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EDITORIAL

Perspective: Sepsis Biomarker Research Requires a Move to the Emergency Department and More Collaboration

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ABSTRACT:
Despite years of research and multiple potential candidate biomarkers for sepsis, few have had sufficient sensitivity or specificity to be integrated into routine practice. There have been only 11 observational studies that have collected samples from patients presenting to the emergency department with suspected sepsis. This has resulted in gaps in the ability to accurately diagnose sepsis in patients presenting with infections and give an accurate prognosis for patients or their families. Recent work has shown the importance of immunothrombosis, particularly in the prognosis for patients admitted to the intensive care unit with sepsis. Significantly some of the most impactful markers are actually decreased. In this perspective we summarize the current sepsis biomarker literature, highlight the limitations, particularly in diagnosis, and suggest some strategies for moving this field forward.

Introduction

Sepsis is a complex syndrome. The pathophysiological processes that develop with infection and progress to sepsis are a result of interactions between the host, the pathogen, as well as environmental and genetic factors. These include the normal innate and acquired inflammatory processes designed to respond to pathogens, as well as intravascular activation of the coagulation cascade to contain pathogen dissemination.[1] This is usually accompanied by physiological changes that result in alterations in vital signs. [2]

The Biomarkers Definition Working Group describes a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[3] Biomarkers play an important role in early detection, monitoring of disease progression, and establishing new therapeutic targets. They are a valuable addition to clinical judgment and improve patient care by enhancing existing prognostic and diagnostic tests. An ideal sepsis biomarker must align with the biological and pathogenic processes and be expressed early in the disease progression.

In their initial review of sepsis biomarkers Vincent and Pierrakos recognized 178 potential candidates [4] and a decade later an additional 80 biomarkers were added, expanding the total count to 258.[5] These reviews highlight 3 important challenges: 1) There is a gap in studies that focus on diagnostics, particularly at the earliest stage of presentation. 2) While many studies evaluate the use of C reactive protein (CRP) and procalcitonin (PCT), these biomarkers cannot always distinguish sepsis from other inflammatory conditions. 3) Aside from studies of PCT and CRP most have been limited to small, often single centre, studies with a lack of standardized reporting for diagnostic [6] and prognostic [7] biomarkers. A recent publication from the Surviving Sepsis Research Committee continues to identify the need for diagnostic biomarkers. [8] Our objective is to discuss these challenges and suggest some methodological strategies to increase the likelihood of having clinically available sepsis biomarkers within this decade.

Sepsis Diagnosis

The World Health Organization has declared sepsis a global health priority, emphasizing the requirement of clear diagnostic strategies for sepsis.[9] The emergency department (ED) is a crucial venue for early diagnosis and timely treatment of sepsis as most cases present to hospital through the emergency department.[10] Every one-hour delay in antibiotic administration is associated with increased in-hospital mortality among septic patients in ED.[11] The Surviving Sepsis Campaign recommends administering intravenous broad-spectrum antibiotics within 1 hour of presentation.[12] Studies of biomarkers have generally enrolled patients at a later stage of sepsis, often from the intensive care unit and hospital wards where other conditions may complicate the findings. To the best of our knowledge, only 11 primary studies have investigated the use of chemical biomarkers for sepsis diagnosis in the emergency department. As summarized in the Table these studies focus primarily on the inflammatory pathways, all but 2 enrolled less than 1000 patients, and most are single centre.

