Section: General Medicine

Systemic Review

PREDICTIVE MODEL AND BIOMARKER FOR EARLY IDENTIFICATION AND RISK STRATIFICATION IN SEPSIS PATIENTS – A SYSTEMIC REVIEW

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Abstract

Background: Sepsis is "a life-threatening organ dysfunction caused by a host's dysfunctional response to infection". However, due to a lack of diagnostic methods and the varied and mysterious character of sepsis, early detection and fast therapies have limitations and are not associated with better outcomes. The response to therapy at a very early stage of sepsis in the emergency department (ED) may be determined by monitoring vital signs and routine biomarker levels during resuscitation. Recent developments in molecular methods have given researchers new tools for discovering novel biomarkers, ranging from genes and proteins in circulating blood cells to metabolites and chemical compounds in bodily fluids. No single biomarker is sufficient to identify the nature and prognosis of sepsis. Hence, individualised sepsis treatment should be followed to overcome the deadly consequences of sepsis. In the era of artificial intelligence, it helps to identify the sepsis prognosis and assist in the treatment by cooperatively working with the biomarker's values.

INTRODUCTION

Sepsis is characterised by life-threatening organ dysfunction caused by an unbalanced host response to an infection.[1] A hyper-inflammatory reaction is frequently followed by an immunosuppressive phase, which can lead to secondary infections and numerous organ failures.[2] Sepsis continues to be a leading cause of mortality and morbidity in critically ill patients despite tremendous improvements in knowledge of the pathophysiology of this clinical illness, hemodynamic monitoring technologies, and resuscitation techniques.[3] Sepsis is reported to affect more than 30 million individuals annually, potentially resulting in 6 million fatalities.[4] Over the past few decades, hospital mortality from sepsis has ranged from 25% to 80%.[5,6] Exotoxins and endotoxins, which are produced by pathogens, are recognised by particular receptors on the surface of monocytes and antigen-presenting cells, such as toll-like receptors, which initiate the septic process.[6] Sepsis is initiated by releasing of numerous factors such as interleukins, interferons, platelet-activating factors, arachidonic acid metabolites, etc.[7] The phrase "cytokine storm" was first used in early preclinical investigations to describe the intense systemic production of proinflammatory cytokines such tumor necrosis factor (TNF), IL-1b, IL-12, and IL-18.[8] Clinical symptoms such as fever, tachycardia, tachypnoea, etc. are also present in a septic event, but none are specific enough to identify the event. Even though many cytokines are raised in a septic event, certain specific biomarkers, such as C-reactive protein (CRP) and procalcitonin levels, serve as an important diagnostic tool in identifying the septic event.[9]

Early Identification of Sepsis

According to a proven fact, sepsis has a mortality rate of 40%. The lack of diagnostic tools is one of the biggest obstacles to early intervention in sepsis. In addition, there is no gold standard for diagnosis.[10] However sepsis can be classified by using certain scoring systems. The widely used scoring systems are SIRS (Systemic Inflammatory Response Syndrome), qSOFA (quick Sequential Organ Failure Assessment),[11] MODS (Multi Organ Dysfunction Syndrome) and APACHE (Acute Physiology, Age and Chronic Health Evaluation).[12,13]

SIRS – These findings are sensitive and have inclusion criteria of body temperature >38 °C or <36° C, heart rate >90 per minute, respiratory rate >20 breaths per minute, and White Blood Cell count below 4,000 or above 12,000 cells/mm3.[11] According to these diagnosis criteria, events that can be cured easily and are not associated with septic events will also be considered sepsis.[14] In 2001, it was determined that the SIRS criteria were insufficient to distinguish between systemic

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inflammation brought on by an infection and sepsis. However, the SIRS criteria were kept in place because of their great sensitivity in predicting systemic inflammation.[11]

qSOFA – This system has inclusion criteria of Respiratory rate >22 per minute, Glasgow coma scale score <15, and Hypotension ≤100 mm Hg.[15] A value of ≥2 shows higher chances of mortality and organ dysfunction. It is quick, simple, and affordable, making it a more trusted source for sepsis diagnosis.[16]

MODS – This operates similarly to SIRS, with a minor alteration compared to SIRS: SIRS describes a process, whereas MODS discuss the process's outcome.[12]

APACHE – This system has the following criteria for inclusion: mean arterial blood pressure (MBP), respiratory rate, arterial oxygen pressure (PaO2), oxygen gradient between alveoli and arteries (PA-aO2), and serum creatinine concentration. These characteristics might serve as the primary outcome markers in patients with sepsis. They are useful for standardising research and assessing patient care quality across intensive care units.[13]

Although many techniques are used, traditional vital sign monitoring and sepsis resuscitation based on vital sign reports play a significant role in therapy. Many veteran physicians use this approach to treat sepsis. Various biological and physiological markers can be used for the assessment/diagnosis. Additionally, there is evidence that these elevated vital sign readings return to normal during the sepsis resuscitation procedure. Therefore, it is still a valuable therapy option.[17]

Predictive Models for Sepsis

Sepsis is simple to treat in its early stages but challenging to identify. Later stages of sepsis are easier to identify but far more challenging to cure.[18] The development of Artificial Intelligence in the medical field enhances clinical practice and patient prognosis. It even helps clinically manage sepsis through specialised algorithms that suggest better antibiotic therapy and hemodynamic optimisations.[19] Machine learning is a branch of artificial intelligence that includes three types of learning methods: supervised (which uses labelled data to create a prediction model, such as for prognostication), unsupervised (which identifies patterns in data and creates groups of subjects with similar characteristics), and reinforcement learning (where a sequential decision process is modelled and optimised). The AI functions by creating algorithms from the existing data of sepsis events, so even with limited availability of vital signs, it can identify the future complications of the event and suggest treatment methods accordingly.[20]

The predictive models use specific values for each disease to understand the sepsis prognosis. For example, even though many factors such as fever, elevated alkaline phosphatase, and aspartate transaminase levels were used as standards for identifying liver injury, recent predictive models show increased RDW levels are one the major underlying factors for the development of sepsis-associated liver injury (SALI).[21] Another important example of the implementation of a predictive model is the identification of new-onset atrial fibrillation (NOAF). Among the standard factors to be considered, measuring C-reactive protein level is as a vital validation tool in identifying the disease-worsening condition.[22]

Simultaneously analysing various factors such as procalcitonin levels (PCT) and C-reactive protein levels (CRP) makes is possible to differentiate between infectious and non-infectious diseases in a septic event. Mid-regional proadrenomedullin (MR-proADM), a new blood biomarker, has been demonstrated to be raised in the early stages of the development of infectious diseases. This serves as a hallmark for identifying microcirculatory damage due to the activation of sepsis.[23]

The patient's medical history helps the physicians anticipate the possible sepsis reactions that can happen to the patient. Men can easily be affected by sepsis due to decreased cell-mediated immune responses, and the male hormone androgen restricts cell-mediated immune responses. And sepsis was more prevalent in patients over 80.[24]

Biomarkers For Sepsis

The innate immune system initiates sepsis by releasing numerous endogenous inflammatory cytokines. There are hundreds of biomarkers circulating in the host system. The biomarker helps to identify the particular type of sepsis and also anticipates the future complications of the susceptible individual.[25] One of the traditional biomarkers for sepsis is C-reactive protein (CRP). CRP is a protein produced by the liver and released into the blood plasma. CRP can distinguish between bacterial and viral illnesses. Elevated blood CRP levels upon admission in ICU patients are associated with a higher probability of organ failure and mortality. The next traditional biomarker for sepsis is procalcitonin (PCT). PCT, a 116-amino-acid protein with a molecular weight of 13 kDa, is a precursor of calcitonin. In response to proinflammatory stimuli, PCT levels rise. PCT levels can distinguish between SIRS and sepsis.[26]

The novel biomarkers widely used in the clinical environment are presepsin and CD64. Presepsin is a soluble form of CD14 found on the surfaces of monocytes and macrophages. During sepsis, presepsin is released into the circulation. Under lipopolysaccharide stimulation, it activates Toll-like receptor 4. It involves the phagocytosis and lysosomal cleavage of microorganisms. In experimental conditions, CD64 is a high-affinity immunoglobulin receptor expressed at low levels on resting neutrophils. It increases abruptly in response to lipopolysaccharide or pro-inflammatory cytokines, making it a promising candidate for a sepsis biomarker. Pro-inflammatory cytokines, including IFN-ɣ, TNF-α, and IL-6, are temporally and quantitatively associated with the expression of

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CD64, whereas IL-10 levels are negatively correlated with CD64 expression. There is evidence of a biphasic expression pattern, with a mild spike after two hours and a more severe increase after six hours. Levels have dropped within 48 hours after the provoking stimuli have been removed.[27]

Other notable biomarkers are central venous oxygen saturation (ScvO2) and lactate. Oxygen supply and consumption imbalances have been found using ScvO2. Low oxygen transport to tissues, increased cellular oxygen extraction, or a combination of the two processes are all indicated by low ScvO2. One of the primary resuscitation aims of early goal-directed treatment is the optimisation of ScvO2. Serum lactate levels are biomarkers to identify tissue hypoxia and anaerobic metabolism. Pyruvate stays in the cytoplasm and is converted to lactate without oxygen, which yields a small amount of ATP that cannot meet the body's metabolic demands. If the lactate levels are >2 mmol/L, the patients have a significant chance of mortality/.[28] Of these biomarkers, procalcitonin (PCT) and heparin-binding protein (HBP) are used as successful biomarkers to differentiate bacterial infections from viral infections.[29]

Genomic and Molecular Biomarkers

Since the human genome is made up of sequences and the extent of genetic diversity in the population was recognised, it has been obvious that a person's genetic composition is likely to have an effect on their clinical presentation as well as on how they respond to therapy and how their condition will turn out.[30] According to a study that was conducted by Molecular Diagnosis and Risk Stratification of Sepsis (MARS), it was found that the importance of four endotypes such as Mars1, Mars2, Mars3, and Mars4 plays an important role in a septic event. Mars1 exhibits significant mortality and impairs the function of the innate and adaptive immune systems. The Mars2 and Mars3 endotypes are involved in pro-inflammatory and innate immune signalling. Mars2 and Mars4 may therefore represent different hyperinflammatory endotypes. Most of the roles played by the Mars3 endotype in adaptive immunological or T-cell pathways support the theory that healthy T-cell functioning influences sepsis outcomes.[31]

Given that live microorganisms isolated from blood may be examined to determine their species and susceptibility to antibiotic treatment, blood culture (BC) reflects the current gold standard for detecting bloodstream infection. However, the practical relevance of BC in diagnosing sepsis is diminished by the long processing time. A traditional PCR-based method is unreliable because it cannot detect the vast and constantly changing range of genotypes that encode extended-spectrum beta-lactamases. PCR-based techniques amplify microbial nucleic acids right from circulation A increase in probably true-positive findings in septic patients was seen using PCR using DNA extracted from whole blood. Recent research indicates that metabolite detection by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and transcriptomic profiling by multiplexed quantitative PCR (qPCR) may have potential in the clinical development of diagnostic tests. These tests may overcome the limitations of single molecules to distinguish between infectious and noninfectious causes of systemic inflammation and assist in determining the patient's immune system status.[32]

Infectious illness susceptibility and response are heritable. It has been discovered that the genetic component of infection-related mortality is five times bigger than the genetic factor of cancer. Like linkage analyses, genome-wide association studies (GWAS) do not need a preexisting hypothesis of candidate genes to test for a relationship with illness. Similar to genetic association studies, GWAS compares the allele frequencies of cases and controls. As a result, misleading biological assumptions regarding crucial genes and disease-related pathways are prevented. Functional single nucleotide polymorphisms in the lymphotoxin - α gene are linked to susceptibility and response to myocardial infarction (MI), according to the first reported example of a GWAS in a complicated illness. To ensure that their discovery was biologically plausible, the researchers used in vitro functional analyses to confirm their GWAS results. GWAS has already been used to uncover illness-associated alleles for Crohn's disease, type 1 diabetes, type 2 diabetes, and age-related macular degeneration. It will also be a key tool for determining disease-associated alleles for infectious diseases.[33]

