



Evolving Definition and Diagnostic Criteria of Sepsis

V. Rakshana^{a#}, A. S. Arunkumar^{at} and Laya Mahadevan^{a*‡}

^a Department of Critical Care Medicine, Saveetha Medical College Hospital, Chennai, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i58B34216

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/76000>

Short Communication

Received 07 October 2021
Accepted 14 December 2021
Published 16 December 2021

ABSTRACT

For many years, the Systemic Inflammatory Response Syndrome (SIRS) criteria were primarily considered for the diagnosis of sepsis, promoting the importance of inflammation. The definition and diagnostic criteria of sepsis has undergone a sizeable metamorphosis from the inception of standardized definitions of sepsis in 1991. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened in Chicago and emphasized that sepsis is an 'ongoing process' of infection and considered SIRS score of two or more for diagnosis of sepsis. SOFA scoring system is an easily calculated system using parameters that are usually obtained during routine care of patients. This ensures that delays are avoided from requirement of any special investigations, making it reproducible in any number of healthcare settings.

Keywords: Healthcare settings; systemic inflammatory response syndrome; chest physicians; sepsis.

1. INTRODUCTION

The lately held Sepsis-three consensus convention defines sepsis as a 'life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. A late evaluation states

that the annual international prevalence of sepsis is at 31.5 million cases, with 19.4 million cases of severe sepsis, ensuing in about 5.3 million deaths [2]. Sepsis related mortality is as much as 40% and about a third of non-survivors die inside forty eight hours of admission to ICU [3].

[#] Undergraduate;

[†] Professor and HOD;

[‡] Assistant Professor;

*Corresponding author: E-mail: laya.luiz@gmail.com;

Mortality in sepsis is highly associated with delays in adequate treatment despite available modern treatment protocols [4]. Since early identification of sepsis and prompt initiation of treatment in the form of antimicrobials and fluid resuscitation reduces the mortality rate, recent protocols have focused on the development of various criteria which are aimed at early identification of sepsis [5-7].

For many years, the Systemic Inflammatory Response Syndrome (SIRS) criteria were primarily considered for the diagnosis of sepsis, promoting the importance of inflammation. Even though, the SIRS Criteria had a high sensitivity (78% - 97% depending on patient population) [8] it yields up to 1 in 8 false negatives in patients with infection and organ failure [9] indicating poor specificity. In an attempt to balance the needs of early diagnosis of sepsis while at the same time have reasonable specificity, the Sepsis-3 Task Force recommended the use of Sequential (Sepsis-related) Organ Failure Assessment score (SOFA) as a tool in identification of septic patients in ICU because SOFA is found to perform better [AUROC; (95%CI)] SIRS : 0.55 (0.54-0.56); SOFA : 0.67 (0.65-0.68); qSOFA : 0.61 (0.60-0.63); SIRS vs SOFA : $p < 0.001$; SIRS vs qSOFA : $p < 0.001$ [10].

Outside the ICU, quick Sequential Organ Failure Assessment score (qSOFA) was introduced for the rapid identification of high risk patients. The qSOFA acts as a risk predictor for patients with known or suspected infection [11].

2. SEPSIS DEFINITIONS OVER THE YEARS

The definition and diagnostic criteria of sepsis has undergone a sizeable metamorphosis from the inception of standardised definitions of sepsis in 1991 [12]. In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened in Chicago and emphasised that sepsis is an 'ongoing process' of infection [12] and considered SIRS score of two or more for diagnosis of sepsis. They also defined severe sepsis and septic shock based on the presence of organ dysfunction and hypotension respectively. For more than two decades Sepsis has been defined as suspected or proven infection in the presence of two or more systemic inflammatory response syndrome (SIRS) criteria [12] (Table 1).

Table 1. Systemic Inflammatory Response Syndrome

Systemic Inflammatory Response Syndrome
Temperature > 38.3 C or < 36°C
Respiratory rate > 20 breaths / min
Heart rate > 90 beats per min
White cell count < 4 or > 12 g/L

In 2001 the second consensus conference with the aim of diagnosing sepsis quicker and more precisely expanded and codified the diagnostic criteria of sepsis [12] by including general parameters, inflammatory parameters, haemodynamic parameters, organ dysfunction parameters and tissue perfusion parameters. It was hoped that use of these clinical, laboratory and monitoring parameters would make the diagnosis of sepsis more reliable thereby aiding quicker treatment and better outcomes. (Table 2).

