PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Nutritional risk factors for all-cause mortality of critically ill patients: a retrospective cohort study
AUTHORS	Wang, Jine; Zheng, Nan; Chang, Xinyi; Qian, Huitao; Han, Yi

VERSION 1 – REVIEW

REVIEWER	Dai, Xiaoyan Guangzhou Medical University
REVIEW RETURNED	15-Aug-2022

GENERAL COMMENTS	In this manuscript, Wang et al. found that PCT, prealbumin, APACHE II and NRS2002 were independent nutritional risk factors for 28-day mortality of critically ill patients. Both prealbumin/PCT ratio and the combination model of PCT, prealbumin and NRS2002, as composite models of inflammation and nutrition, could better predict the prognosis of critically ill patients. Overall, the data in the manuscript is interesting, convincing, and well-organized. There are some concerns listed below: 1. The N number of each panel is missing. 2. The manuscript should be proofread by a native English speaker.

REVIEWER	Leoni , Matteo Luigi Giuseppe Guglielmo da Saliceto Hospital
REVIEW RETURNED	17-Aug-2022

GENERAL COMMENTS	The present study aims to evaluate the prognostic role of nutritional and non-nutritional risk factors for predicting the 28 days outcome of critically ill patients treated with enteral nutrition. Some points should be adequately clarified: - In the introduction and in methods the Authors considered the outcome of patients. Even if in the title and partially in the discussion it is possible to understand that the considered outcome is “mortality” at 28 day, I suggest to clarify the primary outcome of the study in the methods and in the introduction. In fact, “the outcome of critically ill patients” is too generic and it can be interpreted also as clinical complications and not only mortality. - Inclusion criteria: the Authors should clarify when enteral nutrition was started after ICU admission - If we consider the study duration, we can also suppose the presence of COVID-19 patients. Is it true? These patients were excluded from the analysis? The Authors should clarify this point. - It is not completely clear when the potential predictors of clinical outcome were collected. The were collected 2 weeks after the ICU admission? In this case, the clinical utility of the model can be extensively dampened. Generally, mortality predictors are collected

	within 24 hours after ICU admission. - Technically speaking, the authors should change “univariate” and “multivariate” with univariable and multivariable analysis since the meaning is completely different. - How predictors were selected for the multivariable analysis? The is no description in the statistical paragraph. The Authors should adequately implement the methods section of the paper to adequately explain all the steps they used for variables selection - The Authors developed 2 composite models based on inflammatory status and nutritional risk. However, there were no descriptions for variable selections. It seems a progressive collection of variables to increase the AUC of ROC curves to predict the outcome. The Authors should adequately explain the clinical meaning and the mathematical steps they used for the development of composite models. On the contrary, a machine learning approach for the analysis should be appreciated. - For the composite models it is not sufficient the evaluate the global performance of the model reporting AUC, Sen, Spec…it is mandatory to report the B coefficients of the regression or at least the ORs of every variable with the 95% CI along with p values. - Multicollinearity among variables was evaluated before running the regressions? - The Authors report Spearman's correlation coefficient of the variables but they did not evaluate the possibility of non-linear correlation between variables. - Pag. 9 The Authors reported a cut-off value for NRS 2002 and for PCT levels. How these cut-offs were defined? They maximized the sensitivity and specificity of the continuous variable? - The critically ill patients considered in the study are a very heterogeneous group of geriatric patients (surgical + non-surgical patients) consequently, in the discussion, the Authors should evaluate and discuss the possible generalizability of their results. - Reason for ICU admission were not clearly stated. - I suggest implementing the analysis by adding also different complications as secondary end-point of the article and not only mortality. - A clear limit of the study is the absence of model validation. Even if an external validation it is not possible, the Authors can implement an internal validation. For example, they can use the boostrapping. - Prealbumin/PCT was reported in the discussion and in the abstract but no data were reported in the results paragraph. - The authors should discuss why they did not use NUTRIC or mNUTRIC as predictor variables. Since the study is retrospective, almost the mNUTRIC could be calculated.

REVIEWER	Li, Jiaqiong Xuzhou Medical University
REVIEW RETURNED	23-Aug-2022

GENERAL COMMENTS	You had done a lot of hard work to find out that prealbumin/PCT ratio could be a more feasible and accessible combination indicators for prognosis predicting in critically ill patients with enteral nutrition. However, there are still the following issues to be clarified. 1、Data source: to explain clearly that the value of the indicator is the average or the worst value within two weeks after admission. 2、Prediction model：Is the model better with NOMOGRAM？ 3、subgroup analysis: should the value of energy and protein intaked in each group be provided to determine whether the nutritional formulae may be a confounding factor?

