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Systemic failures in septic shock patients: main biomarkers

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Abstract

Sepsis is commonly defined as a life-threatening organ dysfunction caused by an uncontrolled deleterious host response to infection. Septic shock is defined as a subset of sepsis in which there is profound circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than with sepsis alone. Mortality varies for both definitions of sepsis, being 20-30% for sepsis, while for septic shock, this figure can shoot up to between 30% and 50%. Hemodynamic, kidney, lung, sinus, cardiovascular or liver abnormalities are the paramount reasons why these patients are hospitalized. Septic shock can develop immediately soon after hospital admission, but many cases develop it after some time, therefore causing patients to return to hospital treatments once they have already recovered. Therefore, it is crucial to know the markers that could predict and help identify the patients at risk of developing septic shock but also the ones who will develop systemic failures. With this review, we aimed to pool time reliable and cost-effective biomarkers. SIRS criteria, upon their discovery and publication, were a hope to generate a uniform prospective multicentric trial, but SIRS with its 4 criteria is too unspecific and insensitive sign in order to stratify patients. In this study, we aim to review the most important biological markers of organ function that is responsible for systemic failures in patients with septic shock. The early-stage mortal septic shock does not involve laboratory findings. The emergence of morphofunctional abnormalities does not appear abruptly.

Keywords: Severe sepsis; Systemic failure; Inflammation; Biomarkers

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Introduction

Sepsis is commonly defined as a life-threatening organ dysfunction caused by an uncontrolled deleterious host response to infection. Septic shock is defined as a subset of sepsis in which there is profound circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than with sepsis alone. Mortality varies for both definitions of sepsis, being 20-30% for sepsis, while for septic shock, this figure can shoot up to between 30% and 50%.

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predict and help identify the patients at risk of developing septic shock but also the ones who will develop systemic failures. With this review, we aimed to pool time reliable and cost-effective biomarkers. SIRS criteria, upon their discovery and publication, were a hope to generate a uniform prospective multicentric trial, but SIRS with its 4 criteria is too unspecific and insensitive sign in order to stratify patients. In this study, we aim to review the most important biological markers of organ function that is responsible for systemic failures in patients with septic shock. The early-stage mortal septic shock does not involve laboratory findings. The emergence of morphofunctional abnormalities does not appear abruptly.

Septic shock is severe sepsis that results in circulatory, cellular, and metabolic abnormalities to be associated with a greater risk of mortality than sepsis. The sepsis prevalence has increased by 8.9% to 21.9% annually. With a prevalence of 6.0% to 19.0% over 100,000 inhabitants, approximately 10-40% of cases present with severe sepsis, and septic shock can present up to 28% of cases of severe sepsis reported. Moreover, the mortality rate of sepsis/septic shock remains high—around 30-40%. In a retrospective analysis of septic shock-related complications in patients admitted to 71 hospitals in six countries, 32% had hepatic failure, 26.7% circulatory failure, 19.4% kidney failure, and 3.6% required mechanical ventilation in ICUs. Approximately 25% of patients with septic shock who require vasopressors have persistent hypotension after 2 L of normal saline, and the mortality rate is approximately 50%. Among septic shock patients, 10% persistently require high catecholamines, and the mortality rate is more than 40%.

Systemic inflammatory response syndrome (SIRS) and sepsis are prevalent in ICU patients. Thus, it is crucial for a definitive diagnosis and pathophysiological distinction to be made in order to allow a therapeutic approach to be established. Recently, there has been a new definition of Sepsis-3, which recommends that an early screening of septic shock with the assessment of the serum level of lactate is now being recommended in the last hours in several emergency rooms in the world. Associations and randomized clinical trials have shown that mortality is reduced when the diagnosis of sepsis is made early and measures such as abundant cures and the use of broad-spectrum antibiotic therapy/intravenous immunoglobulins are implemented. Also, there is a decrease in resources and/or costs in terms of length of hospitalization and ICU/hospital costs once adequate therapy in septic shock and/or quick sepsis affecting satisfactory patients with sepsis is promptly employed.