In 2016 SEPSIS 3 the Third International Consensus Definitions of Sepsis and Septic shock redefined sepsis as "life-threatening organ dysfunction caused by dysregulated host response to infection" [13]. For the first time the response of the host to the infectious insult was given priority over focus on the infection itself. Thus the updated definitions of SEPSIS 3 emphasis organ dysfunction in the setting of infection, which was quantified using the Sequential Organ Failure Assessment score (SOFA; Table 4) and quick Sequential Organ Failure Assessment (qSOFA) scores for the diagnosis of sepsis in the ICU and ward respectively [14]. SOFA and qSOFA are easily scored utilising parameters collected routinely in a hospital setting, thus making diagnosis easy and quick.

Further Septic shock was defined by Sepsis-3 as "hypotension not responsive to fluid resuscitation" with added requirements for vasopressors to maintain a mean arterial pressure (MAP) > 65 mm Hg or presence of Serum lactate >2 mmol/L. In addition the category of "severe sepsis" as per the 2001 definition was removed. Table 3.

SOFA scoring system is an easily calculated system using parameters that are usually obtained during routine care of patients. This ensures that delays are avoided from requirement of any special investigations, making it reproducible in any number of healthcare settings. Thus SEPSIS 3 is one more attempt at reducing the lead time to diagnosis of sepsis and

ensure early initiation of treatment. Organ dysfunction is defined as an increase in the SOFA score ≥ 2 . Patients presenting with organ dysfunction have an associated 10% mortality risk [11]. Hence these patients need early aggressive resuscitation and stabilisation in an attempt to optimise haemodynamics, improve organ perfusion and ensure early source control.

The quick Sequential Organ Failure Assessment (qSOFA) is another screening tool used at the bedside for early identification of sepsis in the wards. It includes 1 point for each of 3 criteria:

- 1) respiratory rate >22 breathes/ min
- 2) altered mental status: Glasgow Coma Scale (GCS) <15
- 3) Systolic Blood Pressure <100 mm Hg.

A qSOFA score > 2 was found to be significantly predictive of increased all-cause mortality in patients outside ICU [11]. If it is ≥ 2 , the full SOFA score including laboratory results should be used [11]. Though qSOFA has been found to have better specificity in prediction of mortality [14,15] and evolving organ dysfunction [16]. it is criticised to be insensitive as a sepsis screening tool [17,18]. The US Centres for Medicare and Medicaid Services (CMS) SEP-1 quality measure, used to evaluate institutional sepsis bundle compliance, didn't adopt Sepsis-3. SEP-1 is based on SIRS criteria and further defines severe sepsis as sepsis associated with organ dysfunction, hypo-perfusion or hypotension and septic shock as "hypotension not responsive to fluids or serum lactate >4 mmol/L regardless of hypotension." [19,20]. Hence it is based on 2001 International Sepsis Definitions Conference and not on Sepsis-3 definition [12].

Table 2. 2001 Sepsis Criteria

General parameters
Fever
Hypothermia
Tachycardia
Tachypnea
Altered mental status
Significant oedema or positive fluid balance
Hyperglycaemia (in the absence of diabetes)
Inflammatory parameters
Leucocytosis
Leukopenia
Normal white blood cell count with $> 10\%$ immature forms
Plasma C reactive protein >2 SD above normal value
Plasma procalcitonin > 2 SD above normal value
Haemodynamic parameters
Arterial hypotension
Mixed venous oxygen saturation $> 70 \%$
Cardiac index $> 3.5 \text{ l min}^{-1} \text{ m}^{-2}$
Organ dysfunction parameters
Arterial hypoxemia
Acute oliguria
Creatinine increase
Coagulation abnormalities
Ileus
Thrombocytopenia
Hyperbilirubinemia
Tissue perfusion parameters
Hyperlactatemia
Decreased capillary refill or mottling

