EDITORIAL

The Sepsis Score Dilemma: Balancing Precision and Utility

Rajesh Pande[1], Maitree Pandey[2]

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Sepsis definitions given by the 3rd International Consensus Definitions for Sepsis and Septic shock (Sepsis-3) are rather subjective and define Sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more.[1] However, the sepsis population is quite heterogeneous in terms of geographical location, microorganisms involved, site of infection, and immunological response. Despite global initiatives directed to reduce the sepsis burden, there were 48.9 million cases of sepsis reported and 11 million sepsis-related deaths worldwide, representing 20% of all global deaths.[2]

As mortality associated with sepsis remains high, attempts have been made to recognize and quantify sepsis accurately and predict sepsis-related mortality. These include general scores like SOFA, Systemic Inflammatory Response Syndrome (SIRS), Simplified Acute Physiology Score (SAPS III), Sepsis Prediction Model (SPM), Moreno PIRO (predisposition, insult, response, and organ dysfunction), Logistic organ dysfunction system score (LODS), and Oxford acute Severity of illness score (OASIS) for use in the ICU.[3,4] Specific scores like Traumatic Sepsis Score (TSS), and early warning scores like quick SOFA (qSOFA), Universal vital Assessment Score (UVAS), National Early Warning Score (NEWS), and Modified Early Warning Score (MEWS) have been developed for use in locations outside the ICU.[5] Quick SOFA has been abandoned now as its performance was found to be lower than reported earlier and it underestimates risks and adverse outcomes in immunocompromised patients.[6,7]

However, one concern is that many of these scores have been developed and validated in high-income countries (HICs) and may not be equally valid in lower and middle-income countries (LMICs) due to different disease burdens, pathogens involved, and the health infrastructure.[8] The burden of tropical fever-associated sepsis is a major consideration in countries like India. There is no single score that can reliably predict sepsis and associated mortality. Sequential Organ Failure Assessment and SAPS III are more widely used due to their high sensitivity for recognition and mortality prediction in ICU patients compared to other clinical scores. Researchers have also explored various sepsis biomarkers to identify an accurate, easy-to-perform, reproducible, universally available, and cost-effective solution for sepsis detection and mortality prediction. Many biomarkers like procalcitonin (PCT), C-reactive protein (CRP), D-dimer, lactate, cytokines, and pro-adrenomedullin (Pro ADAM) have been explored besides blood biomarkers like neutrophil to leukocyte ratio (NLR), Neutrophil to platelets (NPR) and Neutrophil to monocyte ratios (NMR), and combination biomarkers like CRP-albumin ratio (CAR) have also been used with variable results.

[1]Department of Critical Care Medicine, BLK-Max Super Speciality Hospital, New Delhi, India

[2]Department of Anaesthesiology & Critical Care, Lady Hardinge Medical College, New Delhi, India

Corresponding Author: Rajesh Pande, Department of Critical Care Medicine, BLK-Max Super Speciality Hospital, New Delhi, India, Phone: +91 9810536268, e-mail: rajeshmaitree2000@gmail.com

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In this issue of IJCCM, the study IJCCM_24_468_R1[9] explores the sepsis mortality prediction accuracy of SOFA and SAPS III scores augmented by integrating three biomarkers—PCT, NLR, and CRP, with an assumption that integrating these inflammatory markers with organ dysfunction scores would be more sensitive and specific than either the biomarkers or the scores alone. The augmented versions of these scores were labeled as Pro SOFA and Pro SAPS III respectively. Sequential Organ Failure Assessment and SAPS III data were collected prospectively from 171 ICU patients, and PCT, NLR, and CRP values were measured at the time of enrollment. This was followed by the computation of augmented scores—ProSOFA and ProSAPS III. The relationship among biomarkers, clinical scores, and in-hospital mortality was investigated using multiple logistic regression analysis. Subsequently, the mortality prediction performance of these scores was evaluated using bootstrapping. The prediction performance of ProSOFA and ProSAPS III was compared with SOFA and SAPS III by calculating the Net Reclassification Index (NRI).