Pathophysiology of Septic Shock

Sepsis is defined as a systemic inflammatory response to infection. Although septic shock is the most severe form of sepsis, there is no consensus on its classification, being defined as sepsis-associated hypotension that is unresponsive (non-surviving patients) or responds transiently (surviving patients) to initial fluid resuscitation in combination with the presence of sepsis-induced multi-organ dysfunction. Further clarification of the pathophysiology of septic shock is crucial for the development of appropriate therapies. Severe hypotension during septic shock leads to tissue hypoperfusion by microcirculatory shunting, primarily in splanchnic vessels, further aggravating organ dysfunction.

Multiple organic systems are impaired through complex interactions. First, in response to leukocyte activation and cytokine interactions, changes in microvascular circulation and endothelial function

occur. Then, abnormal energy metabolism, increased oxygen demands in excess of supply, and subsequent tissue hypoxia occur, leading to anaerobic metabolism and lactate production and release in the absence of adenosine triphosphate to fulfill cellular needs. Advances in our understanding of the different pathways of pathophysiology of sepsis have led to the identification of various potential therapeutic strategies that have failed in many clinical trials.

The systemic failures present in the pathophysiology of septic shock will be addressed in this chapter, the last one related to the role of biomarkers, in order to better associate the main findings of the literature review.

Immune Response in Septic Shock

Immune response is the complex reaction of the body in response to the presence of a pathogen in different tissues. The onset of an immune response usually facilitates the clearance of microbial pathogens, which, in the context of infectious disease, prevents the spreading or development of the infectious process. However, given the great diversity of immunologic effectors, the clinical aspects of the immune reaction in primarily infectious diseases are far from being completely understood. As far as septic shock is concerned, immune response is a critical component of the pathophysiological processes that triggers it. A "box model" has been proposed to provide a graphic overview of the pathophysiological studies of sepsis. The scheme considers the human host as a black box, which accommodates the four classical elements of the inflammatory host response to infectious challenge. It has long been recognized that septic patients can present with a variable pattern of inflammation, ranging from an excessive "cytokine storm" with overwhelming immune activation and immunopathology, which is commonly, though not strictly, associated with an initial hyper-inflammatory phase, to a relatively immunosuppressed condition. Most of the current efforts have been devoted to finding a "magic bullet" to modulate the immune component of sepsis and, hopefully, reduce mortality but with overall disappointing results. It was subsequently proposed that inflammation does not kill patients with sepsis but rather the failure to mount an adequate compensatory anti-inflammatory response to sepsis. Given the multifaceted nature of sepsis, it is fairly likely that sepsis does not globally represent a condition of excessive systemic inflammation or immunosuppression but rather a clinical syndrome in which the pathological immune response to a specific pathogen is uncoupled from protective immunity. This would allow for the simultaneous activation and deactivation of immune protective pathways. A thorough characterization of the immune response to the septic challenge is important for the development of new therapeutics and is likely to turn out to also be of help for the identification of potential biomarkers to refine prognosis and treatment of these patients.

Endothelial Dysfunction

Carved within the framework of sepsis pathophysiology, endothelial function has a pivotal position. Endothelium works as a warden in diverse intraorganic compartments, including the cardiovascular system. Production of nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor, and other vasodilators, adjusted by the endothelium, is counterpoised towards vasoconstrictor molecules, such as big endothelin, thromboxane, and platelet aggregation promoters, including thromboxane and von Willebrand factor.

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Given that the endothelial cell plays a role as a junction between the biological cosmos and the connective tissue from inner nuclei of vessels, it is primed to suffer the impairments of an overwhelming septic event, leading to dysfunction with the consequential clinical syndrome of septic shock. Endothelial surgery, a term dubbed by M.W. Merx and M. Bauer, reflects the endothelial heterogeneity in systemic sepsis: capillaries could be "staved", while major arteries dilated. This association between the endothelial "sinusitis" influencing coagulation between two membranes worked as a source of inspiration for the identification of the biomarkers referred to, as all of them are strictly linked to endothelial damage. Basing on these premises, understanding the endothelial tale is essential to effectively dissect the profile of septic shock patients. A review about septic shock biomarkers is ongoing, with a special focus on cardiac and pulmonary indices, including coronary biomarkers and lactate as predictors of decreased creatininemia.

