Acta Biomed 2021; Vol. 92, N. 4: e2021248 DOI: 10.23750/abm.v92i4.11182

Combined Cytokine Scores Assessed at Emergency Department Presentation Predicts COVID-19 Critical Illness

Brandon Michael Henry[1*], *Maria Helena Santos de Oliveira*[2*], *Isaac Cheruiyot*[3], *Stefanie W. Benoit*[4,5], *Justin L. Benoit*[6], *Giuseppe Lippi*[7]

[1]Cardiac Intensive Care Unit, The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA; [2]Department of Statistics, Federal University of Parana, Curitiba, Brazil; [3]School of Medicine, University of Nairobi, Nairobi, Kenya; [4]Department of Pediatrics, University of Cincinnati, College of Medicine, OH, USA; [5]Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, OH, USA; [6]Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH, USA; [7]Section of Clinical Biochemistry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy; *These authors share first authorship of this manuscript.

To the Editor,

Predicting progression to severe coronavirus disease 2019 (COVID-19) is essential for improving allocation of limited healthcare resources and optimizing triage in the emergency department (1). A recent report by Nagant et al. (2), combined cytokine measurements early in hospitalization (0-3 days) for accurate prediction of COVID-19 severity. Owing to observed differences in biomarkers between cohorts and geographical regions (3), as well as heterogeneity in timing of laboratory measurements in the context of the fluctuating course of SARS-CoV-2 infection, we aimed to apply the same cytokine scores for predicting disease course in the Cincinnati COVID-19 Emergency Department (ED) Cohort.

We enrolled adults from the ED with a molecular diagnosis of COVID-19. Blood was drawn during a routine collection under an institutional review board approved waiver of informed consent. Levels of interleukin (IL)-6, 8 and 10 were measured with a Meso Scale Discovery U-Plex assay (Rockville, Maryland, USA). The primary outcome was need for intensive care unit (ICU) admission, whilst need for hospitalization within 30 days of index ED visit and for renal replacement therapy (RRT) were secondary outcomes. Both [IL-6]×[IL-10] and [IL-6]×[IL-8]×[IL-10] scores were computed. Receiver operating characteristic (ROC) curves were used to assess the predictive value of the scores. This study was conducted in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

The final study cohort consisted of 50 patients (60% males; median age, 50.5 years, interquartile range, 40.5-66.0 years), 32 (64%) requiring hospitalization within 30 days of ED visit, 14 (28%) requiring ICU admission, and 8 (16%) requiring RRT. The results are shown in Figure 1. Both IL-6*IL-10 and IL-6*IL-8*IL-10 scores displayed similar predictive performance across the outcomes. IL-6*IL-10 displayed the most optimal performance for predicting the primary outcome (ICU admission) with an AUC of 0.89 (95%CI: 0.78 – 0.99).

We found an [IL-6]×[IL-10] area under the curve (AUC) of 0.89 for predicting ICU admission, identical to that reported by Nagant et al. Given that [IL-6]×[IL-10] and [IL-6]×[IL-8]×[IL-10] displayed similar predictive performance, we suggest the use of [IL-6]×[IL-10] score, as it requires only 2 variables and is simpler to calculate, as well as more cost-effective. The combined use of IL-6 and IL-10 enables identification of patients with predominant