The authors found that CRP had a smaller effect on mortality prediction, but it significantly modified the effect when NLR was low. Risk prediction with high NLR was however independent of CRP. The augmented scores of ProSOFA and ProSAPS III showed a superior prediction accuracy over the original scores ($p < 0.01$). The study emphasizes that integration of PCT into sepsis scores would enhance their mortality prediction values.

The effort to create augmented models for Indian patients by the authors is laudable. Despite the issues with the accuracy of sepsis detection and mortality prediction models, the search must continue as the burden of sepsis and associated mortality in India is high.[10] However, we must be careful in selecting the denominators while developing such models. Procalcitonin, NLR, and CRP have been used in the present study as they are commonly used in clinical

practice but may not be the ideal biomarkers for sepsis detection and mortality prediction. C-reactive protein is an insensitive marker as it does not distinguish between systemic inflammatory response and sepsis. Although there was initial enthusiasm about the diagnostic impact of PCT, the diagnosis of sepsis remains essentially clinical. It is not recommended for sepsis diagnosis or guiding antimicrobial therapy, probably due to considerable variation reported in cutoff values. Procalcitonin remains controversial, as there seems to be no apparent benefit, and its role in mortality prediction remains uncertain. The high cost and limited availability in LMICs are other major concerns regarding their regular use. Currently, serial PCT measurements are only recommended for the de-escalation of antimicrobial therapy.

Many biomarkers like interleukin-6 (IL-6), Pro ADAM, and pentraxin are expensive and not universally available. Combination biomarkers like CAR have also been used. Raised levels of blood biomarkers have been shown to be associated with higher mortality in sepsis, but the sensitivity and specificity for these biomarkers like NLR, NPR, and NMR are low. Different NLR cutoffs used in studies have also resulted in wide variability in the accuracy of prediction. Similarly, the left shift has been shown to be better than NLR, but the problem is it generally rises 12–24 hours after the onset of sepsis. A composite of NLR and NPR has recently been shown to have higher area under curve (AUC) for sepsis-related survival when compared to NLR and NPR separately, but accuracy is a concern due to low sensitivity and specificity. In fact, no biomarker compares to the cardiac biomarker troponin I, which is used to identify acute coronary syndrome with a sensitivity of 95% and specificity of 80%.[11]

Clinical scores like SOFA have also been evaluated in combination with biomarkers for accuracy, and a combination of SOFA with NGAL showed higher sensitivity and specificity for detecting sepsis-associated acute kidney injury (AKI).[12] Another study where SOFA was combined with four biomarkers did not show a better 28-day mortality prediction when compared to the combination of four biomarkers used alone.[13] The present study has another limitation of substantial data loss for the inflammatory biomarkers—29.2% for PCT, 9.9% for CRP, and 2.9% for NLR, which may have affected the accuracy of prediction models. It is a single-center study with 170 patients, and in a country like India, it must be validated in a much broader patient database. As artificial intelligence (AI) is gaining significant ground in critical care, it is also exploited for early detection and mortality prediction in sepsis. In fact, AI-based Sepsis Early Risk Assessment (SERA) algorithm has been found to increase sepsis prediction by 32% with significant reduction in false positives.[14] Similarly a machine learning algorithm "In Sight" using vital signs from EHR was found to predict sepsis 4-hour before its onset and outperformed all sepsis scores.[15] Integration of the ProSOFA and ProSAPS III models with AI would help in its validation on a much larger scale. Considering that India is a global software power, it would be meaningful if we collaborate with IT industries to fast-track such projects which can then be fine-tuned and applied on a mass scale to critically ill patients to identify the sepsis burden and make accurate mortality predictions. The derived output, if meaningful, may be further extended to sepsis therapeutics.

Orcid

Rajesh Pande https://orcid.org/0000-0002-0149-727X
Maitree Pandey https://orcid.org/0000-0003-0220-4106

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