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EVALUATING SEPSIS AND SEPTIC SHOCK: A REVIEW OF DIAGNOSTIC AND PREDICTIVE TOOLS

Rizwanullah[1*], Isha Patel[2], Fardin Akbar Hyderi[3], Hashem Elessawy[4], Moutushi Ahmed[5], Pranaya Rajbhandari[6]

[1*]Department of Medicine, Hayatabad Medical Complex, Pakistan
[2]Department of Medicine, GMERS Medical College, India
[3]Department of Medicine, Bangladesh Medical College, Bangladesh
[4]Department of Medicine, New York Institute of Technology College of osteopathic Medicine, USA
[5]Department of Research, Michigan Advanced Neurology Center, USA
[6]Department of Medicine, Patan Academy of Health Science, Nepal

***Corresponding Author:** Rizwanullah
*Email address: urizwan600@gmail.com

Abstract

Background: Sepsis remains a critical global health issue, contributing to up to 20% of all-cause deaths worldwide, especially within hospital settings. The complexity of sepsis, along with its progression to septic shock, necessitates effective screening and predictive tools for early identification and management.

Objective: This review evaluates the efficacy and utility of various screening and predictive tools used in sepsis and septic shock, including the Sequential Organ Failure Assessment (SOFA) score, quick SOFA (qSOFA) score, modified SOFA (mSOFA), and the Shock Index (SI).

Methods: We conducted a comprehensive review of current literature on these tools' performance in predicting mortality and assessing severity in sepsis. Key studies were analyzed to compare their sensitivity, specificity, and practical application in different clinical settings.

Results: The SOFA score, assessing six organ systems, has demonstrated high accuracy in predicting mortality and organ failure, with changes of 2 or more points indicating sepsis syndrome. The qSOFA score, while useful for rapid identification outside ICU settings, has shown variable sensitivity in diagnosing sepsis and predicting mortality. The SI and mSI have proven valuable in assessing shock severity and predicting hospital admission and mortality. Recent advances include the Phoenix Sepsis Criteria, which offer improved performance in pediatric sepsis identification.

Conclusion: Effective management of sepsis and septic shock relies on integrating multiple screening tools with continuous monitoring of organ functions. While the SOFA score remains a robust tool for assessing acute morbidity, the qSOFA, SI, and mSI scores provide additional insights for rapid triage and severity assessment. Future developments in sepsis criteria, such as the Phoenix Sepsis Criteria, hold promise for enhancing diagnostic accuracy and patient outcomes.

Keywords: Sepsis, septic shock, SOFA score, qSOFA score, Shock Index, modified SOFA score, Phoenix Sepsis Criteria

Introduction

Sepsis, a life-threatening organ dysfunction resulting from a dysregulated response to infection, remains a global health priority, contributing to up to 20% of all-cause deaths worldwide, particularly in hospital settings [1,2]. The rising incidence and mortality rates of sepsis are attributed to an aging population, the prevalence of invasive medical procedures, and widespread antibiotic resistance [3].

Septic shock, a severe form of sepsis, is defined by the need for vasopressor therapy to maintain a mean arterial pressure (MAP) of at least 65 mmHg and a serum lactate level greater than 18 mg/dL after adequate fluid resuscitation [4]. The Sequential Organ Failure Assessment (SOFA) score, used to define sepsis, evaluates six organ systems—respiratory, cardiovascular, neurological, hepatic, hematological, and renal—each scored from 0 to 4, yielding a total score of 0 to 24. The SOFA score can be easily calculated at the bedside without computer software [4,5].

A modified SOFA (mSOFA) score, which substitutes SpO2 for PaO2 and uses the SpO2/FiO2 ratio, may offer similar or improved accuracy in predicting mortality in septic patients [6]. The quick SOFA (qSOFA) score, which includes systolic blood pressure (SBP) <100 mmHg, altered mental status (GCS <15), and respiratory rate ≥22 breaths per minute, is used for rapid identification of infection, particularly outside the ICU. A qSOFA score of 2 or higher is strongly associated with increased mortality in non-ICU patients [8].

