

SIRS, qSOFA, and organ failure for assessing sepsis at the emergency department

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Provenance: This is an invited Editorial commissioned by the Section Editor Zhongheng Zhang (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Williams JM, Greenslade JH, McKenzie JV, *et al.* Systemic Inflammatory Response Syndrome, Quick Sequential Organ Function Assessment, and Organ Dysfunction: Insights From a Prospective Database of ED Patients With Infection. *Chest* 2017;151:586-96.

Submitted Mar 13, 2017. Accepted for publication Apr 20, 2017.

doi: 10.21037/jtd.2017.05.36

View this article at: <http://dx.doi.org/10.21037/jtd.2017.05.36>

Sepsis incidence and mortality rates widely vary among different countries and underlies as a major cause of morbidity and mortality. A recent meta-analysis from high-income countries estimated sepsis annual global incidence at 31.5 million cases, with 19.4 million cases of severe sepsis, resulting in 5.3 million deaths annually (1). Without specific therapies, management relies on infection control and organ support. For these interventions to be most effective, they must be started early, which highlights the need for all health-care workers to be aware of sepsis, so that diagnosis can be made as early as possible. Thus the ability to identify sepsis patients who are at high risk for subsequent deterioration and mortality, starting from prehospital care and emergency department (ED), is crucial since timely recognition and appropriate, effective treatment substantially improves survival. However, sepsis remains as an illness difficult to identify and a gold-standard test for diagnose does not currently exist.

For these reasons, new definitions of septic shock were launched. Accurate diagnostic criteria and consensus definitions have an important role, providing tools for research, benchmarking, performance monitoring, and accreditation. The previous consensus definitions of severe sepsis (sepsis-2) required suspected or proven infection, two or more criteria for the systemic inflammatory response syndrome (SIRS), and organ failure (2,3). The third international consensus definitions for sepsis and septic

shock (sepsis-3) published recently, considered that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the sequential (sepsis-related) organ failure assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10% (4,5). Furthermore, the new definition excludes the concept of SIRS since this term is being considered of not useful anymore. The authors supported this decision mainly based on a retrospective study conducted in Australia and New Zealand by Kaukonen *et al.* (6) in which it was observed that 1 out of 8 patients (12.5%) with sepsis and multiorgan failure did not have at least two SIRS criteria. In addition, they introduced the concept of the quick SOFA (qSOFA) score as a possible predictive tool among patients with suspected infection outside the intensive care unit (ICU) to be used to raise suspicion of sepsis and prompt further action. These data were drawn retrospectively from North American cohorts and a single German cohort. The authors noted that both concepts (qSOFA and sepsis defined as SOFA ≥ 2) need prospective validation in different healthcare settings and their added value in the ED remains actually unknown.

In this regard, a recent prospective work led by Williams and colleagues analyzed in a big Australian cohort of 8,871 patients from the ED admitted with a

diagnosis indicating presumed or potential infection. The authors aimed to determine the prognostic impact of SIRS, and compare the diagnostic accuracy of SIRS and qSOFA for mortality and organ dysfunction. Furthermore, they compared previous (sepsis-2) and novel (sepsis-3) definitions for organ dysfunction. SIRS was present in 1,157 (75.4%) patients with (sepsis-2) organ dysfunction and was associated with increased odds of 30-day mortality (OR 1.8; 95% CI, 1.2–2.7). Similarly, in those with sepsis-3 organ dysfunction 1,561 patients (72.1%) presented with SIRS at ED, and were associated with increased mortality odds (OR 2.2; 95% CI, 1.5–3.1). Although authors conclude SIRS is a useful screening tool for death in ED patients with suspected infection, it is necessary to emphasize that they found 24.6% (sepsis-2) and 27.9% (sepsis-3) of patients with organ dysfunction that did not have SIRS. In other words, approximately a quarter of patients with sepsis plus organ failure did not meet SIRS criteria, and therefore, based on the old definition (sepsis-2), such patients could not have been labelled as sepsis in the ED. This would confirm the findings of Kaukonen *et al.* (6) and support the justification for the change in the definition of sepsis carried out by the third international consensus definitions for severe sepsis and septic shock (4,5). On the other hand, SIRS and qSOFA showed similar discrimination for organ dysfunction (AUROC 0.72 *vs.* 0.73) at ED. qSOFA ≥ 2 was highly specific for identifying organ dysfunction and mortality (96.1% and 91.3% respectively), but sensitivity was poor (29.7% and 49.1% respectively) compared to sensitivity for SIRS ≥ 2 (72.1% and 76.7%). This means that qSOFA ≥ 2 is an excellent tool to predict mortality and organ failure in a fast, easy and inexpensive manner at ED. However, worryingly some patients will be on risk of die or develop organ failure despite showing a qSOFA < 2 , probably because they could have other forms of organ dysfunction not assessed by qSOFA, such as hypoxemia, renal failure, coagulopathy, or hyperbilirubinemia. The consequences of this low sensitivity in a high income ED setting could be limited because mortality rate is expected to be low, and specificity seems a priori more important to avoid overtreatment. In contrast, SIRS has been severely criticized since its high sensitivity, especially in the ICU where 93% of patients had at least two SIRS criteria at some point during their stay (7), can lead to an excessive number of false positives and to an unnecessarily wasting of time and resources. However, this scenario could be different in low and middle income countries where the low sensitivity described for qSOFA is worrisome.