	4、Minor writing mistakes： 29 In addition, patients on whole protein formulae beard(beared) less nutritional risk than those on short peptide formulae. 33 Both prealbumin/PCT ratio and the combination model of PCT, prealbumin and NRS2002（PCT, prealbumin and NRS2002）,as composite models of inflammation and nutrition, could better predict the prognosis of critically ill patients. 47 Since clinical data cannot (could not) be obtained from other centers, no external validation was performed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Major Points:
1. The N number of each panel is missing.

RE: Thank you for your suggestion. We have added the N number of each panel.

2. The manuscript should be proofread by a native English speaker.

RE: Thank you for your suggestion. This manuscript has been polished by Vikas Narang, an English editor from Editage. We have attached the editing certificate as part of the supplementary.

Reviewer: 2

Major Points:
1. In the introduction and in methods the Authors considered the outcome of patients. Even if in the title and partially in the discussion it is possible to understand that the considered outcome is “mortality” at 28 day, I suggest to clarify the primary outcome of the study in the methods and in the introduction. In fact, “the outcome of critically ill patients” is too generic and it can be interpreted also as clinical complications and not only mortality.

RE: Thank you for your suggestion. We have added the primary and secondary outcomes in the introduction and methods section, marked in color, and also showing in below:
In introduction, “Therefor, in this study, we aimed to screen the risk factors for 28-day mortality of critically ill patients, and to establish a composite model of inflammatory and nutritional factors to predict 28-day mortality in critically ill patients.”
In methods, “The primary outcome evaluated in this study was 28-day mortality. Secondary outcomes were 28-day invasive mechanical ventilation (IMV) time and ICU stay.”

2. Inclusion criteria: the Authors should clarify when enteral nutrition was started after ICU admission

RE: Thanks for your advice. We have added the time of enteral nutrition after ICU admission to the inclusion criteria, also showing in below:
Inclusion criteria: (1)… (2)enteral nutrition received within 24-48 hours after admission to ICU. (3)…

3. If we consider the study duration, we can also suppose the presence of COVID-19 patients. Is it true? These patients were excluded from the analysis? The Authors should clarify this point.

RE: Thanks for your concern. There were indeed no COVID-19 patients involved in our study. COVID patients with severe symptoms would be admitted to designated hospitals, or shelter healthcare centers if with minor symptoms.

4. It is not completely clear when the potential predictors of clinical outcome were collected. They were collected 2 weeks after the ICU admission? In this case, the clinical utility of the model can be extensively dampened. Generally, mortality predictors are collected within 24 hours after ICU admission.

RE: Thanks for your comment. We compared the predictor values at admission, the average values within two weeks and the worst values within two weeks after ICU admission. The results showed that the average values within two weeks had highest AUROC to predict 28-day mortality. Therefore, this study applied the average values within 2 weeks as mortality predictors. The table below shows the comparison of these three types of values. (Table please see attached file)

5. Technically speaking, the authors should change “univariate” and “multivariate” with univariable and multivariable analysis since the meaning is completely different.

RE: Thank you for pointing out the mistake, and we have made the correction throughout the manuscript.

6. How predictors were selected for the multivariable analysis? The is no description in the statistical paragraph. The Authors should adequately implement the methods section of the paper to adequately explain all the steps they used for variables selection

RE: Thank you for your comment. We implemented the methods section with more detailed explanation, in the 2nd paragraph of Statistical analysis, also showing as the following “In the multivariable analysis, predictors were selected using forward stepwise regression. Multicollinearity among variables was evaluated before the regressions were conducted.”
Rationale: The relationship between variables and outcomes was analyzed by univariable logistic analysis. Our initial approach was to include all variables in multivariable logistic regression analysis based on their clinical significance. Later on, we applied a more suitable method. We used forward selection method, maximum partial likelihood estimation likelihood ratio test (LR), stepwise regression variable selection method to establish the model. The results showed that APACHE II and PA/PCT were independent risk factors. The current results are more comprehensive and rigor than our initial ones.

7. The Authors developed 2 composite models based on inflammatory status and nutritional risk. However, there were no descriptions for variable selections. It seems a progressive collection of variables to increase the AUC of ROC curves to predict the outcome. The Authors should adequately explain the clinical meaning and the mathematical steps they used for the development of composite models. On the contrary, a machine learning approach for the analysis should be appreciated.