Biomarkers in Septic Shock

Sepsis is characterized as a life-threatening organ dysfunction that can be caused by a dysregulated host response to infection. Septic shock represents a subgroup of sepsis in which underlying circulatory and cellular/metabolic abnormalities are significant enough to considerably increase the risk of lifelong organ damage. Given the danger of delayed identification and the rising number of clinical trials for evidence-based therapy, novel strategies are introduced for the identification, precise diagnosis, and prognosis of biomarkers in patients at high risk of adverse outcomes. The activity of organ support measures is removed in predominant sepsis, and a thorough assessment of comorbidities and functions of survivors is initiated. The analysis is based on a systematic iterative review of the literature. The determination and management of injury are considered standard expectations for patients who receive pediatric intensive care unit (PICU) care.

Septic-set, hosts are currently developing a variety of highly sensitive, very specific coordinated scientific and bench strategies to quantify abnormal gene coding, which is translated into the bloodstream. This appears to establish severe sepsis at a higher potential than procalcitonin infection markers or contemporary opinion. Single-factor biomarkers for the prediction of evolution and response to therapy after severe strong compression are often insufficient. A concerted strategy that produces scientific and is evaluated by bench techniques for the detection of this region specifically in the area of life expectancy is more specific, and researchers are currently established. The biomarkers are emergency physiology scientists and the blood analytes that appear to contribute to the survival of sepsis and confirm the criterion management decisions for hospital and emergency room intensive care-associated practice. The pharmacodynamic study planner should consider the two main areas of attention in determining shock care due to a meta-study of the coordinating efforts in the Sequential Organ-Failure-Test. The initial clinical studies have indicated that the place of death and the systemic changes that commonly occur are the biomarkers.

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Importance of Biomarkers

Biomarkers may be defined as measurable characteristics in tissues, blood, or bodily fluids signifying some biological condition or a fundamental characteristic of a profound physiological or pathological process. Reduced costs, along with laid out and regulated market application by agencies such as the US FDA, have increased interest in biomarker identification and development in the last quarter of the 20th century. Biomarkers for intensive medico-social situations such as diagnosis, prediction, and prognosis of such a common disorder as sepsis, a complex reaction to infection, and its sterile variant, septic shock are under extensive research in terms of specificity, sensitivity, and prognostic functional value.

Pathophysiology of biological systems (auto defense, autoimmune, the endocrine system, cardiovascular system, etc.) behaves not only in time pressure, but also space pressure on various anatomic abodes. Failure in a certain anatomic environment is not only a result of the biomessenger of the organ, tissue, or cell failure, but also that of the disturbance in unsupported local terrain lacking the cytokines needed for activation, growth, maturation, and diversification of the structures functioning for life in this compartment. Medically, many of the physicians do not take into consideration the phylogenetic support in its formation of any biological compartment in terms of a phylogenetic valveless vein subsystem. Phylogenetically, when a lipoproteinuis evolution avails in any compartment it tissues off the life-threatening infections.

Classification of Biomarkers

4.2. Classification of Biomarkers. Biomarkers may be classified into a variety of types that include pathogen detection, endothelial dysfunction, organ dysfunction, immune activation, microcirculation, apoptosis, and multi-biomarkers as well as clinical parameters and genetic information. Every class has specificities, advantages, and disadvantages, but a single biomarker is not able to describe such a complex syndrome. The correct classification of each biomarker ranges from temporal and spatial alteration of such biomarkers to functions, involvement in the host immune response, and specific role in diagnosis or prognosis. It is very useful to better understand all the data on sepsis and stratification methods.