Procalcitonin (PCT) has been considered a promising biomarker for sepsis detection in the emergency department with an AUROC between 0.67 to 0.84; however, it is increased in several conditions, has a low positive predictive value, is downregulated in viral infections and studies have used different cut-off values even from the same centre.[13-16] PCT can also give false results in patients with localized infection, infection with atypical bacteria, patients with severe trauma, recent surgery, and patients on steroids.[5] Similarly, the acute phase reactant C reactive protein (CRP) has limitations of both sensitivity and specificity.[15,17] Presepsin (soluble CD14) performed slightly better than PCT.[16] Pancreatic stone protein, an inflammatory mediator that activates neutrophils, and soluble CD25 (sCD25), an anti-inflammatory mediator, have also shown comparable results to PCT.[14] More recently, the measurement of monocyte distribution width (MDW)[18,19] and Interleukin-6 [20], adjudicated using the current sepsis definition[21] performed better than PCT. The performance of PCT, CRP and MDW appear to be the most promising clinically available biomarkers; however, even the most recent systematic review and meta-analysis was limited by significant heterogeneity.[22] Other biomarkers shown in the Table are limited to small single centre. Future meta-analysis of potential diagnostic biomarkers should separate patients presenting to the ED with those admitted to the intensive care and wards.

Table. Studies of Chemical Biomarkers for Sepsis Diagnosis in the Emergency Department

Biomarker	AUROC analysis (sample size)	References
PCT	1. AUROC 0.72 (859) 2. AUROC 0.80 (513) 3. AUROC 0.67 (66) 4. AUROC 0.82 (152) 5. AUROC 0.84 (102) 6. AUROC 0.80 (142) 7. AUROC 0.82 (158)	1. Liu 2013[16] 2. Magrini 2014[17] 3. Hicks 2014[23] 4. García de Guadiana-Romualdo 2017[14] 5. García de Guadiana Romualdo 2018[15] 6. Song 2019[20] 7. Ling 2023[24]
Presepsin	1. AUROC 0.82 (859) 2. AUROC 0.87 (152)	1. Liu 2013[16] 2. García de Guadiana-Romualdo 2017[14]
CRP	1. AUROC 0.71 (513) 2. AUROC 0.72 (102)	1. Magrini 2014[17] 2. García de Guadiana Romualdo 2018[15]
MDW	1. AUROC 0.73 (2158) 2. AUROC 0.82 (1517)	1. Crowser 2019[19] 2. Hausfater 2021[18]
Other inflammatory markers	1. sPLA2-IIA AUROC 0.93 (51) 2. CD64 AUROC 0.88 (51) 3. IL-6 AUROC 0.89 (142) 4. PTX3 AUROC 0.84 (142) 5. PSP AUROC 0.87 (152) 6. sCD25 AUROC 0.83 (152)	1. Tan 2016[25] 2. Tan 2016[25] 3. Song 2019[20] 4. Song 2019[20] 5. García de Guadiana-Romualdo 2017[14] 6. García de Guadiana-Romualdo 2017[14]
Combination of markers and clinical values	1. PCT+SIRS AUROC 0.92 (66) 2. WBC+MDW AUROC 0.75 (2158) 3. WBC+MDW AUROC 0.83 (1517) 4. qSOFA+PCT AUROC 0.84 (158) 5. NGAL, MMP-6 TIMP-1 with SIRS (no AUROC analysis for diagnosis) (480)	1. Hicks 2014[23] 2. Crouser 2019[19] 3. Hausfater 2021[18] 4. Ling 2023[24] 5. Wang 2014[26]

Abbreviations: PCT= Procalcitonin, CRP= C-reactive protein, sPLA2-IIA= Group II Secretory Phospholipase A2, PSP=Pancreatic stone protein, MDW= Monocyte Distribution Width, NGAL= Neutrophil Gelatinase-Associated LipocalinMMP-9= Matrix Metalloproteinase-9, TIMP-1=Tissue Inhibitor of Matrix metalloproteinases-1, WBC= White blood cell

Given the importance of the coagulation in the early host response to infection[1] future studies should investigate immunothrombotic markers for early sepsis diagnosis[27,28]. We have published a framework for a pragmatic biomarker observational study in the emergency department that integrates sample collection into the usual care.[29].