Table 3. Sepsis-3 definition of Septic Shock

Septic shock Hypotension not responding to fluid resuscitation and requiring vasopressors to maintain MAP > 65 mm Hg (or) Presence of Serum lactate > 2 mmol / L
--

Table 4. Sequential Organ Failure Assessment score

Variables	0	1	2	3	4
Respiratory					
PaO ₂ /FiO ₂	>400	<400	<300	<200	<100
SpO ₂ /FiO ₂	>302	<302	<221	<142	<67
Cardiovascular					
MAP (mm Hg)	>70	>70	Dopamine <5	Dopamine>5,	Dopamine >15 or
Vasopressor doses in mcg/kg/ min			Or any dobutamine	Norepinephrine < 0.1, Phenylephrine < 0.8	Norepinephrine >0.1 Phenylephrine >0.8
Liver					
Bilirubin (mg/dL)	<1.2	1.2-1.9	2.0-5.9	6-11.9	>12
Renal					
Creatininemg/dL)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5
Coagulation (Platelets x 10 ³ / mm ³)	>150	<150	<100	<50	<20
Neurologic (GCS score)	15	13-14	10-12	6-9	<6

According to Sepsis-3, a new increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Whenever the SOFA score is increased, there is increased risk of mortality in those patients
Abbreviations: GCS- Glasgow Coma Scale , FiO₂ – fraction of inspired oxygen, MAP- mean arterial pressure, PAO₂- arterial oxygen pressure, SpO₂- oxygen saturation

Table 5. Definitions of sepsis, severe sepsis and septic shock

Sepsis category	Sepsis-3 Criteria	2001 Sepsis Criteria	CMS SEP-1
Sepsis	SOFA score > 2 + suspected infection	2 of 4 SIRS criteria + suspected infection	2 of 4 SIRS criteria +suspected infection
Severe sepsis	Not applicable	Sepsis + organ dysfunction, hypo-perfusion or hypotension	Sepsis +sepsis – induced organ dysfunction*
Septic shock	Vasopressors to maintain MAP>65 mm Hgin spite of fluid resuscitation or serum lactate >2 mmol/L in the absence of hypovolemia	Sepsis-induced hypotension persisting after IV fluid resuscitation + presence of perfusion abnormalities or organ dysfunction	Lactate >4 mmol/L SBP < 90 mm Hg ,not responding to IV fluids Or MAP <70 mm Hg ,not responding to IV fluid

*Organ dysfunction variables according to CMS SEP-1 include SBP <90 mm Hg or MAP < 70 mm Hg , or a SBP decrease > 40 mm Hg or <2 SD below normal for age or known baseline ; creatinine >2mg/dL or urine output <0.5 ml/kg/hr for > 2 hours ; bilirubin >2 mg /dL; platelet count <100,000; coagulopathy (INR >1.5 or aPTT > 60 sec) lactate > 2 mmol/L

Abbreviations: aPTT – activated partial thromboplastin time; CMS – Centre for Medicare and Medicaid Services; INR – International Normalised Ratio ; MAP – mean arterial pressure; SBP – systolic blood pressure; SD – standard deviation; SIRS – Systemic Inflammatory Response Syndrome; SOFA- Sequential Organ Failure Assessment

3. DISCUSSION

SIRS was the cornerstone in identification of sepsis for a long time. The primary focus with this approach was on inflammation resulting from an infectious insult. However as we now know, inflammation is not unique to infections alone, and is associated with a number of non infectious disease entities. Not surprisingly definitions and scores primarily based on SIRS was found to have low performance for distinguishing infection from non- infectious processes. Recent studies show that SIRS has high sensitivity and low specificity when compared to Qsofa (Sensitivity: SIRS = 78%-97%, SOFA = 5%-42%, qSOFA =56%-93%. Specificity: SIRS= 13%- 48%, SOFA = 92%-99% ,qSOFA = 30%-70%) [8] in identifying sepsis [21-23]. SIRS failed to differentiate systemic inflammation due to infectious and non-infectious insults such as pancreatitis, trauma and hence offered poor outcome prediction [16]. Moreover the use of SIRS criteria failed to define a transition point in risk of death , despite adjustment for baseline characteristics [9]. Because of these drawbacks, more recent management protocols have moved away from SIRS criteria for diagnosis of sepsis and prognostication in these patients.

