Review

Utility of biomarker in sepsis

Nupur Gupta, MD[1] ✉ Akash Agarwal, MD[2]

[1.] Dept of Critical care, Artemis Hospital, Gurugram, India

[2.] Dept. of Anesthesia and Critical Care. Sanar International Hospital, Gurugram, India

Email: 1986.nupur@gmail.com

How to cite the article: Gupta N, Agarwal A. Utility of biomarkers in sepsis. OncoCritiCare2023;1:37-40.

The Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1]

As intensive care units are now protocolising management of sepsis and septic shock in accordance with the surviving sepsis recommendations, the mortality rate of patients with sepsis has reduced significantly, but still continues to be unacceptably high.

With the proportion of culture-negative sepsis being as high as 28% to 49%,[2] where no microbiological proof of an infectious focus is found, diagnosing sepsis many a times poses a challenge to both clinicians and microbiologists.

The increasing rates of inappropriate antibiotic use and the worldwide prevalence of antimicrobial resistance further add to the necessity of diagnosing sepsis at the earliest, enabling prompt and appropriate initiation of treatment.

Biomarkers have a critical role to play in early diagnosis of sepsis. In addition, they can help in a multitude of other ways - by indicating the severity of sepsis, differentiating bacterial from viral and fungal infection, predicting organ dysfunction, helping in prognostication, in antibiotic stewardship and even in evaluating the response to therapy.

Sepsis begins with the activation of an innate immune response mediated by the detection of damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) by pattern-recognition receptors (PRRs) on host cells. Subsequently, pro-inflammatory and anti-inflammatory mediators such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) are released, followed by a rise in the levels of acute phase proteins such as procalcitonin, pro-adrenomedulin, pentraxin-3, and C-reactive protein (CRP). In addition, the serum levels of glycoproteins on cell membranes such as presepsin, soluble triggering receptor expressed on myeloid cell 1 (sTREM-1), and soluble urokinase plasminogen activator receptor (suPAR) may be upregulated, and the expression of CD64, an immunoglobulin receptor, may also be increased.

Owing to this complex pathophysiology of sepsis involving multiple mediators of inflammation, more than 100 different molecules have been proposed as useful biomarkers of sepsis, much more than for any other disease.

While no single biomarker has proven to be a specific indicator of sepsis, rapid detection of key biomarkers could provide the clinician with useful information thereby helping in guiding the treatment.

This review will focus on the diagnostic and prognostic potential of some of the traditional as well as few of the new promising biomarkers.

C–reactive protein (CRP)

CRP, a widely used biomarker to diagnose sepsis, is a protein synthesized by the liver and upregulated by IL–6. It is an acute phase reactant produced in response to nonspecific inflammation, infection and even tissue damage. It helps in the recognition and clearance of foreign pathogens by binding to phospholipids and activating the classic complement pathway. CRP is usually able to differentiate between viral and bacterial infections with levels more than 50mg/dl being associated with bacterial infections 90% of the time.[4] Numerous studies have reported the high sensitivity of CRP for the diagnosis of sepsis, although its low specificity is a primary drawback. The role of CRP in prognostication and predicting increased risk of organ failure is still controversial.[5]

Procalcitonin (PCT)

PCT is a precursor of calcitonin produced by C-cells of the thyroid gland and was first described for the diagnosis of sepsis in 1993. It has since been used widely as a potential biomarker for sepsis. Elevated levels (up to 5000-fold) are seen in response to bacterial toxins within 2 to 4 hrs. In contrast, viral infections downregulate the procalcitonin levels. The diagnostic accuracy of PCT for sepsis has been found have a median sensitivity and specificity of 79%. Higher PCT levels have been associated with increased mortality rates.[6] Moreover, research has shown that PCT levels less than 0.1 ng/mL have been shown to have a high negative predictive value (96.3%) for excluding bacterial infections.[7] Subsequent large, multicentre studies, including the PRORATA trial and the Stop Antibiotics on Procalcitonin Guidance Study (SAPS) validated the use of PCT-guided therapy and showed that PCT can help to reduce antibiotic exposure by shortening treatment duration.[8] Despite being routinely used in clinical practice, PCT has some limitations and has shown to be risen in several other inflammatory conditions aside from bacterial infections such as trauma and surgery.

Cytokines

Another set of biomarkers used commonly in patients of sepsis are the cytokines. Traditionally, the host immune response to sepsis was thought to be characterized by two sequential stages: The initial hyperinflammatory response, where the innate immune system releases proinflammatory cytokines to combat infection by recruiting members of the adaptive system to mount an intense immune response , and , the subsequent stage of compensatory anti-inflammatory response syndrome (CARS), which is a systemic deactivation of the immune system tasked with restoring homeostasis from an inflammatory state. Recent data however suggest that both aspects of the proinflammatory and anti-inflammatory stages of the host immune response often occur concurrently.

