"PROGNOSTIC IMPORTANCE OF RED CELL DISTRIBUTION WIDTH, MEAN PLATELET VOLUME AND NEUTROPHIL LYMPHOCYTE COUNT RATIO IN PATIENTS WITH SEPSIS"

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ABSTRACT

BACKGROUND

Sepsis and septic shock are one of the leading causes of death worldwide. Rapid and precise diagnosis and appropriate antibiotic therapy is necessary to reduce mortality and morbidity in patients with sepsis. Though several biomarkers and scoring systems have been evaluated, prognostic markers to quickly and precisely establish the diagnosis or prognosis of patients with sepsis and septic shock are yet to be evaluated. Hence this study is being done to assess the efficiency of the haemogram parameters RDW, NLCR and MPV as biomarkers in predicting the clinical outcome of patients with sepsis, severe sepsis and septic shock and to study their correlation with SOFA score.

METHODOLOGY

In this prospective observational study, 120 adult patients of both sex with a diagnosis of sepsis and admitted to R.L. Jalappa hospital and research centre, Tamaka, Kolar from January 2018 to July 2019 were included. The haemogram parameters RDW, NLCR and MPV along with SOFA score were compared between the survivors and non survivors groups and its significance in predicting mortality and morbidity like need for ventilatory support, inotropic support, renal replacement therapy and length of ICU stay.

RESULTS

There were 68 males and 52 females in this study. Mortality rate in the study was 34.16%.

The occurrence of LRTI, ARDS showed higher risk of death outcome.

Mean RDW was 14.36±0.61 in the case of survivors and 16.20±0.80 in the case of non-survivors which was statistically significant ($p<0.0001$) with respect to mortality. The mean NLCR was 8.79±0.64 in survivors and 12.09±1.04 in non survivors, the results are statistically significant ($p<0.0001$). Mean MPV was 8.65±0.64 in survivors and 10.40±0.73 in non survivors, the results are statistically significant ($p<0.0001$). The mean SOFA score also had statistically significant correlation (P value <0.001) with respect to non survival. In sepsis patients when SOFA score was cross matched with RDW, NLCR and MPV separately the increase in their values strongly and positively correlated with increase in SOFA score, thus elucidating the usefulness of RDW, NLCR and MPV as prognostic markers in the study of severity of sepsis and the outcome.

CONCLUSION

Red cell distribution width (RDW), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLCR) are quick, cost effective blood tests that can be done even in the resource stricken centers in India. Thus they may be helpful for the treating physician in careful monitoring and aggressive management of severe cases, thus reducing mortality and saving crucial lives.

KEYWORDS:

Sepsis, septic shock, prognostic markers, RDW, MPV, NLCR, SOFA Score.

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LIST OF ABBREVIATIONS

USA	UNITED STATES OF AMERICA
SOFA	SEQUENTIAL ORGAN FAILURE ASSESSMENT
qSOFA	QUICK SOFA
APACHE 2	ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION
RDW	RED BLOOD CELL DISTRIBUTION WIDTH
MPV	MEAN PLATELET VOLUME
NLCR/NLR	NEUTROPHIL TO LYMPHOCYTE COUNT RATIO
RBC	RED BLOOD CELL
ICU	INTENSIVE CARE UNIT
SIRS	SYSTEMIC INFLAMMATORY RESPONSE SYNDROME
BP	BLOOD PRESSURE
SSC	SURVIVING SEPSIS CAMPAIGN
MAP	MEAN ARTERIAL PRESSURE
EPIC-2	EUROPEAN PREVALENCE OF INFECTION IN INTENSIVE CARE
AIDS	ACQUIRED IMMUNODEFICIENCY SYNDROME
MODS	MULTI ORGAN DYSFUNCTION SYNDROME
PAMP	PATHOGEN ASSOCIATED MOLECULAR PATTERNS

TLR	TOLL -LIKE RECEPTORS
NOD	NUCLEOTIDE OLIGOMERIZATION DOMAIN
RIG-i	RETINOIC ACID INDUCIBLE GENE I
TREM 1	TRIGGERING RECEPTORS EXPRESSED ON MYELOID CELL
MDL 1	MYELOID DAP -12 ASSOCIATING LECTIN
NF-kb	NUCLEAR FACTOR -KB
ICAM 1	INTERCELLULAR ADHESION MOLECULE-1
VCAM 1	VASCULAR CELL ADHESION MOLECULE-1
TNF- **α**	TUMOUR NECROSIS FACTOR A
SNP	SINGLE NUCLEOTIDE POLYMORPHISM
GIT	GASTROINTESTINAL TRACT
CNS	CENTRAL NERVOUS SYSTEM
DIC	DISSEMINATED INTRAVASCULAR COAGULATION
ECG	ELECTROCARDIOGRAM
ARDS	ACUTE RESPIRATORY DISTRESS SYNDROME
CRP	C - REACTIVE PROTEIN
SAPS 3	SIMPLIFIED ACUTE PHYSIOLOGY SCORE
RIFLE	RISK INJURY FAILURE LOSS ESRD
ESCCM	EUROPEAN SOCIETY OF CRITICAL CARE MEDICINE

CVC	CENTRAL VENOUS CATHETER
CVP	CENTRAL VENOUS PRESSURE
ROC	RECEIVER OPERATING CHARACTERISTIC
LRTI	LOWER RESPIRATORY TRACT INFECTION
GCS	GLASGOW COMA SCALE
SBP	SYSTOLIC BLOOD PRESSURE
DBP	DIASTOLIC BLOOD PRESSURE
PCT	PROCALCITONIN
CRP	C REACTIVE PROTEIN
PDW	PLATELET DISTRIBUTION WIDTH
CVS	CARDIO VASCULAR SYSTEM
RS	RESPIRATORY SYSTEM
DM	DIABETES MELLITUS
HTN	HYPERTENSION
CKD	CHRONIC KIDNEY DISEASE
COPD	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
CCF	CONGESTIVE CARDIAC FAILURE
IHD	ISCHEMIC HEART DISEASE

INTRODUCTION

PROGNOSTIC IMPORTANCE OF RED CELL DISTRIBUTION WIDTH, MEAN PLATELET VOLUME AND NEUTROPHIL LYMPHOCYTE COUNT RATIO IN PATIENTS WITH SEPSIS

INTRODUCTION

Sepsis is a clinical syndrome characterized by systemic inflammation due to infection, the severity ranging from sepsis to septic shock. Data from the centre for Disease Control and Prevention reveals that sepsis is the leading cause of death in non-coronary intensive care unit patients and the tenth most common cause of death worldwide, the first being heart disease.[1] Despite advances in intensive care and antimicrobial therapy, the incidence of sepsis and related mortality rate has increased over the last thirty years.[2] The mortality rate is estimated at 30% in sepsis and 80% in septic shock in the USA [3] and at 12.8% in sepsis and 45.7% in septic shock in Europe.[4] Reduced rates of reporting may affect estimations in developing countries.

Sepsis or severe sepsis is defined as the harmful systemic response (including some degree of hypofunction) with the proven or suspected microbial etiology. Septic shock is sepsis with hypotension (arterial blood pressure < 90 mmHg below patient's normal blood pressure for at least one hour despite fluid resuscitation) or need for vasopressors to maintain the systolic blood pressure ≥ 90 mmHg or mean arterial blood pressure ≥70 mmHg. The incidence of sepsis and septic shock continues to increase worldwide. The mortality increase has been attributable to patients' advanced age, preexisting comorbidity, immunosuppressive diseases and therapies or infections with multi-drug resistant bacteria, patients with chronic diseases for a long period, and those on medical treatment that circumvent host defenses viz. in-dwelling catheters

and 2 mechanical devices.[5] Invasive bacterial infections are a prominent cause of death around the world-especially among children.

Without consistent and reproducible criteria the extensive pathophysiology associated with sepsis is difficult to diagnose and treat. A delay in the diagnosis and treatment of sepsis will result in the rapid progression of circulatory failure, multiple organ dysfunction and eventually death.[6]

Treatment guidelines are ambiguous. It involves a prolonged hospital stay for patients, while receiving complex therapy. The in-hospital mortality risk of 10% in patients diagnosed with sepsis is widespread and those who develop septic shock increase their mortality risk greater than 40%.[7]

Early diagnosis of severity of sepsis and appropriate treatment is essential for the survival of the patients. There are many biochemical markers, clinical parameters and scoring systems used to assess the severity and in predicting the mortality in patients with sepsis- some of which include- estimating serum procalcitonin levels, clinical scoring systems like Sequential Organ Failure Assessment (SOFA), quick SOFA (qSOFA), Acute Physiology and Chronic Health Evaluation (APACHE II) scoring systems. The degree of severity is most often quantified by the Sequential Organ Failure Assessment (SOFA) score, which can predict the severity and outcome of multiple organ failure. However, calculating SOFA score is cumbersome. Moreover, assessment of the septic patient outcome during treatment needs to be focused on, as currently used clinical and biological criteria are undefined and inadequate for this purpose.

The need for simple, cost effective and easily available, yet reliable markers has pushed researchers in identifying such markers for assessing the severity and predicting the prognosis of sepsis. Several inflammatory biomarkers have been

evaluated in recent years with the high sensitivity, specificity, positive and negative predictive values for the early diagnosis of sepsis as available in literature.

There is an unmet need for predictive tools especially in the resource stricken centers in India to better identify patients with suspected infection likely to progress to a life-threatening state. Such early recognition is particularly important because prompt management of septic patients may improve outcomes.

Red cell distribution width (RDW), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLCR) are quick, cost effective blood tests that can be done even in the resource stricken centers in India. Various biomarkers are being evaluated for early diagnosis of sepsis. RDW, MPV, NLCR are some markers, which have been shown to predict mortality and morbidity of sepsis but has not been fully explored.

The Red Cell Distribution width (RDW) is one of the various biomarkers which have been shown to predict the mortality and morbidity of sepsis.

The Red Cell Distribution Width (RDW) is the coefficient of variation of Red Blood Cell (RBC) volume and is a representation of the RBC size heterogeneity of an individual patient.[8] Recent studies have reported that Red Cell Distribution Width (RDW) is associated with prognosis in Critical Illness, Heart Failure, Acute Myocardial Infarction, Pulmonary Embolism, Pneumonia and Cardiac Arrest.[9-14]

Mean platelet volume (MPV) is an indicator of platelet size and activity, and is easily and cost-effectively measured with the use of automated hematology analyzers. An increased platelet volume and size reflect a thrombotic and inflammatory milieu; thus, MPV has been proposed as a possible marker of platelet function and activation. Several studies have reported that MPV changes are associated with morbidity and mortality in patients with diseases such as sepsis, diabetes mellitus, myocardial infarction, and chronic inflammatory disorders. One study that had been conducted in

intensive care units (ICUs) reported that an elevated MPV was related to a poor prognosis [15].

Research has shown that Neutrophil-lymphocyte count ratio (NLCR) may be considered a novel marker of subclinical inflammation.[16] It represents a combination of two markers; neutrophils, which represent the active nonspecific mediator initiating the first line of defense and lymphocytes, representing the regulatory or protective component of inflammation. Neutrophil-lymphocyte ratio is calculated by dividing the number of neutrophil count by number of lymphocyte count, usually from peripheral blood sample.

In view of the paramount importance of timely diagnosis and the unmet need for predictive tools, we venture to study the behavior of red cell distribution width, mean platelet volume and neutrophil lymphocyte count ratio and their prognostic importance in patients with sepsis.

AIMS & OBJECTIVES

OBJECTIVES OF THE STUDY

- To measure Red cell distribution width (RDW), Mean Platelet volume (MPV), Neutrophil lymphocyte count ratio (NLCR) in patients with sepsis.
- To compare the prognostic value of RDW, MPV, NLCR with Sequential Organ Failure Assessment (SOFA) score among survivors and non-survivors in patients with sepsis.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health concern. Multiple definitions and terminologies are currently in use for sepsis, severe sepsis, septic shock, and organ dysfunction. With Considerable advances made into the pathobiology, the definition for sepsis and septic shock is being revised periodically. A 1991 consensus conference developed initial definitions for sepsis wherein sepsis refers to the presence of an infectious systemic inflammatory response syndrome (SIRS). [17]

Table 1: Consensus Definitions of Sepsis and Related Syndromes

Systemic Inflammatory Response Syndrome (SIRS)	**Two or more of the following:** • Body temperature >38.5°C or <35.0°C • Heart rate >90 beats/minute • Respiratory rate >20 breaths/minute or arterial CO2 tension <32 mmHg or need for mechanical ventilation • White blood cell count >12,000/mm3 or <4000/mm3 or immature forms >10%
Sepsis	SIRS and documented infection (culture or Gram stain of blood, sputum, urine or normally sterile body fluid positive for pathogenic micro-organism; or focus of infection identified by visual inspection - e.g., ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	**Sepsis and at least one sign of organ hypoperfusion or organ dysfunction:** • Areas of mottled skin • Capillary refilling time ≥3 s • Urinary output <0.5 mL/kg for at least 1 hr or renal

	replacement therapy • Lactates >2 mmol/L • Abrupt change in mental status or abnormal electroencephalogram • Platelet count <100,000/mL or disseminated intravascular coagulation • Acute lung injury- acute respiratory distress syndrome • Cardiac dysfunction (echocardiography)
Septic shock	**Severe sepsis and one of:** • Systemic mean Blood Pressure (BP) of <60 mmHg (<80 mmHg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mmHg • Need for dopamine >5 μg/kg/min or norepinephrine or epinephrine <0.25 μg/kg/min to maintain mean BP >60 mmHg (>80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine >15 μg/kg/min or norepinephrine or epinephrine >0.25 μg/kg/min to maintain mean BP >60 mmHg (>80 mmHg if previous hypertension)

The international consensus defines Septic shock as to satisfying the following criteria:

- Arterial hypotension (systolic BP <90 mmHg, mean BP <65mmHg, or reduction in systolic BP > 40 mm Hg from baseline) persisting for at least one hour despite adequate fluid resuscitation (or)
- Serum lactate >4 mmol/L(>36mg/dL) after adequate fluid resuscitation.

(The use of vasopressor agents to correct hypotension does not exclude shock).

As per the Surviving Sepsis Campaign (SSC) guidelines updated in 2012, severe sepsis is defined as sepsis plus sepsis induced organ dysfunction or tissue hypoperfusion.

Septic shock is defined as sepsis induced hypotension persisting despite adequate fluid resuscitation.

The definition was reanalyzed and modified in 2016 and it recommended that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.[7,18] Patients with septic shock can be clinically identified with a presentation of

- Persistent hypotension requiring vasopressors to maintain Mean Arterial pressure (MAP)≥65mmHg and
- Serum lactate >2 mmol/L(>18mg/dL) in the absence of hypovolemia

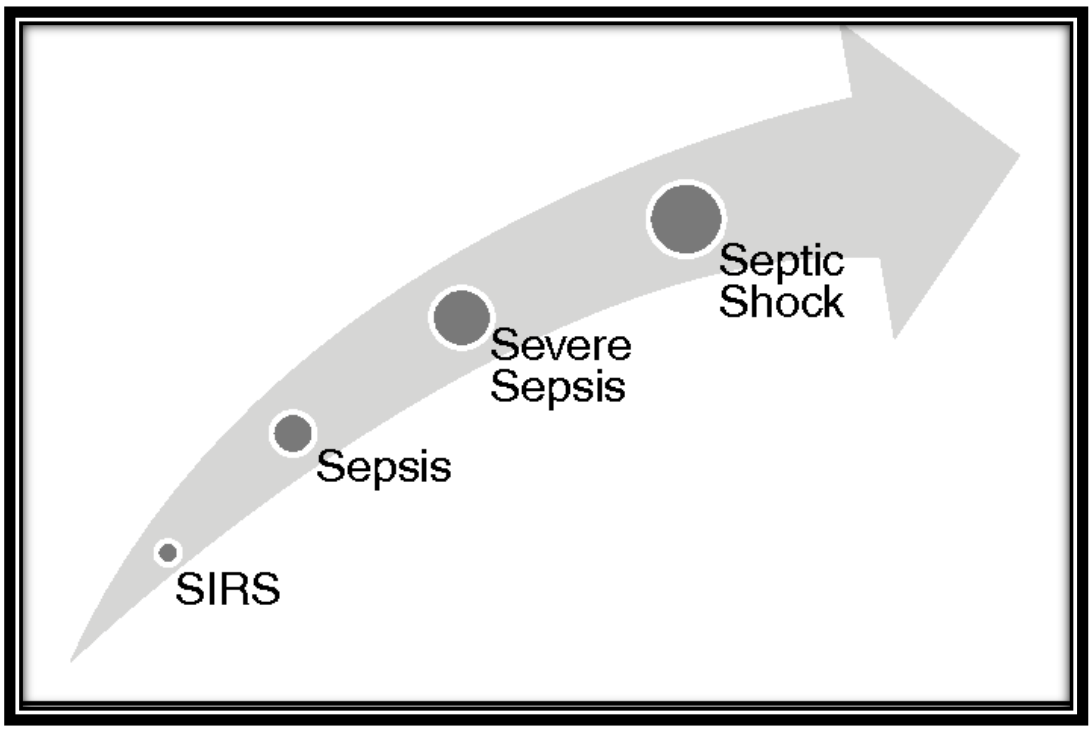


Fig 1. Sepsis - Disease continuum

EPIDEMIOLOGY

Recent estimates indicate that the incidence of sepsis has increased in the past 3 decades.[20] About 1.5 million people in the United States are diagnosed with sepsis every year. The incidence of severe sepsis and septic shock in the United States has increased to 750000 every year (about 3/1000 population).[21] It is reported that, one out of every 4 people admitted with severe sepsis die during hospital stay. There is a similar trend of increase in the incidence of sepsis worldwide. The reason for this increased incidence may be attributed to increase in the lifespan of general population, leading to increase number of ageing population, and the association of chronic diseases like diabetes, cardiac diseases, chronic obstructive pulmonary disease and malignancy. The frequent use of in-dwelling catheter and immunosuppressant's has also contributed to the rise in the number of patients with

sepsis and severe sepsis globally every year. Sepsis has been more commonly associated with African and Afro- American males and also HIV infected individuals. In spite of improvement in health care and treatment modalities, the mortality of patients with severe sepsis and septic shock continues to be high.

ETIOLOGY:

In 2007, a prevalence study was conducted in over 14000 patients in Intensive Care units across more than 70 countries to identify the etiological pattern of sepsis. In the study, 51 % of the patients were considered to be infected, of which respiratory tract infection was found to be most common. In another study conducted by Mayr et.al., respiratory tract infection was found to be the most common cause in adults, followed by bloodstream infection of unspecified etiology, followed in order by genitourinary, abdominal, soft tissue and catheter related infections.[22] Microbial invasion of bloodstream is not essential in all cases of sepsis, as local inflammation can lead to distant organ dysfunction. Studies have shown that only 20 to 40 percentage of cases of severe sepsis and 40 to 70 percentage cases of septic shock yield positive blood culture for bacteria or fungus. More frequent use of broad-spectrum antibiotics in critically ill patients who remain in the ICU for longer periods of time has resulted in a high degree of bacterial resistance over time.[23,24] Antibiotic resistance is challenging, resulting in longer duration of hospital stay and ventilator dependence, although the effect on mortality is uncertain.[25-26] Among causative agents, Gram Negative organisms were found to be the most common cause of sepsis (62%), but, of late, incidence of Gram positive organisms as a cause of sepsis is on the rise and are now becoming almost as common as Gram negative organisms (46%). [20, 27-30] This trend may be due to the greater use of invasive procedures and increasing magnitude

of hospital acquired infections [26]. Recent European prevalence of infection in Intensive Care (EPIC-2) study reported that the incidence of Gram negative organisms to be around 62 % compared to Gram positive organisms at 42%.The study also showed that among individual organisms, Staphylococcus aureus was found to be the most common pathogen (20.5%) followed by Pseudomonas (19.9 %) and Enterobacteriae, particularly E.Coli. A large meta-analysis of more than 500 studies demonstrated that Gram negative bacteremia leads to more mortality than Gram positive bacteraemia[31]. Coagulase negative staphylococci and E coli were the commonest cause of bloodstream infections. Pseudomonas aeruginosa had the highest mortality rate among all (77%). Gram positive pneumonia caused by Staphylococcus aureus 12 was the next common cause (41%). Candida and Acinetobacter species also accounted to high mortality rates (40%).