The shock index (SI), calculated by dividing heart rate (HR) by SBP, is another tool used to assess shock severity, correlating well with the need for hospital or ICU admission, mechanical ventilation, and blood transfusions. However, SI's limitations include its exclusion of diastolic blood pressure (DBP), a valuable indicator of shock severity, and concerns about its applicability across all age groups, particularly in older patients [9-11].

This review emphasizes the significance and utility of these screening and predictive tools in assessing sepsis and septic shock, aiming to improve early recognition and contribute to the development of a more precise definition of sepsis.

Review

Pathophysiology Of Sepsis

Sepsis is a complex condition where pathogenic antigens interact with the body's immune response, disrupting normal homeostasis and causing dysfunctions in cellular, humoral, circulatory, and metabolic systems [12, 13].

Infection

Septic shock begins with an infection that triggers both proinflammatory and anti-inflammatory host responses. These responses can either help eliminate the infection and promote tissue repair or cause organ damage and increase susceptibility to further infections. The response varies based on the pathogen's type, load, and virulence, as well as the patient's genetic and health background, affecting local, regional, and systemic levels [14].

Innate and Adaptive Immune Responses

The innate immune system, comprising cells like neutrophils, natural killer cells, and macrophages, directly combats pathogens and activates the adaptive immune system for targeted responses. It recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) via pattern recognition receptors such as toll-like receptors (TLRs). This recognition triggers metabolic pathways that lead to the formation of the inflammasome, which in turn stimulates the release of pro-inflammatory cytokines like IL-1ß, TNF-α, and IL-6. Excessive inflammasome activity can cause a "cytokine storm" [15].

In the adaptive immune system, activated CD4+ T cells differentiate into T-helper (Th) subsets (Th1, Th2, Th17). Th1 cells aid in memory T cell expansion, CD8+ T cell activation, and microbial elimination, while Th2 cells promote B lymphocyte differentiation and inflammation resolution. Disruptions in the Th1/Th2 balance in sepsis can lead to complications such as persistent

inflammation, immunosuppression, and catabolism syndrome (PICS), characterized by T-cell exhaustion, reduced HLA-DR expression, and increased immune checkpoint molecules, leading to secondary infections and multiple organ dysfunction syndrome (MODS) [16].

Endothelial Dysfunction

Endothelial cells play a critical role in containing bacterial infections. Damage to these cells impairs their ability to release vasodilators and respond to vasoconstrictors, leading to white blood cell and platelet aggregation, and nitric oxide signaling disruption. Sepsis triggers neutrophil recruitment and the release of reactive oxygen species and coagulation-derived proteases, further damaging the endothelium and disrupting microcirculatory blood flow, contributing to organ damage and potential failure [17]. The glycocalyx, essential for vascular barrier function and anti-inflammatory defenses, is particularly vulnerable in sepsis, with its degradation leading to edema and organ failure, especially in the kidneys and lungs [18].

Metabolic Derangement

Sepsis-induced mitochondrial dysfunction occurs through several mechanisms, including the inhibition of the electron transport chain and oxidative stress, leading to reduced cellular energy production and contributing to organ dysfunction. This dysfunction can exacerbate conditions like liver failure, acute kidney injury, and myocardial depression. Sepsis also alters macronutrient metabolism, increasing glycolysis and lipolysis, but impairing the utilization of these nutrients, which can result in the accumulation of toxic byproducts [19].

Coagulopathy

In sepsis, blood clotting is disrupted, involving platelets and neutrophils. Activated platelets interact with leukocytes and neutrophils, producing neutrophil extracellular traps (NETs), which, although protective, can lead to excessive coagulation and thrombus formation. Endothelial damage from bacterial toxins further promotes coagulation by upregulating tissue factor and activating the extrinsic coagulation pathway, leading to thrombin generation and platelet activation, which contribute to the formation of blood clots [20].