Both Proinflammatory markers like TNF-α, IL-1, IL-6, and IL-8, have been shown to be overproduced in sepsis with increased levels showing worsened mortality.[9] Similarly IL 10, the main contributor to CARS has been shown to be high in patients of severe sepsis.[10] However, these cytokines lack specificity as they are also upregulated with sterile inflammation (SIRS), post-surgery, autoimmune disorders, viral infection, and transplant rejection. Additionally, the high cost involved and the difficulty in interpreting these many different cytokines while looking for patterns of upregulation and/or suppression in its relation to the diagnosis of sepsis has proven to be difficult.

Angiopoietins

Angiopoietins (Ang-1 and Ang-2) have been found to be associated with vascular leakage, inflammation, and breakdown of the microvascular endothelium, and therefore have been studied as potential biomarkers in sepsis. While studied mainly in proliferative diseases such as cancer, they have also been associated with inflammation. Ricciuto et al demonstrated that low Ang-1 levels at admission were associated with poor outcome and remained a significant predictor of mortality throughout a 28-day period, while Ang-2 levels correlated with disease severity along with organ dysfunction with levels correlating with tumour necrosis factor-α (TNF-α) and IL-6 levels.[11]

Neutrophil CD64

Neutrophil CD64, a leukocyte surface antigen, also known as Fc receptor 1 (FcR1), is a high-affinity receptor present on neutrophils which binds to monomeric IgG and is involved in both innate and adaptive immune responses by stimulating either phagocytosis or antibody -mediated cytotoxicity. Its expression gets strongly upregulated in response to proinflammatory cytokines of infection within 4–6 hours .[12] Several studies which have looked at neutrophil CD64 expression as a potential biomarker/indicator for detection of sepsis/infection in adults, children, and neonates have demonstrated its higher sensitivity and specificity than CRP, WBC count, neutrophilic and eosinophilic granulocyte counts and even Procalcitonin and IL–6, implying that CD64 index can differentiate between sepsis and SIRS patients in various patient populations.[13]

Soluble Triggering receptor expressed on myeloid cells-1 (sTREM-1)

TREM-1 is a recently discovered member of the immunoglobulin superfamily that is expressed on myeloid cells -1, surface of neutrophils and macrophages. Its expression is upregulated on cells in the presence of bacteria and fungi, but not so in response to non -infectious inflammatory triggers. Its soluble form Strem-1 can be assayed by ELISA from body fluids like plasma, plueral fluid, bronchoalveolar lavage, urine etc. In a clinical study, plasma sTREM-1 levels higher than 60 ng/mL were found to be more accurate than any other clinical or laboratory finding for

indicating infection. A meta-analysis of 11 studies (1795 patients) showed that the pooled sensitivity of plasma sTREM-1 for the diagnosis of sepsis was 79% and the specificity was 80% , thereby concluding a moderate diagnostic performance in differentiating sepsis from SIRS.[14] In another study sTREM-1 was shown to be a mortality predictor as well from infection in a tropical, middle-income country.[15] While studies evaluating sTREM-1 as a potential biomarker are promising, many of other studies contradict whether sTREM-1 has any clinical value, thereby necessitating further analysis.

suPAR

The soluble form of urokinase type plasminogen activator receptor (suPAR) is expressed on various immune cells and is involved in a variety of immunological functions including cell migration, angiogenesis and fibrinolysis. Higher serum levels of suPAR are associated with a higher mortality in patients with an inflammatory response. A recent meta-analysis analysing 17 studies (2,722 patients) reported a AUC of suPAR for discriminating between sepsis and SIRS as 0.81.[16] Many other studies have reported prognostic role of suPAR as well. Other study showed that the mortality rate of bacterial infection increased by 3.37 times with the elevated suPAR level.[17] Owing to its short turnaround times and low production cost, suPAR appears to be a promising biomarker.

Presepsin (sCD14)

Presepsin is a subtype of Soluble N-terminal fragment of the cluster of differentiation marker protein CD14 is expressed on macrophages /monocytes and serves as a receptor for lipopolysaccharides (LPS). In the immune response to sepsis, the serum levels of presepsin are elevated before procalcitonin or IL-6, so it has been proposed as a potential biomarker for the diagnosis of sepsis .[18] A recent prospective study has reported that the serum levels of presepsin in patients with severe sepsis correlated with the SOFA score and presepsin was better than procalcitonin as a biomarker to assess sepsis prognosis and therapeutic effect.[19] Nevertheless, further in-depth analysis of its prognostic value is required

Adrenomedullin

Adrenomedullin (ADM) is a 52-amino acid peptide that is produced mainly in endothelial cells and vascular smooth muscle cells. It is an important mediator of vasodilation and is involved in the regulation of systemic circulation as an autocrine/paracrine vasoactivator. ADM levels are noted to be 20–30 folds higher in septic shock. The mid-regional fragment of pro-adrenomedullin (proADM), is more stable than the ADM peptide, and its levels can be measured in biological fluids. ProADM has been identified in several studies as a prognostic marker for the prediction of mortality in sepsis and septic shock patient. A prospective study at a single centre in Korea measured bio-ADM levels in 215 patients diagnosed with sepsis and septic shock. The levels of bio-ADM in the septic shock group were significantly higher than in the sepsis group, and there was a significant difference between the levels of bio-ADM in the non-survivor and survival groups. The AdrenOSS-1 study also found the levels of bio-ADM to be higher in septic shock patients than in sepsis patients .[20] Since the recent development of the double monoclonal sandwich immunoassay enables bio-ADM measurements, further evaluation, will be required for the clinical use of bio-ADM as a sepsis biomarker.

