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MICROALBUMINURIA : A DIAGNOSTIC AND PROGNOSTIC TOOL IN PATIENTS ADMITTED IN THE HOSPITAL WITH SEPSIS

BY

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MICROALBUMINURIA : A DIAGNOSTIC AND PROGNOSTIC TOOL IN PATIENTS ADMITTED IN THE HOSPITAL WITH SEPSIS ABSTRACT Background "Microalbuminuria, characterized by 30-300 mg/day of albumin excretion in urine, develops rapidly following an acute inflammatory event like sepsis and persists in patients with ensuing complications. It is commonly observed in critically ill individuals and has shown promise not only as an indicator of organ dysfunction and the necessity for vasopressors but also as a predictor of mortality". Still, there is insufficient data, especially in LMICs, to fully understand its utility in projecting death among older sepsis subjects. Hence, this study aimed to evaluate the clinical and microbiological aspects of sepsis, along with assessing the predictive value of urine albumin to creatinine ratio (ACR) or microalbuminuria in elderly sepsis patients treated in hospitals or ICUs. Early prediction of outcomes could lead to more effective and targeted treatments, ultimately improving the overall prognosis for sepsis patients. MATERIALS AND METHODS STUDY SITE:- The research was carried out in the Department of General Medicine at Sri Devraj Urs Academy of Higher Education and Research Centre attached to Sri Devraj URS Medical College affiliated to Sri Devaraj URS Academy of Higher Education and Research Centre, Tamaka, Kolar who fulfil the inclusion and exclusion criteria. STUDY DESIGN:- A prospective cross sectional study STUDY PERIOD:- Samples will be collected from patients during the period of 2022 to 2024 RESULTS In this study, the demographic composition revealed that the majority of participants were males, representing 66.6% of the total sample. In contrast, females constituted 33.4%. This gender distribution indicates a higher prevalence or higher enrolment rate of males in the study. The age range of the participants showed that a significant proportion, 66%, belonged to the 40-70 years age group. This suggests that middle-aged to elderly individuals were more affected or more likely to be included in the study. The average age of the patient was calculated to be 50.32 years with a standard deviation of 17.89 years indicating a wide range age range among the patients The study also suggests mortality rate of 20% , this death rate suggests severity of sepsis ,effective monitoring and intervention needed as early as possible. According to this study albumin creatinine ratio (ACR 2) at 24 hours after admission was measured in urine and median ACR2 among survived patients was 75.00 and among death patients was 187.00 .the p value was 0.049 indicating significant difference.so ACR 2 should be considered as a valuable prognostic marker. CONCLUSION "Microalbuminuria is a promising diagnostic and prognostic tool for critically ill patients, especially those with sepsis. Its rapid, inexpensive, and non-

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PRIOR PERMISSION TO START OF STUDY

The Institutional Ethics Committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has examined and unanimously approved the synopsis entitled **"Micro albuminuria: A Diagnostic and prognostic tool in patients admitted in the hospital with sepsis"** being investigated by **Dr.Lakwan Sakthi** & Dr.Prabhakar.K in the Department of General Medicine at Sri Devaraj Urs Medical College, Tamaka, Kolar. **Permission is granted by the Ethics Committee to start the study.**

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Place: Kolar **DR. D R LAKWAN SAKTHI**

MICROALBUMINURIA : A DIAGNOSTIC AND PROGNOSTIC TOOL IN PATIENTS ADMITTED IN THE HOSPITAL WITH SEPSIS

ABSTRACT

Background

"Microalbuminuria, characterized by 30–300 mg/day of albumin excretion in urine, develops rapidly following an acute inflammatory event like sepsis and persists in patients with ensuing complications. It is commonly observed in critically ill individuals and has shown promise not only as an indicator of organ dysfunction and the necessity for vasopressors but also as a predictor of mortality".

Still, there is insufficient data, especially in LMICs, to fully understand its utility in projecting death among older sepsis subjects. Hence, this study aimed to evaluate the clinical and microbiological aspects of sepsis, along with assessing the predictive value of urine albumin to creatinine ratio (ACR) or microalbuminuria in elderly sepsis patients treated in hospitals or ICUs. Early prediction of outcomes could lead to more effective and targeted treatments, ultimately improving the overall prognosis for sepsis patients.

MATERIALS AND METHODS

STUDY SITE:-

The research was carried out in the Department of General Medicine at Sri Devraj Urs Academy of Higher Education and Research, Tamaka , Kolar -563101

SOURCE OF DATA:-

Individuals coming to R.L.Jalappa Hospital and Research Centre attached to Sri Devraj URS Medical College affiliated to Sri Devaraj URS Academy of Higher Education and Research Centre,Tamaka,Kolar who fulfil the inclusion and exclusion criteria.

STUDY DESIGN:-

A prospective cross sectional study

STUDY PERIOD:-

Samples will be collected from patients during the period of 2022 to 2024

RESULTS

In this study, the demographic composition revealed that the majority of participants were males, representing 66.6% of the total sample. In contrast, females constituted 33.4%. This gender distribution indicates a higher prevalence or higher enrolment rate of males in the study.

The age range of the participants showed that a significant proportion, 66%, belonged to the 40-70 years age group. This suggests that middle-aged to elderly individuals were more affected or more likely to be included in the study. The average age of the patient was calculated to be 50.32 years with a standard deviation of 17.89 years indicating a wide range age range among the patients

The study also suggests mortality rate of 20% . this death rate suggests severity of sepsis ,effective monitoring and intervention needed as early as possible.

According to this study albumin creatinine ratio (ACR 2) at 24 hours after admission was measured in urine and median ACR2 among survived patients was 75.00 and among death patients was 187.00 .the p value was 0.049 indicating significant difference.so ACR 2 should be considered as a valuable prognostic marker.

CONCLUSION

"Microalbuminuria is a promising diagnostic and prognostic tool for critically ill patients, especially those with sepsis. Its rapid, inexpensive, and non-invasive nature makes it suitable for widespread use, including in resource-limited settings. Serial measurements of microalbuminuria offer valuable insights into patient outcomes, enabling healthcare providers to identify high-risk patients early and tailor interventions accordingly. Given its potential to improve patient management and outcomes, microalbuminuria should be considered a standard component of critical care assessment"

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ABBREVIATIONS

LMICs	LOWER MIDDLE INCOME COUNTRIES
SIRS	SYSTEMIC INFLAMMATORY RESPONSE SYNDROME
ICU	INTENSIVE CARE UNIR
APACHE	ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION
SAPS	SIMPLIFIED ACUTE PHYSIOLOGY SCORE
SOFA	SEQUENTIAL ORGAN FAILURE ASSESSMENT
CRP	C REACTIVE PROTEIN
PCT	PROCALCITONIN
ACR	ALBUMIN CREATININE RATIO
LPS	LIPOPOLYSACCHARIDE
TLR	TOLL LIKE RECEPTOR
SSC	SURVIVING SEPSIS CAMPAIGN
LBP	LIPOPOLYSACCHARIDE BINDING PROTEIN
ATP	ADENOSINE TRIPHOSPHATES
ADM	ADRENOMEDULLIN
sTREM 1	SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS
uPAR	UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR
Ang	ANGIOPOIETIN

INTRODUCTION

INTRODUCTION

“Sepsis presents a significant challenge in the healthcare of elderly individuals, often leading to serious illness and death. It manifests as a complex response to infection, serving as a common pathway for fatalities across various infectious diseases globally[1]. In 2017 alone, an estimated 49 million cases of sepsis were reported, contributing to approximately 11 million avoidable deaths, representing about 20% of all global deaths[2]. The burden of sepsis is notably higher in lower-middle-income countries (LMICs), where incidence and mortality rates are at their peak”.

“Patients in intensive care often experience systemic inflammatory response syndrome (SIRS), which, when severe, increases their susceptibility to multiple organ failure[3]. An early manifestation of acute inflammation is the activation of capillary endothelial cells, leading to a rapid rise in capillary permeability to plasma proteins like albumin[4]. The transcapillary escape rate of radio-labeled albumin from circulation significantly rises within 3 hours post-cardiac surgery in patients with infections or malignancies. Research in normal individuals and those with diabetes mellitus or hypertension has also linked urine albumin levels and albumin transcapillary escape rate to systemic endothelial dysfunction[5].

“Sepsis affects 1%–2% of hospitalized patients and stands as a significant cause of morbidity and mortality, ranking as the second leading cause of death globally[6]. Epidemiological studies draw from community or hospital-based data collection methods, such as retrospective chart reviews, discharge diagnoses, death certificates, or prospective observational studies, yielding varying statistics[7]. A robust epidemiological study should be prospective and extended, encompassing a diverse

case mix representative of the disease to allow for broader application of the findings. Most epidemiological data on sepsis originates from Western literature"[8].

Sepsis manifests as a host response to the infecting pathogen, resulting in pathological, physiological, and biochemical abnormalities. It can be categorized as severe sepsis when infection and the host response lead to organ dysfunction (e.g., acute kidney injury, acute liver failure). Septic shock occurs when persistent arterial hypotension due to acute circulatory failure persists despite volume resuscitation[9].

Among adults, sepsis managed in hospitals and intensive care units (ICUs) carries substantial mortality rates of 26.7% and 42.0%, respectively[10]. The factors contributing to these high mortality rates include suboptimal care quality, inadequate healthcare infrastructure, insufficient infection prevention measures, delayed diagnosis, and inappropriate clinical management. Sepsis can lead to severe consequences, even for survivors, causing long-term morbidity and sequelae[11].

Addressing sepsis is not only a costly endeavor but also an essential component of achieving sustainable development goals. However, there is a lack of comprehensive data globally on effective strategies to reduce disability resulting from infection and improve long-term outcomes. Particularly concerning will be the scarcity of information about sepsis among older adults in LMICs.

Timely and accurate diagnosis of sepsis is crucial for better clinical outcomes and is a key aspect of surveillance and clinical care. However, existing diagnostic methods are often expensive or reliant on advanced technology, making them less accessible in LMIC settings. Although biomarkers have garnered considerable interest among sepsis researchers, their affordability and relevance remain limited. Currently, several ICU scoring systems like APACHE II and SAPS II are utilized to forecast mortality[12].

However, these scoring systems are time-consuming and require completion within 24 hours of admission, leading to a delay in administering essential therapies.

Microalbuminuria shows promise as a potential biomarker for enhancing timely and targeted sepsis treatment. he Urine Albumin Creatinine Ratio (UACR) serves as a potential indicator of mortality and morbidity in septic patients[13]. Its primary purpose is to detect urine albumin early in the disease progression, thereby interrupting the disease's further advancement. The glycocalyx layer, which typically acts as a barrier to protein permeability, becomes compromised, leading to increased albumin excretion in the urine from the Glomerulus.

Urine albumin measurements exhibit good specificity and sensitivity in detecting changes in glomerular permeability. Numerous studies have demonstrated the prognostic significance of even small amounts of albumin in urine "(30-300 mg/day)"[14]. Organ dysfunction in critically ill septic patients can be evaluated using SOFA, APACHE II, and APACHE IV. "An increase in SOFA score within the first 48 hours in septic patients predicts mortality rates of at least 50%"[15].

"Similar endothelial dysfunction may occur in non septic inflammatory states. But, it is not known whether the degree of microalbuminuria is different after a septic insult when compared to non infectious ones such as pancreatitis, burns, trauma etc. and, whether it could delineate sepsis in a heterogeneous population of critically ill patients. By drawing an analogy with current biomarkers of sepsis such as procalcitonin (PCT), C-reactive protein (CRP) and the markers of endothelial damage such as the adhesion molecules, which are relatively elevated in sepsis".

"Diffused endothelial dysfunction in sepsis leads to an increase in systemic capillary permeability, the renal component manifesting as microalbuminuria. The degree of

microalbuminuria correlates with the severity of the acute insult, the quantification of which may serve to predict sepsis and mortality in critically ill patients. Aim: To study the trend of microalbuminuria in sepsis patient, to evaluate microalbuminuria as novel biomarker of sepsis, To evaluate the capability of microalbuminuria for the prediction of ICU mortality".

"Microalbuminuria, characterized by 30–300 mg/day of albumin excretion in urine, develops rapidly following an acute inflammatory event like sepsis and persists in patients with ensuing complications. It is commonly observed in critically ill individuals and has shown promise not only as an indicator of organ dysfunction and the necessity for vasopressors but also as a predictor of mortality"[16].

Still, there is insufficient data, especially in LMICs, to fully understand its utility in projecting death among older sepsis subjects. Hence, this study aimed to evaluate the clinical and microbiological aspects of sepsis, along with assessing the predictive value of urine albumin to creatinine ratio (ACR) or microalbuminuria in elderly sepsis patients treated in hospitals or ICUs[17]. Early prediction of outcomes could lead to more effective and targeted treatments, ultimately improving the overall prognosis for sepsis patients.

"In intensive care unit (ICU), prediction of outcome of patients is of vital importance. It helps in planning of early aggressive therapeutic interventions, optimum resource allocation and counselling of the family and/or patient. The two widely adopted systems to predict mortality and morbidity are the acute physiology and chronic health evaluation II (APACHE II)[1] and the simplified acute physiology score II (SAPS II) scores.[2] Although useful to evaluate the outcome, these tools are of limited use in day-to-day practice. Sensitive dynamic and inexpensive prognostic markers that generate

rapid and reliable results are desirable in the ICU setting. Critical illnesses are often characterised by the systemic inflammatory response syndrome (SIRS), the host response to an acute insult. SIRS is a common finding in the ICU patients, which, when severe, can lead to multiple organ failure and finally death.[3] The gold standard for the diagnosis of sepsis is the isolation of causative organism in the culture of appropriate body fluids or tissue, which takes more than 24 h causing delay in the initiation of targeted therapy which in turn impacts the outcome. Hence, the search for early markers of sepsis still continues. Sepsis remains a major global healthcare concern, owing to high morbidity and mortality, despite the advances in medical therapeutics.[4] Targeted therapies probably lose their efficacy due to late administration.[5] Levels of microalbuminuria increase within hours of an inflammatory insult as compared to relatively delayed inductions of procalcitonin (PCT) and C-reactive protein (CRP).[6] Assay of the amount of albumin excreted in a random urine sample, expressed as albumin/creatinine ratio (ACR), is proven to be a simple, validated and reliable test.[7] Several studies in various groups of critically ill patients have established microalbuminuria as a significant prognostic marker of morbidity and mortality in the ICU."

"Early diagnosis of sepsis is of vital importance for patient management and outcome, as early institution of appropriate therapy can be life-saving for the patient. Of the many markers of sepsis available, PCT was considered specific and sensitive in identifying systemic bacterial infections; it has certain limitations such as increases in several non-infectious inflammatory conditions and absence of increase in localised infections.[14,15] CRP is another marker of sepsis, which has limitations of low specificity for the diagnosis of sepsis, slow induction time and lack of correlation with severity of disease, even though it is cheaper".[16,17]

"The levels of microalbuminuria start increasing within hours of an inflammatory insult as against delayed increase in levels of CRP and PCT.[6] Sparse published data are

available regarding biomarkers of sepsis from developing countries like India. In India, utilisation of cost-effective prognostic markers to diagnose this life-threatening condition at the earliest can bring a major difference in the mortality rates. Majority of the data are available from Western countries, but presentation and outcomes in developing countries differ significantly from those in developed countries due to wide variations in the aetiologies and the available healthcare facilities".

