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Unveiling the Significance of Interleukin-6 and Interleukin-10 as Biomarkers for Early Detection and Progression Monitoring of Sepsis.

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Abstract

Sepsis, a life-threatening condition resulting from the body's overwhelming response to infection, poses a significant challenge in healthcare due to its rapid onset and diverse clinical manifestations. Early detection and monitoring of sepsis are critical for timely intervention and improved patient outcomes. Cytokines, small signalling proteins involved in immune responses, play a pivotal role in the complex pathophysiology of sepsis. Cytokines possess a significant trait wherein they exhibit both synergistic and antagonistic actions, rendering them valuable biomarkers. Of these cytokines, interleukin-6 (IL-6) is pivotal in the body's defense against infections and tissue injury, while Interleukin-10 (IL-10) crucially prevents excessive immune cell activation, thereby aiding in immune homeostasis maintenance. Hence these immune molecules, IL-6 and IL-10 have emerged as key biomarkers with the potential to aid in the early identification of infections in sepsis and monitoring its progression. This article reviews the roles and association between pro-inflammatory cytokines like IL-6 and anti-inflammatory cytokines like IL-10 which are crucial for maintaining immune homeostasis and resolving the infection without causing excessive tissue damage. Dysregulation of this balance, as seen in sepsis, can lead to harmful inflammatory responses and organ dysfunction. Monitoring the levels of these cytokines can provide valuable information for diagnosing and managing sepsis. Further, the specific roles of IL-6 and IL-10, shed light on their utility as valuable biomarkers in the clinical landscape of sepsis, aiming to enhance our understanding of their implications for early diagnosis and effective management.

Keywords: Sepsis, Pathophysiology, Organ Dysfunction, Biomarkers, Cytokines, Interleukins (IL-6, IL10), Ageing Population, SOFA, SIRS.

Introduction

The definition of sepsis has undergone a significant evolution over time, reflecting a deeper understanding of its complex pathophysiology. Initially, the 1991 consensus conference established that systemic inflammatory response syndrome (SIRS) in the context of infection would be termed sepsis [1]. This definition was called the 'Sepsis-1'. Subsequent revisions in 2001 included threshold values for organ damage to define sepsis and septic shock and led to the addition of signs and symptoms and challenges in sepsis diagnosis still persisted [2]. A task force consisting of several specialists was established by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine in 2014, resulting in a groundbreaking shift in arly 2016 with the introduction of new definitions aimed at enhancing diagnostic accuracy and clinical relevance [3].

Sepsis is now characterised as a life-threatening organ dysfunction resulting from a dysregulated host response to infection [4, 5]. This innovative definition emphasises the gradual increase in the Sequential Organ Failure Assessment (SOFA) score by two points in response to infection, thereby identifying organ dysfunction. Notably, the SIRS criteria, previously integral to sepsis diagnosis, were eliminated from the updated definitions. The Sepsis-3 Task Force also introduced the quick SOFA (qSOFA) bedside index, designed to identify patients outside critical care units with suspected infection who are at risk of developing sepsis [3, 6].

Recent consensus definitions represent a notable improvement in specificity compared to previous definitions and descriptions, offering a more nuanced framework for identifying and treating sepsis [7]. The emphasis on organ dysfunction as a key criterion increases the clinical relevance of the diagnostic process. Despite

advancements in therapeutic management, the global incidence of sepsis and septic shock has surged since the inception of the first consensus definition (Sepsis-1) in 1991. In 2017, approximately 49 million cases of sepsis and 11 million sepsis-related deaths were reported worldwide, prompting the World Health Organization (WHO) to declare sepsis a global health priority [8]. Several factors contribute to this alarming rise in sepsis incidence. Notably, the ageing population, particularly in Western countries, plays a role. The increased prevalence of invasive medical procedures, widespread use of immunosuppressive drugs and chemotherapy, and the growing challenge of antibiotic resistance also contribute to the escalating sepsis burden.

Despite advancements, septic patients continue to face a substantial risk of in-hospital mortality, accounting for approximately 20% of deaths globally. This underscores the critical importance of addressing sepsis as a high-mortality condition faced in emergency departments worldwide [5, 8]. As research continues to unravel the intricacies of sepsis, ongoing efforts are crucial to refining diagnostic criteria, optimising treatment strategies, and ultimately improving outcomes for individuals affected by this life-threatening condition [9].