Intestinal Microflora

The intestinal microflora plays an important role in the development and maturation of the immune system. The intestinal microbial metabolite profiles of sepsis patients were completely altered compared to healthy people and was found to be associated with an increase in mortality. In a recent study, it was found that the microbiota in sepsis patients is rich in microorganisms related to inflammation, such as *Parabacteroides*, *Fusobacterium*, and *Bilophylloma*. Non survivors showed an abundance in Enterococcus species in their instentinal microflora.[21] However, presence of many confounding factors which cause disruption of the intestinal microbiota such as antibiotic therapy and hospitalization, warrant further studies to understand sepsis associated dysbiosis and its use as potential biomarkers. Research on newly identified classes of biomarkers such as microRNAs, long-non-coding RNAs, or the human microbiome are underway and further clinical studies are warranted to understand their roles as potential biomarkers.

Conflict of interest: Nil

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315:801–810
2. Li, Y., Guo, J., Yang, H. *et al.* Comparison of culture-negative and culture-positive sepsis or septic shock: a

systematic review and meta-analysis. *Crit Care2021;* 25: 167.

3. Biomarkers Definitions Working Group: Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001, 69: 89-95

4. Shaw AC. Serum C-reactive protein and neopterin concentrations in patients with viral or bacterial infection. J Clin Pathol. 1991; 44:596–99.

5. Póvoa P. C-reactive protein: a valuable marker of sepsis. *Intensive Care Med.* 2002; 28:235–43.

6. Wacker C, Prkno A, Brunkhorst FM, et al. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013; 13:426-35.

7. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Am J Clin Pathol. 2011; 135:182-9.

8. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 2010; 375:463-74.

9. Takahashi W, Nakada TA, Yazaki M, Oda S. Interleukin-6 levels act as a diagnostic marker for infection and a prognostic marker in patients with organ dysfunction in intensive care units. Shock. 2016; 46:254–60.

10. Adib-Conquy M, Cavaillon JM. Compensatory anti-inflammatory response syndrome. Tromb Haemost. 2009; 101:36–47.

11. Kumpers P, Lukasz A, David S, et al. Excess circulating angiopoietin-2 is a strong predictor of mortality in critically ill medical patients. Crit Care 2008, 12: R147. 10.1186/cc7130

12. Patnaik R, Azim A, Agarwal V. Neutrophil CD64 a Diagnostic and Prognostic Marker of Sepsis in Adult Critically Ill Patients: A Brief Review. Indian J Crit Care Med 2020; 24:1242–50

13. Li X, Wang J. Diagnostic and prognostic value of neutrophil CD64, IL-6, and PCT in ICU patients with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2023; 35:463-68.

14. Wu Y, Wang F, Fan X, Bao R, Bo L, Li J, Deng X. Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: a systematic review and meta-analysis. Crit Care. 2012 ;16: R229.

15. Wright, S.W., Lovelace-Macon, L., Hantrakun, V. *et al.* sTREM-1 predicts mortality in hospitalized patients with infection in a tropical, middle-income country. BMC Med 2020; 18:159.

16. Huang Q, Xiong H, Shuai T, et al. The clinical value of suPAR in diagnosis and prediction for patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Therapeutic Advances in Respiratory Disease. 2020;14.

17. Ni W, Han Y, Zhao J, Cui J, Wang K, Wang R, Liu Y. Serum soluble urokinase-type plasminogen activator receptor as a biological marker of bacterial infection in adults: a systematic review and meta-analysis. *Sci Rep 6:39481, 2016.*

18. Larsen FF, Petersen JA. Novel biomarkers for sepsis: A narrative review. *Eur J Intern Med.* 2017; 45:46–50

19. Yu H, Qi Z, Hang C, Fang Y, Shao R, Li C. Evaluating the value of dynamic procalcitonin and presepsin measurements for patients with severe sepsis. Am J Emerg Med. 2017; 35:835–841.

20. A, Geven C, Hollinger A, Wittebole X, Chousterman BG, Blet A, Gayat E, AdrenOSS-1 study investigators. Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock-1 (AdrenOSS-1) study. *Crit Care.* 2018; 22:354

21. Haak BW, Wiersinga WJ. The role of the gut microbiota in sepsis. Lancet Gastroenterol Hepatol. 2017; 2:135–143.