RE: Thank you for your comment. Univariable regression showed that NRS2002, prealbumin (PA) and procalcitonin (PCT) affected the 28-day mortality of critically ill patients. NRS2002 and PA are major predictors for nutrition status, and PCT for inflammatory status. Inflammatory and nutritional factors interact in critical illness.
Thus we initially calculated AUROCs of single and composite predictors based on NRS2002, PA and PCT, in order to find out better predictors that could combine inflammatory and nutritional status to predict the outcomes.

According to your advice, we used forward selection method, maximum partial likelihood estimation likelihood ratio test (LR), stepwise regression variable selection method to establish the model. The results directed that APACHE II and PA/PCT were included in the final prediction model. We then performed internal validation of the model. The description is as the following in the results section, 3rd passage, before table 2:
"Univariable regression showed that APACHE II, NRS2002, prealbumin, serum creatinine, urea, AST, PCT, and the ratio of prealbumin to procalcitonin (PA/PCT) affected the 28-day mortality of critically ill patients receiving enteral nutrition ($P < 0.05$). NRS2002 and PA are major predictors for nutrition status, and PCT for inflammatory status. Inflammatory and nutritional factors interact in critical illness. We tried to find out better predictors that could combine inflammatory and nutritional status to predict the outcomes. All candidate factors screened out from univariable regression were entered into a multivariable logistic regression model. The result showed that APACHE II and PA/PCT were included in the final prediction model ($P < 0.05$) (Table 2)"

8. For the composite models it is not sufficient the evaluate the global performance of the model reporting AUC, Sen, Spec…it is mandatory to report the B coefficients of the regression or at least the ORs of every variable with the 95% CI along with p values.

RE: Thanks very much for your advice. The β coefficients of the regression, the ORs of every variable with the 95% CI along with p values have been reported to Table 2.

9. Multicollinearity among variables was evaluated before running the regressions?

RE: Thank you for your comment. Multicollinearity among variables was evaluated before running the regressions. Multicollinearity analysis show that the tolerance is greater than 0.2 and the VIF is less than 10, indicating that there is no multicollinearity. The results are as follows. (Results showing in a table, please see attached file)

10. The Authors report Spearman's correlation coefficient of the variables but they did not evaluate the possibility of non-linear correlation between variables.

RE: Thank you for your comment. In this study, we conducted unpaired t-test for variables with normal distribution and Mann Whitney test for variables with non–normal distribution (Table 1). Thus the Spearman's correlation analysis between variables is no longer required, and the corresponding part in the supplementary materials has been removed.

11. Pag. 9 The Authors reported a cut-off value for NRS 2002 and for PCT levels. How these cut-offs were defined? They maximized the sensitivity and specificity of the continuous variable?

RE: Thank you for your comment. We used the critical value when the Youden's index was the largest as the best cut-off value. Briefly, Youden's index = sensitivity + specificity - 1. This shows that Youden's index maximizes the sensitivity and specificity.

12. The critically ill patients considered in the study are a very heterogeneous group of geriatric patients (surgical + non-surgical patients) consequently, in the discussion, the Authors should evaluate and discuss the possible generalizability of their results.

RE: Thank you for your advice. We discussed the generalizability of our results in the 6th passage of Discussion section, also described as below:
"Although the critically ill patients included in this study are a very heterogeneous group (different ages, comorbidities, surgical and medical causes), the coexistence of inflammation and malnutrition remains a common phenomenon, so the conclusions of this study can be generalized to most critically ill patients."

13. Reason for ICU admission were not clearly stated.

RE: Thank you for your comment. We stated the reasons for ICU admission in Results section, 1st passage, also showing as the following,
"Among the 301 patients, cerebral hemorrhage was the main surgical cause and pneumonia was the main medical cause, with 78 (25.91%) cases of cerebral hemorrhage and 197 (65.45%) cases of pneumonia. Majority of the patients had comorbidities, including 154 (51.16%) cases of hypertension, 110 (36.54%) cases of heart failure, 82 (27.24%) cases of renal failure, 82 (27.24%) cases of cerebral infarction, and 73 (24.25%) cases of diabetes."

14. I suggest implementing the analysis by adding also different complications as secondary end-point of the article and not only mortality.

RE: Thanks very much for your great advice. This is very constructive. We added the secondary outcomes: 28-day invasive mechanical ventilation time and ICU stay, then implemented the analysis in the Methods section (2nd passage), Results section (1st passage) and Table 1.

15. A clear limit of the study is the absence of model validation. Even if an external validation it is not possible, the Authors can implement an internal validation. For example, they can use the boostrapping.