Point-of-Care Testing

Emerging quick diagnostic testing techniques have debuted in clinical microbiology labs, encompassing a wide range of technologies with vastly different levels of complexity, cost, speed, and the capacity to distinguish between one or more infections. When compared to conventional culture methods, technological advancements like matrix-assisted laser desorption ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS) and clinical best practices like active antimicrobial stewardship can result in significant reductions in morbidity, mortality, length of hospitalisation, and costs. Target pathogen DNA sequences can be amplified using pathogen detection techniques based on polymerase chain reaction (PCR). Clinicians benefit from the multiplex PCR assay's capacity to find gene markers for antibiotic resistance, but drawbacks exist. In situ hybridisation-based techniques utilise nucleic acid mimics to identify bacteria in clinical samples rather than traditional DNA or RNA probes. To detect pathogens of interest, a variety of techniques known as "metagenomic shotgun sequencing" sequence nucleic acids from a clinical sample. These assays sequence all the nucleic acids in a specimen using a pathogen-agnostic methodology to identify the causal organism among any background contamination.[34]

Despite recent studies, no gold-standard sepsis biomarker that can be utilised as the sole instrument for precise diagnosis. An ideal sepsis biomarker

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should have traits including the capacity to increase rapidly in response to stimulation and a prolonged elevation to assure discovery and lessen the need for further testing. An analytical test known as a point-of-care (POC) test is crucial in emergency rooms and other settings with limited resources because it gives the user an immediate medical diagnosis. Due to its portability, low blood sample volume requirements, high accuracy, and rapid detection periods, the combination of microfluidics and biosensors has recently attracted interest as an appealing POC testing technology. Popular biocompatible materials used to create microfluidic devices include polymers polydimethylsiloxane (PDMS) and polymethylmethacrylate (PMMA). Multiple clinical sepsis indicators may be found concurrently using microfluidic technology. Unlike conventional laboratory-based testing techniques, microfluidic technology satisfies the WHO "ASSURED" requirements for an optimal POC device. The most effective POC test for sepsis diagnosis may be found by combining microfluidic technology with various materials.[35]

Risk Stratification in Sepsis

When it comes to sepsis, risk stratification and prognostication are especially crucial since high-risk patients may benefit from earlier therapeutic interventions. In contrast low-risk patients may benefit from skipping unneeded operations. According to studies, the length of time after the onset of the illness is crucial for understanding the genetic response at play. Even within the first 24 to 48 hours of sepsis, the host response alters considerably.[36] Presepsin, strongly associated with monocyte-macrophage activity in response to infection, is the most reliable new biomarker. Presepsin levels were low in healthy persons' serum and started to rise in peripheral venous blood within 6 hours of the start of an infection, which was sooner and quicker than PCT and CRP.[37] Foreseeing specific organ dysfunctions is particularly interesting when stratifying patients with sepsis since it may be more therapeutically actionable than merely assigning a patient to a higher-mortality category. For example, anticipating kidney injury might prevent further nephrotoxicity.[36] Physiological-based scoring systems are preferred over diagnosis-based scoring systems as they assess the malfunctioning of organs more precisely.[38] When predicting mortality in general medical or ICU patients, SOFA scores upon admission were performed competitively with (Simplified Acute Physiology Score) SAPS II models. They were only marginally worse than APACHE II/III ratings. Sequential model SOFA scores appear to behave similarly to other organ failure scores. Both the APACHE II/III and SAPS II models performed prognostically better when combined with sequential SOFA derivatives.[39]

Stratified medicine with individualised treatment is the goal of precision medicine, which integrates all biological systems. The future of ICU care will focus on precision medicine, particularly for sepsis management. The fact that patients react to treatments differently should be taken into consideration as a place to start when treating an individual.[40]