This review aims to explore the current state of knowledge surrounding sepsis, delving into its multifaceted aspects. Particularly focusing on the crucial role that interleukins, commonly referred to as cytokines, play as potential biomarkers in the early detection, diagnosis, and monitoring of sepsis progression. The exploration of interleukins as biomarkers not only contributes to a deeper understanding of sepsis pathophysiology but also holds promise for improving clinical strategies that are aimed at reducing the impact of this life-threatening condition.

Stages of Sepsis, Symptoms and Impact on the Quality of life

According to these articles' sepsis can be classified into 3 stages with distinct characteristic features and stage-specific symptoms [10], the risk of progression and the clinical course of sepsis is extensively studied to improve treatment strategies and care [10, 11].

Stage 1: Sepsis

Early sepsis is challenging to identify but may include fever, rapid heartbeat, and breathing changes. A confirmed infection and at least two symptoms are needed for diagnosis. Swift treatment, often with antibiotics, can lead to full recovery.

Stage 2: Severe Sepsis

Severe sepsis involves life-threatening organ dysfunction, marked by symptoms like abnormal heartbeat, decreased urine output, and changes in mental state. Any infection can lead to severe sepsis, with early detection crucial for effective intervention.

Stage Three: Septic Shock

In septic shock, low blood pressure persists despite medical intervention, accompanied by elevated lactate levels. This represents the most dangerous phase, requiring urgent and intensive medical care.

Post-Sepsis Syndrome and Impact on Quality of Life

Sepsis can lead to lingering consequences in the form of post-sepsis syndrome, especially for patients confined to a hospital for an extended period or those who spend time in an intensive care unit (ICU). Post-sepsis syndrome encompasses a collection of symptoms with varying severity and personal and economic consequences. Physical consequences include sleep disturbances, debilitating fatigue, rash, hair loss, painful joints, lack of appetite, shortness of breath, renal failure, cardiovascular events, and swelling of the legs and arms. Survivors of sepsis are likely to experience cognitive impairment, functional disabilities, and psychological impairments, including panic attacks, flashbacks, nightmares, and depression. Ultimately, post-septic syndrome may lead to rehospitalization and a reduced quality of life.

Sepsis is a heterogeneous condition, and individual patient responses can vary. To identify biomarkers this article evaluates the role of cytokines, as biomarkers. Among the cytokines IL-6 and IL-10 are often considered in conjunction with other biomarkers to enhance diagnostic and prognostic accuracy.

What are Cytokines?

Cytokines are small proteins released by cells, crucial for cell-cell interaction. They go by various names based on origin, like Lymphokines, Monokines, Chemokines, and Interleukins. Pleiotropy describes a cytokine affecting different cell types. They exhibit redundancy, with similar functions triggered by different cytokines. Classified by function, cytokines have autocrine, paracrine, and endocrine actions. Cytokine signalling follows a cascade of events, triggering the secretion of multiple cytokines, and importantly cytokines can act synergistically or antagonistically, as shown in figure-1 below and this function is useful for identifying them as Biomarkers in sepsis [12].

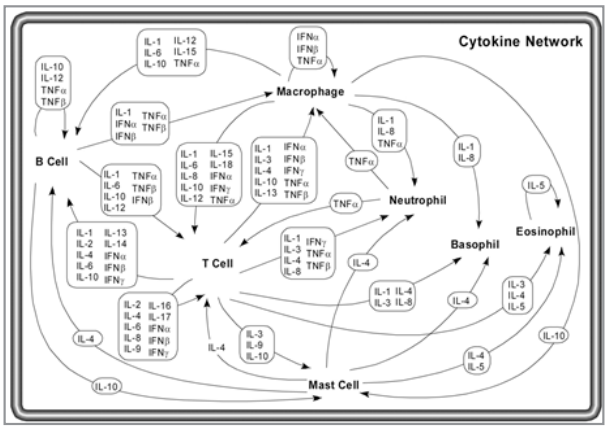

Figure-1: Source:- Zhang Jun-Ming, and Jianxiong An (2007) Cytokines, inflammation, and pain. International anesthesiology clinics 45: 27-37. Image - Cytokine network

This figure-1 shows the cytokine network and the coordinated efforts of different immune cells. Each of these immune cells have different functions and the communication between all of them, to form a robust immune response is facilitated by an array of cytokines and their network.

Interleukins - What are they and Why are they Important?

Interleukins represent a pivotal family of signalling proteins that orchestrate communication within the intricate network of the immune system. These small proteins, also known as cytokines, are produced by various cells, predominantly those of the immune system, and serve as messengers that convey crucial instructions to regulate immune responses and inflammation. Interleukins play a fundamental role in coordinating the body's defence mechanisms against infections, tumours, and other challenges.