4. Main Biomarkers. In 1992, an 'expert consensus' of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) developed the first Consensus Definition of Sepsis, also referred to as Sepsis-1, which included four major criteria. One of the four major criteria required the presence of at least two or more of the following: fever, hypothermia, tachycardia, tachypnea, alteration of white blood cell count. The syndrome was defined accurately and extensively in 2001, with the updated ACCP/SCCM Consensus definition, Sepsis-2, adding a specific term for the progression to severe sepsis and septic shock. However, even with the new definition and levels, as shown in subsequent studies, agreement on what constituted these alterations in vital signs generated in previous studies with values of kappa statistic between 0.26 and 0.96 for sepsis and septic shock. Also, these criteria, demographic data, and paradigm had severe limitations in identifying patients before the onset of severe sepsis, making it almost impossible to plan any research in the emergency departments. Subsequently, these definitions have been updated with new SEPSIS-3 criteria in 2016,

and these new criteria recommend that "sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection" and clinical criteria alone cannot be predicted. In addition, a patient is identified as having sepsis if he/she has an acute increase of at least 2 SOFA points. However, any signs of organ failure that are associated with higher mortality can serve as a prognostic parameter. Established prognostic factors included in the SEPSIS-3 definition include: (1) ScvO2 heart failure, upper value of 67%, (2) Lactate cardiovascular disease, >1 mmol/l, (3) Serum lactate >4 mmol/L, and lactate increase >0.5 mmol/L/h.

Main Biomarkers in Septic Shock

There has been increased interest in identifying biomarkers in blood that could assist in sepsis diagnosis, therapy monitoring, and prognosis. The literature on putative biomarkers is vast and often confusing because so few of these many putative biomarkers have been subjected to comparative evaluation as diagnostic or prognostic tests. Here, we focus on those that appear to be the most empirically evaluated in patients with established sepsis and septic shock, granted that some may be useful specifically as the result of acquisition in clinical trials. The expression of mitochondrial DNA has recently been pinpointed as a potentially promising candidate, though more extensive data in human sepsis patients is needed. Shortcomings with their individual use also stimulate interest in the promise of multiplexing.

Principally, this section discusses markers reflecting immune and endothelial cell activation, dysfunction, turnover, and damage. Sepsis is a clinical syndrome arising from an ongoing dysregulated immune-inflammatory response against an invading pathogen that leads to an imbalance between pro-inflammatory and anti-inflammatory responses, progressive failure of internal organs, and high mortality. The main biomarkers associated with sepsis are shown in this work. The host immune response is the main etiology likely leading to the development of sepsis and, in patients with persisting hypotension despite volume resuscitation, should be minimized through fluid resuscitation. Early antimicrobial broad-spectrum therapy is crucial. A prolonged blood culture sampling should be carried out to identify the pathogen and administer specific therapy. Prompt administration of appropriate antimicrobials has been strongly correlated with improved outcomes in septic shock patients. Septic shock results from an underlying infection that leads to a hyperactive or a hyporeactive state of the organism against it. Circulatory failure often results from damage to the endothelium, which leads to hypovolemia due to capillary leak and arterial vasodilation. Sepsis, severe sepsis, and septic shock are referred to as sepsis condition.

Procalcitonin

Procalcitonin (PCT) is a well-known biomarker used in the diagnosis of septic shock. PCT is the precursor of calcitonin, but it can be detected in the serum of healthy patients. Under physiological circumstances, an amount less than 0.1 ng/mL can be detected. In the early phase of systemic inflammation, PCT levels generally elevate due to the secretion of cytokines. PCT is used to diagnose a likely bacterial infection in clinical settings. Serum levels of PCT are influenced by noninfectious pro-inflammatory stimuli (cardiac shock, extensive surgery, and trauma), but data showed that they are usually low. A main goal is defined to reduce antibiotics during sepsis to decrease an increase of

multidrug-resistant and Clostridioides difficile infections. However, discontinuing their use is very difficult.

We still do not know how to stop antibiotics in patients, and we are unable to wait for the final results of microbiological cultures that generally take at least 48 hours. To overcome these problems, useful diagnostic tools could detect patients with a high probability of having a bacterial or at least a systemic infection even before the presence of severe sepsis or septic shock. Various authors have proved that PCT appears as a diagnostic critical tool in the early stage of sepsis/septic shock if used in serial measurements. It is important to determine if PCT clearance is associated with an improvement in organ dysfunction. PCT should be checked for clinical use in serial measurements more than once in a day in all admitted septic shock patients to the ICU in close relation to the clinical status of the patients for treatment amelioration.

C-reactive Protein

C-reactive protein (CRP) is an annular (pentameric) protein of the class of acute-phase reactive proteins produced mainly in the liver. It is a quantitatively significant and liquid-phase pattern, with a clear kinetic in which the peak of synthesis occurs between 48 and 72 h after the stimulus. It presents a high rate of increase and a slower rate of normalization in the absence of maintaining stimulus. In healthy individuals, its serum levels are very low (<2 mg/L). Although its function is not completely understood, CRP is considered to have a protective role in the inflammatory response because it has shown to present an ability to bind to nuclear and cellular membranes of various microorganisms. It has been shown to activate the complement pathway and may stimulate the phagocytosis of macrophages through the receptors of immunoglobulin (IgG) and complement (CRP).

The involvement of this biomarker in the bacterial, systemic inflammatory response and individual systemic response has made CRP the subject of numerous clinical studies. Our clinical practice and international guidelines have included CRP as a useful biomarker for the evaluation of this type of patient in the first hours after symptoms appear, and after treatment has been initiated. It has also been included in many prognostic scales, such as the sequential organ failure assessment (SOFA) score, the new simplified acute physiology score (SAPS 3) and the quick SOFA (qSOFA) score of sepsis. Its value is not directly related to the degree of organ failure in the acute phase, although low values are clearly related to the absence of organ failure, and high values are related to a high probability of presenting ≥2 organ failure. Its role as a prognostic biomarker closely depends on the strategy used by the clinician for the early diagnosis of this condition. Its diagnostic power is lower than those of the PCT, the WBC and bilirubin, although their association can help in the diagnosis of sepsis.

Lactate

Lactic acidosis is a rare underlying cause of lactatemia in the context of septic shock. The relevance of hyperlactatemia resides in the fact that lactate can be seen as a central end product reflecting the transformation of pyruvate into either energy by the mitochondria or lactate by cytosolic LDH when the oxygen supply is no longer adequate to fulfill the tissue needs. In clinical practice, lactatemia is of interest for several reasons. First, it is a marker reflecting the presence of anaerobic metabolism.

Elevated lactate (point-of-care lactate cut-off ≥ 2 mmol/L) may indicate ongoing tissue hypoperfusion. The parallel between lactate levels and the amount of tissue hypoxia has been repeatedly demonstrated in septic shock. As a consequence, the serial, noninvasive measurement of lactatemia is particularly attractive as it might represent a valuable tool to monitor the patient's response to fluid resuscitation specifically in septic shock. More importantly, studies repeatedly demonstrated that the persistence of hyperlactatemia under proper resuscitation is related to an increased morbidity or mortality, although the definition of normalization (lactate fixed cut-off versus derived formulas) has been extensively discussed.

Prognostic value of lactatemia in septic shock: The assessment of hyperlactatemia as one of the inclusion criteria to define septic shock indirectly highlights the recognition of its prognostic value as the presence of lactate in "sepsis with organ dysfunction" related to a worse prognosis as compared to a simple "severe sepsis". A number of studies have focused on the identification of the optimal measurement timing for lactate to predict outcome in septic shock and found that lactate clearance occurs within six hours in septic patients surviving 28 days. These results have been confirmed in a larger observational cohort study suggesting that a persistent hyperlactatemia is associated with an increased mortality in septic shock.

