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Glycocalyx Components in Prognosis of Sepsis - A Commentary

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Abstract

Objectives: Endothelial glycocalyx shedding has been recognized as a contributor in sepsis pathophysiology. Hence, we attempted to analyse hyaluronan and syndecan (glycocalyx components) as markers of morbidity and prognosis of sepsis by performing serial measurements in these patients.

Design and methods: Subjects were community acquired sepsis, severe sepsis and septic shock patients (150) admitted to ICU of our tertiary care hospital and controls were 50 healthy volunteers. Serum concentrations of markers were measured on days 1,3,5,7 of ICU admission. Survival was assessed after 90 days. Statistical analysis was performed by SPSS version 17.

Results: Hyaluronan and syndecan levels were significantly elevated in all categories of sepsis patients as compared to controls (p<0.001). Levels of both markers were increased in severe sepsis and septic shock patients as compared to sepsis patient group at all-time points. Hyaluronan and syndecan differentiated survivors from non survivors (p<0.001). Unlike non-survivors, in the survivor group, median hyaluronan and syndecan levels decreased significantly (p<0.001) in subsequent measurements. ROC analysis for the prediction of mortality identified cut-offs of 441 ng/ml and 898 ng/ml for hyaluronan and syndecan, respectively. The specificity and negative predictive values were 90% and 90% for hyaluronan and 86% and 91% for syndecan, respectively. Kaplan Meier curves revealed similar results. Both markers correlated significantly with APACHE II and SOFA scores.

Conclusion: These observations indicate that serial measurements of hyaluronan and syndecan are significant prognostic markers for morbidity and survival in sepsis. Further, therapeutic interventional possibilities need to be explored in experimental interventional prospective multi-centre trials.

Commentary

As knowledge of pathophysiological processes advances, newer markers evolve for the prognostic assessment of disease conditions and for identification of possible therapeutic targets. This scenario is especially important for conditions which have still not been addressed satisfactorily, as in case of sepsis. The ACCP/SCCM consensus conference in 1991 defined, sepsis as a systemic response to infection [1]. Martin, in 2003, elaborated on this definition to state that sepsis was "a combination of pathological infection and physiological changes" [2]. Sepsis still culminates in high morbidity and mortality, even more so in the developing countries where resources are limited. Martin et al. in their epidemiological study of over 10,000,000 sepsis patients from 1979 to 2000 reported a decrease in mortality from 27.8% in the first 5 years of this 22-year data, to 17.9% in the last 5 years. In 2005, Moss reported a mortality rate of 20% to 50%, depending on the severity of sepsis [3]. Mayr et al. in 2014 reported an increased incidence and mortality rate of sepsis in the United States over the preceding two decades. This was attributed to the increase in aging population with a consequent increased burden of chronic diseases along with an increased rate of transplants, immunosuppressant therapy, chemotherapy and invasive procedures [4]. In contrast, a report from South India elucidates a mortality rate of 67.5% among adults admitted with severe sepsis [5]. Another 5-year report from one hospital in East India reported a mortality rate 57.9%

[6]. In 2014, we published data from our hospital (a 750-bedded tertiary care hospital in North India) where the observed mortality rate for sepsis patients was 21.12%; this lower rate was attributed to better sepsis management and the use of sepsis bundles in our intensive care units [7]. Thus, even in the better settings, the mortality rate is high and care of the sepsis patient needs improvement.

In 1940, Danielli, during his experiments on the perfused frog legs, demonstrated the existence of an endothelial protective layer called the glycocalyx [8]. It was only in the last two decades that the importance of this layer and its components was confirmed in the pathophysiology of endothelial disruption and sepsis [9]. As yet, there are very few studies reported (many in animal models of sepsis) on these biomarkers and their role in management of sepsis and its resultant hypotension and organ failure. In the study under consideration [10], the abstract of which is reproduced above, the importance of serial estimations of these markers has been emphasized.

Hyaluronan and syndecan have been chosen in this study as representative of the glycocalyx. The lacunae in the knowledge regarding these glycocalyx biomarkers-hyaluronan and syndecan-have been elaborated upon in their introduction, viz whether "these biomarkers are deranged only as an early transient phase or whether this persists during the course of the disease". Also, another aim was to elucidate whether these biomarkers could be used as therapeutic targets in the various stages of sepsis.

Towards this, 50 healthy controls and 150 patients of sepsis (15 with sepsis, 45 with severe sepsis and 90 with septic shock) were enrolled and their serum levels of hyaluronan and syndecan estimated at four time points-days 1, 3, 5, and 7 of ICU admission. Earlier studies have estimated these biomarkers only at one time point, i.e., at the time of admission. But to understand the evolution of these biomarkers through the course of sepsis and its stages, serial measurements would be required during the first week to enable the intensivist to modulate management on basis of these markers towards a better outcome.

This study showed that these glycocalyx biomarkers clearly differentiate between the stages of sepsis (i.e. sepsis, severe sepsis and septic shock), and also between survivors and non-survivors at all-time points. They also demonstrated a significant decreasing trend of the biomarkers in survivors. Therefore, these markers "play an important role in the initiation, severity and progression of sepsis". So how does this impact management of sepsis patients?

First of all, let us consider why serial measurements are better than a single estimation which was done in earlier studies. The day 1 measurement of these markers helps to segregate the patients on basis of severity, but it is the subsequent measurements that help in predicting the outcome; the increasing trends of both markers indicate increasing morbidity and mortality. Hence, serial estimations enhance prognostication of sepsis patients and enable the biomarker-directed intervention in management of these patients.

In addition, this study has elucidated the relevant cut-offs for these biomarkers for prognostication of sepsis patients. A day 7 hyaluronan ≥ 441 ng/ml and a day 5 syndecan ≥ 898 ng/ml gave the best prediction of survival with a high sensitivity (90% and 86%, respectively) and negative predictive value (90% and 91%, respectively).

Lastly, but not the least, can these markers be used as therapeutic targets in severe sepsis and septic shock? The results of this publication indicate that if extensive disruption of the protective latticework of the glycocalyx is prevented, the occurrence of hypotension and organ failure would be reduced. Hence, sepsis patients, in whom the inherent defence mechanisms are weak, could benefit from adjuvant therapy with hyaluronan and/or syndecan. However, verification by multicentric interventional studies is required to elucidate the benefits of the use of hyaluronan and syndecan as therapeutic targets.

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