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OPEN PEER REVIEW

Establishment and Validation of Models Based on Clinical Parameters/Symptoms for Diagnostic and Prognostic Assessment of Neonatal Sepsis

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1 Original submission

3 comments · 9 Jul 2023 – 9 Aug 2023

Referee 1 Reviewer

REJECT 9 Jul 2023

The method must be complete.
On what basis and with what references are the formulas designed?
The abstract is very complete; even its methods section is more complete than the methods section in the main text. The abstract should be briefer.
On what basis are increases in indices such as HGB used?
Hospitalization for more than 7 days is based on the doctor's decision, which is based on the tests, and IL1 plays a role in the decision; it has no value in evaluating the outcome except for longer hospitalizations.
A conclusion section is needed in the manuscript.
Some references are not used in the text.
The presentation of the content is weak.

Referee 2 Reviewer

REJECT 23 Jul 2023

Dear colleague
Thank you for your submission.
- This manuscript has no new message and no novelty.
- It was not determined whether early sepsis or late sepsis was studied.
- Did you conduct the study on term or preterm babies or both? Was gestational age important to you in the study or not?
- You did not specify the exact inclusion and exclusion criteria.

Associate Editor

MAJOR REVISION 9 Aug 2023

Dear Author, please answer these questions:
Patient Population

- Clearly define the inclusion and exclusion criteria for the study population.

- Describe how cases of neonatal sepsis were identified—was identification based on clinical signs, confirmation with blood cultures, or other criteria?

- Provide details on the source of patients—a single hospital or multiple sites? This is important for generalizability.

- Describe how patients were divided into training and validation cohorts. Was this random? Matched?

Model Development

- Explain the process for selecting candidate predictors to include in the models. Was this based on clinical knowledge? Literature review? Statistical approaches like univariate analyses?

- Provide details on the modeling techniques used. For example, logistic regression, decision trees, etc.

- Describe how overfitting was evaluated during model development. Were techniques like bootstrapping or cross-validation used?

- Provide details on any variable selection procedures or criteria for inclusion in final models.

Model Validation

- Describe measures used to assess model discrimination, calibration, and overall performance. Common metrics include AUC, sensitivity, specificity, calibration plots, the Hosmer-Lemeshow test, etc.

- Explain any statistical analyses used to compare model performance between derivation and validation cohorts.

Providing these details on the model development and validation process will allow readers to better evaluate the methodology and generalizability of the models. These are important considerations for prediction model studies.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for your feedback and for the questions concerning our manuscript entitled “Establishment and validation towards clinical parameters/symptoms model for diagnosis and prognostic assessment of neonatal sepsis"(ID: 138660). The comments from reviewers helped us to improve our manuscript.

We did additional analyses of pre-term, added the conclusion section, and detailed the **Methods** section. Hopefully, our revised manuscript will be suitable for publication in your journal. The responds to the queries are listed as the followings.

We are submitting a revised manuscript with changes highlighted in red and a rebuttal letter. Thank you for your time, and please do not hesitate to contact us if you have any further questions.

Best regards

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Reviewer 1:

The method must be complete.
On what basis and reference are the formulas designed?

We added Thanks for your advice. We have simplified the methods section in abstract and added more description in detail in manuscript along with more reference.We completed the methods in the text accordingly as the reviewer suggested.

The abstract is very complete, even the abstract method is more complete than the text method, the abstract should be more brief.

We have simplified the Abstract and added more description in detail in the Methods section accordingly as the reviewer suggested.

On what basis is the indexes such as HGB increasing used?

The indexes were identified based on the pediatric reference range. We added the references in the corresponding position in the text.

Hospitalization duration of more than 7 days is based on the doctor's decision based on the tests and IL1 plays a role in the decision and it has no value in evaluating the outcome except for longer hospitalizations.

That is an interesting question. Though sepsis is often linked with the IL1 family, including IL1a, IL1b, and the IL1 receptor antagonist (IL1ra) [1,2], IL-6, another proinflammatory, was analyzed as one of the 16 indicators analyzed in the current study. Our results showed that IL-6 increasing was identified not only as one of the factors in Model 2 but also as the factors in Prognosic model. Our results was consistent with

those of previous studies [3-5] that also showed that IL-6 is the most potent marker for evaluation of early-onset neonatal sepsis prognosis.

Related references:
1. Berner R, Niemeyer CM, Leititis JU, et al. Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. Pediatric Research. 1998, 44(4): 469 - 477.
2. Atici A, Satar M, Alparslan N. Serum interleukin-1β in neonatal sepsis. Acta Paediatrica. 1996, 85(3): 371 - 374.
3. Memar MY, Alizadeh N, Varshochi M, et al. Immunologic biomarkers for diagnostic of early-onset neonatal sepsis. J Matern fetal Neonatal Med. 2019, 32(1): 143 - 153.
4. Chiesa C, Panero A, Osborn JF, et al. Diagnosis of neonatal sepsis: a clinical and laboratory challenge. Clin Chem. 2004, 50(2): 279 - 287
5. Chiesa C, Pacifico L, Natale F, et al. Fetal and early neonatal interleukin-6 response. Cytokine. 2015, 76(1): 1 - 12

Conclusion part needs in the manuscript.

