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Research Article

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Sepsis Biomarkers: Our Experience and a Review in New Biomarkers

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ABSTRACT

Background: Sepsis represents a dysregulated immune response to infection that leads to organ dysfunction. A wide range of biomarkers, measured by different technologies, are being investigated for sepsis diagnosis, prognosis, and differentiation from Systemic Inflammatory Response Syndrome (SIRS). Early diagnosis of sepsis with improved markers would allow prompt treatment, which is imperative in reducing mortality and morbidity.

Methods: In our case-series study, we enrolled 174 patients who were admitted to and received treatment in the Intensive Care Unit (ICU) of our hospital (sepsis: n = 103, SIRS: n = 71). Specific parameters measured included procalcitonin (PCT), C-reactive protein (CRP), and cytokines (IL-6, IL-8, TNF-alpha).

Results: We observed higher values of laboratory biomarkers in patients with sepsis compared to the SIRS group: PCT 10.2 ± 18.7 ng/ml vs 0.26 ± 0.18 ng/ml, CRP 148 ± 100 mg/L vs 42 ± 45 mg/L, IL-6 286 ± 330 pg/ml vs 21.01 ± 27.5 pg/ml, IL-8 310 ± 292 pg/ml vs 129 ± 32.69 pg/ml, TNF-alpha 131.15 ± 125.96 pg/ml vs 33.55 ± 118.87 pg/ml. A multiple comparison test demonstrated a highly statistically significant difference between groups for PCT, CRP, IL-6, IL-8, TNF-alpha. ROC curve analysis showed high sensitivity (97%) and specificity (93%) for PCT at a threshold of 0.5 ng/ml, and 100% specificity at 2 ng/ml. Other parameters demonstrated lower diagnostic accuracy.

Conclusion: IL-6, IL-8, CRP, and TNF-alpha are sensitive tests for sepsis diagnosis but lack high specificity. PCT is the best marker, as it demonstrates both high sensitivity and specificity. New biomarkers of sepsis: presepsin, pro-adrenomedullin, microRNAs, transcriptomics, proteomics, and markers of neutrophil activation are currently under investigation, but further validation is needed.

Introduction

Sepsis is a cascade of events originating from innate and adaptive immune responses; it is characterized by the activation of various cell types and release of both pro-inflammatory and anti-inflammatory molecules. In the initial phase of sepsis, a predominantly hyper-inflammatory state caused by cellular interactions with the infectious agent develops, followed by a state of immune hypo-responsivity [1,2].

Diagnosing sepsis early is important for its successful management. This necessitated studies to address the usefulness of various biomarkers to diagnose and predict sepsis and to guide antimicrobial therapy. An ideal sepsis biomarker should have high sensitivity and specificity to detect sepsis early for accurate diagnosis [3]. It should provide results through accessible testing methods, aiding healthcare providers in timely interventions [4].

Clinical definition of sepsis requires clear evidence of infection plus the clinical signs of systemic inflammatory response syndrome (SIRS): presence of two or more criteria; fever >38 °C or <36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min, WBC >12 000 cells/mm³ or <4 000 cells/mm³ or >10% of immature forms [5].

A sepsis-associated organ dysfunction is indicated by one of the following criteria: cardiovascular dysfunction (mean arterial pressure 70 mmHg or lower), respiratory organ failure, renal dysfunction (double serum creatinine level), hematologic dysfunction (platelets <80 000/mm³), unexplained metabolic acidosis (pH <7.3), or plasma lactate level double the upper normal limit [6].

The inflammatory process in bacterial infection is normally accompanied by activation of circulating and phagocytic cells, generation of pro- and anti-inflammatory mediators, which serve to localize and control bacterial invasion. In sepsis, this process is generalized, equilibrium in the inflammatory process is lost, and these mediators exert systemic effects.

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Our knowledge of the response system, at all levels, forms the basis of the study for laboratory markers for diagnosis and monitoring of sepsis. In this context, procalcitonin is one of the most studied biomarkers.

PCT, a prohormone of calcitonin, normally synthesized by the C-cells of the thyroid gland, in sepsis is produced ectopically by neuroendocrine cells in the lung and intestine; it consists of a 116-peptide molecule, 13 kDa; synthesis is triggered by bacterial endotoxin and inflammatory cytokines; peak level after 6 hours and half-life of 24–36 h. PCT is currently used as a tool to differentiate bacterial infection from other inflammatory and infectious processes [7]. If there is already SIRS, the effects of PCT are unfavorable. Activated monocytes stimulate PCT production by target cells. In smooth muscle cells that have already contact with pro-inflammatory mediators, PCT stimulates NO production, that supports vascular dilatation. Interferon inhibits PCT production, possibly another reason why PCT is expressed in bacterial infection but not in viral infection.