RE: Thank you for your advice. Internal validation has been added in the Statistics analysis and Results section, and marked in color. Since clinical data could not be obtained from other centers, no external validation was performed. These added results were presented in Figure 3 (new section), also showing as the following: (Results showing in a figure, please see attached file)
"The area under the receiver operating characteristic curve (AUROC) and concordance index (CI) were used to assess the predictive capacity of the prediction model. CIs were obtained by creating 1000 bootstrap samples from the corresponding cohort and replicating the estimation process."

16. Prealbumin/PCT was reported in the discussion and in the abstract but no data were reported in

the results paragraph.

RE: Thank you for your suggestion. We reported Prealbumin/PCT in the Results section (3rd to 5th passages), in table 2 and figure 2, 3, part of the descriptions were also showing as below:
“Univariable regression showed that APACHE II, NRS2002, prealbumin, serum creatinine, urea, AST, PCT, and the ratio of prealbumin to procalcitonin (PA/PCT) affected the 28-day mortality of critically ill patients receiving enteral nutrition ($P < 0.05$).”

17. The authors should discuss why they did not use NUTRIC or mNUTRIC as predictor variables. Since the study is retrospective, almost the mNUTRIC could be calculated.

RE: Thank you for your advice. These have been added in the Discussion section (5th passage), also showing as below:
Guidelines issued by the American Society of Parenteral and Enteral Nutrition in 2016 recommended the use of NRS2002 and NUTRIC scores for the nutritional risk assessment of patients. The NUTRIC score is more complex, involving plenty of parameters including age, APACHE II score, SOFA score, complications, duration of ICU stay and interleukin-6. Therefore, its clinical use is practically limited. Compared to the NUTRIC score, NRS2002 score is simpler and more practical. NRS2002 score is an evidence-based nutritional risk score that can be used to screen nutritional risks for patients, to evaluate the effect of nutritional support, and to predict the clinical outcomes of hospitalized patients. Our results also proved that NRS2002 could be a predictor for 28-day mortality in critically ill patients, and when combined with prealbumin, PCT, transferrin, serum creatinine, urea, and AST levels, its predictive value would be further improved.

Reviewer: 3

Major Points:
1. Data source: to explain clearly that the value of the indicator is the average or the worst value within two weeks after admission.

RE: Thanks for your comment. We compared the predictor values at admission, the average values within two weeks and the worst values within two weeks after ICU admission. The results showed that the average values within two weeks had highest AUROC to predict 28-day mortality. Therefore, this study applied the average values within 2 weeks as mortality predictors. The table below shows the comparison of these three types of values. (Table please see attached file)

2. Prediction model：Is the model better with NOMOGRAM？

RE: Thank you for your suggestion. A nomogram based on the results of multivariable analyses was constructed. These have been added in the Statistics analysis and Results section. These added results were also presented in Figure 2 (new section). (Figure please see attached file)

3. subgroup analysis: should the value of energy and protein intaked in each group be provided to determine whether the nutritional formulae may be a confounding factor?

RE: Thanks for your advice. We compared the calorie and protein intake of all subgroups: peptide-

based formula group (PB), peptide step to whole protein formula group (PW), and whole protein formula group (WP). The results showed that there were no difference among these groups. The statistical results are shown as the following table and figure(Figure and tables showing in the attached file)

Minor writing mistakes：

1. 29 In addition, patients on whole protein formulae beard(beared) less nutritional risk than those on short peptide formulae.

RE: Thanks for pointing out the mistake, it has been corrected as suggested.

2. 33 Both prealbumin/PCT ratio and the combination model of PCT, prealbumin and NRS2002（ PCT, prealbumin and NRS2002）,as composite models of inflammation and nutrition, could better predict the prognosis of critically ill patients.

RE: Thanks for pointing out the mistake, it has been corrected as suggested.

3. 47 Since clinical data cannot (could not) be obtained from other centers, no external validation was performed.

RE: Thanks for pointing out the mistake, it has been corrected as suggested.

VERSION 2 – REVIEW

REVIEWER	Leoni , Matteo Luigi Giuseppe Guglielmo da Saliceto Hospital
REVIEW RETURNED	26-Oct-2022

GENERAL COMMENTS	The article has much improved and it is now ready for publication.

REVIEWER	Li, Jiaqiong Xuzhou Medical University
REVIEW RETURNED	22-Oct-2022

GENERAL COMMENTS	The authors revised and improved manuscript according to the problems asked by reviewers.