It is an important suggestion. We added the conclusion section accordingly.

Some references are not used in the text.

We re-checked the whole manuscript and updated the references. We were sorry for the carelessness.

Content expression is weak

We have made efforts to polish the expression of the entire text.

Reviewer 2:

Than for submission.
- This manuscript has no new message and no novelty.

The etiological agents and symptoms of different types of neonatal sepsis might be quite distinct. No standard diagnosis model based on signs are established for neonatal sepsis to date. Moreover, different pathogen, also means different diagnosis, treatment and prognosis [1-3]. This manuscript aimed to establish and validate the diagnostic models for distinguishing bacteria/virus infection among neonatal sepsis patients, and also a model towards prognostic evaluation. Moreover, the data were collected from Tianjin children's hospital in Tianjin city of China with a population of 13 630 000. The data was a regional representative sample for Northern China. To the best of our knowledge, it is the first diagnostic or prognostic models on neonatal sepsis of this region in China. Therefore, this manuscript provides a novel useful diagnostic tools and also a therapeutic strategy guiding marker for neonatal sepsis.

Related references:
[1].Heller MC, Chigerwe M. Diagnosis and treatment of infectious enteritis in neonatal and juvenile ruminants. Vet Clin North Am Food Anim Pract. 2018, 34(1): 101 - 117.
[2].Sullivan BA, Fairchild KD. Vital signs as physiomarkers of neonatal sepsis. Pediatr Res. 2022, 91(2): 273 - 282.
[3].Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011, 127(5): 817 - 826.
- It was not determined whether early sepsis or late sepsis was studied.

Thanks for your comment. It was early sepsis studied in the current study. we have added description towards these in the Methods section.

- Did you do the study on term or pre-term babies or both? Was the gestational age important

for you in the study or not?

It was an important suggestion. Both term and pre-term babies were included in the current study, and the information of pre-term proportion was added in table 1. As for gestational age, no difference was found between the different gestational age groups in this study (also as shown mentioned in table 1). Therefore, we did not think the gestational age was an important risk factor in our study.

- You did not specify exactly the inclusion criteria and exclusion criteria.

Thanks for your comment. We defined the inclusion and exclusion criteria for the study population in the Method section accordingly.

Associate editor1:
Dear Author please answer these questions
Patient Population
- Clearly define the inclusion and exclusion criteria for the study population

We defined the inclusion and exclusion criteria for the study population in the Method section accordingly.

- Describe how cases of neonatal sepsis were identified - was it based on clinical signs, confirmed with blood cultures, or other criteria?

Cases of neonatal sepsis were identified by clinical signs and confirmed all by blood cultures. We have added these description in the Methods section.

- Provide details on the source of patients - single hospital, multiple sites? Important for generalizability

The source of patients was from single hospital, but the only children's hospital in Tianjin city of China with a population of 13 630 000. Thus, the cases collected in our study could represent those in the city perfectly. We have already added the description for case resource in the Methods section.

- Describe how patients were divided into training and validation cohorts. Was this random? Matched?

The training and validation cohorts were divided by dates of records (cases), records from 2017~2019 was the training cohort while those from 2019~2021 was defined as the validation cohort, and the two cohorts matched perfectly as shown in table 1. We added the related information in the Methods section.

Model Development
- Explain the process for selecting candidate predictors to include in the models. Was this based on clinical knowledge? Literature review? Statistical approaches like univariate analyses?

The candidate predictors were selected based on clinical knowledge and literature review both. The variables selected for multivariate analysis were based on univariate analyses. We added the detail description in the Methods section.

- Provide details on the modeling techniques used. For example, logistic regression, decision trees etc.

We used the Logistic Regression model in the modeling techniques. We detailed the modeling techniques description in the Methods section.

- Describe how overfitting was evaluated during model development. Were techniques like

bootstrapping or cross-validation used?

We used 10-fold cross-validation to evaluate the model fitting during model development. We added the according information in the Methods section.

- Provide details on any variable selection procedures or criteria for inclusion in final models.

Thanks for your suggestion. We added the details on the variable selection procedures in final model in the Methods section.

Model Validation
- Describe measures used to assess model discrimination, calibration, overall performance. Common metrics include AUC, sensitivity, specificity, calibration plots, Hosmer-Lemeshow test etc.

Thanks for your suggestion. We added the related information of AUC, sensitivity, specificity, and calibration plots in the “Apparent performance of the models”, and the related information of Hosmer-Lemeshow test in the “Establishment of the diagnostic models from the training data sets” in the Results section.

- Explain any statistical analyses used to compare model performance between derivation and validation cohorts.

We added the according explanation for statistical analyses in model performance in the Results and Discussion sections.

2 Revision 1

1 comment · 15 Oct 2023

Associate Editor

ACCEPT 15 Oct 2023

No comments