C-reactive protein is an acute inflammatory phase protein produced in the liver, currently believed to be an indicator of inflammation and tissue damage, and is elevated in cases of infection and inflammatory response [8]. CRP is stimulated by IL-6 produced by macrophages. The role of CRP is to bind phosphocholine expressed on the surface of dead cells and some types of bacteria in order to activate the classical complement pathway. CRP production occurs after 6 hours and peak level after 48 hours.

Sepsis is characterized by two phases of hyper-inflammation, where the innate immune system is overactivated leading to production of pro-inflammatory cytokines such as TNF-alpha, IL-1β, IL-6, IL-8, and another period of immunosuppression where both adaptive and innate immunity are acting [9].

Materials and methods

In our study conducted in the laboratory service at the University Hospital Center "Mother Teresa", Tirana, were included 174 recovered patients with symptoms of SIRS and suspected sepsis. The diagnosis of sepsis requires the presence of a presumed or known site of infection (positive blood culture, purulent sputum on respiratory sample, WBC in a normally sterile body fluid, radiographic or physical examination of an infected collection) plus evidence of SIRS.

Quick SOFA (Sequential Organ Failure Assessment) was used to help clinicians recognize possible sepsis in settings other than the ICU. Sepsis should be suspected in patients meeting at least two of three qSOFA criteria: respiratory rate >22 breaths/min, altered mental status, and systolic blood pressure of 100 mmHg or less [10].

For all patients, we evaluated the blood levels of procalcitonin (PCT), C-reactive protein (CRP), IL-6, IL-8, TNF-alpha in addition to routine laboratory tests. Statistical analysis was performed using the statistical software package SPSS version 21.0 (ANOVA test, ROC curves, Tukey HSD test).

Patients were divided into two groups: patients with SIRS and patients with sepsis, following a protocol approved by the Biochemical-Hematological Laboratory Service in collaboration with the respective clinical departments.

Results

The mean values of the study parameters demonstrated: mean PCT levels were much higher in patients with sepsis (10.0 ± 18.7 ng/ml) compared to patients with SIRS (0.3 ± 0.2 ng/ml). The mean CRP levels were considerably higher in patients with sepsis (149.0 ± 100 mg/L) versus the SIRS group (42.3 ± 45.3 mg/L) ($P < 0.001$). Similarly, the mean values for cytokines were higher in the sepsis group versus the SIRS group: IL-8 (310 ± 292 pg/ml) vs (29.5 ± 32.7 pg/ml), IL-6 (286.8 ± 330.7 pg/ml) ($P < 0.001$). TNF-alpha in sepsis (131 ± 254 pg/ml) vs (33.6 ± 118.9 pg/ml) in the SIRS group ($P = 0.010$) (11).

ROC curves demonstrated high sensitivity and specificity for PCT (98% and 93% for PCT 0.4 ng/ml, 97% and 93% for PCT 0.53 ng/ml, and 60% and 100% for PCT 1.99 ng/ml), but lower for other parameters [11].

Tukey HSD test showed significant differences between the two groups respectively: PCT P value <0.001, CRP $P < 0.001$, IL-8 and IL-6 $P < 0.001$, but $P = 0.014$ for TNF-alpha [11].

Discussion

Biomarkers have become essential tools for improving diagnostic accuracy, predicting patient outcomes, and guiding therapeutic decisions. CRP serves as a valuable biomarker in the prompt identification of sepsis, boasting a high degree of sensitivity, yet indicating restricted specificity [12]. Our data showed higher values of CRP in patients with sepsis (149 ± 100.1 mg/L) than in the SIRS group (42.28 ± 45.31 mg/L), but ROC curves showed high sensitivity, while specificity was not very high. For a value of 40 mg/L, sensitivity was 91% and specificity was 62% [11].

Contradictory results have been obtained for TNF-alpha; for example, the treatment of septic patients with anti-TNF antibodies did not affect the clinical outcome of patients [13]. In our study, the level of TNF-alpha was significantly higher in patients with sepsis compared to the SIRS patients ($P = 0.085$); ROC curves showed that the best cut-off for TNF-alpha is 20.7 pg/ml with 64% sensitivity and 72% specificity [11]. This cytokine is not altered only in sepsis but also after surgery or in autoimmune disease and therefore is not specific.