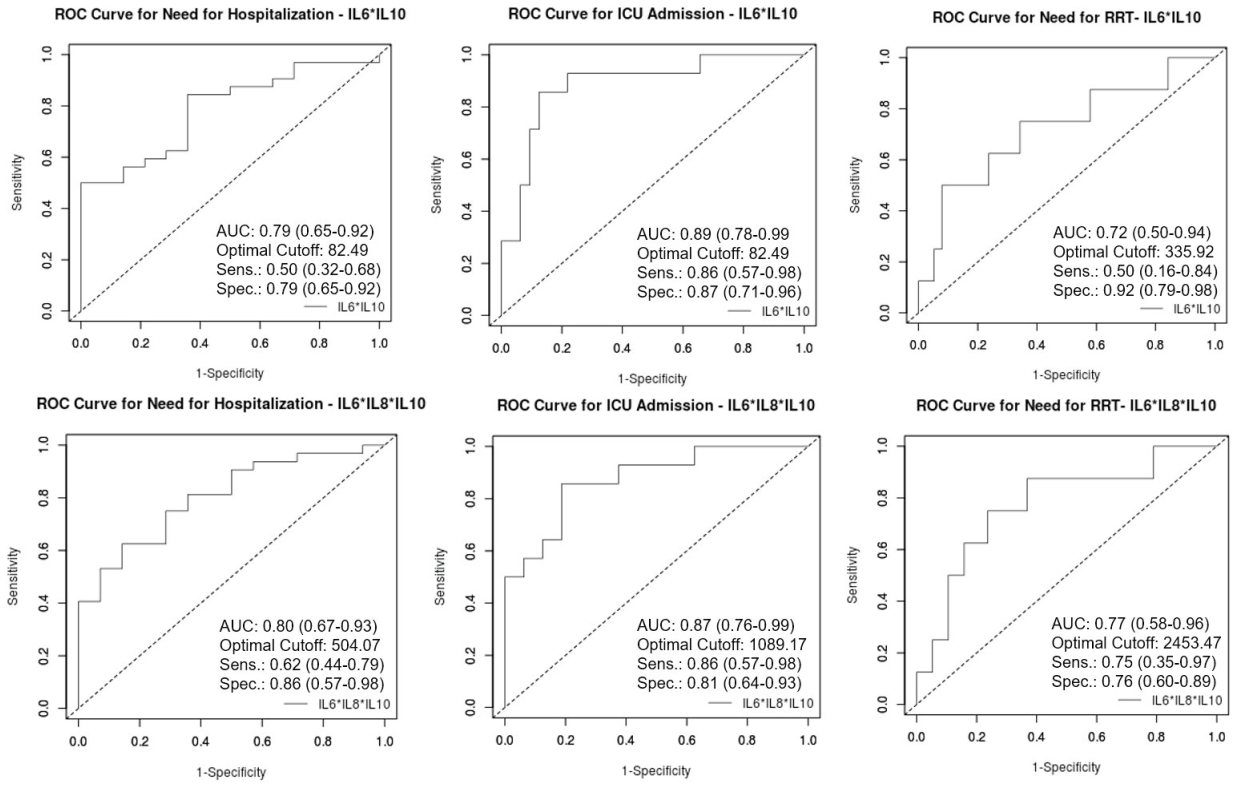

Figure 1. Interleukin-6*Interleukin-10 and Interleukin-6*Interleukin-8*Interleukin-10 ROC Curves for with estimated Area Under the Curve (AUC), sensitivity and specificity values with 95% confidence intervals for need for hospitalization, need for intensive care unit admission, and need for renal replacement therapy (RRT). Optimal cutoffs (pg/mL) were chosen using the Youden index method.

hyperinflammatory response, as well as those who with predominant hypoinflammatory response, both conditions which significantly contribute to development of severe disease (4,5). Notably, we found different cut-offs for our combined cytokine scores compared to those reported by Nagant et al., which may be attributed to pre-analytical and analytical confounders, or differences in sampling day (at ED admission vs. within 0-3 days of hospitalization). Assessment of appropriate cut-offs will hence be required prior to clinical implementation. While these results should be confirmed in larger cohorts, using combined cytokine scores may be useful in risk stratifying COVID-19 patients at ED presentation.

Funding: This study was funded by the University of Cincinnati College of Medicine Special Coronavirus (COVID-19) Research Pilot Grant Program.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 25;58(7):1021–8.
2. Nagant C, Ponthieux F, Smet J, Dauby N, Doyen V, Besse-Hammer T, et al. A score combining early detection of cytokines accurately predicts COVID-19 severity and intensive care unit transfer. International Journal of Infectious Diseases. 2020 Dec 1;101:342–5.
3. Lippi G, Henry BM, Hoehn J, Benoit S, Benoit J. Validation of the Corona-Score for rapid identification of SARS-CoV-2 infections in patients seeking emergency department

care in the United States. Clinical Chemistry and Laboratory Medicine (CCLM). 2020 Aug 10;58(12):e311–3.
4. Henry BM, Benoit SW, Vikse J, Berger BA, Pulvino C, Hoehn J, et al. The anti-inflammatory cytokine response characterized by elevated interleukin-10 is a stronger predictor of severe disease and poor outcomes than the pro-inflammatory cytokine response in coronavirus disease 2019 (COVID-19). Clinical Chemistry and Laboratory Medicine (CCLM) [Internet]. 2020 Nov 25 [cited 2020 Nov 30];1(ahead-of-print). Available from: https://www.degruyter.com/view/journals/cclm/ahead-of-print/article-10.1515-cclm-2020-1284/article-10.1515-cclm-2020-1284.xml
5. Lippi G, Plebani M. Cytokine "storm", cytokine "breeze", or both in COVID-19? Clin Chem Lab Med. 2020;

Correspondence:
Received: 28 December 2020
Accepted: 17 May 2021
Brandon Michael Henry, MD,
Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., Cincinnati, OH, USA 45229
Tel/Fax: 716.598.8610 / Email: brandon.henry@cchmc.org