"A STUDY TO CORRELATE SERUM LACTATE ALBUMIN RATIO TO RAAS SCORING SYSTEM IN SEPSIS IN MICU AT A TERTIARY CARE HOSPITAL-A PROSPECTIVE CROSS SECTIONAL STUDY"

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With reference to the above, we wish to inform you that your proposed research project titled **"A STUDY TO CORRELATE SERUM LACTATE ALBUMIN RATIO TO RAAS SCORING SYSTEM IN SEPSIS IN MICU",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

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LIST OF ABBREVIATIONS

APACHE II - Acute Physiology and Chronic Health Evaluation II

ARDS - Acute Respiratory Distress Syndrome

AKI - Acute Kidney Injury

ALT - Alanine Aminotransferase

AST - Aspartate Aminotransferase

AUC - Area Under Curve

AUROC - Area Under Receiver Operating Characteristic

BUN - Blood Urea Nitrogen

CBC - Complete Blood Count

CI - Confidence Interval

CKD - Chronic Kidney Disease

CRP - C-Reactive Protein

DIC - Disseminated Intravascular Coagulation

DM - Diabetes Mellitus

ESRD - End-Stage Renal Disease

GCS - Glasgow Coma Scale

GFR - Glomerular Filtration Rate

hsCRP - High-Sensitivity C-Reactive Protein

HTN - Hypertension

ICU - Intensive Care Unit

IL - Interleukin

INR - International Normalized Ratio

LA ratio - Lactate to Albumin Ratio

LAR - Lactate-Albumin Ratio

MAP - Mean Arterial Pressure

MEDS - Mortality in Emergency Department Sepsis

MICU - Medical Intensive Care Unit

MODS - Multiple Organ Dysfunction Syndrome

NPV - Negative Predictive Value

OR - Odds Ratio

PaO2/FiO2 - Ratio of Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen

PCT - Procalcitonin

PPV - Positive Predictive Value

PT - Prothrombin Time

PTT - Partial Thromboplastin Time

RAAS - RDW, AGE, APACHE 2, SOFA

RDW - Red Cell Distribution Width

ROC - Receiver Operating Characteristic

RR - Respiratory Rate

SBP - Systolic Blood Pressure

SIRS - Systemic Inflammatory Response Syndrome

SOFA - Sequential Organ Failure Assessment

TNF - Tumor Necrosis Factor

UTI - Urinary Tract Infection

WBC - White Blood Cell

ABSTRACT

Introduction: Sepsis remains a significant global health concern with high morbidity and mortality rates despite advances in critical care medicine. Early identification and risk stratification are crucial for timely interventions. This study aimed to evaluate the correlation between serum lactate-albumin ratio (LAR) and the RAAS (Rapid Alarm Asepsis Score) scoring system, along with other established prognostic markers, in sepsis patients admitted to the Medical Intensive Care Unit (MICU) at a tertiary care hospital.

Methodology: A prospective cross-sectional study was conducted involving 75 patients diagnosed with sepsis according to the Sepsis-3 criteria and admitted to the MICU. Demographic details, clinical characteristics, and laboratory parameters including serum lactate, albumin, procalcitonin (PCT), high-sensitivity C-reactive protein (hsCRP), and red cell distribution width (RDW) were recorded. Established scoring systems including APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment) were calculated. RAAS scores were determined and patients were categorized into four groups. Correlations between LAR, RAAS scores, and other prognostic markers were analyzed.

Results: The study population predominantly comprised elderly patients (46.7% above 60 years) with male preponderance (64%). Most patients had elevated PCT (70.7% with 2-10 ng/mL) and hsCRP (90.7% with >3 mg/L). LAR was elevated (>1.33) in 21.3% of patients. APACHE II scores indicated moderate risk (11-20) in 48% of patients. RAAS categorization showed predominance of Group 3 (60%). RAAS scores demonstrated significant positive correlations with APACHE II ($r=0.533$, $p<0.001$), SOFA ($r=0.268$, $p=0.020$), RDW ($r=0.506$, $p<0.001$), and PCT

levels (p=0.0167). LAR showed a positive but non-significant correlation with RAAS scores (r=0.161, p=0.168). Mean RDW values and APACHE II scores increased significantly across RAAS categories (p<0.001 and p=0.002, respectively).

Conclusion: This study validates the RAAS scoring system as a comprehensive prognostic tool in sepsis, demonstrating significant correlations with established severity markers. While the correlation between LAR and RAAS scores was not statistically significant, the trend toward higher LAR values in higher RAAS categories suggests potential clinical relevance. The integration of multiple biomarkers including LAR and RDW with established scoring systems could enhance risk stratification and guide clinical decision-making in sepsis management. Future larger studies are warranted to further validate these findings.

Keywords: Sepsis, Lactate-albumin ratio, RAAS scoring system, APACHE II, SOFA, Procalcitonin, Red cell distribution width, Risk stratification, Biomarkers, Critical care

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INTRODUCTION

Sepsis remains one of the leading causes of mortality in intensive care units worldwide, representing a complex pathophysiological response to infection that can lead to life-threatening organ dysfunction.[1] Despite significant advances in critical care medicine, the early recognition and accurate prognostication of sepsis continue to present substantial challenges to healthcare providers. The disparity between high-income countries (HICs) and low- and middle-income countries (LMICs) is evident, with LMICs shouldering a significantly greater burden due to limited resources, weaker healthcare systems, and higher disease prevalence.[2]

Sepsis accounts to around 11 million estimated no. of sepsis-related deaths and 19·7% of total deaths globally in 2017. 54% of cases are secondary to infections and 41% secondary to non-communicable diseases. However, there is a decrease in estimated deaths from 1990 to 2017.[3]

Currently, the total burden estimates to 47 000 000 - 50 000 000 Cases per Year. At Least 11 000 000 Die – 1 Death Every 2.8 Seconds. 1 in Every 5 Deaths Worldwide Is Associated With Sepsis. Up to 50%of sepsis survivors suffer from long-term physical and/or psychological effects like post sepsis syndrome. In order to spread awareness on this, the WHO has taken the initiative of considering September 13th of every year as world sepsis day.

The need for reliable, cost-effective, and readily available biomarkers and scoring systems has never been more crucial in guiding therapeutic interventions and improving patient outcomes.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[4] This definition emphasizes the significance of organ dysfunction and highlights the importance of early recognition and intervention. In the medical intensive care unit (MICU) setting, the ability to quickly and accurately assess disease severity and predict outcomes becomes paramount for optimal patient management.

Serum lactate has long been recognized as a crucial biomarker in sepsis, reflecting tissue hypoperfusion and cellular metabolic dysfunction. Elevated lactate levels are associated with increased mortality in critically ill patients, and lactate clearance has been shown to correlate with improved outcomes.[5] The prognostic value of lactate measurement in sepsis has led to its inclusion in various clinical protocols and guidelines for sepsis management, including the Surviving Sepsis Campaign recommendations.

Serum albumin, another significant biomarker, plays multiple vital roles in maintaining physiological homeostasis, including oncotic pressure regulation, anti-oxidant functions, and drug binding. During sepsis, albumin levels often decrease due to increased vascular permeability, reduced synthesis, and increased catabolism.[6] Low albumin levels have been independently associated with poor outcomes in critically ill patients, making it a valuable prognostic indicator.

The combination of these two parameters in the form of the lactate/albumin ratio (LAR) has emerged as a promising prognostic tool in critical care. This ratio potentially offers several advantages over individual parameters, as it combines markers of both tissue perfusion and inflammatory response.[7] Recent studies have

suggested that LAR may provide better prognostic accuracy than either parameter alone in predicting mortality in critically ill patients with sepsis.

The Rapid Acute Assessment Score (RAAS) is a comprehensive scoring system that incorporates three critical components: Red cell Distribution Width (RDW), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) score. Each of these components provides valuable and complementary information for sepsis prognostication.

Red cell Distribution Width (RDW) is a measure of the variability in red blood cell size, which has emerged as a significant prognostic marker in critical illness. Elevated RDW has been associated with increased mortality in sepsis, potentially reflecting underlying inflammatory processes, oxidative stress, and impaired erythropoiesis. Its inclusion in the RAAS enhances the system's ability to capture subtle hematological derangements that may precede overt clinical deterioration.

The APACHE II score is one of the most widely validated and utilized severity-of-illness scoring systems in intensive care. It incorporates twelve physiological measurements, age, and previous health status to provide a comprehensive assessment of disease severity and mortality risk.Within the RAAS framework, APACHE II contributes a robust evaluation of the patient's overall physiological derangement and comorbidity burden.

The SOFA score focuses specifically on organ dysfunction, evaluating six organ systems (respiratory, cardiovascular, hepatic, coagulation, renal, and neurological) on a scale of 0 to 4. As organ dysfunction is central to the definition and pathophysiology of sepsis, the SOFA score's inclusion in RAAS ensures direct assessment of this

critical aspect of sepsis. Sequential SOFA measurements can track disease progression and response to therapy.

The integration of these three components into the RAAS creates a multidimensional evaluation tool that captures different but complementary aspects of sepsis pathophysiology: inflammatory response (RDW), overall disease severity (APACHE II), and specific organ dysfunction (SOFA).This comprehensive approach potentially provides more accurate prognostication than any single component alone.

Understanding the relationship between LAR and RAAS scoring could potentially provide valuable insights into sepsis prognostication. Both tools offer distinct advantages: LAR represents specific pathophysiological derangements through objective laboratory measurements, while RAAS provides a broader assessment of clinical status through readily available physiological parameters.[8] The correlation between these two approaches could help validate their complementary use in clinical practice.

In the context of a tertiary care hospital, where resources for advanced monitoring and laboratory testing are available, the ability to combine and correlate different prognostic tools becomes particularly relevant. Such facilities often manage complex cases of sepsis with multiple organ involvement, requiring sophisticated prognostication for optimal resource allocation and treatment planning.[9] The integration of biochemical markers with clinical scoring systems could potentially enhance the accuracy of outcome prediction and guide more targeted therapeutic interventions.

The timing of prognostic assessment in sepsis is crucial, as early recognition and intervention significantly impact outcomes. Both LAR and RAAS can be calculated relatively early in the course of illness, potentially providing valuable prognostic information when therapeutic interventions are most likely to be effective.[10] However, the dynamic nature of sepsis necessitates ongoing reassessment, and understanding how these parameters change over time may provide additional prognostic value.

AIMS AND OBJECTIVES

Objective:

1. To establish a correlation between serum lactate albumin ratio and RAAS scoring system at different points after admission in the MICU at a tertiary care hospital.

REVIEW OF LITERATURE

HISTORICAL PREVIEW OF SEPSIS

Humanity has fallen victim to countless infectious diseases throughout history, which have caused significant historical shifts. One such example is "The Black Death," which occurred in the late mediaeval era and caused significant social and demographic shifts that preceded the Renaissance.[11]

The word "sepsis," which comes from the Greek word for "decomposition" or "decay," was first used in Homer's poetry approximately 2700 years ago. Later years saw its application in the writings of Galen and Hippocrates. [12] The "Germ theory" of disease was developed in the 1800s, and it was somewhat acknowledged that dangerous microbes were the cause of sepsis. "Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms," according to Hugo Schottmüller's 1914 attempt at the first modern definition.[13] Numerous clinical and experimental studies conducted throughout the 20th century were able to show how crucial the host immune response is to sepsis symptoms.[14]

“We now have a better understanding of sepsis and septic shock thanks to developments in medical science in the late 20th century.” These developments include the identification of inflammatory mediators that stimulate the production of nitric oxide, which causes endothelial damage, activates the coagulation cascade, and ultimately results in organ ischaemia, damage, and death. In the years to come, this understanding will result in innovative methods of treating sepsis.[14]

Definition of Sepsis

Clinicians have tried to diagnose sepsis by combining non-specific physiological and laboratory abnormalities because there is no universally accepted diagnosis of the condition. As a result, international conferences in 1991, 2001, and 2016 all offered definitions of sepsis (Table 1). Guidelines facilitate the effective use of information provided by businesses and guard against disparate user groups' implementations. [15]

A dysregulated host response to infection results in sepsis, a potentially fatal organ failure. Septic shock is a subtype of sepsis where the risk of death is higher due to underlying circulatory, cellular, and metabolic problems than from infection alone. [16] "Because of their rising prevalence and significant pathophysiology, molecular, genetic, and clinical complexity, sepsis and septic shock pose a significant and expanding global burden as well as a challenge for emergency physicians."[16-18]

Table 1: Definitions of Sepsis

Sepsis 1(1991)[19]	Sepsis 2(2001)[20]	Sepsis 3(2016)[16]
Systemic inflammatory response syndrome (SIRS): systemic inflammatory response to a variety of severe clinical insults: Temperature >38°C or <36°C; heart rate > 90 beats per min; respiratory rate > 20 breaths per min or PaCO2 < 32 mmHg; and white blood cell count > 12,000/cu mm, <4000/cu mm, or >10% immature (band) forms Sepsis is a systemic response to infection, manifested by two or	Infection: Documented or suspected and some of the following: General parameters: Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C); heart rate > 90 beats per min or > 2 SD above the normal value for age; tachypnea: respiratory rate > 30 breaths per min; altered mental status; significant edema or positive fluid balance (>20 mL kg−1 over 24 h) Hyperglycemia (plasma glucose > 110 mg dL−1 or	Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. Clinical criteria for sepsis: Suspected or documented infection and an acute increase of ⩾2 SOFA points (Table2) The task force considered that positive qSOFA (quick SOFA) criteria should also

more of the SIRS criteria as a result of infection. Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension; hypoperfusion and perfusion abnormalities may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status Septic shock: Sepsis-induced, with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but not limited to, lactic acidosis, oliguria, or an acute alteration in mental status; patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.	7.7 mM L−1) in the absence of diabetes Inflammatory parameters: Leukocytosis (white blood cell count > 12,000/μL); leukopenia (white blood cell count < 4000/μL); normal white blood cell count with > 10% immature forms; plasma C-reactive protein > 2 SD above the normal value; and plasma procalcitonin > 2 SD above the normal value Hemodynamic parameters: Arterial hypotension (systolic blood pressure < 90 mmHg, MAP < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg in adults or < 2 SD below normal for age, mixed venous oxygen saturation > 70%, cardiac index > 3.5 L min−1 m−2) Organ dysfunction parameters: Arterial hypoxemia "(PaO2/FIO2 < 300); acute oliguria (urine output < 0.5 mL kg−1 h−1 or 45 mM L−1 for at least 2 h); creatinine increase ⩾ 0.5 mg dL−1; coagulation abnormalities (international normalized ratio > 1.5 or activated partial thromboplastin time > 60 s); ileus (absent bowel sounds); thrombocytopenia (platelet count < 100,000 μL−1) Hyperbilirubinemia (plasma total bilirubin > 4 mg dL−1 or 70 mmol L−1) Tissue perfusion parameters: Hyperlactatemia (>3 mmol L−1); decreased capillary refill or mottling"	prompt consideration of possible infection in patients not previously recognized as infected. qSOFA criteria: Altered mental status (GCS score < 15); systolic blood pressure < 100 mmHg; respiratory rate > 22 breaths per min Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. Septic shock can be identified with a clinical construct of sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP ⩾ 65 mm Hg and lactate > 2 mmol L−1 (18 mg dL−1) despite adequate fluid resuscitation

EPIDEMIOLOGY OF SEPSIS

i. Nevertheless, it is challenging to determine the global epidemiological burden of sepsis. Over the past ten years, the prevalence of sepsis has more than doubled, making it one of the leading causes of death in intensive care units (ICUs). [21]

Since the initial consensus definition (Sepsis-1) was established in 1991, the frequency of sepsis and septic shock has steadily increased. In 2017, there were approximately 49 million cases of sepsis and 11 million fatalities worldwide due to sepsis. [22, 23] The World Health Organisation (WHO) made sepsis a worldwide health priority as a result of these findings.[23] There are several reasons for this concerning rise in incidence:

i. Patients' average advancing age, particularly in western nations;
ii. The rise in invasive procedures
iii. The widespread use of chemotherapy and immunosuppressive medications;
iv. Resistance to antibiotics. [24]

Septic patients are at high risk of in-hospital mortality (IHM) despite substantial improvements in therapeutic management; IHM accounts for around 20% of all-cause deaths worldwide, making this combined condition one of the highest-mortality conditions seen in the emergency department (ED).[23, 25]

In underdeveloped nations like India, where sepsis accounts for 60–80% of annual fatalities, the illness continues to pose a significant problem for medical professionals. According to research, the country's epidemiology is dominated by Gram-negative organisms, with a 40% frequency of infections and a 28.3% incidence of severe sepsis

or septic shock. According to a recent prospective study, 56.4% of adults in intensive care units suffer from sepsis.[26]

Surgical patients

One-third of all sepsis cases are surgical patients. According to a recent analysis of surgical sepsis in the United States from 2002 to 2006, postoperative sepsis occurred in 1.2 percent of patients overall following an elective hospital surgery. [27] Depending on the type of surgery and the population under study, postoperative sepsis can range in prevalence from 5% to 30%. It is one of the primary causes of morbidity and mortality in surgical patients. Mortality rates from surgical sepsis typically fall between 10% and 30%.[28]

PATHOPHYSIOLOGY OF SEPSIS

Risk factors for sepsis

- ICU Admission: Hospital-acquired infections affect 50% of patients admitted to the intensive care unit, increasing their risk of sepsis.
- Bacteremia: Sepsis or septic shock were linked to 95% of positive blood cultures.
- Age >65: Sepsis-related mortality is independently predicted by age.