Analyzing data obtained on the level of IL-8 and IL-6, it can be noted that their values were higher in patients with sepsis versus the SIRS group ($P < 0.001$). The best cut-off per IL-8 in ROC curves was 50 pg/ml with sensitivity 82% and specificity 82%, considered the most appropriate recommended for diagnosing sepsis. Analyzing ROC curves for IL-6 for a value of 15 pg/ml, we found 95% sensitivity and 65% specificity, and for a value of 20 pg/ml respectively 88% and 73% [11]. Our results are in full agreement with the studies conducted by different authors in this field [14].

Upon detection of bacteria, the body activates immune cells like macrophages and monocytes, leading to the release of cytokines such as IL-1, IL-6, and TNF-alpha. These cytokines stimulate production of PCT in the liver and other cells. PCT is initially synthesized as a precursor protein known as pre-procalcitonin

[15]. The active form of PCT is produced by proteolytic cleavage of this precursor in response to bacterial toxins and inflammatory mediators. In viral or mild bacterial infections, PCT levels remain stable or slightly elevated. Conversely, during severe infections or sepsis, PCT levels begin to rise within 2–4 h, peaking at 24 h with an increase of hundreds or even thousands of times [15].

In our study, the PCT value was very high (10.2 ± 18.74 ng/ml) in patients with sepsis (range from 0.2 to 100 ng/ml), versus the SIRS group (0.269 ± 0.188 ng/ml) ($P < 0.001$). PCT represented a very high sensitivity and specificity (97% and 93%) for the value of 0.5 ng/ml, and 100% specificity for 1.99 ng/ml, observed in ROC curves[16].

A meta-analysis from 2011 to 2022 included 10 out of 2 457 studies to evaluate the clinical value of PCT [17]. It was shown that PCT levels were significantly elevated in sepsis patients (29.3 ± 85.3 ng/ml), compared to the control group (0.34 ± 8.6 ng/ml) [18]. These studies are in accordance with our study and demonstrate that PCT is an effective and accurate marker for differentiating sepsis from SIRS. Despite these results, PCT was found increased above the upper normal value even in trauma, after surgery, and in pancreatitis.

In our study, we observed the role of PCT, CRP, and cytokines in diagnosing sepsis, but different studies highlight the evolution of sepsis biomarkers and their role in improving early detection, prognosis, and therapeutic decision-making in sepsis management.

Biomarkers of activated neutrophils and monocytes: neutrophil CD64 (Cluster of Differentiation) (NCD64) is a surface receptor on antigen-presenting cells that is upregulated in response to infection and endotoxin exposure; when combined with other markers like CRP, it showed high accuracy in diagnosing sepsis. Inactivated neutrophils rarely express CD64. A study assessing the diagnostic accuracy of neutrophil CD64, PCT, and IL-6 for sepsis found that CD64 exhibited a sensitivity of 88% and specificity of 88% [19].

Presepsin is a novel immune biomarker that exists as a soluble form of CD14. CD14 is a surface glycoprotein, part of the Toll-like receptor (TLR) family, expressed on macrophages and monocytes, with a high affinity for bacterial ligands such as lipopolysaccharides [20]. In the immune response to sepsis, the serum levels of presepsin are elevated before PCT or IL-6; therefore, it is proposed as a potential biomarker for sepsis diagnosis. However, the range of values and their predictive accuracy vary across different studies [20].

sTREM-1 (soluble triggering receptor expressed in myeloid cells-1) is a glycoprotein expressed on the surface of neutrophils, mature monocytes, and macrophages. Infection caused by bacteria can lead to an increased expression of sTREM-1. At present, sTREM-1 is not yet widely adopted in clinical practice, and further studies are needed to establish its clinical utility and standardize its use in routine sepsis management [21].

HMGB1 (High-Mobility Group Box 1) is a non-histone nuclear protein that plays a crucial role in inflammation. It can be secreted by activated macrophages or released during cell necrosis and apoptosis. Identified in 1999 as a late-stage mediator of sepsis, HMGB1 acts as a damage-associated molecular pattern (DAMP), prolonging inflammation by activating macrophages via Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) pathways [22]. Elevated levels of HMGB1 in the later stages of sepsis are often associated with unfavorable outcomes, especially in patients with concurrent chronic inflammatory conditions, leading to higher mortality rates [23].

