"MICROALBUMINURIA AS A BIOMARKER OF SEPSIS AND ITS PROGNOSTIC SIGNIFICANCE IN CRITICALLY ILL PATIENTS – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled **"MICROALBUMINURIA AS A BIOMARKER OF SEPSIS AND ITS PROGNOSTIC SIGNIFICANCE IN CRITICALLY ILL PATIENTS – A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0113014.**

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LIST OF ABBREVIATIONS USED

/Cumm	-	Per cubic millimeter
◦C	-	Degree centigrade
µg	-	Micrograms
^{0}F	-	Degree fahreinheit
ACCP	-	American College of Chest Physicians
ACR	-	Albumin to creatinine ratio
AIDS	-	Aquired immunodeficiency syndrome
ALI	-	Acute Lung Injury
ANP	-	Atrial natriuretic peptide
APACHE II	-	Acute Physiology and Chronic Health Evaluation II
APC	-	Activated Protein C
ARDS	-	Adult Respiratory Distress Syndrome
ATS	-	American Thoracic Society
BC	-	Before Christ
BP	-	Blood pressure
CARS	-	Counter inflammatory response syndrome
CDC	-	Centers for Disease Control
CI	-	Confidence interval
COPD	-	Chronic obstructive pulmonary disease
CORTICUS	-	Corticosteroid Therapy of Septic Shock
CRP	-	C-reactive protein
CT	-	Computed tomography
CVVH	-	Continuous veno venous haemofiltration
CVVHD	-	Continuous veno venous haemodialysis

DIC	-	Disseminated intravascular coagulation
DKA	-	Diabetic ketoacidosis
EC	-	Emergency centre
ECG	-	Electrocardiogram
ED	-	Emergency department
ESICM	-	European Society of Intensive Care Medicine
ESR	-	Erythrocyte sedimentation rate
GCS	-	Glasgow coma scale
GI	-	Gastrointestinal
gm	-	Grams
H/o	-	History of
HIV	-	Acute retroviral syndrome
i.e.	-	That is
ICD-9-CM	-	International Classification of Diseases, Ninth Revision, Clinical Modification
ICU	-	Intensive care unit
IHI	-	Institute for Healthcare Improvement
IL	-	Interleukin
IRO	-	Insult infection, Response, Organ dysfunction
IV	-	Intravenous
kg	-	Kilograms
L	-	Liter
MAP	-	Mean arterial pressure
mg	-	Milligrams
MICU	-	Medical intensive care unit

min	-	Minutes
mL	-	Milliliter
mls/Kg	-	Millilitres per kilograms
mm Hg	-	Millimeters of mercury
mm^3	-	Cubic millimeter
mmol/L	-	Millimole per liter
MODS	-	Multiple organ dysfunction syndrome
mol/L	-	Mole per liter
MRI	-	Magnetic resonance imaging
n	-	Total number
NF-κB	-	Nuclear Factor Kappa B
NPV	-	Negative predictive value
p	-	Probability
PCT	-	Procalcitonin
PIRO	-	Predisposition, Insult infection, Response, Organ dysfunction
PPV	-	Positive predictive value
ProADM	-	Pro-adrenomedullin
PSP	-	Pancreatic stone protein
reg	-	Regenerating protein
SAPS	-	Simplified Acute Physiology Score
SCCM	-	Society of Critical Care Medicine
Scvo2	-	Central Venous Oximetry Catheter
SD	-	Standard deviation
SIRS	-	Systemic inflammatory response syndrome

SIS	-	Surgical Infection Society
SOFA	-	Sequential organ failure assessments
SSC	-	Surviving Sepsis Campaign
sTREM-1	-	Soluble triggering receptor expressed on myeloid cells-1
suPAR	-	Soluble urokinase-type plasminogen activator receptor
TNF	-	Tumour necrosis factor
TNM	-	Tumor node metastasis
UACR	-	Urine albumin to creatinine ratio
US	-	United States
vs	-	Versus
WBC	-	White blood cell
WW II	-	World War II
µmol/L	-	Micromole per litre

ABSTRACT

Background and objectives

There is no single biomarker which can serve as the diagnostic parameter in the diagnosis of sepsis among the patients with SIRS. This study was aimed to evaluate the role of microalbuminuria as a biomarker of sepsis and also to predict ICU mortality.

Methodology

This one year cross sectional study was done from January 2014 to December 2014 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Based on ACCP and SCCM criteria, a total of 65 patients with diagnosis of SIRS enrolled and evaluated for the presence of microalbuminuria at admission and 24 hours after admission.

Results

Most of the patients were males (63.08%) and male to female ratio was 1.70:1. The commonest age group was between 41 to 50 years (27.69%) and the mean age was 51.12 ± 15.87 years. Fever was the common clinical presentation (95.38%). Diagnosis of severe sepsis was noted in 58.46% of the patients. Mortality was note din 56.92% of the patients and length of hospital stay was from 4-7 days in most of the patients (41.54%). UACR at admission was >0.20 in 92.31% of the patients and at 24 hours after admission it was >0.20 in 87.69% of the patients. UACR of >0.20 at admission showed 100% sensitivity in predicting sepsis (83.33% specificity, 98.33% PPV, 100% NPV with positive likelihood ratio of 6) and similar sensitivity pattern was noted with regard to 24 hours

UACR ($p<0.001$). The mean UACR at admission in patients with sepsis was significantly high at admission as well as at 24 hours after admission ($p<0.050$). With regard to mortality, sensitivity of > 0.20 UACR at admission in predicting mortality was 100% with 17.86% specificity, 61.67% PPV and 100% NPV and the positive likelihood ratio was 1.22 which was nearly same for values of UACR at 24 hours after admission. No association was found between length of hospital stay and UACR ($p>0.050$).

Conclusion and interpretation

Microalbuminuria (UACR >0.20) is a reliable biomarker in the determination of sepsis in patients admitted with SIRS but has limited ability in predicting ICU mortality.

Keywords

Microalbuminuria; Sepsis; Systemic inflammatory response syndrome; Urine albumin creatinine ratio;

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INTRODUCTION

The uncontrolled inflammatory response results in systemic inflammatory response syndrome (SIRS). In some individuals this severe inflammatory response is down-regulated; in others it escapes control. In 1992 a consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine (ACCP/ SCCM) proposed a constellation of clinical signs by which SIRS would be recognised.[1] These include tachypnoea, fever or hypothermia, tachycardia and leucocytosis or leukopaenia with a 'left shifted' differential white cell count (increased immature polymorphonucleocytes). It is proposed that every severe insult to the body produces a response with pro- and anti-inflammatory components which together dictates the course of the illness.[2]

SIRS is defined as two or more of Fever >38◦C or < 36◦C; Heart rate >90 beats per minute; Respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg; and Abnormal white blood cell count (>12,000/mm3 or <4,000/ mm3 or >10% bands).[1]

Sepsis represents a continuum of illness due to systemic inflammation caused by an infection that requires prompt recognition and treatment. Sepsis complicated by organ dysfunction is referred to as ''severe sepsis,'' while sepsis complicated by hypotension refractory to adequate volume resuscitation in the absence of an alternate cause has been termed ''septic shock".[3]

In the US alone, the incidence of severe sepsis is over 700,000 annually with an estimated 30% mortality.[4] This represents over 450,000 emergency centre (EC)

visits per year. While some research has been devoted to the study of sepsis in developing countries, its epidemiology in these countries remains poorly described. Despite this, the morbidity and mortality of sepsis in low- and middle-income countries are believed to be disproportionately high, given environmental degradation, widespread malnutrition, and higher rates of bacterial, parasitic, and HIV infection.[5]

Diagnosing sepsis early is vital for patient management and outcome, as early institution of appropriate therapy can be life-saving for the patient. The gold standard for diagnosis of sepsis is the isolation of causative organism in the culture of appropriate body fluids or tissue, which usually takes more than 24 hours causing delay in the initiation of targeted therapy which in turn impacts outcome.[6] For this reason, the search for early marker of sepsis continues.

Currently, there is neither gold standard for diagnosing infection early nor the validated biomarker for the prediction of infection. Though blood cultures processed with standard microbiologic techniques are a frequent diagnostic step, their likelihood of returning with the pathogen of interest depends on a variety of factors, including prior antibiotic therapy. Delays in empiric treatment for sepsis and bacteremia increase mortality as well as length of stay and cost. Making timely recognition of infection and initiation of appropriate therapy is an important goal. Standard blood culture techniques require time with results typically not available for at least 24–48 hours, highlighting the need for rapid diagnosis and risk stratification where biomarkers could be of use.[7]

There have been many attempts to augment clinical decision making with diagnostic tests to increase sensitivity and specificity when diagnosing and treating sepsis and bacteremia. Initial studies employed fever and leukocytosis to define sepsis,[1] though these tests were nonspecific. Subsequent studies focused on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to help in the diagnostic algorithm but suffered from lack of specificity.[7]

As knowledge of sepsis evolved, it became evident that not only direct pathogen effects but also an exuberant inflammatory host response was responsible for the deleterious clinical and laboratory abnormalities. Sepsis is a systemic inflammatory syndrome affecting all organ systems, and biomarkers have focused on a number of pathogen and host responses, including cytokines, cell markers, receptor biomarkers, coagulation, vascular endothelial damage, vasodilation, organ dysfunction, acute phase protein markers, and other systems. Sepsis provokes a systemic host response involving hundreds of mediators that could be potentially used as biomarkers for both diagnosis and prognosis.[8] A recent review detailed nearly 180 biomarkers that have been evaluated including IL-6, IL-8, lactate, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and procalcitonin (PCT).[9] PCT has been the most studied and felt to hold the most promise.[7]

India, with population of 1.2 billion, has one of the highest infectious disease burdens in the world.[7] While systemic data on presentations of acute febrile illness are lacking, 12% of adults (range 1–51%) of those presenting with acute febrile illness will have bacteremia.[10] While sepsis is not interchangeable with bloodstream infections, the majority of research has been done on sepsis as a syndrome and will be evaluated in this review. Availability of diagnostic assays is variable in India,[11]

making diagnosis of these common infections even more difficult. There is great interest in developing decision tools that utilize biomarkers to help aid the rapid diagnosis of bacterial infections. Additionally, due to rising antibiotic resistance on the Indian subcontinent, biomarkers that help with antibiotic stewardship are equally needed. There have been numerous studies evaluating PCT in different clinical scenarios, including sepsis, though the majority of these studies have been in the United States and Europe; there is great opportunity for well-designed studies evaluating biomarkers for sepsis in India.[7]

The host defense in sepsis involves potent inflammatory cascades which release a plethora of pro-inflammatory molecules into the circulation. The endothelium becomes dysfunctional due to the sustained onslaught of these molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak. The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine. The severity of the changes in systemic vascular permeability may be indirectly reflected in the levels of microalbuminuria. Assay of the amount of albumin excreted in a random urine sample, expressed as ACR (albumin/creatinine ratio), is proven to be a simple, validated, and reliable test.[12-15]

This prompted us to evaluate microalbuminuria as a biomarker of sepsis and further to evaluate the ability of microalbuminuria to predict ICU mortality.

OBJECTIVES

The objectives of this study were;

1. To evaluate microalbuminuria as a biomarker of sepsis.

2. To evaluate the ability of microalbuminuria to predict ICU mortality.

REVIEW OF LITERATURE

Historical note on sepsis

Patients with sepsis form a sizable proportion in modern intensive care units. However the medical concept of sepsis is old and historical.

In the past, when medical hygiene was unknown, wound infections were a common and greatly feared complication of surgery. Wound putrefaction (sepsis) was blamed to be the cause.[16]

The word "sepsis" was first introduced by Hippocrates (ca. 460-370 BC) and is derived from the Greek word sipsi ("make rotten"). Ibn Sina (979-1037 BC) observed the coincidence of blood putrefaction (septicaemia) and fever. This concept of sepsis was prevalent until the 19th century. Only few examples of pathophysiological investigations are known. Herrmann Boerhave (1668-1738), a doctor in Leyden, postulated that toxic substances in the air were the cause for sepsis.[16]

At the beginning of the 19th century, the chemist Justus von Liebig expanded the theory by claiming that the contact between wounds and oxygen was responsible for the development of sepsis.[16]

Ignaz Semmelweis (1818-1865) was the first researcher to develop a modern view of sepsis. In 1863, more than 15 years after his findings, he published his work "Aetiology, terminus and prophylaxis of puerperal fever" (Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers).[16]

The French chemist Louis Pasteur (1822-1895) discovered that tiny single cell organisms caused putrefaction. He called them bacteria or microbes and deducted that these microbes could be causing disease. He also made the significant discovery that bacteria in fluids could be killed by heating. This meant that a fluid could be sterilised.[16]

Joseph Lister (1827-1912) drew a correlation between Semmelweis' observations, and Pasteur's findings and by scientific studies, first with animals, then with humans, he examined the effects of skin and instrument disinfection with carbolic acid (the so-called antiseptic method). By doing so, Lister was able to drastically reduce post-amputation mortality.[16]

In 1887, Robert Koch (1843-1910) introduced steam sterilisation and thus refined Lister's techniques.[16]

In Germany the physician H. Lennhartz, who worked as medical director at Eppendorf Hospital, initiated the change in the understanding of sepsis from the ancient concept of putrefaction to the modern view of a bacterial disease. His student Hugo Schottmüller (1867-1936), in 1914 paved the way for a modern definition of sepsis: "Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms." Thus, for the first time, a source of infection as the cause of sepsis came into focus. Schottmüller explained: "A therapy should not be directed against bacteria in the blood but against the released bacterial toxins (...)." This concept was well ahead of his time.[16]

Although antiseptic procedures meant a huge medical breakthrough, it was apparent that a number of patients still developed sepsis. During that pre-antibiotic time, the death rate was very high. These patients often had a very low blood pressure. This condition was called septic shock. Only with the introduction of antibiotics after WW II could the death rate of sepsis be reduced further. With technological progress, intensive care medicine started to develop and sepsis cases soon became the main patient fraction in intensive care units (ICU).[16]

In 1967 Asbough and colleagues observed a severe lung disease which developed in intensive care patients with severe shortness of breath, loss of lung compliance, and diffuse alveolar infiltration. This disease was called Adult Respiratory Distress Syndrome (ARDS) and was often a fatal complication. It was soon understood that sepsis patients were more prone to this complication. Apart from that, it was deduced that the development of ARDS was the result of an inflammatory reaction caused by substances produced in the diseased body.[16]

In the 1980s it was discovered that this inflammatory reaction was not only apparent in the lungs but in the whole body. Hence it was inferred that the onset of sepsis did not derive from an infectious focus alone, but that the host response against infection had a role in its development.[16]

In 1989, US-American ICU specialist Roger C. Bone (1941-1997) defined sepsis, which is still valid today: "Sepsis is defined as an invasion of microorganisms and/or their toxins into the bloodstream, along with the hosts reaction against this invasion."[16]

Definition

In 1992, the American College of Chest Physicians (ACCP) / Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS) as well as sepsis, severe sepsis, septic shock and MODS (multiple organ dysfunction syndrome).[1] The introduction of SIRS was intended to define a clinical response to a non-specific insult, either infectious or non-infectious in origin. SIRS is defined as 2 or more of the following:[3]

SIRS: 2 or more of the following variables:

- Fever >38◦C or < 36◦C
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg
- Abnormal white blood cell count (>12,000/mm3 or <4,000/ mm3 or >10% bands)

Bacteremia: Presence of bacteria within the blood stream (SIRS or sepsis)

Sepsis: SIRS plus a documented or presumed infection.

Severe sepsis: The aforementioned sepsis criteria with associated organ dysfunction, hypoperfusion or hypotension.

Sepsis induced hypotension: Presence of a systolic BP <90 mmHg or a reduction of > 40 mmHg from baseline in the absence of other causes of hypotension."

Septic shock: Persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation.

Multiorgan dysfunction syndrome (MODS): State of physiological derangements in which organ function is not capable of maintaining homeostasis.

In 2001, an International Sepsis Definition Conference[3] was sponsored by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS) to revisit the 1992 sepsis guidelines.[1] Based on this conference a consensus document was developed, concluding that there was not enough evidence to support a change to the previous definitions. This document expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience. Besides, the document developed a classification scheme for sepsis, called PIRO (Predisposition, Insult infection, Response, Organ dysfunction), that will stratify patients on the basis of their predisposing conditions, the nature and extent of the insult (in the case of sepsis, infection), the nature and magnitude of the host response, and the degree of concomitant organ dysfunction. This provided a basis for introducing PIRO as a hypothesis-generating model for future research.[3,17,18]

Predisposition (P) was the new element which was added to the IRO model proposed by John Marshall and based on the TNM system used in oncology patients. Factors that predispose patients to outcome in sepsis include genetic factors, environment, cultural factors and pre-existing diseases.[3,17,18]

Infections (I) have four aspects that have a significant impact on outcome: The site, extent, source (hospital vs. community-acquired, etc) and type of organism.

Besides, the immune status of a patient predispose to opportunistic infections, and alter the prognosis.[3,17,18]

Response (R) is affected by several factors, such as, age, type of invading microorganism, genotype and co-morbidities. The use of biomarkers to stratify the degree of response is one of the most promising elements for diagnosis and risk assessment in the future. Given the complexity of the immune response in sepsis a single static measurement of a biomarker (pro-calcitonin or any other biomarker) may not be as important as a dynamic assessment of change over time. The level of organ dysfunction is similar to that of metastatic disease in cancer.[3,17,18]

The evaluation of organ dysfunction has evolved from describing it in all-or-nothing terms to use organ failure scores to describe the degree of organ dysfunction developing over the course of critical illness. [3,17,18]

The participants in this conference gave priority to the facilitation of bedside diagnosis over standardized sepsis entry criteria for clinical trials. The conclusions of this conference can be summarized as: [3]

- The current concepts of sepsis, severe sepsis, and septic shock seem to be robust definitions and should remain as described 10 yrs ago.
- Current definitions do not allow for precise staging of the host response to infection.
- Signs and symptoms of sepsis are more varied than the initial criteria established in 1991.[1]
- A list of these signs and symptoms, for the diagnosis of sepsis is presented.

Diagnostic criteria for sepsis[3]

General

- Fever (>38.3 ^{0}C)
- Hypothermia (core temperature <36 ^{0}C)
- Heart rate>90/min or more than two SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant oedema or positive fluid balance
- Hyperglycaemia

Inflammatory Leukocytosis

- Leukopenia
- Normal WBC count with greater than 10% bands
- Plasma C-reactive protein>2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

Hemodynamic

- Hypotension: SBP<90 mmHg, MAP<70 mmHg, or an SBP decrease> 40 mmHg in adults or< 2 SD below normal for age.

Organ dysfunction

- Creatinine increase
- Coagulopathy
- Hypoxaemia

- Ileus
- Oliguria
- Thrombocytopenia
- Hyperbilirubinemia

Tissue perfusion

- Hyperlactatemia
- Decreased capillary refill or mottling

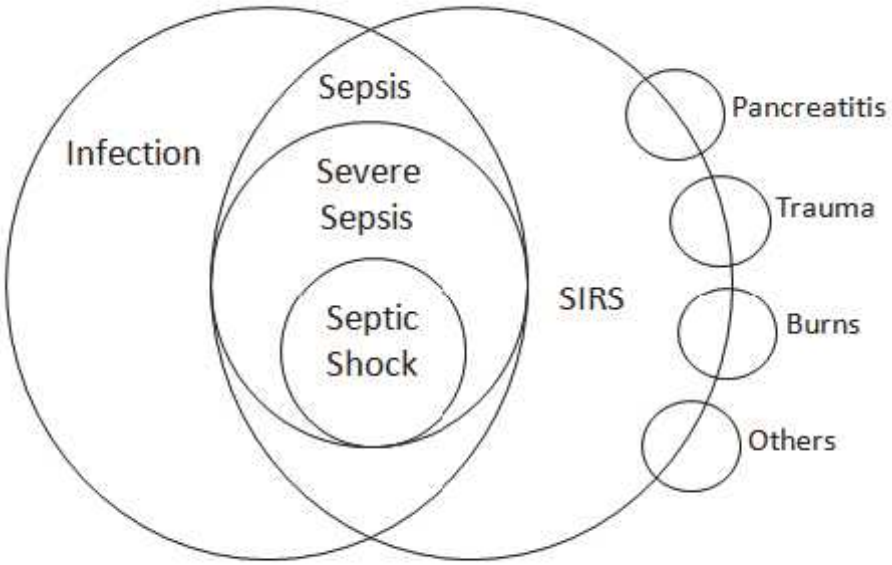


Figure 1. The relationship between infection, systemic inflammatory response syndrome (SIRS) and sepsis syndromes[18]

The future lies in developing a staging system that will characterize progression of sepsis. A new system, PIRO, is proposed for characterizing and staging the host response to infection.[18]

Epidemiology

The epidemiology of severe sepsis and septic shock is not well known mainly due to the absence of population based prospective cohort studies.[19] The prevalence of severe sepsis and septic shock in patients admitted to intensive care units is 11-30% and 6-10%, respectively. The reported rates of severe sepsis from different studies ranged from 50 to 104 per 100.000 population, with an incidence of 300/100.000 in a single study from the United States.[4]

Studies using data from admissions to emergency departments and intensive care units have also found increasing rates of severe sepsis and septic shock in the last decade. In 1990, the Centers for Disease Control (CDC), based on data from the National Hospital Discharge Survey, estimated that there were 450,000 cases of sepsis per year in the United States.[20]

Angus, using ICD-9-CM codes, in a large observational cohort study (n=6,621,559) in the United States in 1995, identified 192,980 cases of severe sepsis which represents an estimated incidence of 3.0 cases per 1,000 population, 2.26 cases per 100 hospital discharges, and 11 percent of all admissions to the ICU.[4]

However, the accuracy of ICD-9-CM coding for the identification of specific medical conditions remains controversial, and Martin[21] suggested that Angus's estimates[4] may overstate the incidence of severe sepsis by as much as a factor of two to four. Martin et al.[21] identified 10,319,418 cases of sepsis from an estimated 750 million hospitalizations in the United States over a 22-yr period, with an increase in frequency from 82.7 cases per 100,000 population in 1979 to 240.4 cases per

100,000 population in 2000, therefore there was an annualized increase in the incidence of sepsis of 8.7 percent.

In a recent prospective, observational study in Iceland, the incidence of severe sepsis and septic shock was 0.48 per 1,000 inhabitants ≥18 years of age per year [95% confidence intervals (CI) 0.42-0.55].[22]

Sepsis in India

Sparse data are available from India regarding sepsis and related syndromes. In contrast to western countries where Gram-negative sepsis is the predominant cause, other uncommon causes such as falciparum malaria, leptospirosis, enteric fever, tuberculosis cause sepsis, septic shock and MODS18 in India in critically ill patients.

In a study[23] from New Delhi, 132 of 387 patients with sepsis, who fulfilled the criteria for severe sepsis/septic shock were considered for analysis. The most common suspected site of infection was the lung (45.5%), followed by urinary tract (21.2%) and abdomen (16.7%). While the ICU mortality in young patients (< 60 years of age) was 45.6%, the mortality was 60.7% in the old (> 60 years of age but < 80 years of age) and 78.9% in very old (> 80 years of age) patients (P = 0.035). The relative risk (RR) for dying in the old and very old subjects was 1.125 and 1.487, respectively as compared to the young patients. There was an increased need for organ support in the elderly and very elderly population as compared to the younger population. On multivariate analysis, the age of patient was the only variable found to be an independent predictor of ICU mortality [P = 0.002, OR: 1.038, 95% confidence interval (CI): 1.014–1.062]. These observations suggest that increasing

age is an important independent predictor of death in critically ill patients in the Indian scenario.

Age predilection

There is a direct relationship between advanced age and the incidence of severe sepsis, septic shock, with a sharp increase in incidence in elderly people .[4,24]

Race

Epidemiologic studies have shown a higher incidence of severe sepsis and septic shock in black people, suggesting a possible genetic predisposition. Alternatively, a higher prevalence of renal disease and diabetes in the black population might explain the higher incidence of these syndromes.[21]

Besides, a higher incidence of severe sepsis and septic shock in black people could be related to the higher percentage of black people living in poverty. The mean age of black people afflicted has been found to be lower than white population. A higher infection rate and a higher risk of acute organ dysfunction has been noted in blacks compared to white population, suggesting racial factors contributing to sepsis.[25]

Lastly, race specific genetic polymorphisms in the host response to infection may predispose certain racial groups to increased incidence or worse outcomes with sepsis.[29]

Sex

Men are more likely than women to develop sepsis, with a mean annual relative risk of 1.28 (95% CI 1.24-1.32).[21] However, it is not clear whether this difference could be due to a higher prevalence of comorbidities in men, or whether women are protected against the inflammatory changes that occur in severe sepsis and septic shock.[4,21] Female gender has been found to substantially decrease the risk of developing severe sepsis, independent of other patient and surgical risk factors, after elective surgery.[27]

Comorbidities

Patients with severe sepsis and septic shock frequently have underlying comorbidities which predispose them to infections and may have an additive contribution to mortality.

Sources of severe sepsis and septic shock

The lung is the primary source of infection both in severe sepsis and in septic shock, followed by the abdomen, the urinary tract, soft tissues and primary blood stream infection.[28,29]

Microorganisms that cause severe sepsis and septic shock

The proportion of severe sepsis and septic shock with unidentified pathogen is about one third. In some studies the infection was not documented in 40% of cases, possibly due to the increase in empiric antibiotic treatment. The percentage of positive blood culture increases with the severity of the sepsis syndrome. Traditionally, Gram-negative bacilli - mostly represented by *Escherichia coli*,

Pseudomonas aeruginosa, *Klebsiella pneumonia* - were more prevalent than Gram-positive cocci - *Staphylococcus aureus*, *Streptococcus pneumonia*, *Enterococcus* spp. - . However, Gram-positive microorganisms have become the most common microorganisms isolated in recent studies. The percentage of polymicrobial infection as well as the proportion of multiresistant bacteria like *Pseudomonas* and methicillin-resistant *Staphylococci*, has significantly increased over time.[18,29] The incidence of fungi has also been reported to be increasing in recent years.

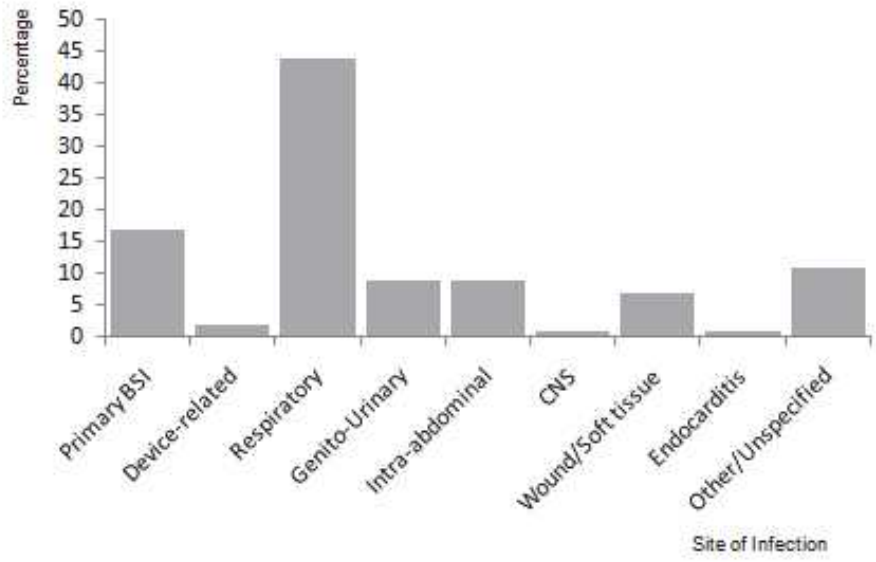


Figure 2. Sources of severe sepsis[4]

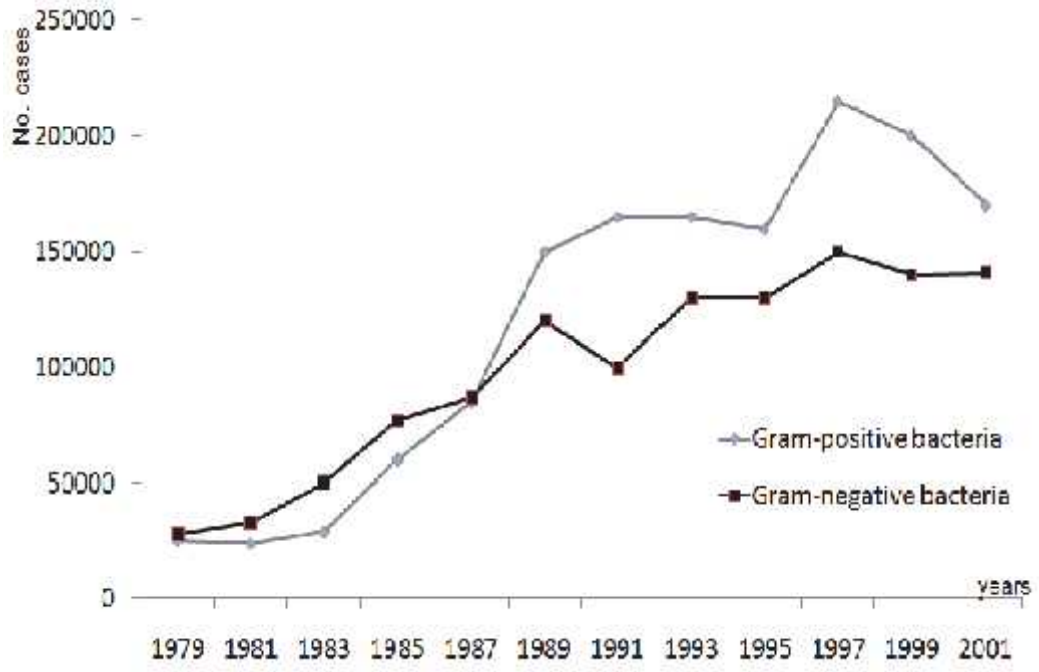


Figure 3. Cases of severe sepsis according to the causative origin[21]

Age influences the etiology of severe sepsis and septic shock in the pediatric population. In the neonatal period the most frequent microorganisms isolated are group B streptococci. Enteric bacilli, such as *Escherichia coli*. *Listeria monocytogenes,* enterococci, *Haemophilus influenzae*, and *Streptococcus pneumoniae* are less common pathogens isolated.[18]

The incidence of coagulase-negative staphylococci, *Staphylococcus aureus*, gram-negative bacilli, and fungi are increasing in the pediatric population as a consequence of the advances in neonatology. *S. pneumoniae, Neisseria meningitidis,*and *H. influenzae* type B are common pathogenes beyond the neonatal period.[18]

Immunodeficiency predispose children to some specific microorganisms. Gram negative bacteria, alpha-hemolytic streptococci, Viridans group streptococci

and cytomegalovirus are predominantly isolated neutropenic patients. *Streptococcus pneumoniae,P. aeruginosa, Staphylococcus aureus,* and *Haemophilus influenza type B* are commonly found in patients with acquired immunodeficiency syndrome; *Streptococcus pneumoniae, Salmonella* spp., *Haemophilus influenza type B,* and *N. meningitides* are predominant in patients with asplem.[18]

Morbidity

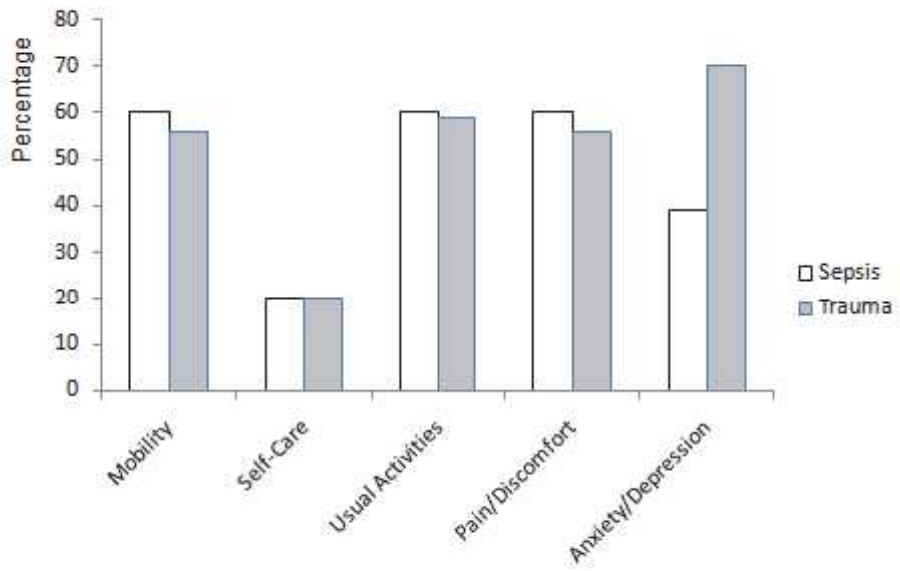


Figure 4. Quality of life of 164 patients with sepsis or trauma after 2 years following ICU admission using the EuroQol 5D questionnaire.[30]

Half of severe sepsis survivors are readmitted to hospital within a year, and their quality of life is comparable with survivors of polytrauma. Jagodič et al.[30] studied the long-term survival and quality of life of patients treated in a surgical ICU for sepsis or trauma, and found that the quality of life (assessed after 2 years following ICU admission using the EuroQol 5D questionnaire) was reduced to the

same level in both groups, and 82% of patients reported a problem (moderate or extreme) in at least one dimension of EuroQol 5D.