Recent studies have shown that there has been an increased incidence of sepsis among paediatric population over the past decade. This has been largely due to the disproportionate increase in the incidence of sepsis among neonates, particularly among the low birth weight category[32]. Again, respiratory tract infections were found to be the most common cause of sepsis even among paediatric population (49%) followed by primary bacteremia (18.1%).

RISK FACTORS

Risk factors for severe sepsis can broadly be divided into risk factors for infection, contingent upon developing infection, and risk factors for organ dysfunction.

Bacteremia

Patients with bacteremia often developed systemic consequences of infection. In a study conducted in 2015 in South Korea in patients with sepsis, whose blood cultures

were positive for either bacteria or fungi, about 95% of positive blood cultures were associated with sepsis severe sepsis or septic shock

Sex and race

Sepsis has been found to be more common among male gender and black people (African and Afro- American)

Environmental factors

There exists an inverse relationship between socioeconomic status and the risk for development of sepsis.[33]

Age

Elderly patients, particularly above 65 years, are at increased risk of developing sepsis.

The incidence of sepsis increases with age, and older adults above 65 years of age have an increased risk of mortality from sepsis compared to their younger counterparts. Age is also an independent prognostic marker in sepsis. Elderly individuals need greater nursing care and close monitoring. Studies have shown that in-hospital mortality rates are higher among elderly individuals affected with sepsis.

Immunosuppression

Immunosuppression is an important risk factor for the development of sepsis. Conditions that affect the host defense mechanisms and those drugs that lead to immunosuppression make the patient more vulnerable for developing frequent infections and their poor immunity make them candidates for the development of sepsis. Some of these conditions include renal failure, diabetes, neoplasms, hepatic failure, AIDS, patients on corticosteroid therapy or immunosuppressant medications. The risk of progression to severe sepsis, septic shock and Multi Organ Dysfunction

Syndrome (MODS) is more common among immunosuppressed individuals which may lead to high mortality.

Malignancy and diabetes

Diabetes and malignancies alter the immune system resulting in an increase in the risk for developing sepsis. Studies have shown that there is high incidence of nosocomial infections among patients with diabetes, particularly among patients with poor glycemic control.

Community acquired pneumonia

Patients who developed community-acquired pneumonia were found to have an increased risk of developing sepsis and an increased risk of progression to severe sepsis and septic shock.

Genetic factors

There is confirmatory evidence from experimental and clinical studies that genetic factors can increase the risk of infection in few cases. Monogenic defects underlie vulnerability to specific infection, but genetic factors are typically genetic polymorphisms. Genetic studies of susceptibility to infection have initially focused on defects of antibody production or a lack of T- cells, phagocytes, natural killer cells or complement, but recently genetic defects that impair the recognition of pathogens by the innate immune system have been recognized. Study by Sorensen et al., suggests that genetic factors may play a crucial role in outcomes of infectious diseases compared with cardiovascular disease. In this study, children whose biological parents died due to infectious causes had an 8 fold increased risk of death due to infections[34]. In comparison, the increased risk of death due to cardiovascular causes was four fold if their biological parents died of cardiovascular causes.

PATHOPHYSIOLOGY

The normal host responds to any infection in a peculiar fashion aiming towards localizing and restricting the bacterial invasion. The host responds by triggering the activation of circulating macrophages resulting in the production of pro-inflammatory and anti-inflammatory cytokines. When microbial organisms enter the host, it responds by triggering the innate immune cells, particularly macrophages, to identify and bind to the microbial components. This process may occur as follows.

- When the microorganisms enter the host, the host immune cells have certain pattern recognition receptors on their cell surface that identify and attach to the Pathogen

Associated Molecular Patterns (PAMP) [1] of the microorganism. There are three major groups of Pattern Recognition Receptors:

1) Toll -like receptors (TLR)

2) Nucleotide oligomerization domain (NOD) leucine Rich repeat proteins and

3) Retinoic acid inducible gene I (RIG-i) like helicases.

The host immune cells also contain triggering receptors expressed on myeloid cell (TREM-1) and Myeloid DAP -12 associating Lectin (MDL-1) on their surface which identify and bind to the microorganisms[2].The binding of Toll like receptors triggers a signaling cascade by activating the cytosolic nuclear factor -kb (NF-kb). The activated NF-kb migrate from the cytoplasm to the nucleus, attaches itself to the transcription sites, and trigger the activation of a large set of genes resulting in the release of pro-inflammatory cytokines like Tumor necrosis factor-Alpha,Interleukin-1, chemokines like Intercellular Adhesion Molecule-1(ICAM -1) and Vascular Cell Adhesion Molecule-1(VCAM-1) and nitric oxide. The polymorphonuclear leukocytes also get activated and express adhesion molecules on their surface that leads to their

aggregation and margination to the vascular endothelium. The polymorphonuclear leukocytes then undergo a series of steps such as rolling, adhesion, diapedesis, and chemotaxis to move to the site of injury.[35] The poly morphonuclear leukocytes now release inflammatory mediators at the site of injury which leads to the cardinal signs of 16 local inflammation. This process is regulated by the release of pro-inflammatory and anti - inflammatory mediators by the macrophages at the site of injury that is triggered by the invasion of tissue by the microorganisms.[36-38]

The balance in the pro-inflammatory and anti- inflammatory mediators control and regulate the inflammatory process, which leads to homeostasis, overcoming of the infectious insult and ultimately results in tissue repair and healing[39]. When this inflammatory response to infection exceeds the boundary of local environment and becomes a more generalized response, it leads to widespread tissue damage and is called sepsis. In the absence of any infectious etiology, this process is called Systemic Inflammatory Response Syndrome (SIRS). The reason why the localised immune response sometimes crosses the local environment leading to sepsis is still not clear.

- It may be due to the direct effect of microorganisms or their toxic products. Bacterial cell wall components like endotoxin, peptidoglycan, muramyl dipeptide and lipotechoic acid and bacterial products like Staphylococcal enterotoxin-B, toxic shock syndrome toxin-1, pseudomonas exotoxin A, and M-protein of hemolytic group A streptococci may contribute to the progression of a local infection to sepsis.[40-42]
- Large quantities of pro-inflammatory cytokines released during sepsis may spill into the bloodstream leading to the progression of local infection to sepsis. These include tumor necrosis factor-alpha and interleukin-1 whose

plasma levels peak early and eventually decrease to undetectable levels. There is strong evidence that TNF - α has an important role to play in sepsis.[43, 44]

- The complement system is a protein cascade which helps in clearing pathogens.[45, 46] There is proven evidence in animal studies that activation of complement system plays a vital role in sepsis. [47, 48]

Genetic susceptibility

Single nucleotide polymorphism (SNP) is the commonest type of genetic variation. Various SNPs are associated with high degree of susceptibility to infection. Some of these include SNPs of genes that encode cytokines like TNF-α, IL-10, IL-18,IL-1 receptor antagonist, IL-6 and Interferon gamma; cell surface receptors like CD14, MD2, toll-like receptors 2 and 4; lipopolysaccharide ligands like lipopolysaccharide binding protein, bactericidal permeability increasing protein, mannose-binding lectin, heat shock protein 70,angiotensin I-converting enzyme, and caspase-12. [49]

SYSTEMIC EFFECTS OF SEPSIS

When the immune response to bacterial invasion becomes generalized, it leads to widespread cellular injury. Organ dysfunction eventually follows this cellular injury. The precise mechanism of cellular injury is not understood, but various mechanisms have been proposed explaining the process of cellular injury. These include tissue ischemia, cytopathic injury and an altered rate of apoptosis.

A) TISSUE ISCHEMIA

During sepsis there occurs a significant derangement in metabolic auto- regulation which is the process that matches oxygen availability to changing tissue oxygen demand. Moreover, during sepsis, microcirculatory and endothelial lesion frequently develops. These lesions decrease the cross sectional area available for tissue oxygen exchange reading to tissue ischemia and cellular injury[50].

B) CYTOPATHIC INJURY

The pro- inflammatory mediators released during sepsis may lead to mitochondrial dysfunction through a variety of mechanisms, like direct inhibition of respiratory enzyme complexes, oxidative stress damage and mitochondrial DNA breakdown.[51] Such mitochondrial injury leads to cytotoxicity.

C) APOPTOSIS

Apoptosis is the primary mechanism by which senescent or dysfunctional cells normally get eliminated. It is the principal process by which inflammation gets terminated once an infection has subsided. The pro-inflammatory cytokines that are released during sepsis delay the process of apoptosis in the activated macrophages and neutrophils, disrupting the normal inflammatory response mechanism and leading to the development of multiple organ failure. In addition to this, there is also an extensive apoptosis of lymphocytes and dendritic cells which alters the immune response that occurs during sepsis. The extent of lymphocytic apoptosis correlates with the severity of sepsis and the level of immunosuppression. Apoptosis has also been found to occur in epithelial cells, endothelial cells and parenchymal cells. Several animal studies have shown that inhibiting the process of apoptosis has been protective from organ dysfunction.[52,53]

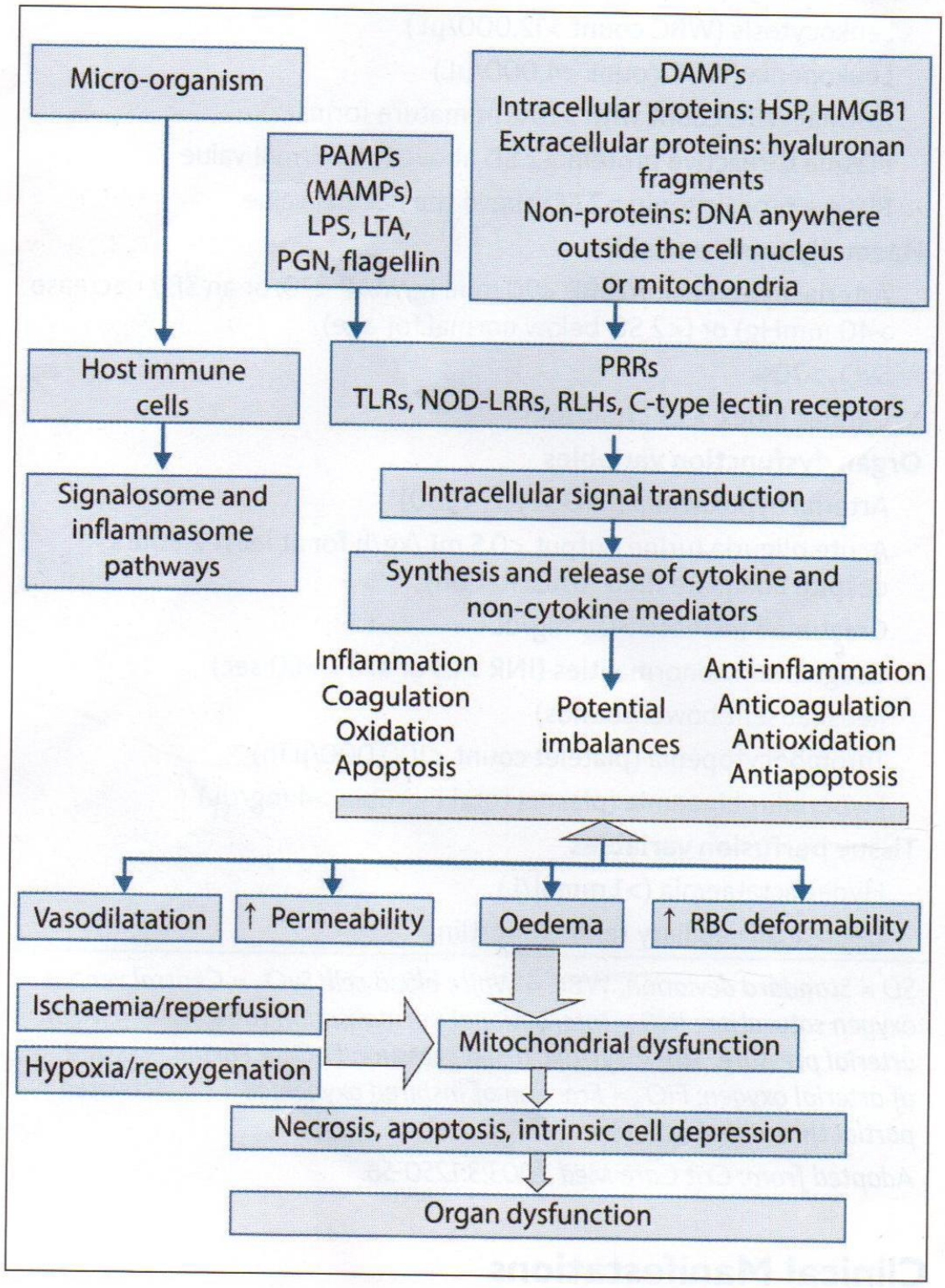


Fig 2a. Pathophysiology of sepsis - Flow chart

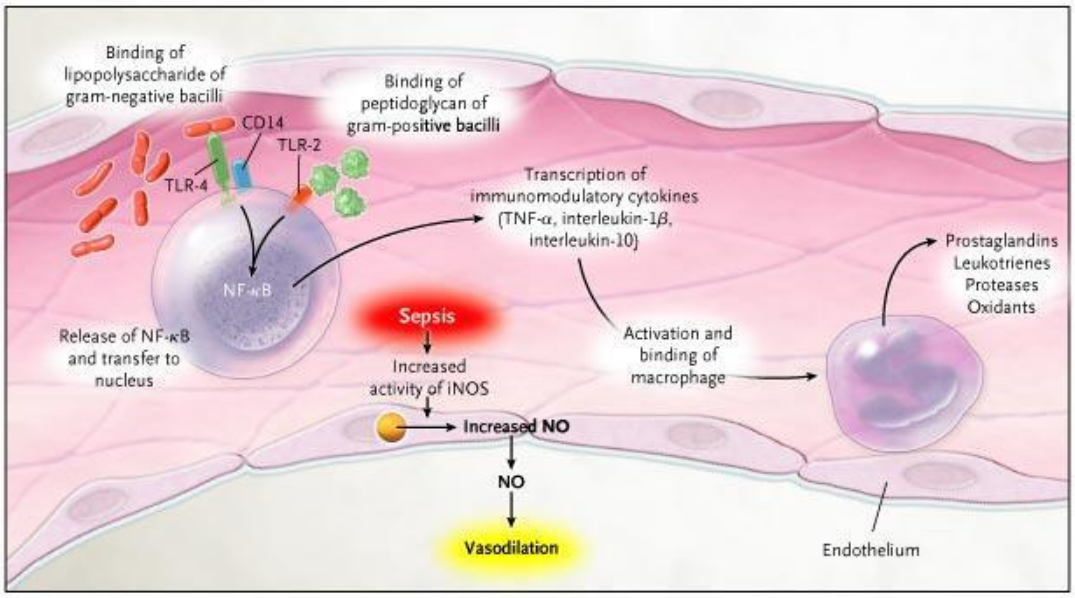


Fig 2b. Pathophysiology of sepsis and septic shock

ORGAN SPECIFIC EFFECTS OF SEPSIS

The cellular injury accompanied by the release of pro-inflammatory and anti - inflammatory mediators leads to the development of organ failure. Multi organ dysfunction is not uncommon.

Circulation:

Circulatory dysfunction leads to diffuse vasodilatation resulting in hypotension.

Inflammatory mediators like nitric oxide and prostacyclin are released by the endothelial cells in sepsis to induce appropriate vasodilatation for the purpose of improving metabolic auto - regulation. But diffuse vasodilation occurs as unintended consequences of these inflammatory mediators, which results in hypotension. Nitric oxide, particularly is believed to play an important role in the process of vasodilatation during septic shock.[54,55] When nitric oxide reaches the systemic circulation, it depresses the auto regulation at all the- central, regional and micro regional levels of circulation. Vasodilatation is not the only cause of hypotension in sepsis. It may also be due to the redistribution of intravascular fluid which occurs as a

consequence of increased endothelial permeability and reduced arterial vascular tone. In addition to these diffuse effects on circulation, there are also localized effects.

 During sepsis myocardial depressant substances that are released into the circulation impair the systolic and diastolic ventricular performance of the heart. The myocardium may still be able to use the Frank- Starling law and maintain the cardiac output in normal individuals. But patients with pre-existing cardiac disease are often unable to increase their cardiac output appropriately, further contributing to hypotension.

Sepsis is associated with a reduction in the number of functional capillaries as a result of which there is subnormal oxygen extraction through the micro circulation.

 Sepsis induces phenotypic changes to endothelial cells. This occurs through direct and indirect interactions between the endothelial cells and components of the bacterial wall. These phenotypic changes lead to endothelial dysfunction, which is associated with coagulation abnormalities, reduced leukocytes, decreased red blood cell deformability, upregulation of adhesion molecules, adherence of platelets and leukocytes and degradation of the glycocalyx structure.[56] Diffuse endothelial activation results in widespread tissue edema.

 Micro particles from circulating and vascular cells also participate in the deleterious effects of sepsis-induced intravascular inflammation [57].

Lung

Endothelial injury that occurs in the pulmonary vasculature during sepsis impairs capillary blood flow and leads to increased micro vascular permeability. This leads to interstitial and alveolar edema. The neutrophil entrapment in the pulmonary vasculature further amplifies the injury, the end result being pulmonary edema and

hypoxemia. This type of pulmonary edema that occurs in sepsis is called as acute respiratory distress syndrome.

Gastrointestinal tract

The circulatory abnormalities that occur in sepsis disrupt the GIT‘s normal barrier function, leading to translocation of bacteria and endotoxin from the gut into the systemic circulation, thus further amplifying the septic process.

Liver

Liver dysfunction can contribute to the initiation and progression of sepsis. Normally, the reticulo endothelial system of the liver is the first line of defence in clearing bacteria and bacteria-derived products that enter the portal system from the gut. Liver dysfunction can prevent the elimination of enteric-derived endotoxin and bacteria-derived products, which results in direct spillover of these harmful products into the systemic circulation. [58, 59]

Kidney

Sepsis is often associated with acute kidney injury. The renal hypoperfusion that occurs in sepsis leads to organ dysfunction. Systemic hypotension, direct renal vasoconstriction, release of cytokines such as Tumor Necrosis Factor, may also contribute to renal injury.

Nervous system

Central nervous system complications occur very commonly in septic patients. Encephalopathy and peripheral neuropathy are the commonest complications.