Other studies have investigated this issue. In a recent multicenter prospective cohort study by Freund and colleagues involving 879 patients with suspected infection treated at the ED, the qSOFA was better than SIRS at predicting in-hospital mortality with an AUROC of 0.80 (AUROC, 0.65) and severe sepsis (AUROC, 0.65) (8). In this cohort a qSOFA ≥ 2 had an in-hospital mortality rate of 24% versus 3% for patients with a qSOFA < 2 . In contrast, in another recent report, predictive validity of qSOFA is evaluated in a retrospective analysis of the large Australian and New Zealand Intensive Care society (ANZICS) Adult Patient Database of admissions to adult general ICUs (9). Among more than 184,000 patients with an infection-related primary diagnosis admitted to 182 ICUs, the authors reported that the predictive value of qSOFA in the ICU setting was inferior to SOFA score. A SOFA score ≥ 2 points were present in 90.1%; 86.7% manifested 2 or more SIRS criteria and 54.4% had a qSOFA ≥ 2 points. Based on AUROC analysis, SOFA showed a significantly high prognostic accuracy for in hospital mortality, greater than SIRS or qSOFA did, with AUROCs of 0.75, 0.58 and 0.60 respectively. Probably, interventions like intubation plus mechanical ventilation, sedation, etc. can alter the validity and generability of qSOFA and SIRS in the critical care setting. Therefore SOFA (and/or other more complex scores) remains as the only reliable prognostic score in this scenario.

These are the first large studies analyzing the role of qSOFA and SIRS prospectively and/or in a large number of patients. The main message is valuable: both, SIRS and qSOFA are useful tools for predicting mortality and organ failure outside the ICU, but this utility disappears in the critical ill setting. The high specificity of qSOFA confers great value for the screening of those patients with a presumed infection more likely to develop a life-threatening organ dysfunction (or as some authors suggest, to detect other potentially lethal pathologies like heart attack or pulmonary embolism). So the presence of two or more of these criteria can be used to prompt clinicians to further evaluate the patient for the presence of infection and/or organ dysfunction, to start or adapt treatment, and to consider transfer the patient to an ICU. However not all is perfect, and ideally it would be necessary to reassess the risk of bias because of low sensitivity. Perhaps a possible solution could add other simple clinical parameters or biomarkers like lactate (10) or other novel biomarkers (11). Therefore, based on the most recent findings, and until qSOFA sensitivity is not somewhat improved, qSOFA is meant to be

used to raise suspicion of sepsis and prompt further action only outside the ICU setting.

Interestingly, Williams and colleagues also find that overall organ dysfunction according to both sepsis-2 and sepsis-3 definitions provided similar estimates of mortality risk. However, their analyses showed that mortality associated with each individual organ dysfunction varied widely despite the same SOFA threshold. Thus, even at SOFA cut offs of three or more points, gastrointestinal and haematological organ system dysfunction remains less important for prognostication than dysfunction in the other systems (OR mortality not higher than 2.5 for both *vs.* OR >7.5 for the rest of organs). So authors point out for first time in literature the poor calibration of the SOFA score between organ systems. As authors point, it might be related to the use in the ED setting (ideally SOFA was designed for use in critically ill patients with multiorgan failure) or to the fact that the SOFA has not been updated from 1996. As the original authors of SOFA recognized, the criteria used and especially the individual values for each of the parameters evaluated in the SOFA score should not be considered as definitive, but can be altered when sufficient data are collected (12). So these limitations in the SOFA score could limit its validity between ED patients and also affect sepsis-3 organ dysfunction criteria. Again, it might be reduced by recalibrating the score with contemporary patient data.

Finally, despite all these circumstances, 29% of patients with sepsis-3 organ dysfunction [639] did not meet sepsis-2 criteria for organ dysfunction presented with an acute increase in total SOFA of two or more, since that increase occurred in different organ systems. Mortality for those patients was significantly less than for those with sepsis-2 organ dysfunction at 30 days (difference 3.6%, 95% CI; 0.8–6.4%), but not at one year (difference –2.6%; 95% CI, –6.8% to 1.5%). In other words, the new definition (sepsis-3) seems to be reliable and it was able to detect more cases of sepsis than the old (sepsis-2) classification did, contrary to the opinion of other authors who defended just the opposite (13).

In summary, Williams and colleagues offer us an observational, robust and well-designed study. They have enrolled the largest cohort of ED patients with suspected infection to compare the different definitions of sepsis for assessment of the proposed “sepsis-3” criteria. As conclusion, qSOFA, outside the ICU in the high income settings where it has been tested, appears a simple, rapid, inexpensive, and valid way to identify—among patients

with suspected infection—those at a higher risk of having or developing organ failure and sepsis. However it seems necessary to look for options to improve its low sensitivity. Until then, it does not replace the role of SIRS in the emergency setting. However, both SIRS and qSOFA are not adequate methods for assessing severity in the critical care setting. Finally, novel definition of sepsis based on SOFA ≥ 2 seems accurate and safe, although as authors demonstrate a new and exhaustive validation of the different organic systems evaluated by SOFA scale is necessary in order to improve as far as possible the accuracy of the scale and its applicability to sepsis detection in all possible scenarios with special attention to those outside the ICU environment.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Andaluz D, Ferrer R. SIRS, qSOFA, and organ failure for assessing sepsis at the emergency department. *J Thorac Dis* 2017;9(6):1459-1462. doi: 10.21037/jtd.2017.05.36