" nutritional therapy like the one described in a previous manuscript of Mclave et al (Ref: McClave SA, Beth E. Taylor BE, Martindale RG et al. Guidelines for the provision and assessment of Nutrition Support Therapy in the Adult Critically Ill Patients. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N). 2016.)

- Neverthless, inspite of best of our efforts to meet the target, goals in some patients for various reasons were not met (low nutritional adequacy) and that exactly was the premise to see how well the targeted approach effects the clinical outcome.

- In Discussion pg 13 Line 56 the statement that only three studies have examined targeted nutrition therapy and NUTRIC score does not seem to be accurate; in addition to several papers in your reference list, a quick Pubmed search turns up several papers with just a few listed here:

- Acehan, S., Gulen, M., Isıkber, C., Unlu, N., Sumbul, H. E., Gulumsek, E., & Satar, S. (2021). mNUTRIC tool is capable to predict nutritional needs and mortality early in patients suffering from severe pneumonia. Clinical nutrition ESPEN, 45, 184-191. https://doi.org/10.1016/j.clnesp.2021.08.030.

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- Ata Ur-Rehman, H. M., Ishtiaq, W., Yousaf, M., Bano, S., Mujahid, A. M., & Akhtar, A. (2018). Modified Nutrition Risk in Critically Ill (mNUTRIC) Score to Assess Nutritional Risk in Mechanically Ventilated Patients: A Prospective Observational Study from the Pakistani Population. Cureus, 10(12), e3786. https://doi.org/10.7759/cureus.3786.

- Alramly, M. K., Abdalrahim, M. S., & Khalil, A. (2020). Validation of the modified NUTRIC score on critically ill Jordanian patients: A retrospective study. Nutrition and health, 26(3), 225-229. https://doi.org/10.1177/0260106020923832.

- Sutrisnawati, I., Darmono, D., Murbawani, E., Puruhita, N., Probosari, E. 2021. Correlation between nutric score and adequacy of energy and protein intake with duration of mechanical ventilation in the intensive care unit Dr. Kariadi Hospital, Semarang-Indonesia. Bali Medical Journal 10(1): 392-396. DOI:10.15562/bmj.v10i1.2196

- Though prima facie it seems that a lot of studies are done on mNUTRIC score but if we look carefully those by, Acehan et al, Wang et al, Ata Ur-Rehman et al, Alramly et al have seen only one time association of mNUTRIC with clinical parameters like predicting mortality, duration of mechanical ventilation, length of stay etc. While Sutrisnawati et al observed only the correlation of energy and protein adequacy with duration of MV and not NUTRIC score. As mentioned in our discussion only 3 studies have seen the association of

the nutrition therapy i.e., nutritional adequacy provided with mNUTRIC score in the ICU, hence we have mentioned about only those 3 studies.

- In Discussion, pg 12, Line 48-51: Suggest revising the sentence to Similarly, other studies have reported a longer duration of ventilator days apart from longer duration of hospital stay. 6, 13, 14 Reference 27 is an ASPEN consensus guideline and would not provide sufficient evidence for "similar studies" - you would need to cite the one reference from these guidelines. Also, this guideline reference is older than #3 in your reference list and therefore you should only use #3 as it is more current. However, you still need a primary reference here and not a guideline document.

- As suggested, the line on page 17, line 48-51 has been revised in the manuscript.
- As rightly pointed out by the reviewer, the reference no. 27 (ASPEN guideline) has been replaced with original study (Sutrisnawati et al. Bali Medical Journal. 2021) rather than the reference for a guideline.
- However, reference #3 has been retained as it is the latest ASPEN guidelines.

- Lastly, the paper should end with mentioning Limitations followed by a Conclusion paragraph. For help with formatting a research paper, checklists from the EQUATOR Network are particularly useful. In this case, the STROBE checklist would be used.

- The manuscript has been revised as per the reviewer's suggestion, and the limitations and conclusion of the study have been added as per the STROBE checklist on page no.19.

- The tables and figures are very helpful and easy to understand.
- References are relevant, appropriate, and sufficiently recent. There are now several published papers on mNUTRIC and mortality outcome since 2019.

We thank the reviewer for the appreciation.

Reviewer #2: The authors present an interesting study regarding use of the mNUTRIC score and its impact on survival in patients with cirrhosis admitted to the ICU.

Questions/concerns:

1) The manuscript would benefit from a review grammar.

2) The authors indicate that the number one reason for admission was altered mental status. This is an interesting finding. Can you comment on the use of lactulose in this population? What is the impact on nutritional status or the ability to administer nutrition to patients who are receiving lactulose?

We thank the esteemed reviewer for this comment. Considering the ill effects of lactulose on gut, like bloating, diarrhea and abdominal distension and its consequent effect on nutritional therapy, lactulose is not used in our ICU, instead, polyethylene glycol is used routinely.