Interleukin-6

The last biomarker to comment on is the interleukin-6 (IL-6), which has been called the pivot of the main pro-inflammatory and anti-inflammatory cytokine mutually regulated with IL-10 and has been related to sepsis prognosis. Interleukin-6 is the key inducer of acute-phase response and has other numerous biological effects, including inflammatory response, hematopoiesis, lipid metabolism, hyperplasia, anti-lipoprotease genes, T/B cell differentiation, and antibody production. In serum, IL-6 is detectable 1-2 h after onset until around day 5 of sepsis onset. It has been associated with the development of sepsis-related complications in different studies and has also been classified as an IL-6 predictor score of ICU mortality at the beginning of sepsis. It is known that it enhances adhesion molecule expression and exocytosis. IL-6 also inhibits the release of acetylcholine from autonomic nerve endings. In general, the activity of the IL-6 system increases with age and a higher body mass index, while dieting and concomitant diseases such as cardiovascular or kidney diseases result in reduced activity of the IL-6 system. Hypertriglyceridemia, hyperleptinemia, and the TNF system also result in increased IL-6 activity. Pro-inflammatory cytokines such as TNF induce IL-6 release, while anti-inflammatory cytokines such as IL-1RA and IL-10 inhibit IL-6 release. IL-6 is also regulated at the hepatocyte level, which decreases with age or sepsis. The half-life of IL-6 in the circulation is 5-6.8 min, which is the shortest among the sepsis biomarkers. IL-6 can be released into the systemic circulation or localized to the lungs and peritoneal membranes. Decousus et al. have reported in a rat saline lung lavage sepsis model. Therefore, measuring IL-6 serum would be helpful as a biomarker of sepsis activity and also for monitoring clinical signs of the disease using a serial approach, despite the fact that its predictive values for septic shock or patients' death are coincident. Recently, Çelik et al. concluded that plasma IL-6 determination at 12 h provided a high specificity for establishing sepsis.

There is no doubt regarding the role of IL-6 or its level in the broader or more precise issue of being a marker for sepsis in general or septic shock. One study has concluded that IL-6 determination can be used to identify septic shock onset with or without sepsis. Another valuable role of IL-6 is in terms of patient management. Mice treated with an IL-6 inhibitor had reduced levels of hepatic injury and elevated anti-inflammatory IL-4 and IL-10 expression, whereas Croft et al. have recently concluded that BMS-981550, an IL-6 inhibitor, had no effect on the outcome of adult patients with severe community-acquired pneumonia and it has been only recommended during thrombotic events. It should also be mentioned that the decline or failure of IL-6 levels in severe sepsis or septic shock patients who are not responding to therapy to survive may predict a poor outcome. More recently, another trial about targeting sepsis-induced Immunoparalysis is a multicenter study, discussing benefits in modulating IL-6, has been designed. Additionally, in the second international consensus sepsis definitions, considering the existent evidence, a pre-ICU admission random plasma lactate concentration apparent was implicitly included in the newly outlined septic shock criteria and no mentioning of IL-6 broader or more precise issue has been mentioned. However, IL-6 determination would offer an interesting alternative or complement to lactate as an indicator of endothelial failure and organ impairment when it would evolve in broad clinical use.

Diagnostic and Prognostic Value of Biomarkers

One of the biggest challenges for healthcare professionals is early disease recognition. This is currently where the problem lies with septic shock. All the currently used systemic biomarkers can be divided into two parts: those with a diagnostic value and those with a prognostic value. The proposed diagnostic values of biomarkers are based both on basic quantities of the specific marker and on different combinations with other markers. In the last decade, special attention has been paid to the diagnostic importance of presepsin. It is a new novel marker. The level of sTREM-1 is significantly higher in patients with septic shock than in critically ill patients without an infection. The level of PCT starts to rise an average of 2-4 h after an infection is detected. The quick release of ADRENOMEDULLIN is considered to be connected with the crucial impact of the inflammatory system on vessels in which the endothelium synthesizes a considerable part of ADRENOMEDULLIN. Based on the driven conclusion, it is possible to determine the level of this peptide 1 h after the detection of a bacterial infection.