The term "interleukin" reflects the initial understanding that these signalling molecules primarily acted between leukocytes (white blood cells). However, it is now recognized that interleukins exert their influence on a broader range of cells, including non-immune cells, contributing to the dynamic interplay of the immune response. Interleukins are named in the chronological order of their discovery rather than any functional or structural features [11]. They are named in the abbreviated form 'IL' followed by the number as per discovery, that is, IL1, IL2, IL3 and so on. There are about 40 known interleukins as per existing knowledge as presented in this article, and each differs in their cell origin and has distinct functions in the immune regulation. Interleukins along with the coordinated effort of other factors play a pivotal role in the pro and anti-inflammatory responses [13, 14]. They are actively being explored for a spectrum of conditions, including infectious diseases, autoimmune disorders, and cancer. The study of interleukins continues to uncover the complexities of immune regulation, offering valuable insights into the mechanisms underlying health and disease. There is an increasing potential for targeted interventions that can regulate immune responses, leading to improved patient outcomes [15].

Cytokines in the Pathophysiology of Sepsis

Sepsis, unlike uncomplicated and localized infections, manifests as an intricate disturbance in the finely tuned immunological balance between inflammation and anti-inflammation. The imbalance in pro- and anti-inflammatory pathways induces a widespread release of cytokines, mediators, and pathogen-related molecules leading to the subsequent activation of coagulation and complement cascades. The onset of sepsis is characterized by the identification of pathogen-derived molecular patterns (PAMPs) like endo- and exotoxins, lipids, or DNA sequences, as well as endogenous host-derived danger signals known as damage-associated molecular patterns (DAMPs). These molecules act as initiating signals, triggering the activation of specific receptors, including toll-like receptors (TLRs) located on the surface of antigen-presenting cells (APCs) and monocytes. This activation initiates the clinical syndrome of sepsis by inducing the transcription of genes involved in inflammation, cell metabolism, and adaptive immunity [16].

While the activation triggers upregulation of both pro-inflammatory and anti-inflammatory pathways, the resulting inflammation plays a crucial role in causing progressive tissue damage, ultimately leading to multi-organ dysfunction. Many patients experience concurrent immunosuppression, marked by the downregulation of activating cell surface molecules heightened apoptosis of immune cells, and T cell exhaustion. This state, known as 'immuno-paralysis,' observed in the later stages of the disease renders affected patients susceptible to nosocomial infections, opportunistic pathogens, and viral reactivation [17, 18].

Table 1: showing a clear breakdown of the events and their descriptions in a concise manner.

Event	Description
Binding of PAMPs and DAMPs to TLRs	This initiates signal transduction on APCs and monocytes.
Signal Transduction	Results in the translocation of NF-κB into the cell nucleus.
Expression of Early Activation Genes	Including proinflammatory interleukins (IL-1, IL-12, IL-18), tumor necrosis factor-alpha (TNF-α), and interferons (IFNs).
Induction of Additional Cytokines	Such as IFN-γ, IL-6, IL-8, and activation of complement and coagulation pathways.
Downregulation of Adaptive Immune System	Through negative feedback mechanisms.
Outcome during Early Sepsis	Marked by an increase in both pro-inflammatory and anti-inflammatory cytokines.
Individualized Immunological Phenotype	Resulting in hypo- or hyper-responsiveness, posing diagnostic challenges.

The intricate interplay of inflammatory and anti-inflammatory responses during the course of sepsis and septic shock is depicted in Figure 2.

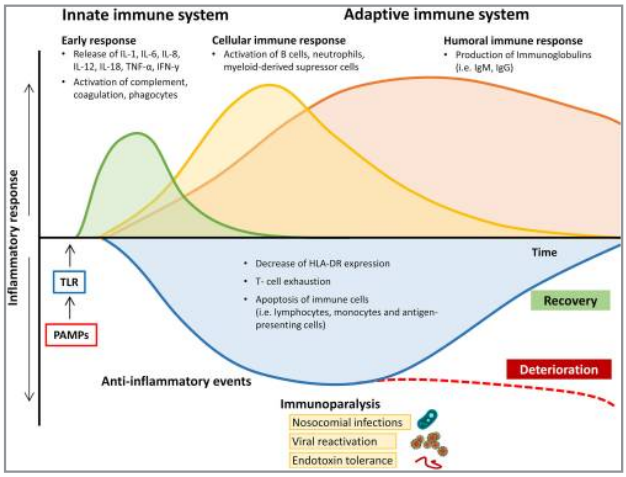

Figure 2: Source:- Dominik Jarczak, Stefan Kluge, Axel Nierhaus (2021) Sepsis-Pathophysiology and Therapeutic Concepts. Frontiers in medicine 8: 628302.

The dynamic changes in human leukocyte antigen-D related (HLA-DR), immunoglobulin M/G (IgM/G), IL, IFN-γ, PAMPs, TNF-α, and TLRs illustrate the complexity of the immune system's reactions during sepsis progression. Understanding these molecular and cellular events is crucial for developing targeted therapeutic strategies and advancing our knowledge of sepsis pathophysiology.

Complications and Factors Associated with Sepsis

In cases of sepsis triggered by an invasive pathogen, the underlying mechanism involves intricate inter- and intracellular signalling through cell-surface receptors. This initiates complex signal transduction mechanisms common to various types of sepsis. The septic activation of the autonomic nervous system places an immense burden on the heart, inducing a state of global cardiac hypokinesis, hypotension, and hypoperfusion. This heightened cardiac strain worsens ischemia due to excessive coagulation within the organs, further contributing to tissue pathology. Ultimately, these converging mechanisms lead to a hypotensive, electrolyte-imbalance patient, experiencing organ failure at varying rates due to ischemic injury, hypoxemia, and pro-inflammatory tissue damage [19, 20]. The inflammatory stage of sepsis can persist for varying durations, these infections are often attributed to commensal flora or opportunistic bacteria that would not normally colonise a healthy individual [20].

A significant concern during late-stage sepsis is the reactivation of latent viruses, which can lead to increased morbidity and mortality, [21, 22].

Role of Interleukins in Sepsis

Interleukins play a critical role in the pathophysiology of sepsis, a condition characterised by a dysregulated host response to infection, often leading to systemic inflammation and multiple organ dysfunction. During sepsis, the immune system is activated to combat the invading pathogens. Interleukins, which are a group of signalling proteins that facilitate communication between immune cells, are released in response to infection.

(i) Pro inflammatory cytokines

These are commonly produced by functionally active macrophages and are involved in the up-regulation and expression of the inflammatory responses [23, 24]. This class of cytokines are also the effectors of autoimmune response [25]. They play a key role in the body's defence against infections and tissue injury. They stimulate immune cells to move towards the site of infection or injury and enhance the immune response.

Table 2: Summarises the role of Interleukins in sepsis

Cytokines/Mediators	Functions	Examples
Interleukin-1α (IL-1α)	Initiating and amplifying immune response	Attract inflammatory cells
IL-1β	Promoting inflammation to combat pathogens	Promote immune cell activation
IL-6	Regulating overall inflammatory milieu	Regulate inflammatory response
Tumour Necrosis Factor-α (TNF-α)	Attract inflammatory cells	Promote immune cell activation
IL-20 family	Contribution to pro-inflammatory network	Amplify immune response
Leukaemia Inhibitory Factor (LIF)	Modulate immune response	Induce cytokine production
Interferon-gamma (IFN-γ)	Enhance immune response	Stimulate immune cell activity
Oncostatin M (OSM)	Regulate inflammatory milieu	Promote immune cell migration
Ciliary Neurotrophic Factor (CNTF)	Promote cell survival	Regulate inflammatory response
Transforming Growth Factor-β (TGF-β)	Modulate immune response	Suppress immune activity
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Stimulate immune cell production	Promote immune cell proliferation

IL-8	Attract neutrophils to site of inflammation	Enhance inflammatory response
IL-11	Modulate immune response	Induce acute phase protein production
IL-12	Promote differentiation of T cells	Enhance immune response
IL-17	Induce cytokine production	Promote tissue inflammation
IL-18	Enhance IFN-γ production	Modulate immune response
IL-33	Amplify Th2 response	Regulate immune cell function
Chemokines	Attract immune cells to site of inflammation	Regulate leukocyte trafficking

This multifaceted involvement emphasises the potential significance of IL-6 in the context of sepsis. Numerous studies have documented elevated IL-6 production in sepsis patients, strongly indicating its association with the development of this critical condition. Specifically, research has shown that IL-6 levels are heightened in patients with sepsis, with even more pronounced increases in those experiencing shock or severe sepsis. Notably, patients who were under severe sepsis exhibited higher IL-6 levels, reinforcing the hypothesis that IL-6 is a key cytokine in the pathophysiology of severe sepsis. Furthermore, an increased IL-6 level was correlated with the highest risk of mortality in sepsis patients, highlighting its potential as a prognostic indicator. Among the diverse array of cytokines induced during sepsis, plasma IL-6 demonstrates the most robust correlation with the severity of sepsis and mortality rate [26].

(ii) Anti-inflammatory cytokines

These are described as a series of immunoregulatory molecules that control the activity of pro-inflammatory cytokine response, to prevent hyper-inflammation and its side effects by initiating counter responses.

Major anti-inflammatory cytokines include some interleukins (IL-1 receptor antagonist, IL-4, IL-6, IL-10, IL-11, and IL-13), leukaemia inhibitory factor, interferon-alpha, and transforming growth factor beta (TGF-beta).

IL 10 is primarily produced by key immune cells like CD4+ Th2 cells, monocytes, and B-cells, acting as a regulatory force to maintain immune balance. When our immune system is in combat mode, releasing various signalling molecules or cytokines, IL-10 steps in to exert its inhibitory influence. Specifically, it has a powerful ability to suppress the expression of Th1 cytokines, such as IL-2 and IFN-γ. The action of IL-10 doesn't halt at Th1 cytokines—it extends to a broader spectrum of pro-inflammatory signals. Upon binding to its high-affinity IL-10 receptor, IL-10 effectively dampens the production of TNF-α, IL-1, IL-6, IL-8, IL-12, GM-CSF, MIP-1α, and MIP-2α. Importantly, this inhibition occurs in various immune cells, including monocytes, macrophages, neutrophils, and natural killer (NK) cells [27]. In the context of sepsis, IL-10 emerges as a critical player in the pathophysiology of this condition. Studies have reported that IL-10 levels are significantly elevated in patients with severe sepsis, with a positive correlation observed between IL-10 levels and sepsis severity as well as mortality rates. The measurement of serum cytokines has provided valuable insights, indicating that an increased IL-10-to-TNF-α ratio is associated with a higher risk of death in sepsis patients. Persistent overproduction of IL-10 is identified as a key risk factor for the severity and fatal outcome of sepsis, suggesting a state of profound immunosuppression in these patients [28].

Therefore, pro-inflammatory cytokines initiate and amplify the immune response during infections or tissue damage, while anti-inflammatory cytokines regulate and resolve this response, preventing excessive inflammation and promoting healing. The balance between these two types of cytokines is crucial for maintaining a properly functioning immune system and preventing chronic inflammatory conditions.

In a normally functioning host, inducible IL-6 serves a distinctive role during acute responses: it acts to curtail the levels of proinflammatory cytokines while safeguarding the levels of anti-inflammatory cytokines. Furthermore, IL-6 plays a proactive role in stimulating the production of IL-1 receptor antagonist, an anti-inflammatory mediator. This dual action highlights that IL-6 can exert a protective effect, contributing to the delicate balance required for an effective and controlled immune response.

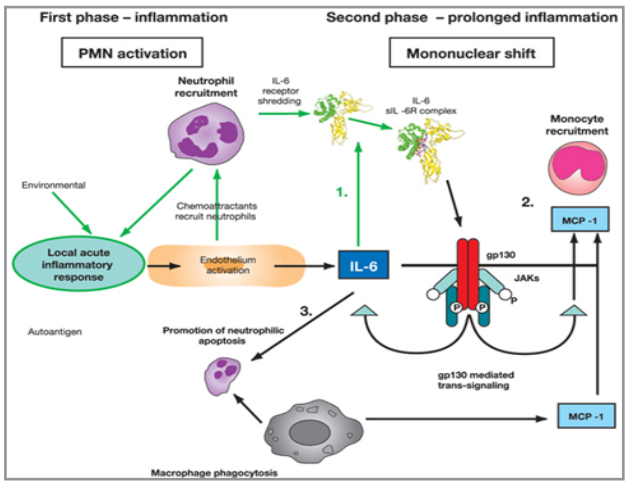

Figure 3: Source:- Cem Gabay (2006) Interleukin-6 and chronic inflammation. Arthritis research & therapy 8: S3.

After an acute inflammatory response, IL-6 binds to sIL-6R in Stage 1. In Stage 2, trans-signalling via gp130 induces monocyte recruitment, facilitated by JAK and MCP. Stage 3 involves prolonged IL-6 triggers neutrophil apoptosis, promoting phagocytosis, and resulting in mononuclear accumulation at the injury site. The overall process contributes to the transition from acute to chronic inflammation.

Disruptions in leukocyte trafficking control, such as continuous IL-6 production may hold significance at the onset of chronic disease. Notably, IL-6 profoundly influences the nature of the immune response by dictating the recruitment, activation, and apoptotic clearance of distinct leukocyte subpopulations, including neutrophils, monocytes, and lymphocytes.

The reduction in neutrophil presence at the inflamed site is not just attributable to their exit but is also linked to a programmed cell death process - apoptotic elimination which is crucial for inflammation resolution. This mechanism is often accompanied by anti-inflammatory signals, with IL-6 being a notable mediator. Furthermore, the transition from a neutrophil-dominated environment to an accumulation of monocytes is a precisely orchestrated process to strike a delicate balance between proinflammatory and anti-inflammatory elements within the immune response, to bring in resolution of inflammation and facilitate tissue repair [29].

Inflammatory Response Initiation by IL-10

Interleukin-10 (IL-10) is a multifaceted cytokine with diverse phenotypic effects. Initially identified as a product of T helper 2 cells with the ability to inhibit T helper 1 cell activation, it is now recognized to be produced by a wide range of activated immune cells. These include B cells, mast cells, granulocytes (such as neutrophils, basophils, and eosinophils), macrophages, dendritic cells, and various T cell subsets. IL-10's primary actions are generally characterised as anti-inflammatory, inhibitory, or self-regulating. It acts as a negative feedback regulator, by exerting control and contributing to the resolution of inflammation through autocrine and paracrine mechanisms. The immunosuppressive effects of IL-10 are extensive and operate at both cellular and humoral levels.

IL-6 and IL-10 as Biomarkers in Sepsis and other Diseases

The evaluation of cytokines IL-6, IL-10, and IL-8, along with their heightened concentrations, unveils crucial insights into immune status and the activation of the immune system, in a study on breast cancer. These cytokines emerge as noteworthy biomarkers for forecasting and tracking the progression of breast cancer, thereby aiding in its effective management. The findings also suggested that these cytokine levels also hold the potential to identify the specific stage of breast cancer [30]. A case-control study exploring the -1082(A/G) polymorphism within the promoter region of the IL-10 confirms a distinct correlation between sepsis susceptibility and the mentioned polymorphism. Specifically, the A allele of the -1082 polymorphism was implicated in heightened sepsis susceptibility, while the G allele was linked to an increased production of interleukin 10 and a higher mortality rate in severe sepsis cases [31]. Further, age-related mortality and hypothermia were associated with the induction of IL-6 and IL10 contributing to the increased susceptibility to physiological stressors such as infection and sepsis [32].

In severe sepsis and sepsis shock the role of the IL6-174 G/C promoter genotypes in patients observed IL6 serum concentrations were highest in patients with the GG genotype, followed by CG and lowest in CC genotype individuals [33, 34]. Research highlights the crucial role of timely and consistent anti-inflammatory reactions, characterised by an elevated IL-10 versus TNF-α. ratio, in signalling severe illness and unfavourable outcomes among individuals experiencing severe sepsis. When evaluating serum levels of IL-10 and the IL-10 versus TNF-α ratio in conjunction with established sepsis scoring systems, these parameters prove to be valuable indicators for closely monitoring patients and discerning those with a potentially challenging prognosis [24].

Conclusion

IL-6 plays a pivotal role in sepsis by mediating the immune response as soon as infection occurs, influencing both the initiation and resolution of inflammation. The delicate balance between the interleukins proinflammatory (IL-6) and anti-inflammatory (IL-10) effects is crucial, and dysregulation contributes to sepsis pathogenesis. As sepsis advances, IL-6 facilitates a shift towards an anti-inflammatory state, modulating the immune response by inhibiting proinflammatory cytokines and promoting anti-inflammatory cytokines like IL-10. Elevated IL-6 levels in sepsis patients serve as a biomarker for severity. Meanwhile, IL-10's role is context-dependent; in the early hyperinflammatory phase, it helps control inflammation, but prolonged production can lead to immunosuppression, increasing susceptibility to secondary infections. IL-10's nuanced role necessitates careful consideration in therapeutic strategies, factoring in the sepsis stage and individual patient characteristics for a balanced outcome. Thus, both IL-6 and IL-10 serve as valuable predictive biomarkers for assessing sepsis progression.

Declarations

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