Acute respiratory distress syndrome, myocardial dysfunction, acute renal failure and chronic dysfunction, disseminated intravascular coagulation (DIC), and liver failure are all common sequels of severe sepsis and septic shock. Furthermore, recent evidence shows that septic shock in elderly persons leads to significant long-term cognitive and functional disability as a consequence of prolonged tissue hypoperfusion.[31]

Mortality

The Centers for Disease Control and Prevention has estimated that sepsis is the tenth leading cause of death overall in the United States.[32] Severe sepsis is considered to be the most common cause of death in noncoronary critical care units. The deaths related to severe sepsis exceed the number of persons with other diseases that attract public awareness, such as breast cancer and AIDS.[33] The mortality rates of severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively.[18]

The global in-hospital mortality rate in 624 patients with sepsis syndromes admitted to the ICU in our hospital was 37.7%, 55.9% and 66.2% in sepsis, severe sepsis and septic shock respectively. However the related mortality to infection was quite lower (7.7%, 16.7% and 30.1% in sepsis, severe sepsis and septic shock respectively).[18]

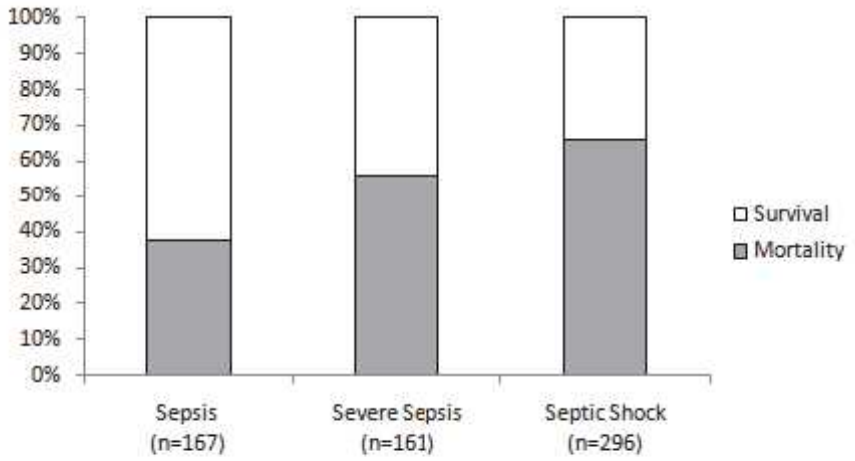


Figure 5. Mortality rate according to sepsis diagnostic criteria[18]

The crude mortality rate of septic shock is decreasing, but patients with septic shock still have a high excess risk of death than critically ill patients who are nonseptic. Annane et al in an epidemiological study analyzed 100,554 intensive care unit admissions on the Collège des Utilisateurs de Bases de données en Réanimation (CUB-Re´a) database, collected from 22 hospitals over a 8-year period, 1993 to 2000, and found an overall frequency of septic shock of 8.2 per 100 admissions, and a crude mortality of 60.1% that declined from 62.1% (in 1993) to 55.9 (in 2000) ($p<0.001$). As compared with matched intensive care unit admissions without sepsis, the excess risk of death due to septic shock was 25.7 (95% confidence interval, 24.0–27.3) and the matched odds ratio of death was 3.9 (95% confidence interval, 3.5–4.3).[29]

The severity of severe sepsis and septic shock do not markedly depend on the source of infection or on its causative microorganism. On the contrary, mortality is directly related to the occurrence of organ failure in sepsis, and this relationship has remained consistent among patients of different races and sexes. However, organ failure scores have difficulty in quantifying the contribution that preexisting organ dysfunction adds to risk.[18]

The patient's underlying comorbidities are directly related to mortality in several studies. The index of McCabe and Jackson is one of the most useful scores used in epidemiological and clinical studies to quantify underlying consitions. APACHE II, Simplified Acute Physiology Score (SAPS II) and the sequential organ failure assessments (SOFA) are prognostic scores based on bedside evaluation which are widely used to predict the prognosis of severe sepsis and septic shock. The hospital mortality of severe sepsis is about 30% according to several studies, but this rate has been found much lower in children and previously healthy adults.[18]

Mirzanejad et al found that mortality from pneumococcal bacteremia varied from 3.2% in children to 43% in the elderly.[34] This fact suggest attributable mortality of sepsis may be much less than the commonly observed 30% and that the mechanism by which sepsis causes death is highly dependent on individual patient factors, many of which may not be reversible by single antisepsis agents.[4]

Patients with sepsis who had an organ failure have higher mortality. Besides, organ failure has a cumulative effect on outcomes. Mortality in patients without organ failure is approximately 15 percent, whereas it reaches 70 percent in patients

with three or more failing organs (classified as having severe sepsis and septic shock).[18]

A hospital survey of patients with SIRS done by Pittet et al.[35] revealed an overall in-hospital incidence of 542 episodes/1000 hospital days. In comparison, the incidence in the ICU was 840 episodes / 1000 hospital days. Rangel-Frausto et al.[36] published a prospect survey of patients admitted to a tertiary care center that revealed 68% of hospital admissions to surveyed units met criteria for SIRS. The incidence of SIRS increased as the level of unit accuity increased. Progression of SIRS was noted to be: 26% developed sepsis, 18% developed severe sepsis and 4% developed septic shock within 28 days of admission. The mortality rates were 7% (SIRS), 16% (sepsis), 20% (severe sepsis) and 46% (septic shock). The medial time interval from SIRS to sepsis was inversely related to the number of SIRS criteria (2, 3 or all 4) met.

Pittet et al.[36] also demonstrated that control patients had the shortest hospital stay, while patients with SIRS, sepsis and severe sepsis respectively required progressively longer hospital stays.

Clinical features

Despite having a relatively common physiologic pathway, numerous triggers exist for SIRS and patients present in a variety of manners. A thorough history is critical in determining the proper evaluation of the patient with SIRS as the differential diagnosis is extremely broad.[37]

Infectious causes

- Bacteremia
- Bacterial sepsis
- Cellulitis
- Cholecystitis
- Community-Acquired Pneumonia
- Diabetic foot infection
- Erysipelas
- HIV (acute retroviral syndrome)
- Infective endocarditis
- Influenza
- Intra-abdominal infections
- Meningitis
- Necrotizing fasciitis
- Nosocomial pneumonia
- Pelvic inflammatory disease
- Prostatitis
- Pseudomembranous colitis (Clostridium difficile)
- Pyelonephritis
- Septic arthritis
- Toxic shock syndrome
- Urinary tract infection
- Viral syndrome

Non infectious causes[38]

- Acute mesenteric ischemia
- Alcohol withdrawal
- Burns
- Cirrhosis
- Connective tissue disease
- Deep venous thrombosis
- Dehydration
- DKA
- Drug overdose
- Drug reaction
- Electrical injuries
- Erythema multiforme
- Gastrointestinal bleeding
- Gout
- Hemorrhagic shock
- Intestinal perforation
- Malignancy
- Myocardial infarction
- Pancreatitis
- Peripheral ischemia
- Pulmonary embolism
- Toxic epidermal necrolysis
- Transfusion reactions

- Trauma

The clinician's history should be focused around the chief complaint with a pertinent review of systems. Patients should be questioned regarding constitutional symptoms of fever, chills and night sweats which may help differentiate infectious from noninfectious etiologies. The timing of symptom onset may also guide a differential diagnosis towards either an infectious, traumatic, ischemic or inflammatory etiology.[37]

Pain, especially when localized, may guide a health care worker in both differential diagnosis and evaluation. While it is beyond the scope of this chapter to provide a differential for pain in the various body parts, a physician should carefully evaluate the duration, location, radiation, quality and exacerbating factors associated with the pain to help establish a differential diagnosis.[37]

Patients' medications should be reviewed. Medication side effects or pharmacologic effects either induce or mask SIRS (i.e. Beta Blockers will prevent tachycardia). Recent changes in medications should be addressed to rule out drug-drug interactions or a new side effect. Allergy information should be gathered and specifics of reaction should be obtained.[37]

Careful review of initial vital signs is an integral component to making the diagnosis. Monitoring of vital signs periodically during the initial evaluation period is necessary as multiple other factors (stress, anxiety, exertion of walking to the examination room, etc) may lead to a false diagnosis of SIRS. A focused physical examination based on patient's complaints is adequate in most situations. Evaluation for evidence of hypoperfusion (skin mottling, mental status changes, delayed

capillary refill and decreased urinary output) should be done in all patients. Patients unable to provide any history should undergo a complete physical examination including a rectal examination to rule out a perirectal abscess or gastrointestinal bleeding.[37]

The clinical features of severe sepsis vary significantly, depending on multiple factors including host characteristics, site and severity of infection, and time course of sepsis before therapy.[39]

Pathophysiology

SIRS, independent of the etiology, has the same pathophysiology with minor differences, in inciting cascades. Many consider the syndrome as a self defense mechanism, which uses inflammation as the body's response to nonspecific insults that arise from chemical, traumatic or infectious stimuli. The inflammatory cascade is complex and involves humoral and cellular responses, complement and the cytokine cascades. The relationship between these complex interactions and SIRS was best summarized by Bone RC[40] as a three stage process.

Stage I

Following an insult, there is local cytokine production with the goal of inciting an inflammatory response thereby promoting wound repair and recruitment of the reticular endothelial system.[38,40]

Stage II

Small quantities of local cytokines are released into circulation to improve the local response. This leads to growth factor stimulation and the recruitment of

macrophages and platelets. This acute phase response is typically well controlled by a decrease in the proinflammatory mediators and by the release of endogenous antagonists. The goal is homeostasis.[38,40]

Stage III

If homeostasis is not restored, a significant systemic reaction occurs. The cytokine release leads to destruction rather than protection. A consequence of this is the activation of numerous humoral cascades and the activation of the reticular endothelial system and subsequent loss of circulatory integrity. This leads to end organ dysfunction.[38,40]

Bone RC[41] also endorsed a multi-hit theory behind the progression of SIRS to organ dysfunction and possibly MODS. In this theory, the event that initiates the SIRS cascade "primes the pump." With each additional event, an altered or exaggerated response occurs, leading to progressive illness. The key to preventing the multiple hits is adequate identification of the cause of SIRS and appropriate resuscitation and therapy. Depending on the inciting factors, many SIRS states resolve without specific intervention.[38,40]

Trauma, inflammation or infections lead to the activation of the inflammatory cascade. When SIRS is mediated by an infectious insult, the inflammatory cascade is often initiated by endotoxin or exotoxin. Tissue macrophages, monocytes, mast cells, platelets and endothelial cells are able to produce a multitude of cytokines. Cytokines Tissue Necrosis Factor-α (TNF) and Interleukin 1 (IL-1) are first released and initiate several cascades. The release of IL-1 and TNF (or the presence of endotoxin or exotoxin) leads to cleavage of the

Nuclear Factor Kappa B (NF-κB) inhibitor. Once the inhibitor is removed, NF-κB is able to initiate the production of mRNA that will induce the production of other pro-inflammatory cytokines. Interleukins 6 (IL-6) and 8 (IL-8) and Interferon-gamma are the primary pro-inflammatory mediators induced by NF-κB. TNF and IL-1 have been shown to be released in large quantities within 1 hour of an insult and have, both local and systemic effects. They are responsible for fever and the release of stress hormones (norepinephrine, vasopressin and activation of the renin-angiotensin-aldosterone system). Other cytokines, especially IL-6, stimulate the release of acute phase reactants such as C-reactive protein. Infection has been shown to induce a greater release of TNF than does trauma, which therefore leads to a greater release of IL-6 and IL-8. This is suggested to be the reason for a higher fever associated with infection than trauma.[38]

The cumulative effect of this inflammatory cascade is an unbalanced state with inflammation and coagulation dominating. To counteract the acute inflammatory response, the body is equipped to reverse this process via counter inflammatory response syndrome (CARS). Interleukin 4 (IL-4) and 10 (IL-10) are cytokines responsible for decreasing the production of TNF, IL-1, IL-6 and IL-8. The acute phase response also produces antagonists to TNF and IL-1 receptors. These antagonists either bind the cytokine and thereby inactivate it or block the receptors. The balance of SIRS and CARS is a critical factor in determining a patients outcome.[38]

Sepsis is a complex condition starting from an infective stimulus and resulting in an exaggerated immune response. The inflammatory response that was

initiated to fight the infection ultimately leads to damage of various organs through out the body.[41]

During the onset of sepsis, the inflammatory system becomes hyperactive, involving both cellular and humoral defence mechanisms Endothelial and epithelial cells, as well as neutrophils, macrophages and lymphocytes, produce powerful pro-inflammatory mediators, especially tumour necrosis factor- (TNF-), interleukin (IL)-6, IL-1 and IL-8. Simultaneously, robust production of acute-phase proteins, such as C-reactive protein, occurs and humoral defence mechanisms such as the complement system are activated, resulting in production of pro-inflammatory mediators, including C5a, the complement split product. C5a ultimately enhances cytokine and chemokine production. Furthermore, the coagulation system becomes activated through various mechanisms, often resulting in disseminated intravascular coagulopathy.[41]

The hallmarks of the sepsis are excessive inflammation, excessive coagulation and suppression of fibrinolysis. In addition endogenous Activated Protein C which modulates coagulation, controls inflammation and supports fibrinolysis is also decreased. There is considerable variability in response which is almost certainly to a large degree genetically determined. Those with a tendency to produce excessive cytokines and TNF will have a greater inflammatory response. Simultaneously, the initial vascular damage results in neutrophil activation, neutrophil-endothelial cell adhesion, and further elaboration of inflammatory cytokines. In tissues already prone to dysfunctional oxygen uptake and metabolism, this vascular injury promotes further tissue hypoxia through regional hypo perfusion. This uncontrolled cascade of inflammation and coagulation fuels the progression of

sepsis, resulting in tissue hypoxia and ischemia with resultant organ dysfunction and death.[41]

Laboratory evaluation

In order to completely assess SIRS, a minimum of a complete blood cell count with differential to evaluate for leukocytosis or leucopenia in required. Routine laboratory tests will often include a basic metabolic profile while other lab tests should be individualized based on history and physical examination findings. Patients seen in an outpatient physician's office or emergency room will require a different evaluation than a currently hospitalized patient with new onset SIRS. The selection of imaging studies depends on the differential diagnosis that is being considered.[38]

Sedimentation rates and C-reactive proteins are not sensitive in distinguishing between causes of SIRS but may be helpful in certain circumstances. The lack of specificity significantly diminishes the clinical role of acute phase reactants in narrowing the differential diagnosis, but when elevated, may have a role in monitoring response to treatment. Procalcitonin levels have shown variable clinical utility in differentiating infectious from noninfectious causes. However lack of routine availability in most hospitals limits their usefulness. Research is currently under way to evaluate other potentially useful acute phase reactants.[38]

Laboratory and imaging studies to consider in a patient with SIRS[38]

Primary

- Complete blood count with differential
- Comprehensive metabolic panel

- Urinalysis

Secondary

- Amylase/Lipase
- Blood cultures
- Cardiac enzymes and ECG
- C-reactive protein and ESR
- Influenza nasal swab (November-March)
- Lactic acid level
- Legionella urine antigen
- Pneumococcal urine antigen
- Spinal fluid analysis
- Sputum culture (if suspecting pneumonia)
- Urine cultures

Radiographic

- Chest radiograph
- Abdominal radiograph
- Soft tissue radiographs
- CT of abdomen and pelvis
- CT of chest
- CT or MRI of the brain
- CT or MRI of soft tissue
- Lower extremity ultrasound
- Right upper quadrant ultrasound

Diagnosis of sepsis is not easy. Making an early, accurate diagnosis of septic

shock is vital in increasing survival rates. The signs and symptoms of severe sepsis may be subtle. Although the components of SIRS are non specific, the combination of suspected infection and the presence of SIRS may help alert the clinician to a possible diagnosis of sepsis. Although hypotension is another clinical sign that may signal the onset of septic shock, patient may present with severe sepsis and clinically significant global tissue hypoxia in its absence. Metabolic markers such as serum lactate and arterial base deficit may help to identify the severe cases. A single lactate measurement of 4mmol/l or more at initial presentation is associated with an increased rate of mortality.[42]

There may well be signs of altered mentation and abnormalities of renal and liver function test, as well as coagulation abnormalities. At least two blood cultures and cultures from other sites are indicated before commencement of antibiotic therapy. Diagnostic studies such as Ultra sound and CT scan should be performed promptly.[41]

D dimmers are grossly elevated in sepsis. Levels of Protein C are lowered which has therapeutic implications. The potential role of biomarkers for diagnosis of infection in patients presenting with severe sepsis remains undefined. Perhaps the most common considerations as diagnostic biomarkers for sepsis have been C-reactive protein and Procalcitonin. Despite initial enthusiasm for their potential diagnostic strengths,[43] they have failed to accurately differentiate sepsis from similar critical illnesses.