- Immunosuppresion: Patients with immunosuppressive medications, HIV, liver disease, and renal failure are more susceptible to sepsis.
- They are more vulnerable to diabetes and cancer because they can change the immune system.

- Prior hospital stays are associated with the use of antibiotics, which raises the risk of contracting resistant bacteria.
- A number of single nucleotide polymorphisms have been investigated, although they are not directly accountable.

Microbiology of sepsis:

Over time, the prevalence of detectable microorganisms in sepsis/septic shock has changed; currently, Gram-positive bacteria predominate, and fungal sepsis has grown in clinical and epidemiological significance.

Staphylococcus aureus and Streptococcus pneumonia are the two most commonly identified pathogens among Gram-positive bacteria.

Escherichia coli, Klebsiella, and Pseudomonas species are the most often found Gram-negative bacteria.

"Candida species, which are frequently seen in immunocompromised or neoplastic patients receiving long-term treatment with chemotherapeutic and immunosuppressive medications, play the most important role among the fungal infections linked to the illness." [29]

"The respiratory tract/pulmonary parenchyma accounts for 43 percent of sepsis-related infections, followed by the urinary system (16 percent), the belly (14%), the head, which is linked to a fever of undetermined origin (FUO) (14%), and other sites/causes (13%)." [29]

Our knowledge of the immunology and molecular pathobiology of sepsis has significantly changed. In the past, it was believed that the hyperimmune host response to a specific infection was the main cause of haemodynamic signs of sepsis. [16] Nonetheless, a substantial amount of research on the molecular causes of sepsis has

uncovered a far more intricate and subtle interaction between the infectious agent and host that results in the variety of sepsis symptoms.

Innate immunity and inflammatory mediators

The activation of innate immune cells, which are mostly composed of neutrophils, monocytes, macrophages, and natural killer cells, is the initial stage in the start of the host response to the infection. [30] "Pathogen-associated molecular patterns (PAMPs), such bacterial endotoxins and fungal β-glucans, attach to certain pattern recognition receptors on these cells to accomplish this." "Damage-associated molecular patterns (DAMPs), which can be intracellular material or molecules released from dead or damaged host cells, like ATP and mitochondrial DNA, are another source of such interactions." "Toll-like receptors (TLRs), C-type leptin receptors, NOD-like receptors (nucleotide-binding oligomerisation domain), and RIG-1-like receptors (retinoic acid inducible gene 1) are among the receptors on monocytes and macrophages that these bind to. Proinflammatory cytokines such as TNFα, IL-1, and IL-6 are released as a result of the activation of intracellular signal transduction pathways. Furthermore, some pattern recognition receptors, like the NOD-like receptor group, have the ability to group together to form larger protein complexes known as inflammasomes, which are involved in the production of caspases, which are involved in programmed cell death, and important cytokines like IL-1β and IL-18. Leukocyte activation and proliferation, complement system activation, endothelial adhesion molecule and chemokine expression upregulation, tissue factor synthesis, and hepatic acute phase reactant induction are all brought on by proinflammatory cytokines." The aforementioned immune response is exaggerated in sepsis, which causes collateral damage and host cell and tissue death.

Dysregulation of hemostasis

The inflammatory and coagulation cascades are both activated at the same time in sepsis, indicating a crossover between the inflammatory and haemostatic pathways. This interaction can range from fulminant disseminated intravascular coagulation (DIC) to moderate thrombocytopenia. There are several contributing factors to the dysregulation of coagulation in sepsis. The release of tissue factor from damaged endothelium cells is assumed to be the primary cause of sepsis's hypercoagulability (additional sources include monocytes and polymorphonuclear cells). [31] In fact, blockage of tissue factor has been demonstrated to completely prevent inflammation-induced thrombin generation in in vitro experimental models of bacteremia and endotoxemia. [32] The coagulation cascade is then systemically activated by tissue factor, leading to the formation of platelet-fibrin clots, activation of platelets, and thrombin generation. Local perfusion abnormalities brought on by these microthrombi may result in tissue hypoxia and organ failure.

"The anticoagulant effects of protein C and antithrombin, which ordinarily moderate the coagulation cascade, are also diminished in addition to the procoagulant effect mentioned above." Thrombomodulin, which is triggered by thrombin, transforms protein C into its active version, known as activated protein C. "Then, by working with activated protein S to degrade factors Va and VIIIa, activated protein C produces an anticoagulant action. By reducing neutrophil and monocyte adherence to the endothelium and inhibiting TNFα, IL-1β, and IL-6, it is also known to have strong anti-inflammatory effects." The coagulation cascade can spread uncheckedly in individuals with acute systemic inflammation, like sepsis, because of low amounts of protein S, downregulated thrombomodulin, and lowered plasma levels of protein C.[33]

Sepsis also results in a decrease in fibrinolysis in addition to the hypercoagulability already mentioned. [34] Vascular endothelial cells release tissue plasminogen activators in response to elevated TNFα and IL-1β levels. The resulting rise in plasminogen activator inhibitor type 1 (PAI-1) blunts the resulting increase in plasmin activation. Reduced fibrinolysis and fibrin clearance are the overall results, which help to sustain microvascular thrombosis.

Immunosuppression

"Remarkably, a protracted state of immunosuppression frequently replaces the initial proinflammatory state of sepsis. Because of apoptosis and a diminished reaction to inflammatory cytokines, there is a reduction in the quantity of T cells (both cytotoxic and helper)."[35] Postmortem examinations of intensive care unit patients who passed away from sepsis revealed a widespread reduction in CD4+ and CD8+ T cells, which were primarily detected in lymphoid organs including the spleen. Also, studies have shown that endotoxins cause a reduction in the production of important cytokines as TNF and IL-6.[36] There was less chemotaxis in response to IL-8 and fewer chemokine receptors produced by neutrophils in septic individuals.[37]

"These results imply that a septic's immune system is unable of mounting a successful defence against secondary bacterial, viral, or fungal infections. It has been hypothesised that early lymphopenia can function as a biomarker for immunosuppression in sepsis, after a study revealed that a low lymphocyte count early in sepsis (day 4 of diagnosis) is predictive of both 28-day and 1-year death."[38]

Cellular, tissue, and organ dysfunction

Reduced oxygen transport to and utilisation by cells due to hypoperfusion is the fundamental mechanism causing tissue and organ failure in sepsis. Sepsis is characterised by circulatory dysfunction, which leads to hypoperfusion. [39] "According to several research, the incidence of septic cardiomyopathy ranges from 18% to 60%. It is believed to be connected to circulating cytokines, including TNFα and IL-1β, which can impair cardiac myocytes' mitochondrial function and induce sadness." Septic cardiomyopathy's primary characteristics are its abrupt onset and reversibility. Second, unlike in cardiogenic shock, the decreased left ventricular ejection fraction is accompanied by increased left ventricular compliance and either normal or low left ventricular filling pressures. [40] Numerous investigations have demonstrated that sepsis is associated with both systolic and diastolic dysfunction, as well as decreased stroke volumes and elevated end-diastolic and end-systolic volumes. [41] "However, a clear impact of cardiac depression on mortality has not yet been proven. Additionally, sepsis causes a state of hypotension and distributive shock due to the dilatation of the arteries and veins (caused by inflammatory mediators) and the resulting decrease in venous return. All three elements of the microvasculature—capillaries, venules, and arterioles—are dilated. This is made worse by the loss of endothelial barrier function brought on by changes in tight junctions and endothelial cadherin, which causes intravascular fluid to flow into the interstitial space. When combined with the previously mentioned microvascular thrombosis, all of the aforementioned alterations in the body's haemodynamics may cause tissues and organs to be hypoperfused. Lactic acid is thus produced as a consequence of enhanced anaerobic glycolysis in cells. Furthermore, mitochondrial dysfunction and a decrease in ATP levels are brought on by the reactive oxygen species (ROS)

generated by the inflammatory response. Cellular damage results from these processes. A large portion of sepsis's morbidity and mortality are caused by the more general changes in the tissue and organs that are discussed below." [14]

The endothelium undergoes major changes, including enhanced leukocyte adhesion, vasodilation, disruption of its barrier function, and the development of a procoagulant condition. As a result, oedema fluid builds up in the bodily cavities, subcutaneous tissue, and interstitial spaces.[14]

Lungs[42] - Interstitial and alveolar oedema are caused by endothelial damage in the pulmonary vasculature, which also increases microvascular permeability and disrupts pulmonary capillary blood flow. The damage to the alveolar capillary membrane is started and intensified by neutrophil trapping in the pulmonary microcirculation. One common symptom of these impacts is ARDS. Acute lung damage occurs in up to 40% of individuals with severe sepsis.

Type I alveolar pneumocyte destruction, endothelial cell injury and destruction, platelet and leukocyte aggregate deposition, and type II pneumocyte repair and hyperplasia are all signs of acute lung injury, a spectrum of pulmonary dysfunction brought on by parenchymal damage. Numerous additional mediators are produced as a result of neutrophil and macrophage migration into the interstitium and alveoli, which damages the alveolar and epithelial cells.

Early on, acute lung injury can be reversed, but most of the time, the host reaction is out of control, and the acute lung injury develops into acute respiratory distress syndrome. Neutrophils, lymphocytes, and fibroblasts continue to infiltrate. There is type II pneumocyte proliferation and persistent alveolar inflammatory exudate. There will be a resolution if this can be stopped. If not, lung fibrosis and progressive respiratory failure occur. An aggressive healing process that results in an

overabundance of fibroblasts infiltrating the body and the production of collagen and other extracellular matrix (ECM) proteins causes a restrictive defect that ultimately leads to respiratory failure in the late stage of acute respiratory distress syndrome.

Kidney — "It is common for acute renal failure to accompany sepsis. Uncertainty surrounds the processes by which sepsis causes acute renal failure. One cause is acute tubular necrosis brought on by hypoperfusion and/or hypoxaemia. Renal damage may also result from cytokine release, direct renal vasoconstriction, and systemic arterial hypotension. Since sepsis has been linked to normal or even enhanced renal blood flow due to the transfer of blood flow from the cortical to the medullary area, septic acute renal failure is not solely caused by hypoperfusion. Microcirculatory failure, an inflammatory response brought on by pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), and a bioenergetic adaption response that includes tubular cell cycle arrest machinery are all linked to these macrovascular alterations. As a result, the mechanism of kidney damage during sepsis could be understood as a bio-energetic adaptation of tubular epithelial cells to peritubular microvascular dysfunction caused by dysregulated inflammation."[14]

GIT –"The natural barrier function of the gut is suppressed by endothelial damage and other circulatory irregularities, which permits bacteria and endotoxins to move into the systemic circulation and exacerbate the septic response. This is corroborated by a prospective cohort research that discovered that the development of multiple organ dysfunction syndrome was predicted by increased intestinal permeability as measured by the urine excretion of oral lactulose and mannose."[43]

Nervous system — The central nervous system is often affected by sepsis before other organ systems are involved. The pathophysiology of altered sensorium (encephalopathy), the most frequent CNS consequence, is not well understood. One

study reported a high rate of brain abscesses, neurotransmitter disruption, and oxidative stress; however, due to the identified pathology's variability, it is unclear whether haematogenous infection is the primary aetiology. Changes in metabolism and modifications in cell signalling by inflammatory mediators have been connected to CNS disease. Increased leukocyte infiltration, exposure to toxins, and active cytokine trafficking across the blood-brain barrier are all likely caused by blood-brain barrier breaches. According to somatosensory evoked potential, functional alterations in the central nervous system are preceded by both mitochondrial malfunction and microvascular damage.

The parasympathetic nervous system may mediate systemic inflammation during sepsis, according to mounting evidence. During sepsis, afferent vagus nerve stimulation increases the release of corticotropin-releasing hormone (CRH), ACTH, and cortisol. Subdiaphragmatic vagotomy can inhibit these effects. [44]

A catabolic condition is known to result from sepsis. Muscle is broken down quickly and significantly to create amino acids for gluconeogenesis, which powers the immune cells. Hyperglycemia is another condition that can be brought on by elevated insulin resistance.[14]

Figure 1: Pathogenesi of Sepsis

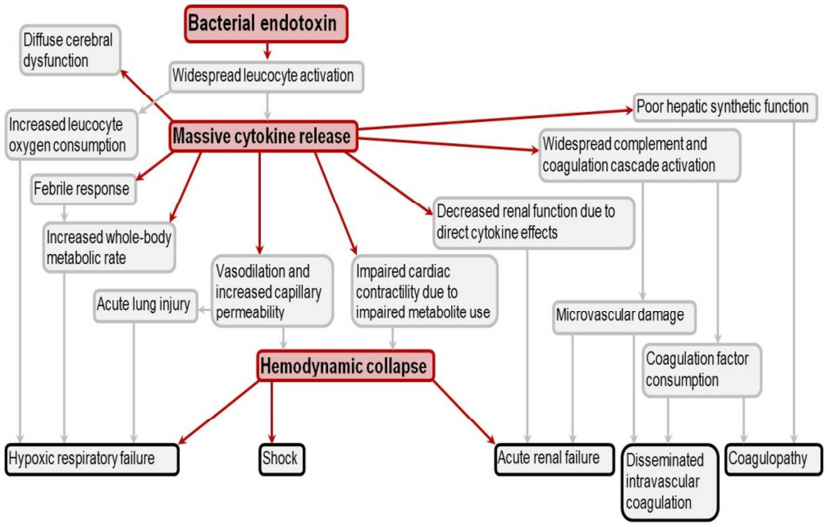


Figure 2: Pathophysiology of Organ Dysfunction In Sepsis

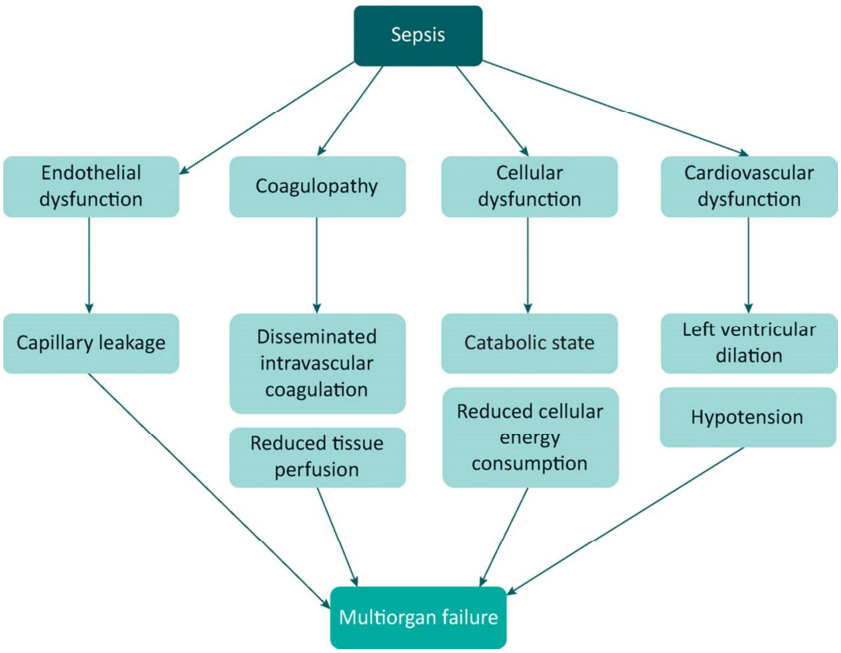
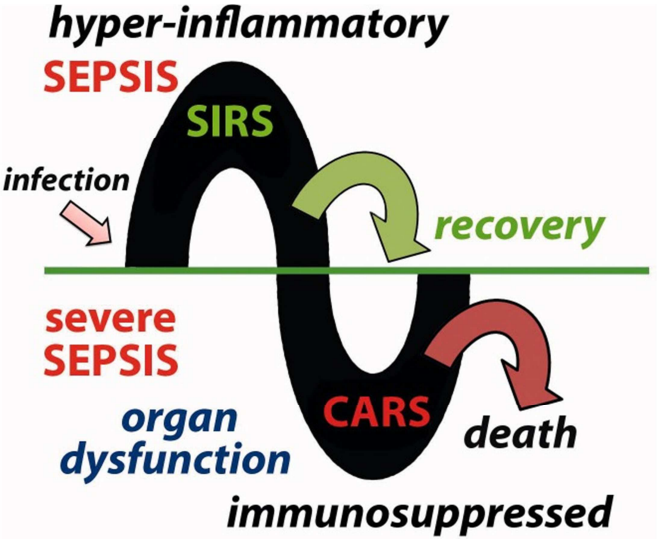


Figure 3: Sepsis may be divided into two phases.



CLINICAL MANIFESTATIONS OF SEPSIS[45]

Particularly in individuals recovering from surgery, sepsis symptoms and indicators can be mild and sometimes confused with signs of other conditions (such as delirium, pulmonary embolism, or intrinsic cardiac failure). Patients with sepsis usually have tachypnea, diaphorea, tachycardia, and fever, but their blood pressure is normal. There can be additional indications of the causing infection. Confusion or a reduction in awareness may be an early indicator of sepsis or septic shock, especially in the elderly or very young. Despite a drop in blood pressure, the skin paradoxically gets warmer. Later, there is peripheral cyanosis and mottling, and the extremities turn pale and cold. Additional symptoms and indicators unique to the organ in question, such as oliguria and dyspnoea, are brought on by organ malfunction.