Pentatraxin-3 (PTX3) and adrenomedullin (ADM) are commonly used as prognostic biomarkers; PTX3 belongs to the pentraxin family. It plays a crucial role in the acute-phase response to inflammation and infection. It is synthesized by various cell types, including macrophages, dendritic cells, mesenchymal cells, fibroblasts, and glial cells, in response to pathogenic stimuli or inflammatory conditions [24]. Elevated PTX3 levels in blood samples have consistently been associated with more severe cases of sepsis and unfavorable outcomes.

ADM (adrenomedullin) is primarily produced by vascular smooth muscle and endothelial cells and can be synthesized in various tissues, including the adrenal cortex, kidneys, lungs, blood vessels, and heart. Research has demonstrated that ADM levels correlate with sepsis severity, organ failure, and 30-day mortality, highlighting its diagnostic and prognostic utility [25].

Novel diagnostic biomarkers: circular RNAs, first discovered in viruses in 1970, have been increasingly identified in various cells with the advancement of bioinformatics techniques. Recent studies propose circular RNAs as valuable markers for sepsis diagnosis due to their involvement in immune response and the regulation of microRNAs, but this remains in the research phase [26].

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally and are currently under investigation as potential biomarkers for sepsis. High levels of microRNA-155 expression have been linked to a poor prognosis in sepsis patients [27].

Omics technologies, including genomics, transcriptomics, proteomics, and metabolomics, are referred to as the systematic measurement at the level of DNA, RNA, protein, and metabolite levels, and omics technologies have resulted in the delineation of newer biomarkers in sepsis and sub-phenotyping in sepsis patients. By integrating clinical indicators and advanced biomarkers, personalized treatment strategies can be developed, improving outcomes in sepsis cases [28].

Sepsis is a multifaceted condition with diverse pathophysiological mechanisms and relying on a single biomarker that reflects different aspects of the immune response, inflammation, and organ dysfunction, a more comprehensive evaluation of the patient's condition can be achieved. For instance, PCT indicates bacterial infection, while elevated lactate levels indicate tissue hypoperfusion and organ dysfunction; a combination of these markers can provide insight into both the infectious and metabolic aspects of sepsis. A combination of CRP and IL-10, TNF-alpha, first as general markers of inflammation, while cytokines are associated with immune response, can offer a comprehensive evaluation of the inflammatory cascade in sepsis [29].

Given the complexities of the sepsis response, panels of biomarkers or models combining biomarkers and clinical data are necessary, as well as specific data analysis methods, which broadly fall under the scope of machine learning (machine learning is a class of mathematical methods that attempt to generate knowledge and insight from large databases). A variety of machine learning algorithms have been applied to the question of sepsis diagnosis, prognostication, and phenotyping, most of which belong to the realms of supervised learning (sepsis diagnosis and prognosis) or unsupervised learning (to define phenotypes) [30].

Conclusion

Sepsis represents a dysregulated immune response to infection that leads to organ dysfunction. Early diagnosis of sepsis with improved markers would allow prompt treatment, which is imperative in reducing morbidity and mortality. A wide range of biomarkers, measured by different technologies, are being investigated for sepsis diagnosis, prognosis, and differentiation from SIRS [31]. IL-6, IL-8, CRP, and TNF-alpha are sensitive tests for sepsis diagnosis but lack high specificity. PCT is the best marker, as it demonstrates both high sensitivity and specificity, but it can be found elevated even in trauma, pancreatitis, and after surgery. New biomarkers of sepsis, such as PTX3, pro-adrenomedullin, microRNAs, transcriptomics, proteomics, and markers of neutrophil activation, are currently under investigation, but further validation is needed.

Because no single marker is likely to provide sufficient diagnostic and prognostic information, a multimarker approach, combining traditional and novel biomarkers, may offer the best strategy for improving sepsis diagnosis and management. Standardizing the interpretation of multi-biomarker panels poses a challenge [29].

Given the complexity of the sepsis response, panels of biomarkers and clinical data are necessary. Due to the complexity, high dimensionality, and/or large size of datasets involved, specific data analysis tools-loosely termed machine learning-become required. Machine learning, in conjunction with routine clinical and biological data, has potential in precision medicine and enrichment in adult and pediatric sepsis, but most of the literature on machine learning models and biomarkers in sepsis remains limited to small cohorts and retrospective studies [30].

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