 Encephalopathy: The pathogenesis of the encephalopathy is poorly defined. A high incidence of brain microabscesses was noted in one study, but the significance of hematogenous infection as the principal mechanism remains uncertain.

 Peripheral neuropathy: Studies suggest that at least 25 percent of patients admitted to medical or surgical intensive care units have some degree of acquired paresis.[60,61]. Affected patients manifest a sensorimotor polyneuropathy characterized by limb muscle weakness and atrophy, reduced or absent deep tendon reflexes, sensory loss to light touch and pin prick, and relative preservation of cranial nerve function61.The mechanism of axonal injury in this condition is unknown. CNS dysfunction may be attributed to changes in metabolism and alterations in cell signaling due to the release of inflammatory mediators.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

The clinical manifestation of patients with sepsis includes signs and symptoms that are common to any septic response and those manifestations that occur as a complication of the septic response. Moreover, some of the clinical manifestations can give a clue to the primary etiology contributing to the sepsis. Most patients are hyperthermic, whereas some patients may be normothermic or hypothermic. Hypothermia is commonly seen in elderly, neonates and alcoholics. Hyperventilation producing respiratory alkalosis is a very common early manifestation in sepsis. Disorientation, confusion and other manifestations of encephalopathy can develop early. Blood glucose levels increase in septic patients, particularly in diabetics. Protein catabolism is accelerated. Serum albumin levels decrease due to impaired hepatic synthesis and due to the movement of albumin into the interstitial spaces.

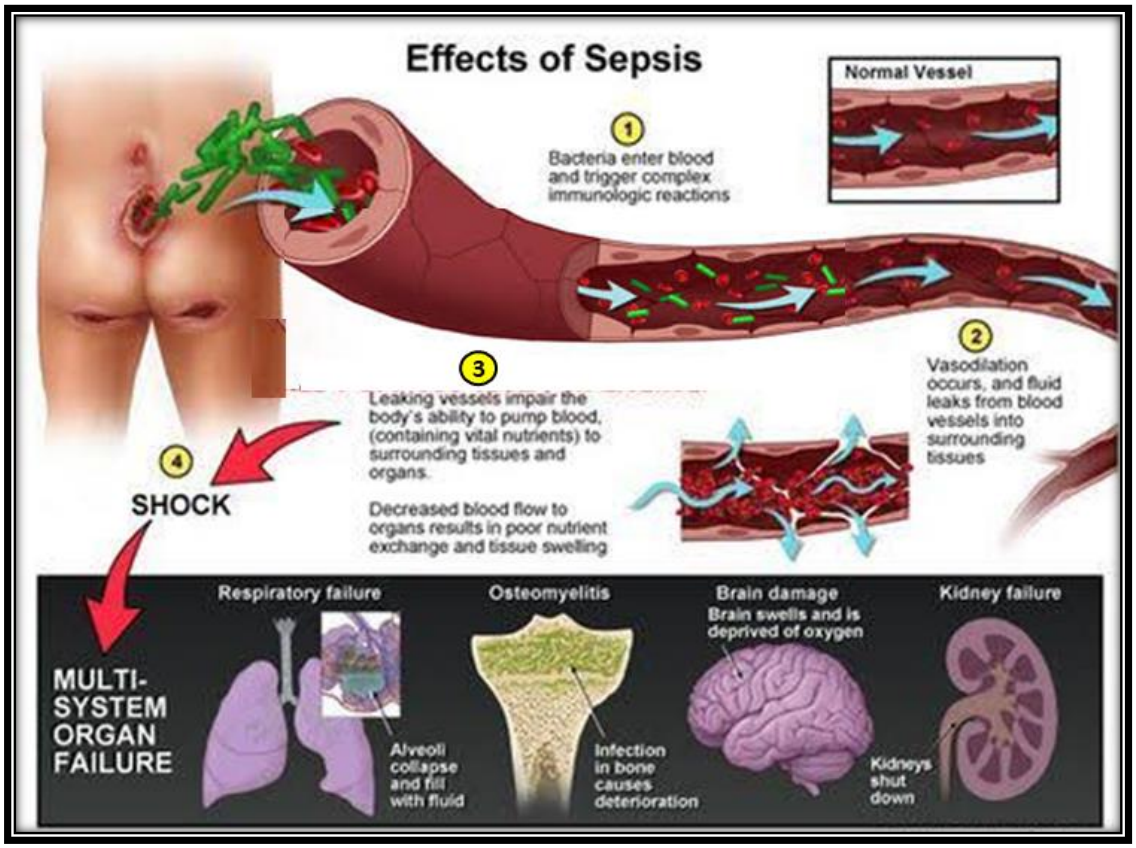


Fig 3. Effects of sepsis

COMPLICATIONS

Cardio pulmonary complications

Alveolar epithelial injury and increased alveolar capillary permeability leads to increased pulmonary water content. This interferes with gas exchange and produces arterial hypoxemia. Ultimately acute lung injury and acute respiratory distress syndrome will result. Hypotension occurs as a result of hypovolemia and generalized redistribution of blood flow in sepsis. Dehydration may further contribute to hypotension. Also, as a part of the septic response, the myocardial function becomes depressed within the first 24 hours in most patients with sepsis. In patients with no preexisting cardiac failure, the cardiac output is usually maintained in spite of the myocardial depression. The myocardial function restores to normal over several days.

So the primary cause of hypotension is usually a decreased systemic vascular resistance.

Renal complications

Oliguria, azotemia, proteinuria are the commonest renal complications. Most renal failure occurs due to acute tubular necrosis as a result of hypovolemia and hypotension.

Coagulopathy

Thrombocytopenia is common in patients with sepsis. In patients with DIC, the platelet counts are very low, usually less than 50000. The exact mechanism for thrombocytopenia is unclear.

Neurological complications

Confusion, altered sensorium (acute encephalopathy) occurs as early manifestation of sepsis. Studies show that encephalopathy occurs in around 20 to 60 percentage of septic patients at some point during the course of illness.

Immunosuppression

Patients with severe sepsis often become immune suppressed. This leads to increased risk for secondary infection and difficulty in controlling the primary infection.

LABORATORY INVESTIGATIONS AND DIAGNOSIS

The most common laboratory findings that are seen in sepsis include neutrophilic leukocytosis, thrombocytopenia and hyperbilirubinemia. Urine analysis may show mild to moderate proteinuria. Leukopenia may be seen in some individuals. Peripheral smear may reveal neutrophilia with neutrophils containing toxic granules. In severe sepsis, thrombocytopenia usually worsens and may be associated with prolonged thrombin time, decreased fibrinogen levels and elevated D -dimer levels suggesting

DIC. Serum creatinine and blood urea nitrogen levels are commonly elevated in patients with severe sepsis and septic shock, indicating renal hypoperfusion and acute kidney injury. Arterial blood gas analysis usually reveals high anionic gap metabolic acidosis though in many patients early arterial blood gas analysis may show respiratory alkalosis as a result of hyperventilation. The most common ECG abnormality seen is sinus tachycardia. Chest X-ray may reveal underlying pneumonia or features of acute respiratory distress syndrome (ARDS). Bacteremia is very common and blood cultures may reveal the causative organism. In case of suspected urinary tract infection, urine cultures are helpful. In patients with in-dwelling catheter or soft tissue infections, swabs taken from the catheter or wound should be sent for culture.

DIAGNOSTIC AND PROGNOSTIC MARKERS

There is no specific diagnostic test for sepsis. Several diagnostic and prognostic markers are being studied by researchers in patients with sepsis. Some of these biomarkers which are proved to be helpful in the diagnosis and predicting the severity and outcome to some extent are discussed below.

C - reactive protein:

CRP levels are being used extensively as a non-specific marker of inflammation. Several studies have demonstrated the increase in CRP levels in patients with sepsis[62, 63]. As CRP levels are also increased in many other inflammatory conditions like rheumatoid arthritis, crohns disease, myocardial infarction, CRP is a nonspecific marker of sepsis. Because baseline CRP levels are often raised in these comorbid chronic inflammatory conditions, changes in concentrations over time and serial monitoring of CRP levels in patients with sepsis are more useful than single values [64, 65].

Procalcitonin

Many studies have shown that procalcitonin levels are elevated in patients with sepsis[66]. Several studies have validated procalcitonin to be a more reliable marker of sepsis than CRP, and that, it can be used to distinguish between sepsis caused by bacteria and other organisms [67, 68].There is also evidence based data that higher procalcitonin levels are associated with increased mortality thus making it a good prognostic marker as well [69].

Cytokine Levels

Various inflammatory cytokines, that are key mediators of the sepsis response, have been studied for their role as biomarkers of sepsis, some of which include IL-6, TNFα and IL-8. The serum levels of these inflammatory cytokines have been shown to be increased in patients with sepsis.[70]

Soluble Triggering Receptor Expressed on Myeloid Cells-1

Serum levels of sTREM-1 are found to be elevated in patients with sepsis. [71-74] Several studies have suggested that they are more sensitive and specific for infection than other markers such as CRP and procalcitonin.[71,72] A decrease in sTREM-1 levels over time was associated with a good prognosis in patients with sepsis.[75]

CD 64

Neutrophilic CD 64 expression have been studied in patients with sepsis and were found to have moderate sensitivity and specificity in the diagnosis of sepsis.[76,77]

Clot Waveform Analysis

Toh et al have established in their studies on patients diagnosed with sepsis and severe sepsis, the optical transmission waveform obtained during measurement of the activated partial thromboplastin time showed a biphasic pattern. The presence of this abnormal waveform has been used to support a diagnosis of sepsis [78]

PREDICTION OF OUTCOME OF SEPSIS: SCORING SYSTEMS

Severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions.

APACHE II (Acute Physiology and Critical Health Evaluation score)

The APACHE II score is one of the many scoring systems available such as SOFA, SAPS III, RIFLE to assess the prognosis of individual patients based on the set of laboratory values and the patient's sign of illness both acute and chronic illness. For APACHE II scoring, the input data should be that of the initial 24 hours of the patient's entry into the ICU.

SOFA SCORE

In 1994, The European Society of Critical Care Medicine (ESCCM), developed a simple and objective score, the Sequential Organ Failure Assessment (SOFA) Score as a system for measuring the status of the patient in the ICU.[79,80] The organ dysfunction in sepsis is recommended to be identified by an acute change in total SOFA score $\geq$ 2 points consequent to infection. The Sequential Organ Failure Assessment (SOFA) score allows for calculation of both the number and the severity of organ dysfunction in six organ systems, i.e., respiratory, coagulatory, liver, cardiovascular, renal, and neurologic. The score can measure individual or aggregate organ dysfunction. Different variables and parameters are included in each of the organ system. The function of each is scored from 0 (the Normal function-unless the patient has a previously known co-morbidity like cirrhosis, chronic kidney disease etc) to 4 (the most abnormal condition), giving a possible score of 0 to 24 on each day of ICU stay. The sum of the highest score per individual during the entire ICU stay is

considered the Maximal SOFA score. A higher SOFA score is associated with an increased probability of mortality[81].

The value of SOFA score> 15 is supposed to predict a mortality of 90%. Mean SOFA score is the average of all total SOFA scores in the entire period of ICU stay. Studies reveal that mean SOFA score for the first 10 days is significantly higher in non-survivors. Aditi Jain et al made prospective study on patients of age between 15 and 80 years admitted to ICU over 8 weeks period and concluded that there is a high correlation of ΔSOFA score (significance p<0. 0001) and the mortality[82]. The maximum score in survivors (3.92 ±2.17) was significantly lower than that of non-survivors (8.9 ± 3.45), while duration of the stay did not correlate with the survival (p = 0.461).

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Table 2: SOFA Scoring system

qSOFA score

SOFA score computation is a tedious procedure and uses a treatment related variable (doses of vasopressor agents). Laboratory variables, namely, PaO2, platelet count, creatinine level and bilirubin level are needed for full computation. The qSOFA score focuses on only three clinical variables- hypotension (Systolic blood pressure ≤ 100mm Hg), altered mental status and tachypnea (respiratory rate > 22/min), the presence of at least two of these criteria strongly predicts the likelihood of poor outcome in patients with clinical suspicion of sepsis in the non-ICU environment. This definition, nevertheless, does not offer clear criteria for sepsis diagnosis. In this context, sepsis raises multiple problems of diagnosis and prognosis, and further studies are necessary to identify useful criteria for establishing a rapid and correct diagnosis and quick and effective treatment.

OTHER BIOMARKERS

Extensive studies have been done on identifying specific markers for rapid diagnosis in order to improve the clinical management of sepsis. The literature focuses on RDW and NLCR i.e., the haemogram parameters which are easy to evaluate, and which do not incur additional costs to routine analysis. Normally red cell size variation is known as anisocytosis. The red blood cell distribution width (RDW) represents an index of the heterogeneity of the erythrocytes (anisocytosis) which is calculated by dividing the standard deviation of erythrocyte volume by the mean corpuscular volume (MCV) and multiplying by 100 to express the result as a percentage.

Structure of the Red cell

Among the cells of human tissues mature RBCs are unique, in the sense that they normally lack nuclei and cytoplasmic structures such as Lysosomes, endoplasmic reticulum and mitochondria. Hence they cannot carry out protein synthesis, and are unable to undergo mitosis and mitochondrial oxidative reactions. RBCs are biconcave discs of 7-8μm in diameter, but their shape changes to a parachute- like configuration in the capillaries whose diameter, is less than that of RBCs in the biconcave disc form. As the membrane of red cell is elastic they resume biconcave shape. Once they re-enter the large blood vessels, loss of flexibility or elasticity leads to membrane damage and change in shape. This leads to diminished life span.

RED CELL DISTRIBUTION WIDTH (RDW)

Red cell distribution width is an index of variation in RBC size or RBC volume. Most automated instruments produce a quantitative assessment of the variation in red cell volume indicated by RDW which corresponds to the microscopic analysis of the degree of anisocytosis. The RDW derived from pulse height analysis can be expressed either as (SD) standard deviation in fl or as the percent of coefficient of variation (CV) of the measurements of red cell volume.

RDW-SD is a measurement of width of RBC size distribution histogram and it is measured by calculating the width at the 20% height level of the RBC size distribution histogram. Hence RDW-SD is not influenced by the average RBC size, that is, mean corpuscular volume.

RDW-CV is calculated from standard deviation and MCV by the formula.

RDW-CV (%) = 1 SD of RBC volume / MCV x 100% Since RDW- CV is obtained mathematically from MCV it is affected by changes in average size of RBCs.

Normal reference ranges of RDW in adults:

RDW - SD 39-46 fl

RDW - CV 12-14%

Significance of elevated RDW

- Early diagnosis of nutritional deficiency (d/t) iron, B12 and folic acid.
- Differentiation of iron deficiency anaemia from thalassemia.
- Differentiation of megaloblastic anaemia from other causes of macrocytosis
- Identification of Red cell fragmentation, agglutination and dimorphic red cells in peripheral smear examination.

Red cell distribution width in sepsis

Recent studies have been focusing on evaluating RDW's prognostic value and use for the diagnostic role in sepsis. Literature reveals that as RDW is a means of evaluating the variability in size of erythrocytes it has been used widely in the differential diagnosis of anemia [83].Since RDW is a marker of unspecific inflammation, it can show high value in many other diseases such as heart failure, stroke, peripheral arterial disease or chronic pulmonary diseases [84].Red cell distribution width (RDW) represents an indicator which can vary in sepsis, under the influence of pro-inflammatory cytokines (TNFα, IFNδ, IL-1β, IL-6)[85],released during the inflammatory process. These cytokines cause inefficient erythropoiesis resulting in structural and functional changes of erythrocytes, with volume variations and increased RDW.

Elevated value of RDW can also appear in nutritional deficiencies such as iron deficiency anaemia, vitamin B12 or folate deficiency anaemia, or in blood transfusions[86]. Kim et al. evaluated the predictive role of RDW regarding the short and medium-term mortality in elderly patients with severe sepsis and septic shock and

concluded that every one percent (1%) increase in RDW is equivalent to a 15% increase in the mortality rate in the first 30 days [87]. Lorente et al. showed that RDW is a low-cost procedure which should be routinely performed to identify the risk of death in sepsis. In this study, the prognostic value of RDW was compared with other biomarkers such as serum malondialdehyde and TNFα, [88]

In a study on 349 patients, the function of RDW in predicting septic outcome in sepsis through the statistically significant association with APACHE II score and with hospital mortality rate. ($p<0.0001$) was presented. This study demonstrated that an RDW value over 16% is concurrent with a higher APACHE value and risk of death[84]. RDW was also considered a good predictor of the length of hospitalization for septic patients admitted to intensive care units [89].

The biomarker RDW proved its usefulness as an outcome measure because an ascending trend of RDW in the first 72 hours of admission is associated with an unfavourable prognosis, even though the initial values were normal [90]. Chen et al. analysed almost 7000 adult patients with sepsis, with a mortality rate of 6.8%. In this study, patients who died had higher initial values of RDW than the survivors (15.7% versus 13.8%). There were also established threshold values; for RDW over than 15.6%, the risk of death was 16.7%, for RDW between 14 – 15.6% it was 7.3%, and for RDW under 13.1% the mortality rate was 1.6%. Thus, RDW was considered to be a superior mortality predictive factor to SIRS criteria, the MEDS (Mortality in Emergency Department Sepsis) or CURB65 scores [91].

Mean platelet volume (MPV)

Platelets play an important role in the pathophysiology of sepsis. Platelets cause activation of the innate immune system as mentioned in figure below. Hence thrombocytopenia may be associated with dysregulated host response.[15]

Even though low platelet count is common in sepsis, cause of death is rarely due to bleeding. Platelets release various cytokines that interact with leukocytes and endothelium to cause micro thrombi formation. These mechanisms are useful in containing sepsis in localised infection whereas in severe infections it becomes maladaptive and dysregulated leading to multiorgan dysfunction.[15]

Thrombocytopenia in sepsis is caused by decreased production or increased destruction of platelets. The etiology of thrombocytopenia is multi-factorial. However the most common cause of thrombocytopenia is platelet activation followed by platelet consumption, platelet destruction or thrombus formation. The bone marrow tries to compensate this by increase in platelet production which leads to release of immature platelets into peripheral circulation. Young platelets have large surface area. Moreover platelets change their shape from discoid to spherical along with formation of pseudopods during platelet activation to achieve a large surface area.[15]

A typical range of platelet volumes is **9.4- 12.3 fL**(femtolitre).

It is an indicator of platelet size and activity, and is easily and cost-effectively measured with the use of automated hematology analyzers. An increased platelet volume and size reflect a thrombotic and inflammatory milieu; thus, MPV has been proposed as a possible marker of platelet function and activation. Several studies have reported that MPV changes are associated with morbidity and mortality in patients with diseases such as sepsis, diabetes mellitus, myocardial infarction, and chronic inflammatory disorders. [15].

SIGNIFICANCE OF NLCR

Neutrophil/lymphocytes count ratio (NLCR) has been the focus of several recent studies as it is accessible, cheap and readily determined. The importance of this parameter is related to the pathophysiological mechanism of SIRS, which is characterised by an increased number of circulating leucocytes, due to the increased number of neutrophils, the first line of antimicrobial defence. On the other hand, lymphocytopenia appears as a consequence of lymphocyte margination and redistribution in the lymphatic system, with accelerated apoptosis [92]. Normally there are 4000-11000 WBCS/ micro litre in the human blood. Of these granulocytes are the most numerous. Young granulocytes have horse shoe shaped nuclei that become multilobed as the cells grow older. Most of them contain neutrophilic granules.

Neutrophils

Neutrophils have cytoplasmic granules that contain biologically active substances involved in inflammatory reactions. The average half- life of a neutrophil in the circulation is 6 hours. They are attracted to the endothelial surface by selectins and they roll along it. Neutrophil adhesion molecules of the integrin family helps them to get bound to selectins.

They insinuate themselves through the walls of the capillaries by a process known as diapedesis. Many of those that leave the circulation enter the GI tract and are lost from the body. Neutrophilic granules contain various proteases and in addition they also contain enzymes such as NADPH oxidase, catalase and myeloperoxidases. NADPH oxidase is associated with a sharp increase in oxygen intake and metabolism in the neutrophil, (Respiratory burst) and this reaction generates plenty of free O-radicals. The myeloperoxidase catalyses the conversion of Halides and cyanides to

their corresponding acid forms. These acids in turn are potent oxidants by themselves. In addition to myeloperoxidase and NADPH oxidase neutrophil granules also contain an elastase and two metalloproteinases.

The total body neutrophils can be divided into circulating pool (CGP) and marginating granulocyte pool. In these two pools, the cells are equal size and they are in constant equilibrium. MGP represents the neutrophils involved in adhesion and rolling along the endothelial cells in post capillary venules and they are not found in blood obtained by venepuncture. So the neutrophil content actually represents about half of the total no of neutrophils in the vascular compartment.

Lymphocytes

Lymphocytes are motile non phagocytic cells. There are many subpopulations of lymphocytes which interact with each other and with cells of the monocyte macrophage system. They help in maintaining both humoral and cell mediated immunity. Proliferating lymphocytes are enriched with enhanced levels of enzyme n-terminal deoxyribonucleic acid transferase. It is found in immature lymphoid cells in the bone marrow and thymocytes, but not in mature lymphocytes. Adenosine de aminase is present in large amounts in Tlymphocytes and it is necessary for their immune function.

Inflammation

Inflammation is naturally a protective mechanism against invasion of microbes and toxins. The inflammatory response consists of 2 main components- a vascular reaction and a cellular reaction. Both the reactions are mediated by chemical factors that are derived from plasma proteins or cells produced as a result of inflammatory response.

Mechanisms

Endothelial dysfunction secondary to cellular response of blood components heralds the onset of inflammation. Endothelial dysfunction leads to impaired production of nitric oxide and prostacylins. This leads to the depletion of anti-atherogenic, antithrombotic and vasodilator properties of the vascular endothelium.

Zahorec first proposed the use of the ratio of neutrophil and lymphocyte counts [neutrophil lymphocyte count ratio (NLCR)] as an marker of infection in clinical Applications. [93] Loonen et al., demonstrated that NLCR is a rapidly available biomarker, and appears most promising in differentiating patients with BSI from those without BSI for subsequent pathogen identification.[94] NLCR is considered to be superior to other biomarkers such as CRP, leukocytes count or neutrophils count, as a predictor for bacteremia in patients admitted to emergency or intensive care units.[95] In a study of 40 patients with severe sepsis, Okashah et al., highlighted NLCR superiority regarding sensitivity, specificity, positive and negative predictive values to other parameters like lactate, CRP, neutrophils count, lymphocytes count, or leucocytes count.[96] The same study showed the usefulness of NLCR in prognostic evaluation attributing to the statistically significant correlation with two severity scores, APACHE II ($p=0.01$) and SOFA ($p=0.01$).

Recently, attempts have been made to establish threshold values for NLCR for predicting the severity and outcome of the disease. A more recent study showed that an initial value of NLCR over 10 could be correlated with an unfavorable prognosis, as assessed by the number of SIRS criteria, the presence of organ failure or septic metastasis at admission.

Despite the low number of investigated patients, this study intended to substantiate the prognostic role of NLCR in sepsis through the statistically significant correlations

with APACHE IV (p=0.01) and APS (p=0.01) scores and with the estimated rate of mortality (p=0.01)[97]. A retrospective study, which included 2311 patients with bacteremia concluded that a value of NLCR over seven on admission, represented an independent increased mortality rate risk factor [98].

The predictive role of NLCR has been evaluated not only in septic patients but also in patients with tumors, cardiovascular diseases or intestinal inflammatory diseases. The initial value of this indicator was correlated with the outcome and with the survival rate in patients with different types of cancers: pulmonary, breast, prostatic, pancreatic, oesophageal [99], colorectal [100] or hepatocellular carcinoma followed by liver transplant [101].Several studies, published in cardiovascular medicine domain, showed the prognostic role of NLCR in patients with an acute coronary syndrome, aortocoronary bypass or congestive heart failure [102],[103]. Ertas et al. indicated that NLCR was useful in the prognosis of patients with thromboembolic Stroke.[104] On the other hand, a high correlation between NLCR and the outcome of patients with gangrenous appendicitis was demonstrated, and was shown to be superior to other parameters like fever, CRP, Leucocytes number or the Glasgow scale.[105]

MANAGEMENT OF SEPSIS

Early Management

For patients with severe sepsis or septic shock, (i) stabilization of the airway and breathing and (ii) restoration of perfusion to the peripheral tissues should be should be done immediately, by supplemental oxygenation and monitored continuously with pulse oximetry.

Intubation and mechanical ventilation if needed should not be delayed.[106, 107] Following initial stabilization, chest radiographs and arterial blood analysis should be

obtained in combination with other clinical parameters to diagnose acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), which frequently complicate sepsis.

Central venous Catheter (CVC)

After the assessment of airway and perfusion, inserting a central venous catheter will be beneficial with most patients with severe sepsis and septic shock for infusion of intravenous fluids, infusion of blood product and infuse medications. In addition, CVC can be used to monitor the central venous pressure (CVP) and the central venous oxyhaemoglobin saturation (ScvO2). Few studies have shown that, management of septic shock guided by ScvO2 reduce the mortality. [108]

Restoration of Perfusion

Once the presence of hypoperfusion has been established, early restoration of perfusion is vital to prevent or reduce multi organ dysfunction. The goals for resuscitation of circulation include maintaining central venous pressure (CVP) 8 to 12 mmHg, a mean arterial pressure (MAP) ≥65 mmHg and a urine output ≥0.5 mL/kg per hour. Intravenous fluid administration should be started as early as possible.

Intravenous fluids

Large volume infusions of IV fluids are the main stay of initial therapy in patients with severe sepsis or septic shock. Fluid should be administered as rapidly infused boluses [109,110].

The volume status, blood pressure, peripheral perfusion and the presence of lung signs (to rule out pulmonary edema) must be monitored before and after each bolus.

Intravenous fluids should be administered carefully and a more restrictive approach should be followed with respect to fluid resuscitation in patients at risk and who have developed acute lung injury or ARDS.[111] The ideal fluid of choice can be either crystalloids like 0.9 % normal saline or Ringer's Lactate or colloids like 4% albumin or pentastarch. Though 0.9 % normal saline is the most commonly used and preferred fluid of choice for many clinicians, the usefulness of crystalloids have been studied extensively.

In a SAFE (Saline versus Albumin Fluid Evaluation) trial, nearly 7000 critically ill patients were studied after being randomly assigned to receive 4% albumin to one group and normal saline to another group. It was observed that, after 28 days, there was no difference in the outcome between the two groups. In another trial called VISEP trial, a similar comparison was done between two groups. One group received penta- starch (colloid) and another group received Ringer's lactate (crystalloid). The trial was stopped due to an increased trend in 90 day mortality among patients who received pentastarch [112]. Generally, crystalloids like normal saline/ Ringer's lactate are preferred due to the higher cost of colloid.

Vasopressors and Inotropes

In the treatment of severe sepsis and septic shock, though vasopressors are second line agents, intravenous vasopressors are the next step in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema[113]. The choice of vasopressor agents have been studied. Use of norepinephrine in most patients were recommended and phenylephrine (a pure alpha-adrenergic agonist) was observed to be useful when tachycardia or arrhythmias preclude the use of agents with beta adrenergic activity[106,114] When the ScvO2 remains <70 percent after optimization

of intravenous fluid and vasopressor therapy, additional therapies such as inotropic therapy or red blood cell transfusion could be considered.

IDENTIFYING AND REMOVING THE SEPTIC FOCUS

The primary therapeutic intervention involves the identification and treatment of the primary site or sites of infection, the other interventions being purely supportive [115-117]. A careful history and physical examination may yield clues to the source of sepsis and help guide microbiologic evaluation. For example, the presence of a urinary or intravenous catheter increases the chances that these are the source of infection. The catheters should be removed immediately and changed if warranted. Gram staining and culture of samples from the suspected source of infection should be collected as early as possible and sent to reliable laboratory without contamination. Source control measures should be undertaken since undrained foci of infection may not respond to antibiotics alone. For examples, abscesses should be drained as early as possible.

ERADICATION OF INFECTION

Antimicrobial regimen

Intravenous antibiotic therapy should be started immediately after obtaining culture samples, since early initiation of antibiotic therapy is associated with lower mortality [118].The choice of antibiotics depends on the patient's history with suspected source of infection and targeting suspicious pathogens, recent antibiotics received [119], comorbidities, clinical context (eg, community- or hospital-acquired), Gram stain data, and local resistance patterns [106,120-123].

Generally clinicians prefer starting broad-spectrum antibiotics when the potential pathogen or infection source is not immediately obvious.

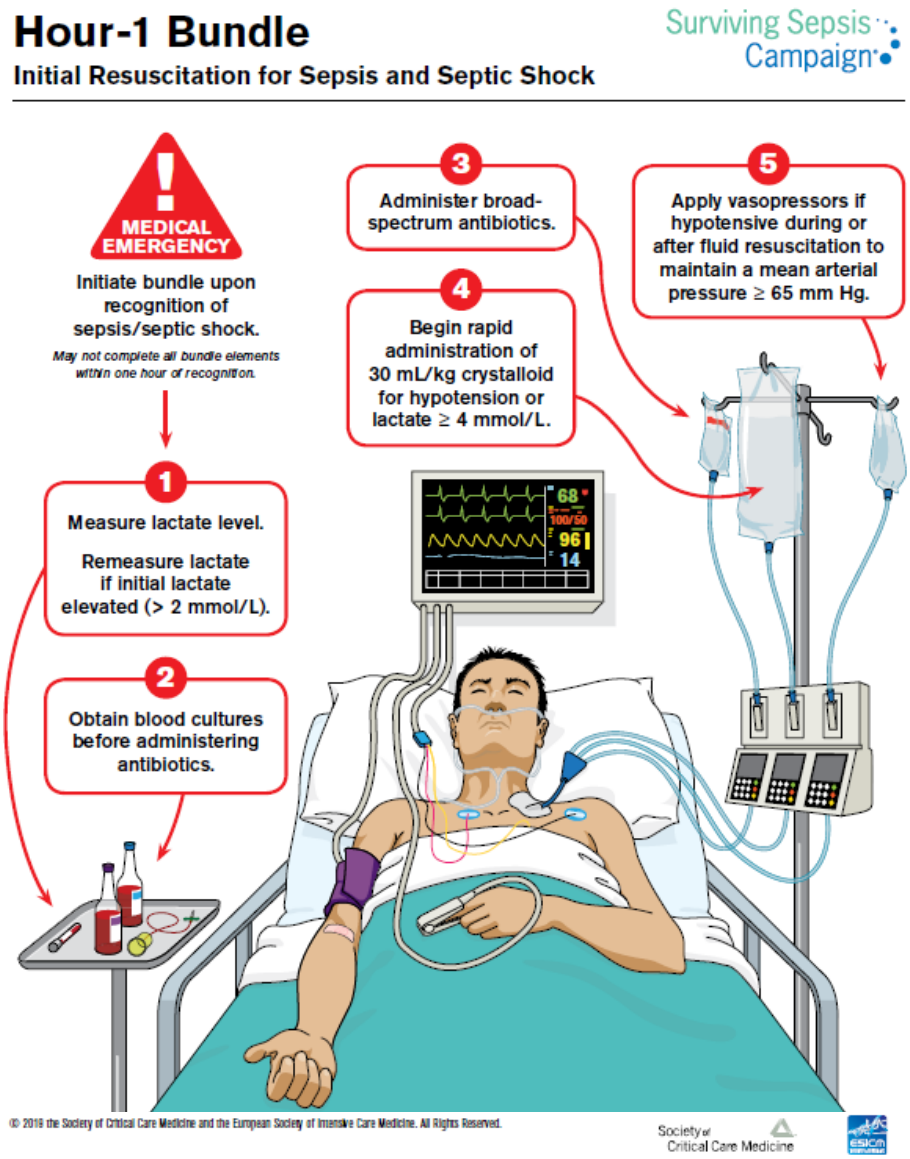


Fig 4. SURVIVING SEPSIS CAMPAIGN BUNDLE

Literature reveals that extensive work has been done in the diagnostic and early treatment of sepsis in developed countries. Research is still going on in the identification of markers to diagnose sepsis, severe sepsis and septic shock from SIRS. More of research is needed to identify biomarkers in this area in developing countries. Hence this study is undertaken to find the effectiveness of the biomarkers Red cell distribution width (RDW) Mean platelet volume (MPV) and Neutrophil-Lymphocyte count ratio (NLCR) as prognostic markers of sepsis and to correlate it with SOFA score in predicting the outcome.

MATERIALS & METHODS

MATERIALS AND METHODS

The study was performed at R.L. Jalappa hospital and research centre, Tamaka, Kolar from January 2018 to July 2019 after obtaining the approval of Institutional Ethical Committee.

Study design: A single-center, prospective observational study.

Inclusion criteria:

- Patients > 18 years of age with sepsis (diagnosed as per "The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)".

Exclusion criteria:

- Patients with pre-existing organ dysfunction prior to infection (chronic kidney disease, decompensated liver disease, cardiac disease).
- Patients with Blood loss >10% blood volume.
- Blood product transfusion in the week before admission.
- Patients with haematological diseases such as anaemia, hypersplenism, haematological malignancy, metastatic bone marrow infiltration by malignancy, recovery after bone marrow hyperplasia.
- Recent chemotherapy.
- Pregnant individuals.

Sample size:

The study subjects were patients admitted to R.L. Jalappa hospital and research centre, Tamaka, Kolar presenting with the syndrome of sepsis and who were selected according to the inclusion criteria. The sample size was determined according to the formula:

$$n = \left(\frac{Z_{\alpha/2} \cdot \sigma}{E}\right)^2$$

where,

n = Sample size, σ = Population standard deviation

E = Margin of error and Zα/2 is normal deviate for two-tailed alternative hypothesis at a level of significance; for example, for 5% level of significance, Zα/2 is 1.96 and for 1% level of significance it is 2.58. The confidence level is estimated at 95% Standard deviation 2.2 With a z value of 1.96 the confidence interval or margin of error is estimated at ± 0.05. Assuming that 80 percent is considered as power of the study, the minimum sample size required for the study is calculated to be 75 Taking into account 20% attribution rate sample size was calculated to be 75+15 = 90 A total of 120 samples were collected at the end of the study.

Method of collection of data:

Informed written consent from all the patients who met inclusion and exclusion criteria for the study was procured before conducting the study.

Clinical, and laboratory data were obtained and studied before administration of broad spectrum antibiotics. Patients were assessed for sepsis and septic shock (Society of Critical Care Medicine Conference definitions)[7]. Blood samples were collected and analyzed within 3 hrs from the time of presentation. RDW, MPV, NLCR were obtained from the values measured.

The principles of initial resuscitation (fluid therapy, vasopressors, inotropic support) and infection issues (source identification and control, appropriate antibiotic therapy) were followed regularly and the outcome studied. SOFA score was recorded at admission in the emergency ward or ICU for studying the in- hospital outcome. RDW, MPV, Neutrophil count, Lymphocyte count and calculation of NLCR were done at the time of admission. All patients were followed up at the hospital until the time of discharge, death or maximum period of 14 days. Major adverse events in the form of shock requiring inotropic support, ventilator requirement, need for renal replacement therapy and death were recorded. The correlation studies of RDW, MPV, NLCR, and SOFA score is done and their prognostic value among survivors and non-survivors in patients with sepsis compared.

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test or Fischer's exact test** (for 2x2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables.

Correlations were performed with **Pearson Correlation coefficient**.

SOFA score, RDW, MPV and NLR were further analyzed using the receiver operating characteristic (ROC) and optimal cut-off points were chosen for the calculation of sensitivity, specificity. A test that predicts an outcome no better than chance has an area under the ROC curve of 0.5. An area under the ROC curve above 0.8 indicated fairly good prediction.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data

RESULTS

RESULTS

One twenty patients were included in the study, and the observations of these patients were compiled and analyzed.

Distribution of subjects according to age group among survivor and non-survivor

The age of patients ranged from 20 to 99 years.

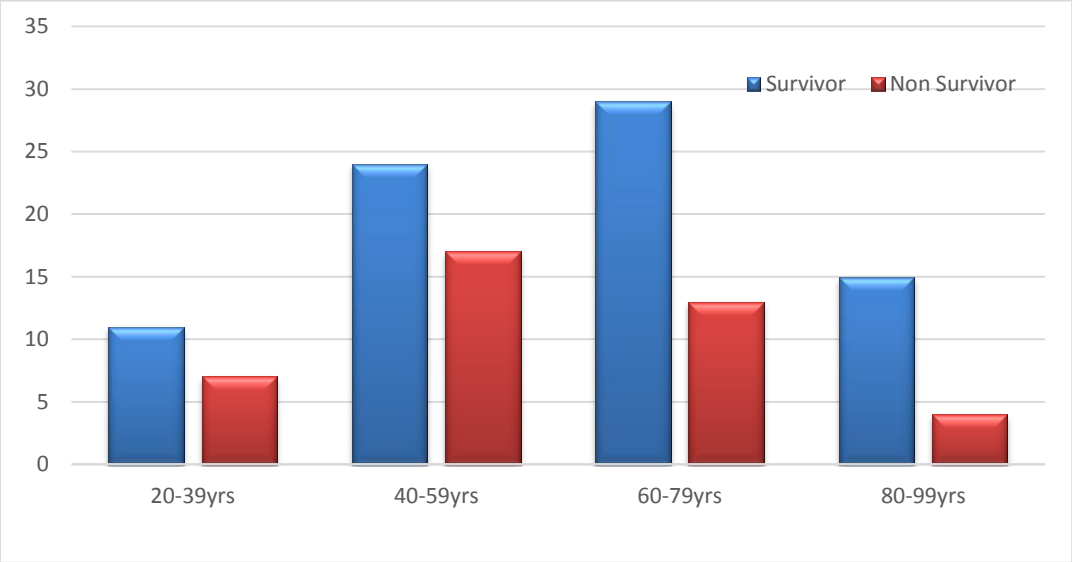
The patients in the study were divided into 4 age groups, viz., 20-39 years, between 40 to 59 years, between 60 to 79 years and 80 to 99 years. There were 11 patients (13.9%) survivors and 7 (17.1%) non survivors in between 20 to 39 years age group, 24 (30.4%) survivors and 17 (41.5%) non survivors in between 40 to 59 years age group, 29 (36.7%) survivors and 13 (31.7%) non survivors in between 60 to 79 years age group and 15 (19.0%)survivors and 4 (9.8%) non survivors in between 80 to 99 years of age group as shown in Table 3, Figure 5.