Multi-Omnics Approaches

Biomarkers are molecular indicators which are used to identify abnormal process of the human body.[41] The focus of the quest for biomarkers has switched from conventional protein and cytokine markers to systems-based techniques because of the enormous promise of biomarkers for individualized therapy in sepsis.[42] In order to examine genomes and explain physiological or pathophysiological processes, genomics requires enormous data sets that may be collected using recombinant DNA techniques, DNA sequencing, and bioinformatics tools. Sepsis is a polygenic condition started by infection, much like many clinical disorders. Patients' vulnerability to infection and how they react to it are determined by genetic variables.

Proteomics - The collection of all proteins that are produced by an organism is known as the proteome. Analysis of the expression, location, function, and interaction of proteomes is provided by proteomics.

Metabolomics - Molecular weights smaller than 1000 kDa in metabolites in healthy or pathological settings are the focus of the growing omics technique known as metabolomics. This method may be used to examine biochemical occurrences in cells, tissues, or organs and to assess the severity of disorders.[41]

Transcriptomics - The transcriptome is the set of all RNA transcripts (both coding and non-coding) in a cell under a certain situation. The modification in the expression of particular genes can be used as a diagnostic for sepsis since transcription patterns differ in relation to different disorders.[43]

The early stages of sepsis are characterized by both proinflammatory and antiinflammatory responses, despite the fact that sepsis is an inflammatory illness. The immunological features of sepsis were identified using a bioinformatics study of three gene datasets (GSE95233, GSE57065, and GSE28750). Recent studies found that patients Differentially expressed genes (DEGs) were particularly enriched for pathways related to innate immunity, T-cell biology, antigen presentation, and NK cell activity. Most of these genes' real-time PCR expression levels were consistent with the patterns found by microarray analysis.[44]

Clinical Implications and Future Directions

Significant progress has been made in identifying subphenotypes of critical care syndromes, with significant implications for the future of critical care; however, many obstacles must still be removed to translate subphenotypes into clinical practice and fully realise the potential of precision medicine. The discovery of new disease subgroups has grown exponentially in recent years due to advancements in genomes, transcriptomics, proteomics, and metabolomics, as well as the development of data processing tools. Insights into pathophysiology, opportunities to find commonalities between

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syndromes, and the development of useful new treatments could all result from pursuing subphenotypes, which could change the definition of critical illness to one based on biological similarity rather than clinical symptomatology.[45] There is currently no proven treatment for sepsis, despite advancements in patient care with early goal-directed therapy and enhanced support measures. The development of Omics-based technologies and their use in sepsis patients have revealed further unrecognised abnormalities in the genome, metabolome, and proteome that represent the underlying pathophysiology of illness at a molecular level. They are now the subject of investigation. Artificial intelligence is anticipated to play a key role in guiding research in managing sepsis as big data analytics enter the healthcare sector and help organise the vast collections of Omics-produced data. Recently, healthcare practice has focused on using artificial intelligence algorithms as instruments for prognostic and diagnostic enrichment. Investments in processing power and infrastructure are necessary to collect, process, and organise the vast volumes of patient data on the way to sepsis precision medicine.[46]

CONCLUSION

Sepsis is distinguished as a heterogeneous illness by the complex immune-inflammatory response to an infection, whether suspected or proven. Detecting sepsis without a gold standard is challenging and unstable. Even though it is still in the early stages of development, using more modern, precise techniques like immunomodulators offers a potential study area. Simple yet effective clinical techniques for sepsis evaluation and prognostication have been developed using scores like the APACHE-II and sequential organ failure assessment (SOFA). Multigene transcriptomics can increase sepsis's diagnostic and prognostic precision over existing testing methods by assessing the host response to infection. Improved multiplexing capabilities in microfluidic technology make evaluating more biomarkers at once possible. To create better identification methods and to continue research into studies that will enhance the diagnosis of sepsis in Emergency Department patients, clinicians should embrace and adapt to evolving technology.

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