Tools for Evaluation of Sepsis

Sepsis is a complex clinical syndrome marked by multiorgan failure due to the body's exaggerated response to infections. On the other hand, septic shock is characterized by a severe drop in blood pressure and abnormal lab findings such as high lactate levels despite sufficient fluid resuscitation [21]. Patients with sepsis present with a wide range of symptoms, including general fatigue, fever, tachycardia, tachypnea, confusion, and reduced urine output. Some may exhibit skin mottling and prolonged capillary refill times. Diagnostic markers for sepsis include elevated lactate levels, white blood cell counts, and increased plasma C-reactive protein or procalcitonin levels [22]. Given the diverse symptoms and lab results, various tools like SI, MSI, SOFA, qSOFA, and mSOFA are utilized to improve the triaging process and risk stratification, aiding in the early identification of critically ill patients to enhance outcomes through early goal-directed therapy [23].

Shock Index (SI)

The Shock Index (SI) is crucial for the early detection and evaluation of critical illness in emergency settings and for monitoring resuscitation progress. Research by Rady et al. indicated that an SI of 0.9 or higher predicts a higher priority for treatment in the emergency department (ED) and a greater likelihood of hospital admission and intensive care, compared to relying on pulse or blood pressure alone [24]. Another cohort study of 58,336 adults revealed that SI values between 0.5 and 0.7 were associated with lower admission likelihood and inpatient mortality, while SI >1.2 was nearly 12 times more likely to result in admission compared to standard SI. In a separate study of 295 patients with severe sepsis, those with a sustained SI >0.8 had a 38.6% chance of needing vasopressors within 72 hours, compared to 11.6% for those without sustained high SI levels [25,26].

SI has also been evaluated for predicting hemodynamic response to volume expansion, with a study showing that patients with a central venous pressure (CVP) ≥8 mmHg and SI ≤1 were unlikely to respond to volume expansion, while those with SI >1 were more likely to be fluid-responsive [27]. Additionally, Berger et al. found that SI ≥0.7 was as effective as SIRS in predicting hyperlactatemia and 28-day mortality, with SI ≥1.0 being the most specific predictor [24]. Jouffroy's study of 114 septic shock patients indicated that an SI >0.9 can predict increased mortality risk in prehospital settings [28].

Modified Shock Index (mSI)

The modified Shock Index (mSI), which includes heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) by dividing HR by mean arterial pressure (MAP), provides a more comprehensive assessment of stroke volume and systemic vascular resistance [27]. Jayaprakash et al. found that mSI >1.3 was associated with a higher risk of myocardial dysfunction and ICU mortality [29]. Althunayyan et al. reported that mSI ≥1 was sensitive in predicting ICU admission, shock, and mortality, while mSI ≥1.3 was linked to sepsis, hyperlactemia, ICU admission, and 28-day mortality with a specificity range of 59-100% [23]. Zhang et al. found that pre-vasopressor SI, mSI, and diastolic SI (dSI) were significantly associated with three-day mortality in septic shock patients [30].

SOFA score

The SOFA score is a tool used to assess acute morbidity in critical illness and has been validated in various settings. A change in SOFA score of 2 or more is indicative of sepsis syndrome [31]. Innocenti et al. found that the SOFA score was higher in septic patients with adverse outcomes regarding 28-day mortality and ICU admission [32]. Khwannimit et al. demonstrated the SOFA score's accuracy in predicting hospital mortality with an AUC of 0.880 and its utility in predicting 30-day mortality and multiple organ failures [33]. Peng et al. showed that SOFA had greater sensitivity and specificity for predicting septic shock compared to qSOFA and SIRS [34].

qSOFA score

The qSOFA score, which includes components like SBP <100 mmHg, altered mental status (GCS <15), and RR ≥22 breaths per minute, is used to identify sepsis and septic shock but has limitations in sensitivity. Wani et al. found that qSOFA had poor sensitivity for diagnosing sepsis and predicting 28-day mortality [35]. Maitra et al. noted qSOFA's poor sensitivity in predicting in-hospital mortality for suspected infection patients [36]. In contrast, Baig et al. found that qSOFA had high sensitivity and specificity in predicting mortality in severe sepsis and septic shock patients [37].