The most significant role of a diagnostic value is minimizing the disadvantage of starting the effective antibiotic treatment during the first hour of diagnosis, which leads to lower mortality in septic shock. Recently, one of the more interesting studies that proves the diagnostic value of diagnostic biomarkers is presepsin. Prosepsin (a fragmented part of CD14) is a novel promising biomarker in systemic infection, sepsis as well, and bacteremia. Prosepsin has a high optimal cut-off value of 645 pg/mL in severe sepsis in predicting in-hospital mortality with good sensitivity and specificity. Prosepsin reflects the bacteremia as well. In the guidelines from 2015, it has been stated that clinicians should find a marker such as ADRENOMEDULLIN, ANP, PCT, Cg-1, endothelium, and other markers to be very useful for guiding the treatment in septic shock. Some of them take part in evaluating distribution of a vasopressor, positive result of volume test, prediction of improvement of tissue perfusion, and

monitoring of vasopressor use. In some cases, the serum level is mentioned as infection variables. It, however, mentioned tissue perfusion energies. Overall, clinicians should measure a specific biomarker on decision to change the treatment strategy. In most of markers, it is possible to adapt in cautions before doing the measurement of precise biomarker. Whether sepsis evaluation might be at the optimal level by using one or more biomarkers for such tasks. By determining specific timely variables. There are always options. Clinical symptoms and signs are valuable for diagnosing and evaluating only those patients who may make mistakes.

Current Challenges and Future Directions

An optimal panel of plasma and genetic biomarkers, as well as miRNA patterns or exosomes for the definitive diagnosis and progression prediction of septic shock, could be proposed to undergo clinical trials. This piece of advice for clinicians lies at the end of the latest systematic review. Moreover, circulating cellular mRNA and cell-free PAI-1 for the diagnosis of sepsis were recommended for further research. However, it has not been stated how to improve and continue the retrospective and prospective full range of methodological study development on the subject according to standard Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria. Dealing with the search for new biomarkers for early diagnostics of septic shock is significantly challenging due to the high complexity of pathophysiology, unexplained causes of variability in results, multiple confounding and signaling factors influencing the reliability of detection tests, medication, and services. It is advisable to generate accurate epidemiological data to conduct studies characterizing the properties of biomarkers and their potential use in clinical practice under real-life conditions. It is also recommended to conduct studies examining the cost-effectiveness associated with conducting different long-term monitoring strategies in septic shock. It seems that determining a program for the use of biomarkers in monitoring sepsis and the starting mode for selective de-escalation plays crucial significance.

The request for dealing with the research on the combination of measurements using a biomarker of the immune system and biomarker of the cardiovascular system is noteworthy. This idea will undoubtedly require independent analysis due to the methodological requirements and the need for separate apparatus. A significant result of such studies may be the possibility of conducting large studies that could finally allow the determination of positive and negative predictive values, relative risk, and odds ratio. Such studies, however, are only possible on the basis of multicenter cooperation. For now, patient-dedicated therapy with selected medications is necessary. In our opinion, these should be inhibitors of HMGB1 protein, which binds to DNA and is responsible, among others, for the induction of an inflammatory response. Moreover, a diagnostic assessment should be performed to check the concentration and, most importantly, to determine the ratio of apoptotic to active platelets.

Conclusion

Septic shock and subsequent patient death may be related to systemic failures, which are often characterized as maldistribution of microcirculatory flow, triggering an imbalance in oxygen and nutrient supply. Additionally, an increase in permeability, downregulation, or suppression of the cardiovascular system may further decompensate the failing microcirculatory system.

An early prediction of the onset of sepsis triggers a great deal of development of biomarkers to diagnose and monitor critically ill patients. Among them, few emerge with highly predictable values for the outcome in patients having the outcome mortality in the Emergency Department (ED) time window. This review allows readers to understand the systemic failures associated with septic shock and the role of main biomarkers during this critical condition. The significance lies in the indication that the mortality rate after 12-hour admission in the ED is approximately 37%. Mortality is mainly related to the absence of "Guideline-based therapy" and "appropriate antibiotics" prescription, conditioned by the absence of diagnosis or an early-stage full septic shock diagnosis without treatment compliance. SIRS-based guidelines have shown a positivity value of 39% for ED septic shock patients with a 2% false-negative rate. Following the recent definitions, the main causes of mortality are the development of systemic failures; the combination of microcirculatory and cardiovascular failure can deeply affect the outcome. Necessary therapies targeting these combined failures were not well described. Thus, the administration of catecholamines to target possible microvascular failure is a more common and straightforward practice.

Conflict of Interest

No conflicts of interest were declared by the authors.

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Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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