Table 3:- Distribution of subjects according to age group among survivor and non-survivor

Age group	Survivor		Non Survivor		P Value
	N	%	N	%	
20-39yrs	11	13.9%	7	17.1%	0.424
40-59yrs	24	30.4%	17	41.5%	
60-79yrs	29	36.7%	13	31.7%	
80-99yrs	15	19.0%	4	9.8%	
Total	79	100%	41	100%	

P value 0.424, there was no statistically significant difference found between survivor and Non survivor with respect to age.

Figure 5:- Graph showing distribution of subjects according to age group among survivor and non-survivor



Distribution of subjects according to sex among survivor and non-survivor

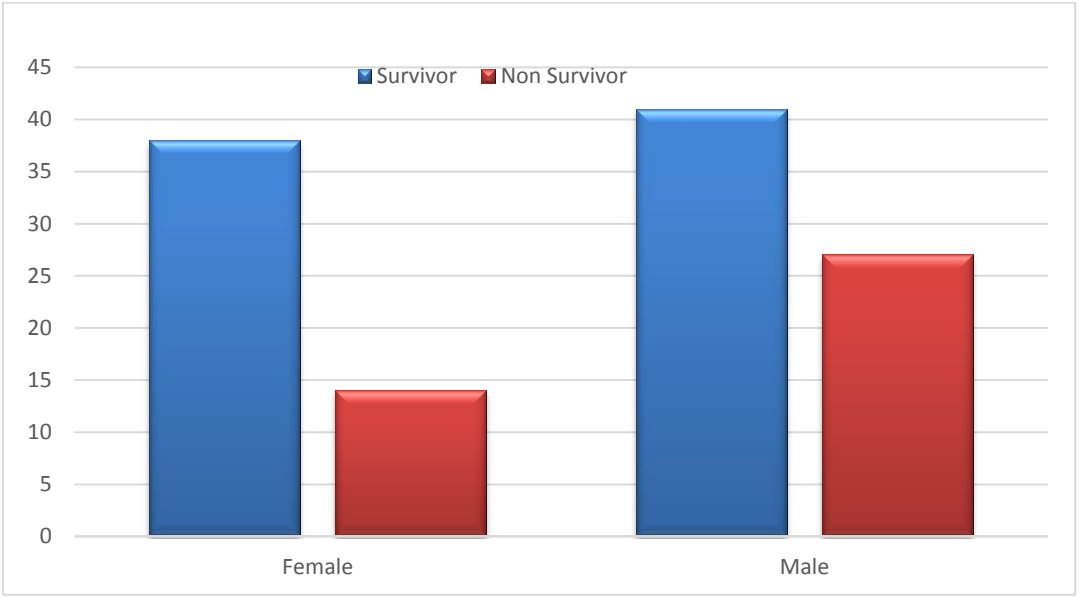
Among 120 patients included in the study, 38 (48.1%) survivors and 14 (34.1%) non survivors were females; and among males 41 (51.9%) survivors and 27 (65.9%) non survivors.

Table 4:- Distribution of subjects according to sex among survivor and non-survivor

Sex	Survivor		Non Survivor		P value
	N	%	N	%	
Female(52)	38	48.1%	14	34.1%	0.176
Male(68)	41	51.9%	27	65.9%	
Total	79	100%	41	100%	

P value 0.176, there was no statistically significant difference found between survivor and Non survivor with respect to sex.

Figure 6:- Graph showing distribution of subjects according to sex among survivor and non-survivor



Frequency distribution of symptoms among survivor and non-survivor

Among all the patients included in the study, in survivors 62 (78.5%) had fever, 3 (3.8%) had headache, 35 (44.3%) had cough, 25 (31.6%) had breathlessness, 21 (26.6%) had altered sensorium, 10 (12.7%) had vomiting, 1 91.3%) had decreased urine output and 5 (6.3%) had abdominal pain.

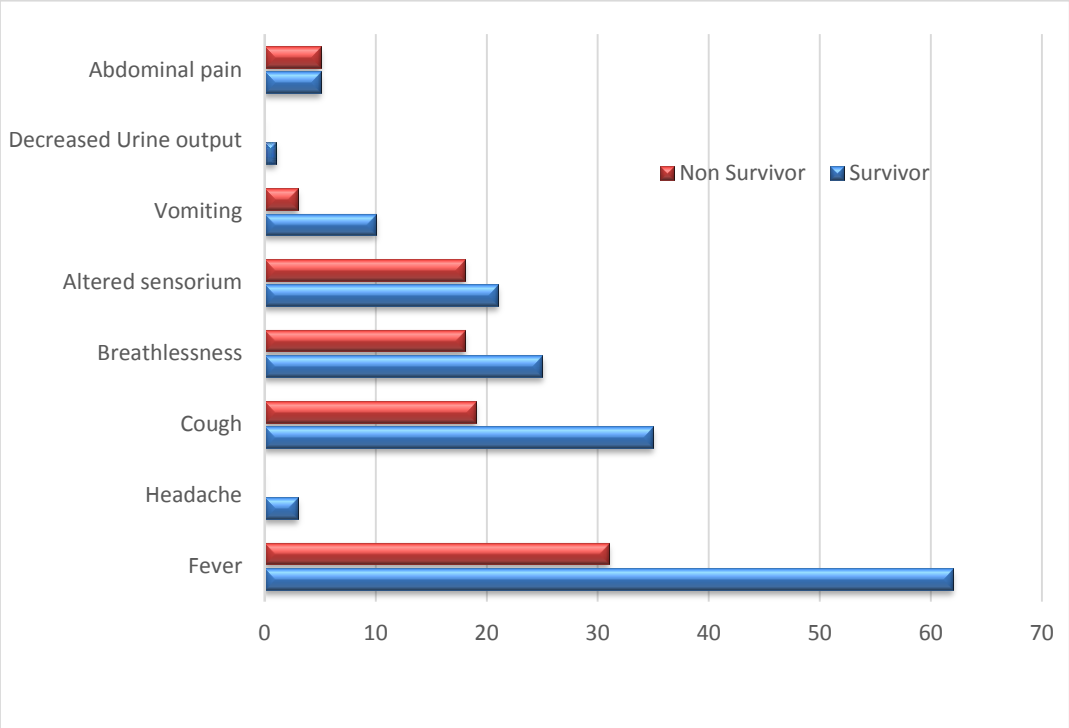
Among all the patients included in the study, in non survivors 31 (75.6%) had fever, 19 (46.3%) had cough, 18 (43.9%) had breathlessness, 18 (43.9%) had altered sensorium, 3 (7.3%) had vomiting, and 5 (12.2%) had abdominal pain.

Table 5:- Frequency distribution of symptoms among survivor and non-survivor

	Survivor		Non Survivor		P value
	N	%	N	%	
Fever	62	78.5%	31	75.6%	0.818
Headache	3	3.8%	0	.0%	0.550
Cough	35	44.3%	19	46.3%	0.847
Breathlessness	25	31.6%	18	43.9%	0.229
Altered sensorium	21	26.6%	18	43.9%	0.066
Vomiting	10	12.7%	3	7.3%	0.539
Decreased Urine output	1	1.3%	0	.0%	1.00
Abdominal pain	5	6.3%	5	12.2%	0.197

There was no statistically significant difference found between survivor and Non survivor with respect to any of the symptoms.

Figure 7:- Graph showing Frequency distribution of symptoms among survivor and non-survivor



Distribution of subjects according to diagnosis among survivor and non-survivor

Among all the patients included in the study, in survivors 6 (7.6%) had acute GE, 8 (10.1%) had cellulitis, 46 (58.2%) had LRTI, 2 (2.5%) had LRTI+ ARDS, 7 (8.9%) had meningitis, 1 (1.3%) had neuroinfection(encephalitis) and 9 (11.4%) had urosepsis.

Among all the patients included in the study, in non survivors 1 (2.4%) had acute GE, 15 (36.6%) had LRTI, 13 (31.7%) had LRTI + ARDS, 2 (4.9%) had meningitis, and 10 (24.4%) had urosepsis.

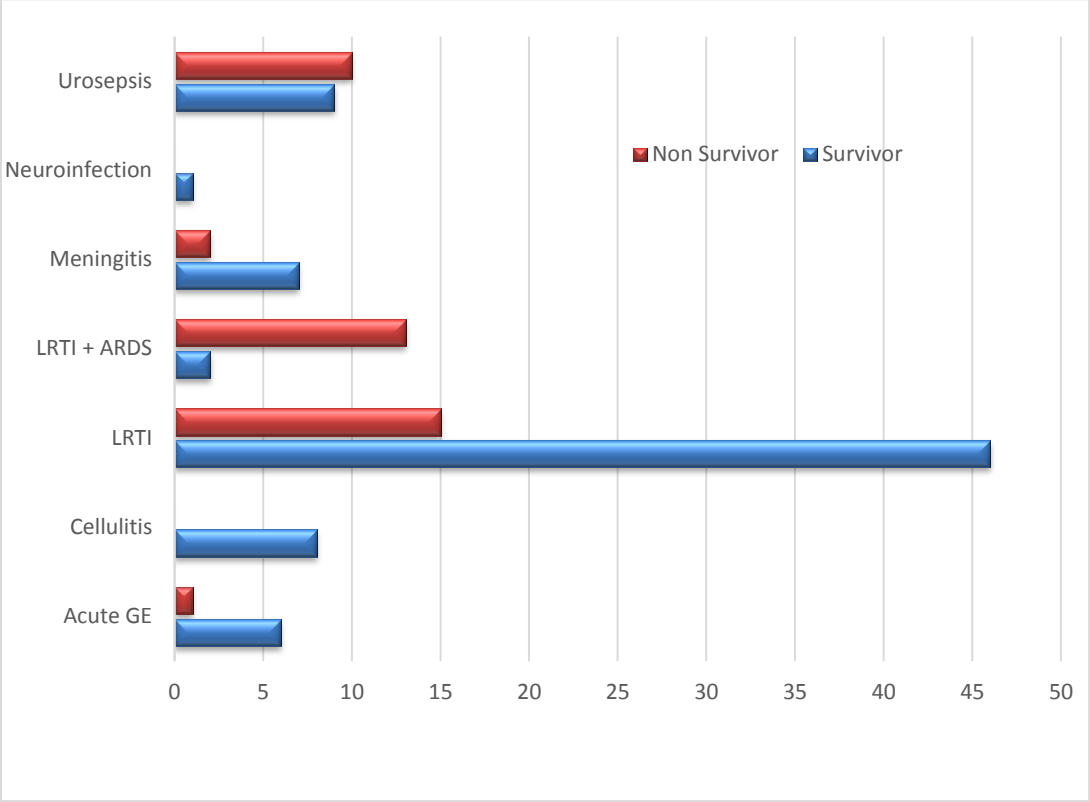
Table 6:- Distribution of subjects according to diagnosis among survivor and non-survivor

	Survivor		Non Survivor		P value
	N	%	N	%	
Acute GE	6	7.6%	1	2.4%	0.420
Cellulitis	8	10.1%	0	.0%	0.050
LRTI	46	58.2%	15	36.6%	0.034
LRTI + ARDS	2	2.5%	13	31.7%	<0.001
Meningitis	7	8.9%	2	4.9%	0.717
Neuroinfection(encephalitis)	1	1.3%	0	.0%	1.00
Urosepsis	9	11.4%	10	24.4%	0.111
Total	79	100%	41	100%	

P value <0.001, there was a statistically significant difference found between survivor and Non survivor with respect to LRTI, LRTI+ ARDS.

There was no statistically significant difference found between survivor and Non survivor with respect to other diagnosis like Acute GE, Cellulitis, Meningitis, neuro infection and Urosepsis .

Figure 8:- Graph showing Distribution of subjects according to diagnosis among survivor and non-survivor.



Distribution of subjects according to cultured organism among survivor and non-survivor

Among all the patients included in the study, of 79 survivors 65 (82.3%) had no organism, 3 (3.8%) had acinetobacter species, 1 (1.3%) had AFB, 1 (1.3%) had candida albicans+ acinetobacter, 7 (8.9%) had E. Coli, 1 (1.3%) had Klebsiella oxytoca and 1 (1.3%) had Klebsiella pneumonia, Acinetobacter.

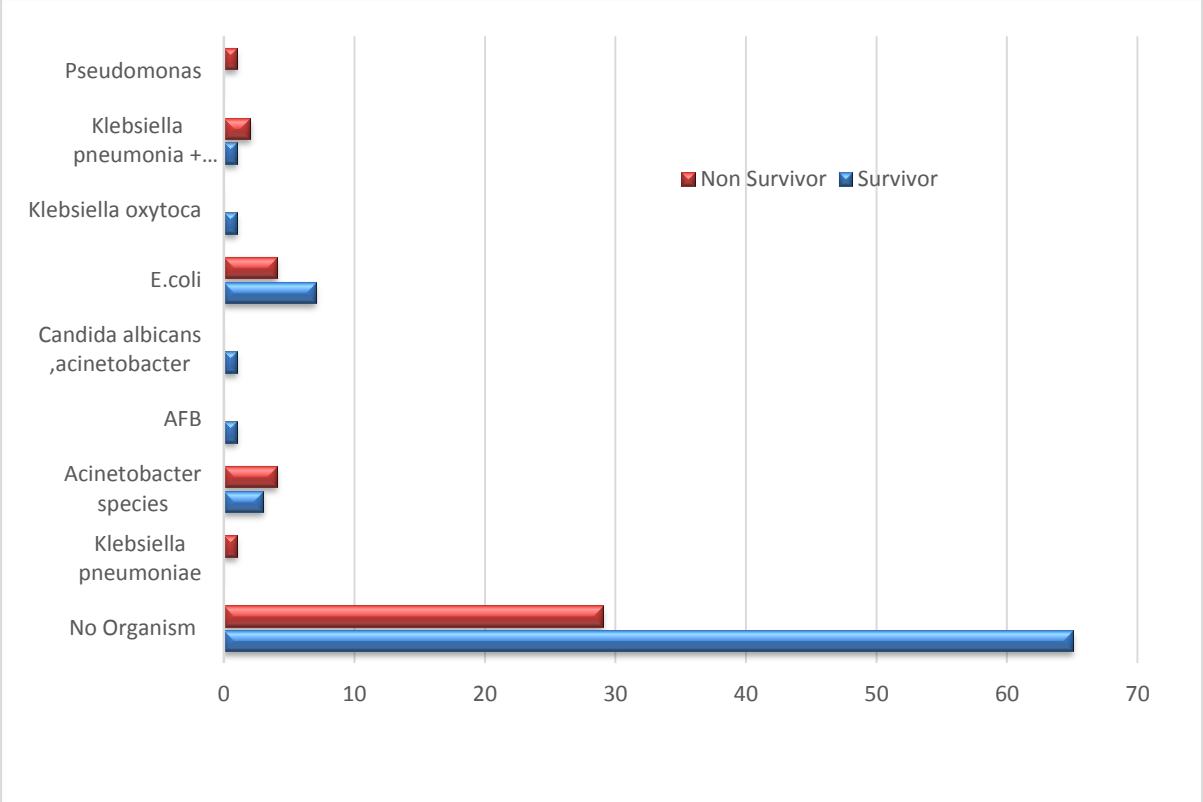
Among all the patients included in the study, of 41 non survivors 29 (70.7%) had no organism, 1 (2.4%) had Klebsiella pneumonia 4 (9.8) had acinetobacter species, 4 (9.8%) had E. Coli, 2 (4.9%) had klebsiella pneumonia + acinetobacter and 1 (2.4%) had pseudomonas.

Table 7:- Distribution of subjects according to cultured organism among survivor and non-survivor

	Survivor		Non Survivor		P value
	N	%	N	%	
No Organism	65	82.3%	29	70.7%	0.216
Klebsiella pneumoniae	0	.0%	1	2.4%	0.683
Acinetobacter species	3	3.8%	4	9.8%	0.864
AFB	1	1.3%	0	.0%	0.764
Candida albicans ,acinobacter	1	1.3%	0	.0%	0.764
E.coli	7	8.9%	4	9.8%	0.871
Klebsiella oxytoca	1	1.3%	0	.0%	0.764
Klebsiella pneumonia +Acinetobacter	1	1.3%	2	4.9%	0.220
Pseudomonas	0	.0%	1	2.4%	0.683

There was no statistically significant difference found between survivor and Non survivor with respect to cultured organism

Figure 9:- Graph showing Distribution of subjects according to cultured organism among survivor and non-survivor.



Distribution of subjects according to Co morbidities among survivor and non-survivor

Among all the patients included in the study, in survivors 69 (87.3%) had co-morbidity, and 10 (12.7%) had no co- morbidity.

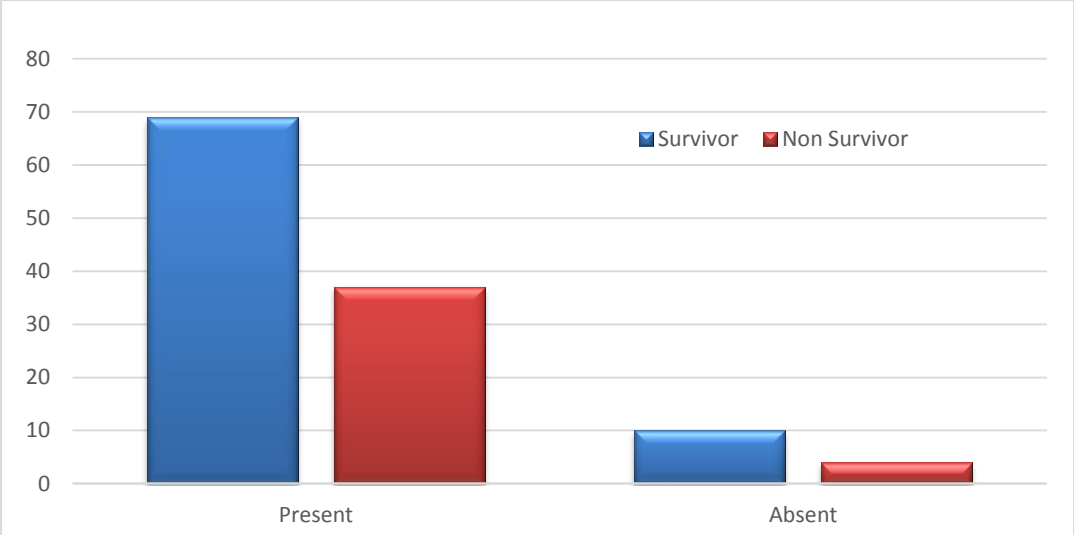
Among all the patients included in the study, in non survivors 37 (90.2%) had showed co- morbidity, and 4 (9.8%) had showed no co- morbidity.

Table 8:- Distribution of subjects according to Co morbidities among survivor and non-survivor

Co morbidities	Survivor		Non Survivor		P value
	N	%	N	%	
Present	69	87.3%	37	90.2%	0.770
Absent	10	12.7%	4	9.8%	
Total	79	100%	41	100%	

P value 0.770, there was no statistically significant difference found between survivor and Non survivor with respect to co morbidities.

Figure 10:- Graph showing distribution of subjects according to Co morbidities among survivor and non-survivor



Distribution of subjects according to Ventilator Support among survivor and non-survivor

Among all the patients included in the study, in survivors 50 (63.3%) had no ventilator support, and 29 (36.7%) had ventilator support.

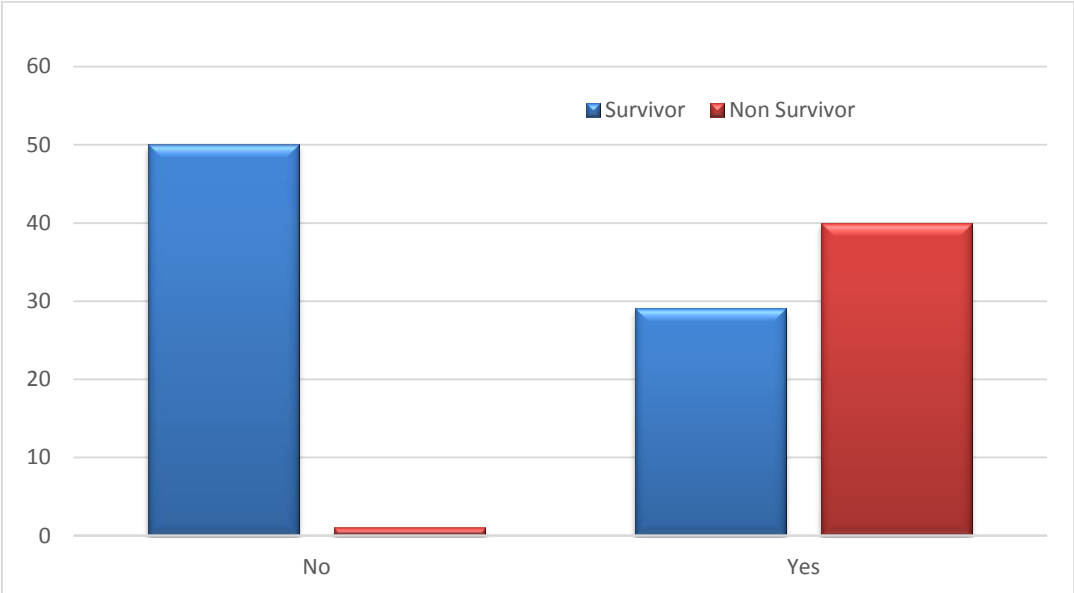
Among all the patients included in the study, in non survivors 1 (2.4%) had no ventilator support and 40 (97.6%) had ventilator support.

Table 9:- Distribution of subjects according to Ventilator Support among survivor and non-survivor

	Survivor		Non Survivor		P value
	N	%	N	%	
No	50	63.3%	1	2.4%	<0.001
Yes	29	36.7%	40	97.6%	
Total	79	100%	41	100%	

P value <0.001, there was a statistically significant difference found between survivor and Non survivor with respect to Ventilator Support.

Figure 11:- Graph showing distribution of subjects according to Ventilator Support among survivor and non-survivor



Distribution of subjects according to inotropic support among survivor and non-survivor

Among 79 survivors included in the study, 37 (46.8%) had no inotropic support, and 42 (53.2%) had inotropic support.

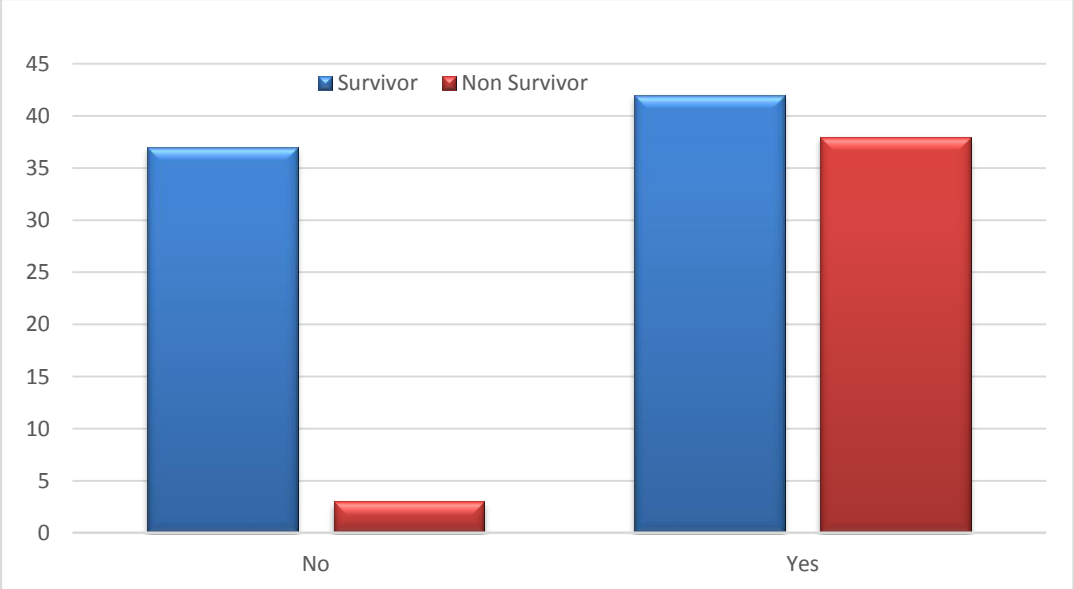
Among 41 non survivors included in the study, 3 (7.3%) had no inotropic support, and 38 (92.7%) had inotropic support.

Table 10:- Distribution of subjects according to inotropic support among survivor and non-survivor

	Survivor		Non Survivor	
	N	%	N	%
No	37	46.8%	3	7.3%
Yes	42	53.2%	38	92.7%
Total	79	100%	41	100%

P value <0.001, there was a statistically significant difference found between survivor and Non survivor with respect to inotropic support.

Figure 12:- Graph showing Distribution of subjects according to inotropic support among survivor and non-survivor



Distribution of subjects according to renal replacement therapy among survivor and non-survivor

Among 79 survivors included in the study, 69 (87.3%) had no renal replacement therapy, and 10 (12.7%) had renal replacement therapy.

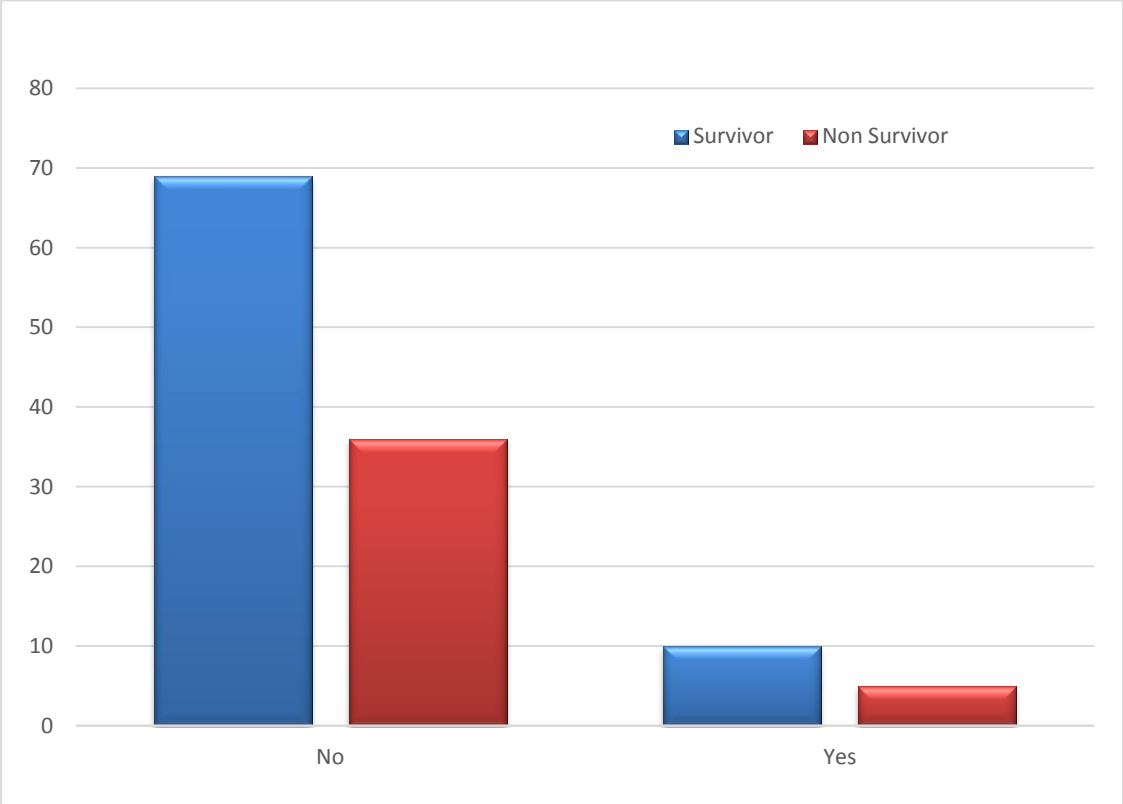
Among 41 non survivors included in the study, 36 (87.8%) had no renal replacement therapy, and 5 (12.2%) had renal replacement therapy.

Table 11:- Distribution of subjects according to renal replacement therapy among survivor and non-survivor

	Survivor		Non Survivor		P value
	N	%	N	%	
No	69	87.3%	36	87.8%	0.942
Yes	10	12.7%	5	12.2%	
Total	79	100%	41	100%	

P value 0.942, there was no statistically significant difference found between survivor and Non survivor with respect to renal replacement therapy.

Figure 13:- Graph showing Distribution of subjects according to renal replacement therapy among survivor and non-survivor



Distribution of subjects according to SOFA Score among survivor and non-survivor

Among 79 survivors included in the study, 46 (58.2%) had SOFA score between 1-5, 30 (38.0%) had SOFA score between 6-.10 and 3 (3.8%) had SOFA score between 11-15.

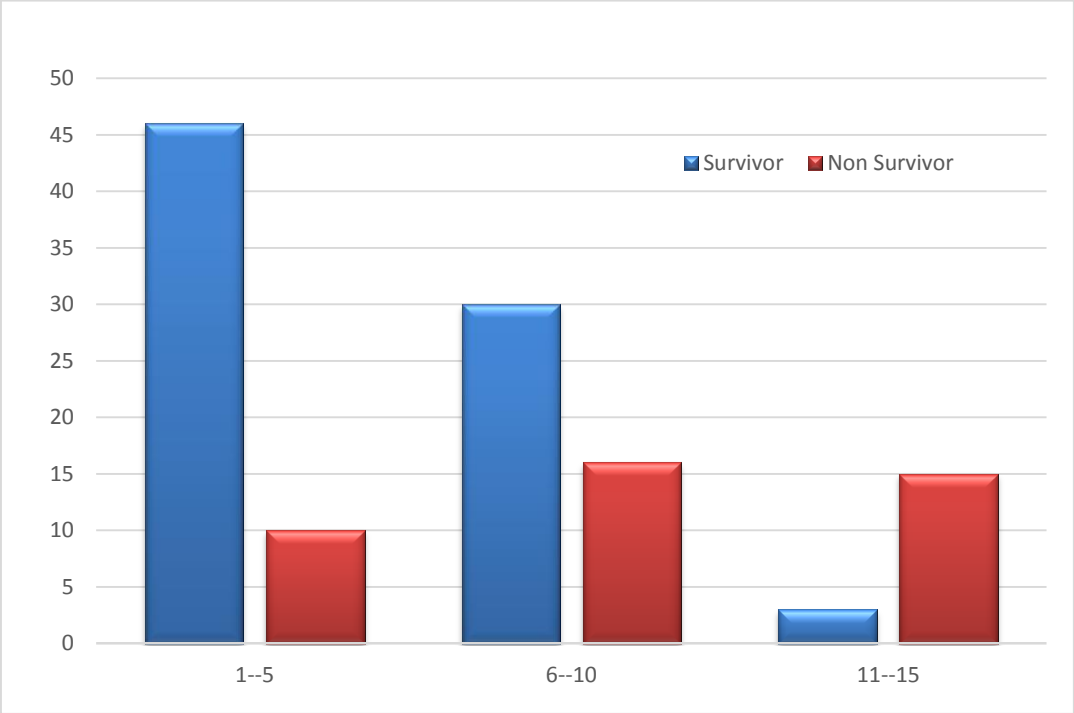
Among 41 non survivors included in the study, 10 (24.4%) had SOFA score between 1-5,16 (39.0%) had SOFA score between 6-.10 and 15 (36.6%) had SOFA score between 11-15.

Table 12:- Distribution of subjects according to SOFA Score among survivor and non-survivor

	Survivor		Non Survivor		P value
	N(79)	%	N(41)	%	
1-5	46	58.2%	10	24.4%	<0.001
6-10	30	38.0%	16	39.0%	
11-15	3	3.8%	15	36.6%	

P value <0.001, there was a statistically significant difference found between survivor and Non survivor with respect to SOFA Score.

Figure 14:- Graph showing Distribution of subjects according to SOFA Score among survivor and non-survivor



Comparison of blood pressure, pulse and GCS among survivor and non-survivor

Among all the patients included in the study, in survivors the mean pulse rate was 102, mean DBP was 70, mean SBP was 109 and mean GCS was 14. P= <0.001

Among all the patients included in the study, in non survivors the mean pulse rate was 115, mean DBP was 57, mean SBP was 91 and mean GCS was 12. P= <0.001

Table 13:- Comparison of blood pressure, pulse and GCS among survivor and non-survivor

	Survivor		Non Survivor		P value
	Mean	SD	Mean	SD	
Pulse(bpm)	102	13	115	16	<0.001
DBP (mm/hg)	70	15	57	10	<0.001
SBP (mm/hg)	109	32	91	19	<0.001
GCS	14	2	12	2	<0.001

There was a statistically significant difference found between survivor and non-survivor with respect to systolic blood pressure, diastolic blood pressure, pulse and GCS

Comparison of SOFA Score, RDW, NLR and MPV among survivor and non-survivor

Among all the patients included in the study, survivors had a mean SOFA score of 5, RDW of 14.3, NLR of 8.7 and MPV of 8.6. P= <0.001

Among all the patients included in the study, non survivors had a mean SOFA score of 9, RDW of 16.2, NLR of 12.09 and MPV of 10.40. P= <0.001

Table 14:- Comparison of SOFA Score, RDW, NLR and MPV among survivor and non-survivor

	Survivor		Non Survivor		P value
	Mean	SD	Mean	SD	
SOFA score	5	3	9	3	<0.001
RDW	14.3684	.6193	16.2049	.8050	<0.001
NLR	8.7975	.6471	12.0951	1.0435	<0.001
MPV	8.6532	.6435	10.4098	.7376	<0.001

There was a statistically significant difference found between survivor and non-survivor with respect to SOFA Score, RDW, NLR and MPV

Table 15:- Correlation of SOFA score with RDW, NLR and MPV

		SOFA score
RDW	Pearson Correlation	0.465**
	P value	<0.001
NLR	Pearson Correlation	0.318**
	P value	<0.001
MPV	Pearson Correlation	0.400**
	P value	<0.001

RDW had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.001 with a Pearson's coefficient of 0.465.

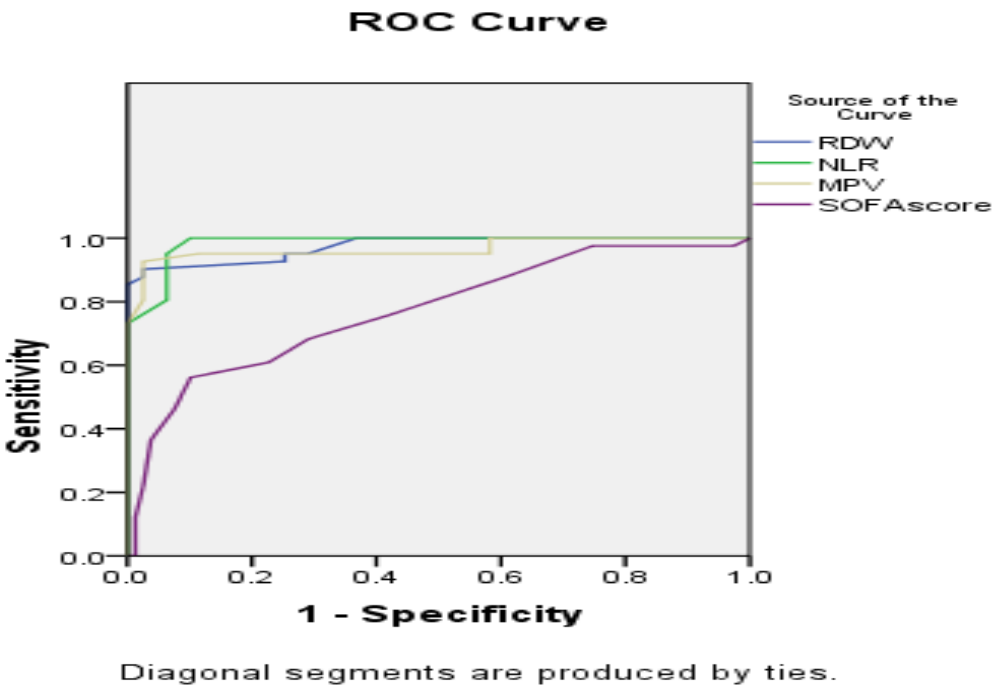
NLR had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.001 with a Pearson's coefficient of 0.318.

MPV had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.001 with a Pearson's coefficient of 0.400'

Table 16:- Comparison of SOFA score, RDW, NLR and MPV with respect to sensitivity and Specificity

	SOFA Score	RDW	NLR	MPV
Cut off value	>8	>15.2	>10.1	>9.4
Sensitivity	56.10	90.24	100.00	92.68
Specificity	89.87	97.47	89.87	97.47

Figure 15:- Graph showing the receiver operating characteristic (ROC) curves comparing red cell distribution width (RDW), Sequential Organ Failure Assessment (SOFA), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLR)



	AUC	95% CI	P Value
RDW	0.973	0.926 to 0.994	<0.001
NLR	0.984	0.943 to 0.998	<0.001
MPV	0.966	0.916 to 0.990	<0.001
SOFA Score	0.772	0.687 to 0.844	<0.001

Area under the curve for NLR was 0.984 (95% CI 0.943 to 0.998) with significant P value <0.001 which was best among the four parameters compared.

Area under the curve for RDW was 0.973 (95% CI 0.926 to 0.994) with significant P value <0.001 which was second best.

Area under the curve for MPV was 0.966 (95% CI 0.916 to 0.990) with significant P value <0.001.

Area under the curve for SOFA Score was 0.772 (95% CI 0.687 to 0.844) with significant P value <0.001.

DISCUSSION

DISCUSSION

Lee JH et al; published a retrospective study in 2018 which dealt with the utilization of MPV as a prognostic factor for the patients with pneumonia in the ICU. Although the essential investigation of the study is not entirely similar to ours, this study was considered as both of them contain the inspections which dealt with the comparison of SOFA score with MPV of both the survival as well as non-survival groups.[15]

The mean APACHE II score as well as was the mean SOFA score was calculated which were found to be 19.6 ± 6.5, and was 7.9 ± 2.9, respectively. When the isolated MPV and platelet count values are analyzed corresponding to the survival and non-survival groups at admission, it was found that it was devoid of significant difference in between the aforementioned blood indices and the survival as well as non-survival groups.

Contrastingly, our study reported a statistically significant difference between survivor and non-survivor with respect to SOFA score, and MPV. While the study by Lee JH et al; depicted 8.2±1.1 and 8.3±1.5 MPV readings to the survivor and nor survivor group, respectively generating a p value of 0.452, our study demonstrated a mean of 8.65$\pm$0.64 and 10.40$\pm$0.73 for the survivor and nor survivor group, respectively, clocking p value at <0.001.