Our present study aims at evaluating microalbuminuria as a marker for sepsis

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

AIM:-

"The study aims at evaluating microalbuminuria as a marker (diagnostic and prognostic) for sepsis".

OBJECTIVES:-

- The primary objective is to detecting microalbuminuria as indicator of sepsis within 24 hours.
- The secondary objective is to assess the prognostic value of microalbuminuria for patient mortality.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

“Sepsis is a significant global health challenge and is a primary cause of mortality among people in emergency units. Annually, it impacts over 900,000 individuals in the US, with an incidence of 536 cases per 100,000 person-years[18].

THE INTERNATIONAL CONSENSUS PANEL :

PANEL 1: In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to Infection.

The panel proposed the term ―severe sepsis‖ to describe instances in which sepsis is complicated by acute organ dysfunction , and ―septic shock‖ as sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia.

PANEL 2: In 2003, a second consensus panel concluded that signs of a systemic inflammatory response such as tachycardia or an elevated white cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions.

PANEL 3 : The European Society of Intensive Care Medicine and the Society of Critical Care Medicine convened a task force of 19 critical care, infectious disease, surgical, and pulmonary specialists in January 2014. The group engaged in interactive Review of Literature 6 discussions via 4 face-to-face meetings between January 2014 and January 2015, email correspondence , and voting.Existing definitions were revisited in light of an enhanced appreciation of the pathobiology and the availability of large electronic health record databases and patient cohorts. The Third International Consensus 2015 has improved the understanding of pathobiology and the formation of a new definition for sepsis . Sepsis is a multifaceted host response to an infecting

pathogen that may be significantly amplified by endogenous factors . The original conceptualization of sepsis as an infection with at least 2 of the 4 SIRS criteria focused solely on inflammatory excess. However , the validity of SIRS as a descriptor of sepsis pathobiology has been challenged. Sepsis is now recognized to involve early activation of both pro and anti-inflammatory responses,33 along with major modifications in non-immunologic pathways such as cardiovascular, neuronal , autonomic , hormonal, bioenergetic, metabolic, and coagulation, 31,34,35 all of which have prognostic significance. Organ dysfunction, even when severe , is not associated with substantial cell death.

Despite recent advancements, standardized protocols, and increased physician awareness over the last decade, survival rates have notably improved, yet mortality rates still range between 20% and 37%, resulting in 270,000 deaths each year in the United States[19,20]. Initially, 80% of sepsis cases are managed in emergency departments, while the remaining cases develop during hospitalization for other conditions.

Key risk factors for sepsis include age 65 or older, malnutrition, chronic illnesses, immunosuppression, recent surgical procedures or hospital stays, and the presence of indwelling medical devices[21].

Notably, about 1/3 rd of sepsis instances occur in the postoperative phase. Despite some patients recovering well enough for hospital discharge, they face higher rates of readmission .and mortality in 12 months, along with significant decrease in physical and intellectual function compared to controls".

Sepsis is characterized by SIRS (systemic inflammatory response syndrome) and the presence of known or suspected infection.

Microalbuminuria in sepsis and its prognostic factors in critically ill patients showed that the degree of albuminuria is dependent on the intensity of the inflammatory responses, and therefore microalbuminuria reflects disease severity found to be prevalent in a broad spectrum of critically ill patients.

Procalcitonin (PCT) has been used as a sensitive and specific marker for systemic infections, but it is also known to increase in other non-infectious inflammatory conditions and may remain normal in localized infections.

C-Reactive Protein (CRP) is another marker which is used but it is nonspecific, takes time to rise and does not correlate with the severity of the disease.

As compared to PCT and CRP, levels of microalbuminuria increase within hours of inflammatory injury.

The levels of microalbuminuria were significantly high among the patients with sepsis at admission as compared to those without sepsis. These levels continued to remain significantly high among the non-survivors, whereas they had dropped among those who survived.

" The effect of the inflammatory cascade that occurs in response to sepsis damages the endothelium of the capillaries with damage to the glycocalyx layer of endothelium which normally acts as a barrier against passage of albumin across the capillary wall. Damage to the glycocalyx results in increased permeability of the capillaries with resultant loss of albumin into urine" .

"Intestinal integrity is compromised in subjects with T2DM and the activation of LPS TLR4 signalling might play an important role in the development of microalbuminuria in T2DM. so microalbuminuria in diabetes patients should be excluded from study".

" Levels of microalbuminuria increase within hours of an inflammatory insult as compared to relatively delayed inductions of procalcitonin (PCT) and C-reactive protein (CRP).Assay of the amount of albumin excreted in a random urine sample, expressed as albumin/creatinine ratio (ACR), is proven to be a simple, validated and reliable test. ACR2 had the highest value among ACR1, ACR2 and APACHE II for predicting mortality".

In intensive care units a highly accurate biomarker is required for the early diagnosis of sepsis. Additional studies should be performed measuring microalbuminuria levels in larger populations of ICU patients before this technique can become an accepted part of clinical practice".

DEFINITION:-

"The International Consensus Definitions for Sepsis and Septic Shock by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine", were integrated into the "Surviving Sepsis Campaign (SSC) International guidelines in 2016"[22,23]. This update simplified terminology, recognizing only sepsis and septic shock as official terms. "Sepsis" is characterized as high mortality organ dysfunction resulting from a imbalanced host responses to infection, while "Septic shock" accompanies sepsis by dysfunctions in metabolic, cellular and circulatory levels, correlating with heightened mortality rate[24].

Formerly septic shock was idealised by hypotension, but it's understood now that hypotension can manifest later, with tissue hypoperfusion preceding it. The diagnosis of septic shock now includes lactate values one of the indirect indicator of tissue blood flow, alongside the need for a vasopressor therapy to maintain a mean arterial pressure

above 65mm Hg[25]. Throughout this text, the word “Sepsis” encompasses both “sepsis and septic shock” unless explicitly stated otherwise.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

“According to Sepsis-3 guidelines no longer include the systemic inflammatory response syndrome (SIRS) criteria. However, these criteria still play a role in identifying acute infections. SIRS is characterized by the presence of at least two of the following four criteria: a temperature above 100.4°F (38°C) or below 96.8°F (36°C), a heart rate exceeding 90 beats per minute, a respiratory rate surpassing 20 breaths per minute or a partial pressure of carbon dioxide below 32 mm Hg, and a white blood cell count above 12,000 per μL (12 × 109 per L), below 4,000 per μL (4 × 109 per L), or with more than 10% immature forms”[26-28].

“The sensitivity of the SIRS criteria in detecting sepsis is approximately 50% to 60%, and around one in eight ICU-admitted patients with sepsis does not meet these criteria”. A drawback of the SIRS criteria is their potential presence in non infectious manifestations like “autoimmune disorders , vasculitis , pancreatitis , burns , trauma , recent surgical interventions”[29].

SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE and q SOFA:-

“Sepsis incorporates both full Sequential Organ Failure Assessment(SOFA) and a simplified system known as quick SOFA (qSOFA) to assist in diagnosis. The qSOFA was specifically designed to aid clinicians in identifying potential sepsis cases outside of the ICU setting. Patients having at least 2 of the 3 qSOFA standards—namely, respiratory rate of twenty two cycles/min or greater, altered sensorium, and SBP of 100mm/Hg or less-needs further examinations for sepsis suspicion. However, the qSOFA's effectiveness is restricted by the relatively low sensitivity (around 50 percent)

and its tendency to flag patients who are in the later stages of sepsis. Despite these limitations, Sepsis-3 incorporates qSOFA due to its convenience, as it does not require laboratory tests and can be quickly administered. Until more advanced diagnostic tools become available, clinicians should consider sepsis for patients exhibiting a good score on either "SIRS criteria or qSOFA"[30-34].

On other,SOFA score, approved by "Society of Critical Care Medicine", is utilized in emergency settings to know in hospital deaths. It evaluates extent of six organ dysfunction in critically ill patients.SOFA is initially evaluated upon intensive care admission and then every 48 hours thereafter. A rise in the SOFA score of at least two points from baseline (typically assumed as zero before sepsis in patients without known pre existing organ dysfunction) indicates acute organ dysfunction, suggesting a diagnosis of sepsis and correlating with a mortality increase exceeding 20%.

EPIDEMIOLOGY:-

The incidence of severe sepsis outside modern ICUs, especially in parts of the world in which ICU care is scarce is largely unknown. Extrapolating from treated incidence rates in the United States, Adhikari et al estimated up to 19 million cases worldwide per year. The true incidence is presumably far higher.

ETIOLOGY:-

Infections of the genitourinary , gastrointestinal, , respiratory systems along with skin or soft tissue infections constitute the majority of cases, contributing to over 80% of all instances. In contrast, infections related to indwelling devices, endocarditis, and meningitis or encephalitis individually make up about 1% of sepsis cases each[35,36]. Among these, pneumonia stands out as the leading cause of sepsis.

"Gram-negative (62%) or Gram-positive (47%)" bacterial microbes are primary culprits behind sepsis, with some patients harboring multiple microbial organisms. A minority of sepsis cases are attributed to fungal, viral, or parasitic infections[37].

Approximately half of sepsis-treated patients, termed as having culture-negative sepsis, will not have a determined source of infection. Respiratory infections are most prone for culture negative, while infections of the urinary tract are more prone to yield culture positive.

OVER ALL APPROACH:-

Despite advancements in science over the past two decades, the management approach for sepsis has remained largely consistent. The primary evolution lies in the introduction of many interventions which should be completed within specific timeframes[38]. The implementation of these sepsis care protocols has demonstrated a reduction in mortality due to sepsis and must be adopted across every healthcare facility.

Following the initial stabilization of the airway and respiratory functions, patient diagnosed as sepsis must undergo "sepsis bundle protocol", further comprising of fluid resuscitation, antibiotic administration ,measurement of lactate, and obtaining the cultures, all approximately in 3 hrs of presentation[39]. If hypotension persists despite fluid resuscitation, vasopressor therapy is initiated. Furthermore, for suspected infections requiring surgical or other interventional management (such as those involving the abdomen, gallbladder or biliary system, urinary system, joints, skin, and soft tissues), early consultation with surgical specialists for infection source control is recommended[40].

DIAGNOSIS:-

The presentation of sepsis varies depending on the initial infection source, often becoming evident only in the later stages of disease when symptoms and signs are pronounced.multiple clinical conditions that mirror infections and must be included which are acute pulmonary embolism , acute pancreatitis , acute myocardial infarction, adrenal crisis, acute transfusion reaction, thyrotoxicosis and acute alcohol withdrawal.[41,42].

In order to enhance diagnosis of sepsis, physicians should gather comprehensive history, lab, clinical and radiological data that support the presence of infection and organ dysfunction. Table 1 provides an overview of data regarding “sepsis and septic shock”.

TABLE 1: CLINICAL MANIFESTATIONS OF SEPSIS AND SEPTIC SHOCK

Clinical Manifestations of Sepsis and Septic Shock

System	Clinical findings	Comments
Cardiac	Tachycardia, hypotension, warm and flushed skin (vasodilation), poor capillary refill, new murmur	Shock results from redistribution of intravascular circulation, peripheral vasodilation, and myocardial depression; patients with hypotension as the initial presentation of sepsis have a twofold increased risk of death; early echocardiography should be considered, if available, for sepsis management
Constitutional	Fevers or rigors, malaise or myalgia, diaphoresis, anorexia	Fever is the most common manifestation of sepsis but may be absent, especially in older adults and people with chronic alcohol abuse or immunosuppression; hypothermia on presentation may be associated with higher mortality
Dermatologic	Ecchymosis or petechiae; bullous lesions; erythematous, fluctuant, purulent lesions; ulceration; rash; splinter hemorrhage; erythema	Should be distinguished from direct bacterial invasion (e.g., abscess, cellulitis, erysipelas), lesions secondary to sepsis (e.g., disseminated intravascular coagulation), lesions secondary to vasculitis or microemboli (e.g., endocarditis); areas of indwelling devices (e.g., vascular, dialysis, and pleural catheters) should be evaluated
Gastrointestinal	Abdominal pain, distention, rigidity, decreased bowel sounds, diarrhea (bloody or nonbloody), emesis	Early imaging is recommended for further evaluation; suspected surgical abdomen requires immediate consultation; major blood loss from gastrointestinal hemorrhage is uncommon in sepsis
Genitourinary	Dysuria, frequency, hematuria, pyuria, lower abdominal pain, costovertebral tenderness, vaginal discharge or bleeding	Imaging should be considered early to rule out renal obstruction or renal abscess; pelvic inflammatory disease should be considered in sexually active women; placental abruption and threatened, inevitable, or incomplete miscarriage should be considered in pregnant patients; retained products of conception should be considered in the postpartum period
Musculoskeletal	Joint pain; joint swelling; regional muscle pain, with or without edema; crepitus; saddle anesthesia; extremity weakness	A septic joint requires early orthopedic consultation; suspected necrotizing soft tissue infection (e.g., pain out of proportion to examination findings, crepitus, skin eruption) requires immediate general surgical consultation; spinal abscess, spinal osteomyelitis, and diskitis require immediate neurosurgical consultation
Neurologic	Headache, altered mental status, neck stiffness or rigidity, seizures	Older adults may present with subtle agitation or irritation; lumbar puncture is diagnostic for central nervous system infection; computed tomography of the head should be performed before lumbar puncture in patients with a history of immunosuppression, new seizure, papilledema, or focal neurologic deficit
Pulmonary	Upper: sore throat, dysphagia, trismus Lower: cough, shortness of breath, pleuritic chest pain, tachypnea or hyperventilation	Most common source of sepsis; pulmonary embolus should be considered early in the diagnosis if risk factors are present; acute lung injury and acute respiratory distress syndrome are late complications; computed tomography of the chest, thoracentesis, and chest tube placement may be needed for suspected parapneumonic effusion or empyema

SYMPTOMS:-

While febrile illness is frequently observed in sepsis cases, its absence does not rule out sepsis completely. Hypothermia induced by sepsis and lack of febrile illness are common in aged adults and individuals with long term alcohol misuse and compromised immune systems. Primary abnormality is hypotension noted in roughly

"40%" of sepsis subjects[43,44]. In older adults, generalized weakness, agitation or irritability, and altered mental status may be the sole indications of sepsis.

LABORATORY TESTING:-

Lab assessments must encompass a overall blood count with basic and differential metabolic picture, measurements of lactate levels , procalcitonin levels and liver enzyme levels, coagulator levels and urine analysis. Evaluating blood samples may elucidate extent on acidbase imbalances, those may be prevalent in "sepsis" that often stem from tissue hypoperfusion[45] (leading to lactic acidosis) and renal dysfunction.

Clinicians are advised to secure peripheral blood cultures preferably 2 sets (which includes one from a central venous line, if possible) alongside cultures from urine sample , stool sample , sputum sample and samples from other areas (in cases of abscesses, ulcers, or drainage)[46]. Fluid cultures from cerebrospinal, joint, pleural, and peritoneal sources should be obtained based on clinical necessity.

IMAGING:-

Radiological investigations must encompass chest x-ray and further evaluations performed like warranted (such as 2D Echo for endocarditis suspected subjects, chest CT for COPD or pleural effusion, and abdominal/pelvic CT for renal or abdominal abscesses)[47].

SEPSIS BIOMARKERS:-

Procalcitonin serves as an inflammation marker generated by cytokines and bacterial endotoxins, commonly used to indicate bacterial sepsis[48]. Meanwhile, serum lactate level plays a crucial role in sepsis diagnosis, treatment, and prognosis.

A procalcitonin concentration below 0.05 ng/mL is considered normal, with levels below 0.25 ng/mL suggesting a low likelihood of bacterial sepsis. Procalcitonin levels typically elevate within four hours post-infection onset, peaking between 12 to 48 hours. These levels correlate significantly with sepsis severity; for instance, "septic shock" patients in need of vasopressors showed average procalcitonin levels of "32.7 ng/mL", contrasting "9.6 ng/mL" for those having sepsis but not in shock[48-51]. Due to its short half-life, procalcitonin levels aid in therapy response monitoring and guide discontinuation of antibiotics, especially in pneumonia of bacterial origin. Failure in decreasing procalcitonin by 80% within seventy two hours is linked to higher deaths among in-hospital patients.

Elevated lactates in sepsis subjects result from "tissue hypoxia , aerobic glycolysis or reduced clearance (e.g due to hepatic dysfunction). Lactate results surpassing 18 mg/dL (2 mmol/L) is definitive indicator for septic shock per Sepsis criteria[52,53,54]. Even in patients with normal blood pressure, increased lactate levels shouldn't be overlooked in sepsis cases. Regular lactate measurements, every 4 to 6 hours until normalization, are recommended". Overall mortality is reduced in lactate guided fluid resuscitation compared to nil lactate monitoring. Failure by clearing lactate during sepsis treatment necessitates a reassessment of appropriate source of control

Biomarkers of sepsis

An ideal biomarker can be objectively measured and reflects normal biological and pathogenic processes as well as responses to therapeutic interventions. Many trials have identified potential biomarkers. More than 170 biomarkers have been studied for use in evaluation of sepsis . Development of sepsis changes the expression and activity of thousands of endogenous mediators of inflammation, coagulation, and intermediary metabolism. Even when biomarkers start at equal values, the effect of inflammatory responses can cause these values to change in opposite directions

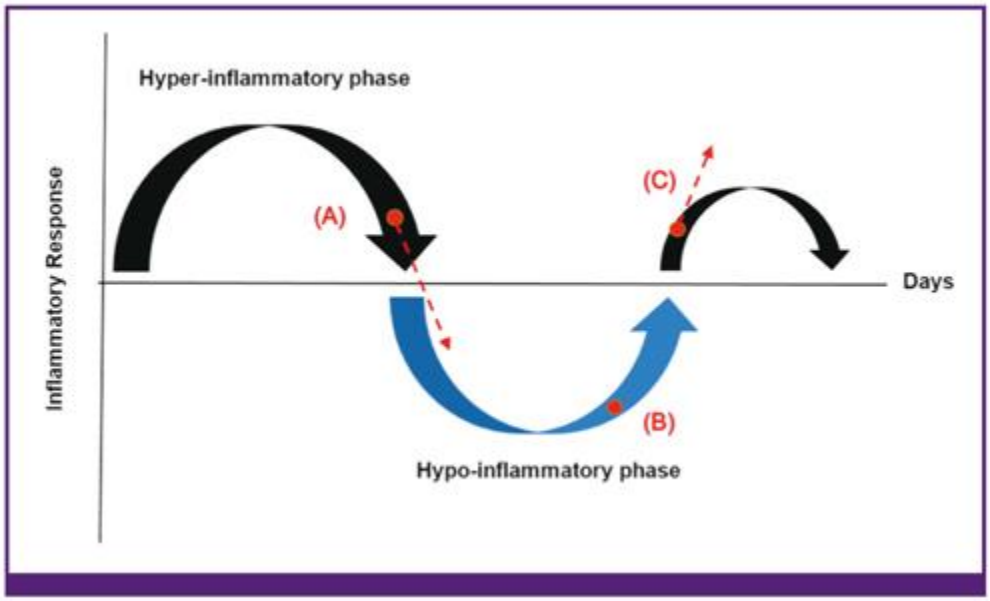

FIGURE 1 : INFLAMMATORY RESPONSE

While early diagnosis is helpful, biphasic or repeated biphasic models of sepsis make it difficult to predict mortality and prognosis based on initial biomarker levels. Nevertheless, the ideal biomarkers could play a role in sepsis screening, early diagnosis, risk stratification, critical assessment, and prognosis prediction ,which can improve outcomes

. This review will discuss the major measurable sepsis biomarkers that have been proposed for clinical use.

1. Markers for early response to sepsis

The traditional sepsis model is the immune response activated when TLR expressed on the macrophage recognizes LPS in cell walls of gram-negative bacteria. This is an example of pattern recognition receptors (PRR) and pathogen-associated molecular patterns (PAMP). This recognition stimulates secretion of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6. Various inflammatory cytokines and LPS have therefore been studied as sepsis biomarkers.

1) Cytokines and chemokines

TNF-α, IL-1β, and IL-6 are cytokines responsible for mediation of the initial innate immune system response to injury or infection. These proinflammatory cytokines contribute to fever, activate endothelial cells, attract circulating polymorphonuclear cells (PMNs), and enter the circulatory system. Studies have demonstrated increased blood cytokine levels in patients with sepsis. However, levels of these cytokines also increase after trauma, surgery, stroke, or with autoimmune diseases. Use of these inflammatory cytokines to diagnosis sepsis is difficult because they are nonspecific and unable to differentiate infection from inflammation. TNF-α and IL-6 levels have been reported to be related to organ damage and mortality, making them potentially useful prognosis predictors. However, a clinical trial of pretreatment with polyclonal ovine anti-TNF fragment antigen binding fragments (CytoFab) showed no difference in 28-day mortality. The conflicting reports could be explained by the short half-life (the half-life of TNF, for example, is 17 minutes) and earlier peak concentration of proinflammatory cytokines than other biomarkers. IL-1β levels are not elevated to the

same degree as TNF. Therefore, neither TNF nor IL-1β has proven to be useful as major biomarkers of sepsis.

TABLE 2 : ROLE OF BIOMARKERS

Role of biomarkers
Screening patients at risk of sepsis
Establish early diagnosis that helps the initial management of sepsis
Risk stratification to identify patients at risk of poor outcome
Monitoring the response of intervention
Predict outcomes
Requisites for useful biomarkers
Objectively measured
Have reference standard
Reproducibility of test
Have well-known kinetics
Cost-effectiveness
Reflect normal biologic process, pathologic process or pharmacologic response to therapy

It is difficult to translate certain clinical condition into particular cytokine profile, which could be caused by and is the result of complex inflammatory responses. Recent studies have proposed that measurement of multiple cytokines correlates well with disease severity and prognosis. Combined biomarkers will be addressed later.

2) Lipopolysaccharide-binding protein

LPS-binding protein (LBP), mainly synthesized in the liver, is a polypeptide that binds LPS. The LPS-LBP complex initiates signal transduction according to LBP level. This complex complex has a dual action, enhancing and inhibiting LPS signaling at low and higher levels, respectively . Serum LBP level increases several-fold in sepsis, making it useful for diagnosis . It may also be effective as a predictive marker for disease

severity and outcomeHowever, LPS and LBP levels are affected by administration of antibiotics and generally do not correlate to the clinical course of sepsis. Therefore, it is of limited use as a sepsis biomarker.

2. Markers for late response to sepsis

TNF-α and IL-1β are released within minutes of exposure to LPS. In the late 1990s, investigators found that LPS-treated mice died after serum TNF-α and IL-1β returned to basal levels, suggesting that mediators other than TNF-α might contribute to death. There are two well-known inflammatory mediators, high-mobility group box 1 (HMGB1) protein and macrophage migration inhibitory factor (MIF), which are important in late phase of severe infections.

1) High-mobility group box 1 protein

HMGB1 is a cytoplasmic and nuclear protein that is undetectable in healthy subjects. It is released by activated monocytes or necrotic tissues during infection or injury. This proinflammatory cytokine reaches detectable levels after 8-12 hours and plateaus after 18-32 hours. Plasma HMGB1 concentration has been shown to increase in patients with severe sepsis and septic shock and is correlated with the degree of organ failure. In a prospective study, HMGB1 measurements on day 3 discriminated survivors from non-survivors with a sensitivity and specificity of 66% and 67%, respectively. HMGB1 levels greater than 4 ng/mL on day 3 were associated with a 5.5-fold increased risk of death (95% confidence interval [CI]: 1.3-23.6).

2) Macrophage migration inhibitory factor

The other "late" proinflammatory molecule, MIF normally circulates at low levels of 2-10 ng/mL. Plasma MIF concentration increases during infection and very high levels

have been found in cases with severe sepsis and septic shock.A recent study concluded that high MIF levels serve as an early indicator of poor outcome in sepsis .These results imply that late mediators such as HMGB1 and MIF could predict sepsis prognosis.

3. C-reactive protein

Tillet & Francis first discovered C-reactive protein (CRP) in a patient with lobar pneumonia in 1930. It was identified as a protein responsible for precipitating C polysaccharide during the acute phase of *Streptococcus pneumonia* infection . CRP was also found in patients with endocarditis or rheumatic fever. Its response is stronger in acutely ill patients; levels decrease as patients recover. These characteristics make CRP a member of the class of acute-phase reactants. CRP is an old biomarker used most commonly in clinical settings. It is a nonspecific marker of inflammation that also increases after surgery, burns, myocardial infarctions, and rheumatic diseases. The sensitivity and specificity of CRP as a marker for bacterial infections are 68-92% and 40-67%, respectively. Its low specificity and inability to differentiate bacterial infections from non infectious causes of inflammation makes CRP of limited diagnostic value. However, CRP shows promise for evaluating sepsis severity and prognosis. CRP plasma levels have been shown to correlate with the severity of infection. A rapid decrease in CRP levels has been reported to correlate with good response to initial antimicrobial therapy in septic patients. CRP is a useful biomarker to monitor treatment response. However, hasty interpretation or antibiotic guidance within 1-2 days after starting empirical antibiotic treatment is problematic in many clinical situations. Clinicians cannot interpret changes in CRP levels without considering the kinetics of this marker.

4. Procalcitonin

Procalcitonin (PCT) is a precursor of calcitonin, a calcium regulatory hormone secreted from thyroid tissue in healthy individuals. In infectious conditions, PCT is released from nearly all tissues including lung, liver, kidney, pancreas, spleen, colon, and adipose tissues. In 1993, PCT was first described as a marker elevated in bacterial infections. In 2008, PCT was proposed as an adjunctive diagnostic marker to differentiate acute bacterial infection from other inflammatory states by the American College of Critical Care Medicine and the Infectious Diseases Society of America . In a systematic review and meta-analysis, PCT was found to be more specific (specificity 81% [95% CI: 67-90%]) than CRP (67% [95% CI: 56-77%]) for differentiating bacterial infection among hospitalized patients .The cutoff median PCT value in this meta-analysis was 1.1 ng/mL (interquartile range: 0.5-2.0 ng/mL). PCT cutoffs for diagnosis of sepsis or guidance of antibiotic choice have not yet been fully determined; the sensitivity and specificity of this marker for diagnosis of sepsis are affected by different cutoff values. PCT values need to be further evaluated according to different sites of infection, hosts, and pathogens. Another recent meta-analysis showed that PCT is a useful marker for early diagnosis of sepsis in critically ill patients, with sensitivity and specificity of 77% (95% CI: 72-81%) and 79% (95% CI: 74-84%), respectively. PCT levels are also elevated after surgery, cardiogenic shock, heat shock, acute graft-versus-host disease, and immunotherapy such as granulocyte transfusion, which could limit its usefulness as a sepsis biomarker . PCT has also drawn attention because it can be used for guidance of antibiotic stewardship to reduce inappropriate use of antibiotics.However, many experts recommend that PCT-guided decision-making should be an adjunctive method based on consideration of the patient's clinical course.

5. Lactate

Serum lactate levels can reflect tissue hypoperfusion and anaerobic metabolism in severe sepsis and septic shock. At a cellular level, energy production depends on glucose and oxygen metabolism. Glycolysis converts glucose to pyruvate and yields 2 adenosine triphosphates (ATPs). Pyruvate then enters the Krebs cycle, which produces more ATPs. However, in hypoxic circumstances, pyruvate is instead converted to lactate. Elevated lactate levels and lactate-to-pyruvate ratios result mostly from increased glycolysis and lactate production as well as limited tissue oxygenation. Elevated levels are also related to impaired hepatic lactate clearance and mitochondrial dysfunction. Several studies have demonstrated that elevated lactate levels are related to mortality in patients with sepsis. In a retrospective study of critically ill patients, serum lactate levels greater than 2 mmol/L on admission were associated with a 1.94-10.89-fold increased mortality compared to levels below 2 mmol/L. In a large study of 1,278 patients with infections, those with lactate levels above 4 mmol/L had higher in-hospital mortality rates than patients with lactate levels less than 2.5 mmol/L (28.4% vs. 4.9%) . Another study has reported that sustained hyperlactatemia is predictive of in-hospital mortality.In contrast, however, early lactate clearance was associated with improved outcomes in patients with severe sepsis and septic shock .A recent systematic review further confirmed the utility of monitoring serial blood lactate and its value as a predictive marker of in-hospital mortality. Recently, data from a retrospective study by the Vasopressin Septic Shock Trial and a single-center septic shock cohort (St. Paul's Hospital cohort) have suggested that even minimal increases in arterial lactate concentration within the reference range (1.4-2.3 mmol/L) may predict 28-day mortality (sensitivity and specificity of 86% and 27%, respectively). Furthermore, the data suggested that patients with lactate levels below 1.4 mmol/L might benefit from

vasopressin infusion.Therefore, lactate screening and monitoring may be a valuable tool for risk stratification and to predict sepsis outcome.

6. Mid-regional proadrenomedullin

Like PCT, proadrenomedullin (proADM) is a kind of "hormokine" that encompasses the cytokine-like behavior of hormones during inflammation and infections. Adrenomedullin (ADM) is a 52-amino-acid peptide produced by the adrenal medulla. ADM is produced during physiological stress and has various functions including vasodilation and anti-inflammatory and antimicrobial effects . Plasma ADM concentration and ADM gene expression increases in patients with sepsis . However, ADM is rapidly cleared from the circulation, making measurements unreliable. Therefore, instead of ADM, serum quantification of the mid-regional fragment of proADM has been studied. Recent clinical data have shown that circulating mid-regional proADM levels are significantly higher in patients with sepsis than in patients with systemic inflammatory response syndrome (SIRS) [64]. A recent study of febrile patients with hematologic malignancies reported that proADM could predict localized bacterial infections and differentiate sepsis from SIRS. In addition, proADM is responsible for hypotension associated with severe sepsis, which has been proposed as a good marker for risk assessment and predicting sepsis prognosis. If further data support these findings on the predictive value of proADM, it could be useful as both a prognostic marker and a diagnostic marker for early stages of localized infections.

7. Cell surface markers and soluble receptors

1) CD64

CD64 is a membrane glycoprotein with increased expression in patients with bacterial infections. CD64 expression increases hours after activation of innate immunity; it is not expressed by PMN in healthy individuals. Therefore, CD64 expression can reflect very early stages of infection and help to both make early diagnosis and predict prognosis. The CD64 index has been suggested to be predictive of positive bacterial cultures and a useful test for management of sepsis and other significant bacterial infections. Another study demonstrated that the CD64 index is higher in febrile adult patients with bacterial infections, with a sensitivity of 87% (95% CI: 79-92%), and that high CD64 expression is related to survival. In contrast, it has been reported that CD64 indices greater than 2.2 are specific (89% specificity [95% CI: 83-94%]) but less sensitive (63% sensitivity [95% CI: 55-71%]) to predict bacterial infections in critically ill patients. A systematic review and meta-analysis concluded that CD64 could be a marker for bacterial infection with a pooled sensitivity and specificity of 79% (95% CI: 70-86%) and 91% (95% CI: 85-95%), respectively. However, because published studies have low methodological quality, further studies are needed to verify these findings.

2) Soluble triggering receptor expressed on myeloid cells 1

Soluble triggering receptor expressed on myeloid cell 1 (sTREM-1) is a soluble form of TREM-1, a glycopeptide receptor expressed on the surface of myeloid cells such as PMNs, mature monocytes, and macrophages. TREM-1 expression increases in bacterial or fungal infection. A prospective study by Gibot et al. suggested that the sensitivity and specificity of sTREM-1 for diagnosis of sepsis are comparable to that of CRP and PCT . A meta-analysis reported that the sensitivity and specificity of sTREM-1 to

diagnose bacterial infections were 82% (95% CI: 68-90%) and 86% (95% CI: 77-91%), respectively. Another recent meta-analysis showed that plasma sTREM-1 had only moderate diagnostic performance to differentiate sepsis from SIRS . A prospective study at a single center in Korea reported that sTREM-1 levels on admission were independently significant for survival in patients with severe sepsis . In addition, rapid decrease of sTREM-1 is correlated with better outcome . Therefore, sTREM-1 may be useful for sepsis diagnosis or predicting sepsis prognosis. The usefulness of sTREM-1 as a biomarker requires further evaluation in clinical settings either measured alone or combined with other biomarkers.

3) Soluble urokinase plasminogen activator receptor

First described in 1990, urokinase plasminogen activator receptor (uPAR) is a surface signaling receptor expressed on most leukocytes . uPAR was originally thought to assist directional invasion of migrating cells, but is now known to be involved in multiple immunological functions including cellular adhesion, differentiation, proliferation and angiogenesis, as well as migration . During inflammatory processes, uPAR is cleaved from the cell surface by proteases and released as soluble uPAR (suPAR). It is measurable in blood and body fluids including urine, cerebrospinal fluid, bronchial washing fluid, and saliva. suPAR plasma levels reflect immune activation in response to bacterial or viral infection, cancer, burns, and rheumatic diseases. suPAR levels are significantly higher in patients with sepsis than those without and also higher in critically ill patients than control patients. However, recent studies have demonstrated that suPAR has a lower diagnostic value for sepsis (areas under receiver operating characteristic curves [AUC-ROC] of 0.62) than CRP or PCT . Several studies have suggested suPAR to be an informative marker for severity of sepsis. In a prospective study of 543 acutely-ill patients, baseline suPAR levels were significantly associated

with 30 day- and 90 day-mortality after adjusting for age, CRP, and Charlson's comorbidity index.In a recent systematic review, suPAR was superior to other biomarkers, including CRP, PCT, and sTREM-1 for predicting prognosis. Overall, suPAR might have better prognostic value to predict mortality instead of diagnosing sepsis.

8. Angiopoietin

Angiopoietin (Ang)-1 and -2 are endothelial-derived vascular growth factors that play opposing roles during sepsis. Ang-1 stabilizes the endothelium, whereas Ang-2 facilitates loss of endothelial integrity and vascular leakage. Ang-1 or Ang-2 activates the transmembrane endothelial tyrosine kinase Tie2, which mediates the quiescent, healthy state of blood vessels. Ang-2 plays a crucial role in induction of inflammation . Elevated levels of circulating Ang-2 are associated with sepsis with multi-organ dysfunction, which is indicative of impaired vascular endothelial integrity. A cohort study revealed that elevated Ang-1 and lower Ang-2 levels were observed in sepsis survivors . The endothelium and Ang-Tie2 receptor ligand system have been the recent focus of ongoing sepsis studies.

9. Combined biomarkers and sepsis scoring systems

We have discussed several sepsis biomarkers. Numerous biomarkers have been evaluated for clinical use in sepsis, with moderate to good sensitivity and specificity for diagnosis and prognosis. However, the results of measuring a single biomarker are inconclusive in clinical settings. Owing to this limitation, combination approaches measuring multiple biomarkers have recently been introduced. "Scoring systems" have also been developed, which use both clinical and laboratory markers. In 2003, the infection probability score (IPS) was introduced to assess the probability of infection

in critically ill patients. The IPS ranges from 0 to 26 points, and includes patient body temperature (0-2 points), heart rate (0-1 points), respiratory rate (0-1 points), white blood cell counts (0-3 points), CRP (0-6 points), and sepsis-related organ failure assessment score (0-2 points). The AUC-ROC of IPS was 0.82 for predicting the probability of infection. Patients with <14 points have only a 10% risk of infection [93]. Several clinical examples of combinations of biomarkers and scoring for sepsis are shown below

TABLE 3 :OTHER BIOMARKERS AND SEPSIS

Authors [references]	Markers	Outcome	Results
Bozza et al. [27]	MCP-1, APACHE-II	Predict 28-day mortality	AUC-ROC of 0.89
Selberg et al. [44]	PCT, C3a	Differentiate sepsis from SIRS	AUC-ROC of 0.93[a]
Kofoed et al. [82]	suPAR, sTREM-1, MIF, CRP, PCT, WBC	Differentiate bacterial infection from SIRS	AUC-ROC of 0.88
Gibot et al. [91]	sTREM, PCT, CD64	Diagnose sepsis	AUC-ROC of 0.95[b]
Shapiro et al. [92]	NGAL, protein C, IL-1ra	Predict severe sepsis, septic shock, and death	AUC-ROC of 0.80, 0.77, and 0.79[c]
Kofoed et al. [94]	suPAR, sTREM-1, MIF, age	30-day and 180-day mortality	AUC-ROC of 0.93 and 0.87
Harbarth et al. [95]	Temperature, HR, BP, WBC, PCT	Differentiate sepsis from SIRS	AUC-ROC of 0.94

Combined biomarkers and inclusion of sepsis scoring systems showed better AUC-ROC values than single biomarkers. Theoretically, combining multiple markers can improve diagnostic and prognostic values, because sepsis is composed of multiple immune responses with various changes in cytokines and biomarkers. However, which and how many combinations of biomarkers are most informative have not yet been investigated for use as a high-throughput technology. Cost-effectiveness and comprehensive clinical interpretation must also be evaluated.

MICROALBUMINURIA:-

Microalbuminuria is a medical condition characterized by the presence of a slightly elevated amount of albumin in the urine. Normally, only small traces of albumin are found in urine, but when the kidneys are not functioning optimally, they may allow more albumin to pass through into the urine. In medical terms, it typically defined as an albumin excretion rate of 30-300 mg/twenty four hours or a urinary albumin creatinine ratio (UACR) of 30-300 mg/g creatinine in a spot urine sample[55]. This condition is often considered a marker for early kidney damage or dysfunction, particularly in conditions like diabetes, hypertension, and certain systemic diseases.

Definition: Microalbuminuria is typically defined as a" urinary albumin excretion rate (UAER) of 30-300 mg per 24 hours or a urinary albumin-to-creatinine ratio (UACR) of 30-300 mg/g creatinine in spot urine sample".

Measurement: It is usually calculated using a spot urine test or a 24-hour urine collection. The albumin concentration is compared to creatinine levels to calculate the UACR, which is a more accurate reflection of albumin excretion adjusted for variations in urine concentration.

Causes and Risk Factors:

Kidney Damage: Microalbuminuria often indicates early kidney damage or dysfunction, especially in conditions like diabetic nephropathy, hypertensive nephropathy, and glomerulonephritis.

Systemic Diseases: It can also be associated with systemic diseases such as diabetes mellitus, hypertension, cardiovascular disease, and metabolic syndrome.

Inflammation and Infection: Inflammatory conditions, infections, and certain medications can temporarily increase urinary albumin levels, but persistent elevation suggests underlying kidney issues".

Clinical Significance:

"Early Detection of Kidney Disease: Microalbuminuria is an important marker for detecting early kidney disease, often preceding significant changes in renal function.

Prognostic Indicator: Elevated microalbuminuria levels are associated with an increased risk of progressive kidney disease, cardiovascular events, and mortality, particularly in diabetic patients.

Cardiovascular Risk Marker: Microalbuminuria is also considered a marker for increased cardiovascular risk, independent of traditional risk factors like hypertension and hyperlipidemia.

Monitoring and Management: Regular monitoring of microalbuminuria is essential for managing conditions like diabetes and hypertension, as it helps assess kidney function and guide treatment strategies to prevent or delay progression to more severe kidney disease stages".

Diagnosis and Treatment:

Diagnosis: Microalbuminuria is diagnosed through urine tests, often as part of routine screening for kidney function in high-risk individuals or as a follow-up to abnormal findings in other tests.

Treatment: Management involves addressing underlying conditions contributing to microalbuminuria, such as optimizing blood glucose control in diabetes, controlling blood pressure, reducing protein intake, and avoiding nephrotoxic medications[56,57].

Microalbuminuria serves as an important clinical marker for early kidney damage and increased cardiovascular risk. Regular monitoring and appropriate management are crucial in individuals with microalbuminuria to prevent or delay the progression of kidney disease and associated complications.

MICROALBUMINURIA IN RELATION TO SEPSIS:-

Microalbuminuria, in the context of sepsis, serves as an early indicator of renal impairment and systemic inflammatory response. Here are the medical aspects:

Renal Dysfunction Marker: Microalbuminuria indicates renal impairment during sepsis. It reflects compromised glomerular filtration function, allowing increased albumin passage into the urine, often preceding overt kidney injury.

Prognostic Value: Elevated urinary albumin levels correlate with poorer prognoses in septic patients, indicating a higher risk of adverse outcomes such as increased mortality rates and prolonged hospital stays.

Inflammatory Response: Sepsis triggers a systemic inflammatory cascade, contributing to renal dysfunction and microalbuminuria. Inflammatory mediators disrupt glomerular barrier integrity, facilitating albumin leakage into the urine.

Treatment Monitoring: Monitoring microalbuminuria aids in evaluating treatment response in septic patients. Reductions in microalbuminuria levels over time may signify improved renal function and resolution of systemic inflammation.

Clinical Management: Healthcare professionals managing septic patients should closely monitor renal function, including assessing urinary albumin excretion. Comprehensive care involves addressing the underlying infection, supporting organ function, and ongoing assessment of vital signs and laboratory parameters, including markers of renal function like microalbuminuria/

MANAGEMENT :-

FLUID RESUSCITATION:-

Initial importance should be given in managing earlier stage sepsis which involves vascular access and beginning fluid resuscitation. Patients diagnosed with sepsis should receive an intravenous crystalloid at a rate of 30 mL per kg within the first three hours. Administering an initial 1-L bolus over 30 minutes is a standard approach, followed by additional fluid resuscitation through repeat bolus infusions. This method of intravenous fluid administration helps improve preload and cardiac output , thereby enhancing O2 delivery . However, it's crucial to note that the hemodynamic effects of fluid boluses in sepsis are temporary, lasting only about 60 mins

Several separate studies have indicated no significant changes in twenty eight day mortality outcomes with resuscitation using either colloid (such as albumin) or crystalloid (like normal saline or Ringer lactate). Nonetheless several studies showed a slight advantage in mortality with the use of albumin. Inspite this ,use of crystalloids are recommended for fluid resuscitation due to their widespread availability and lower cost. Crystalloid solutions can be unbalanced (like 0.9% normal saline) or balanced (like Ringer lactate or Plasma-Lyte A)[58]. Large-volume resuscitation with an unbalanced crystalloid can lead to issues like hyperchloremic acidosis, coagulopathy, and acute kidney injury, encouraging an increased use of balanced crystalloids.

New trials with balanced crystalloids using normal saline in unstable patients showed a minor mortality advantage (10.4% vs 11.2% not significant statistically) and a reduced incidence of kidney damage(14.4% vs 15.3% significant statistically) with the use of balanced crystalloids[59,60]. However the trial showed a mixed patient statistics with sepsis as the important criteria in only small percentage of subjects.

Despite of whatever fluids used, regular fluid balance reassessment is essential even after the primary resuscitation phase in order to prevent both dehydration and fluid overload. Monitoring parameters such as dynamic blood pressure response, lactate clearance for tissue perfusion assessment, and urine output (targeting 0.5 mL per kg per hour or more) can help avoid fluid overload, mainly in patients who already have conditions like “chronic renal disease , heart failure, or acute lung injury”. Various other methods, such as ultrasonography to assess inferior vena cava collapsibility, pulse pressure variation, and the passive leg raise test, can aid in determining fluid tolerance and responsiveness for optimal fluid management[61].

In the later stages of sepsis management, fluid administration should be restricted. By 72 hours, the goal for net fluid balance should be close to zero (where the patient voids an amount equal to the fluids given) or slightly negative (where the patient voids slightly more than the fluids given). Increased positive fluid balance within seventy two hours was associated with a higher mortality.

ANTI-MICROBIAL THERAPY:-

Numerous studies suggest that starting appropriate antibiotic treatment early leads to better clinical outcomes. The exact timing, however, remains contentious. The Surviving Sepsis Campaign (SSC) guidelines recommend administering antibiotics within the first hour, yet achieving this within clinical settings can be challenging.

Moreover, this one-hour guideline lacks clear validation . In January 2019, the "Society of Critical Care Medicine and the American College of Emergency Physicians" jointly advised against the 1 hour goal.

"A cumulative study of eleven trials involving 16,178 subjects, aged 18 years or older, presenting to emergency departments with severe sepsis or septic shock[62,63] found no difference in mortality between patients receiving antibiotics within three hours of triage and those getting them within one hour after sepsis recognition. This analysis underscores the importance of early antibiotic use but couldn't pinpoint the optimal timing for maximum benefit".

"A recent retrospective study of over 10,000 sepsis patients in emergency departments showed higher one-year mortality rates in those receiving antibiotics after three hours compared to those getting them earlier[64]. Notably, there was no notable difference in mortality rates between subjects receiving antibiotics within 1hour vs. after 1hour, indicating that the one-hour target might not necessary. The study suggested that administering antibiotics within 90 minutes of sepsis onset could prevent one death per 61 patients".

Initial antibiotic therapy should be broad and empirical, tailored to the suspected infection site, likely pathogen, clinical context (community vs. hospital-acquired), and local resistance patterns. Using inappropriate antibiotics can increase mortality rates by up to 34%. Therapy should be refined based on culture results and identified pathogens to reduce antimicrobial resistance, drug toxicity, and treatment costs.

"There's no agreement on de-escalating combination antibiotic therapy, especially in culture negative sepsis. Factors like clinical progress, biomarker trends (e.g., decreasing procalcitonin levels)[65,66], and fixed treatment durations guide decision-

making. Most sepsis-related infections require seven to 10 days of antibiotic therapy, although specific cases like endocarditis or osteomyelitis may need longer treatment durations".

TABLE 4 :THERAPY FOR SPECIFIC SEPSIS RELATED CONDITIONS

Therapy	Clinical application	Evidence*	Comments
Blood product therapy (packed red blood cells transfusion)	Packed red blood cells transfusion is recommended only when the hemoglobin level is 7 g per dL (70 g per L) or less in the absence of myocardial ischemia, severe hypoxemia, or acute hemorrhage	Strong: Compared with a transfusion threshold of 9 g per dL (90 g per L), a threshold of 7 g per dL had a similar mortality rate with fewer transfusions and adverse events in patients with septic shock	In the TRISS trial, the lower-threshold group received a median of 1 unit of blood, and the higher-threshold group received a median of 4 units
Blood product therapy (platelets)	Platelets are recommended when counts are less than 10×10^3 per μL (10×10^9 per L) regardless of bleeding risk or when counts are less than 20×10^3 per μL (20×10^9 per L) when bleeding risk is significant; the goal is a platelet count of 50×10^3 per μL (50×10^9 per L) or greater for active bleeding, need for surgery or planned invasive procedures	Weak: No RCTs assessing the use of prophylactic platelets in patients with sepsis or septic shock	Platelet transfusion criteria were extrapolated from patients with therapy-induced thrombocytopenia; patients with sepsis are more susceptible to bleeding
Corticosteroids	Hydrocortisone (200 mg per day) is recommended in patients with septic shock that is not responsive to vasopressor therapy and fluid resuscitation	Weak: Hydrocortisone significantly reduced mortality in patients with relative adrenal insufficiency	RCTs and meta-analyses continue to show conflicting results
Glycemic control	Insulin is recommended when two consecutive blood glucose measurements are greater than 180 mg per dL (10 mmol per L); blood glucose should be monitored every one to two hours and then every four hours once insulin dosing is stable	Strong: Intensive blood glucose control did not improve mortality and had a 13-fold increase in the risk of hypoglycemia	Although several medical organizations recommend a blood glucose target between 140 and 180 mg per dL (7.8 and 10 mmol per L), the SSC does not endorse specific lower-threshold blood glucose ranges
Lactate monitoring	A lactate measurement is recommended at the time of sepsis suspicion; if the level is greater than 18 mg per dL (2 mmol per L), repeat measurement every four to six hours until levels have normalized	Weak: Lactate clearance is associated with a reduction in mortality but not length of hospitalization	Lactate may be elevated by increased aerobic glycolysis in response to stress or decreased clearance due to hepatic dysfunction; rising lactate levels should prompt reassessment of perfusion
Nutrition	Enteral nutrition should be used instead of parenteral nutrition if possible; dextrose infusion should be administered over the first seven days	Strong: Meta-analysis of critically ill and surgical patients demonstrated no benefit in mortality with early parenteral nutrition	Initiation of parenteral nutrition within the first seven days is not recommended
Sodium bicarbonate therapy	Not recommended in patients with hypoperfusion-induced lactic acidemia with a pH of 7.15 or greater	Weak: Two blinded, crossover RCTs did not show any benefit with sodium bicarbonate therapy	Use of sodium bicarbonate is associated with sodium and fluid overload, decreased ionized calcium levels, and increased lactate levels

VASOPRESSOR THERAPY:-

Norepinephrine is the primary vasopressor used in treating shock associated with sepsis when initial fluid bolus doesn't elevate mean arterial pressure(MAP) to 65mmHg or above. Prompt initiation of vasopressors within the first hour after initial fluid therapy

significantly enhances patient survival. The delay in starting vasopressor treatment in septic shock patients escalates mortality by 5% per hour.

Starting with norepinephrine of 2 to 5 mcg/min and adjusting up to 36 to 90mcg/min is recommended to attain the target MAP. If norepinephrine fails to reach this goal, vasopressin (up to 0.03units/min) can be added as secondary option , followed by epinephrine (20 to 50mcg per minute) if necessary.

Vasopressors are administered through central venous(CV) catheter with ongoing BP monitoring via arterial line. In cases where central venous catheter placement is delayed, peripheral administration of norepinephrine is acceptable, especially when septic shock is not responding to further fluid resuscitation attempts. This approach is preferred over excessive fluid administration. The risk of tissue damage from using vasopressors through a peripheral venous catheter for a short period is minimal. It's crucial to titrate vasopressor dosages to maintain optimal hemodynamics and limit their use to the shortest duration necessary.

TABLE 5: MANAGEMENT OF SEPSIS RELATED CONDITIONS

Therapy	Clinical application	Evidence*	Comments
Source control (infection)	Appropriate cultures should be obtained before initiation of antibiotics if possible; intravascular access devices should be removed; early surgical or interventional radiology consultation is recommended	Strong: Observational studies reveal reduced survival when source control exceeds six to 12 hours	In the absence of septic shock or fungemia, patients with intravascular catheters may be treated with a longer duration of antibiotics; sepsis from a urinary source has the lowest mortality, whereas sepsis from ischemic bowel has the highest mortality
Stress ulcer prophylaxis	Recommended for patients with risk factors for gastrointestinal bleeding (mechanical ventilation of more than 48 hours, coagulopathy, preexisting liver disease, renal replacement therapy, multiorgan failure)	Strong: Prophylaxis reduces upper gastrointestinal tract bleeding only in patients with risk factors	Proton pump inhibitors were shown to be more effective than histamine H_2 antagonists in preventing gastrointestinal bleeding; there is concern for possible *Clostridioides difficile* infection and increased risk of pneumonia with use of proton pump inhibitors
Vasopressor therapy	Norepinephrine is the first-line vasopressor agent for hypotension that is not responsive to fluid resuscitation; vasopressin or epinephrine may be added as a second-line agent	Strong: Multiple studies recommend norepinephrine as the initial vasopressor with a target mean arterial pressure of 65 mm Hg or greater	A higher mean arterial pressure does not improve mortality but increases arrhythmias; dopamine can be used as an alternative to norepinephrine in select patients with low risk of tachyarrhythmias and bradycardia
Venous thromboembolism prophylaxis	Low-dose unfractionated heparin or low-molecular-weight heparin is recommended unless contraindicated	Strong: Several trials of acutely ill patients demonstrated a reduction in venous thromboembolism with pharmacologic prophylaxis	The use of low-molecular-weight heparin is preferred over unfractionated heparin; mechanical devices are recommended if pharmacologic prophylaxis is contraindicated

Additional strategies to enhance survival in septic shock are corticosteroids (although their efficacy was debated), blood product transfusions, glycemic control, nutritional support, and addressing the sources of infection.

An adjunctive approach was explored in a recent small retrospective observational study that compared standard care by adding “IV ascorbic acid (1,500mg every 6 hours) , hydrocort (50mg every 6 hours), and thiamine (200mg every 12 hours) in sepsis patients. This intervention group exhibited reduced mortality (8.5% vs 40% ,$P < .001$) and decreased reliance on vasopressor therapy compared to control group”.Study's main drawback was its sample size of 94 patients, yet it sparked some interest, leading to more ongoing clinical trials to determine the therapy's efficacy more comprehensively[67-70].

Innovatively, a recent analysis of over 20,000 patient records pinpointed those with the highest sepsis-related mortality risk using clinical phenotypes derived from 27 biomarkers. This study identified four distinct phenotypes. Patients with the lowest mortality rates (5%) required minimal vasopressors, while those with the high death rate(40%) exhibited “liver dysfunction and septic shock”. This underscores sepsis's clinical diversity, although further research is crucial before integrating these clinical phenotypes into routine clinical decision-making.

TABLE 6 : KEY RECOMMENDATIONS FOR PRACTICE OF SEPSIS RELATED CONDITIONS

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
In settings other than the intensive care unit, the quick Sequential Organ Failure Assessment (https://www.mdcalc.com/qsofa-quick-sofa-score-sepsis) can help clinicians recognize possible sepsis early in the evaluation.[9,12-14]	B	Validation studies and retrospective analysis of observational studies
Sepsis care protocols decrease sepsis-related mortality and should be implemented in all medical facilities.[21-24]	B	Multiple prospective cohort trials
Patients with sepsis should complete the sepsis bundle (fluid resuscitation, antibiotics, lactate measurement, and cultures) within three hours of presentation.[24-27]	B	Systematic reviews and retrospective trials
As part of fluid resuscitation, patients with sepsis should receive an intravenous crystalloid at 30 mL per kg.[21]	C	Expert consensus guideline
Norepinephrine is the first-line vasopressor agent for patients with septic shock if initial fluid resuscitation fails to restore mean arterial pressure to 65 mm Hg or greater.[21,28,29]	A	Multiple studies with head-to-head comparisons of norepinephrine and other vasopressors and a meta-analysis showing that norepinephrine reduces sepsis-related mortality

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://

MATERIALS AND METHODS

MATERIALS AND METHODS:-

STUDY SITE:-

The research was carried out in the Department of General Medicine at Sri Devraj Urs Academy of Higher Education and Research, Tamaka , Kolar -563101

SOURCE OF DATA:-

Individuals coming to R.L.Jalappa Hospital and Research Centre attached to Sri Devraj URS Medical College affiliated to Sri Devaraj URS Academy of Higher Education and Research Centre,Tamaka,Kolar who fulfil the inclusion and exclusion criteria.

STUDY DESIGN:-

A prospective cross sectional study

STUDY PERIOD:-

Samples will be collected from patients during the period of 2022 to 2024

SAMPLE SIZE CALCULATION:-

Sample Size:

Sample size was estimated by using the proportion of microalbuminuria in subjects who admitted for sepsis was 68.3% from the study by Mamatha TR et al. using the formula

$$\textbf{Sample Size} = \frac{Z_{1-\alpha/2}^{2}\, P\,(1-P)}{d^2}$$

$Z_{1-\alpha/2}$ = is standard normal variate(at 5% type 1 error ($P<0.05$) it is 1.96 and at 1% type1 error($P<0.01$) it is 2.58).As in majority of studies P values are considered significant below 0.05 hence 1.96 is used in formula.

P= Expected proportion in population based on previous studies or pilot studies

d= Absolute error or precision

P = 68.3% or 0.683

q = 31.7% or 0.317

d = 10% or 0.10

Using the above values at 95% Confidence level a sample size of 84 subjects will be included in the study. Considering 10% Nonresponse a sample size of 84 + 8.4 ≈ 93 minimum subjects will be included in the study.

STUDY POPULATION:- 93

INCLUSION CRITERIA:-

- "Adults patients >18 years patient fulfilling SIRS criteria (two or more of the following) :
- Temperature less than or equal to 36deg Celsius or more than or equal to 38deg Celsius
- Heart rate more than or equal to 90bpm
- Respiratory rate more than or equal to 20 breaths/min
- White blood cell count more than or equal to 12,000 or less than or equal to 4,000 cells/mm3"

EXCLUSION CRITERIA:-

- "Patients with pre-existing chronic kidney disease (Patients on long term renal replacement therapy/sonological features of chronic kidney disease).
- Type 2 diabetes mellitus and hypertension
- Patients with proteinuria due to renal and post renal causes.
- Female patients with menstruation or pregnancy".

METHODOLOGY:-

"Patients coming to R.L.Jalappa Hospital and Research Centre which is attached to Sri Devraj URS Medical College affiliated to Sri Devaraj URS Academy of Higher Education and Research Centre,Tamaka,Kolar who fulfil the inclusion and exclusion criteria have been taken into the study

Patient or the patient attenders will be explained about entire procedure and informed consent will be taken in their own understandable language.

Information will be collected through a pre tested proforma for each patient . Detailed history will be sourced from the subject or from relatives of the subject or immediate bystander accompanying the subject.

Demographic data, history, clinical examination will be recorded in the study proforma. A thorough clinical evaluation will be carried out and recorded in the protocol. Temperature, Heart rate, Respiratory rate, Blood pressure will be recorded.

Relevant laboratory investigations - Complete hemogram, Blood culture and sensitivity ,C Reactive protein, Blood urea, Serum creatinine, Serum electrolytes, Random blood sugar, Erythrocyte sedimentation rate will be done and recorded.

Routine urine analysis, Urine culture and sensitivity will be recorded.

Sputum culture and sensitivity, chest x ray will be done in required patients.

Urine spot samples will be collected at the time of admission for Albumin Creatinine Ratio 1 (ACR1) and Albumin Creatinine Ratio 2 (ACR2) at 24hrs of admission".

VARIOUS METHODS USED FOR ANALYSIS:-

UACR

FIGURE 2 : COMPARISION OF ALBUMINURIA WITH EGFR FOR PROGNOSIS

				Albuminuria categories		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Stages	**G1**	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Key to Figure:
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst.
Green: Low Risk (if no other markers of kidney disease, no CKD)
Yellow: Moderately Increased Risk
Orange: High Risk
Red: Very High Risk
Deep Red: Highest Risk

STATISTICAL ANALYSIS:-

Data will be entered into Microsoft excel data sheet and will be analyzed using SPSS 22 version software. Categorical data will be represented in the form of Frequencies and proportions.

Chi-square will be used as test of significance. Continuous data will be represented as mean and standard deviation. Independent t test will be used as test of significance to identify the mean difference. P value <0.05 will be considered as statistically significant.

RESULTS

RESULTS

DEMOGRAPHIC DATA

TOTAL SAMPLES -93

SURVIVORS -75

NON SURVIVORS-18

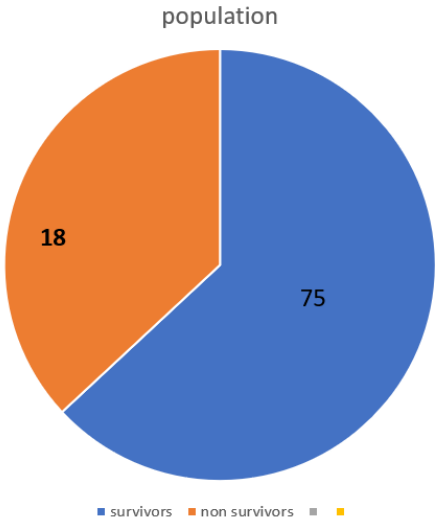

Figure 3 shows the demographic data of the study participants. Out of 93 participants ,18 patients were non survivors and 75 were survivors

GENDER

TOTAL-93

MALE-62

FEMALE-31

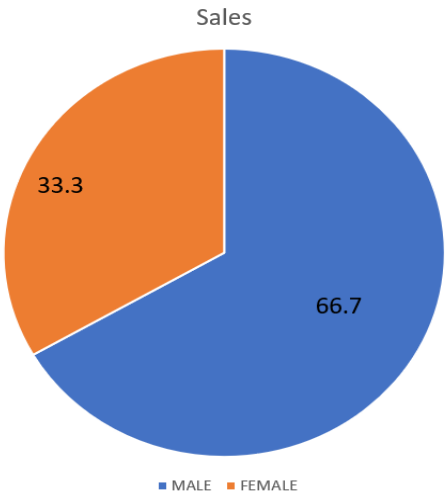

Figure 4 depicts the gender of the study participants. Were 62 of them were male and 31 were female. In percentage we can tell that 66.7% were male and 33.3% were female

AGE DISTRIBUTION

AGE GROUP	AGE	PERCENTAGE
18-20	2	2.2
21-30	4	4.3
31-40	11	11.8
41-50	22	23.7
51-60	24	25.8
61-70	25	26.9
>70	5	5.4
TOTAL	93	100

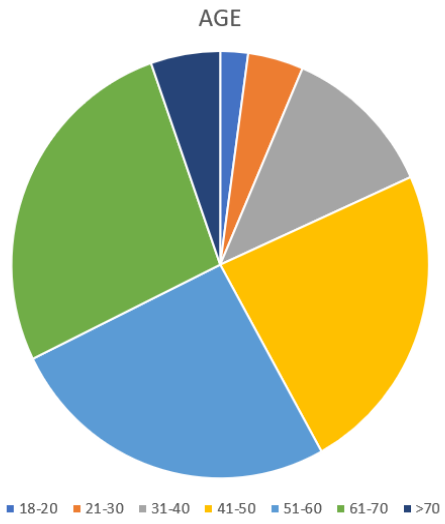

Table 7 and Figure 5 shows the age distribution of the study participants. 2 of them belonged to the age group of 18-20 which is 2.2%, 4 in the range of 21-30 which is 4.3%, 11 between 31-40 years which is 11.8%, 22 in the range of 41-50 years which is 23.7%, 24 in the range of 51-60 years which is 25.8% , 25 in between 61-70 years which is 26.9% , more than 70 years there were 5 participants which is about 5.4%

UACR AT ADMISSION

TOTAL PATIENTS	93
NORMAL	7
MICROALBUMINURIA	84
MACROALBUMINURIA	2

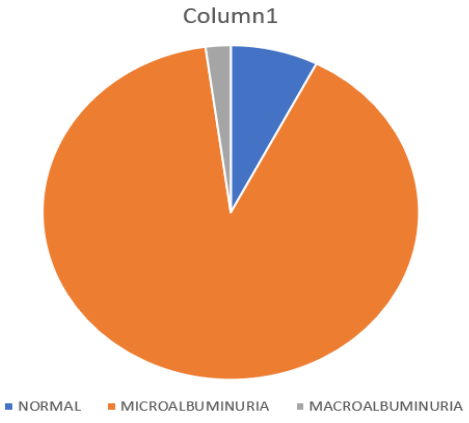

Table 8 and Figure 6 represents the UACR at admission.

The UACR was normal in 7 participants , microalbuminuria was seen in 84 participants and in 2 participants macroalbuminuria was observed.

COMPARISSION OF UACR 1 AND UACR 2

	MEAN UACR 1	MEAN UACR 2
SURVIVORS	58.00	116.05
NON SURVIVORS	142.00	189.11

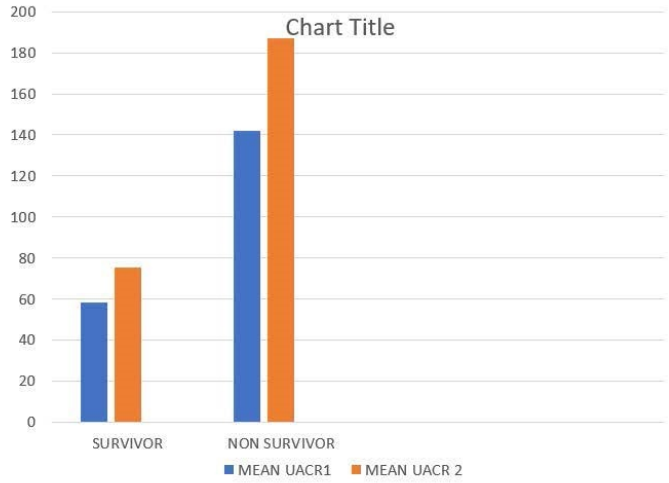

Table 9 and Figure 7 represents the comparison of UACR 1 & UACR 2.The mean UACR 1 for survivors were 58.0 and for non-survivors it was 142.00. The mean UACR 2 for survivors was 116.05 and for non – survivors was 189.11

TO PREDICT MORTALITY BY COMPARING UACR 1 WITH UACR 2

	DECREASED UACR AFTER 24 HOURS	INCREASED UACR AFTER 24 HOURS
SURVIVORS	53	22
NON SURVIVORS	4	14

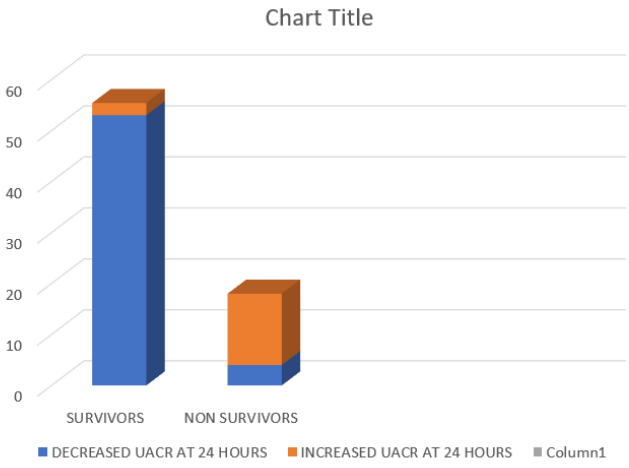

Table 10 and Figure 8 represents the mortality by comparing UACR 1 with UACR 2,

the decrease in UACR after 24 hours is seen in 53 of survivors and 4 among non survivors. Increase in UACR after 24 hours is seen in 22 of survivors and 14 among non survivors

RESULTS:

In this study, the demographic composition revealed that the majority of participants were males, representing 66.6% of the total sample. In contrast, females constituted 33.4%. This gender distribution indicates a higher prevalence or higher enrolment rate of males in the study.

The age range of the participants showed that a significant proportion, 66%, belonged to the 40-70 years age group. This suggests that middle-aged to elderly individuals were more affected or more likely to be included in the study. The average age of the patient was calculated to be 50.32 years with a standard deviation of 17.89 years indicating a wide range age range among the patients

The study also suggests mortality rate of 20% . this death rate suggests severity of sepsis ,effective monitoring and intervention needed as early as possible.

According to this study albumin creatinine ratio (ACR 2) at 24 hours after admission was measured in urine and median ACR2 among survived patients was 116.05 and among death patients was 189.11 .the p value was 0.049 indicating significant difference.so ACR 2 should be considered as a valuable prognostic marker.

DISCUSSION

DISCUSSION

"Sepsis continues to be a significant global healthcare challenge due to its high rates of morbidity and mortality, even with advancements in medical treatments. Despite the progress in medical technology and therapeutic interventions, sepsis remains a leading cause of death in intensive care units (ICUs) worldwide. One of the main challenges in managing sepsis is the timely and accurate diagnosis of the condition. The effectiveness of targeted therapies diminishes significantly when administered late, making early detection crucial for improving patient outcomes[71]. As of now as there is no proper method to diagnosis sepsis as early as possible".

"Sepsis is defined as intense host defense response that initiates powerful inflammatory cascades, releasing numerous pro-inflammatory molecules into the bloodstream. This overwhelming inflammatory response can lead to widespread tissue damage and organ dysfunction. The endothelium, which lines the interior surface of blood vessels, becomes dysfunctional due to the persistent attack from these inflammatory molecules and concurrent oxidative stress. A key early event in sepsis is the loss of barrier integrity, resulting in systemic capillary leakage. This increased permeability allows fluids and proteins to leak out of the circulatory system, leading to tissue edema and further impairing organ function. In the kidneys, this increased capillary permeability manifests as elevated excretion of albumin in the urine".

Microalbuminuria, defined as the "excretion of 30–300 mg of albumin per day in the urine, which rapidly occurs following an acute inflammatory insult like sepsis and persists in patients with complications". This condition is frequently observed in severly ill patients and has demonstrated potential indicator of "organ failure, vasopressor requirement, and mortality". Studies have shown that microalbuminuria

can outperform traditional scoring systems like Acute Physiological and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA)" scores in detecting outcomes in critically ill patients.

Similar endothelial dysfunction can occur in non-septic inflammatory conditions. However, it is unclear whether the degree of microalbuminuria differs following a septic insult compared to noninfectious conditions such as pancreatitis, burns, or trauma, and whether it could distinguish sepsis in a diverse population of critically ill patients. Current sepsis biomarkers like "procalcitonin (PCT), C-reactive protein (CRP), and markers of endothelial damage such as adhesion molecules" are markedly increased in sepsis[72]. Drawing a parallel with these biomarkers, it is hypothesized that microalbuminuria would show a similar pattern of elevation in sepsis

To test this hypothesis, our study aimed to explore the diagnostic role of microalbuminuria by measuring its levels in patients with and without sepsis. A secondary objective was to assess the ability of microalbuminuria to predict ICU mortality. Early diagnosis of sepsis is crucial for patient management and outcomes, but no reliable method currently exists. Culturing body fluids, the gold standard for sepsis diagnosis, often yields negative results and takes at least 24 hours[73], potentially delaying targeted therapies. Procalcitonin (PCT) is considered specific and sensitive for identifying systemic bacterial infections, but it also increases in several non infectious inflammatory conditions, does not rise in localized infections, and has a relatively high turnaround time for the LUMI test. C-reactive protein (CRP), a less expensive alternative, is limited by its low specificity for sepsis diagnosis, slow induction time, and lack of correlation with disease severity.

“Microalbuminuria may provide an indirect measure of changes in systemic vascular permeability. Testing the albumin-to-creatinine ratio (ACR) in a random urine sample is a simple, validated, and reliable method. Microalbuminuria levels rise within hours of an inflammatory insult, unlike the relatively delayed increases of PCT and CRP. Numerous studies across various groups of critically ill patients have consistently established microalbuminuria as a significant prognostic marker for morbidity and mortality in the ICU”.

“In our present study, 93 participants were included, with a male preponderance of 66.6% and females constituting 33.4%. The majority of the participants were in the age group of 61-70 years, constituting 26.9%, followed by those in the age group of 51-60 years, constituting 25.8%. The mean age of the participants was 50.32 years. Of the 93 study participants, 84 presented with UACR at the time of admission, and most developed UACR within 24 hours, indicating that 87% of the participants presented with microalbuminuria”.

“On admission, microalbuminuria was found to be significantly elevated in patients with sepsis compared to those without. At 24 hours, UACR was significantly elevated in the non-survivors. The ACR test is done on a regular basis in the hospital laboratory and results can be made available as early as 30 minutes. The ACR can also be estimated by the ICU nurses themselves, as a point-of-care test, within 15 min, as shown in Gosling *et al*'s study.[18]

The pathophysiological cause of microalbuminuria in general is not fully understood, but defects in both the glomerulus and the tubules have been implicated. In acute inflammation, microalbuminuria is surmised to be a result of the endothelial glomerular

leak in the kidneys, which is a manifestation of systemic increases in capillary permeability due to an intense inflammatory onslaught on the endothelium".

De Gaudio et al. evaluated 55 post-operative patients developed sepsis during ICU course and found that Post-operative patients developing sepsis, unlike those with an uncomplicated postoperative evolution, showed an increase in glomerular permeability which was revealed by ACR. The increase in the ACR was positively correlated to the increase in SOFA score, while it had no relation to the PaO2/FIO2 ratio . We found the same positive correlation between ACR and SOFA in our study that confirms the strong agreement between ACR and clinical scoring systems in septic patients.

In a study by Gosling et al., Microalbuminuria was compared with mortality, APACHE II and SAP II scores. Median (95% confidence interval) ACR at admission for survivors (n = 115) and non-survivors (n = 25) were 37.2 (31.9-57.5) and 157.5 (70.8-361.1) mg/g, respectively (p = 0.0002). For 92 surgical, trauma, and burn patients, of whom 81 survived, ACR of > 52.2 mg/gm gave a sensitivity for the death of 100%, specificity of 59%, the positive predictive value of 25%, and negative predictive value of 100%. Mortality probability receiver operator characteristic curve areas for ACR, APACHE II, and SAP II were 0.843 (p < .0001), 0.793 (p = 0.0004), and 0.770 (p = 0.0017), respectively. In this study (Gosling et al.), its cut-off level is much closer to our level in spite; it was used in a different category of patients. This may indicate the widespread possible benefit of ACR in different patient categories rather than only septic patients.

In Bhadade et al., significantly higher levels of microalbuminuria were found among patients with sepsis as compared to those without sepsis. The levels decreased in survivors with sepsis after 24 hours, whereas they continued to remain almost at the

same levels among those without sepsis. The change in microalbuminuria levels over 24 hours can be used to measure the effectiveness of therapy. Persistence of high levels or increasing trend of microalbuminuria levels over 24 hours was found to be a predictor of a poor outcome. A high level of microalbuminuria at 24 hours and increasing trend of microalbuminuria also predicted mortality better than APACHE II and SOFA scores. The point of difference is that authors in this study measure ACR at 24 hours and not early as we did which may give earlier prognostic value in our study.

In a study by Thorevska et al., They confirmed a high prevalence of microalbuminuria in critically ill patients and suggested that an albumin-creatinine ratio ≥ 100 mg/g is an independent predictor of mortality and hospital stay [17].

A study done by Rivers et al[74]. postulates the possibility of inflammation-induced defects in the glycocalyx layer of the endothelium being responsible for higher levels of microalbuminuria in sepsis. It has been shown that the glycocalyx of the fenestrated glomerular capillaries acts as a barrier to protein permeability, and enzymatic degradation of this layer increases the passage of albumin across the glomerulus, which is in line with our present study findings. A possible explanation for the reductions of median levels after 24 hours of ICU admission could be the effect of therapeutic interventions on the attenuation of the inflammatory process and pacifying effects on the endothelium.

The study reported a mortality rate of 20%. The median ACR2 at 24 hours of admission was 75.0 among survivors, while among non-survivors, it was significantly higher at 187.0. The p-value of 0.049 indicates that the difference is statistically significant,

thereby establishing the prognostic significance of microalbuminuria in sepsis patients. These findings are consistent with studies conducted by Spapen and De Gaudio et al.,[75] which used microalbuminuria as a tool to document the effect of treatment with high doses of N-acetylcysteine, an antioxidant, and low-dose hydrocortisone, respectively, in severe clinical sepsis.

The concept that is prevailing is that Micro albuminuria is nothing but a systemic capillary inflammation indicated by the presence of inflammatory biomarkers such as C-reactive protein, TNF-α, soluble intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (30-32). Studies that show the association between MA and acute respiratory distress syndrome (ARDS) provide further support. In patients with trauma, Pallister and colleagues (33, 34) demonstrated that albumin excretion rate which is measured within 8 hours after the admission predicted the development of ARDS, and the underlying mechanism was an increase in the systemic capillary leakage. However, another study conducted in patients with sepsis showed that ACR did not correlate to EVLW and PaO2 /FiO2 , and thus concluded microalbuminuria does not point out to increased systemic capillary permeability in septic shock. One explanation for this is that in the later study, the population had very low levels of serum albumin, and hypoalbuminemia may influence the urinary albumin excretion. Another explanation is that EVLW is not completely determined by pulmonary vascular permeability; other factors, including volume status, cardiac function and severity of lung injury, all contribute to EVLW. In our study, ACR was significantly correlated with AKI development, proving that an increase in urinary albumin excretion was correlated with increases in systemic capillary leakage. The kidneys receive about 25% of the cardiac output, and small changes in glomerular permeability will lead to notable changes in microalbuminuria, and thus kidneys are

sensitive to permeability changes . Numerous studies have investigated the association of ACR and outcomes in critically ill patients, and the correlation can be found in a variety of clinical settings. Thorevska N et al (37) evaluated the association of ACR and clinical outcomes in 104 mixed ICU patients and found that ACR >100 mg/g was an independent predictor of mortality and hospital stay. In surgical patients, ACR measured on arrival to the ICU was able to significantly differentiate survivors from nonsurvivors (38). Abid et al (39) measured ACR serially and divided study subjects into 2 groups: one with decreasing ACR and the other with increasing ACR. They found that patients with increasing ACR had significantly higher mortality rates and corresponding higher degrees of illness severity. A similar result was replicated in a medical ICU by Thorevska et al (37). Mortality was a secondary outcome in our study, and consistent with previous findings, ACR was significantly higher in nonsurvivors than in survivors. Thus, together with conventional illness severity scores, the measurement of ACR on entry to the ICU can provide additional information on patient outcome, which can help to target patients who will most benefit from prophylactic strategies such as avoidance of nephrotoxic exposure, maintenance of renal blood flow and early initiation of renal replacement therapy.

To our knowledge, no prior study has investigated the role of microalbuminuria in diagnosing sepsis. Although our findings indicate that the urine albumin-to-creatinine ratio (UACR) may not have strong discriminant value for sepsis diagnosis, its advantages include being a noninvasive, inexpensive, and readily available bedside screening test. It can help identify patients with Systemic Inflammatory Response Syndrome (SIRS) who do not have sepsis, as demonstrated in a study conducted by Gosling et al[(76)].

In summary, microalbuminuria presents a promising avenue for early diagnosis and prognosis in sepsis management. While more research will be necessary to fully establish diagnostic utility, its role as a prognostic marker is well-supported. This simple and cost-effective test could enhance the timely identification and treatment of sepsis, ultimately improving patient outcomes in the ICU.

CONCLUSION

CONCLUSION

Microalbuminuria is a promising diagnostic and prognostic tool for critically ill patients, especially those with sepsis. Its rapid, inexpensive, and non-invasive nature makes it suitable for widespread use, including in resource-limited settings. Serial measurements of microalbuminuria offer valuable insights into patient outcomes, enabling healthcare providers to identify high-risk patients early and tailor interventions accordingly. Given its potential to improve patient management and outcomes, microalbuminuria should be considered a standard component of critical care assessment.

Non-invasive: The test requires only a urine sample, which is non-invasive and easy to obtain, reducing patient discomfort and risk.

Early Indicator: Microalbuminuria levels rise within hours of an inflammatory insult, providing an early warning sign of sepsis or other critical conditions, unlike some traditional biomarkers that may take longer to elevate.

Predictive Value: Serial measurements of microalbuminuria can track changes over time, offering continuous insights into a patient's condition and helping to identify those at risk of deterioration.

Serial measurements of microalbuminuria can serve as a helpful measure in the clinical assessment of critically ill patients at risk of a worse prognosis. For instance, patients who do not exhibit significant microalbuminuria during the first six hours of ICU admission are less likely to have sepsis, providing early reassurance and guiding clinical decision-making. Furthermore, after 24 hours, the absence of elevated microalbuminuria levels strongly predicts ICU survival, with predictive accuracy comparable to established scoring systems like the APACHE II.

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ANNEXURES

ANNEXURES

PATIENT INFORMATION SHEET

STUDY TITLE: " MICROALBUMINURIA :A DIAGNOSTIC AND PROGNOSTIC TOOL IN PATIENTS ADMITTED IN HOSPITAL WITH SEPSIS

GUIDE : DR.PRABHAKAR .K

STUDY CONDUCTED BY: DR. D .R. Lakwan sakthi

STUDY LOCATION: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar.

Microalbuminuria occurs due to changes in glomerular permeability within few hours of inflammation in sepsis. It reflects generalised endothelial damage throughout the vasculature. So, microalbuminuria serves as marker of sepsis. The measurement of microalbuminuria at the time of admission and after 24 hour of admission can be taken as prognostic indicator of mortality in critically ill patients.

All Patients diagnosed with Urinary microalbuminuria will be included in this study. Patients in this study will undergo routine investigations,cbc,rft,lft,serum albumin,urinary microalbumin.The principal investigator will bear the expenses of special investigations required for the study .

Your participation is the study will help us to use the outcomes of this study for future subjects and will bring to limelight the importance and potentiate the clinical application of micro albuminuria as a diagnostic and prognostic tool for sepsis.

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study, we will collect information (as per proforma) from you or a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee.

There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

The purpose of the study is explained in detail to us and all information collected is for study purpose only. The data collected is submitted to the department of General Medicine, SDUMC, Kolar and confidentiality ensured .The merits and demerits explained briefly to us.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH

TAMAKA, KOLAR - 563101.

INFORMED CONSENT FORM

Title : **MICROALBUMINURIA : A DIAGNOSTIC AND PROGNOSTIC TOOL IN PATIENTS ADMITTED IN HOSPITAL WITH SEPSIS**

Principal investigator: Dr. D.R.Lakwan Sakthi

I, Mr./Mrs./Miss . …….. have been explained in my own understandable language,that I will be included in the above mentioned study ,being conducted in RL JALAPPA HOSPITAL.

I have been explained that my clinical findings,investigations,treatment and prognosis will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary and I can withdraw from the study any time and this will not affect my relation with my doctor or treatment for my ailment.

I have been explained about the risk/benefit of the study.

I understand that the medical information produced by this study will become part of institutional records and will be kept confidential by my said institute.

I agree not to restrict the use of any data or result that arise from this study provided such a use is only for scientific purpose(s).

I have principal investigator mobile number for enquiries.

I have been informed that standard of care will be maintained throughout the treatment period.

I in my sound mind give full consent to be added in the part of this study.

Investigator: Dr. D.R.Lakwan sakthi

Phone number : 76393656565

Name	Signature	Date	Time
Patient:			
Witness:			
Primary Investigator/ Doctor:			

ಶ್ರೀ ದೇವರಾಜ್ ಉರ್ಸ್ ಆಸ್ಪತ್ರೆ, ತಮಕಾ, ಕೋಲಾರ - 563101

<u>ತಿಳುವಳಿಕೆಯುಳ್ಳ ಒಪ್ಪಿಗೆಯ ನಮೂನೆ</u>

ನಾನು , Mr/Mrs/Miss_____ನನ್ನ ಸ್ವಂತ ಅರ್ಥವಾಗುವ ರೀತಿಯಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ

ಭಾಷೆ, ಮೇಲೆ ತಿಳಿಸಿದ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನನ್ನು ಸೇರಿಸಿಕೊಳ್ಳಲಾಗುವುದು

ಆರ್.ಎಲ್ ಜಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ.

ನನ್ನ ಕ್ಲಿನಿಕಲ್ ಸಂಶೋಧನೆಗಳು, ತನಿಖೆಗಳು, ಚಿಕಿತ್ಸೆ ಮತ್ತು ಎಂದು ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ

ಮುನ್ನರಿವು ಮೌಲ್ಯಮಾಪನ ಮತ್ತು ಅಧ್ಯಯನ ಉದ್ದೇಶಕ್ಕಾಗಿ ದಾಖಲಿಸಲಾಗುತ್ತದೆ.

ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಭಾಗವಹಿಸುವಿಕೆಯು ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿದೆ ಮತ್ತು ನಾನು ಮಾಡಬಹುದು ಎಂದು ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ

ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹಿಂದೆ ಸರಿಯಿರಿ ಮತ್ತು ಇದು ನನ್ನೊಂದಿಗಿನ ನನ್ನ ಸಂಬಂಧದ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ

ನನ್ನ ಕಾಯಿಲೆಗೆ ವೈದ್ಯರು ಅಥವಾ ಚಿಕಿತ್ಸೆ.

ಅಧ್ಯಯನದ ಅಪಾಯ/ಪ್ರಯೋಜನದ ಬಗ್ಗೆ ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ.

ಈ ಅಧ್ಯಯನದಿಂದ ಉತ್ಪತ್ತಿಯಾಗುವ ವೈದ್ಯಕೀಯ ಮಾಹಿತಿಯು ಭಾಗವಾಗುತ್ತದೆ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ

ಸಾಂಸ್ಥಿಕ ದಾಖಲೆಗಳ ಮತ್ತು ನಾನು ಹೇಳಿದ ಸಂಸ್ಥೆಯಿಂದ ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುವುದು.

ಈ ಅಧ್ಯಯನದಿಂದ ಉಂಟಾಗುವ ಯಾವುದೇ ಡೇಟಾ ಅಥವಾ ಫಲಿತಾಂಶದ ಬಳಕೆಯನ್ನು ನಿರ್ಬಂಧಿಸದಿರಲು ನಾನು ಒಪ್ಪುತ್ತೇನೆ

ಅಂತಹ ಬಳಕೆಯನ್ನು ವೈಜ್ಞಾನಿಕ ಉದ್ದೇಶ(ಗಳು)ಗಾಗಿ ಮಾತ್ರ ಒದಗಿಸಲಾಗಿದೆ.

ವಿಚಾರಣೆಗಾಗಿ ನಾನು ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಯ ಮೊಬೈಲ್ ಸಂಖ್ಯೆಯನ್ನು ಹೊಂದಿದ್ದೇನೆ.

ಸಂಪೂರ್ಣ ಗುಣಮಟ್ಟದ ಆರೈಕೆಯನ್ನು ನಿರ್ವಹಿಸಲಾಗುವುದು ಎಂದು ನನಗೆ ತಿಳಿಸಲಾಗಿದೆ

ಚಿಕಿತ್ಸೆಯ ಅವಧಿ.

ಈ ಅಧ್ಯಯನದ ಭಾಗದಲ್ಲಿ ಸೇರಿಸಲು ನನ್ನ ಉತ್ತಮ ಮನಸ್ಸಿನಲ್ಲಿ ನಾನು ಸಂಪೂರ್ಣ ಒಪ್ಪಿಗೆಯನ್ನು ನೀಡುತ್ತೇನೆ.

ತನಿಖಾಧಿಕಾರಿ : Dr.D.R. ಲಕ್ಷ್ಮಾನ್ ಶಕ್ತಿ

ದೂರವಾಣಿ ಸಂಖ್ಯೆ : 7639356565

ಹೆಸರು	ಸಹಿ	ದಿನಾಂಕ	ಸಮಯ
ರೋಗಿಯ :			
ಸಾಕ್ಷಿ:			
ವೈದ್ಯರು/ಪ್ರಾಥಮಿಕ ತನಿಖಾಧಿಕಾರಿ :			

PROFORMA

Particulars of the patients

NAME :

AGE : ____ YEARS

SEX : MALE

OCCUPATION :

LOCATION :

HOSPITAL NUMBER :

DATE AND TIME OF ADMISSION : __/__/20__ AT __:__ AM/PM

DATE OF DISCHARGE :__/__/20__

ADMISSION DIAGNOSIS :

BRIEF HISTORY :

SYMPTOMS ON PRESENTATION :

□ Fever

□ Hypothermia

□ Tachyacardia

□ Confusion or disorientation

□ Hyperventilation

□ Shortness of breath

PRIOR TREATMENT :

□ YES □ NO

PROVIDER:

SUPPORTIVE:

TREATMENT :

PAST HISTORY :

□ DIABETES MELLITUS

□ HYPERTENSION

□ LIVER DISORDER

□ CARDIOVASCULAR DISEASE

□ RENAL DISORDER

□ TUBERCULOSIS

□ BRONCHIAL ASTHMA

PERSONAL HISTORY :

- DIET :
- APPETITE :
- SLEEP :
- BOWEL AND BLADDER :
- HABITS :
- SOCIOECONOMIC STATUS :

GENERAL PHYSICAL EXAMINATION:

- Height: ____cms
- Weight : ____ kgs
- BMI : ____kg / m

VITAL DATA

- Pulse: ___ bpm

• Temperature:____oF

• BP: ____ mmHg

• Respiration rate: ____ cpm

• SpO2 : ____% @ RA

SYSTEMIC EXAMINATION :

• Per abdomen:

• Respiratory system:

VENTILATORY SUPPORT :

• Cardio vascular system:

• Central nervous system :

GCS :

INVESTIGATIONS:

Routine:

CBC

• HB : ____ gm%

• TC :____ Thousands/mm3

• DC : N___% L ___% E___% M____% B____%

• PCV :____ %

• PLATELETS :____ Thousands/mm3

ESR

RFT

• UREA :___ mg/dL

• SERUM CREATININE :____ mg/dL

• NA+ :____mEq/L

• K+ :_____mEq/L

RBS : ____ mg/dL

LFT

• TOTAL BILIRUBIN : ____ mg/dl

• DIRECT BILIRUBIN : ____ mg/dl

• AST : ____ U/L

• ALT : ____ U/L

• ALP : ____ U/L

• TOTAL PROTEIN : ____ g/dL

• GGT : _____ U/L

SERUM ALBUMIN : ____g/Dl

URINARY MICRO ALBUMIN : ____mg/day

BLOOD CULTURE AND SENSITIVITY :

CHEST X-RAY :

TREATMENT :

FINAL OUTCOME :

MASTERCHART

s.no	age	Gender	religion	address	Socioeconomic status	Cause of sepsis	Temperature (FARENHEIT)	Heart rate(BPM)	Respiratory rate(CPM)	BLOOD PRESSURE (MM HG)	HEMOGLOBIN (g/dl)	Wbc TH/MM3	PLATELET COUNT TH/MM3	RBS (MG/DL)	BLOOD UREA (MG/DL)	SERUM CREATININE (MG/DL)	SODIUM (mEq/L)	POTASSIUM (mEq/l)	Crp(mg/L)	ESR(mm/hr)	UACR1	UACR2	SURVIVOR
1	33	male	muslim	urban	lower	MENINGOENCEPHALITIS	99.5	123	22	110/70	11.8	13.00	145	189	54	1.0	130	4.3	positive	positive	24	37	yes
2	52	male	hindu	rural	Lower middle	BRONCHOPNEUMONIA	98	100	28	100/70	12.7	14.40	190	114	43	0.9	136	3.2	positive	positive	39	72	yes
3	18	male	hindu	urban	Lower middle	CELLULITIS	101	109	20	80/40	10.8	16.23	123	94	87	2.3	128	3.6	positive	positive	83	65	yes
4	41	female	hindu	rural	lower	CATHETER SITE SEPSIS	103	104	18	90/60	9.7	19.56	220	167	65	1.7	146	4.1	positive	positive	130	232	no
5	58	male	hindu	rural	Lower middle	URINARY TRACT INFECTION	102.1	116	18	100/80	11.0	15.34	176	156	46	1.5	138	4.6	positive	positive	115	110	yes
6	64	male	hindu	rural	middle	PYELONEPHRITIS	99	98	25	110/80	10.8	24.20	120	112	90	3.4	150	5.4	positive	positive	329	286	yes
7	23	male	muslim	urban	upper	VIRAL FEVER	97.9	97	22	130/80	13.0	17.20	34	109	36	0.8	145	4.0	positive	positive	27	45	yes
8	57	male	hindu	rural	Lower middle	BRONCHOPNEUMONIA	99.5	117	32	100/60	12.7	14.40	156	94	56	1.5	136	3.7	positive	positive	54	37	yes
9	36	female	hindu	rural	Lower middle	URINARY TRACT INFECTION	98.6	108	17	110/80	11.5	13.00	212	187	49	1.1	134	4.3	positive	positive	96	49	yes
10	69	male	muslim	urban	lower	PYREXIA OF UNKNOWN ORIGIN	104	110	25	90/70	14.0	22.10	325	124	40	0.7	143	4.8	positive	positive	19	76	yes
11	34	male	hindu	rural	Lower middle	MENINGOENCEPHALITIS	100.5	120	22	90/50	10.9	26.00	112	130	76	1.4	132	3.8	positive	positive	78	139	no
12	26	male	muslim	urban	Upper middle	CELLULITIS	103	132	26	80/50	11.7	24.60	176	145	94	3.0	128	3.6	positive	positive	34	178	no
13	45	male	hindu	urban	lower	VIRAL FEVER	98.2	89	17	140/80	9.4	14.00	23	112	111	2.8	140	4.8	positive	positive	112	143	yes
14	47	female	muslim	rural	lower	BRONCHOPNEUMONIA	99	96	30	100/70	10.6	17.90	212	190	39	1.0	128	4.3	positive	normal	23	54	yes
15	38	male	hindu	rural	Lower middle	VIRAL FEVER	99.5	107	22	120/80	12.0	11.50	18	176	33	1.1	142	3.9	positive	positive	56	89	no
16	58	male	hindu	rural	Lower middle	CATHETER RELATED SEPSI	98.8	113	20	90/60	8.8	16.00	169	87	56	2.4	119	4.4	positive	positive	196	176	yes
17	72	female	christian	rural	lower	BRONCHOPNEUMONIA	99.4	119	27	110/70	8.4	19.00	134	143	76	1.4	135	3.4	positive	positive	110	75	yes
18	51	male	muslim	urban	lower	INFECTIOUS DIARRHEA	98.6	124	16	90/60	12.4	13.34	221	119	59	2.5	128	2.7	positive	positive	90	223	no
19	43	male	hindu	rural	Lower middle	PYELONEPHRITIS	99.5	134	18	130/80	10.3	22.20	155	102	165	4.2	131	4.7	positive	positive	58	167	no
20	69	female	hindu	rural	lower	VIRAL FEVER	98.7	115	17	100/80	11.0	11.27	20	190	29	0.8	136	3.8	positive	positive	278	230	yes
21	27	female	hindu	rural	Lower middle	URINARY TRACT INFECTION	97.6	93	22	120/70	10.7	13.54	178	134	64	1.7	142	4.6	positive	positive	58	43	yes
22	48	male	hindu	rural	lower	BRONCHOPNEUMONIA	99.6	89	26	100/60	14.8	11.55	165	111	57	1.3	129	2.9	positive	positive	83	79	yes
23	62	male	hindu	rural	Lower middle	CHOLECYSTITIS	99.4	110	20	130/80	11.8	18.50	190	142	49	1.1	149	3.9	positive	positive	25	39	yes

24	45	female	hindu	rural	Upper middle	THROMBOPHLEBITIS	99.5	98	19	140/70	13.0	10.86	163	113	30	0.8	144	4.3	positive	positive	119	72	yes
25	55	male	hindu	rural	upper	MENINGOENCEPHALITIS	102	135	25	100/70	10.0	23.30	145	178	56	1.8	132	3.5	positive	positive	148	83	yes
26	63	female	hindu	urban	lower	URINARY TRACT INFECTION	101.5	124	19	110/70	12.8	13.27	165	127	87	1.4	127	3.7	positive	positive	40	34	yes
27	41	male	hindu	rural	lower	INFECTIOUS DIARRHEA	104	156	20	90/60	13.2	15.43	128	103	118	2.4	125	3.2	positive	positive	89	245	no
28	59	male	christian	rural	Lower middle	VIRAL FEVER	102	105	20	100/70	14.0	12.40	32	176	90	2.1	154	3.5	positive	positive	93	106	yes
29	48	male	hindu	rural	Lower middle	CATHETER RELATED SEPSIS	97.6	90	21	90/60	9.8	16.43	235	212	119	3.3	143	5.2	positive	positive	237	220	yes
30	66	female	hindu	rural	Lower middle	URINARY TRACT INFECTION	99.4	87	18	90/50	12.2	14.32	323	110	67	1.3	139	3.3	positive	positive	17	70	yes
31	41	male	hindu	urban	Upper class	BRONCHOPNEUMONIA	99.4	102	28	100/60	9.6	21.24	456	212	87	0.9	125	3.9	positive	positive	149	117	yes
32	68	male	hindu	rural	Lower middle	CELLULITIS	99.3	108	26	110/70	10.4	17.00	114	89	50	1.2	130	3.0	positive	positive	58	30	yes
33	33	female	hindu	rural	lower	CATHETER RELATED INFECTION	100.4	96	21	130/70	13.6	14.23	234	167	112	3.0	142	5.3	positive	positive	243	190	yes
34	56	male	muslim	urban	middle	INFECTIOUS DIARRHEA	97.4	99	19	80/50	8.9	19.43	320	159	87	3.6	131	2.9	positive	positive	118	120	yes
35	62	male	hindu	rural	Lower middle	BRONCHOPNEUMONIA	99.8	113	30	68/40	9.7	27.00	167	190	63	1.9	134	3.6	positive	positive	73	62	yes
36	68	male	hindu	rural	lower	BRONCHOPNEUMONIA	97.5	123	22	110/70	13.5	3.00	89	143	18	1.0	140	3.3	positive	positive	289	258	yes
37	62	female	hindu	rural	Lower middle	INFECTIOUS DIARRHEA	101.6	135	16	100/60	11.2	15.34	234	176	58	1.8	119	4.4	positive	positive	125	87	yes
38	47	male	hindu	urban	middle	BRONCHOPNEUMONIA	98.9	96	22	100/60	11.9	12.23	187	97	76	2.0	133	2.8	positive	positive	72	79	yes
39	55	male	hindu	rural	lower	MALARIA	103	145	19	110/80	12.1	18.48	56	134	48	1.0	143	4.1	positive	positive	312	289	yes
40	31	male	hindu	rural	middle	DENGUE FEVER	99.6	106	18	100/60	11.8	11.00	34	142	40	0.8	134	3.9	positive	positive	38	65	yes
41	54	male	hindu	rural	lower	CHOLECYSTITIS	99.4	100	20	110/70	13.7	23.00	212	119	49	1.1	128	3.3	positive	positive	120	110	yes
42	71	male	hindu	rural	Lower middle	MENINGOENCEPHALITIS	96.9	90	26	80/50	10.6	2.00	190	156	62	1.4	138	3.0	positive	positive	256	345	no
43	58	male	muslim	urban	lower	URINARY TRACT INFECTION	97.8	98	22	90/40	15.8	12.45	165	112	74	1.6	131	4.2	positive	positive	149	167	yes
44	52	male	hindu	rural	middle	BRONCHOPNEUMONIA	99.5	102	34	120/70	11.4	13.00	172	189	43	1.0	125	4.9	positive	positive	194	193	yes
45	44	male	hindu	rural	lower	INFECTIOUS DIARRHEA	104	137	14	90/50	13.0	14.30	342	110	97	2.3	129	3.0	positive	positive	134	148	no
46	56	female	hindu	rural	Upper middle	CHOLECYSTITIS	98	123	18	100/60	11.2	12.45	220	167	68	1.4	133	4.4	positive	positive	178	144	yes
47	66	male	hindu	rural	Lower middle	INTRAABDOMINAL INFECTION	98.7	96	22	80/50	13.9	30.00	112	109	59	1.9	129	2.9	positive	positive	48	73	yes
48	54	male	hindu	rural	Lower middle	CELLULITIS	103	134	20	90/60	10.8	27.00	154	106	110	2.6	132	2.5	positive	positive	128	109	yes
49	45	female	hindu	rural	middle	BRONCHOPNEUMONIA	99.3	102	27	100/80	9.3	13.00	176	153	43	0.7	140	3.6	positive	positive	90	112	no

50	59	male	hindu	rural	lower	THROMBOPHLEBITIS	98.4	89	23	110/60	11.8	11.50	190	178	39	1.0	143	3.5	positive	positive	85	80	yes
51	73	female	hindu	rural	Lower middle	INFECTIOUS DIARRHEA	103.5	117	18	78/50	10.6	19.00	145	84	76	1.7	127	3.3	positive	positive	67	47	yes
52	33	male	hindu	urban	middle	CATHETER RELATED SEPSI	100.6	108	18	90/50	8.5	16.00	219	206	111	5.9	129	3.4	positive	positive	98	87	no
53	69	male	hindu	rural	Middle	BRONCHOPNEUMONIA	104.6	143	26	130/80	12.2	21.34	178	134	45	1.1	138	4.6	positive	positive	134	116	yes
54	43	female	hindu	rural	Lower middle	BRONCHOPNEUMONIA	99.3	127	29	100/60	9.8	15.67	143	123	38	0.6	128	4.8	positive	positive	186	122	yes
55	63	male	hindu	rural	lower	LUNG ABSCESS	102.8	132	30	120/70	9.3	22.45	89	106	78	2.0	136	3.9	positive	positive	56	123	no
56	30	female	christian	rural	Lower middle	UROSEPSIS	99.2	120	22	90/50	10.1	17.45	176	80	104	2.8	121	3.4	positive	positive	78	92	yes
57	68	male	hindu	rural	middle	INFECTIOUS DIARRHEA	98.9	98	19	100/60	14.3	2.86	39	112	86	1.9	132	2.8	positive	positive	110	54	yes
58	66	female	hindu	rural	middle	BRONCHOPNEUMONIA	101	116	25	110/60	12.3	13.45	220	109	50	1.0	137	3.3	positive	positive	46	36	yes
59	47	male	hindu	rural	Upper middle	CELLULITIS	103.4	127	16	80/40	12.4	32.00	145	78	107	3.1	128	4.9	positive	positive	32	119	no
60	55	male	hindu	rural	Lower middle	BRONCHOPNEUMONIA	101	114	27	100/70	18.8	17.40	172	198	75	2.1	140	4.3	positive	positive	100	87	yes
61	75	female	muslim	urban	lower	TYPHOID FEVER	100.6	86	17	100/60	9.7	13.00	78	110	40	1.0	142	3.5	positive	positive	36	47	yes
62	19	male	hindu	rural	Lower middle	FEVER OF UNKNOWN ORIGIN	99.8	95	24	120/80	13.3	18.34	231	122	37	0.7	135	3.8	positive	positive	76	65	yes
63	25	male	hindu	rural	middle	MENINGOENCEPHALITIS	102.8	118	21	110/60	10.9	25.45	27	98	67	1.5	129	4.6	positive	positive	29	65	yes
64	63	male	hindu	rural	lower	PULMONARY TUBERCULOSIS	101	106	26	100/50	9.8	22.87	165	74	50	1.O	127	3.0	positive	positive	91	78	yes
65	67	female	hindu	rural	Lower middle	CELLULITIS	104	143	18	110/60	10.5	29.00	125	134	48	1.1	120	4.7	positive	positive	106	91	yes
66	44	female	hindu	rural	Upper middle	SPLEENIC ABSCESS	97.9	97	19	90/50	9.4	24.67	234	83	89	2.1	132	3.7	positive	positive	204	187	yes
67	39	male	hindu	urban	Lower middle	SEPTIC ARTHRITIS	99.6	113	22	110/60	10.7	21.34	543	145	70	1.2	138	3.5	positive	positive	189	170	yes
68	56	male	hindu	rural	middle	PULMONARY TUBERCULOSIS	99.5	105	25	100/60	8.9	16.45	134	123	59	1.3	123	3.9	positive	positive	76	58	yes
69	61	male	hindu	rural	lower	BRONCHOPNEUMONIA	100.6	117	22	110/70	10.7	19.34	212	189	45	0.9	134	3.1	positive	positive	110	104	yes
70	44	female	hindu	rural	lower	UROSEPSIS	99.7	94	18	90/50	11.4	17.34	155	127	90	2.4	142	4.2	positive	positive	145	132	yes
71	65	male	hindu	rural	Lower middle	CELLULITIS	100.3	106	16	80/50	12.2	28.36	176	160	87	2.2	130	3.4	positive	positive	97	112	yes
72	63	female	hindu	rural	middle	LIVER ABSCESS	103.7	104	19	110/60	9.3	21.63	190	127	69	1.7	157	3.9	positive	positive	190	204	yes
73	32	male	muslim	urban	Lower middle	BRAIN ABSCESS	99.8	94	19	90/60	10.9	22.00	276	185	102	2.1	146	2.6	positive	positive	167	225	no
74	64	female	hindu	rural	Lower middle	FEVER OF UNKNOWN ORIGIN	97.6	87	22	110/70	13.5	14.54	194	177	45	1.0	134	3.9	positive	positive	109	87	yes
75	65	female	hindu	rural	lower	BACTERIAL MENINGITIS	98.6	105	19	80/50	11.6	15.62	156	163	54	1.2	140	4.8	positive	positive	211	174	yes

76	46	male	hindu	rural	middle	DENGUE FEVER	99.0	113	17	90/50	13.0	14.67	45	116	43	1.0	145	3.9	positive	normal	55	78	yes
77	51	male	hindu	rural	Lower middle	PULMONARY TUBERCULOSIS	102	123	26	100/60	10.2	13.87	126	203	65	1.3	132	2.8	positive	positive	39	24	yes
78	68	female	hindu	rural	middle	TYPHOID	100.9	117	21	120/60	11.0	19.04	76	89	34	0.9	138	4.3	positive	positive	163	134	yes
79	47	male	muslim	rural	Lower middle	CEREBRAL MALARIA	99.7	106	22	110/80	9.7	3.65	102	134	87	2.2	130	4.4	positive	positive	189	197	yes
80	63	male	hindu	urban	lower	LEPTOSPIROSIS	101	113	18	100/60	11.6	13.23	12	110	101	2.1	133	3.8	positive	positive	99	47	yes
81	55	female	hindu	rural	Lower middle	UNKNOWN BITE WITH CELLULITIS	100.5	112	19	110/70	13.2	19.08	450	1871	56	1.2	146	4.3	positive	positive	70	54	yes
82	47	male	hindu	rural	Lower middle	MENINGOENCEPHALITIS	101	107	17	120/90	12.6	24.09	151	98	69	1.5	122	3.0	positive	positive	290	298	no
83	69	female	christian	rural	lower	URINARY TRACT INFECTION	99.7	105	22	120/70	12.0	13.22	209	134	56	1.2	135	4.0	positive	positive	56	34	yes
84	34	male	muslim	rural	Lower middle	DENGUE FEVER	99.9	98	26	110/60	13.6	19.25	10	93	43	1.0	134	3.7	positive	positive	127	139	yes
85	49	female	hindu	rural	Lower middle	CELLULITIS	100.4	119	19	70/40	11.7	23.67	110	132	40	0.9	123	4.8	positive	positive	110	115	yes
86	62	male	hindu	rural	lower	SPONTANEOUS BACTERIAL PERITONITIS	102	108	23	80/50	10.4	16.79	190	79	118	2.4	136	4.5	positive	positive	40	57	no
87	76	female	hindu	urban	Lower middle	PULMONARY TUBERCULOSIS	101.7	112	32	110/80	7.6	12.98	105	118	37	1.0	132	2.6	positive	positive	234	203	yes
88	53	male	hindu	rural	middle	UROSEPSIS	99.8	97	20	90/50	8.3	16.34	246	90	89	3.0	119	4.2	positive	positive	204	319	no
89	42	male	muslim	rural	Lower middle	CATHETER RELATED SEPSIS	102.9	106	18	140/70	6.9	22.09	298	112	78	4.9	125	5.9	positive	positive	145	176	yes
90	67	male	hindu	rural	middle	CELLULITIS	104.6	145	19	100/70	11.9	11.90	160	161	80	2.0	132	3.2	positive	positive	129	98	yes
91	56	female	hindu	rural	lower	BRONCHOPNEUMONIA	102.7	134	22	110/60	12.4	15.32	132	156	48	1.1	148	2.9	positive	positive	110	87	yes
92	48	male	hindu	urban	Lower middle	MENINGITIS	101	119	17	100/70	9.2	16.76	105	189	45	0.8	130	4.2	positive	positive	107	113	yes
93	58	female	hindu	rural	lower	LUNG ABSCESS	103.6	122	29	90/60	8.7	31.00	220	148	65	1.3	127	3.0	positive	positive	187	298	no