DIAGNOSIS OF SEPSIS[46]

Clinical symptoms; monitoring of heart rate, blood pressure, and oxygen levels; complete blood count (CBC) with electrolyte panel, creatinine, and lactate; and differential

Central venous oxygen saturation (ScvO2), PaO2, and invasive central venous pressure (CVP) measurements

• Blood, urine, and other possible infection sites, such as surgery patients' wounds

When a patient with a known illness exhibits organ malfunction or systemic indications of inflammation, sepsis is suspected. Similar to this, a patient exhibiting otherwise inexplicable symptoms of systemic inflammation should have a history, physical examination, and tests, such as blood cultures, cultures of other suspect bodily fluids, and urinalysis and urine culture (especially in patients with indwelling catheters), to assess for infection. Depending on the probable cause, ultrasonography (such as the Rapid Ultrasound for Shock and Hypotension (RUSH) Examination), CT, or MRI may be necessary in patients with a suspected surgical or hidden cause of sepsis. Although they are not specific, blood levels of procalcitonin and C-reactive protein are frequently raised in cases of severe sepsis and may help with identification. The diagnosis is ultimately clinical.

"As clinically warranted, other causes of shock (such as hypovolemia and myocardial infarction [MI]) should be checked out using the history, physical examination, electrocardiogram, and serum cardiac markers. Sepsis-induced hypoperfusion can produce ECG signs of cardiac ischaemia, such as nonspecific ST-T wave abnormalities, T-wave inversions, and supraventricular and ventricular arrhythmias, even when MI is not present."

Early identification of organ failure is crucial. Although other grading systems have been developed, the fast SOFA score (qSOFA) and the sequential organ failure assessment score (SOFA score) have been verified in terms of mortality risk and are quite easy to use. "There is no need to wait for test results to determine the qSOFA

score, which is determined by the Glasgow Coma Scale, respiration rate, and blood pressure. The qSOFA score is a more accurate indicator of inpatient mortality for patients with a suspected infection who are not in the intensive care unit (ICU) than the SOFA score and SIRS. The SOFA score is a more accurate indicator of in-patient mortality for patients with a suspected infection in the intensive care unit (ICU) than both the qSOFA score and the systemic inflammatory response syndrome (SIRS)."

Patients with ≥ 2 of the following criteria meet criteria for SIRS and should have further clinical investigation:

- Temperature > 38° C (100.4° F) or < 36° C (96.8° F)
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or PaCO2 < 32 mm Hg
- White blood cell count > 12,000/mcL (12 × 10^9/L), < 4,000/mcL (4 × 10^9/L) or > 10% immature (band) forms

Figure 4: SIRS and qSOFA scoring

SIRS criteria (two or more)	qSOFA criteria (two or more)
36 > Temperature >38	Systolic blood pressure <100 mmHg
Respiratory rate > 22/min	Respiratory rate >20/min
Heart rate > 90 bpm	Glasgow Coma Scale ≤14
4000> White cell count >12,000	

SIRS: Systemic Inflammatory Response Score; qSOFA: quick Sequential Organ Failure Assessment.

"The **SOFA score** is somewhat more robust in the ICU setting, but requires laboratory testing."

Figure 5: SOFA scoring

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

"Serum electrolytes, BUN (blood urea nitrogen), creatinine, PCO2, liver function, arterial blood gases (ABGs), CBC, and chest x-ray are all tracked. Treatment can be guided by measuring serum lactate levels, central venous oxygen saturation (ScvO2), or both. Polymorphonuclear leukocytes can be as low as 20%, and the white blood cell (WBC) count can be either higher (> 15,000/mcL [> 15 × 109/L]) or lower (< 4,000/mcL [< 4 × 109/L]). Depending on the severity of sepsis or shock, the patient's immunologic condition, and the cause of the infection, the WBC count may rise or fall during sepsis. WBC alterations brought on by sickness trends may be obscured by concurrent corticosteroid therapy, which raises WBC counts."

"As a partial remedy for lactic acidemia, hyperventilation with respiratory alkalosis (low PaCO2 and elevated arterial pH) happens early. Typically, blood and serum lactate levels rise as serum bicarbonate levels fall. Blood pH falls and metabolic acidosis gets worse as shock deepens. A lower PaO2:FIO2 ratio and occasionally overt hypoxaemia with PaO2 < 70 mm Hg are symptoms of early hypoxemic respiratory failure. Acute respiratory distress syndrome (ARDS) can cause diffuse

infiltrates to show up on the chest x-ray. Renal insufficiency typically causes a progressive rise in BUN and creatinine. Although overt hepatic failure is rare in patients with normal baseline liver function, bilirubin and transaminases may increase."

In situations when the precise kind of shock is unknown or when significant fluid amounts (such as > 4 to 5 L balanced crystalloid within 6 to 8 hours) are required, haemodynamic assessments using a central venous or pulmonary artery catheter may be utilised.

In the intensive care unit, bedside echocardiography is a useful and noninvasive substitute for traditional haemodynamic monitoring. In contrast to other types of shock, when cardiac output is usually lowered and peripheral resistance is increased, septic shock causes an increase in cardiac output and a decrease in peripheral vascular resistance.

Unlike hypovolemic, obstructive, or cardiogenic shock, septic shock is unlikely to have aberrant CVP or pulmonary artery occlusive pressure (PAOP).

"Relative adrenal insufficiency, or normal or slightly raised baseline cortisol levels that do not rise noticeably in response to further stress or exogenous adrenocorticotropic hormone [ACTH], is a condition that many patients with severe sepsis experience. Serum cortisol can be measured at 8 AM to assess adrenal function; a level less than 5 mcg/dL (less than 138 nmol/L) is insufficient. An alternative method is to assess cortisol levels both before and after injecting 250 mcg of synthetic ACTH; a rise of less than 9 mcg/dL (less than 248 nmol/L) is deemed inadequate."

BIOMARKERS OF SEPSIS[47]

❖ **"Pro-inflammatory cytokines as markers of the hyper-inflammatory phase of sepsis"**

The cytokines that mediate the innate immune system's early reaction to damage or infection are TNF, IL-1β, and IL-6. Endothelial cells are activated by TNF and IL-1β, which draws circulating polymorphonuclear leukocytes (PMNs) to the area. Fever and other systemic symptoms are also brought on by their entering the bloodstream. In addition to stimulating a change in bone marrow cell production that results in the generation of more PMNs, IL-6 increases the liver's synthesis of the so-called acute phase reactants, such as CRP. Thus, these three cytokines are primarily in charge of SIRS's characteristics and may also be helpful as sepsis biomarkers.

❖ **"PCT and CRP as biomarkers of sepsis"**

Both PCT and CRP are proteins that are generated in reaction to inflammation and/or infection. Apart from lactate, they are perhaps the two most commonly utilised clinical tests to identify and treat sepsis patients.

❖ **"Biomarkers of complement proteins in sepsis"**

"By opsonising the surfaces of microbes with a portion of complement protein 3 (C3) known as C3b, complement proteins improve phagocytosis. Pro-inflammatory peptides such C5a, a cleavage product of complement protein 5, are also produced when the complement cascade is activated. The focus has been on C5a as a potentially helpful biomarker, and there is strong evidence that complement plays a part in fostering the inflammatory state in sepsis."

❖ **"Biomarkers of activated neutrophils and monocytes in sepsis"**

"As was already established, the bone marrow produces more PMNs as a result of increasing levels of the pro-inflammatory cytokine IL-6. This stimulation may also result in PMN precursors leaving the bone marrow before they have fully developed, depending on the degree of inflammation." One of the requirements for SIRS is either a rise in the overall quantity of PMNs in circulation or a rise in the proportion of immature forms. In sepsis patients, circulating PMNs are already activated by cytokines, which causes alterations in their appearance. PMN activation in bacterial infection is indicated by toxic granulations, which are higher concentrations of antimicrobial chemicals in the main granules, and Döhle bodies, which are endoplasmic reticulum aggregates. By employing quantitative flow cytometry to measure the amounts of certain cell differentiation markers on the PMN cell surface, PMN activation can be identified much earlier. Although other activation indicators have also been investigated as sepsis biomarkers, the main focus has been on CD64, a receptor with a high affinity for the Fc region of the immunoglobulin molecule."

"Monocytes also express activation markers as CD64, CD11b, and TREM-1. However, the soluble form of the receptor for advanced glycation end-products (RAGE) has been the focus of research on monocyte activation markers as possible biomarkers of sepsis."

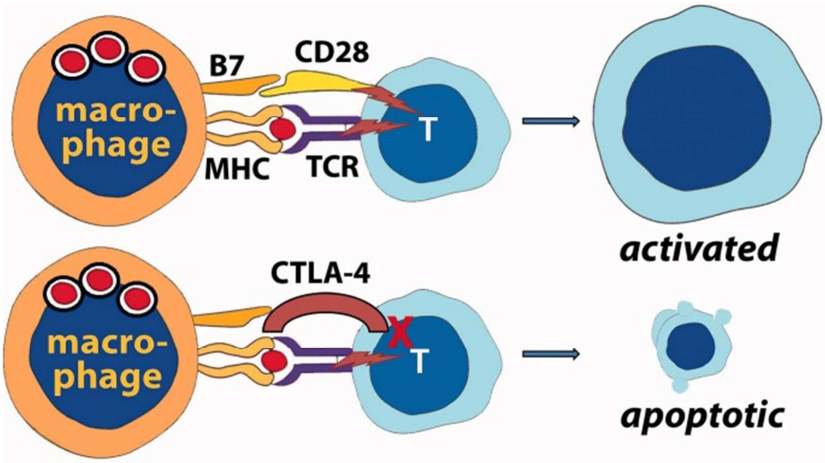
❖ **"Detection of infectious organisms and their products in sepsis"**

"As sepsis indicators, PAMPs generated by microbes and DAMPs released during tissue damage have both been studied."

❖ **"Biomarkers of the immunosuppressive phase of sepsis"**

"More than 15 years ago, Bone acknowledged the significance of CARS, which occurs after the hyper-inflammatory state in septic patients. A number of indicators of the immunosuppressive stage of sepsis have drawn a lot of interest lately (Figure 4)."

Figure 6: "There is strong evidence that adaptive immunity is compromised in patients suffering from severe sepsis. The Class II MHC proteins that present foreign peptides to the TCR may no longer be expressed by macrophages (or monocytes). But more significantly, T-cells increase the production of CTLA-4, a different ligand for the co-stimulator B7 on the cell that presents the antigen. Interaction with CTLA-4 causes T-cell inresponsiveness and, ultimately, death by apoptosis, as opposed to co-stimulation and T-cell activation, which would happen if B7 coupled with CD28."



❖ **Biomarkers of organ dysfunction in sepsis**

"Physicians can determine whether end-organ malfunction has caused a patient's clinical condition to progress from sepsis to severe sepsis using a number of established standard laboratory tests." Acute physiology and chronic health

evaluation (APACHE) and SOFA are two physiological scoring systems that use some of these to determine the level of critical illness in hospitalised patients. Liver and renal disease are indicated by elevated bilirubin and creatinine values, respectively. However, the blood lactate level is the most commonly used biomarker for organ dysfunction.

LACTATE AS A PROGNOSTIC MARKER IN SEPSIS

Normal lactate metabolism

Manufacturing Lactate generation in humans at rest has been calculated to be around 20 mmol/kg/day (range: 0.9 to 1.0 mmol/kg/hour) using carbon isotopes. Although a wide variety of cells can release lactate into the bloodstream, it is unknown how much lactate each organ or tissue produces and uses at rest. An astounding 800 to 1,800 millilitres per minute of lactate clearance has been calculated by examining the elimination of injected sodium L-lactate. This suggests that 60 to 120 mmol of lactate are eliminated every hour at a concentration of 1 to 2 mmol/L, and that all of the blood can be cleansed of lactate every 3 to 4 minutes. [48]

"Glycolysis in the cytosol produces lactate from pyruvate. Lactate dehydrogenase (LDH), an enzyme that promotes lactate synthesis and typically keeps a steady lactate to pyruvate ratio of roughly 10:1, keeps its concentration in balance with pyruvate. Therefore, it stands to reason that any circumstance that raises pyruvate generation will also raise lactate generation. Crucially, the production of lactate from pyruvate releases NAD+, a key electron acceptor during glycolysis, which may help to promote the production of glycolytic energy. Glycolysis is impossible without an effective cytosolic mechanism to recycle NAD+ from NADH."

Removal

The liver and kidneys can either directly oxidise lactate or use it as a source of glucose for metabolism.

Gluconeogenesis

The Cori cycle (gluconeogenesis) is the process by which muscle or other tissues produce it and the liver and kidney convert it into glucose. One of the main sources of glucose in humans is lactate, which is quantitatively the most significant gluconeogenic precursor. Although the kidneys are responsible for about 30% of lactate metabolism, hepatocytes are the primary site of oxidative lactate absorption. Half of the total lactate conversion to glucose is caused by the kidneys' transformation of lactate into glucose.[49]

Oxidation

"In addition to being converted to glucose by the Cori cycle, lactate is also eliminated by oxidation (through the citric acid cycle and pyruvate). At rest, around half of the lactate that is accessible is eliminated through oxidation, while during activity, 75–80% of it is. This finding implies that lactate functions as a bioenergetic fuel under stress and can be used to both deliver extra glucose and spare blood glucose utilisation."[50]

Lactate use during stress

At rest, lactate is taken up and oxidised by the heart. Fast pacing, βadrenergic stimulation, exercise, and shock all cause an increase in myocardial lactate uptake. Lactate is a greater source of pyruvate than glucose and can make up as much as 60%

of the myocardial oxidative substrate during hyperlactatemia. The majority of the heart's energy requirements during shock are met by oxidising lactate. Lactate infusion improves cardiac performance in patients with acute heart failure, cardiogenic shock, and septic shock, as well as cardiac output in anaesthetised pigs. In fact, circulatory failure and early animal mortality are linked to systemic lactate depletion. [51]

When metabolic demand rises, the human brain transforms into a lactate consumer. About 7% of the brain's energy needs at rest and up to 25% during exercise are met by lactate. In the conscious, healthy human brain, neurones oxidise blood lactate, and astrocytes convert it to glycogen. During hyperlactatemia, lactate's role as a source of brain energy rises.[52]

Source of lactate in sepsis[53]

There is ongoing discussion and investigation regarding the physiological cause of lactate production during sepsis. According to recent evidence, SAHL may be caused by additional non-hypoxic factors.

Increased lactate production

"Lactic acid is continuously produced by the human body, and its levels peak when cellular oxygen demand rises or oxygen supply falls. Unlike elevated oxygen demand, hypoxia not only causes lactate to be produced directly, but it also prevents Hypoxia-inducible Factor 1-alpha (HIF1a) from degrading and encourages its transcriptional activation (60). HIF-1a regulates lactate generation and glycolysis in a variety of ways. By stimulating the transcription of glycolytic enzymes and membrane transporters, it improves glycolysis and raises glucose flux. At the same time, when HIF-1a is activated, the expression of LDHA, an enzyme essential for lactate

synthesis, is increased, which raises lactate levels. Increased oxygen consumption by activated immune cells during the hyperinflammatory phase of sepsis causes tissue hypoxia, which stabilises the transcription factor HIF-1a and subsequently raises lactate generation. For instance, Toll-like receptors (TLRs) trigger modifications in glycolytic metabolism, which are essential for dendritic cell activation. Anaerobic ATP synthesis also proves advantageous in low-oxygen environments that are characteristic of infection and inflammation. This is in line with a prior finding that HIF-1a increases dendritic cells' glycolysis triggered by lipopolysaccharide (LPS). Consequently, elevated oxygen requirements during inflammatory reactions highlight an essential adaptation of activated immune cells to the augmentation of lactate generation that is dependent on HIF-1a."

A substantial increase in pro-inflammatory cytokines is a hallmark of sepsis in its early stages. Pro-inflammatory cytokines, particularly interleukin (IL)-1b, have been shown in numerous investigations to be important mediators of aerobic glycolysis and lactate generation.

"Notably, during sepsis, increased lactate generation in response to infection is a common occurrence that can happen in almost all cells. In a process dependent on the T cell receptor (TCR), early T cell activation (minutes to hours) boosts aerobic glycolysis and redirects pyruvate to lactate synthesis. Neutrophils have a low mitochondrial respiration rate and a strong glycolytic activity. According to reports, lactic acid can be secreted by human neutrophils through a monocarboxylate transporter."

"Recent data suggests that during immunological reactions, activated ECs primarily rely on glycolysis rather than OXPHOS for ATP synthesis because of their low mitochondrial concentration, which in turn promotes lactate buildup."

Impaired catabolism of lactate

Lactic acidosis will develop if the body collects a significant amount of lactic acid. In response, its clearing necessitates effective techniques. The primary mechanism for maintaining lactate homeostasis is catabolism, which is the process by which the enzyme lactate dehydrogenase B (LDHB) transforms lactate into pyruvate. Pyruvate then contributes to the irreversible elimination of lactate by entering the mitochondrial TCA cycle for further oxidation and energy generation via pyruvate dehydrogenase (PDH). Pyruvate dehydrogenase dysregulation and mitochondrial malfunction reduce OXPHOS in severe sepsis, which disrupts the TCA cycle. In turn, this speeds up the buildup of lactate in sepsis. Interestingly, new data from preclinical and clinical research suggests that sepsis reduces PDH activity. According to reports, sepsis patients' peripheral blood mononuclear cells have significantly less PDH activity and quantity than those of the control group. Subsequent investigation revealed that sepsis non-survivors have lower levels of PDH activity than survivors. Crucially, these individuals showed an inverse relationship between baseline lactate levels and PDH activity, indicating that PDH dysregulation plays a role in elevated lactate levels in sepsis.

