Quest to predict Mortality in Sepsis: Will We ever get It Right?

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Sepsis definition has undergone quantum shift over the last 3 decades. From using host systemic inflammatory response syndrome (SIRS) to identify sepsis,1,2 we have now moved to define sepsis as a life-threatening organ dysfunction due to dysregulated host response to infection.3 More importantly predicting mortality in sepsis has been a challenge and continues to remain a challenge due to the heterogeneity of patients and also the various scoring systems used.4

Through the various definitions and criteria used Sepsis-1 was developed using SIRS criteria. Four SIRS criteria were defined, namely tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36°C), and leucocytosis or leukopenia (white blood cells >12000/mm³ or <4000/mm³). Patients who met two or more of these criteria fulfilled the definition of SIRS and sepsis was defined as infection of suspected infection leading to SIRS. The SIRS concept had its validity challenged over the next decade because of onset of inflammation in absence of infection like pancreatitis, burns, and other disease processes. A 2001 task force led by Levy et al.5 identified this, however, due to lack of alternate evidence-based criteria, same definition was continued but they expanded the list of diagnostic criteria thus giving rise to Sepsis-2 criteria.

It was in 2016 Society of Critical Care Medicine and European Society of Intensive Care Medicine6 relooked at criteria to identify sepsis and compared SIRS to other methods like logistic organ dysfunction score (LODS) and sequential organ failure assessment (SOFA) score. The authors concluded that SOFA score was more predictive in assessing the severity of organ dysfunction in a septic patient. The predictive value for in hospital mortality of septic patients was more with SOFA (10%) as compared to SIRS.6,7 They also concluded that LODS and SOFA had similar prediction capacity, however, due to its ease of calculation SOFA was recommended. They further concluded that lack of complete variables of SOFA and complexity of method may result in late recognition of sepsis, hence a simplified method quick SOFA (qSOFA) was introduced for early and ease of identification. Quick SOFA consisted of three variables: hypotension—systolic blood pressure <100 mm Hg, altered mental status, and tachypnea—respiratory rate >22/min. A qSOFA of ≥2 predicted organ dysfunction.

The simplified definition came with its own criticism. William et al.8 very eloquently demonstrated the lack of sensitivity of qSOFA in identifying early sepsis, a stage in which the treatment is most effective. This qSOFA cannot be relied upon as a screening tool for patients presenting to hospital. However, it could still be useful in patients who are admitted to hospital with suspected sepsis. Moving from an inflammatory-based definition in Sepsis-1 and -2 to a more syndromic-based definition in Sepsis-3 we have certainly made the diagnostic criteria wide. The term organ dysfunction in new Sepsis-3 criteria still remains a difficult one to understand as many organs have more than one function and also the inappropriate host response how to measure that. With these lacunas in the definition its ability to predict mortality also becomes varied. In 2017 Raith et al.9 performed a retrospective analysis of 184,875 patients admitted to Australian and New Zealand intensive care units (ICUs) with primary infection-related diagnosis. They compared the increase in SOFA, SIRS, and qSOFA by two or more points, respectively, and looked at the patient’s outcomes. The study was conducted in 182 ICUs from 2000 to 2015. They concluded that SOFA had a greater accuracy in prognosticating mortality in admitted ICU adult patients as compared to SIRS or qSOFA. When compared between SIRS and qSOFA they found that SIRS was better in prediction of in hospital mortality.

In this edition, Bhattacharya et al.10 have attempted to compare ability of SIRS, SOFA, and qSOFA in predicting mortality in sepsis. To conduct a prospective study looking at predictability of SIRS, SOFA, and qSOFA in ICU patients is very challenging technically and logistically, due to the complexity of collecting data, presentation of patient directly to hospital, or been referred from a peripheral center and previous treatment received have all been shown to influence the sepsis outcomes. The authors must be commended for this. The authors have used the Sepsis-2 definition of severe sepsis and septic shock and correlated it to sepsis and septic shock by the Sepsis-3 definition. We are well aware of the limitation of comparison as on looks at the inflammatory syndrome and the Sepsis-3 looks at dysregulated response and organ dysfunction. This has resulted in a very complex interpretation of sepsis, severe sepsis, and septic shock patients. If we take the current Sepsis-3 definition then only 96 of the total 122 patients (78.6%) fulfill the Sepsis-3 criteria. This emphasized that identification of sepsis could have been done using the current definition only. One of the important study findings is the distribution of septic patients as per etiology of sepsis. Scrub typhus was 30.32% followed by pneumonia 25.41% and urinary tract infection 17.21%. The overall mortality was 61/122 (50%), which is a bit higher than most studies. However, the important point to note is scrub typhus patients forming more than 30% of total sample size. Scrub typhus is a tropical infection, while its prevalence in Indian subcontinent is well documented it is difficult to interpret or predict mortality in this group of patients as none of the criteria SIRS, SOFA, or qSOFA ever had such a large population of tropical infections in their validation studies. Hence the applicability of these scores in this population of patients is unique and probably requires further studies. Also, deep diving into the mortality data reveals 78% mortality in septic shock patients and 32% in severe sepsis patients. This is due to the two different definitions used to identify sepsis.

The ability of SIRS, SOFA, and qSOFA to predict mortality is well appreciated and comparable to some of the other studies in literature. The highest area under the receiver operating characteristic curve in predicting mortality is the SOFA score followed by the qSOFA and SIRS scores. The highest sensitivity was seen for SIRS score >2 (91.80%) with the highest specificity for a SOFA score on the second day after admission >12 (83.61%). They have very clearly demonstrated that predication of mortality by SOFA is most specific followed by qSOFA and SIRS is highly sensitive but specificity is very poor.

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Where do we go from here is the big question? While studies have clearly shown SOFA to be superior and specific in predicting mortality, the complexity and several variable availability remain the limiting factor in measuring SOFA in every patient. With qSOFA we do have limited ability to diagnose sepsis in its early stage when the treatment is most effective. It is very clear that SIRS has lost steam due to its poor specificity. Also in a heterogeneous patient population like India where tropical diseases form a major chunk of admissions, how justified are we in using the sepsis definition, which was never tested against such group of patients.

I believe we in the subcontinent will have to conduct studies in our patient population, just like Bhattacharya et al. and come out with our very own sepsis definition and mortality prediction model. I am confident with the large pool of patients we have across the country, such a study would be a landmark in identification of sepsis and predicting mortality.

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References