LETTER TO EDITOR

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Definition of Sepsis and Novel Biomarkers for Sepsis

Sepsisin Tanımı ve Sepsis İçin Yeni Biyobelirteçler

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Dear Editor,

Sepsis is a clinical syndrome with high mortality that can progress with multiple organ failure as a result of the body's abnormal and inappropriate host response to infection. In order to determine some definitions that could be used in sepsis patients and make it easier for clinicians to recognize and categorize these patients, a conference was held for the first time in Northbrook in 1991 by the American College of Chest Physicians/Society of Critical Care Medicine. SIRS (systemic inflammatory response syndrome) criteria were defined for the first time (Sepsis-1 criteria) (1). Since there is no gold standard method for the diagnosis of sepsis, the definition of sepsis was insufficient and unclear for many clinicians until 2001, the 'International Sepsis Definitions Meeting' was held in Washington in December 2001 in order to correct the existing definitions and increase their accuracy and reliability (Sepsis-2 criteria) (2). These criteria were used until 2016. Sepsis definition was updated in 2016 by the European Intensive Care Medical Association and the Intensive Care Medical Association due to the correct understanding of the pathophysiology of sepsis, the terms described in 1991 and 2001 being used interchangeably or unnecessarily, the SIRS criteria not having high specificity in sepsis patients, and the understanding that they only address the excessive inflammatory response (Sepsis-3 criteria) (3). With these updates, the diagnosis of sepsis was changed to the diagnosis of the body's inappropriate inflammatory response to infection, it was accepted that the SIRS criteria do not always indicate the infection status and that it can occur in many hospitalized patients, and these criteria were abandoned. In addition, the diagnosis of severe sepsis was also abandoned. According to these criteria, sepsis is defined as a clinical syndrome with high mortality that can progress with multiple organ failure as a result of the body's abnormal and uncontrolled host response to infection.

There is no specific biomarker for sepsis. In the literature, there are many ideal biomarker studies but the definition of sepsis is so vague. Since there is no standard for distinguishing infection, it is difficult to distinguish sepsis from SIRS that is especially non-infectious.

Platelets are the basic cells of hemostasis. However, recent studies have shown that they also play a role in inflammation (4,5). Studies have shown that mortality increases in patients with decreased platelet function and thrombocytopenia due to sepsis, and that it plays a role in determining the prognosis in patients who stay in the ICU for more than five days and subsequently develop thrombocytopenia (6).

Lactate is formed as a result of the catabolism of the intermediate metabolite pyruvate, which occurs as a result of glycolysis, by the lactate dehydrogenase enzyme under anaerobic conditions (7). Due to tissue hypoperfusion in sepsis, hyperlactatemia occurs as a result of the decrease in oxygen delivery and the shift of the primary energy source for cells to anaerobic glycolysis, and it also occurs as a result of the reprogramming of glucose metabolism seen in immune system cells (8).

Procalcitonin is produced by C cells of the thyroid gland in healthy individuals in the absence of inflammation. Serum procalcitonin levels rise 2-4 hours after an inflammatory stimulus. After reaching its peak value at the 6th hour, it maintains its plateau value for up to 8-24 hours and its plasma half-life is 24 hours. Apart from systemic infection, causes such as shock, trauma, surgery, burn injury, pancreatitis, and chronic kidney disease can also induce procalcitonin production. Among all these reasons, the highest levels were detected in sepsis. Procalcitonin is also used as a marker of serious bacterial infections and organ failure due to sepsis (9,10). In 2016, its use was approved by the Food and Drug Administration (FDA) on the grounds that procalcitonin monitoring helps predict 28-day mortality in patients with sepsis and septic shock.

SCUBE-1 is a cell surface protein identified by recent studies within the SCUBE gene family. EGF-like repetitive structures have been shown to function as an adhesive module in mediating platelet-matrix and platelet-platelet interactions. Although these soluble EGF-like portions of SCUBE-1 do not induce platelet aggregation per se, they

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can potentiate ristocetin-induced platelet agglutination (11,12). In a study conducted in Turkey, including 187 patients, it was reported that SCUBE-1 is an independent prognostic factor in septic patients (13).

CD14 is a co-receptor located on the membrane of myeloid cells that helps the presentation of lipopolysaccharides to toll-like receptor-4 and lipopolysaccharide-binding protein. These lipopolysaccharides are found especially in the cell walls of bacteria phagocytosed by macrophages, monocytes, and neutrophils. After stimulation of the receptor, the membranous part of CD14 is destroyed and its level decreases, while sCD14 is secreted from the cell. It is then converted to presepsin, sCD14-ST (subtype), by cathepsin D and other proteases. The characteristics of presepsin are that it is measured in healthy individuals, increases in the early stage of infection, and is directly proportional to the activity of innate immunity (14). Presepsin has recently attracted the attention of various clinical research groups as a prognostic biomarker in sepsis. The biological activity of presepsin has not been elucidated in detail. However, it has been identified as a moderating factor. Plasma presepsin levels can be considered an indicator of activated innate immune effector cells in response to invasive pathogens (15).

Copeptin is a glycopeptide molecule consisting of 39 amino acids located at the C-terminus of pre-pro-vasopressin and was first identified in 1972. During the release of arginine vasopressin from the pituitary, they are released in equal molar amounts together with a peptide molecule called neurophysin. It is not yet clear whether copeptin has a physiological role or whether it is a nonfunctional protein found as a residue after arginine is separated from vasopressin (16). High copeptin levels serve as a prognostic marker for adverse outcomes in sepsis, shock, pneumonia, stroke, acute coronary syndrome, and diabetes (17).

As a result, the definition of sepsis is newly taking shape in the literature. However, there is no ideal sepsis biomarker. Researchers should be encouraged to work on new markers in this field.

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