As sepsis management has evolved, integrating SOFA and qSOFA with continuous monitoring of specific organ functions is crucial. Monitoring cardiovascular, respiratory, renal, and hepatic functions is essential for detecting and managing sepsis-related complications and guiding targeted interventions. The Phoenix Sepsis Criteria, developed by the Society of Critical Care Medicine (SCCM), assess multiple organ systems and have shown better performance in identifying pediatric sepsis and septic shock compared to other criteria [38,39].

MSOFA

The Modified Sequential Organ Failure Assessment (MSOFA) score is a clinical tool designed to assess organ dysfunction in critically ill patients, particularly in resource-limited settings such as during a mass influx of patients in a disaster or pandemic. This score simplifies the traditional Sequential Organ Failure Assessment (SOFA) score by requiring only one laboratory measurement, making it more practical for emergency use. The MSOFA score evaluates five organ systems—respiratory, cardiovascular, central nervous system, renal, and liver—on a scale from 0 to 4, with a maximum score of 19, whereas the SOFA score assesses six organ systems with a maximum score of 24. Notably, the MSOFA replaces some laboratory measurements with clinical assessments; for

instance, it uses the SpO2/FIO2 ratio instead of the PaO2/FIO2 ratio and evaluates liver function through clinical signs of jaundice rather than relying on bilirubin levels. Studies have demonstrated that the MSOFA score can predict mortality and the need for mechanical ventilation as effectively as the SOFA score, thereby serving as a valuable tool for triage in critical care environments. The development and validation of the MSOFA score have been documented in research, highlighting its effectiveness and ease of implementation in challenging situations (40).

Conclusion

In conclusion, the accurate and timely assessment of sepsis and septic shock remains pivotal in improving patient outcomes and reducing mortality. The use of various screening tools such as the SOFA, qSOFA, and SI scores provides valuable insights into the severity and progression of sepsis, each with its strengths and limitations. While SOFA remains a robust tool for assessing organ dysfunction and predicting mortality, qSOFA offers a rapid assessment approach, especially outside the ICU. The SI and mSI provide additional context for evaluating shock severity and guiding resuscitation efforts. Integrating these tools with continuous monitoring and advancements in criteria, such as the Phoenix Sepsis Criteria, enhances our ability to identify and manage sepsis effectively. Continued research and refinement of these tools are essential for optimizing early detection and treatment strategies, ultimately improving patient outcomes in sepsis care.