The most exciting development in the last 2 years is the recognition of "soluble triggering receptor expressed on myeloid cells-1" (sTREM-1) as a potential

biomarker for sepsis.[44] For this marker, a level greater than 60 ng/mL was more accurate than any other clinical and laboratory findings indicating infection.[41]

Treatment

The development of new treatment modalities has resulted in a spate of treatment algorithms, often promulgated by medical societies and healthcare improvement organizations. As these modalities have rolled out, increasing levels of evidence have emerged to support or refute their utility in treating patients with sepsis. One of the greatest endeavours to date is the Surviving Sepsis Campaign (SSC) that was originally launched in 2002 with the stated goal to reduce mortality by 25%. The primary method to achieve this goal was the development of evidence-based sepsis care guidelines that were published in 2004 and recently revised in 2008.[45]

The Institute for Healthcare Improvement (IHI) has highlighted sepsis as an area of focus and has identified several deficiencies that may cause suboptimal care of patients with severe sepsis. These deficiencies include inconsistency in the early diagnosis of severe sepsis and septic shock, frequent inadequate volume resuscitation without defined endpoints, late or inadequate use of antibiotics, frequent failure to support the cardiac output when depressed, frequent failure to control hyperglycemias adequately, frequent failure to use low tidal volumes and pressures in acute lung injury, and frequent failure to treat adrenal inadequacy in refractory shock.[41]

The management of patient with sepsis is influenced more by appropriate treatment with antibiotics and fluids than by specific intensive care. Therefore early

intervention should never be delayed pending admission to the intensive care unit. The early and aggressive treatment of septic shock has been well documented in the survival sepsis campaign which is based on the best current practice.[41]

The cornerstones of treatment are infection control, haemodynamic stabilization, and modulation of the septic response.[41]

Infection Control

Infection control is vital if the patient is to have any chance of survival. Appropriate broad-spectrum antibiotics must be given within the first hour of recognition of sepsis after obtaining various cultures. Evidence clearly shows that delay or inadequate antibiotic treatment results in poorer outcome. For every hour lost mortality climbs by 9%.[46]

Haemodynamic Stabilization

In septic shock there is extensive cardiovascular derangement. Hypotension is caused by myocardial depression, pathological vasodilatation and extravasation of circulating volume due to widespread capillary leak. The initial resuscitative effort is to attempt to correct the absolute and relative hypovolemia by refilling the vascular tree. There is no evidence to support one type of fluid crystalloid or colloid is superior to the other. There is good evidence that early well directed aggressive volume resuscitation improves outcome of sepsis.[3] During the first 6 hours of resuscitation the goals of initial resuscitation are a Central venous pressure of 8-12 mm Hg, Mean arterial pressure (MAP) ≥ 65 mmHg, Urine output ≥ 0.5 mL/kg/hr and a central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65%, respectively

Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-centre study.[47] Resuscitation directed toward the previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce in hospital, 28-days as well as 60 days mortality rate.

If Scvo2 or SVo2 of 70% or 65%, respectively, is not achieved with fluid resuscitation to the central venous pressure target, then transfusion of packed red blood cells to achieve a hematocrit of ≥ 30% and/or administration of a dobutamine infusion (up to a maximum of 20 µg/kg/min) be used to achieve this goal.[41]

It is important to remember that vasopressors should be utilized not only when fluids fail to reverse hypotension, but also during resuscitation to maintain minimally adequate blood pressure. Traditionally, the use of noradrenalin in patients with shock has been restricted by the fear of excessive vasoconstriction that may result in end-organ hypo perfusion. In the past it was usually given only when other vasopressin agents failed, and thus such patients were predicted to have a poor outcome. Recent studies indicate that the fear of deleterious effect was unwarranted and that noradrenalin may have a role as a first-line vasopressor agent in patients with septic shock.[41]

Vasopressin should be considered in refractory shock despite high dose conventional vasopressors. Vasopressin is an endogenously produced hormone that is deficient in many patients with septic shock. Exogenously administered vasopressin in physiologic replacement doses may act synergistically with other vasopressor agents, and has been associated with early withdrawal of

catecholamine.[41]

Most studies have evaluated short-term infusions of vasopressin at 0.08 U/minute or less as add-on therapy in patients requiring adrenergic agents. The results show that starting vasopressin in patients with septic shock increases systemic vascular resistance and arterial blood pressure, thus reducing the dosage requirements of adrenergic agents.[48] These effects are rapid and sustained. Substantial enhancement of urine output due to increased glomerular filtration rate, was shown in several studies. A few studies demonstrated clinically significant reduced cardiac output or cardiac index after vasopressin administration, necessitating cautious use in patients with cardiac dysfunction.[41]

Modulation of Septic Response

There are a number of ways to modulate the septic response. These include use of steroids, tight glucose control and the use of Activated Protein C. Septic shock causes adrenal suppression which can be confirmed by measuring cortisol levels or by using the synacthan test. Compared to placebo, the administration of low dose of hydrocortisone (200-300 mg/day in divided doses) to patients with septic shock decreases the need for vasopressors[49] and lowers the mortality rate.[50]

Low dose hydrocortisone should only be given to non responders of the synacthan test, but in practice all patients receive this treatment until the result of the test are received. Following the Corticosteroid Therapy of Septic Shock (CORTICUS) study there is now an increasing trend towards restricting the use of low dose hydrocortisone only to patients with refractory hypotension who are already on high doses on vasopressors.[51]

The trial did show a faster resolution of septic shock in patients who received steroids but failed to show a mortality benefit with steroids therapy. Close control of blood glucose has been shown to increase survival in critically ill septic patients. When conservative (10–11.1 mol/L) glycemic control was compared with tight control (4.4-6.1 mmol/L) in a multi centre, randomized controlled trial, tight control lead to a significant reduction in mortality (8% versus 4-6%), p < 0-04 and improved morbidity at 12 months.[52]

Activated Protein C

Human activated Protein C (APC) is an endogenous regulator of coagulation. In order for protein C in the plasma to become activated, it must combine with thrombin and thrombomodulin along with the endothelial protein C receptor. With endothelial damage this activation does not take place resulting in its deficiency. Therefore APC supplementation is a rational therapeutic option. APC has an important role in the management of severe sepsis. It protects against the disruption of the endothelial cell membrane, improves micro circulatory perfusion, and has anti inflammatory, procoagulant, fibrinolytic and anti apoptotic activity. APC must ideally be started within the first 24 hours of the onset of septic shock.[41]

Other beneficial strategies in sepsis

Low tidal volume ventilation: using normal or high tidal volume (10-12mls/Kg) ventilation will cause over expansion of the normal lung segments. This will in turn result in inflammatory mediators being released in the lung tissue. The consequences of this are the development of Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS). Therefore it is crucial to use low tidal

volume ventilation (6ml/kg) to keep plateau airway pressure less than 30 cm of water.[53,54]

High volume haemofilteration: In the past five years, many studies have been conducted to evaluate and demonstrate benefits of increasing the volume of ultra filtration and replacement fluid during continuous renal replacement therapy[55,56] particularly in complex and very severe syndromes such as severe sepsis and septic shock, associated with or without acute renal failure.

In general, the high-volume approach provides higher clearances for middle/high molecular weight solutes than a simple diffusive transport, continuous veno venous haemodialysis (CVVHD) or a convection-based transport at lower volumes, continuous veno venous haemofiltration (CVVH). These solutes seem to be primarily involved in the Systemic Inflammatory Response Syndrome, which characterizes the sepsis syndrome, and their efficient removal may thus be beneficial.[57]

Alternative approaches have been based on more efficient removal of inflammatory mediators by high cut-off hemofilters, which are characterized by an increased effective pore size. Most commercially available hemofilters do not permit a substantial elimination of cytokines because of the low cut-off point of their membranes. The use of high cut-off hemofilters is a new and effective approach to cytokine removal, but it has potentially harmful side effects, such as the loss of essential proteins like albumin.[58]

Because the reversibility of this disease and the resultant mortality may be greatest during the earliest stages of presentation, proper sepsis management should

not be confined within the walls of an Intensive Care Unit. Specific emphasis on appropriate triage to ensure prompt diagnosis of the high-risk patient is vital to the launch of a coordinated and cooperative effort by the primary treating clinician and the intensivist**.**[41]

Potential complications of SIRS[38]

- Anemia
- ARDS
- Cardiovascular decompensation
- Deep venous thrombosis
- DIC
- Electrolyte abnormalities
- GI Bleeding and stress gastritis
- Hyperglycemia
- IV catheter related bacteremia
- Renal failure
- Respiratory failure

Biomarkers of sepsis

Sepsis is systemic inflammatory response syndrome (SIRS) caused by infection. However, infections can be difficult to confirm. Fever, tachycardia, hypotension, and other vital sign abnormalities found in SIRS are not specific for infection and overlap with noninfectious etiologies presenting with systemic inflammation. There is no gold standard for diagnosing infection, and though blood cultures processed with standard microbiologic techniques are a frequent diagnostic

step, their likelihood of isolating the pathogen depends on a variety of factors, including prior antibiotic therapy.[59]

Delays in empiric treatment for sepsis and bacteremia increase mortality as well as length of stay and cost, making timely recognition of infection and initiation of appropriate therapy an important goal.[7,60] Standard blood culture techniques require time with results typically not available for at least 24–48 hours, highlighting the need for rapid diagnosis and risk stratification where biomarkers could be of use.[7]

There have been many attempts to augment clinical decision making with diagnostic tests to increase sensitivity and specificity when diagnosing and treating sepsis and bacteremia. Initial studies employed fever and leukocytosis to define sepsis,[1] though these tests were nonspecific. Subsequent studies focused on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to help in the diagnostic algorithm but suffered from the same lack of specificity. As our knowledge of sepsis evolved, it became evident that not only direct pathogen effects but also an exuberant inflammatory host response was responsible for the deleterious clinical and laboratory abnormalities.[7]

Sepsis is a systemic inflammatory syndrome affecting all organ systems, and biomarkers have focused on a number of pathogen and host responses, including cytokines, cell markers, receptor biomarkers, coagulation, vascular endothelial damage, vasodilation, organ dysfunction, acute phase protein markers, and other systems. Sepsis provokes a systemic host response involving hundreds of mediators that could be potentially used as biomarkers for both diagnosis and prognosis.[8]

Inspite of availability of reliable diagnostic methods for detecting bacterial infections, these are not widely available or accessible in routine practice in developing countries and confirmation of diagnosis of bacterial infection is done mainly in referral hospitals or research facilities.[7] An ideal biomarker for bacterial infections should facilitate early rapid diagnosis, predict the course and prognosis of the disease and guide therapeutic decisions (*e.g*. antibiotic stewardship).[7]

Leucocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), pro-adrenomedullin (ProADM), serum procalcitonin (PCT), mid-regional pro-atrial natriuretic peptide (ANP), pancreatic stone protein (PSP)/regenerating protein (reg), interleukin-6 (IL-6), IL-8, IL-27, soluble urokinase-type plasminogen activator receptor (suPAR) among others, have been studied as potential biomarkers to facilitate diagnosis and aid prognostication in bacterial sepsis.[61]

Microalbuminuria

A hallmark of the systemic inflammatory response syndrome (SIRS) accompanying infection is endothelial cell injury and resultant capillary permeability. This is particularly evident in renal glomeruli, where basement membrane permeability is increased at baseline allowing leakage of serum proteins, notably albumin, into the urine.[62.63] Recent studies have shown that microalbuminuria at intensive care unit (ICU) admission is associated with increased morbidity and mortality.[63,64] Therefore, evidence of microalbuminuria in ED sepsis patients may be associated with adverse outcomes. Sepsis is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release a

plethora of pro-inflammatory molecules into the circulation.[65] The endothelium becomes dysfunctional due to the sustained onslaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak.[66] The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine.[67]

Microalbuminuria, defined as 30–300 mg/day of albumin excretion in the urine, occurs rapidly after an acute inflammatory insult such as sepsis and persists in patients with complications.[68-73]

Microalbuminuria may serve as a means of indirectly quantifying changes in systemic vascular permeability. Assay of the amount of albumin excreted in a random urine sample, expressed as ACR, is a simple, validated and reliable test.[12] Levels of microalbuminuria increase within hours of an inflammatory insult as compared to relatively delayed inductions of PCT and CRP.[74]

The pathophysiological cause of microalbuminuria in general is not known, but defects in both the glomerulus and the tubules have been implicated. In acute inflammation, microalbuminuria is surmised to be a result of the endothelial glomerular leak in the kidneys that is a manifestation of the systemic increases in capillary permeability, due to an intense inflammatory onslaught on the endothelium.[14,75] It is postulated that, the possibility of inflammation induced defects in the glycocalyx layer of the endothelium being responsible for higher levels of microalbuminuria in sepsis. It has been shown that the glycocalyx of the fenestrated glomerular capillaries acts as a barrier to protein permeability and (enzyme) degradation of the layer increases the passage of albumin across the glomerulus.[76]

A possible explanation for the reductions of median levels after 24 hours of ICU admission could be the effect of therapeutic interventions on the attenuation of the inflammatory process and pacifying effects on the endothelium. It is speculated that, early targeted interventions may help in the preservation of the glycocalyx from further degradation that might mitigate increases in vascular permeability.[77] The same logic might also explain the observed decreases in the median ACR levels in patients with sepsis as compared to the patients without sepsis. One can therefore envisage the possible utility of microalbuminuria in monitoring the effect of therapy too.[14]

Overall, urine ACR is significantly higher in the sepsis cohort in comparison to other systemic inflammatory diseases that probably indicates a distinct yet unknown pathophysiology. Serial monitoring of bedside urine albumin-creatinine measurement may potentially aid clinical assessment in the early identification of patients with sepsis that requires early targeted therapy. Another potential application may be in excluding patients at risk at 24 hours of admission. The 24 hours ACR assessment predicts ICU survival and may have the potential to monitor the efficacy of therapeutic interventions delivered, such as fluid resuscitation, appropriate antibiotics, vasopressors and inotropes that affect the endothelium.[14,15]

Literature

A study conducted by Thorevska et al to ascertain the prevalence and prognostic significance of Microalbuminuria in critically ill patients concluded the high prevalence of microalbuminuria in critically ill patients and significance of Albumin Creatinine Ratio >100mg/g as independent predictor of ICU mortality.[64]

A study conducted by Makris et al to evaluate whether clinically significant Microalbuminuria is an early marker of capillary dysfunction that accompanies Systemic Inflammatory Response Syndrome concluded that significant and persistent microalbiminuria is positively co related with organ dysfunction. Monitoring of urinary albumin levels might serve as sensitive marker of inflammation and disease deterioration.[78]

A study conducted by Gopal et al to find, does microalbuminuria predict illness severity in critically ill patients, a systematic review, concluded that microalbuminuria may hold promise as predictor of illness severity and mortality in ICU.[79]

A study conducted by Abid et al to evaluate predictive value of microalbuminuria in the development of multi organ failure in ICU patients, concluded that analysis of Microalbuminuria over first 48hours of an ICU admission may provide useful means of identifying sepsis patients.[80]

A study conducted by Todi et al to evaluate the degree of microalbuminuria as a diagnostic tool in predicting sepsis in critically ill patients, concluded that absence of significant microalbuminuria at the time of ICU admission is unlikely to be associated with sepsis.[81]

A study conducted by Basu et al to find microalbuminuria as a novel biomarker of sepsis in critically ill patients concluded the absence of significant microalbuminuria on ICU admission is unlikely to be associated with sepsis. At 24hours, absence of elevated levels of microalbuminuria is strongly predictive of ICU survival.[14]

METHODOLOGY

This study was done under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design and duration

This study was a one year cross sectional study.

Study period

The study was conducted from January 2014 to December 2014.

Place

The present study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum which is a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Adult patients admitted in ICU with systemic inflammatory response syndrome (SIRS) and/or sepsis during the study period at KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belgaum were enrolled in the study.

Sample size

The study included a total of 65 patients with systemic inflammatory response syndrome (SIRS).

Sampling procedure

The sample size was determined based on the following formula.

Sample Size (n) = 2^2 x sensitivity x (100–sensitivity) / (10% of sensitivity)^2

Therefore, $n = 4 \times 86^{82} \times (100 - 86) / (0.1 \times 86)^2$

$n = 2^2 \times 86 \times 14 / 9^2$

$n = 59.45 \approx 60$

However, 65 patients fulfilled the selection criteria hence were included in the study.

Selection criteria

Inclusion Criteria

- Patients with systemic inflammatory response syndrome (SIRS) and/or sepsis as defined by American College of Chest Physicians and Society of Critical Care Medicine.[3]
- Patients aged 18 and above.
- Patients with ICU stay of more than 24 hours.

Exclusion Criteria

- Patients with anuria, hematuria.
- Patients with preexisting chronic kidney disease.
- Patients with proteinuria due to renal and post renal causes.
- Patients with urinary tract infection.

- Female patients with menstruation or pregnancy.

Ethical clearance

The study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum prior to the commencement.

Informed consent

The patients fulfilling the selection criteria were briefed about the study and those who expressed their willingness to participate in the study were enrolled after obtaining a written informed consent (Annexure–I).

Data collection

On admission at intensive care unit, the on duty physician collected the demographic data of the patients along with relevant history of current illness and past medical history. Further these patients underwent clinical examination followed by systemic examination.

Investigations

Patients were subjected to following investigations.

- Complete blood count
- C reactive protein
- Blood urea
- Serum creatinine
- Serum electrolytes
- Random blood sugar

- Urine analysis
    - Routine
    - Microscopy
    - Albumin creatinine ratio
- Blood culture and sensitivity

All these findings were noted on a predesigned and pretested proforma (Annexure-II).

Procedure

At the time of admission and again after 24 hours, patients were assessed for vital signs and symptoms of systemic inflammatory response syndrome (SIRS) and/or infection. Infection was delineated by presence of clinical signs and laboratory markers of inflammation along with presence of polymorphonuclear cells in a normally sterile body fluid and/or culture or gram stain of body fluids showing a pathogenic microorganism and/or radiological or visual evidence of an infective focus.

The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions were used to delineate patients with SIRS, sepsis, severe sepsis and septic shock.

<u>Definition of systemic inflammatory response syndrome (SIRS)</u>

- Body temperature < 36°C or > 38°C
- Heart rate > 90 beats per minute
- Respiratory rate

- > 20 breaths per minute or,
- An arterial partial pressure of carbon dioxide <4.3 kPa (32 mmHg)

- White blood cell count
  - < 4000 cells/mm^3 (4 x 109 cells/L) or
  - > 12,000 cells/mm^3 (12 x 109 cells/L), or
  - The presence of > 10% immature neutrophil band forms.

Severe sepsis

- Fulfilling at least ≥ 2 of SIRS criteria.
- Associated or suspected source of infection
- One or more of the following
  - Evidence of end organ damage
    - Elevated creatinine levels, > 120 μmol/L or
    - Altered mental status, GCS < 14
  - Serum lactate levels of ≥ 4mg/dL
  - Episode of hypotension (<90/60 mmHg), which responds to initial fluid resuscitation.

Septic shock

- Fulfilling at least ≥ 2 or more of SIRS criteria
- Associated or suspected source of infection
- Persistent hypotension (<90/60 mmHg) which does not respond to adequate fluid resuscitation.

On the basis of the above, patients were divided into two groups: patients *without sepsis* and patients with *sepsis* [patients with severe sepsis and septic shock].

Study variables

Estimation of urinary albumin creatinine ratio (UACR)

Spot urine samples were collected at the time of admission and again at 24 hours, for quantification of UACR. Urine samples were received in the biochemistry lab and stored at -20°C till analysis. Urinary microalbumin was measured by the immunoturbidimetric method and urinary creatinine by modified kinetic Jaffe reaction.[83]

Microalbuminuria

Microalbuminuria was defined by UACR values between 30 to 300 mg/g. UACR of >300 mg/g was considered as clinical proteinuria. Trend of microalbuminuria was assessed from the change of UACR value at admission to the UACR value at 24 hours. A UACR of ≥ 0.20 was considered as microalbuminuria.[84]

Outcome

The outcome was considered as survival and mortality.

Length of hospital stay

The length of hospital stay was determined as stay from the date of admission to discharge.

Statistical methods

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analysed using SPSS version 20. The categorical data was expressed in terms of rates, ratios and percentages and the continuous data was expressed in terms of mean ± standard deviation. The association between the outcome, clinical and demographic characteristics was tested using Chi-square test or Fisher's exact test. Continuous data was compared using independent sample 't' test. The accuracy of UACR in discriminating the survival at admission and 24 hours after admission was determined by calculating sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio. At 95% confidence interval, a probability (p) value of ≤ 0.050 was considered as statistically significant.

RESULTS

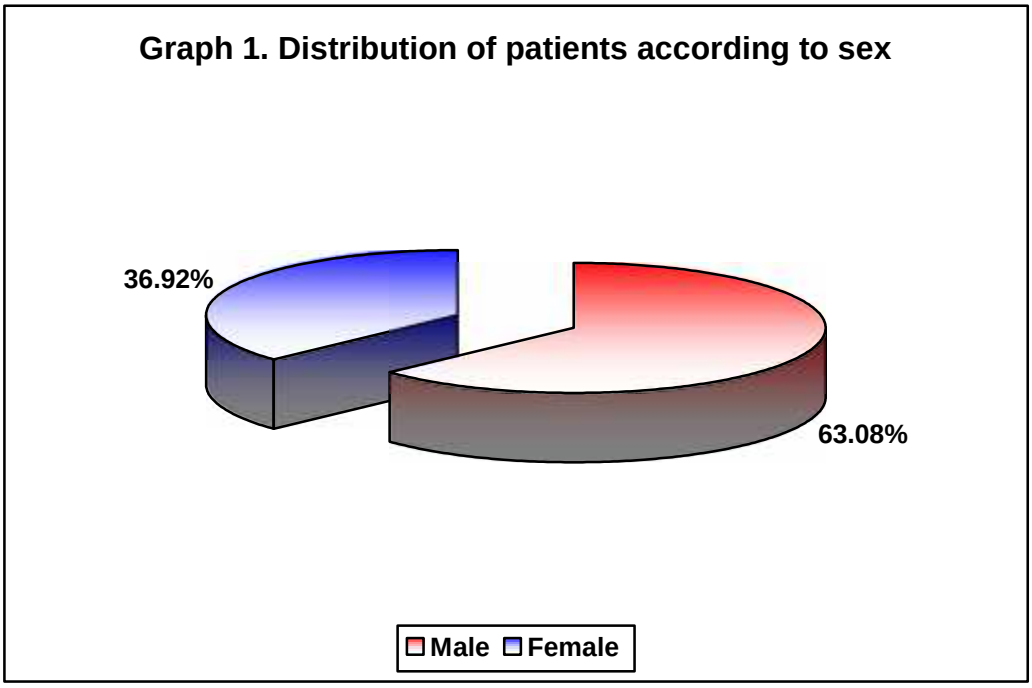
The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

A total of 65 adult patients admitted in ICU with the diagnosis of SIRS as defined by American College of Chest Physicians and Society of Critical Care Medicine from January 2014 to December 2014 were studied.

The data obtained was analysed and the final results were tabulated and interpreted as below.

Table 1. Distribution of patients according to sex

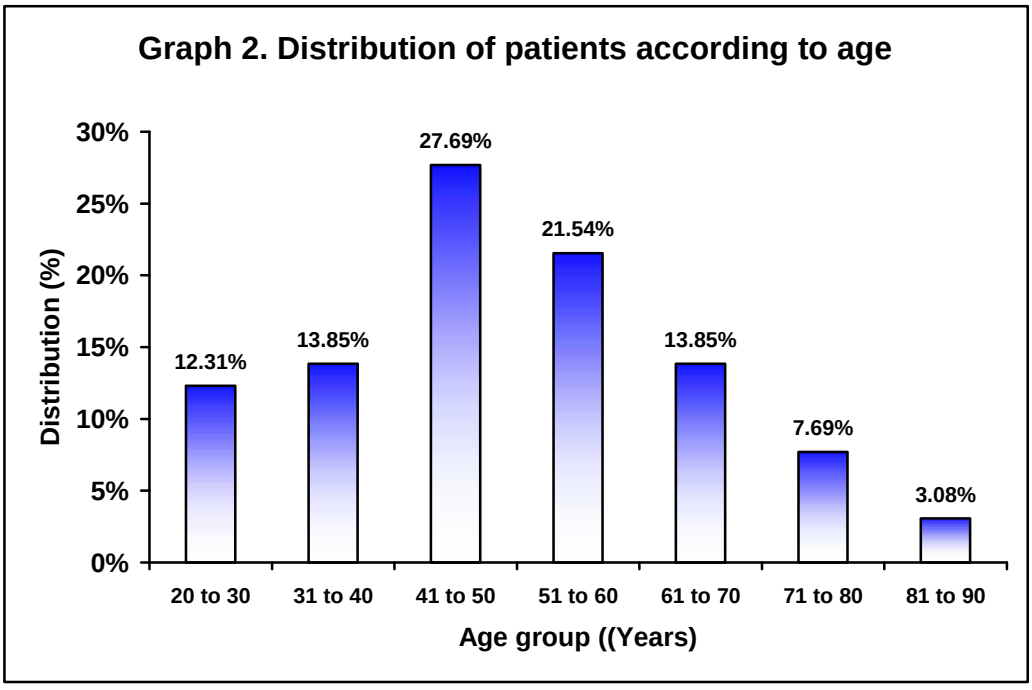
Sex	Distribution (n=65)	
	Number	**Percentage**
Male	41	63.08
Female	24	36.92
Total	**65**	**100.00**



In the present study most of the patients were males (63.08%). The male to female ratio was 1.70:1.

Table 2. Distribution of patients according to age

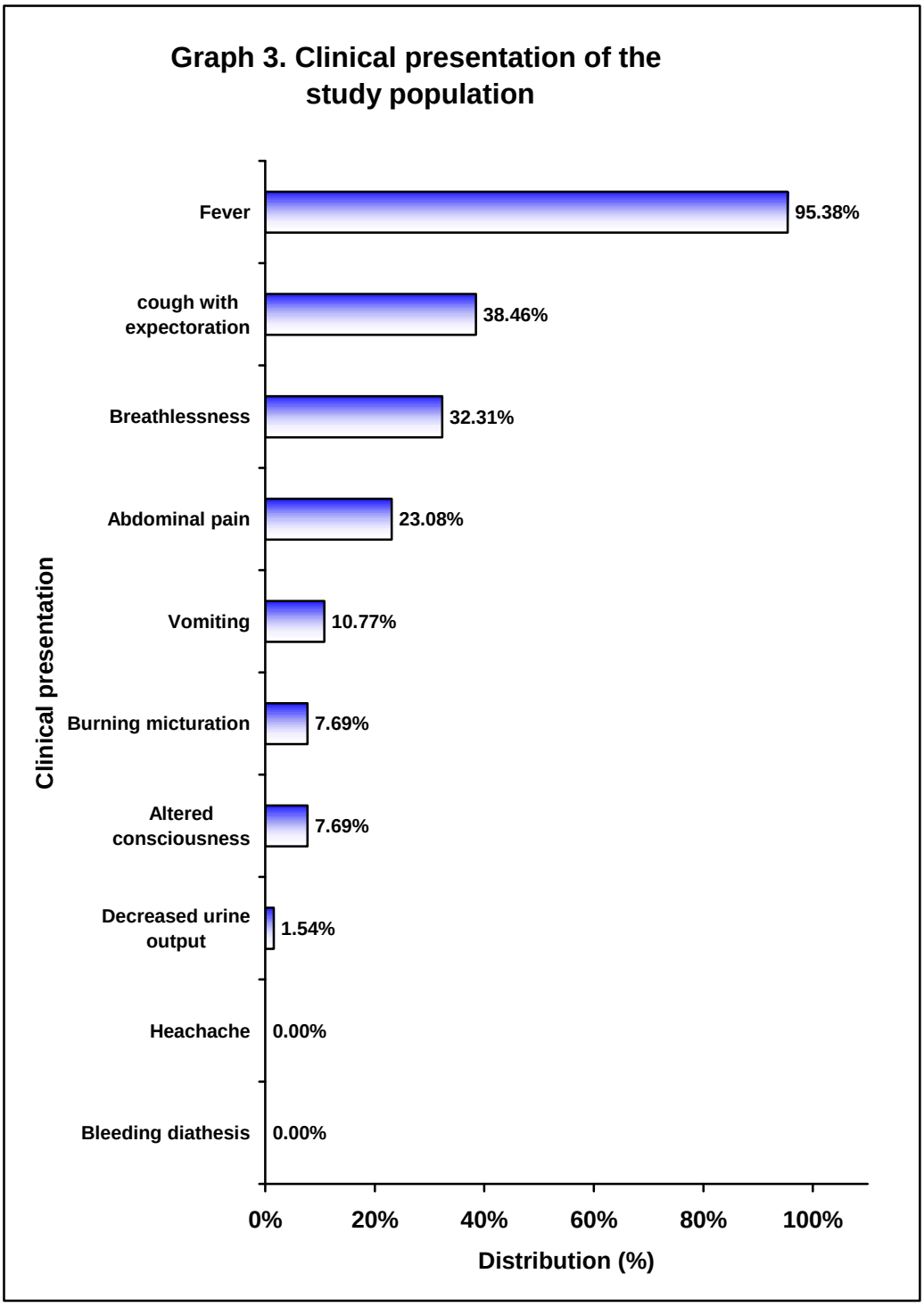
Age group (Years)	Distribution (n=65)	
	Number	**Percentage**
20 to 30	8	12.31
31 to 40	9	13.85
41 to 50	18	27.69
51 to 60	14	21.54
61 to 70	9	13.85
71 to 80	5	7.69
81 to 90	2	3.08
Total	**65**	**100.00**



In this study 27.69% of the patients were aged between 41 to 50 years and 21.54% were aged between 51 to 60 years.

Table 3. Clinical presentation of the study population

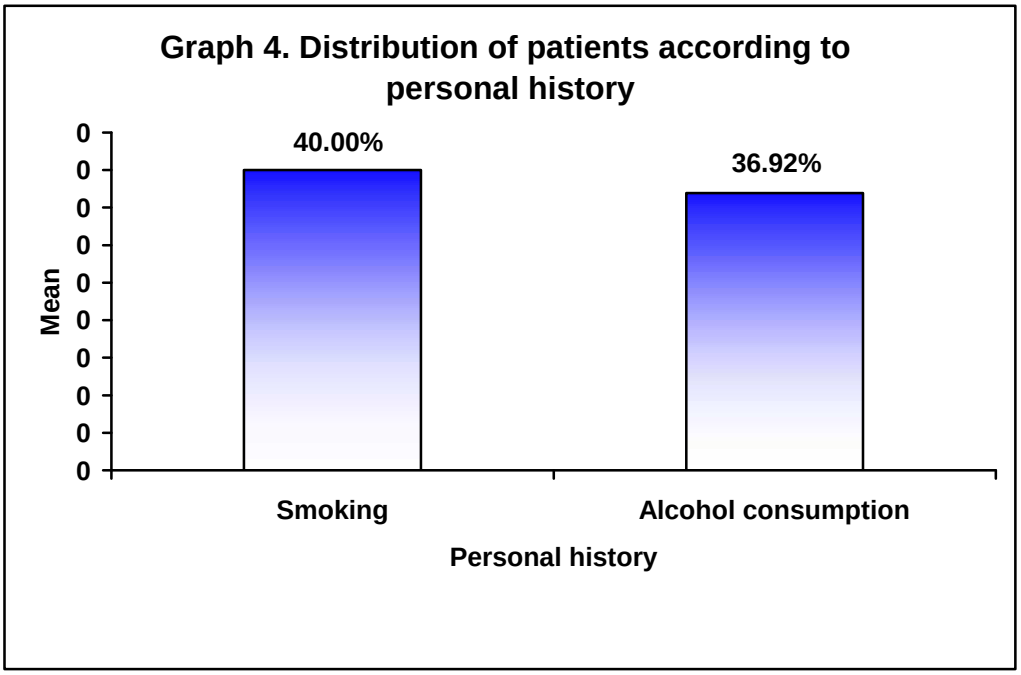
Clinical presentation	Distribution (n=65)	
	Number	**Percentage**
Fever	62	95.38
Cough with expectoration	25	38.46
Breathlessness	21	32.31
Abdominal pain	15	23.08
Vomiting	7	10.77
Burning micturation	5	7.69
Altered consciousness	5	7.69
Decreased urine output	1	1.54
Heachache	0	0.00
Bleeding diathesis	0	0.00



In the present study fever was the common clinical presentation (95.38%) followed by cough with expectoration (38.46%), breathlessness (32.31%) and abdominal pain (23.08%).

Table 4. Distribution of patients according to personal history

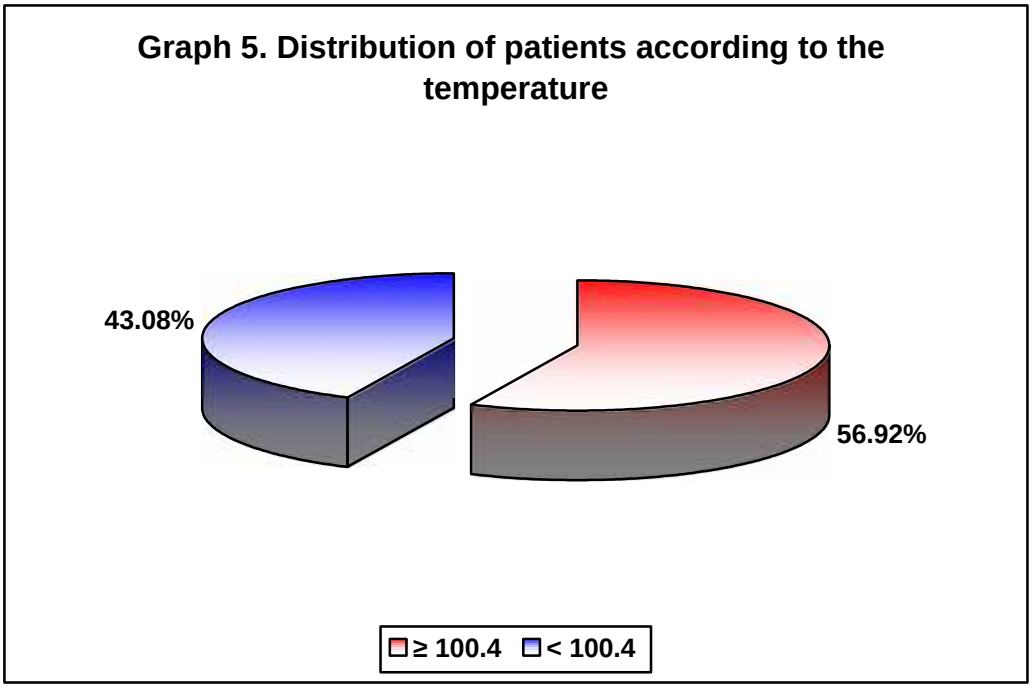
Personal history	Distribution (n=65)	
	Number	**Percentage**
Smoking	26	40.00
Alcohol consumption	24	36.92



In this study, history of smoking and alcohol consumption was present in 40% and 36.92% of the patients.

Table 5. Distribution of patients according to the temperature

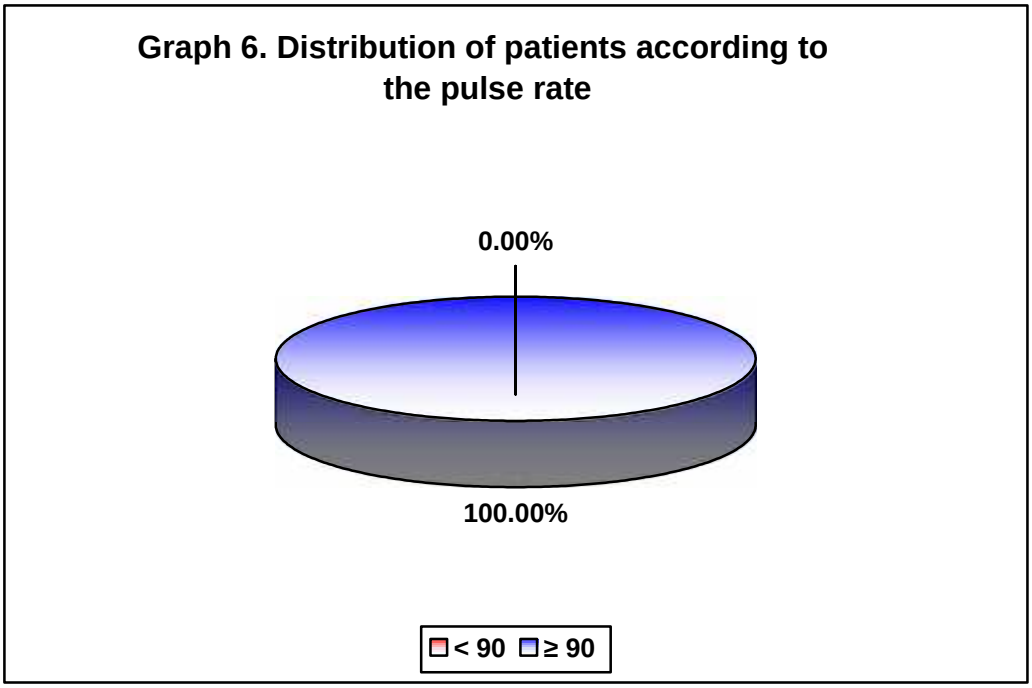
Temperature (^{0}F)	Distribution (n=65)	
	Number	**Percentage**
≥ 100.4	37	56.92
<100.4	28	43.08
Total	**65**	**100.00**



In the present study 56.92% of the patients had temperature of ≥ 100.4 ^{0}F.

Table 6. Distribution of patients according to the pulse rate

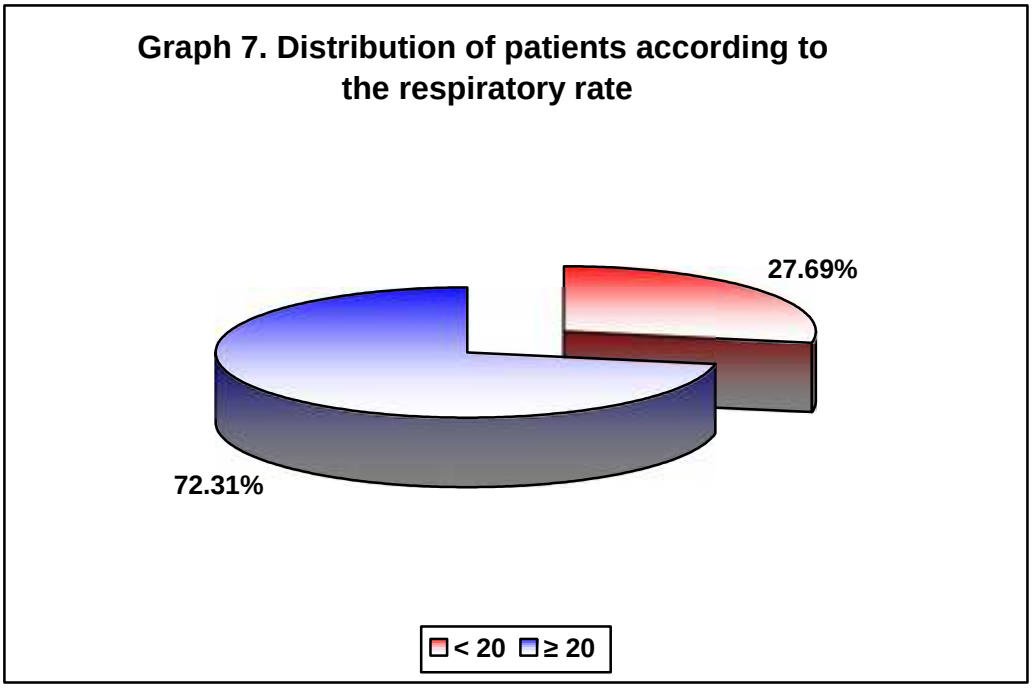
Pulse rate (/Minute)	Distribution (n=65)	
	Number	**Percentage**
< 90	0	0.00
≥ 90	65	100.00
Total	**65**	**100.00**



In this study all the patients had pulse rate of ≥ 90 / minute (100%)

Table 7. Distribution of patients according to the respiratory rate

Respiratory rate (/Minute)	Distribution (n=65)	
	Number	**Percentage**
< 20	18	27.69
≥ 20	47	72.31
Total	**65**	**100.00**

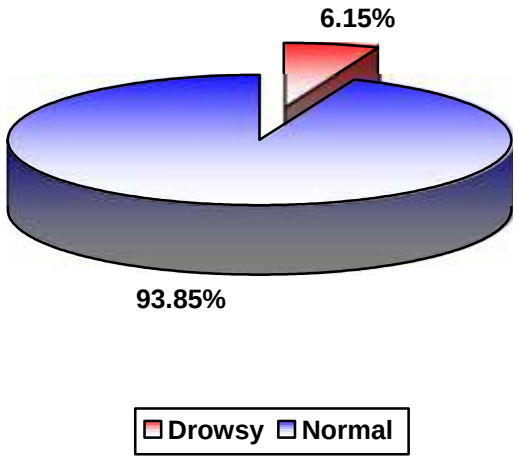


In this study majority (72.31%) of the patients had respiratory rate of ≥ 20 per minute

Table 8. Distribution of patients according to the findings on CNS examination

Findings	Distribution (n=65)	
	Number	**Percentage**
Drowsy	4	6.15
Normal	61	93.85
Total	**65**	**100.00**

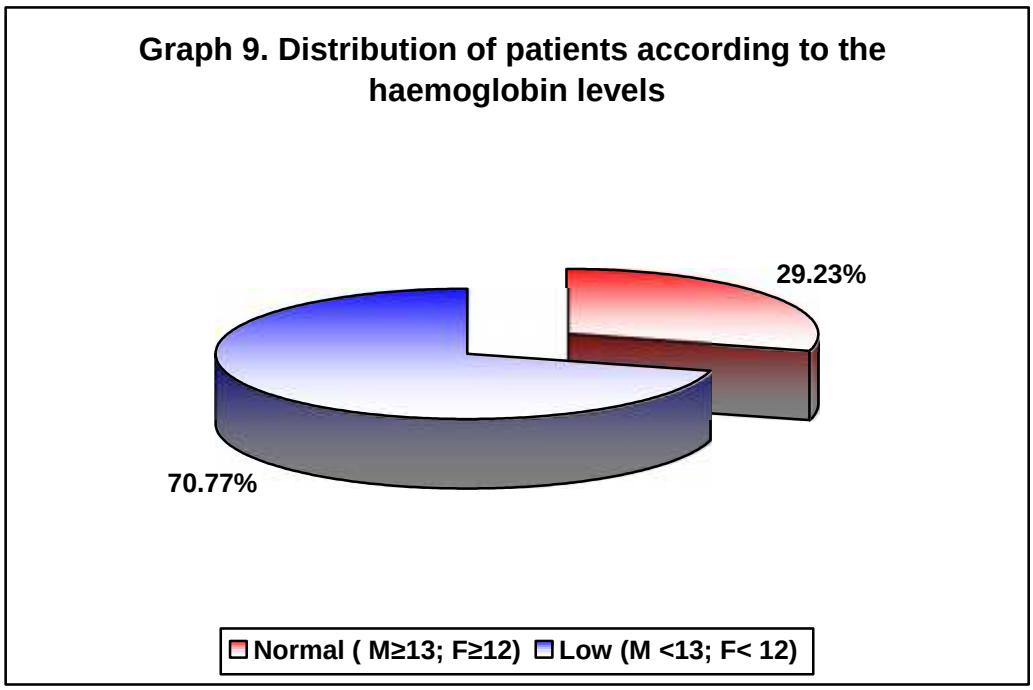
Graph 8. Distribution of patients according to the findings on CNS examination



In this study, drowsiness was noted in 6.15% of the patients.

Table 9. Distribution of patients according to the haemoglobin levels

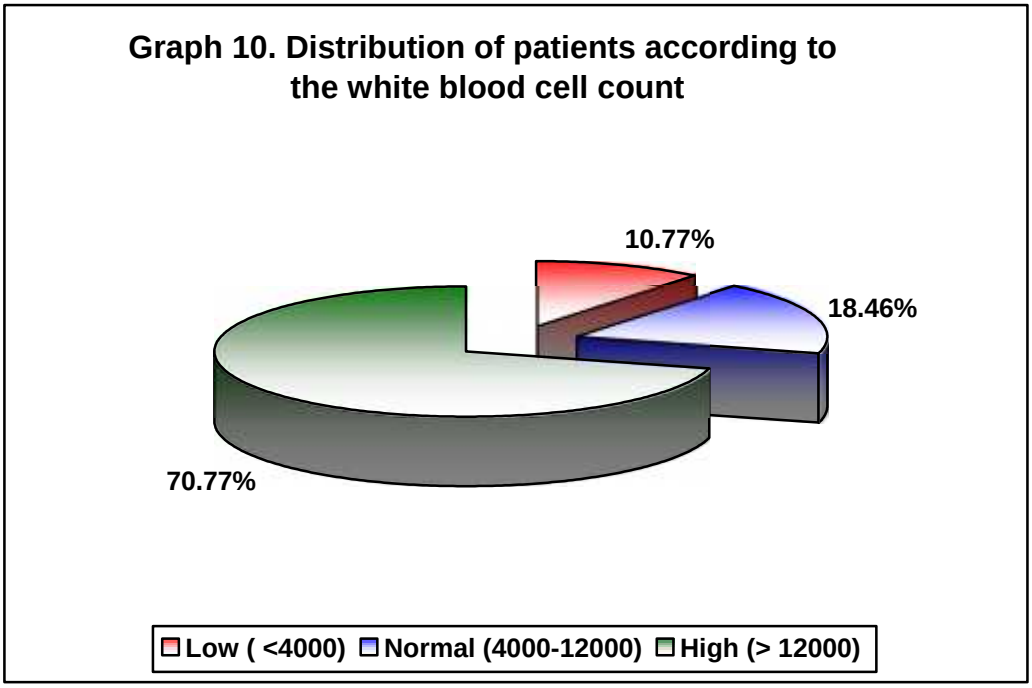
Haemoglobin (gm%)	Distribution (n=65)	
	Number	**Percentage**
Normal (M≥13; F≥12)	19	29.23
Low (M<13; F<12)	46	70.77
Total	**65**	**100.00**



In the present study majority of the patients had low haemoglobin levels (70.77%).

Table 10. Distribution of patients according to the white blood cell count

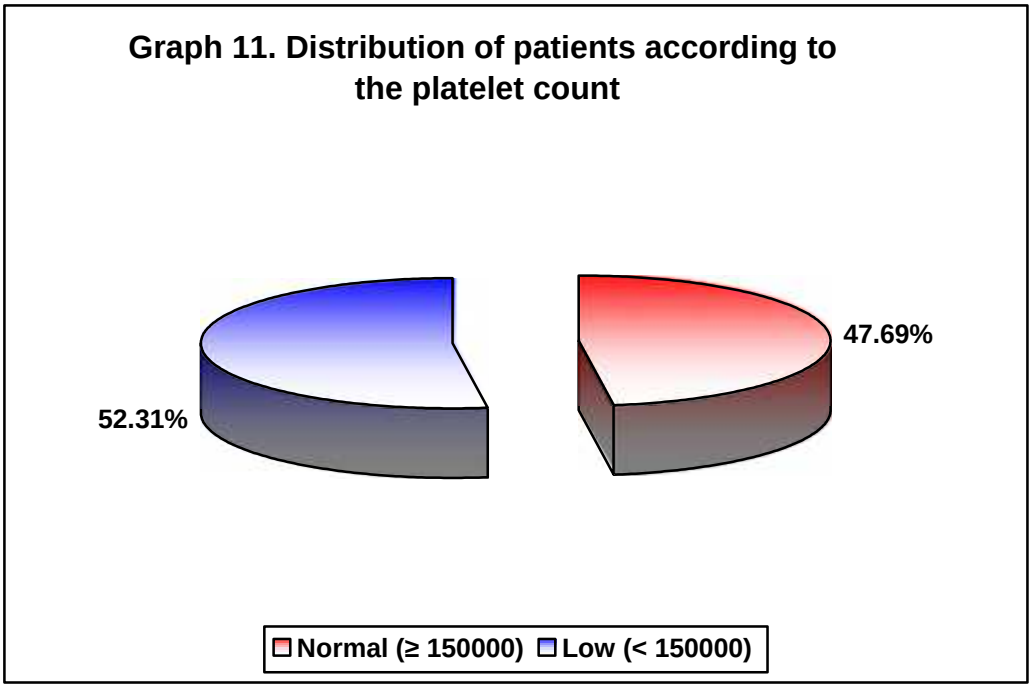
WBC (/Cumm)	Distribution (n=65)	
	Number	**Percentage**
Low (<4000)	7	10.77
Normal (4000-12000)	12	18.46
High (>12000)	46	70.77
Total	**65**	**100.00**



In this study 70.77% of the patients had raised while blood cell count (>12000 /Cumm)

Table 11. Distribution of patients according to the platelet count

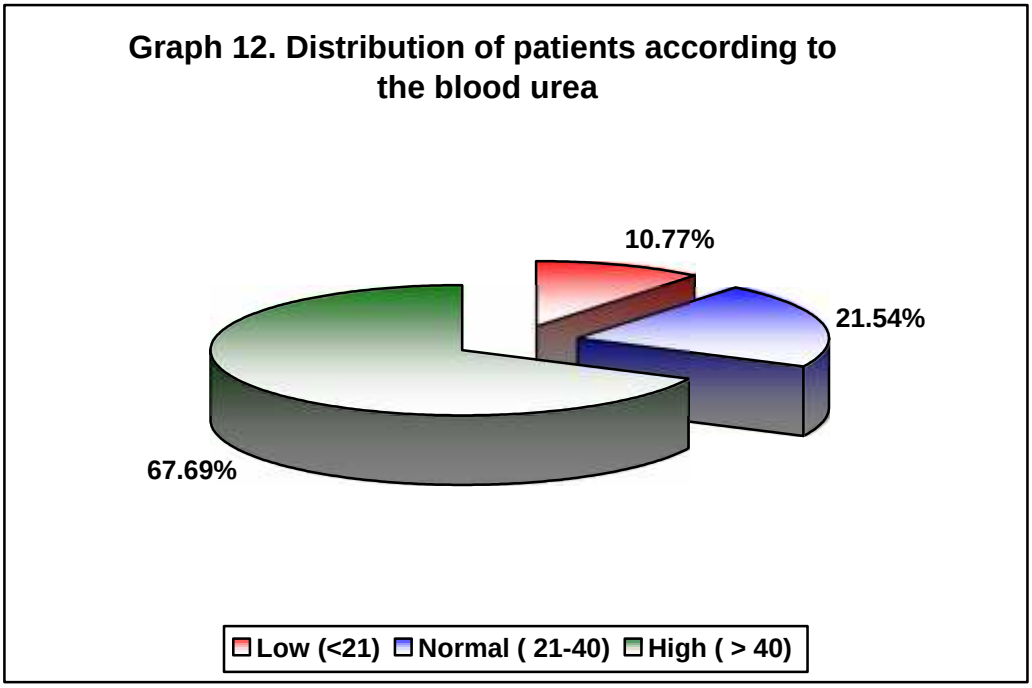
Platelet count (/Cumm)	Distribution (n=65)	
	Number	**Percentage**
Normal (≥ 150000)	31	47.69
Low (< 150000)	34	52.31
Total	**65**	**100.00**



In the present study platelet count was < 150,000 /Cumm in 52.31% of the patients.

Table 12. Distribution of patients according to the blood urea

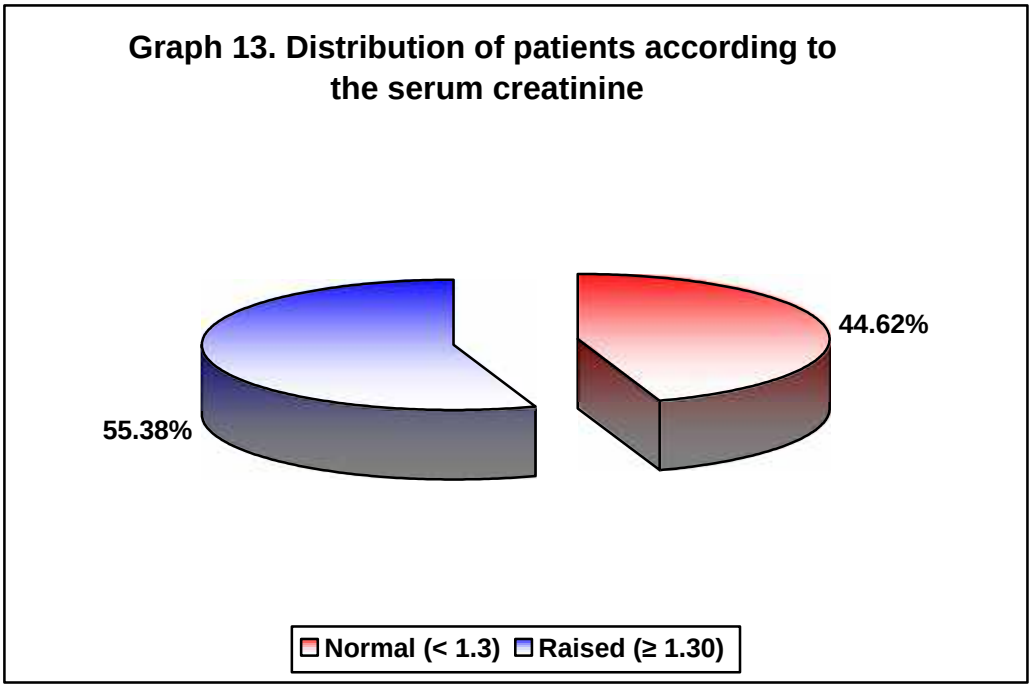
Blood urea (mg/dL)	Distribution (n=65)	
	Number	**Percentage**
Low (<21)	7	10.77
Normal (21-40)	14	21.54
High (>40)	44	67.69
Total	**65**	**100.00**



In this study blood urea levels were > 40 mg/dL in 67.69% of the patients.

Table 13. Distribution of patients according to the serum creatinine

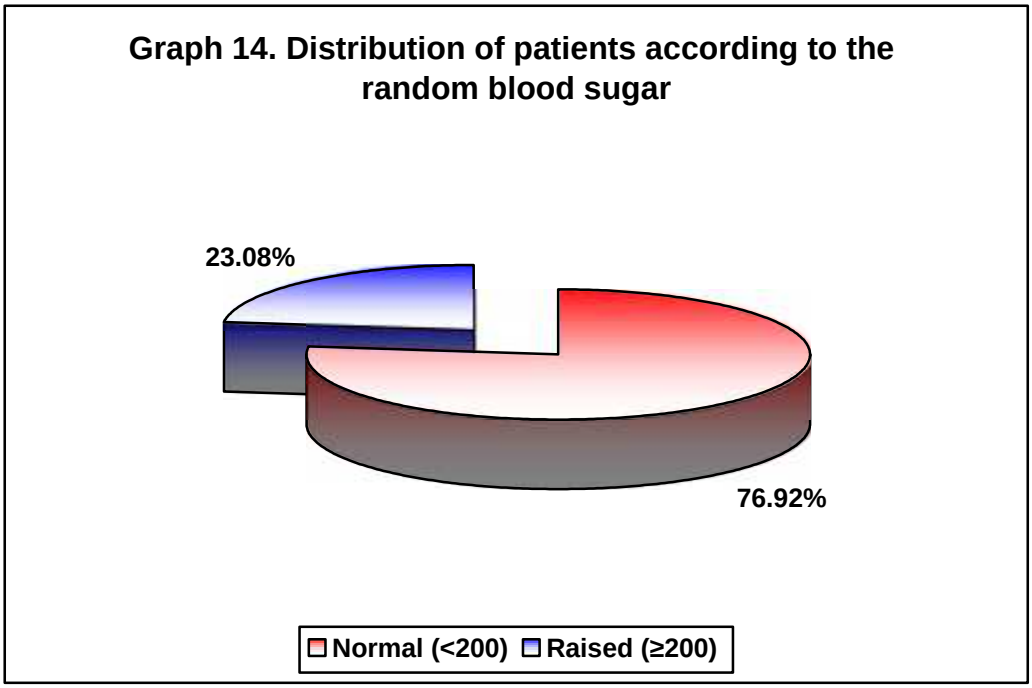
Serum creatinine (mg/dL)	Distribution (n=65)	
	Number	**Percentage**
Normal (< 1.3)	29	44.62
Raised (≥ 1.30)	36	55.38
Total	**65**	**100.00**



In the present study 55.38% of the patients had raised serum creatinine (≥1.30 mg/dL).

Table 14. Distribution of patients according to the random blood sugar

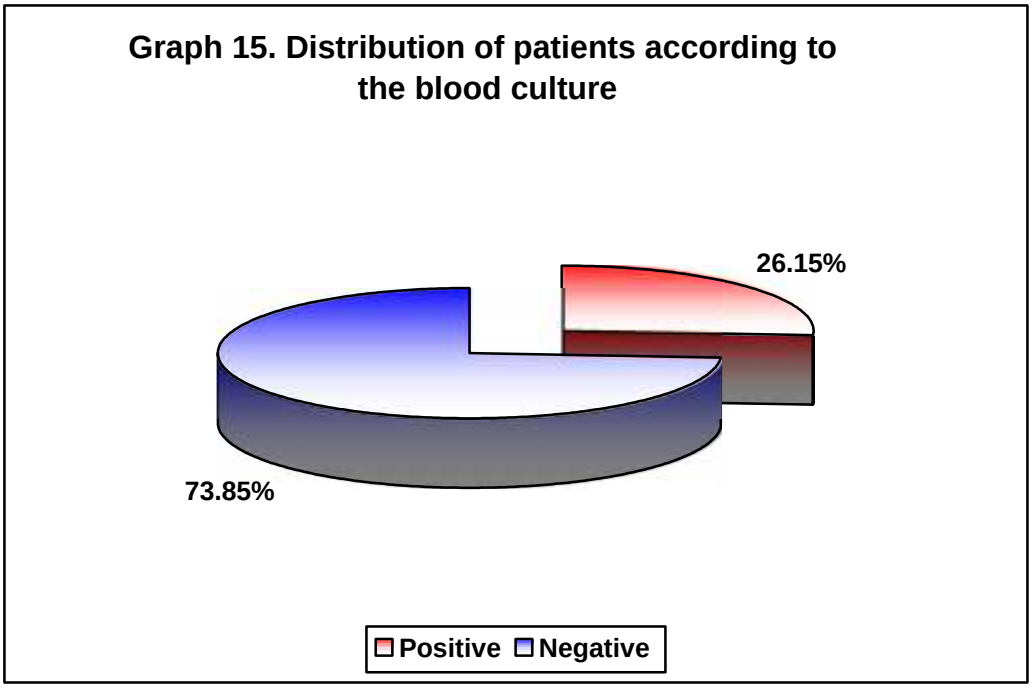
Random blood sugar (mg/dL)	Distribution (n=65)	
	Number	**Percentage**
Normal (<200)	50	76.92
Raised (≥200)	15	23.08
Total	**65**	**100.00**



In this study 23.08% of the patients had higher random blood sugar levels (≥200 mg/dL).

Table 15. Distribution of patients according to the blood culture

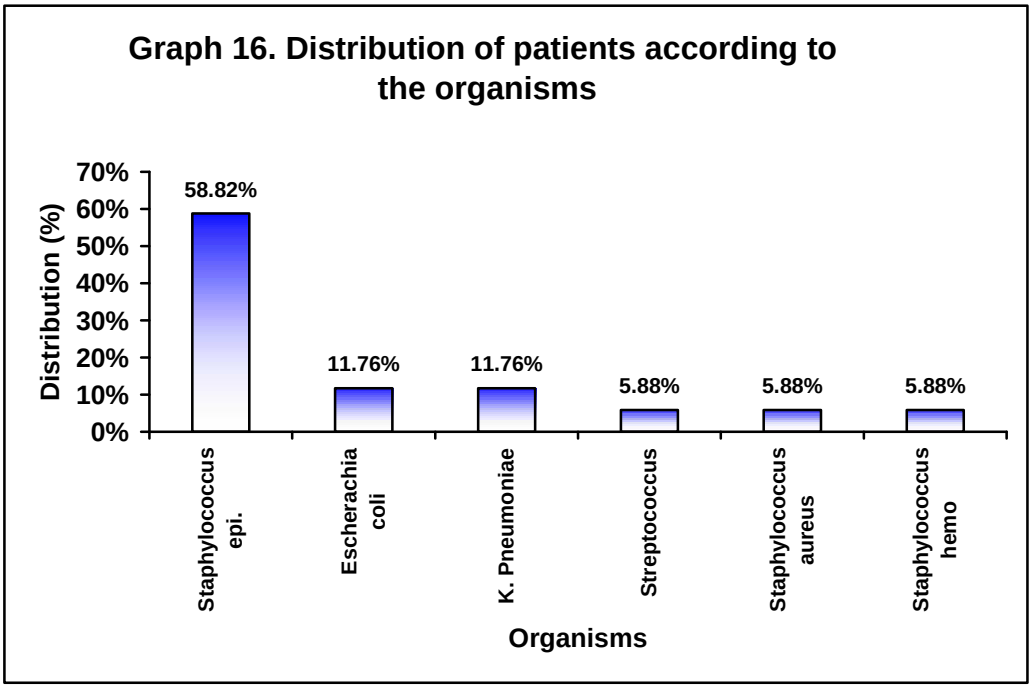
Culture	Distribution (n=65)	
	Number	**Percentage**
Positive	17	26.15
Negative	48	73.85
Total	**65**	**100.00**



In this study 26.15% of the patients had positive blood culture.

Table 16. Distribution of patients according to the organisms

Organisms	Distribution (n=17)	
	Number	**Percentage**
Staphylococcus epidermidis	10	58.82
Escherachia coli	2	11.76
K. pneumoniae	2	11.76
Streptococcus	1	5.88
Staphylococcus aureus	1	5.88
Staphylococcus hemo	1	5.88
Total	**17**	**100.00**

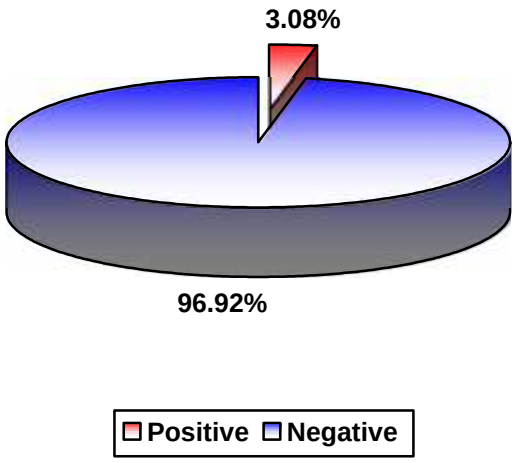


In the present study commonest organism isolated was staphylococcus epidermidis (58.82%) followed by escherachia coli and K. pneumoniae (11.76%).

Table 17. Distribution of patients according to the urine culture

Culture	Distribution (n=65)	
	Number	**Percentage**
Positive	2	3.08
Negative	63	96.92
Total	**65**	**100.00**

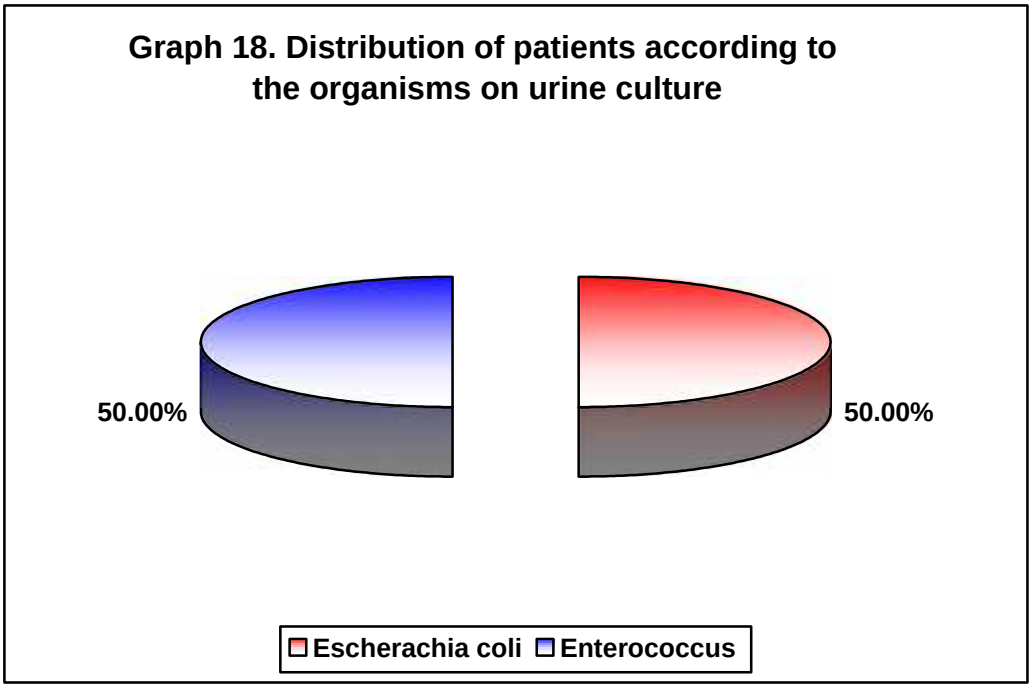
Graph 17. Distribution of patients according to the urine culture



In this study urine culture was positive in 3.08% of the patients.

Table 18. Distribution of patients according to the organisms on urine culture

Organisms	Distribution (n=2)	
	Number	**Percentage**
Escherachia coli	1	50.00
Enterococcus	1	50.00
Total	**2**	**100.00**



In the present study of the 2 patients with positive urine culture 1 each had Escherachia coli (50%) and enterococcus (50%).

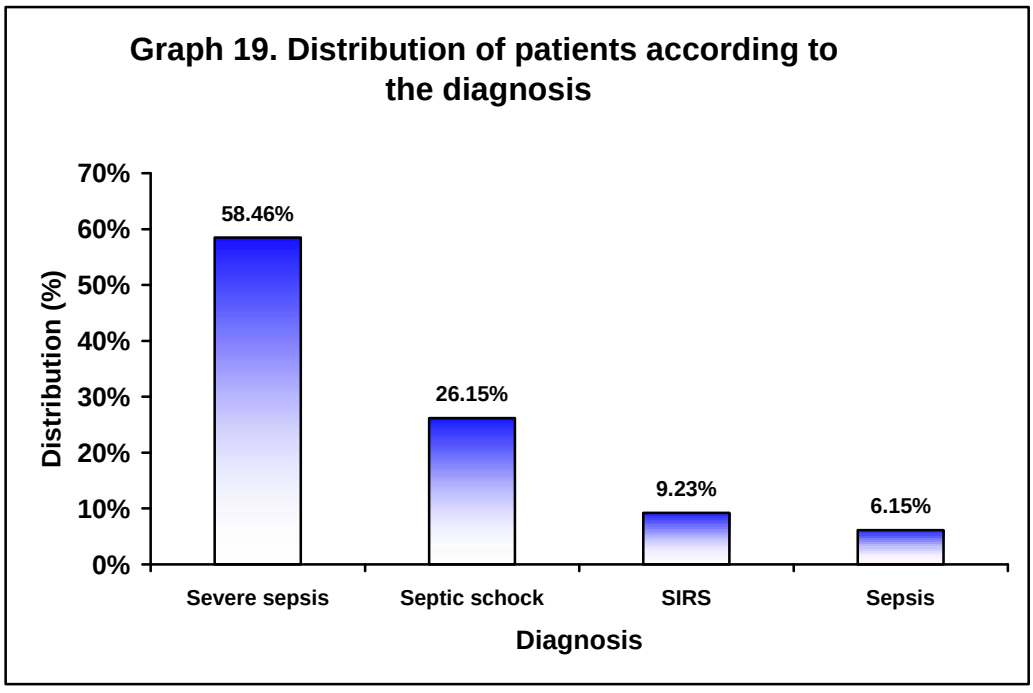
Table 19. Distribution of patients according to the primary diagnosis

Diagnosis	Distribution (n=65)	
	Number	**Percentage**
Pneumonia	24	36.92
Cellulitis	15	23.08
Acute gastroenteritis	6	9.23
COPD	4	6.15
Acute bacterial encephalitis	2	3.08
Blood transfusion reaction	2	3.08
Viral fever with thrombocytopenia	2	3.08
Cirrhosis	1	1.54
Gluteal Abscess	1	1.54
Hepatic encephalopathy	1	1.54
Liver abscess	1	1.54
Meningitis	1	1.54
Oral mucormycosis	1	1.54
Peritonitis	1	1.54
ARDS	1	1.54
Bacterial meningitis	1	1.54
Viral meningoencephalitis	1	1.54
Total	**65**	**100.00**

In the present study the commonest diagnosis was pneumonia (36.92%) followed by cellulitis (23.08%).