Hui-Bing Zhang et al; published a study in 2016 which discussed about the utilization of red cell distribution width, platelet distribution width and neutrophil-lymphocyte count ratio as a factor for triage of sepsis. Although the study didn't specifically deal with survivors and non survivors, but its inclusion in our study was due to its primal objective vested in the observation and comparison of blood indices with traditional

parameters CRP and PCT for finding the prognosis of sepsis in patients with or without positive blood cultures.

In this study, the sensitivity, specificity, were calculated and analysis of ROC curves was done to compare the blood indices in patients with positive blood culture to those without. The Area under the ROC curve of each tested marker were as follows RDW (0.621), NLR (0.718) and the highest being PCT (0.829). While the study had not considered the potentiality of MPV as one of the comparative factors for the prognosis of sepsis, it had contemplated platelet distribution width (PDW) for the same. The Area under the ROC curve is (0.636). The p value for the same are as follows RDW (0.023), NLR (<0.001), PCT (<0.001) and PDW (0.010). [124]

Comparative analysis with our study in the terms of Area under the ROC curve for RDW, NLR and MPV demonstrates a similarity especially of NLR. In our study while the p value for RDW, NLR and MPV remain <0.001 denoting its significance, the Area under the ROC curve are as follows RDW (0.973), NLR (0.984) and MPV (0.966).

In a study by Martins EC et al; which dealt with the consideration of NLR in the estimation of early diagnosis of sepsis, the focus was on the early diagnosis of sepsis as it is one of the prime causes of hospitalization and mortality in adult intensive care units. The parameters studied are low cost and easy to implement by health services in low and middle income countries like ours.

In this study the ROC curve values of NLR, band neutrophils and total leukocytes are calculated and analyzed for their potentiality in successful sepsis prediction which were 0.62, 0.98 and 0.51 respectively. [125]

While our study had not considered the ROC curve values of band neutrophils and total leukocytes, the ROC curve values of NLR is almost same 0.984.

Rahul PN and Anita SP published a paper in the year 2018 which investigates the importance of MPV in severe sepsis. While the subjects in the study was divided upon the criteria of either being expired or shifted out of the ward, our study divided the subjects on the basis of being either survived or not survived.

They demonstrated that gender differences does not significantly influence either in shifting out or in the expiry of the patients, similarly our study too reported that there was a desolation in the difference found between survivor and Non survivor with respect to gender.

Coming to the diagnosis, the study by Rahul PN and Anita SP demonstrated that majority of the patients who were expired suffered from pneumonia. Similarly in our study, majority of the patients who were expired suffered from LRTI, ARDS. They found that there was a significant difference in MPV Day 1 between Expired and Shift out groups with a t value of 3.92 and a $p<0.01$. Also there was a significant difference in Highest MPV between Expired and Shift out groups. [126] Our study has similar findings with MPV of 8.6 among survivors and 10.4 among non survivors.

Gupta A and Gupta R published a study in the first quadrant of 2019 which speaks volumes about the prognostic implications of hematological indices in sepsis patients. In this study 117 patients were taken into the study and were analyzed for a period of 7 days.

The study showed that there was higher number of patients in male gender (56.41%) than there were females (43.58%). The predisposition of males was higher in both

survivor as well as non survivor groups (54.25%) and (62.21%) respectively. when compared to females (45.74%) and (45.74%) respectively. Similarly in our study, the male predisposition is higher when compared to females in both the survivor as well as non survivor groups although there was no statistical significance. The males in survivor and non survivor groups are 51.9% and 65.9% respectively. The females in survivor and non survivor groups are 48.1% and 34.1% respectively.

While this study reported a significant increase in the standard deviation of RDW in the non-survivor group, its significance for the total and survivor group of septic patients is not observed. A significant change in NLCR was observed in the survivor group, its significance for the non survivor group of septic patients is not observed [127]

Similarly, our study however demonstrated significance in the RDW, NLCR between survivors and non survivors group ($p<0.001$).

Coming to the other indices, significant differences in the mean and SD values of MPV, PDW and PLCR on observation day 1 and 7 was lacking which summarizes the dearth of major prognostic implication in patients with sepsis. Contrastingly, our study demonstrated significance ($p<0.001$) in the MPV in both survivors and well as non survivors group.

From all the above studies, we concluded that Red cell distribution width (RDW), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLCR) are quick, cost effective blood tests which have been shown to predict mortality and morbidity of sepsis. In our study, we had included patients age greater than 18 years of both the genders in which 38 (48.1%) survivors and 14 (34.1%) non survivors were female; and 41 (51.9%) survivors and 27 (65.9%) non survivors were male, there was

no statistically significant difference found between survivor and Non survivor with respect to age and sex. The incidence of sepsis was slightly higher among male patients compared to females. In our study the mortality rate in patients above 60 years of age was found to be the highest (75%) among all age groups. This is in correlation with many studies that have been conducted worldwide that have observed that there was an increased mortality rate among elderly patients diagnosed with sepsis. The most common presenting symptom among non survivors was fever followed by cough and altered sensorium. The most common source of infection was respiratory tract followed by urinary tract infections. This was partly in correlation with the study conducted by Mayr et al[21] respiratory tract infection accounted to the highest etiology of sepsis followed by bloodstream and site unspecified infections.

In survivors 69 (87.3%) had showed co- morbidity, and 10 (12.7%) had showed no co- morbidity and in non survivors 37 (90.2%) had showed co- morbidity, and 4 (9.8%) had showed no co- morbidity (P value 0.770), there was no statistically significant difference found between survivor and Non survivor with respect to co morbidities in our study.

The SOFA score was calculated with the available laboratory parameters during admission. The SOFA scores during admission correlated well with the outcome of the patients. Those patients with scores less than 5 had a better survival rate and short duration of hospital stay. Those patients with the SOFA scores above 10 had a high mortality rate. In the survivors group, SOFA scores more than 10 during admission had a prolonged duration of hospital stay and also developed complications. These patients needed vigorous intervention compared to those with a SOFA score of less than 10 during admission.

In survivors the mean of 5 had SOFA score, 14.3 had RDW, 8.7 had NLR and 8.6 had MPV (P= <0.001). In non survivors the mean of 9 had SOFA score, 16.2 had RDW, 12.09 had NLR and 10.4 had MPV (P= <0.001).

In sepsis patients when NLCR was cross matched with SOFA score, there was a strong and positive correlation shown in a similar way as RDW correlates with SOFA score at admission as well as with MPV.

SUMMARY

SUMMARY

- This prospective, analytical, comparative study was conducted in 120 patients of both sexes
- The age of patients ranged from 20 to 99 years. The patients in the study were divided into 4 age groups, viz., 20-39 years, between 40 to 59 years, between 60 to 79 years and 80 to 99 years. There were 11 patients (13.9%) survivors and 7 (17.1%) non survivors in between 20 to 39 years age group, 24 (30.4%) survivors and 17 (41.5%) non survivors in between 40 to 59 years age group, 29 (36.7%) survivors and 13 (31.7%) non survivors in between 60 to 79 years age group and 15 (19.0%) survivors and 4 (9.8%) non survivors in between 80 to 99 years of age group.
- Among all the patients included in the study, 38 (48.1%) survivors and 14 (34.1%) non survivors were female; and 41 (51.9%) survivors and 27 (65.9%) non survivors were male.
- Among all the patients included in the study, in survivors 62 (78.5%) had fever, 3 (3.8%) had headache, 35 (44.3%) had cough, 25 (31.6%) had breathlessness, 21 (26.6%) had altered sensorium, 10 (12.7%) had vomiting, (91.3%) had decreased urine output and 5 (6.3%) had abdominal pain.
- Among all the patients included in the study, in non survivors 31 (75.6%) had fever, 19 (46.3%) had cough, 18 (43.9%) had breathlessness, 18 (43.9%) had altered sensorium, 3 (7.3%) had vomiting, and 5 (12.2%) had abdominal pain.
- Among all the patients included in the study, in survivors 6 (7.6%) had acute GE, 8 (10.1%) had cellulitis, 46 (58.2%) had LRTI, 2 (2.5%) had LRTI+ ARDS, 7 (8.9%) had meningitis, 1 (1.3%) had neuroinfection and 9 (11.4%) had urosepsis.
- Among all the patients included in the study, in non survivors 1 (2.4%) had acute GE, 15 (36.6%) had LRTI, 13 (31.7%) had LRTI + ARDS, 2 (4.9%) had meningitis, and 10 (24.4%) had urosepsis.

- Among all the patients included in the study, in survivors 65 (82.3%) had no organism, 3 (3.8%) had acinetobacter species, 1 (1.3%) had AFB, 1 (1.3%) had candida albicans acinetobacter, 7 (8.9%) had E. Coli, 1 (1.3%) had Klebsiella oxytoca and 1 (1.3%) had Klebsiella pneumonia, Acinetobacter.
- Among all the patients included in the study, in non survivors 29 (70.7%) had no organism, 1 (2.4%) had Klebsiella pneumonia 4 (9.8) had acinetobacter species, 4 (9.8%) had E. Coli, 2 (4.9%) had klebsiella pneumonia, acinetobacter and 1 (2.4%) had pseudomonas.
- Among all the patients included in the study, in survivors 69 (87.3%) had showed co-morbidity, and 10 (12.7%) had showed no co- morbidity.
- Among all the patients included in the study, in non survivors 37 (90.2%) had showed co- morbidity, and 4 (9.8%) had showed no co- morbidity.
- Among all the patients included in the study, in survivors 50 (63.3%) had no ventilator support, and 29 (36.7%) had ventilator support.
- Among all the patients included in the study, in non survivors 1 (2.4%) had no ventilator support, and 40 (97.6%) had ventilator support.
- Among all the patients included in the study, in survivors 37 (46.8%) had no inotropic support, and 42 (53.2%) had inotropic support.
- Among all the patients included in the study, in non survivors 3 (7.3%) had no inotropic support, and 38 (92.7%) had inotropic support.
- Among all the patients included in the study, in survivors 69 (87.3%) had no renal replacement therapy, and 10 (12.7%) had renal replacement therapy.
- Among all the patients included in the study, in non survivors 36 (87.8%) had no renal replacement therapy, and 5 (12.2%) had renal replacement therapy.
- Among all the patients included in the study, in survivors 46 (58.2%) had SOFA score between 1-5, 30 (38.0%) had SOFA score between 6-.10 and 3 (3.8%) had SOFA score between 11-15.

- Among all the patients included in the study, in non survivors 10 (24.4%) had SOFA score between 1-5, 16 (39.0%) had SOFA score between 6-.10 and 15 (36.6%) had SOFA score between 11-15.
- RDW had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.0001 with a Pearson's coefficient of 0.465.
- NLR had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.0001 with a Pearson's coefficient of 0.318.
- MPV had a positive correlation with SOFA score. This correlation is statistically significant as the p value is < 0.0001 with a Pearson's coefficient of 0.400'
- Area under the curve for NLR was 0.984 (95% CI 0.943 to 0.998) with significant P value <0.001 which was best among the four parameters compared.
- Area under the curve for RDW was 0.973 (95% CI 0.926 to 0.994) with significant P value <0.001 which was second best.
- Area under the curve for MPV was 0.966 (95% CI 0.916 to 0.990) with significant P value <0.001.
- Area under the curve for SOFA Score was 0.772 (95% CI 0.687 to 0.844) with significant P value <0.001.

CONCLUSION

CONCLUSION

Various biomarkers are being evaluated for early diagnosis of sepsis. RDW, MPV, NLCR are some markers, which have been shown to predict mortality and morbidity of sepsis.

In our study, the efficiency of RDW, NLCR along with MPV as biomarkers of sepsis has been made and the correlation of the SOFA score with RDW, NLCR and MPV in predicting the outcome of patients has been studied.

In sepsis patients when SOFA score was cross matched with RDW, NLCR and MPV separately the increase in their values strongly and positively correlated with increase in SOFA score, thus elucidating the usefulness of RDW, NLCR and MPV as prognostic markers in the study of severity of sepsis and the outcome.

Red cell distribution width (RDW), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLCR) are quick, cost effective blood tests that can be done even in the resource stricken centers in India. Thus they may be helpful for the treating physician in careful monitoring and aggressive management of severe cases, thus reducing mortality and saving crucial lives.

LIMITATIONS

1. Since RDW, NLCR and MPV levels are affected by many conditions, their levels without other inflammatory indicators such as C-reactive protein, procalcitonin gamma-glutamyl transferase etc, may not give exact information about patients' inflammatory status.
2. Only the circulating neutrophil and lymphocyte counts were analyzed but the different subpopulations of the lymphocytes had not been explored.
3. Patients` underlying diseases could alter the NLCR levels. Age and comorbidities are associated with the severity of sepsis and mortality. Genuine report of co morbidity could not be acquired from the patients.
4. The time elapsed between the blood sampling and the measuring of RDW may significantly affect the RDW levels. Intra-day cell count variations also may be considered. All these necessitate future prospective clinical research.
5. The study is a prospective observational study in a single institution in a short duration with less sample size of 120. For validation of the results, the sample size should be large.

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ANNEXURES

INFORMED CONSENT FORM

PATIENT INFORMATION SHEET

Name of the Project	Prognostic importance of Red Cell Distribution Width, Mean Platelet Volume and Neutrophil Lymphocyte Count Ratio in patients with Sepsis
Name of the Principal investigator	Dr. Minni Meka
Name of the Organization	Sri Devaraj Urs Academy of Higher Education and Research , Tamaka, Kolar

SUBJECT'S NAME: AGE: HOSPITAL NUMBER:

Purpose of the study: Septic shock is a major healthcare problem, affecting millions of people worldwide. it has been shown that prompt diagnosis and early administration of antibiotic therapy considerably improves the outcomes of septic patients.

Despite advances in modern medicine, sepsis remains the primary cause of death. Prediction of outcome from disease has become an essential component of health science. So, various scoring systems have been developed to predict outcome of sepsis. There is no perfect model of severity score to predict mortality. Red cell distribution width (RDW), mean platelet volume (MPV) and neutrophil lymphocyte count ratio (NLCR) are quick, cost effective blood tests that can be done even in the resource stricken centres in India. Although readily available their prognostic value in patients with sepsis has not been fully explored.

In view of the paramount importance of timely diagnosis and the unmet need for predictive tools, we venture to study the behaviour of red cell distribution width, mean platelet volume and neutrophil lymphocyte count ratio and their prognostic importance in patients with sepsis.

Voluntary Participation: Your participation in this study is entirely voluntary. There is no compulsion to participate in this study. You will be in no way affected if you do not wish to participate in this study. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study. Further you are at liberty to withdraw from the study at any time. We assure you that your withdrawal will not affect your treatment by the concerned physician in any way.

Procedure: We will be collecting a small volume of blood (6ml) from your arm. The sample will be used for pathological and biochemical testing.

Duration: The research takes place over a period of 1 year.

Risks: No drug will be tested on you. Blood will be collected using a sterile and disposable needle and syringe.

Confidentiality: All information collected from you will be kept confidential and will not be disclosed to anyone except if required by law. Only the project investigators will have access to identification details.

Sharing the results: The results obtained from this study will be published in scientific or medical journals or medical conferences.

We will not compel you at any time during this process; also, we would greatly appreciate your cooperation in the study. We would like to get your consent to participate in the study.

For any information you are free to contact the investigator. This study has been reviewed and approved by the Institutional Ethics Committee and has been started only after their formal approval. This document will be stored in the safe locker of Medicine department and a copy given to you for your information.

For any further clarification you can contact the study investigator:

Dr. Minni Meka (Post graduate)

Department of General Medicine

SDUMC , KOLAR

Contact No : 8951598258

CERTIFICATE OF CONSENT

Declaration by the participant:

I have been invited to take part in this research study. I have been asked to participate in this study because I satisfy the eligibility criteria.

I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study.

I have had the opportunity to ask questions I might have about the testing, the procedure, the associated risk, alternatives and limitations and any questions that I asked have been answered to my satisfaction by a qualified health professional.

I understand that I remain free to withdraw from the study at any time and this will not change my future care.

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for medical research, test validation or education as long as my privacy is maintained.

Subject name:

(Parents / Guardians name):

Date:

Signature / Thumb impression:

ತಿಳಿವಳಿಕೆಯ ಸಮ್ಮತಿ ನಮೂನೆ

ರೋಗಿಯ ಮಾಹಿತಿ ನಮೂನೆ

ಯೋಜನೆಯ ಹೆಸರು	ಸೆಪ್ಸಿಸ್ ಹೊಂದಿರುವ ರೋಗಿಗಳಲ್ಲಿ ಕೆಂಪು ಕೋಶ ವಿತರಣೆ ಅಗಲದ, ಪ್ಲೇಟ್ಲೆಟ್ ಪರಿಮಾಣ ಮತ್ತು ನ್ಯೂಟ್ರೋಫಿಲ್ ಲಿಂಫೋಸೈಟ್ ಎಣಿಕೆ ಗಣನ ಅನುಪಾತದ ಪ್ರಜ್ಞಾವಿಸ್ತಾರಕ ಪ್ರಾಮುಖ್ಯತೆ
ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿ ಹೆಸರು	ಡಾ. ಮಿನ್ನಿ ಮೆಕಾ
ಸಂಸ್ಥೆಯ ಹೆಸರು	ಶ್ರೀ ದೇವರಾಜ್ ಉರ್ಸ್ ವೈದ್ಯಕೀಯ ಕಾಲೇಜು ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರ, ತಮಕ, ಕೋಲಾರ

ಪಾಲ್ಗೊಳ್ಳುವವರ ಹೆಸರು: ವಯಸ್ಸು: ಸಂಖ್ಯೆ:

ಅಧ್ಯಯನದ ಉದ್ದೇಶ: ಸೆಪ್ಟಿಕ್ ಆಘಾತವು ವಿಶ್ವದಾದ್ಯಂತ ಲಕ್ಷಾಂತರ ಜನರ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುವ ಪ್ರಮುಖ ಆರೋಗ್ಯ ಸಮಸ್ಯೆಯಾಗಿದೆ. ಪ್ರತಿಜೀವಕ ಚಿಕಿತ್ಸೆಯ ಪ್ರಾಂಪ್ಟ್ ರೋಗನಿರ್ಣಯ ಮತ್ತು ಆರಂಭಿಕ ಆಡಳಿತವು ಸೆಪ್ಟಿಕ್ ರೋಗಿಗಳ ಫಲಿತಾಂಶಗಳನ್ನು ಗಣನೀಯವಾಗಿ ಸುಧಾರಿಸುತ್ತದೆ ಎಂದು ತೋರಿಸಲಾಗಿದೆ.
ಆಧುನಿಕ ಔಷಧಗಳಲ್ಲಿನ ಪ್ರಗತಿಗಳ ಹೊರತಾಗಿಯೂ, ಸೆಪ್ಸಿಸ್ ಮರಣದ ಮುಖ್ಯ ಕಾರಣವಾಗಿದೆ. ರೋಗದಿಂದ ಬರುವ ಫಲಿತಾಂಶದ ಭವಿಷ್ಯವು ಆರೋಗ್ಯ ವಿಜ್ಞಾನದ ಒಂದು ಪ್ರಮುಖ ಅಂಶವಾಗಿದೆ. ಆದ್ದರಿಂದ, ಸೆಪ್ಸಿಸ್ನ ಫಲಿತಾಂಶವನ್ನು ಊಹಿಸಲು ವಿವಿಧ ಸ್ಕೋರಿಂಗ್ ವ್ಯವಸ್ಥೆಗಳನ್ನು ಅಭಿವೃದ್ಧಿಪಡಿಸಲಾಗಿದೆ. ಮರಣದಂಡನೆಯನ್ನು ಊಹಿಸಲು ತೀವ್ರತೆಯ ಸ್ಕೋರ್ನ ಪರಿಪೂರ್ಣ ಮಾದರಿ ಇಲ್ಲ. ಕೆಂಪು ಕೋಶ ವಿತರಣೆ ಅಗಲ, ಪ್ಲೇಟ್ಲೆಟ್ ಪರಿಮಾಣ ಮತ್ತು ನ್ಯೂಟ್ರೋಫಿಲ್ ಲಿಂಫೋಸೈಟ್ ಎಣಿಕೆ ಅನುಪಾತ ಅರ್ಥೈಸಿಕೊಳ್ಳುವುದು ತ್ವರಿತ, ವೆಚ್ಚದ ಪರಿಣಾಮಕಾರಿ ರಕ್ತ ಪರೀಕ್ಷೆಗಳು, ಇದು ಭಾರತದಲ್ಲಿನ ಸಂಪನ್ಮೂಲ ಬಾಧಿತ ಕೇಂದ್ರಗಳಲ್ಲಿ ಸಹ ಮಾಡಬಹುದು. ಸೆಪ್ಸಿಸ್ ಹೊಂದಿರುವ ರೋಗಿಗಳಲ್ಲಿ ಅವರ ಪ್ರಜ್ಞಾವಿಸ್ತಾರಕ ಮೌಲ್ಯವು ಸುಲಭವಾಗಿ ಪರಿಶೋಧಿಸಲ್ಪಟ್ಟಿಲ್ಲವಾದರೂ ಸಂಪೂರ್ಣವಾಗಿ ಪರಿಶೋಧಿಸಲಾಗಿಲ್ಲ.