In terms of identifying patients at risk of mortality , qSOFA is most sensitive while SOFA is most specific. (Sensitivity: SIRS =96%-98%, SOFA = 27%-73%, qSOFA = 98%-100%. Specificity: SIRS =7%-44%, SOFA = 74%-98%, qSOFA =17%- 65%) [8].

SEPSIS 3 redirects the focus on diagnosis of sepsis to the presence of organ dysfunction. SOFA provides a better outcome prediction in patients with sepsis. Presence of even mild organ dysfunction in the presence of sepsis increase mortality multi fold when compared to those without organ dysfunction. Hence all patients presenting with suspected sepsis needs to be carefully evaluated for the presence of organ dysfunction. On the other hand patients presenting with features of organ dysfunction need to be thoroughly evaluated for unrecognised infections. Having a complete SOFA scoring done in the ward setting may be difficult as it relies on oxygen parameters obtained from arterial blood gas values and also platelet counts and bilirubin values for identification of coagulation and liver failure respectively, parameters that may typically not be available routinely in the wards. Hence for the early identification of patients at risk of rapid

deterioration a bedside assessment tool called qSOFA was introduced.

qSOFA is a simple triaging tool consisting of three easily obtained components: respiratory rate, Glasgow Coma Scale and systolic blood pressure and is found to be marginally superior to a full SOFA scoring outside the ICU. It can be very easily used in the wards by any healthcare worker. A qSOFA value >2 is predictive of increased all- cause mortality in patients outside ICU [11] These patients need urgent further evaluation to rule out organ dysfunction and sepsis. Though qSOFA performs well as a predictor of mortality it performs poorly as a diagnostic tool in identification of sepsis. Hence it provides a general assessment of severity independent of the infection and may be considered a warning signal in the clinical decision-making process to identify those at higher risk of mortality in a non ICU setting [24]. The recently published Surviving Sepsis Campaign guideline 2021, makes a strong recommendation against using qSOFA as a sole screening tool for the identification of sepsis or septic shock when compared to SIRS, National early warning score (NEWS) or modified early warning score(MEWS) [25]. Studies have shown that qSOFA is more specific but less sensitive than SIRS in identifying organ dysfunction due to infection [26,27]. Similar results were seen when QSOFA was compared with NEWS and MEWS [28]. However in ICU environment SOFA demonstrated significantly greater capacity compared with qSOFA and SIRS criteria for predicting mortality. {[AUROC ; (95% CI)]} SIRS = 0.64 ;(0.62-0.66), qSOFA = 0.66 (0.64-0.68), SOFA = 0.74 (0.73 -0.76) }.The relationship between SOFA scores and risk of death has been confirmed in a variety of patient subgroups including sepsis [11,29,30].

4. CONCLUSION

Among all the available sepsis diagnostic criteria, SIRS has high sensitivity but poor specificity in identification of sepsis, while SOFA score is very specific. qSOFA does well in the non ICU setting in recognising patients at high risk of deterioration but must not be used as a sole tool in identification of sepsis. It is more specific but less sensitive than SIRS in identification of sepsis. qSOFA and SIRS scoring system are easy to use as they are based on clinical variables that are commonly recorded. However SOFA scoring requires more extensive evaluations based on further laboratory