3) I have concerns with the last paragraph on page 11, you state that "most of the time appropriate nutritional interventions are relegated to the background" though you have indicated that nutrition support/therapy is on of the top 3 most important considerations for managing a critically ill cirrhotic patient. Why in your facility is nutritional support being relegated to the background? This seems to be an institutional problem and should be more clearly described. I would argue that the majority of high functioning ICU do not "relegate nutritional support to the background"

The general statement made on page 11 "most of the time appropriate nutritional interventions are relegated to the background", did not refer to our institute, rather it was a general statement towards nutritional practice in the ICU at our institute nutrition is of utmost importance as there is a fully functional department of Clinical Nutrition, headed by a Gastroenterologist along with a full time devoted faculty focusing on patient care, academics and research with almost 10 students working on nutrition related projects. Hence this was a general statement and did not refer to our institute.

2nd Editorial decision
01-Jun-2022

Ref.: Ms. No. JCTRes-D-22-00038R1
Identifying the critically ill cirrhotics who benefit the most from nutrition therapy: The mNUTRIC score study
Journal of Clinical and Translational Research

Dear Dr. Benjamin,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jul 01, 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:

Dear authors,

Thank you for submitting your revision to JCTR.

I have perused over the manuscript and found numerous irregularities between what is alluded to in the rebuttal versus what has been actually implemented. Here are a few examples. Please note that specific comments or comments that pertain to a specific section often serve as blanket statements that can be extended to other sections of the manuscript. We expect that you understand this concept and implement it fundamentally throughout the next revision.

1. The word "cirrhotics" still appears at numerous locations throughout the manuscript, especially the abstract. This raises concern about the integrity of your revision, as I am sure you understand.
2. The manuscript is replete with grammar/spelling errors and linguistic/syntax mistakes. Phrases are abbreviated but then the abbreviations are not used (e.g., length of ICU stay). The manuscript is sloppy and needs to be corrected by a native speaker. Please contact the editorial office if help is needed with contracting a third party service.
3. Please write the narrative using whole sentences. The section "Study design: Prospective observational study" for example falls short of anything resembling a complete sentence. This also pertains to the "Definition of terms" section as well as other regions in the manuscript.
4. Answering the reviewers' queries in the rebuttal is not sufficient. The implicit value of their comments are that their queries are also addressed in the manuscript. Please ensure that this is the case for all applicable comments, such as the comments on the data collection.

5. Please be accurate in your reporting and rebutting. For example, who assigned the disease severity scores?

Please address these concerns to the fullest extent; only then will we be able to further process your manuscript.

Kindest regards,

Michal Heger
Editor

Authors' response

Point to point to reply to reviewer's comments

I have perused over the manuscript and found numerous irregularities between what is alluded to in the rebuttal versus what has been actually implemented. Here are a few examples. Please note that specific comments or comments that pertain to a specific section often serve as blanket statements that can be extended to other sections of the manuscript. We expect that you understand this concept and implement it fundamentally throughout the next revision.

1. **The word "cirrhotics" still appears at numerous locations throughout the manuscript, especially the abstract. This raises concern about the integrity of your revision, as I am sure you understand.**

We are very sorry to have missed changing the word "cirrhotic" to "patient with cirrhosis" in the manuscript. The corrections have been now made throughout the manuscript including the abstract.

2. **The manuscript is replete with grammar/spelling errors and linguistic/syntax mistakes. Phrases are abbreviated but then the abbreviations are not used (e.g., length of ICU stay). The manuscript is sloppy and needs to be corrected by a native speaker. Please contact the editorial office if help is needed with contracting a third party service.**

- The linguistic mistakes have been corrected with professional help. We hope that your esteemed journal finds it appropriate.

- As rightly suggested the abbreviations for the terms which have not been repeated and used only once have been removed.

3. Please write the narrative using whole sentences. The section "Study design: Prospective observational study" for example falls short of anything resembling a complete sentence. This also pertains to the "Definition of terms" section as well as other regions in the manuscript.

- As suggested, complete sentences have been used to define the study design and various terms used. The desired appropriate changes have been made in the manuscript.

4. **Answering the reviewers' queries in the rebuttal is not sufficient. The implicit value of their comments are that their queries are also addressed in the manuscript. Please ensure that this is the case for all applicable comments, such as the comments on the data collection.**

We are very sorry, the reply to the comment of data collection has been added in the manuscript.

5. Please be accurate in your reporting and rebutting. For example, who assigned the disease severity scores?

- We are sorry to have missed out the incorporation of the answer to the question "who performed the data collection?" into the manuscript. The following statements pertaining to data collection have been incorporated in the manuscript: "The disease severity scores were calculated with the help of online calculators (SOFA: https://www.mdcalc.com/sequential-organ-failure-assessment sofa-score, APACHE II: https://www.mdcalc.com/apache-ii-score, CTP: https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality, MELD:https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older) using the necessary parameters collected from the daily bedside hospital records by the student investigator HT, a fellow in Clinical Nutrition."

3rd Editorial decision
27-Jul-2022

Ref.: Ms. No. JCTRes-D-22-00038R2
Identifying critically ill patients with cirrhosis who benefit from nutrition therapy: The mNUTRIC score study
Journal of Clinical and Translational Research

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

Journal of Clinical and Translational Research
Peer review process file 08.202205.009

Comments from the editors and reviewers: