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Prognostic value of platelet to lymphocyte ratio in sepsis outcome prediction

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Abstract
Sepsis represents a complicated illness occuring when the body's immune response to infections disturbs, resulting in an uncontrolled inflammation as well as compromised immune system. Such condition is attributed to infections acquired in both community as well as hospital settings, with a special emphasis on (ICUs). In fact, it represents the primary etiology for mortality within ICUs, accounting for almost 50% of all. Hence, it represents a worldwide health issue with substantial economic consequences. Therefore, it is crucial to finding prognostic as well as diagnostic biomarkers for preventing related complications as well as decreasing death rates through commencing therapy prior to permanent damage occurence. A one-hour delay while managing sepsis is believed to be linked to a 7-10 percent rise within sepsis-related fatalities. Consequently, several attempts have been undertaken for discovering a feasible biomarker, helping detect those having sepsis or possess higher chances for mortality. Of all the biomarkers investigated for sepsis, (CBC) metrics, involving the (NLR) as well as (PLR), have the potential to be useful.

Keywords: Lymphocyte, sepsis outcome, ratio

Introduction
As to the 2021 SSC recommendations regarding sepsis as well as septic shocks: Sepsis represents a potentially fatal condition characterized by organs' malfunction due to a compromised immune reaction to infections [1]. Various scoring systems have been employed for evaluating organs' malfunction severity through by quantifying anomalies based on clinical observations, laboratory testing, as well as therapeutic treatments. Scoring systems variations have also resulted in inconsistent reporting. The prevailing measure utilized currently, is the Sequential Organ Failure Assessment (SOFA) (formerly known as the Sepsis-related Organ Failure Assessment). Higher SOFA scores exhibits a correlation with a greater death probability [2].

Etiology
- Gram-negative sepsis prevalence has decreased to 25-30% in 2000. Gram-positive MOs are responsible for a significant proportion, falling between 30% and 50%, of reported cases. Etiology remains polymicrobial in nature within 11-19% of cases.
- Fungi, viruses as well as parasites are responsive for fourteen percent of cases [3].
- Finally, cultures could exhibit negative findings within thirty percent of instances, particularly among those having community-acquired sepsis managed with antibiotics prior to hospitalization [3].

Predisposing factors for septic shock [4]
a) DM
b) Lymphoproliferative disorders
c) Cirrhosis
d) Invasive interventions or devices
e) Burns
f) Intravenous Drug Abuse
g) Chronic Organ Failure
h) Long-term antibiotic regimen

i) Cancer
j) Neutropenia

Sepsis Biomarkers

The NIH defines a biomarker as a measurable characteristic indicating a normal or diseased condition, or a specific drug's response. They exhibit reliability as well as accuracy, making them valuable for diagnosing specific conditions. Additionally, they aid in early detection, determining the disease's progression, predicting outcomes, as well as intervention mechanisms [5].

Established biological markers:

a) Lactate: Currently, it is advised to utilize it as a SSC Hour-1 sepsis bundle component for individuals having sepsis [6], and an elevated lactate is part of the Sepsis-3 definition of septic shock Additionally, an increased lactate level is involved in the Sepsis-3 definition of septic shock, which is recommended to be utilized as a resuscitation's guide through reducing serum lactate among those having raised lactate levels [1].

b) C-reactive protein: Some of its functions involve activating platelets, promoting chemotaxis, as well as boosting cell-mediated immunity through phagocytosis stimulating [7]. Such protein is also utilized for those having trauma, distinguishing sepsis of a noninfectious systemic inflammatory response syndrome. A substantial elevation of this protein during the first four days following injuries serves as a dependable infection indicator [8].

c) B-type natriuretic peptide: BNP represents a cardiac hormone inducing natriuresis, diuresis, as well as vasodilation. Ventricular myocardium produces it as a reaction to the heart muscle's stretching. Its major function involves controlling cardiac pressure as well as maintain the intravascular homeostasis [9]. Septic shock is characterized as a disorder causing profound blood pressure alterations.

d) Procalcitonin: represents a diagnostic tool currently utilized for distinguishing bacterial infection from other inflammatory as well as infectious conditions [10]. Numerous research have addressed, measuring PCT's serum levels could be effective in guiding antibiotic therapy. Additionally, it is utilized for safely minimizing the unnecessary medications' administration, hence lowering the sepsis treatment negative events as well as preventing antibiotic-resistant bacteria emergence [11].

Promising biomarkers

1. **Receptor for advanced glycation end products:** (RAGE) represents a standard recognized receptor involved in several physiological as well as pathological processes, including DM complications, cancer, atherosclerosis, as well as inflammation [12].
2. **Nitric oxide: (**NO) represents a highly reactive produced naturally inside the body by three isoforms of nitric oxide synthase enzyme: neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), as well as endothelial NOS (eNOS or NOS3). These molecules play a substantial role in maintaining cardiovascular balance. Hence, studies havekik0, concentrated on their impact on heart disease caused by sepsis [13].
3. **Haptoglobin:** While it is well acknowledged that liver is the primary site of Hp synthesis, research indicates that it is also expressed in several other organs involving lungs, kidneys, heart, spleen, thymus, as well as brain [14]. Some reports address that Hp levels are affected by the acute inflammatory. Additionally, such protein exhibits an antibacterial as well as antioxidant role. [15, 16].
4. **Cytokines as biomarkers:** Sepsis can be divided into two phases: a hyperinflammation phase, where the innate immune system overactivated, thus producing proinflammatory involving TNF, IL-1b, IL-6, as well as IL-8, followed by a immunosuppression subsequent phase where both adaptive as well as innate immunity are acting [17]. Septic individuals participating in clinical trials exhibited a pro-inflammatory cytokines elevation [18, 19].
5. Clinical scores lack effectiveness in early infection detection in critically-ill individuals; yet, integrating such scores with biomarkers enables prompt as well as precise sepsis diagnosis. Combining the (MEWS), a monitoring measure for sepsis, with blood lactate levels proved to be effective in promptly identifying the disease [20].

Platelets to lymphocyte ratio (PLR)

Platelets are dynamic blood cells that, in conjunction with coagulation factors, play a crucial role in hemostasis, or hemorrhage prevention. They exhibit interactions with each other and with leukocytes as well as endothelial cells, for inspecting vascular bed for damaged areas, where they subsequently undergo activation [21].

Platelets role in sepsis

Platelets exhibit the ability for either directly or indirectly interacting with many bacteria, viruses, fungi, protozoan pathogens, as well as their byproducts, thus helping eliminate such pathogens. Such interaction is influenced by factors involving characteristics as well as bacterial concentration, interaction duration. Additionally, it includes numerous processes. Indirect contacts may occur via the plasma proteins binding, involving fibrinogen, von Willebrand factor, complement proteins, or IgG. Such proteins operate as bridges between infections as well as platelets, or they can interact with bacterial toxins [22].

Sepsis induced thrombocytopenia

In sepsis situations, peripheral processes play a more significant role in causing thrombocytopenia, making a myelogram unnecessary unless there are particular circumstances. The most prevalent mechanism for platelet consumption is by thrombin-mediated platelet activation. Severe sepsis may lead to (DIC), a condition where coagulation is activated throughout the body, causing intravascular fibrin development as well as small and mid-sized vessels blockage. As an aquired diseases, DIC is linked to numerous clinical conditions, especially septicemia [23].

Lymphocytes represent a subtype of leukocytes (WBCs) found in the immune system of most vertebrates. They involve**:**

a) T lymphocytes: They are essential for regulating the antimicrobial phagocytic as well as cytotoxic activities of cells involved in innate immune response [24].

b) B lymphocyte: Has a crucial part in the protective

immune response of the host. B cells secrete cytokines, display antigens to T lymphocytes, and undergo differentiation into antibody producing cells. Antibodies attachment to bacteria may enhance the process of bacterium opsonization as well as promote phagocytosis [25].

c) **Natural killer cells:** Possess both cytotoxic capabilities as well as immunoregulatory roles, involving cytokines secretion such as IFN-γ, TNF-α, as well as (GM-CSF) [26].

Lymphocytes role in sepsis

1. **T lymphocytes:** T-cell compartment is crucial in controlling the immune response effector phase. T lymphocytes, namely CD4+ and CD8+ cells, (TH) cells, primarily play a role in controlling the immune response [27]. The first subgroups identified were labeled as TH1 as well as TH2 cells, distinguished by their specific production of two cytokines, IFN-γ and IL-4, respectively [28].
2. **B lymphocyte:** B lymphocyte clones produces antibodies. Which is triggered by antigens plays a crucial role in effectively eliminating various pathogens throughout the immune response. B cells may also function as efficient antigen-presenting cells for delivering microbial antigens to T lymphocytes [29].
3. **Natural killer cells:** NK cells likely have a direct role in the innate immune system's antibacterial response since they have the ability to identify pathogen-associated molecular patterns [30].

Blood lymphocyte

Dysfunction occurrence in sepsis has been well acknowledged, characterized by severe lymphopenia as well as reduced lymphocyte T CD4+, CD8+, and NK cells [31]. Nevertheless, investigations have shown that immunosuppression occurs in both peripheral blood cells as well as in organs of individuals died from sepsis, leading to increased interest in lymphocyte malfunction during sepsis [32].

Platelet-to-Lymphocyte Ratio (PLR)

PLR has been a useful indicator in the last ten years for detecting changes in platelet and lymphocyte levels caused by acute inflammation as well as prothrombotic conditions. [33]. The global interest in the value of PLR in laboratory diagnostics of a wide variety of diseases is reflected since 2008 and then get more interest [34].

Its usage was documented in the neoplastic diseases' prognostic prediction, involving hepatocellular carcinoma as well as breast cancer [35]. Accumulating data indicates that high (PLRs) are closely linked to elevated systemic inflammation, thus potentially playing a role in prognosis as well as progression of several conditions, involving atherosclerosis. [35] as well as DM [36]. An increased PLR suggests an increased thrombotic/inflammatory response in the host, which is associated with higher among septic cases [37]. And since 2017 the value of PLR with sepsis as a prognostic marker for sepsis outcome had a great interest. Normal range PLR across all ages for men and women were 92.88 ± 28.70 for men and 108.02 ± 32.99 in females.it vary according to age and sex [38].

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