References

1. World Health Organization. Global Report on the Epidemiology and Burden of Sepsis: Current Evidence, Identifying Gaps and Future Directions. Geneva: World Health Organization; 2020.
2. Yealy DM, Mohr NM, Shapiro NI, Venkatesh A, Jones AE, Self WH. Early care of adults with suspected sepsis in the emergency department and out-of-hospital environment: a consensus-based task force report. Ann Emerg Med. 2021; 78:1-19. doi: 10.1016 /j.annemergmed.2021.02.006.
3. Vakkalanka JP, Harland KK, Swanson MB, Mohr NM. Clinical and epidemiological variability in severe sepsis: an ecological study. J Epidemiol Community Health. 2018;72:741-5. doi: 10.1136/jech-2018-210501.
4. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10. doi: 10.1001 /jama.2016.0287.
5. Moreno R, Rhodes A, Piquilloud L, et al. The Sequential Organ Failure Assessment (SOFA) Score: has the time come for an update? Crit Care. 2023;27:15. doi: 10.1186/s13054-022-04290-9.
6. Raymond NJ, Nguyen M, Allmark S, Woods L, Peckler B. Modified Sequential Organ Failure Assessment sepsis score in an emergency department setting: retrospective assessment of prognostic value. Emerg Med Australas. 2019;31:339-46. doi: 10.1111/1742-6723.13154.
7. Emadi SA, Baradari AG, Charati JY, et al. SOFA and modified SOFA score for assessing outcomes among trauma patients in intensive care unit. Int J Surg Open. 2022;47:100559. doi: 10.1016/j.ijso.2022.100559.
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. 2020;15:63. doi: 10.1186/s13017-020-00343-y.
9. Talmor D, Jones AE, Rubinson L, Howell MD, Shapiro NI. Simple triage scoring system predicting death and the need for critical care resources for use during epidemics. Crit Care Med. 2007;35:1251-6. doi: 10.1097/01.CCM.0000262385.95721.CC.
10. Liu YC, Liu JH, Fang ZA, et al. Modified shock index and mortality rate of emergency patients. World J Emerg Med. 2012;3:114-7. doi: 10.5847/wjem.j.issn.1920-8642.2012.02.006.
11. Singh A, Ali S, Agarwal A, Srivastava RN. Correlation of shock index and modified shock index with the outcome of adult trauma patients: a prospective study of 9860 patients. N Am J Med Sci. 2014;6:450-2. doi: 10.4103/1947-2714.141632.

12. Font MD, Thyagarajan B, Khanna AK. Sepsis and septic shock - basics of diagnosis, pathophysiology and clinical decision making. Med Clin North Am. 2020;104:573-85. doi: 10.1016/j.mcna.2020.02.011.
13. Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840-51. doi: 10.1056/NEJMra1208623.
14. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ. 2016;353. doi: 10.1136/bmj.i1585.
15. Liu D, Huang SY, Sun JH, et al. Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. Mil Med Res. 2022;9:56. doi: 10.1186/s40779-022-00422-y.
16. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. Am J Respir Crit Care Med. 2020;202:361-70. doi: 10.1164/rccm.201910-1911TR.
17. Giustozzi M, Ehrlinder H, Bongiovanni D, et al. Coagulopathy and sepsis: pathophysiology, clinical manifestations and treatment. Blood Rev. 2021;50:100864. doi: 10.1016/j.blre.2021.100864.
18. Salomão R, Ferreira BL, Salomão MC, Santos SS, Azevedo LC, Brunialti MK. Sepsis: evolving concepts and challenges. Braz J Med Biol Res. 2019;52. doi: 10.1590/1414-431X20198595.
19. Wasyluk W, Zwolak A. Metabolic alterations in sepsis. J Clin Med. 2021;10:2412. doi: 10.3390/jcm10112412.
20. Arora J, Mendelson AA, Fox-Robichaud A. Sepsis: network pathophysiology and implications for early diagnosis. Am J Physiol Regul Integr Comp Physiol. 2023;324 doi: 10.1152/ajpregu.00003.2023.
21. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers. 2016;2:16045. doi: 10.1038/nrdp.2016.45.
22. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet. 2018;392:75-87. doi: 10.1016/S0140-6736(18)30696-2.
23. Althunayyan SM, Alsofayan YM, Khan AA. Shock index and modified shock index as triage screening tools for sepsis. J Infect Public Health. 2019;12:8226. doi: 10.1016/j.jiph.2019.05.002.
24. Berger T, Green J, Horeczko T, et al. Shock index and early recognition of sepsis in the emergency department: pilot study. West J Emerg Med. 2013;14:168-74. doi: 10.5811/westjem.2012.8.11546.
25. Balhara KS, Hsieh YH, Hamade B, Circh R, Kelen GD, Bayram JD. Clinical metrics in emergency medicine: the shock index and the probability of hospital admission and inpatient mortality. Emerg Med J. 2017;34:89-94. doi: 10.1136/emermed-2015-205532.
26. Lanspa MJ, Brown SM, Hirshberg EL, Jones JP, Grissom CK. Central venous pressure and shock index predict lack of hemodynamic response to volume expansion in septic shock: a prospective, observational study. J Crit Care. 2012;27:609-15. doi: 10.1016/j.jcrc.2012.07.021.
27. Pramudyo M, Bijaksana TL, Yahya AF, Putra IC. Novel scoring system based on clinical examination for prediction of in-hospital mortality in acute coronary syndrome patients: a retrospective cohort study. Open Heart. 2022;9. doi: 10.1136/openhrt-2022-002095.
28. Jouffroy R, Pierre Tourtier J, Gueye P, et al. Prehospital shock index to assess 28-day mortality for septic shock. Am J Emerg Med. 2020;38:1352-6. doi: 10.1016/j.ajem.2019.11.004.
29. Jayaprakash N, Gajic O, Frank RD, Smischney N. Elevated modified shock index in early sepsis is associated with myocardial dysfunction and mortality. J Crit Care. 2018;43:30-5. doi: 10.1016/j.jcrc.2017.08.019.
30. Zhang TN, Hao PH, Gao SY, Liu CF, Yang N. Evaluation of SI, MSI and DSI for very early (3-day) mortality in patients with septic shock. Eur J Med Res. 2022;27:227. doi: 10.1186/s40001-022-00857-y.
31. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score-development, utility and challenges of accurate assessment in clinical trials. Crit Care. 2019;23:374. doi: 10.1186/s13054-019-266