Furthermore, the lactic acid cycle or Cori cycle can be used to eliminate excess lactate. Lactate in the bloodstream travels to the liver, where hepatocytes use it for gluconeogenesis, the process by which glucose is created again. Additionally, it can be released into the urine by the kidneys or oxidised and eliminated by other tissues. We must admit, though, that hepatic and renal failure are widespread in septic shock and severe sepsis, and that they may be a factor in sepsis hyperlactatemia. The finding that increased lactate levels are associated with higher Sequential Organ Failure Assessment (SOFA) and fast SOFA (qSOFA) scores lends credence to this idea.

Hyperlactatemia can also result from other disorders such peripheral shunting and increased adrenergic stimulation, however it is unknown how common these conditions are and how important they are clinically in sepsis patients.

Alternative explanations for sepsis-associated hyperlactatemia[54]

Aerobic glycolysis mediated by adrenaline A more plausible explanation for SAHL is increased aerobic glycolysis brought on by inflammation linked to sepsis. Stated differently, SAHL is a metabolic state shift rather than a reaction to problems with cell oxygenation. According to this theory, when the pace of glucose metabolism surpasses the mitochondria's oxidative capacity, an altered metabolic state results. A greater use of glucose results in the production of pyruvate. As a result, pyruvate is generated more quickly than PDH can convert it to acetyl CoA. Due to a mass effect, this raises the concentration of pyruvate within cells, which in turn raises lactate synthesis. This theory makes sense and is straightforward. It's crucial to evaluate the observations that back it up, though.

"Increased protein catabolism (sepsis-induced muscle proteolysis), as seen by a rise in the mRNA of proteolytic genes in skeletal muscle, also raises pyruvate concentration." This results in the release of amino acids such as alanine, which is then converted by alanine aminotransferase into pyruvate and then lactate. In sepsis, there is a strong correlation between endogenous and exogenous catecholamines and hyperlactatemia. They enhance the activity of the Na+/K+-ATPase pump by stimulating the β2-receptor. Studies on both humans and animals have shown that adrenaline enhances the production of lactate by increasing the activity of the Na+/K+ ATPase.

Adrenergic activation in sepsis may also raise lactate, which has rational biochemical causes. Epinephrine stimulates glycogenolysis and glycolysis with simultaneous ATP

generation and activation of the Na+/K+-ATPase pump by raising cyclic AMP. ADP is produced as a result of this activation's consumption of ATP. By stimulating phosphofructokinase, ADP reactivates glycolysis, producing more pyruvate and, in turn, more lactate (Figure 3). Furthermore, when ouabain completely blocked muscle lactate generation, Levy and colleagues further validated the involvement of Na+/K+-ATPase pump stimulation. Clinically significant, the capacity to enhance lactate generation and glycolysis in response to adrenaline stimulation is linked to a better prognosis in shock patients, indicating that this is an adaptive response.

Lactate concentration in resuscitation fuids

In people who are haemodynamically stable, intravenous injection of lactated Ringer's solution did not appear to aggravate metabolic acidosis or raise circulating lactate concentrations following a 1 L infusion over 60 minutes. Lactate levels only significantly increase when big amounts (180 mL/kg/h) are infused. Conversely, Ringer's solution's buffering effect, which has a stronger anion difference in physiology, may raise blood pH.

Lactate level thresholds[55]

- Normal lactate levels are less than 1.0 mmol/L in all age groups.
- Lactate levels greater than 2.0 mmol/L represent hyperlactataemia and should be reviewed by a clinician with experience in managing deteriorating patients, and treatment started as advised.
- A lactate of 4.0 mmol/L significantly increases the risk for both morbidity and mortality, and requires urgent treatment and escalation through the health service organisation’s rapid response system.

- A lactate less than 2 mmol/L does not preclude a diagnosis of sepsis, especially in a paediatric patient and/or when low systolic blood pressure or signs of organ dysfunction are present.

"Recognition of lactate in sepsis/ septic shock"[53]

❖ **Early observations**

"German physician-chemist Johann Joseph Scherer noted the presence of lactic acid in seven case reports of young women who died during childbirth as early as 1843 (24). These patients were diagnosed with cerebral haemorrhage, hemorrhagic shock, subsequent peritonitis, and perimetritis (24). Scherer postulated that with such severe disorders, there was an increase in lactic acid generation. Future research into the diagnostic and prognostic potential of lactic acid in a variety of situations is made possible by Scherer's groundbreaking case reports, which are regarded as the foundational evidence of lactic acid as an indicator of septic and hemorrhagic shock."

"High lactate levels in patients with circulatory failure and shock were frequently seen in clinical practice during the 1960s and 1980s. Blood lactate levels have been proven to provide a critical prognostic marker and to identify the severity of shock, accurately predicting outcomes even prior to the development of severe hypotension. These investigations also revealed that lactic acid plays a significant role in the metabolic acidosis seen in early shock. Studies have demonstrated a good association between the levels of lactate from venous blood in the pulmonary artery, right atrium, or superior vena cava and arterial levels. Huckabee proposed that assessing "excess lactate," or an unbalanced increase in lactate levels in relation to pyruvate, provides a more accurate assessment of oxygen debt. Lactate levels alone, however, might be a more straightforward and accurate predictive indication of the severity of shock,

according to Weil et al. In terms of severe sepsis/septic shock, these early studies were imprecise, but they were accurate for a large number of later trials."

❖ **Recognition in sepsis**

Cohen and Woods proposed in the late 1980s that either type A hyperlactatemia, which is caused by an insufficient oxygen supply, or type B hyperlactatemia, which is caused by causes unrelated to tissue hypoxia, could be the cause of elevated lactate levels. "Despite its seeming simplicity, this strict classification can be difficult to apply in complex clinical situations, especially when it comes to sepsis-related hyperlactatemia, which some people classify as type A and others as type B." The intricacy and range of the intricate kinetics involved in the synthesis and utilisation of lactate by tissues are, in fact, concealed by this classification. Hyperlactatemia can also result from peripheral shunting and increased adrenergic stimulation, however it is unknown how common these conditions are and how important they are clinically in sepsis patients. Despite this, lactate is a useful indicator that is crucially unaffected by blood pressure for determining tissue hypoxia and disease severity. Sequential blood lactate measures can indicate subsequent multiple organ failure, and research has shown that blood lactate levels are a better predictor of septic shock outcomes than oxygen-related metrics. "Clinical researchers at the time recognised the importance of blood lactate levels of 4 mmol/L or higher in the context of early goal-directed therapy."

Inclusion in clinical guidelines

The 1992 definition of septic shock and severe sepsis included lactate as a sign of hypoperfusion. [56] Lactate was identified as a symptomatic assessment of treatment endpoints and a measure of severity in the first version of the Surviving Sepsis

Campaign (SSC) guidelines. [57] According to guidelines, individuals with septic shock or suspected severe sepsis should have their serum lactate levels measured within six hours. When lactate levels exceed 4 mmol/L, early resuscitation treatment is required. Furthermore, lactate clearance is associated with reduced morbidity and mortality in septic shock and severe sepsis, which is consistent with SSC's emphasis on treating tissue hypoperfusion early in resuscitation. According to studies, a lactate clearance of less than 10% offers good sensitivity and specificity when used as a predictor of hospitalization-related morbidity and mortality. Furthermore, a review of the pertinent database found that patients benefit clinically from the guidelines' emphasis on lactate measurement. The notion that lactate can direct the management of sepsis has been confirmed by later research..[53]

Risk stratification

"There is growing evidence that using lactate levels to stratify sepsis risk is feasible. Blood lactate concentrations higher than 0.75 mmol/L, for instance, may be used by clinicians as an indicator to identify patients who are at an increased risk of death, according to a retrospective multi-center study. [58] Even in the absence of hypotension, patients with moderate lactate levels and suspected infections in the emergency room are at moderate to high risk of dying. This implies that in critical illnesses, such as sepsis, lactate levels have a significant predictive significance. Notably, it has been observed that lowering mortality does not necessarily need changing therapies based on surrogate physiological targets from invasive catheter measures. This is consistent with research showing that serial blood lactate monitoring is just as successful as catheter-based assessments. Additionally, studies show that lactate clearance is linked to lower mortality rates in patients in critical condition, providing the best predictive value for therapeutic use."[53]

Integration into diagnosis and treatment algorithms

"The Sepsis-3 definition of septic shock, which is differentiated from sepsis by the requirement that vasopressors maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level exceeding 2 mmol/L without hypovolemia, emphasises the critical role of lactate. Even in cases where sepsis has not yet been diagnosed, lactate levels are advised for screening undifferentiated adult individuals. 58 Furthermore, knowing why lactate levels increase might help improve treatment plans, particularly when determining how aggressively to give fluids to patients, according to Gattinoni et al. It was proposed that values near normal can indicate successful resuscitation even if lactate levels do not completely return to normal."[60]

Lactate albumin Ratio[61]

The most prevalent protein in plasma, albumin, serves as a protein reserve and is the primary protein carrier that preserves acid-base balance. It also significantly contributes to oncotic pressure. Additionally, albumin inhibits platelet aggregation and binds to antithrombin to have antioxidant, immunological, and anticoagulant effects. Albumin is a long-term nutritional indicator that is only produced in the liver. But in critical sickness, albumin is also a negative acute-phase reactant. Because of decreased liver synthesis in response to inflammatory chemicals and catabolism brought on by the increased protein and energy needs, albumin levels sharply decline during sepsis. Furthermore, increased microvascular permeability may push albumin into extravascular compartments, further exacerbating hypoalbuminemia, while liver dysfunction during sepsis may reduce albumin synthesis. In hospitalised patients, low albumin is an independent predictor of poor outcomes and has been associated with increased morbidity. Moreover, albumin has a substantial correlation with the

outcome of sepsis patients.

With encouraging results, recent studies have examined the prognostic usefulness of the combination of the aforementioned indicators expressed as a ratio, specifically the lactate to albumin ratio (LAR), in acute inflammation, severe infections, and critical illness. According to recent research, the LAR plays a predictive function in sepsis. Studies on the dynamics of the LAR in the early stages of sepsis and its correlation with the severity and prognosis of sepsis are few, nevertheless.

SCORING SYSTEMS FOR SEPSIS PATIENTS

Florence Nightingale initially addressed the subject of medical treatment outcome assessment in 1863. [62] At first, clinicians' subjective assessments were used to predict outcomes in critical illness. The necessity for quantitative and clinically meaningful surrogate outcome measures to assess the efficacy of treatment procedures arose from the intensive care unit's (ICU) fast development. For this reason, scoring systems have been created and used. critical care unit outcomes are influenced by a number of characteristics that are present on the patient's first day and later throughout their stay in the critical care unit. Although numerous grading systems have been created for these groups, only few are actually put to use. A number of these systems are simply referred to by their acronym. A scoring system typically consists of two components: a probability model (an equation that indicates the likelihood of a patient's hospital death) and a score (a number corresponding to the severity of the sickness).[63]

There are several screening scores for predicting sepsis mortality.

- quick Sequential Organ Failure Assessment (qSOFA)
- National Early Warning Score (NEWS)
- Sequential organ failure assessment (sofa)

- ❖ Systemic Inflammatory Response Syndrome (SIRS) Score
- ❖ Mortality In Emergency Department Sepsis (MEDS) Score
- ❖ Sepsis Patient Evaluation In The Emergency Department (SPEED) Score
- ❖ Sepsis Severity Score (SSS)
- ❖ Acute Physiology and Chronic Health Evaluation (APACHE)

- RAAS scoring

The prognosis of the patient's health status is ascertained, the effectiveness of various treatment plans is compared, and patients who need a more aggressive surgical approach are identified using these scoring systems.

RAAS scoring system

By combining these four clinical parameters into a single score, the RAAS scoring system—which stands for "Red Blood Cell Distribution Width (RDW), Age (AGE), SOFA (Sequential Organ Failure Assessment), and APACHE II (Acute Physiology and Chronic Health Evaluation II)—allows healthcare providers to better predict a patient's prognosis and guide treatment decisions. In other words, a higher RAAS score indicates a greater severity of sepsis.

Components:

The score is calculated by assigning points based on the values of a patient's RDW, age, SOFA score, and APACHE II score.

APACHE II

The APACHE II severity of disease classification system was created in 1985 utilising a database of intensive care unit patients from North America. It provides a

general estimate of disease severity using a point score based on the results of 12 routine physiologic measurements (collected within 24 hours of admission), age, and prior health condition. Based on these measurements, an integer score between 0 and 71 is then calculated; higher scores indicate a more serious illness and a higher chance of dying. Acutely unwell patients can be prognostically stratified using APACHE II scores, which can also help researchers compare the effectiveness of novel or alternative treatment approaches. A variable receives zero points if it has not been measured. The APACHE II score, the primary diagnostic category for which the patient is hospitalised to the intensive care unit, and whether or not the patient needed emergency surgery are used to predict hospital mortality. Using the logistic regression equation and specially designed beta coefficients, the predicted risk of hospital death is determined. [52] This scoring system's main drawback is that many individuals have multiple co-morbid diseases, making it challenging to choose just one primary diagnostic category. Furthermore, time bias exists because the physiological variables are all dynamic and subject to various influences, such as continuous resuscitation and treatment. This is a crucial factor to take into account when treating patients in the intensive care unit, particularly in light of the recent emphasis on the significance of early goal-directed therapies. Predicted mortality may be overestimated as a result of all these factors..[64]

Figure 7: Acute physiologic and chronic health evaluation (APACHE II)

A: Acute physiological score (12 variables)

Physiologic variable	High abnormal range				Normal range	Low abnormal range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature rectal (°C)	≥41	39-40.9	-	38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.0
Mean arterial pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart rate-ventricular response	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate per minute-non-ventilated or ventilated	≥50	35-490		25-34	12-24	10-11	6-9		≤5
Oxygen: A-a DO_2 or PaO_2 (Torr)									
FiO_2 ≥0.5 record A-a DO_2	≥500	350-499	200-349		≤200	PO_2 61-70		PO_2 55-60	PO_2 <55
FiO_2 <0.5 record only PaO_2					PO_2 >70				
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum HCO_3 (mmol/L)-only if no ABGs	≥52	41-51.9		32-40.9	23-31.9		18-21.9	15-17.9	<15
Serum sodium (mmoL/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium (mmoL/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		≤2.5
Serum creatinine (μmoL/L)	≥350	200-340	150-190		60-140		<60		
Hematocrit (%)	≥60		50-50.9	46-49.9	30-45.9		20-29.9		≤20
White blood cell count (×1,000/mm³)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow coma score=15 minus actual GCS									

B: Age points		C: Chronic health points			Apache II score
Age (years)	Points	History	Points for elective surgery	Points for emergency surgery	Sum of A+B+C
≤44	0	Liver: Biopsy-proven cirrhosis and documented portal hypertension or prior episodes of hepatic failure	2	5	A: APS
45-54	2	Cardiovascular: NYHA Class IV	2	5	B: Age points
55-64	3	Respiratory: e.g., severe COPD, hypercapnia, home O_2, pulmonary hypertension	2	5	score
65-74	5	Immunocompromised	2	5	C: Chronic health
≥75	6	Renal: Chronic dialysis	2	5	point score
Total score					

APACHE: Acute physiology and chronic health evaluation; A-a DO_2: Alveolar-arterial oxygen tension difference; PaO_2 (Torr) arterial oxygen tension; FiO_2 (%): Fractional concentration of inspired oxygen; HCO_3: Bicarbonate; ABG: Arterial blood gas; NYHA: New York heart association; COPD: Chronic obstructive pulmonary disease. To compute predicted death rates for groups of acutely ill patients, the individual risk of hospital death is calculated with the following equation; the individual risks are then summed up and the value is divided by the total number of patients. $R/1\text{-}R = -3.517 + (\text{APACHE II score} \times 0.146) + (0.603, \text{only if post-emergency surgery}) + (\text{diagnostic category weight as shown below})$, where R is the estimated risk of hospital death

SOFA

The European Society of Intensive Care Medicine developed the SOFA method in 1994 at a consensus meeting, and it underwent additional revisions in 1996. 30 The SOFA subjective score was assessed on 1449 patients by Vincent et al.65 in 1998. This score, which ranges from 0 to 4, was created to measure the severity of a patient's disease based on data on the degree of organ dysfunction in six different organ failures. The lowest mortality is indicated by one failing plus a respiratory failure; death ranges from 65% to 74% for all other combinations. The maximal score plus the maximal change have been examined in later analyses, which have demonstrated that the latter has a lesser prognostic value than the former. The temporal history of the patient's condition throughout the duration of the ICU stay is

also taken into consideration. Despite the lack of a direct correlation between SOFA score and death, two published prospective studies can be used to approximate the risk of mortality. [30]

A reliable prognostic predictor is the sequential evaluation of organ dysfunction in the initial days of intensive care unit admission.

Red Cell Distribution Width (RDW)[66]

Red blood cell (RBC) size heterogeneity is represented by the red cell distribution width (RDW), which is the coefficient of variance of RBC volume. Increased red cell breakdown, malnutrition, and blood transfusions all raise RDW. RDW is impacted by iron, vitamin B12, and folate deficits. Elevated RDW has been linked to biomarkers of chronic inflammation, including C-reactive protein and erythrocyte sedimentation rate.

The mean corpuscular volume of erythrocytes and its standard deviation are used to compute the red cell distribution width (RDW). Many acute and chronic disorders can change it. In patients with acute heart failure, pancreatitis, pulmonary embolism, acute renal failure, stroke, influenza, and sepsis, many authors demonstrated a correlation between high RDW and unfavourable outcomes. Anisocytosis is shown by RDW, which reflects the variation in erythrocyte volume.

Establishment of RAAS Scoring System for Sepsis and Investigate the Correlation Between Different RAAS Scores and Prognosis of Patients with Sepsis[67]

Assign parameter values based on the CUTOFF values of various parameters and various variable ranges. The MODS scoring system and the APACHE II scoring system's assignment methods serve as the foundation for the parameter assignment. In

order to confirm the impact of RAAS on prognosis assessment in sepsis patients, Within 24 hours of admission, patients' APACHE II, SOFA, and matching RAAS scores were determined. By comparing the AUC area of the three scoring systems, the predictive impact of RAAS on sepsis patients was assessed. The AUC area of the single RDW and the three scoring systems were computed.

The total mortality of sepsis patients corresponding to four distinct RAAS scoring intervals and the mortality of patients with varying RAAS scores were computed after the scores were split into four intervals (GROUP-1:0–1, GROUP-2:2–3, GROUP-3:4–5, and GROUP-4:6).

REVIEW OF RELATED ARTICLES

Mahashabde ML et al (2024)[68] determined that a high L/A ratio and the SOFA score at ICU admission were independent risk factors for ICU admission and were linked to a poor prognosis and unfavourable outcomes. In order to prevent negative outcomes, individuals with a high L/A ratio and SOFA score should be detected early and treated vigorously. In contrast to using serum lactate alone, the current study shows that adding serum albumin and lactate levels to the L/A ratio greatly improves predictive accuracy.

Kabra R et al (2023)[69] The purpose of this research is to evaluate the serum lactate/albumin (L/A) ratio's effectiveness as a sepsis syndrome prognostic indicator. With a sensitivity of 100% and a specificity of 88%, this study discovered that the L/A ratio was an exceptional predictive value for predicting death and hospital stay (discharge) among sepsis participants when compared to lactate and albumin alone.

Huang Y et al (2022)[67] To examine the short-, medium-, and long-term high risk of death in patients with sepsis diagnosed early in the emergency department (ED), a modified scoring system based on the RDW, AGE, SOFA, and APACHE II score (RAAS score) was created. They came to the conclusion that the RAAS score system is a new and trustworthy way to forecast the short- and medium-term mortality of sepsis patients. The death rate for sepsis patients steadily rises as the RAAS score rises.

Bou Chebl R et al (2021)[70] The purpose of this prospective study is to confirm that the L/A ratio to lactate has a better predictive value in sepsis and septic shock. They came to the conclusion that in sepsis patients, the L/A ratio is a more accurate indicator of in-hospital mortality than lactate. The septic shock subgroup did not exhibit this superiority. As a better predictive tool for sepsis patients, the authors advocate using the ratio early in the emergency department.

Bou Chebl R et al (2020)[71] Examining the predictive efficacy of the lactate to albumin (L/A) ratio in comparison to lactate alone in predicting morbidity and death in sepsis patients is the goal of this study. They came to the conclusion that for in-hospital mortality in adult septic patients, the L/A ratio performs better as a predictive indicator than initial serum lactate.

MATERIALS AND METHODS

Study design: Prospective cross-sectional study

Study area: Department of General Medicine, J.N. Medical College, Belagavi, Karnataka, India.

Study period: Research study was conducted from January 2023 to December 2023. Below is the work plan.

Table 1: Work plan of the study with percentage of allocation of study time and duration in months

Work plan	% of allocation of study time	Duration in months
Understanding the problem, preparation of questionnaire.	5-10%	January 2023 to March 2023
Pilot study, Validation of questionnaire, data collection and manipulation	Upto 80%	April 2023 to June 2023
Analysis and interpretation	5-10%	July 2023 to September 2023
Dissertation write-up and submission	5-10%	October 2023 to December 2023

Sample size: The minimum sample size formula based on prevalence rate is

$$n = \frac{z_\alpha^2 P(1-P)}{d^2}$$

where P is the prevalence rate and d is the percentage likely difference in the prevalence.

z_α is linked with the level of significance. For 5% level of the significance $z_\alpha = 1.96$.

Ref: Enter here the name of the article and the author.

The parameter considered in the calculation is the rate of mortality in ICU among severe sepsis cases which is 56%

With P = 56% and d = 20% of P = 11.2%, the sample size is 75.

Sampling Method: Consecutive sampling

- **Inclusion criteria:**

Age > 18 years

1. Patients diagnosed with sepsis.
2. Sepsis is defined according to sepsis 3 definition as a life-threatening organ dysfunction caused by dysregulated host response to infection.

Exclusion criteria:

1. Pregnant females
2. Patients lesser than 18 years of age
3. Patients not meeting sepsis 3 criteria
4. Septic shock.
5. Patients with recent blood transfusion.
6. Known cases of chronic liver diseases
7. Patients with history of chronic/acute alcohol abuse

METHODOLOGY:

This prospective cross-sectional study was conducted in the Medical Intensive Care Unit (MICU) at a tertiary care hospital in Belagavi from January 2023 to December 2023. The study aimed to establish a correlation between serum lactate albumin ratio and RAAS components (RDW width, Apache 2 score, and SOFA score) at different time points after MICU admission.

Study Population and Sample Selection

All patients above 18 years of age admitted to the MICU with a diagnosis of sepsis during the study period were considered for inclusion. The diagnosis of sepsis was based on the Sepsis-3 criteria, which defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Written informed consent was obtained from all participants or their legal representatives before enrollment in the study.

Patient Assessment and Data Collection

Upon admission to the MICU, detailed clinical history and physical examination findings were recorded for all enrolled patients. Vital parameters including temperature, blood pressure, heart rate, respiratory rate, and Glasgow Coma Scale were documented. The RAAS score was calculated for each patient at admission and at predetermined intervals during their MICU stay.

Laboratory Investigations

Blood samples were collected from all patients at admission and at specified intervals for various laboratory investigations. Complete blood count, including Red Cell

Distribution Width (RDW), was performed using an automated hematology analyzer. Mini renal profile, including blood urea nitrogen and serum creatinine, was assessed to evaluate renal function. Liver function tests were conducted to assess hepatic parameters including serum albumin levels.

Arterial blood gas (ABG) analysis was performed to measure serum lactate levels and assess acid-base status. Blood samples for culture were collected under strict aseptic precautions before the initiation of antimicrobial therapy. Urine analysis was conducted, and samples were sent for culture and sensitivity testing to identify potential urinary tract infections.

Calculation of Parameters

The lactate albumin ratio (LAR) was calculated by dividing the serum lactate level (mmol/L) by the serum albumin level (g/dL) obtained from the same blood sample. RDW was obtained directly from the complete blood count report. APACHE II score was calculated using twelve physiologic measurements, age, and previous health status. SOFA score was calculated using parameters from six organ systems (respiratory, coagulation, liver, cardiovascular, central nervous system, and renal).

Quality Control Measures

All laboratory investigations were performed in the hospital's accredited laboratory following standard operating procedures. Regular calibration of equipment and internal quality control measures were maintained throughout the study period. Double data entry and random cross-checking were performed to ensure data accuracy.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee. Patient confidentiality was maintained throughout the study period, and all procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Duration of Follow-up

Patients were followed up during their entire MICU stay. Laboratory parameters and clinical scores (RDW, APACHE II, and SOFA) were recorded until either discharge from MICU, death, or transfer to another facility. This allowed for comprehensive analysis of the temporal relationship between LAR and RAAS components.

Documentation and Record Keeping

All patient data, laboratory reports, and calculated scores were systematically documented in individual case record forms. Electronic backup of all data was maintained with appropriate security measures to ensure data protection and confidentiality.

STATISTICAL ANALYSIS

Data was entered in excel sheet and analyzed using SPSS version 21. Results were presented in tabular and graphical forms Mean, median, standard deviation and ranges were calculated for quantitative data. Qualitative data were expressed in terms of frequency and percentages. Student t test (Two Tailed) was used to test the significance of mean and P value <0.05 was considered significant.

RESULTS

Table 1 and Graph 1 show the distribution of patients according to age. The majority of patients (46.7%) were above 60 years of age, followed by those in the 51-60 years age group (22.7%). The younger age groups had fewer patients, with only 1.3% under 20 years, 10.7% in the 21-30 years range, 8% in the 30-40 years range, and 10.7% in the 41-50 years range. This indicates that sepsis predominantly affected the elderly population in this study.

Table 1: Distribution of patients according to age

Age (in years)	Frequency	Percentage
<20	1	1.3%
21-30	8	10.7%
30-40	6	8%
41-50	8	10.7%
51-60	17	22.7%
>60	35	46.7%
Total	**75**	**100%**

Graph 1: Distribution of patients according to age

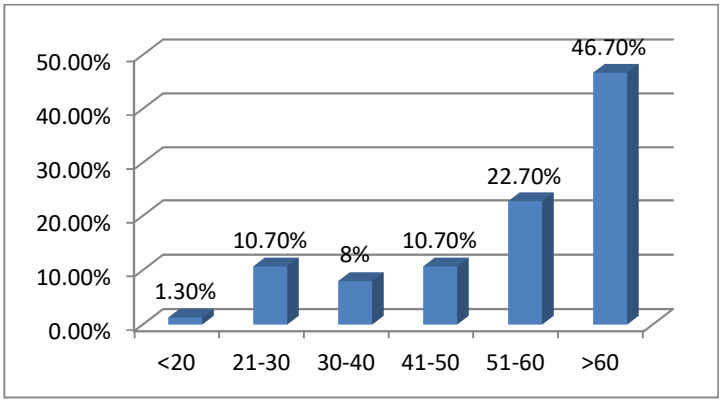


Table 2 and Graph 2 show the distribution of patients according to gender. Males comprised 64% of the study population, while females accounted for 36%. This suggests a higher prevalence of sepsis among male patients in the MICU at the tertiary care hospital.

Table 2: Distribution of patients according to gender

Gender	Frequency	Percentage
Female	27	36%
Male	48	64%
Total	**75**	**100%**

Graph 2: Distribution of patients according to gender

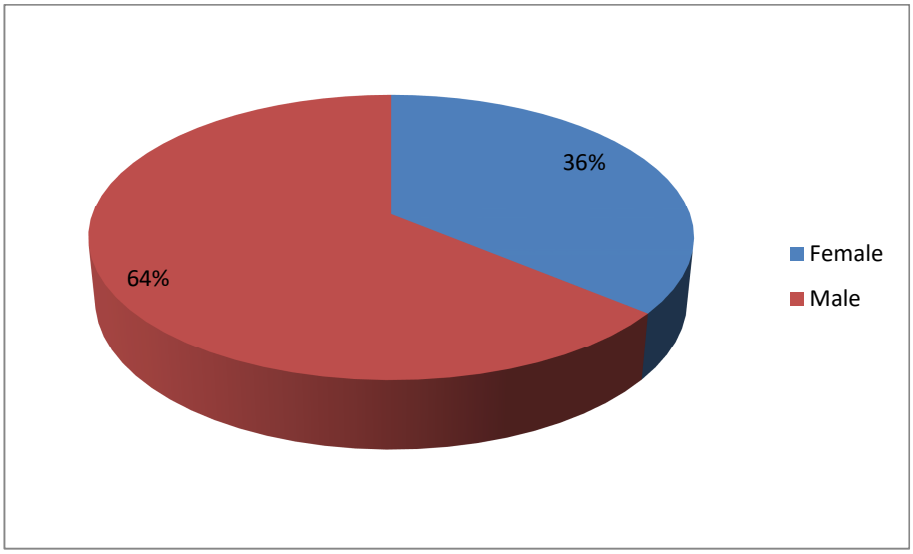


Table 3 and Graph 3 show the distribution of patients according to diagnosis. The most common diagnoses were Cellulitis, Chronic Kidney Disease, and Pneumonia, each accounting for 13.3% of cases. Other significant diagnoses included Acute Kidney Injury (9.3%), Acute Gastroenteritis (8%), and Heart Failure/Infarct (8%). Less common diagnoses included Poisoning and Polytrauma (2.6% each) and Lung Abscess (4%).

Table 3: Distribution of patients according to Diagnosis

Diagnosis*	Frequency	Percentage
Abdominal Tuberculosis	4	5.3%
Acute Gastroenteritis	6	8%
Acute Kidney Injury	7	9.3%
Cellulitis	10	13.3%
Poisoning	2	2.6%
Pyelonephritis	4	5.3%
Chronic Kidney Disease	10	13.3%
Sepsis	4	5.3%
Dengue encephalopathy	5	6.6%
Hypertensive encephalopathy	4	5.3%
Lung Abcess	3	4%
Pneumonia	10	13.3%
Polytrauma	2	2.6%
Status Epilepticus	4	5.3%
Heart Failure/Infarct	6	8%
Subacute Hemorrhage	2	2.6%
Total	**75**	**100%**

*multiple responses

Graph 3: Distribution of patients according to Diagnosis

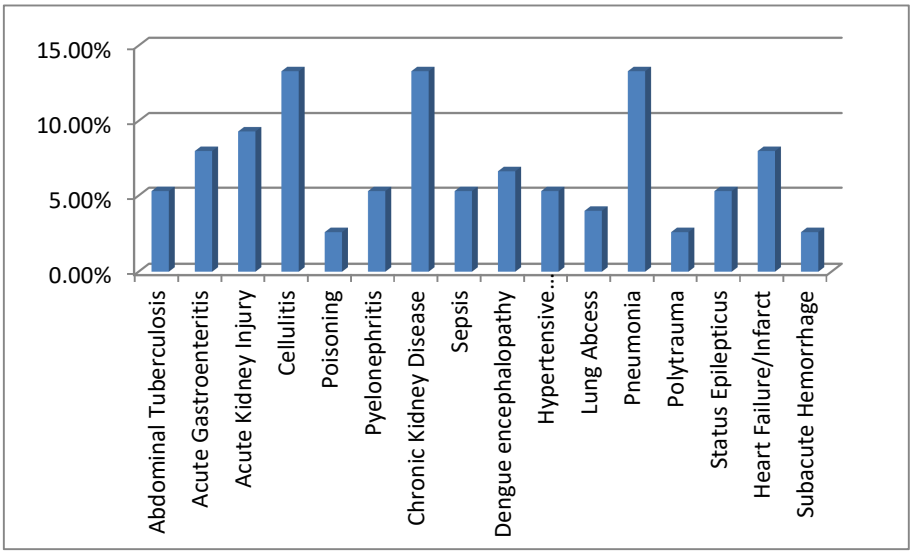


Table 4 and Graph 4 show the distribution of patients according to the presence of hypertension and diabetes. The majority of patients (41.3%) had no comorbidities. However, 29.3% had both hypertension and diabetes, 22.7% had hypertension alone, and 6.7% had diabetes alone. This indicates that hypertension was more prevalent than diabetes among the sepsis patients in this study.

Table 4: Distribution of patients according to Presence of hypertension and diabetes

Co-morbidity	Frequency	Percentage
Diabetes	5	6.7%
Hypertension	17	22.7%
Hypertension and diabetes	22	29.3%
None	31	41.3%
Total	**75**	**100%**

Graph 4: Distribution of patients according to Presence of hypertension and diabetes

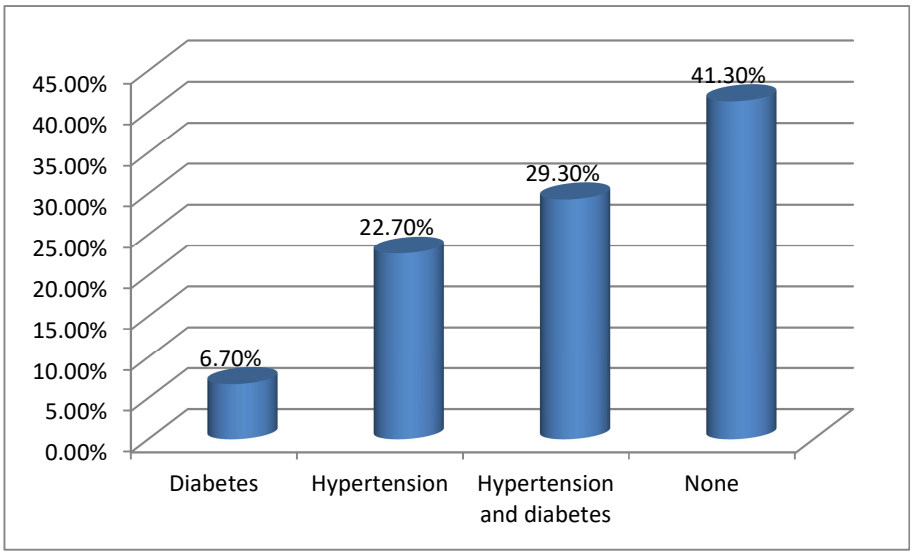


Table 5 and Graph 5 show the distribution of patients according to Procalcitonin (PCT) levels. The majority of patients (70.7%) had PCT levels between 2-10, indicating moderate to high risk. Only 10.7% had low-risk PCT levels (0.05-0.5), while 18.7% had possible risk levels (0.5-2). This demonstrates that most sepsis patients in the study had significantly elevated PCT levels.

Table 5: Distribution of patients according to Procalcitonin Levels

PCT	Frequency	Percentage
0.05-0.5 (Low risk)	8	10.7%
0.5-2 (Possible Risk)	14	18.7%
2-10 (Moderate to high risk)	53	70.7%
Total	**75**	**100%**

Graph 5: Distribution of patients according to Procalcitonin Levels

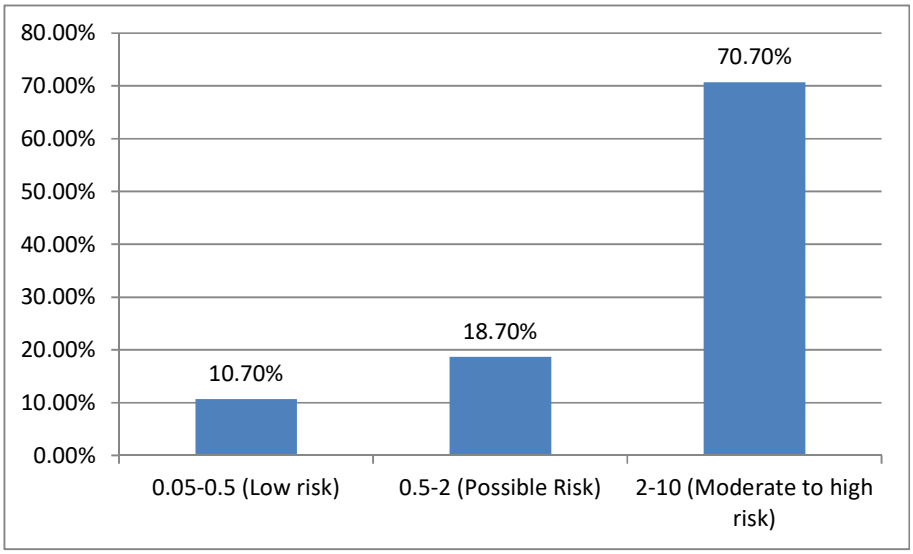


Table 6 and Graph 6 show the distribution of patients according to high-sensitivity C-reactive protein (hsCRP) levels. An overwhelming majority (90.7%) of patients had hsCRP levels greater than 3, indicating possible risk, while only 9.3% had low-risk levels (1-3). This suggests that hsCRP is a sensitive marker for inflammation in sepsis patients.

Table 6: Distribution of patients according to hsCRP Levels

hsCRP	Frequency	Percentage
1-3 (Low risk)	7	9.3%
>3 (Possible Risk)	68	90.7%
Total	**75**	**100%**

Graph 6: Distribution of patients according to hsCRP Levels

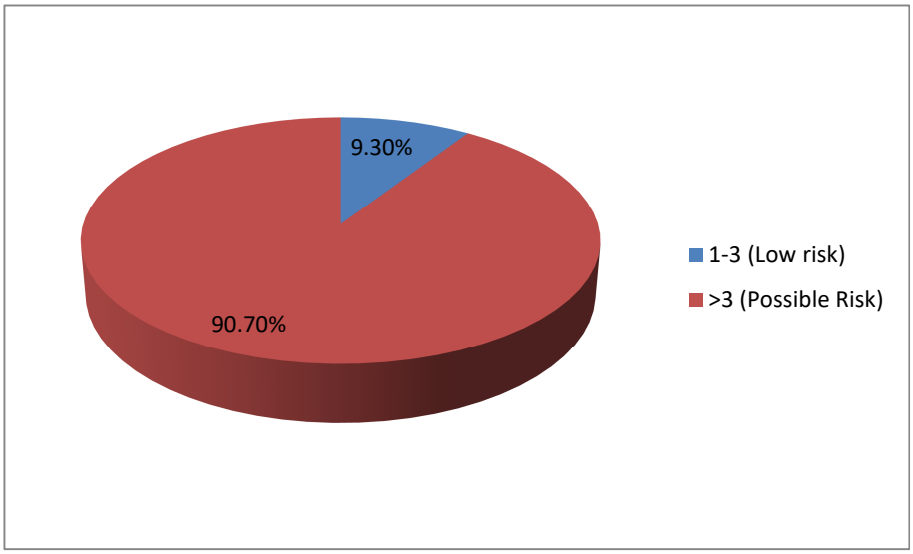


Table 7 and Graph 7 show the distribution of patients according to Lactate to Albumin (LA) ratio. Most patients (78.7%) had normal LA ratios (0.5-1.33), while 21.3% had ratios above 1.33, indicating possible risk. This suggests that the LA ratio may not be elevated in all sepsis cases.

Table 7: Distribution of patients according to Lactate to Albumin ratio

LA	Frequency	Percentage
0.5-1.33 (Normal)	59	78.7%
>1.33 (Possible Risk)	16	21.3%
Total	**75**	**100%**

Graph 7: Distribution of patients according to Lactate to Albumin ratio

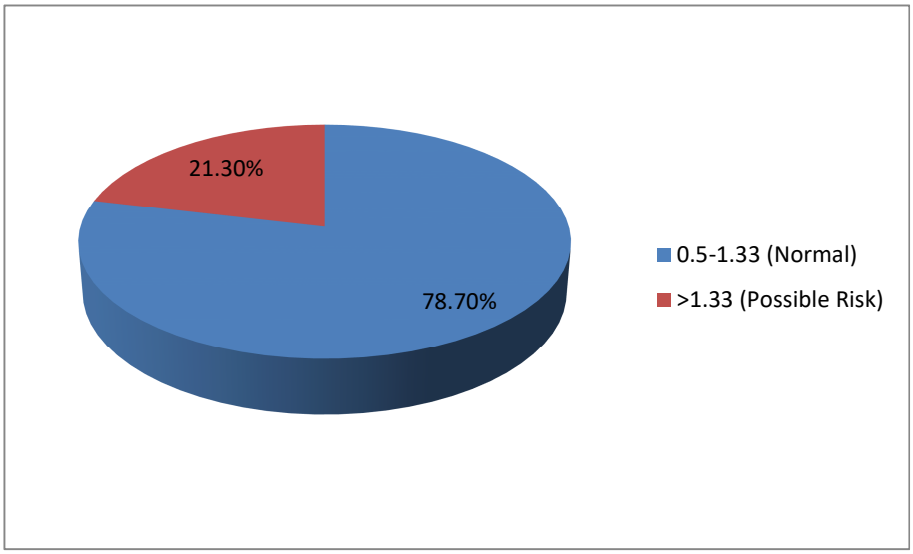


Table 8 and Graph 8 show the distribution of patients according to APACHE II scores. Nearly half (48%) of the patients had moderate risk scores (11-20), 44% had low-risk scores (0-10), and only 8% had high-risk scores (21-30). This distribution indicates that most sepsis patients in the study had low to moderate severity based on APACHE II scoring.

Table 8: Distribution of patients according to APACHE II scores

APACHE II scores	Frequency	Percentage
0-10 (Low risk)	33	44%
11-20 (Moderate Risk)	36	48%
21-30 (High Risk)	6	8%
Total	**75**	**100%**

Graph 8: Distribution of patients according to APACHE II scores

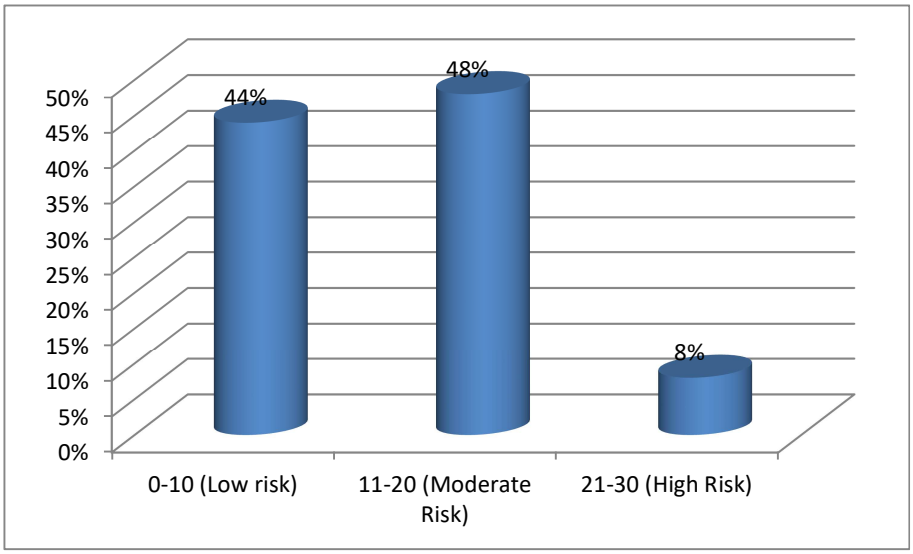


Table 9 and Graph 9 show the distribution of patients according to RAAS categories. The majority (60%) of patients fell into Group 3, followed by Group 2 (26.7%), Group 4 (8%), and Group 1 (5.3%). This suggests that the RAAS scoring system classified most patients in the higher risk categories.

Table 9: Distribution of patients according to RAAS categories

RAAS	Frequency	Percentage
Group 1	4	5.3%
Group 2	20	26.7%
Group 3	45	60%
Group 4	6	8%
Total	**75**	**100%**

Graph 9: Distribution of patients according to RAAS categories

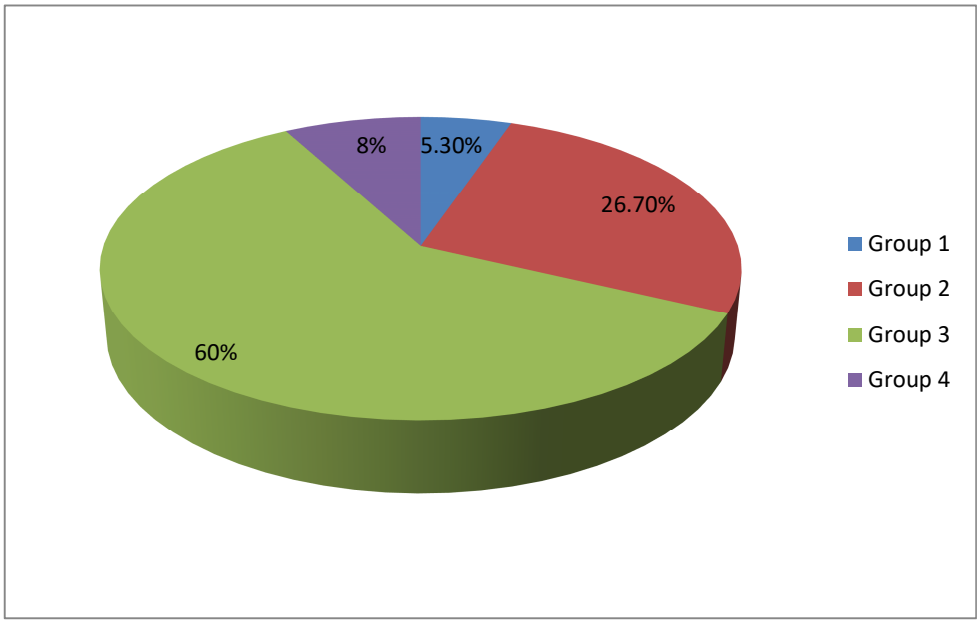
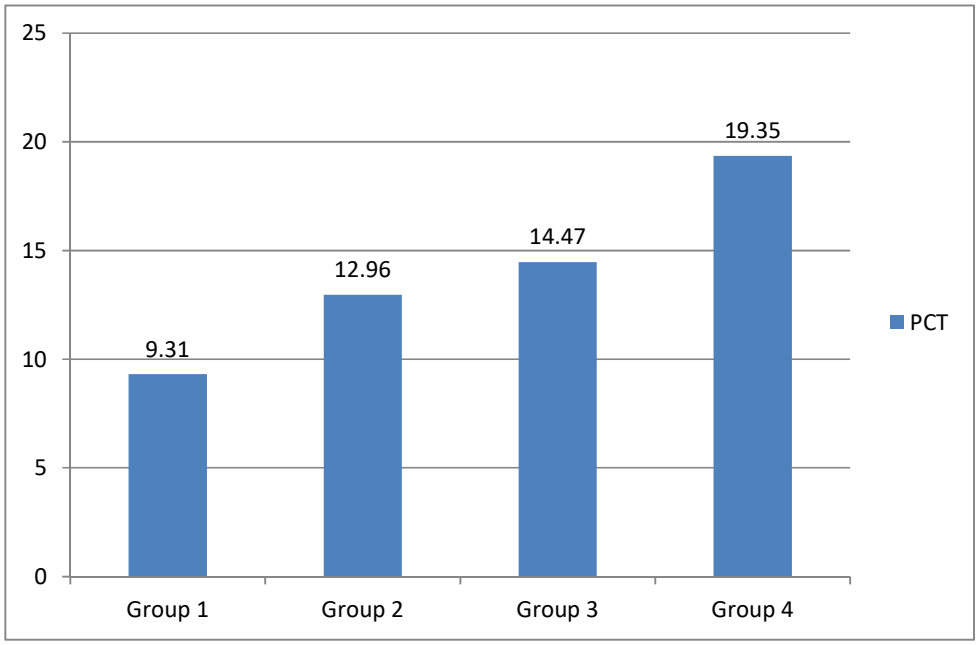


Table 10 and Graphs 10a-10e show the distribution of patients according to RAAS categories and their comparison with other scores. Significant differences ($p<0.05$) were observed in PCT, hsCRP, RDW, SOFA, and APACHE II scores across the four RAAS groups. The mean values of PCT, RDW, SOFA, and APACHE II increased progressively with higher RAAS groups, while hsCRP showed a decreasing trend. This suggests that the RAAS categories effectively stratify patients with different severity levels.

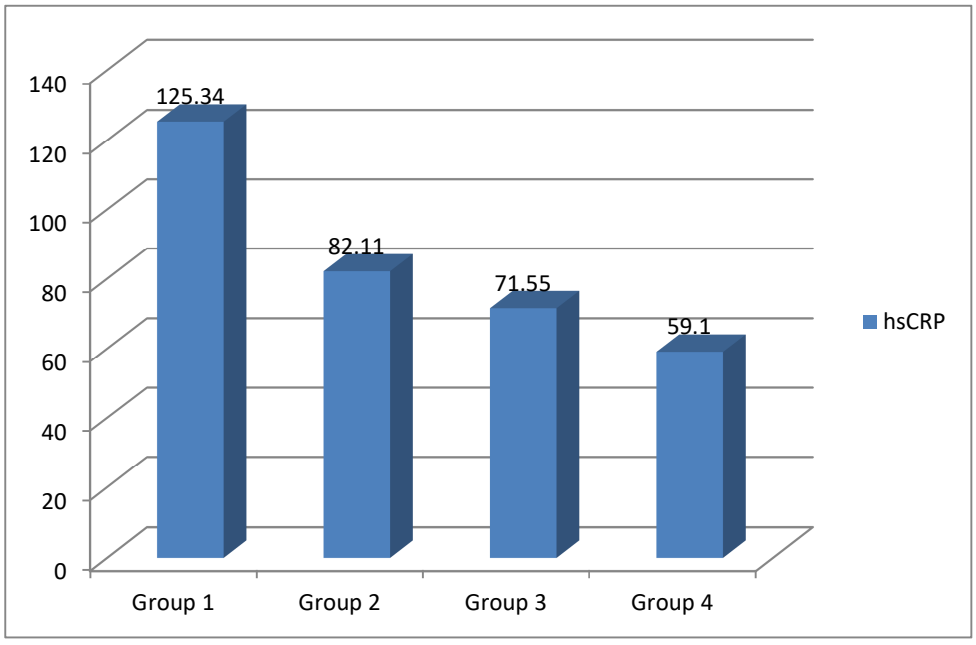
Table 10: Distribution of patients according to RAAS categories and their comparison with other scores

RAAS	Group 1	Group 2	Group 3	Group 4	P value
PCT	9.31 ± 10.36	12.96 ± 34.07	14.47 ± 32.54	19.35 ± 14.49	**0.0167**
hsCRP	125.34 ± 145.92	82.11 ± 81.78	71.55 ± 95.53	59.1 ± 66.32	**<0.001**
RDW	12.75 ± 0.47	14.18 ± 0.78	17.84 ± 2.32	17.25 ± 1.76	**<0.001**
Albumin	2.8 ± 0.74	2.86 ± 0.819	2.69 ± 0.54	2.78 ± 0.66	0.812
Lactate	2.92 ± 1.57	3.01 ± 1.13	3.71 ± 1.83	3.39 ± 1.86	0.421
SOFA	4.75 ± 1.5	4.25 ± 1.86	6.1 ± 2.43	5.6 ± 1.34	**0.021**
APACHEII	11.0 ± 3.46	11.5 ± 5.64	15.7 ± 5.24	19.8 ± 1.92	**0.002**
LA ratio	1.1 ± 0.77	1.15 ± 0.64	1.46 ± 0.89	1.37 ± 0.81	0.490

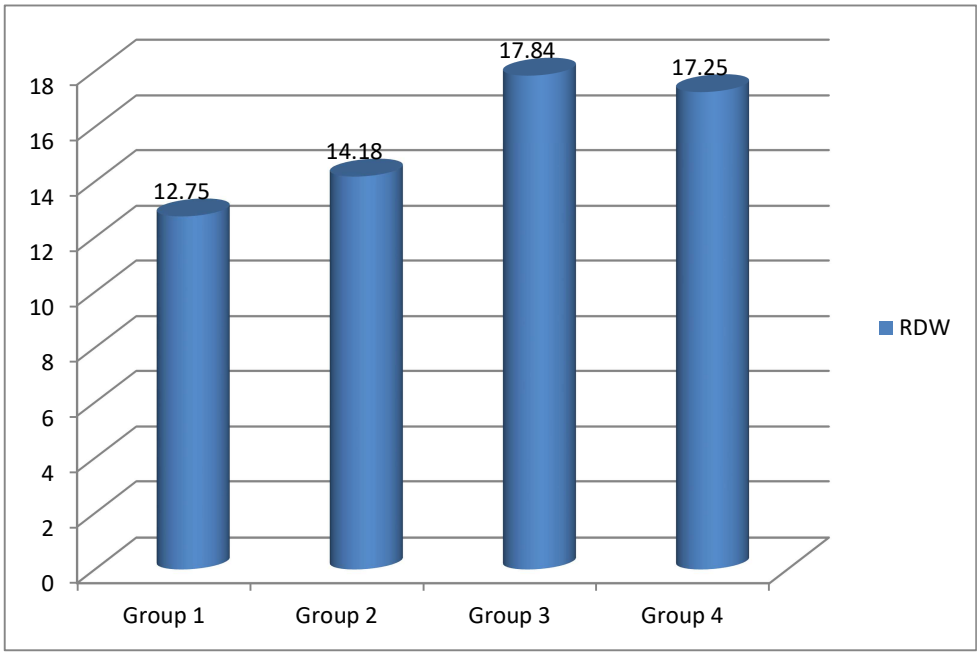
Graph 10a: Comparison of PCT among RAAS groups



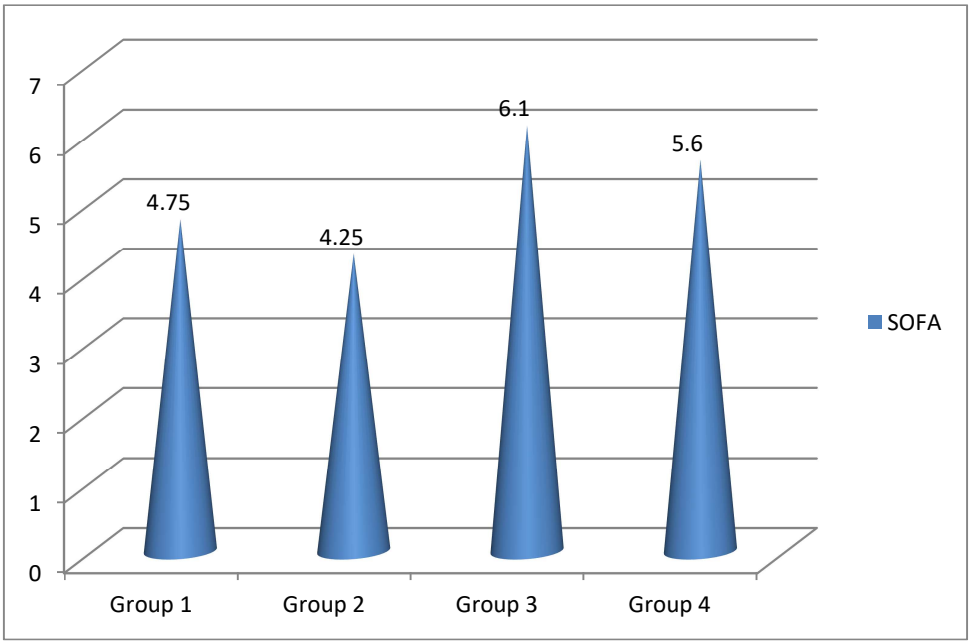
Graph 10b: Comparison of hsCRP among RAAS groups



Graph 10c: Comparison of RDW among RAAS groups



Graph 10d: Comparison of SOFA among RAAS groups



Graph 10e: Comparison of APACHEII among RAAS groups

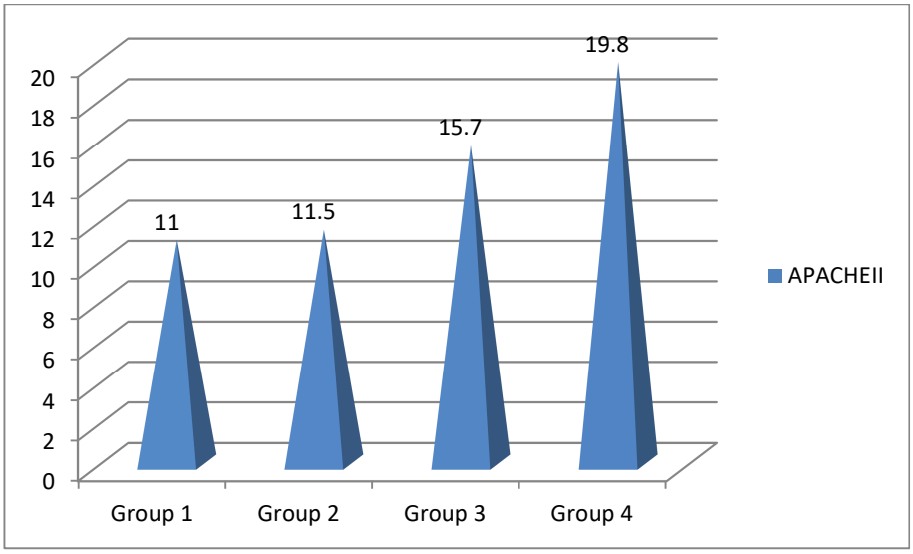


Table 11 and Graph 11 show the correlation between RAAS and different variables. Significant positive correlations were observed between RAAS and SOFA (r=0.268, p=0.020), RAAS and APACHE II (r=0.533, p<0.001), and RAAS and RDW (r=0.506, p<0.001). The correlations with LA ratio, albumin, and lactate were not statistically significant. This indicates that RAAS correlates well with established severity scores (SOFA and APACHE II) and with RDW.

Table 11: Correlation between RAAS and different variables

RAAS	Correlation co-efficient	P value
LA	0.161	0.168
SOFA	0.268	**0.020**
APACHE II	0.533	**<0.001**
Albumin	-0.126	0.281
Lactate	0.146	0.210
RDW	0.506	**<0.001**

Graph 11: Correlation coefficients between RAAS and different variables

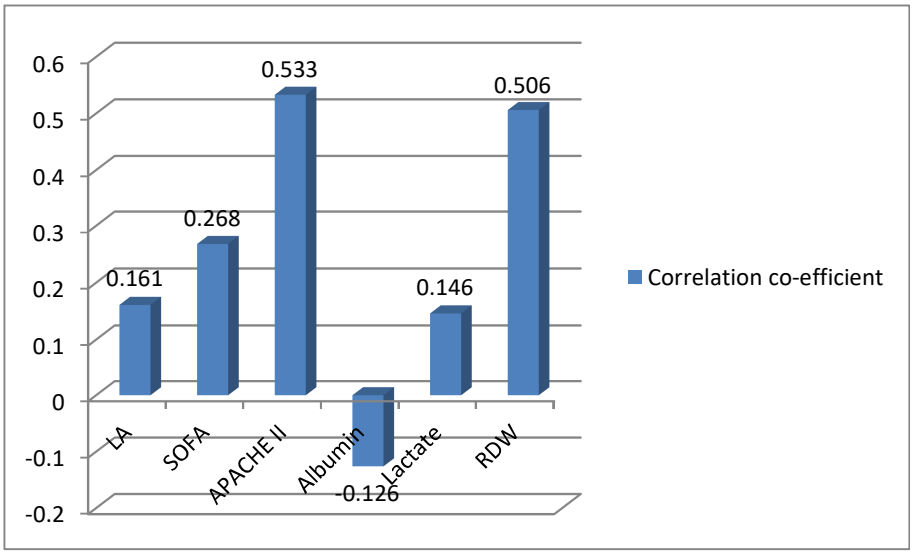
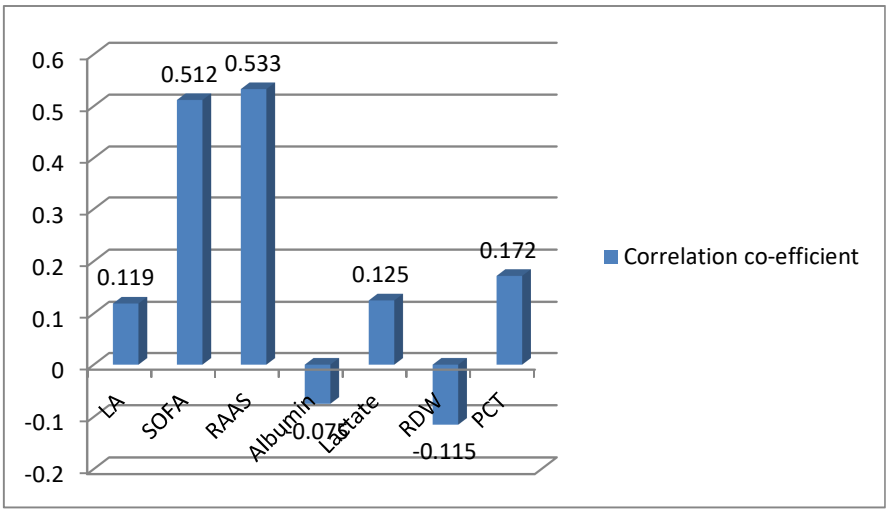


Table 12 and Graph 12 show the correlation between different variables and APACHE II. Significant positive correlations were observed between APACHE II and SOFA ($r=0.512$, $p<0.001$) and between APACHE II and RAAS ($r=0.533$, $p<0.001$). The correlations with other variables, including LA ratio, albumin, lactate, RDW, and PCT, were not statistically significant. This further supports the relationship between RAAS and established severity scores.

Table 12: Correlation between different variables and APACHE II

APACHE II	Correlation co-efficient	P value
LA	0.119	0.309
SOFA	0.512	**<0.001**
RAAS	0.533	**<0.001**
Albumin	-0.075	0.525
Lactate	0.125	0.286
RDW	-0.115	0.452
PCT	0.172	0.295

Graph 12: Correlation co-efficients between different variables and APACHE II



Inter-parameter Correlations

The correlations between the three parameters (PCT, RDW, and SOFA) were minimal, suggesting that these parameters capture different aspects of patient condition. PCT and SOFA showed the strongest inter-parameter correlation at r = 0.1383, while PCT and RDW showed a slight negative correlation (r = -0.0615), as did RDW and SOFA (r = -0.0871) (Table 13).

Table 13: Correlations between Clinical Parameters

Parameter Pair	Pearson's Correlation Coefficient (r)
PCT and RDW	-0.0615
PCT and SOFA	0.1383
RDW and SOFA	-0.0871

Combined Parameter Analysis

Five different weighting schemes were evaluated to assess whether a combination of PCT, RDW, and SOFA could achieve a stronger correlation with APACHE II than any individual parameter. The strongest correlation was achieved with weights based on each parameter's individual correlation strength with APACHE II ($r = 0.4827$), which assigned 64% weight to SOFA, 22% to PCT, and 14% to RDW. Emphasizing SOFA in the combined score (50% weight) yielded the second-strongest correlation ($r = 0.4117$) (Table 14).

Notably, the correlation-based weighting scheme produced a correlation coefficient that was slightly lower than SOFA alone, indicating that the addition of PCT and RDW in this proportion did not substantially enhance the predictive capability beyond what SOFA already provides.

Table 14: Combined Parameter Correlations with APACHE II Score

Weighting Scheme	Parameter Weights	Correlation with APACHE II (r)
Equal weights	PCT (33%), RDW (33%), SOFA (33%)	0.3246
Correlation-based weights	PCT (22%), RDW (14%), SOFA (64%)	0.4827
SOFA emphasized	PCT (25%), RDW (25%), SOFA (50%)	0.4117
PCT emphasized	PCT (50%), RDW (25%), SOFA (25%)	0.2635
RDW emphasized	PCT (25%), RDW (50%), SOFA (25%)	0.2017

Multiple Correlation Analysis

The multiple correlation coefficient (R) for the combination of PCT, RDW, and SOFA with APACHE II was 0.5234, indicating a moderate overall correlation. The multiple coefficient of determination (R^2) was 0.2739, suggesting that these three parameters together explain approximately 27.39% of the variance in APACHE II scores (Table 15). This represents a meaningful improvement over using SOFA alone, which explains approximately 26.2% (0.512^2) of the variance.

Table 15: Multiple Correlation Analysis

Statistic	Value	Interpretation
Multiple correlation coefficient (R)	0.5234	Moderate correlation
Multiple coefficient of determination (R^2)	0.2739	27.39% of variance explained

DISCUSSION

This prospective cross-sectional study provides valuable insights into the relationship between serum lactate-albumin ratio, RAAS scoring system, and established prognostic markers in sepsis patients admitted to the MICU of a tertiary care hospital. Our findings demonstrate that the RAAS scoring system correlates significantly with validated prognostic tools such as APACHE II and SOFA scores, suggesting its utility as a comprehensive assessment tool for sepsis severity.

The significant positive correlation between RAAS scores and procalcitonin levels, along with the strong correlation with RDW values, further validates the RAAS system as a reliable indicator of sepsis severity and potential outcomes. While the correlation between LAR and RAAS scores did not reach statistical significance, we observed a trend toward higher LAR values in patients with higher RAAS categories, indicating potential clinical relevance that warrants further investigation in larger cohorts.

Our demographic analysis revealed a predominance of elderly patients and those with comorbidities, particularly hypertension and diabetes, emphasizing the need for heightened vigilance and targeted interventions in these vulnerable populations. The diverse spectrum of diagnoses leading to sepsis in our study underscores the complexity of sepsis pathophysiology and the need for a multidisciplinary approach to management.

The integration of multiple biomarkers and scoring systems, as demonstrated in our study, could potentially enhance risk stratification and guide clinical decision-making in sepsis management. Early identification of high-risk patients using readily available markers such as LAR, RDW, and RAAS scores may facilitate timely interventions and improve outcomes.

Despite certain limitations, including the relatively small sample size and single-center design, our study contributes meaningfully to the existing evidence base on sepsis prognostication. Future larger multicenter studies with longitudinal follow-up are recommended to further validate our findings and explore their implications for clinical practice. The potential incorporation of LAR and RDW into existing sepsis assessment protocols could represent a cost-effective approach to enhancing prognostic accuracy in resource-limited settings.

In conclusion, this study highlights the complex interplay between various biomarkers and scoring systems in sepsis and underscores the potential value of integrating multiple parameters for comprehensive risk assessment. The RAAS scoring system, complemented by biomarkers such as LAR and RDW, offers promising avenues for enhancing sepsis management and improving patient outcomes.

MERITS OF THE STUDY

- Prospective design, which reduces recall bias and allows for standardized data collection protocols
- Comprehensive assessment of multiple biomarkers and severity scores (PCT, hsCRP, LAR, RDW, APACHE II, SOFA) allowing for comparative analysis
- Use of established sepsis criteria (Sepsis-3) for patient inclusion, ensuring alignment with current consensus definitions
- Implementation of quality control measures for laboratory investigations, enhancing reliability of biomarker measurements
- Systematic documentation and calculation of scores at predefined time points, allowing for temporal analysis
- Inclusion of both clinical and laboratory parameters, providing a comprehensive assessment of patient status

- Investigation of novel biomarker ratios (LAR) that may offer cost-effective prognostic information compared to complex scoring systems
- Statistically significant correlations identified between RAAS and established severity scores (SOFA and APACHE II), suggesting clinical relevance
- Diverse patient population with various underlying diagnoses, potentially increasing the generalizability within sepsis patients
- Ethical considerations appropriately addressed, including informed consent and institutional review board approval

LIMITATIONS OF THE STUDY

- Single-center study conducted at a tertiary care hospital in Belagavi, which may limit generalizability to other healthcare settings or geographical regions
- Cross-sectional design that provides correlational data but cannot establish causality between LAR and RAAS components
- Relatively small sample size (n=75), which may limit statistical power, especially for subgroup analyses
- Consecutive sampling method used instead of random sampling, which could introduce selection bias
- Short follow-up period limited to MICU stay, preventing assessment of long-term outcomes and prognostic value
- Heterogeneous study population with multiple underlying diagnoses and comorbidities, which may confound the relationship between LAR and RAAS components
- Exclusion of patients with septic shock, limiting applicability to the full spectrum of sepsis severity

- Potential confounding from treatment interventions (e.g., fluid resuscitation, antimicrobial therapy) not accounted for in the analysis
- Lack of external validation of the findings in an independent cohort
- Multiple comorbidities (58.7% had either diabetes, hypertension, or both) may have influenced the biomarker levels independent of sepsis severity

SUMMARY

INTRODUCTION

Sepsis remains a significant global health concern with high morbidity and mortality rates despite advances in critical care medicine. Early identification and risk stratification are crucial for timely interventions. This study aimed to evaluate the correlation between serum lactate-albumin ratio (LAR) and the RAAS (Rapid Alarm Asepsis Score) scoring system, along with other established prognostic markers, in sepsis patients admitted to the Medical Intensive Care Unit (MICU) at a tertiary care hospital.

Objective:

1. To establish a correlation between serum lactate albumin ratio and RAAS scoring system at different points after admission in the MICU at a tertiary care hospital.

MATERIAL AND METHODS

A prospective cross-sectional study was conducted involving 75 patients diagnosed with sepsis according to the Sepsis-3 criteria and admitted to the MICU. Demographic details, clinical characteristics, and laboratory parameters including serum lactate, albumin, procalcitonin (PCT), high-sensitivity C-reactive protein (hsCRP), and red cell distribution width (RDW) were recorded. Established scoring systems including APACHE II (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sequential Organ Failure Assessment) were calculated. RAAS scores were determined and patients were categorized into four groups. Correlations between LAR, RAAS scores, and other prognostic markers were analyzed.

RESULTS

The key findings of our study can be summarized as follows:

1. **Demographic and Clinical Characteristics**:

- Age distribution revealed a predominance of elderly patients, with 46.7% above 60 years and 22.7% in the 51-60 age group.
- Gender distribution showed male predominance (64%) compared to females (36%).
- The most common diagnoses leading to sepsis were pneumonia, chronic kidney disease, and cellulitis (13.3% each), followed by acute kidney injury (9.3%).
- Regarding comorbidities, 29.3% had both hypertension and diabetes, 22.7% had hypertension alone, and 6.7% had diabetes alone, while 41.3% had no documented comorbidities.

2. **Biomarker and Scoring System Results**:

- Procalcitonin levels indicated moderate to high risk (2-10 ng/mL) in 70.7% of patients.
- High-sensitivity C-reactive protein was elevated (>3 mg/L) in 90.7% of patients.
- Lactate-albumin ratio was elevated (>1.33) in 21.3% of patients, suggesting increased risk.
- APACHE II scores showed low risk (0-10) in 44% of patients, moderate risk (11-20) in 48%, and high risk (21-30) in 8%.

- RAAS categorization showed predominance of Group 3 (60%), followed by Group 2 (26.7%), Group 4 (8%), and Group 1 (5.3%).

3. **Correlation Analyses**:

    - RAAS scores demonstrated significant positive correlations with:
        - APACHE II scores ($r=0.533$, $p<0.001$)
        - SOFA scores ($r=0.268$, $p=0.020$)
        - RDW values ($r=0.506$, $p<0.001$)
        - Procalcitonin levels ($p=0.0167$)
    - RAAS scores showed significant negative correlation with hsCRP levels ($p<0.001$)
    - Lactate-albumin ratio showed a positive but non-significant correlation with RAAS scores ($r=0.161$, $p=0.168$)
    - No significant correlation was observed between RAAS scores and albumin levels ($r=-0.126$, $p=0.281$) or lactate levels alone ($r=0.146$, $p=0.210$)

4. **Comparative Analyses**:

- Mean RDW values increased significantly across RAAS categories, from 12.75±0.47% in Group 1 to 17.84±2.32% in Group 3 ($p<0.001$)
- Mean APACHE II scores increased progressively across RAAS categories, from 11.0±3.46 in Group 1 to 19.8±1.92 in Group 4 ($p=0.002$)

- Mean procalcitonin levels showed an increasing trend across RAAS categories, from 9.31±10.36 ng/mL in Group 1 to 19.35±14.49 ng/mL in Group 4
- Mean lactate-albumin ratio showed a trend toward higher values in Group 3 (1.46±0.89) compared to Group 1 (1.1±0.77), although not statistically significant (p=0.490)

These results support the validity of the RAAS scoring system as a comprehensive prognostic tool in sepsis and highlight the potential complementary role of biomarkers such as LAR and RDW in risk stratification. The significant correlations between RAAS scores and established prognostic markers (APACHE II, SOFA, PCT, RDW) underscore its utility in sepsis severity assessment, while the trend toward higher LAR values in higher RAAS categories, albeit not statistically significant, suggests potential clinical relevance that warrants further investigation in larger studies.

CONCLUSION:

This study validates the RAAS scoring system as a comprehensive prognostic tool in sepsis, demonstrating significant correlations with established severity markers. While the correlation between LAR and RAAS scores was not statistically significant, the trend toward higher LAR values in higher RAAS categories suggests potential clinical relevance. The integration of multiple biomarkers including LAR and RDW with established scoring systems could enhance risk stratification and guide clinical decision-making in sepsis management. Future larger studies are warranted to further validate these findings.

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ANNEXURE – I - INFORMED CONSENT FORM

" A STUDY TO CORRELATE SERUM LACTATE ALBUMIN RATIO TO RAAS SCORING SYSTEM IN SEPSIS IN MICU AT A TERTIARY CARE HOSPITAL-A PROSPECTIVE CROSS SECTIONAL STUDY"

Name of Student/Principal Investigator:

Name of Guide/Co Investigators: MD (GENERAL MEDICINE)

PROFESSOR AND UNIT CHIEF, OF GENERAL MEDICINE

J.N.MEDICAL COLLEGE, BELAGAVI

Introduction:

- Sepsis is a life-threatening complication of infection and characterized by physiologic, pathologic, and biochemical abnormalities.
- It is the tenth most common cause of death globally.
- The incidence of sepsis and septic shock is reported to be increasing according to ICD 9 CM which is almost 50% higher in the last decade.
- Despite acknowledgment represented by the Third consensus definition for sepsis and septic shock and the surviving sepsis campaign, there are still important gaps in the diagnosis and identification of sepsis.
- Sepsis is defined as a dysregulated host response to infection that leads to acute organ dysfunction.
- Diagnostic criteria -

Sepsis- f(threat to life|organ dysfunction|dysregulated host response| infection).

Where sepsis is the dependent variable. It is a function of 4 independent variables linked in a causal pathway, one conditional upon the other.

- Many infection-specific biomarkers and molecular diagnostics are under study to help discriminate sterile inflammation from infection, but these tools are not commonly used.
- A clinician's acumen is still crucial to the diagnosis of infection. The primary physiologic manifestations of organ dysfunction can be assessed quickly at the bedside with various scoring systems.
- This study aims to correlate lactate albumin ratio (which already has an established positive correlation with sepsis) to RAAS scoring system (which is a superior scoring system used to assess the prognosis of sepsis)
- A strong correlation between a biomarker ratio and a scoring system is anticipated to strengthen the authenticity of each.

Explanation of procedure: The patients will be selected according to the aforementioned inclusion and exclusion criteria.

Vitals will be recorded and samples will be collected for the following at the time of admission.

1)Complete blood count
2)Mini renal
3)Liver function test
4) ABG
5) Blood culture
6) Urine analysis
7) Urine culture

Patients will be followed up on days 7 and 21 (or last day of hospital stay) after admission and the use of vasopressors, steroids and other medications that can alter the serum lactate levels will be noted.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case the you decide to withdraw your participation, you are free to do so. However, you are requested to convey the decision to the principal investigator.

Possible benefits from participating in the study: An early diagnosis will be helpful to determine further course of treatment**.** The data gathered will help the population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from the you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from the you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: The patient will not receive any payment for participating in this study.

The cost of investigations done during the course of the study will be paid by the principal investigator**.** (Strike out which is not applicable)

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purposes and or presented to scientific groups. However, the patients identity will never be revealed.

Questions: In case of any questions with regard to this study, you are free to contact:

If you have any questions or complaints with regard to your right as a study participant you may contact Dr Harsha Hegde, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, we are not waving any of your legal rights

CONSENT STATEMENT

I am making a voluntary decision to participate in the study**" A STUDY TO CORRELATE SERUM LACTATE ALBUMIN RATIO TO RAAS SCORING SYSTEM IN SEPSIS IN MICU AT A TERTIARY CARE HOSPITAL-A PROSPECTIVE CROSS-SECTIONAL STUDY"**

My signature below indicates that I have decided to participate and I have read the information provided above or the information provided above has been read to me in the language that I understand best. I was given the opportunity to ask questions and that they have been answered to my satisfaction.

Name of the participant:

Signature or left thumb impression of the participant:

Name of the witness:

Signature or left thumb impression of the witness:

Name of the investigator:

Signature of the investigator:

ANNEXURE – II

MASTER CHART

	AGE/SEX	IP NUMBER	DIAGNOSIS	HTN/DM	PCT	HSCRP	RDW	ALBUMIN	LACTATE	SOFA	APACHE2	L:A	RAAS	FERRITIN	D-DIMER
1	55/F	10073605	NET TUMOR STAGE 4	HTN	100		18.3	2	6	6	22	3	5		
2	67/M	10074330	STATUS EPILEPTICUS	NA	6		19.2	1.6	3.08	5	18	2.375	6		
3	86/M	10072209	AOCKD/PNEUMONIA	DM/HTN			12.3	3.8	2.54	4	8	0.66	3		
4	69/F	10074223	METABOLIC ENCEPHALOPATHY	HTN/DM	0.18		17.1	2.4	6	4	18	2.5	3		
5	65/M	10073963	LUNG ABSCESS	NA	1.31	274	23.9	2.9	2.1	5	19	0.72	6	806	926
6	28/M	10073955	HIE/ASPIRATION PNEUMONIA	NA	30		19	2.5	5	5	19	2	5		
7	58/M	10074398	HYPERTENSIVE ENCEPHALOPATHY	HTN/DM	6.75		13	2.8	2.07	3	14	0.73	1		
8	76/F	10072876	PNEUMONIA	HTN/DM	5	45.6	18.5	1.7	3.82	5	20	2.24	9		
9	21/M	10074863	SEPSIS	NA	22		19	2.9	2.1	4	19	0.72	5		
10	38/F	10075187	EMPHYSEMATOUS PYELONEPHRITIS	DM	88.2		19.9	2.4	8.34	5	19	3.47	5		
11	50/M	10074983	PNEUMONIA	NA	44		17.8	4	2.2	2	16	0.55	2		
12	30/F	10075376	VIRAL PNEUMONIA	NA	8.28	208	15	2.3	2.11	5	8	0.7	3		
13	60/M	10072937	DENGUE ENCEPHALOPATHY	HTN/DM			17.8	1.8	3.97	7	3	2.2	3		
14	59/M	10075578	AOCKD	HTN/DM			16.4	3.2	2.95	6	21	0.92	4		
15	73/M	10074174	AKI	HTN/DM	4.73		17.4	3	3	6	18	1	5		
16	71/M	10073855	AECOPD	HTN			20	3.2	2.38	5	23	0.74	6		
17	23/F	10074905	ABDOMINAL TB	NA	47		18	2.4	6.41	5	19	2.67	5		
18	58/M	10073008	PNEUMONIA	HTN	1.85		15.2	4.5	2.23	2	18	0.49	3		
19	66/F	10075588	UROSEPSIS	HTN/DM	1.56		14.7	2.6	2.05	4	19	0.78	3		
20	76/M	10074226	ASPIRATION PNEUMONIA	HTN/DM	2.41		14.8	2	2.5	5	9	1.25	3		
21	67/F	10075565	AOCKD/UROSEPSIS	HTN	20		15.6	2.9	3.35	6	24	1.13	5		
22	57/M	10074246	CELLULITIS	HTN	6.83		18.8	2.3	8.23	5	11	3.57	4		
23	60/M	10072937	DENGUE ENCEPHALOPATHY/ASPIRATION PNEUMONIA	NA	2.38		15.1	2.3	3.97	8	19	1.72	4		
24	75/F	10074931	RCC	NA	4.81		15.5	2.6	2.6	5	11	1	5		
25	38/M	10076493	PHENOL POISONING	HTN	100		16	4.5	3.8	4	3	0.66	4		
26	48/F	10075939	ACUTE GE	NA	6.78		14	2	5.44	5	18	2.72	2		
27	74/F	10075921	UROSEPSIS	NA	42.8		15.1	2.6	3.91	9	20	1.19	5		
28	58/F	10076177	DIABETIC FOOT	HTN/DM	88		17.2	2.7	2.08	6	20	0.77	5		
29	25/M	10076167	POLYTRAUMA	NA	14.7		17.2	2.2	3.73	16	18	1.69	5		
30	75/M	10075949	EPIDIDYMO ORCHITIS	DM	5.35		18.2	2.7	4.2	7	8	1.55	4		
31	72/M	10076635	MYOSITIS	HTN/DM	2.14	209	16	2	2	4	15	2	4		
32	88/M	10075774	GREAT TOE GANGRENE	HTN/DM			18.5	3.1	2.76	5	19	0.89	6		
33	84/M	10074935	LRTI/SOCKD	HTN	23.6	12.2	16	3.1	6.67	8	20	2.15	6		
34	64/M	10076426	UROSEPSIS/IHD	HTN	100	286	17	2.9	6.82	11	16	2.35	4		
35	25/F	10076725	PHENYL CONSUMPTION	NA			14	2	3.35	2	4	1.6	2		
36	55/M	10076727	MENINGOENCEPHALITIS	NA	19.4	567	17.1	2.6	2	5	4	0.76	4		

37	65/F	10076774	SAH	HTN	6.23		16.4	3	3.3	6	20	1.1	5		
38	64/M	10076557	R MCA INFARCT	NA	5.41		15.1	1.8	1.39	7	22	0.77	4		
39	60/F	10077013	CELLULITIS/PNEUMONIA	HTN/DM	2.39		19.8	3.8	6.27	9	20	1.65	5		
40	42/F	10077527	ACUTE GE	DM	20.7		16	1.9	2	2	7	1.05	3		
41	24/F	10077170	ACUTE PANCREATITS/PYELONEPHRITIS	NA	5.89		20.6	2.9	2.9	6	16	1	4		
42	38/F	10077471	TB ARTHRITIS/PNEUMONIA	NA	0.09		20.7	3.2	3	6	9	0.93	4		
43	62/M	10076120	PNEUMONIA	NA	2.11		13.8	2.6	1.14	4	8	0.43	1		
44	69/M	10078048	UROSEPSIS/AOCKD	HTN	1.8		15.8	2.2	1.44	4	20	0.65	5		
45	76/M	10075212	CELLULITIS	HTN/DM	95.7		20.3	2.8	3	4	12	1.07	4		
46	63/F	10078015	COPD	HTN/DM	20		20.5	3.6	2.81	2	6	0.78	3		
47	75/M	10073963	LUNG ABSCESS	NA	4		23.9	3	2.29	2	7	0.76	4		
48	56/F	10073761	NEUTROPENIC SEPSIS	HTN	5.62		21.7	2.4	1.8	8	14	0.74	4		
49	47/M	10078125	CELLULITS/AKI	NA	98.9		14.6	2.2	2.11	7	17	0.95	2		
50	49/M	10077560	PYREXIA OF UNKNOWN ORIGIN	NA	100		17.3	3.1	2.55	7	18	0.82	5		
51	60/M	10077839	THROMBOCYTOPENIC FEVER	HTN	42		12.1	3.8	4.06	6	14	1.06	1		
52	82/F	10077728	ACUTE HEART FAILURE/ACUTE GE	HTN	14.8		17.6	3.4	2.5	7	11	0.73	4		
53	31/M	10076693	PNEUMONIA	NA	7.72		14	3	1.72	8	11	0.57	2		
54	63/F	10078015	COPD	HTN/DM	5		20.5	3.6	2.81	3	7	0.78	3		
55	26/M	10077578	AKI	HTN	20		14.9	3.6	3.99	7	7	1.1	2		
56	76/M	10079413	PNEUMONIA	HTN/DM	2.12		15	3.5	2.33	8	20	0.66	5		
57	54/M	10079247	CELLULITIS/AKI	NA			16	2.7	2.65	9	14	0.98	4		
58	75/M	10079230	PNEUMONIA/CKD	HTN/DM	100		15	2.7	3.09	9	20	1.14	5		
59	65/M	10079263	CKD/IHD	HTN/DM			17.7	3.5	4.28	5	21	1.22	5		
60	32/F	10080084	VIRAL HEPATITS	NA	64.8		16	3	2.64	5	10	0.88	4		
61	48/F	10079411	PNEUMONIA	HTN/DM	1.07	68.2	18	2.4	2.18	5	19	0.9	5		
62	72/M	10079799	PNEUMONIA/ACUTE GE	NA	100		16	2.9	4	8	15	1.37	5		
63	60/M	10079302	AKI/PYELONEPHROTIS	HTN	2.38	107	16	2.4	2.43	8	24	1.01	5		
64	35/M	10078366	JEJUNOSTOMY/IHD	HTN	2.8		17	3	2.5	2	7	0.83	4		
65	52/F	10078064	UTI/PNEUMONIA	HTN/DM	1.74	136	15	2.8	2.57	4	10	0.91	2		
66	69/F	10079400	PNEUMONIA	NA	22		13	2	4.43	6	8	2.21	1		
67	70/F	10080389	ACUTE GE	HTN	2.2		14	2.4	3.21	4	18	1.39	3		
68	56/M	10080928	AKI	HTN			18	2	4.4	5	12	2.2	4		
69	51/F	10080711	OP/C/C GANGRENOUS BOWEL	NA			14	3	3.34	4	7	1.11	2		
70	90/M	10081234	ACUTE GE/AKI	NA	18		15	2.1	4	4	12	1.9	4		
71	61/M	10080092	RIIT FOOT DIABETIC ULCER	DM	100		14	3.7	3.41	4	19	0.92	3		
72	47/M	10081266	APLASTIC ANEMIA SECONDARY TO VIRAL INFECTION	NA	23		16	2	7.8	5	15	3.9	4		
73	72/M	10081383	PYELONEPHRITIS	NA	100		14.4	1.9	5	5	19	2.63	4		
74	17/M	10081571	PNEUMONIA	NA	2.8		16	2.8	2	4	15	0.7	4		
75	66/M	10081829	PVD WITH WET GANGRENE	T2DM	100		18	2	6.8	4	12	3.4	4		