Peer Review Report

Review Report on Prognostic Role of IL-34 in Sepsis and Sepsis-Induced Acute Lung Injury: Preliminary Results and Future Directions

Original Research, Acta Biochim. Pol.

Reviewer: Emanuele Martorana
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EVALUATION

Q 1 **Please summarize the main findings of the study.**

The authors study the role of interleukin-34 (IL-34) as a prognostic biomarker in patients with sepsis, including those with sepsis-induced acute lung injury (ALI). In particular they shows how elevated IL-34 levels are associated with sepsis severity and poor outcomes, including higher APACHE II and SOFA scores.
Furthermore IL-34 is identified as an independent risk factor for 28-day mortality in sepsis patients, with a proposed critical threshold of 130.05 pg/ml for high-risk individuals (values above the threshold indicates an higher survival rate).
While IL-34 levels are higher in sepsis patients with ALI, its prognostic significance within this subgroup is limited and requires further exploration.

Q 2 **Please highlight the limitations and strengths.**

The work done by authors explores the under-investigated role of IL-34 in sepsis and ALI for risk detection and prognosis, using advanced statistical methods like ROC, Cox regression and Kaplan-Meier.
A limitation is the in-depth study of a single biomarker, other cytokines were not so well analyzed, restricting the broader understanding of inflammatory pathways.

Q 3 **Please comment on the methods, results and data interpretation. If there are any objective errors, or if the conclusions are not supported, you should detail your concerns.**

In the methods, the clarity in describing patient grouping, cytokine assays, and statistical analyses ensures transparency and reproducibility, which are essential strengths for this type of study. The results have a systematic presentation of findings and reliance on robust statistical evidence are indeed laudable. The interpretation of data explain well the connections between IL-34 levels and sepsis severity is appropriate and aligns with the study's aim.
My critique regards the exclusion of other key biomarkers, to deepen this point, it could suggest which biomarkers might have been most relevant and how their inclusion could enrich the understanding of IL-34's role in the inflammatory cascade. Additionally, the critique could discuss whether the intervals and time points for IL-34 monitoring were optimally chosen to reflect the cytokine's dynamic behavior in sepsis.

Check List

Q 4 **Please provide your detailed review report to the editor and authors (including any comments on the Q4 Check List)**

This study provides valuable insights into the role of IL-34 as a potential prognostic biomarker in sepsis, particularly its correlation with sepsis severity and 28-day mortality. The findings underscore the potential of IL-34 as a useful tool for early risk stratification, aiding in identifying patients at higher risk of adverse outcomes. However, several limitations of the study must be considered when interpreting the results. The relatively small sample size and the single-center design constrain the generalizability of the findings, raising the need for caution before applying them in broader clinical practice.

1) Consider revising the title to reflect the preliminary nature of the findings, given the limitations in sample size and generalizability. A more cautious title might be for example: Prognostic Insights of IL-34 in Patients with Sepsis and Acute Lung Injury: Preliminary Findings and Future Directions

2) The introduction lacks a clear rationale for the choice of IL-34, which seems to be driven solely by the limited availability of patient serum. The authors begin by introducing sepsis and ALI, then proceed to discuss the relevance of IL-34, while omitting the significance of key biomarkers such as IL-6, CRP, IL-8, TNF-α, IL-1β, and their combinations, which have well-established roles in sepsis detection and prognosis (citations below). Please, add the rationale for focusing exclusively on IL-34 without considering these other biomarkers. Consider, in future studies, the potential combination of the available biomarkers to improve the predictive value and risk stratification.
-Li, Jianying et al. “Prognostic value of inflammatory cytokine detection for sepsis patients in ICU: a meta-analysis.” American journal of translational research vol. 16,6 2612-2621. 15 Jun. 2024, doi:10.62347/NYLM7723
-Carcò, Daniela et al. “Combination of Interleukin-6, C-Reactive Protein and Procalcitonin Values as Predictive Index of Sepsis in Course of Fever Episode in Adult Haematological Patients: Observational and Statistical Study.” Journal of clinical medicine vol. 11,22 6800. 17 Nov. 2022, doi:10.3390/jcm11226800
-Zeng, Gongbo et al. “Combination of C-reactive protein, procalcitonin, IL-6, IL-8, and IL-10 for early diagnosis of hyperinflammatory state and organ dysfunction in pediatric sepsis.” Journal of clinical laboratory analysis vol. 36,7 (2022): e24505. doi:10.1002/jcla.24505

3) Enhance references in the introduction section for the role of IL-34 in inflammatory disease, for example, by including recent works:
-Jacobs, Max C, and W Joost Wiersinga. “Interleukin-34: A New Player in the Sepsis Arena.” Critical care medicine vol. 46,6 (2018): 1032-1033. doi:10.1097/CCM.0000000000003113
-Lin, Xue et al. “Interleukin-34 Ameliorates Survival and Bacterial Clearance in Polymicrobial Sepsis.” Critical care medicine vol. 46,6 (2018): e584-e590. doi:10.1097/CCM.0000000000003017

4) Line 113: The phrase "We will try our best.." is informal for a scientific manuscript, please correct.

5) Line 191,...,200: Why did the authors analyze longitudinal data for only 22 patients? The motivation for this choice is unclear in the paper, and there are no details about the selection criteria for these patients. Additionally, the statement that 86.4% of patients showed a decrease in IL-34 over time requires clarification, are these patients all from the survival group? While it is noted that 2 out of 3 patients (13.6%) with an increase in IL-34 levels died, this finding holds limited significance without knowing the outcomes in the larger 86.4% cohort. Please explain.

6) In the manuscript, particularly in the statistical section, the method used to combine biomarker values is not clearly explained. Please clarify this aspect.

7) In discussing the association between IL-34 levels and 28-day mortality, the authors mention the increase in AUC when the SOFA score is added but overlook the improvement in sensitivity seen in the combination. Please highlight this aspect in the text, as sensitivity is particularly important in clinical screening scenarios, even at the risk of false positives.

8) Line 239, cardinality of ALI group missed.

9) Line 246, details the proportions of non-survivors.

10) In the Discussion section clarify this points:
- Emphasize the study's limitations. While IL-34 shows potential as a prognostic marker, the small sample size and single-center design limit the generalizability of the findings;
- Add comparison with other inflammatory markers;
- Changes over time of IL-34 could be used to monitor patient response?

11) It would add value to the work if the authors could provide a file with the anonymized data used in the study.

Q 5 **Is the English language of sufficient quality?**

Yes.

Q 6 **Is the quality of the figures and tables satisfactory?**

Yes.

Q 7 **Does the reference list cover the relevant literature adequately and in an unbiased manner?**

No.

Q 8 **Are the statistical methods valid and correctly applied? (e.g. sample size, choice of test)**

Yes.

Q 9 **Are the methods sufficiently documented to allow replication studies?**

Yes.

Q 10 **Are the data underlying the study available in either the article, supplement, or deposited in a repository? (Sequence/expression data, protein/molecule characterizations, annotations, and taxonomy data are required to be deposited in public repositories prior to publication)**

No.

Q 11 **Does the study adhere to ethical standards including ethics committee approval and consent procedure?**

Yes.

Q 12 **Have standard biosecurity and institutional safety procedures been adhered to?**

Not Applicable.

QUALITY ASSESSMENT

Q 13	Originality	
Q 14	Rigor	
Q 15	Significance to the field	
Q 16	Interest to general audience	
Q 17	Quality of the writing	
Q 18	Overall quality of the study