32. Innocenti F, Tozzi C, Donnini C, De Villa E, Conti A, Zanobetti M, Pini R. SOFA score in septic patients: incremental prognostic value over age, comorbidities, and parameters of sepsis severity. Intern Emerg Med. 2018;13:405-12. doi: 10.1007/s11739-017-1629-5.
33. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the accuracy of three early warning scores with SOFA score for predicting mortality in adult sepsis and septic shock patients admitted to intensive care unit. Heart Lung. 2019;48:240-4. doi: 10.1016/j.hrtlng.2019.02.005.
34. Peng Y, Zhang W, Xu Y, et al. Performance of SOFA, qSOFA and SIRS to predict septic shock after percutaneous nephrolithotomy. World J Urol. 2021;39:501-10. doi: 10.1007/s00345-020-03183-2.
35. Wani ZA, Gulzar K, Yatoo H, Kole T. Validation of 'Quick Sequential Organ Failure Assessment Score' as a screening tool for early identification of sepsis patients in the emergency department. Cureus. 2023;15 doi: 10.7759/cureus.39251.
36. Maitra S, Som A, Bhattacharjee S. Accuracy of quick Sequential Organ Failure Assessment (qSOFA) score and systemic inflammatory response syndrome (SIRS) criteria for predicting mortality in hospitalized patients with suspected infection: a meta-analysis of observational studies. Clin Microbiol Infect. 2018;24:1123-9. doi: 10.1016/j.cmi.2018.03.032.
37. Baig MA, Sheikh S, Hussain E, Bakhtawar S, Subhan Khan M, Mujtaba S, Waheed S. Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. Turk J Emerg Med. 2018;18:148-51. doi: 10.1016/j.tjem.2018.08.002.
38. Schlapbach LJ, Watson RS, Sorce LR, et al. International Consensus Criteria for Pediatric Sepsis and Septic Shock. JAMA. 2024;331: 665-74. doi: 10.1001/jama.2024.0179.
39. Sanchez-Pinto LN, Bennett TD, DeWitt PE, et al. Development and validation of the Phoenix criteria for pediatric sepsis and septic shock. JAMA. 2024;331:675-86. doi: 10.1001/jama.2024.0196.
40. Grissom CK, Brown SM, Kuttler KG, Boltax JP, Jones J, Jephson AR, Orme JF Jr. A modified sequential organ failure assessment score for critical care triage. Disaster Med Public Health Prep. 2010 Dec;4(4):277-84. doi: 10.1001/dmp.2010.40. PMID: 21149228; PMCID: PMC3811929.