ಸಕಾಲಿಕ ರೋಗನಿರ್ಣಯದ ಪ್ರಾಮುಖ್ಯತೆ ಮತ್ತು ಭವಿಷ್ಯಸೂಚಕ ಪರಿಕರಗಳ ಅಗತ್ಯವಿಲ್ಲದ ಅಗತ್ಯತೆಯ ದೃಷ್ಟಿಯಿಂದ, ಕೆಂಪು ಕೋಶ ವಿತರಣೆ ಅಗಲದ ನಡವಳಿಕೆಯನ್ನು ಅಧ್ಯಯನ ಮಾಡಲು ನಾವು ಪ್ರಯತ್ನಿಸುತ್ತೇವೆ, ಪ್ಲೇಟ್ಲೆಟ್ ಪರಿಮಾಣ ಮತ್ತು ನ್ಯೂಟ್ರೋಫಿಲ್ ಲಿಂಫೋಸೈಟ್ ಎಣಿಕೆ ಅನುಪಾತ ಮತ್ತು ಸೆಪ್ಸಿಸ್ನ ರೋಗಿಗಳಲ್ಲಿ ಅವರ ಪ್ರಾಗ್ನೊಸ್ಟಿಕ್ ಪ್ರಾಮುಖ್ಯತೆಗಳನ್ನು ಅಧ್ಯಯನ ಮಾಡಲು ನಾವು ಪ್ರಯತ್ನಿಸುತ್ತೇವೆ.

ಸ್ವಯಂಪ್ರೇರಿತ ಭಾಗವಹಿಸುವಿಕೆ: ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆ ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂಪ್ರೇರಿತವಾಗಿರುತ್ತದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಯಾವುದೇ ನಿರ್ಬಂಧವಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಯಾವುದೇ ರೀತಿಯಲ್ಲಿ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನೀವು ಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದ ಒಪ್ಪಿಕೊಳ್ಳುವುದಾದರೆ ಮಾತ್ರ ಹೆಬ್ಬೆರಳು ಅನಿಸಿಕೆಗೆ ನೀವು ಸಹಿ / ನೀಡಬೇಕಾಗಿದೆ. ಮತ್ತಷ್ಟು ನೀವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನದಿಂದ ಹಿಂಪಡೆಯಲು ಸ್ವತಂತ್ರರಾಗಿರುತ್ತಾರೆ. ನಿಮ್ಮ ಹಿಂತೆಗೆದುಕೊಳ್ಳುವಿಕೆಯು ನಿಮ್ಮ ಚಿಕಿತ್ಸೆಯನ್ನು ಯಾವುದೇ ರೀತಿಯಲ್ಲಿ ಯಾವುದೇ ವೈದ್ಯರ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ ಎಂದು ನಾವು ನಿಮಗೆ ಭರವಸೆ ನೀಡುತ್ತೇವೆ.

ವಿಧಾನ: ನಿಮ್ಮ ತೋಳಿನಿಂದ ನಾವು ಸ್ವಲ್ಪ ಪ್ರಮಾಣದ ರಕ್ತವನ್ನು (6 ಮಿಲಿ) ಸಂಗ್ರಹಿಸುತ್ತೇವೆ. ಮಾದರಿ ರೋಗ ಮತ್ತು ಜೈವಿಕ ಪರೀಕ್ಷೆಗಾಗಿ ಬಳಸಲಾಗುತ್ತದೆ.

ಅವಧಿ: ಸಂಶೋಧನೆಯು 1 ವರ್ಷ ಅವಧಿಯವರೆಗೆ ನಡೆಯುತ್ತದೆ.

ಅಪಾಯಗಳು: ನಿಮ್ಮ ಮೇಲೆ ಯಾವುದೇ ಔಷಧಿ ಪರೀಕ್ಷಿಸಲಾಗುವುದಿಲ್ಲ. ರಕ್ತವನ್ನು ಒಂದು ಬರಡಾದ ಮತ್ತು ಬಿಸಾಡಬಹುದಾದ ಸೂಜಿ ಮತ್ತು ಸಿರಿಂಜ್ ಬಳಸಿ ಸಂಗ್ರಹಿಸಲಾಗುತ್ತದೆ.

ಗೋಪ್ಯತೆ: ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಿದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿರಿಸಲಾಗುವುದು ಮತ್ತು ಕಾನೂನಿನ ಅಗತ್ಯವಿದ್ದರೆ ಹೊರತುಪಡಿಸಿ ಯಾರಿಗಾದರೂ ಅದನ್ನು ಬಹಿರಂಗಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ಯೋಜನೆಯ ಶೋಧಕರು ಮಾತ್ರ ಗುರುತಿನ ವಿವರಗಳಿಗೆ ಪ್ರವೇಶವನ್ನು ಹೊಂದಿರುತ್ತಾರೆ.

ಫಲಿತಾಂಶಗಳನ್ನು ಹಂಚಿಕೆ: ಈ ಅಧ್ಯಯನದಿಂದ ಪಡೆದ ಫಲಿತಾಂಶಗಳನ್ನು ವೈಜ್ಞಾನಿಕ ಅಥವಾ ವೈದ್ಯಕೀಯ ನಿಯತಕಾಲಿಕಗಳಲ್ಲಿ ಅಥವಾ ವೈದ್ಯಕೀಯ ಸಮಾವೇಶಗಳಲ್ಲಿ ಪ್ರಕಟಿಸಲಾಗುತ್ತದೆ.

ಈ ಪ್ರಕ್ರಿಯೆಯಲ್ಲಿ ನಾವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ನಿಮ್ಮನ್ನು ಒತ್ತಾಯಿಸುವುದಿಲ್ಲ; ಸಹ, ನಾವು ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮ ಸಹಕಾರವನ್ನು ಬಹಳವಾಗಿ ಶ್ಲಾಘಿಸುತ್ತೇವೆ. ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನಿಮ್ಮ ಒಪ್ಪಿಗೆಯನ್ನು ಪಡೆಯಲು ನಾವು ಬಯಸುತ್ತೇವೆ.

ಯಾವುದೇ ಮಾಹಿತಿಗಾಗಿ ನೀವು ತನಿಖೆದಾರನನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತವಾಗಿರುತ್ತೀರಿ. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೀತಿಶಾಸ್ತ್ರ ಸಮಿತಿಯಿಂದ ಪರಿಶೀಲಿಸಲಾಗಿದೆ ಮತ್ತು ಅನುಮೋದಿಸಲಾಗಿದೆ ಮತ್ತು ಅವರ ಔಪಚಾರಿಕ ಅನುಮೋದನೆಯ ನಂತರ ಮಾತ್ರ ಪ್ರಾರಂಭಿಸಲಾಗಿದೆ. ಈ ಡಾಕ್ಯುಮೆಂಟ್ ಅನ್ನು ಮೆಡಿಸಿನ್ ಇಲಾಖೆಯ ಸುರಕ್ಷಿತ ಲಾಕರ್ನಲ್ಲಿ ಮತ್ತು ನಿಮ್ಮ ಮಾಹಿತಿಗಾಗಿ ನಿಮಗೆ ನೀಡಿದ ಪ್ರತಿಯನ್ನು ಸಂಗ್ರಹಿಸಲಾಗುತ್ತದೆ.

ಮತ್ತಷ್ಟು ಸ್ಪಷ್ಟೀಕರಣಕ್ಕಾಗಿ ನೀವು ಅಧ್ಯಯನ ಶೋಧಕವನ್ನು ಸಂಪರ್ಕಿಸಬಹುದು:
ಡಾ. ಮಿನ್ನಿ ಮೆಕಾ (ಸ್ನಾತಕೋತ್ತರ ಪದವಿ)
ಜನರಲ್ ಮೆಡಿಸಿನ್ ಇಲಾಖೆ
SDUMC, ಕೋಲಾರ್
ಸಂಪರ್ಕ ಸಂಖ್ಯೆ: 8951598258

ಪರಿಶೀಲನೆ ಪ್ರಮಾಣೀಕರಣ

ಪಾಲ್ಗೊಳ್ಳುವವರ ಘೋಷಣೆ:

ಈ ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳಲು ನನಗೆ ಆಹ್ವಾನಿಸಲಾಗಿದೆ. ನಾನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಪಾಲ್ಗೊಳ್ಳುವಂತೆ ಕೇಳಿದೆ ಏಕೆಂದರೆ ನಾನು ಅರ್ಹತಾ ಮಾನದಂಡಗಳನ್ನು ಪೂರೈಸುತ್ತೇನೆ.

ನಾನು ಓದಿದ್ದೇನೆ ಅಥವಾ ನನಗೆ ಓದುತ್ತಿದ್ದೇನೆ ಮತ್ತು ಅಧ್ಯಯನದ ಉದ್ದೇಶ, ಬಳಸಲಾಗುವ ಕಾರ್ಯವಿಧಾನ, ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ನನ್ನ ಪಾಲ್ಗೊಳ್ಳುವಿಕೆಗೆ ಸಂಬಂಧಿಸಿರುವ ಲಾಭ ಮತ್ತು ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗಪಡಿಸುವ ಮಾಹಿತಿಯ ಸ್ವರೂಪವನ್ನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ಪರೀಕ್ಷೆ, ಕಾರ್ಯವಿಧಾನ, ಸಂಬಂಧಿತ ಅಪಾಯ, ಪರ್ಯಾಯಗಳು ಮತ್ತು ಮಿತಿಗಳನ್ನು ನಾನು ಹೊಂದಿರಬಹುದಾದ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ನನಗೆ ಅವಕಾಶವಿದೆ ಮತ್ತು ಯೋಗ್ಯ ಆರೋಗ್ಯ ವೃತ್ತಿಪರರಿಂದ ನನ್ನ ತೃಪ್ತಿಗೆ ನಾನು ಕೇಳಿದ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳಿಗೆ ಉತ್ತರ ನೀಡಲಾಗಿದೆ.

ನಾನು ಯಾವ ಸಮಯದಲ್ಲಾದರೂ ಈ ಅಧ್ಯಯನದಿಂದ ಹಿಂದೆಗೆದುಕೊಳ್ಳಲು ಮುಕ್ತವಾಗಿರುತ್ತೇನೆ ಮತ್ತು ಇದು ನನ್ನ ಮುಂದಿನ ಕಾಳಜಿಯನ್ನು ಬದಲಿಸುವುದಿಲ್ಲ ಎಂದು ನಾನು ಅರ್ಥಮಾಡಿಕೊಂಡಿದ್ದೇನೆ.

ನಾನು, ಈ ಗೌಪ್ಯತೆ ನಿರ್ವಹಿಸಲ್ಪಡುವವರೆಗೆ ವೈದ್ಯಕೀಯ ಸಂಶೋಧನೆ, ಪರೀಕ್ಷೆ ಮೌಲ್ಯಮಾಪನ ಅಥವಾ ಶಿಕ್ಷಣಕ್ಕಾಗಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹ ಮತ್ತು ಪ್ರಕಟಣೆಯನ್ನು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಳ್ಳುತ್ತೇನೆ ಮತ್ತು ಒಪ್ಪುತ್ತೇನೆ.

ರೋಗಿಯ ಹೆಸರು:
(ಪಾಲಕರು / ಪೋಷಕರ ಹೆಸರು):
ದಿನಾಂಕ:
ಸಹಿ / ಹೆಬ್ಬೆರಳು ಗುರುತು:

IEC CERTIFICATE

SDUAHER

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH

SRI DEVARAJ URS MEDICAL COLLEGE

Tamaka, Kolar

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No. SDUMC/KLR/IEC/08 /2017-18 Date: 29-11-2017

CERTIFICATE

This is to certify that the ethics committee of Sri Devaraj Urs Medical College, Kolar in its meeting conducted on **29-11-2017** has unanimously approved the synopsis for the dissertation entitled **"Prognostic importance of red cell distribution width, Mean platelet volume and neutrophil lymphocyte count ratio in patients with sepsis"** to be submitted to Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, by **Dr.Minni Meka,** Postgraduate student in the department of **General Medicine** at Sri Devaraj Urs Medical College, Kolar

Member Secretary
Institutional Ethics Committee
SDUMC, Tamaka Kolar

Member Secretary
Institutional Ethics Committee
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Tamaka, Kolar,

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PROFORMA

PROGNOSTIC IMPORTANCE OF RED CELL DISTRIBUTION WIDTH, MEAN PLATELET VOLUME AND NEUTROPHIL LYMPHOCYTE COUNT RATIO IN PATIENTS WITH SEPSIS

Case no:	Date:
Name:	UHID no:
Age: Gender:	Address:

- HISTORY OF PRESENTING ILLNESS:

- PAST MEDICAL HISTORY: HTN: ☐ DM: ☐
  Others:

- PERSONAL HISTORY: Smoking: ☐ Alcohol intake: ☐

GENERAL EXAMINATION:

	Day 1	Day 2	Day 3	Day 4	Day 5
Pulse rate					
Blood Pressure					
GCS					

CVS-

RS-

PA-

CNS-

DIAGNOSIS-

INOTROPIC SUPPORT: ☐ VENTILATORY SUPPORT: ☐

RENAL REPLACEMENT THERAPY: ☐

OUTCOME: DISCHARGE: ☐ DEATH: ☐

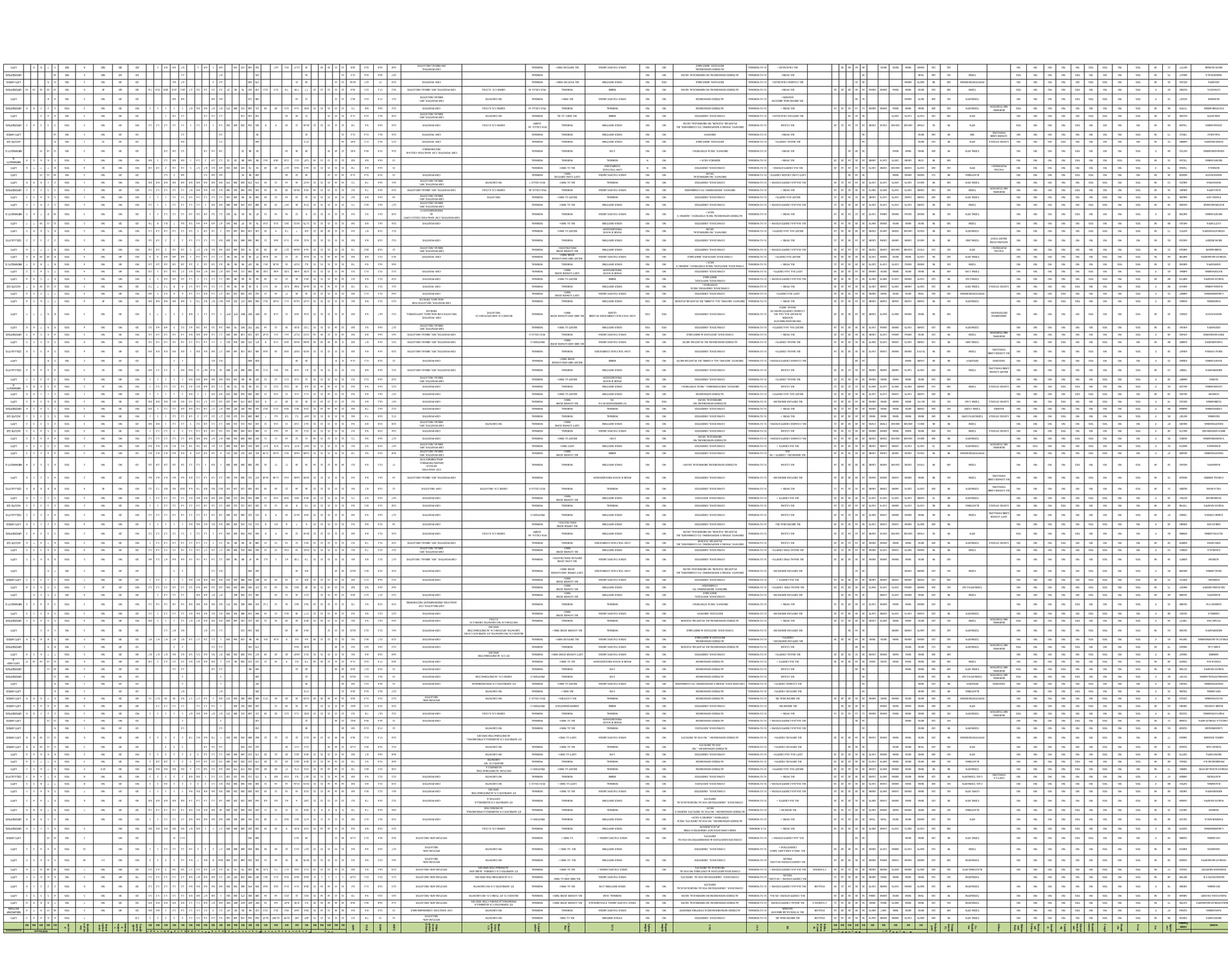
Investigations	Day 1	Day 2	Day 3	Day 4	Day 5
Hemoglobin					
MCV					
RDW					
MPV					
TLC Neutrophils- Lymphocytes-					
PLATELET COUNT					
BLOOD UREA					
S. CREATININE					
S. BILIRUBIN					
URINE OUTPUT					

CXRAY:
CULTURES:
USG/other scans (if any):

SOFA score	Day 1	Day 2	Day 3	Day 4	Day 5

SIGNATURE OF GUIDE

MASTER CHART



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