Sepsis Prognosis

Sepsis remains a disease with a hospital mortality of 20-30%, and a subsequent 5-year mortality of 50%.[30] Similar to presentations in the ED, deviations in vital signs from baseline, as measured by early warning scores, have prognostic value to predict deterioration and recognize those patients who may develop sepsis from hospital acquired infections.[31] This significant mortality is attributed to recurrent hospitalizations as well as an increase in cardiovascular disease, particularly with patients with pre-existing diabetes.[32-34] Providing patients and their families with a short- and long-term mortality and morbidity prognosis will aid in end-of-life decision making. It also provides clinicians with a reason to monitor inflammatory and thrombotic markers for the sickest septic patients.

While PCT, CRP, IL-6 and presepsin may have diagnostic potential, a recent systematic review did not show any prognostic potential for predicting mortality when measured at baseline on admission to the ICU[35], suggesting that a single measurement of this inflammatory biomarkers may not be sufficient and different markers will be required. In contrast, a systematic review of showed that

elevations in pancreatic stone protein had an OR of 2.7 to predict ICU mortality. [36]. Other markers such serum S100B, a biomarker of sepsis-associated encephalopathy, have more organ specific prognosis.[37] All these systematic reviews have limitations for movement into routine clinical practice due to both biases in the study designed and significant heterogeneity in the included patient populations. In addition, there is primarily a focus on the inflammatory pathways.

Our group has focused on the role of immunothrombosis in sepsis pathophysiology, and the importance of temporal measurements. Plasma cell free DNA (cfDNA), released into the circulation through the formation of neutrophil extracellular traps (NETS), induces coagulation through the intrinsic pathway. In a pilot study, elevations in cfDNA were associated with ICU mortality, occurred within 24 hours of ICU admission, and persisted for up to 28 days.[38]. A subsequent multicentre observational study again showed the importance of cfDNA on the first day of ICU admission with sepsis to predict sepsis mortality[39] with reduced levels of circulating intrinsic DNaseI.[40] The importance of cfDNA as a prognostic marker recently been validated in a systematic review. [41]

Two additional prognostic immunothrombosis biomarkers have come from our studies. Protein C is a natural anticoagulant and reduced levels in septic ICU patients, particularly those that do not return to normal, are associated with increased mortality.[38,39] The prognostic value of reduced Protein C has been confirmed in a systematic review.[42] Persistent thrombocytopenia is a poor prognostic sign in sepsis,[43] and the protease A Disintegrin-like and Metalloprotease with Thrombospondin type Motif 13 (ADAMTS13) is an important regulator of Von Willebrand Factor (VWF), responsible for cleaving VWF multimers and limiting platelet aggregation. We have shown that septic ICU patients have reduced ADAMT13 levels and activity; persistently low levels is a potential marker of poor prognosis.[44] This work shows that not all biomarkers need be elevated to be important.

Conclusions

The sheer volume of potential diagnostic and prognostic biomarkers for sepsis continues to rise with the progressive understanding of sepsis pathophysiology including individual and group phenotypic responses. More recent systematic reviews and meta-analysis have attempted to pull multiple smaller observational studies together; however, without standardization of patient cohorts, attempts to limit biases and variations in technical methods, translation into practice will not occur. To overcome this important obstacle, we have the following recommendations.

1. Biomarker studies should ideally be pragmatic multinational, multicentre observational studies with published protocols and standardized reporting. The clinical characteristic of these patients should be described to the same detail as a randomized clinical trial. Validation studies in a separate population are important.
2. Investigators should justify studies that seek to address both diagnostic and prognostic markers. Patient populations should be recruited from cohorts that have biggest impact. More diagnostic studies are needed in patients presenting with community acquired infections.
3. Analytical methods should be harmonized and cut points agreed by statistical analysis. Engagement of clinical chemists will support the rapid translation into practice.

Collaboration within the international sepsis community and funders is needed to achieve these goals and finally have biomarkers in routine practice.

Conflicts of Interest Statement: AFR is the Scientific Director of Sepsis Canada, a national research network funded by the Canadian Institutes of Health Research. She is funded by a research chair from Hamilton Health Sciences. She holds a patent for a combination of clinical and biomarkers for sepsis prognosis. JA and AFR have filed a patent for a biomarker panel for sepsis diagnosis.

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