investigations. Patients presenting with organ dysfunction as identified through SOFA scores of 2 or more are at higher risk of mortality.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801-10.
2. Fleischmann C, Scherag A, Adhikari NKJ, et al; International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. *Am J Respir Crit Care Med*. 2016;193(3):259-272
3. Blanco J, Muriel-Bombín A, Sagredo V, et al. Incidence, organ dysfunction and mortality in severe sepsis: a Spanish multicentre study. *Crit Care* 2008;12:R158.
4. Pruinelli L, Westra BL, Yadav P, Hoff A, Steinbach M, Kumar V, et al. Delay within the 3-hour surviving sepsis campaign guideline on mortality for patients with severe sepsis and septic shock. *Crit Care Med*. 2018;46:500–5.
5. Sprung CL, Sakr Y, Vincent J-L, Le Gall J-R, Reinhart K, Ranieri VM, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely ill Patients (SOAP) study. *Intensive Care Med*. 2006;32:421–7.
6. Dulhunty JM, Lipman J, Finfer S. Does severe non-infectious SIRS differ from severe sepsis? *Intensive Care Med*. 2008;34:1654–61.
7. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.
8. Koch, C., Edinger, F., Fischer, T, et al . Comparison of qSOFA score , SOFA score and SIRS criteria for the prediction of infection and mortality among surgical intermediate and intensive care patients. *World J Emerg Surg* 15, 63 (2020).
9. Kaukonen KM, Bailey M, Pilcher D, et al. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015;372:1629-38.
10. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. *Intensive Care Med*. 1996;22:707–10.
11. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:762–74.
12. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250–6.
13. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552.
14. Freund Y, Lemachatti N, Krastinova E, et al. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. *JAMA*. 2017;317(3):301-308.
15. Donnelly JP, Safford MM, Shapiro NI, et al. Application of the Third International Consensus Definitions for Sepsis (Sepsis-3) classification: a retrospective population-based cohort study. *Lancet Infect Dis*. 2017;17(6):661-670.
16. Park HK, Kim WY, Kim MC, et al. Quick sequential organ failure assessment compared to systemic inflammatory response syndrome for predicting sepsis in emergency department. *J Crit Care*. 2017;42:12-17.
17. Raith EP, Udy AA, Bailey M, et al. Prognostic accuracy of the SOFA score,

- SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. *JAMA*. 2017;317(3):290-300.
18. Haydar S, Spanier M, Weems P, et al. Comparison of qSOFA score and SIRS criteria as screening mechanisms for emergency department sepsis. *Am J Emerg Med*. 2017;35(11):1730-1733.
 19. Dellinger RP. The future of sepsis performance improvement. *Crit Care Med*. 2015;43(9):1787-1789.
 20. Faust JS, Weingart SD. The past, present, and future of the Centers for Medicare and Medicaid Services Quality Measure SEP-1. *Emerg Med Clin North Am*. 2017;35(1):219-231.
 21. Franchini S, Scarallo L, Carlucci M, Cabrini L, Tresoldi M. SIRS or qSOFA? Is that the question? Clinical and methodological observations from meta-analysis and critical review on the prognostication of patients with suspected sepsis outside the ICU. *Intern Emerg Med*. 2019;14:593–602.
 22. Jiang J, Yang J, Jin Y, Cao J, Lu Y. Role of qSOFA in predicting mortality of pneumonia. A systematic review and meta-analysis. *Medicine*. 2018;97(40):e12634.
 23. Fernando, S. M. et al. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection. A systematic review and meta-analysis. *Ann Intern Med*. 2018;168:266–275.
 24. Giamarellos-Bourboulis EJ, Tsaganos T, Tsangaris I, Lada M, Routsis C, Sinapidis D, et al. Validation of the new Sepsis-3 definitions: proposal for improvement in early risk stratification. *Clin Microbiol Infect*. 2017;23:104e9.
 25. Evans L, Rhodes A, Alhazzani W et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine*. 2021;49(11):e1063-e1143
 26. Fernando SM, Tran A, Taljaard M, et al. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection: A systematic review and meta-analysis. *Ann Intern Med*. 2018;168:266–275
 27. Herwanto V, Shetty A, Nalos M, et al. Accuracy of quick sequential organ failure assessment score to predict sepsis mortality in 121 studies including 1,716,017 individuals: A systematic review and meta-analysis. *Crit Care Explor*. 2019;1:e0043
 28. Liu VX, Lu Y, Carey KA, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. *JAMA Netw Open*. 2020; 3:e205191.
 29. Wendlandt B, Bice T, Carson S, Chang L. Intermediate care units: a survey of organization practices across the United States. *J Intensive Care Med*. 2020;35:468–71.
 30. Krebs ED, Hassinger TE, Guidry CA, Berry PS, Elwood NR, Sawyer RG. Non-utility of sepsis scores for identifying infection in surgical intensive care unit patients. *Am J Surg*. 2019;218:243–7.

© 2021 Rakshana et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/76000>