Table 20. Distribution of patients according to the diagnosis

Diagnosis	Distribution (n=65)	
	Number	**Percentage**
Severe sepsis	38	58.46
Septic shock	17	26.15
SIRS	6	9.23
Sepsis	4	6.15
Total	**65**	**100.00**

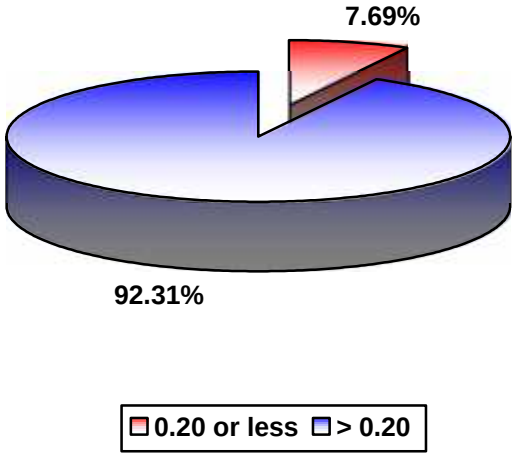


In this study severe sepsis was the commonest diagnosis noted in 58.46% of the patients followed by septic shock which was noted in 26.15% of the patients.

Table 21. Distribution of patients according to the UACR at admission

UACR	Distribution (n=65)	
	Number	**Percentage**
0.20 or less	5	7.69
> 0.20	60	92.31
Total	**65**	**100.00**

Graph 20. Distribution of patients according to the UACR at admission

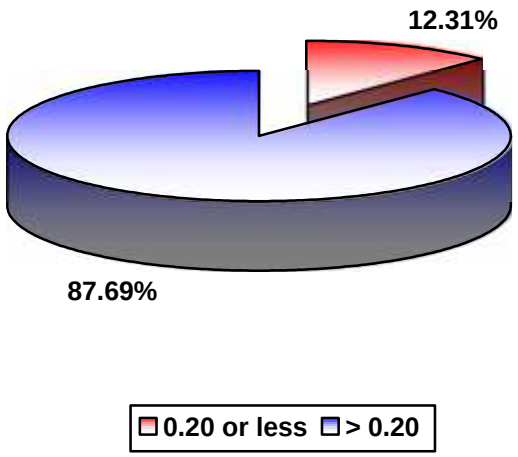


In this study UACR at admission was >0.20 in 92.31% of the patients.

Table 22. Distribution of patients according to the UACR at 24 hours after admission

UACR	Distribution (n=65)	
	Number	**Percentage**
0.20 or less	8	12.31
> 0.20	57	87.69
Total	**65**	**100.00**

Graph 21. Distribution of patients according to the UACR at 24 hours after admission



In the present study UACR 24 hours after admission was > 0.20 in 87.69% of the patients.

Table 23. Association of sepsis with UACR

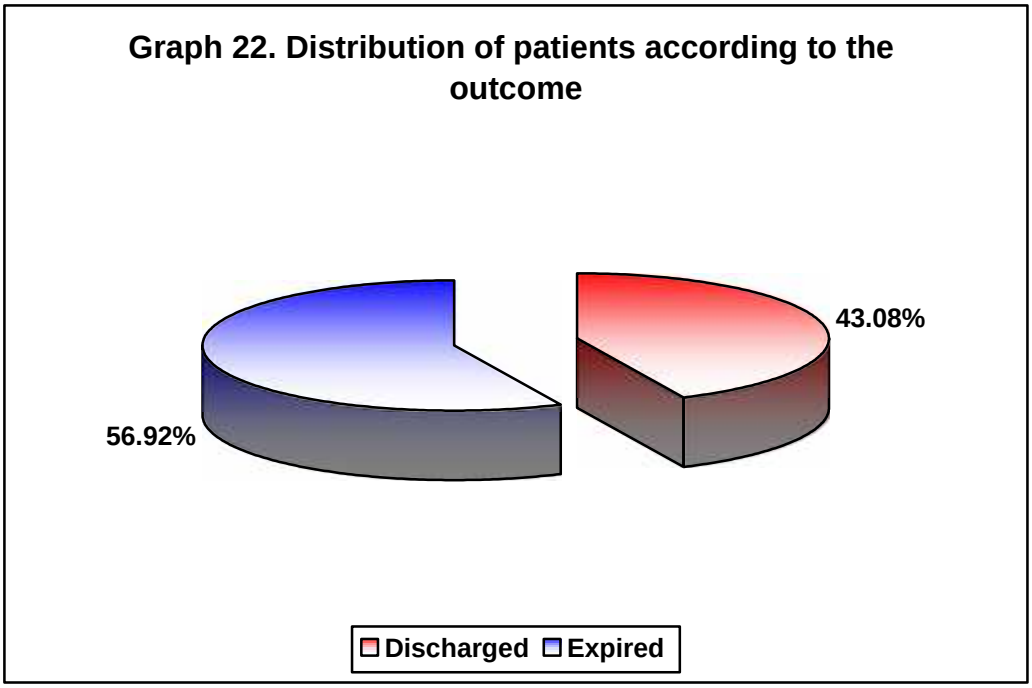
Interval	UACR	Diagnosis				Total		'p' value
		Sepsis		SIRS				
		No.	%	No.	%	No.	%	
At admission	> 0.20	59	98.33	1	1.67	60	100.00	**<0.001**
	≤ 0.20	0	0.00	5	100.00	5	100.00	
	Total	**59**	**90.77**	**6**	**9.23**	**65**	**100.00**	
24 hours After admission	> 0.20	56	98.25	1	1.75	57	100.00	**<0.001**
	≤ 0.20	3	37.50	5	62.50	8	100.00	
	Total	**59**	**90.77**	**6**	**9.23**	**65**	**100.00**	

In the present study out of 60 patients with UACR of >0.20 at admission, 98.33% had sepsis (p<0.001). The sensitivity of > 0.20 UACR at admission was 100% with 83.33% specificity, 98.33% PPV and 100% NPV and the positive likelihood ratio was 6.

Out of 57 patients with UACR of >0.20 at 24 hours after admission, 98.25% had sepsis (p<0.001). The UACR of >0.20 at 24 hours after admission was 94.92% sensitive and 83.33% specific with PPV of 98.25% and NPV of 62.5%. The positive likelihood ratio was 5.69.

Table 24. Distribution of patients according to the outcome

Outcome	Distribution (n=65)	
	Number	**Percentage**
Discharged	28	43.08
Expired	37	56.92
Total	**65**	**100.00**



In this study 56.92% of the patients expired and 43.08% recovered.

Table 25. Association of outcome with UACR

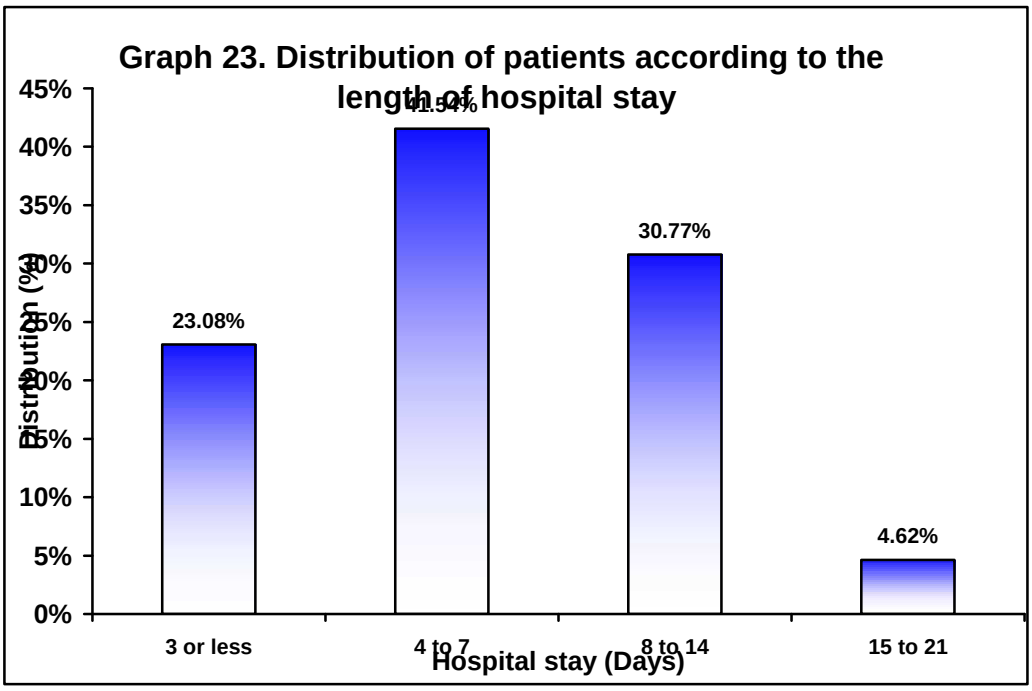
Interval	UACR	Outcome				Total		'p' value
		Expired		Improved				
		No.	%	No.	%	No.	%	
At	> 0.20	37	61.67	23	38.33	60	100.00	**0.012**
admission	≤ 0.20	0	0.00	5	100.00	5	100.00	
	Total	**37**	**56.92**	**28**	**43.08**	**65**	**100.00**	
24 hours	> 0.20	37	64.91	20	35.09	57	100.00	**0.001**
After	≤ 0.20	0	0.00	8	100.00	8	100.00	
admission	**Total**	**37**	**56.92**	**28**	**43.08**	**65**	**100.00**	

In the present study out of 60 patients with UACR of >0.20 at admission, 61.67% of the patients expired (p=0.012). The sensitivity of > 0.20 UACR at admission in predicting mortality was 100% with 17.86% specificity, 61.67% PPV and 100% NPV and the positive likelihood ratio was 1.22.

Out of 57 patients with UACR of >0.20 at 24 hours after admission, 64.91% of the patients expired (p=0.001). The UACR of >0.20 at 24 hours after admission was 100% sensitive and 28.57% specific in predicting mortality with PPV of 64.91% and NPV of 100% . The positive likelihood ratio was 1.40.

Table 26. Distribution of patients according to the length of hospital stay

Hospital stay (Days)	Distribution (n=65)	
	Number	**Percentage**
3 or less	15	23.08
4 to 7	27	41.54
8 to 14	20	30.77
15 to 21	3	4.62
Total	**65**	**100.00**



In the present study most of the patients had hospital stay between 4 to 7 days (41.54%) followed by 8 to 14 days (30.77%).

Table 27. Association of length of hospital stay with UACR

Interval	Hospital stay	UACR				Total		'p' value
		>0.20		≤0.20				
		No.	%	No.	%	No.	%	
At	3 or less	15	100.00	0	0.00	15	100.00	0.495
admission	4 to 7	25	92.59	2	7.41	27	100.00	
	8 to 14	17	85.00	3	15.00	20	100.00	
	14 to 21	3	100.00	0	0.00	3	100.00	
	Total	**60**	**92.31**	**5**	**7.69**	**65**	**100.00**	
24 hours	3 or less	13	86.67	2	13.33	15	100.00	1.000
After	4 to 7	24	88.89	3	11.11	27	100.00	
admission	8 to 14	17	85.00	3	15.00	20	100.00	
	14 to 21	3	100.00	0	0.00	3	100.00	
	Total	**57**	**87.69**	**8**	**12.31**	**65**	**100.00**	

In the present study no association was found between length of hospital stay and UACR assessed at admission (p=0.495) as well as after 24 hours after admission (p=1.000).

Table 28. Comparison of mean UACR with diagnosis

Interval	Diagnosis				p value
	Sepsis		SIRS		
	Mean	SD	Mean	SD	
UACR at admission	0.98	0.54	0.27	0.28	0.003
UACR at 24 hours	1.17	0.66	0.40	0.06	0.008

In this study mean UACR at admission in patients with sepsis was significantly high at admission (0.98 ± 0.54 vs 0.27 ± 0.28; p=0.003) as well as at 24 hours after admission (1.17 ± 0.66 vs 0.40 ± 0.06; p=0.008).

Table 29. Comparison of mean UACR with outcome

Interval	Outcome				p value
	Expired		Improved		
	Mean	SD	Mean	SD	
UACR at admission	1.15	0.52	0.58	0.42	<0.001
UACR at 24 hours	1.58	0.40	0.46	0.42	<0.001

In the present study significantly higher mean UACR value was noted at admission in patients who expired (1.15 ± 0.52 vs 0.58 ± 0.42; p<0.001) and at 24 hours after admission (1.58 ± 0.40 vs 0.46 ± 0.42; p<0.001) compared to those who improved.

Table 30. Characteristics of the study population

Variable	Mean		Median	Range	
	Mean	SD		Minimum	Maximum
Age (Years)	51.12	15.87	50	20	84
Temperature	100.41	2.18	101	88	104
Pulse (/Minute)	112.49	9.57	110	90	140
Respiratory rate (/Minute)	24.69	7.42	27	11	36
Systolic BP (mm Hg)	83.78	12.32	80	60	110
Diastolic BP (mm Hg)	59.02	8.29	60	40	80
Haemoglobin (gm%)	11.06	3.24	11.10	2.00	18.50
White blood cell count (/Cumm)	16700.00	11049.53	14000	1300	54300
Platelet count (/Cumm)	158227.69	140012.64	123000	5000	764000
Blood urea (mg/dL)	72.57	52.62	68	12	320
Serum creatinine (mg/dL)	1.88	1.15	1.5	0.57	6.50
Random blood sugar (mg/dL)	163.29	101.93	129	51	590
UACR at admission	0.91	0.56	0.81	0.09	2.83
UACR 24 hours	1.10	0.69	1.26	0.09	2.69
Length of stay (Days)	6.49	4.01	6	2	21

The clinical and biochemical profile of patients admitted is as shown in table 30.

DISCUSSION

Sepsis remains a major global health care concern, owing to high morbidity and mortality, despite the advances in medical therapeutics.[64] Sepsis is characterized by SIRS(systemic inflammatory response syndrome) and the presence of known or suspected infection.[78]

It is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release plethora of pro-inflammatory molecules into circulation.[79] The endothelium becomes dysfunctional due to sustained onslaught of inflammatory molecules. An early event is loss of barrier integrity leading to systemic capillary leak.[7] The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in urine.[81]

Biomarkers of sepsis such as PCT and CRP which are considered specific and sensitive in identifying systemic bacterial infections hold much promise for rapid diagnosis and risk stratification. Despite extensive research, no single biomarker can yet serve as the lone diagnostic parameter. There is still a need for robust cost effective analyses in sepsis which will be of keen interest in India to determine potential rational implementation strategies. While there are publications in India evaluating various biomarkers in sepsis, the level of evidence is still not such to make definitive recommendations for use.[7]

Assay of amount of albumin excreted in random urine sample, expressed as Albumin Creatinine Ratio is simple, validated and reliable test. Levels of microalbuminuria increases within hours of inflammatory insult.[14,15] Hence the

present study was undertaken to evaluate microalbuminuria as a biomarker of sepsis and further to evaluate the ability of microalbuminuria to predict ICU mortality.

This one year cross sectional study was done in Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 65 adult patients admitted in ICU with the diagnosis of SIRS defined by ACCP and SCCM were enrolled. All the patients were evaluated for microalbuminuria at admission and 24 hours after admission.

In the present study male preponderance was noted that is, nearly two thirds of the patients (63.08%) were males and the male to female ratio was 1.70:1. A similar study by Basu S. et al.[14] also reported 62.8% of the males and 37.2% females. Our observations were also similar to the study by Bhadade RR et al.[13] where 67.2% of the patients were males and 32.8% of the patients were females.

In this study 27.69% of the patients were aged between 41 to 50 years and 21.54% of the patients between 51 to 60 years. The youngest patients was aged 20 years and the oldest patient was aged 84 years. The mean age was 51.12 ± 15.87 years and median age was 50 years. The mean age observed in the present study was similar to that of a study by Drumheller BC et al.[62] who reported mean age of 51.2 ± 17.0 years. However, the mean age observed in the in the present study differed from the similar studies reported in India by Basu S. et al.[14] and Bhadade RR et al.[13] who reported median age of 63.5 years and 33 years.

In the present study fever was the commonest clinical symptom noted in 95.38% followed by cough with expectoration in 38.46%, breathlessness in 32.31% and abdominal pain in 23.08%. With regard to SIRS criteria, all the patients (100%)

had pulse rate of >90 /minute, 56.92% of the patients had temperature of ≥ 100.4 ^{0}F, and majority (72.31%) of the patients had respiratory rate of ≥ 20 per minute. Drowsiness was present in 6.15% of the patients. With regard to haematological profile, majority of the patients had low haemoglobin levels (70.77%) and while blood cell count >12000 /Cumm (70.77%) while platelet count was <150,000 /Cumm in 52.31% of the patients. Renal profile revealed raised blood urea levels (>40 mg/dL) in 67.69% of the patients and 55.38% of the patients had raised serum creatinine (>1.30 mg/dL). The blood culture was positive in 26.15% of the patients and commonest organism isolated was staphylococcus epidermidis (58.82%) followed by escherachia coli (11.76%) and K. pneumoniae (11.76%). Urine microscopy revealed positive urine culture in 2 (3.08%) patients and 1 each had Escherachia coli (50%) and enterococcus (50%).

In this study, primary reason for the ICU admission was pneumonia which was noted in 36.92% of the patients followed by cellulitis in 23.08%. A similar study by Basu S. et al.[14] reported the primary reasons for admission to ICU as acute respiratory failure (COPD) (19.14%) followed by gastrointestinal bleeding (11.70%), congestive heart failure (5.31%), acid base electrolyte disturbance (5.31%), and other causes (58.51%). However in the present study COPD was the cause of ICU admission in 6.15% of the patients and acute gastroenteritis was noted in 9.23% of the patients.

In this study out of 65 patients, 38 (58.46%) patients developed severe sepsis and 17 (26.15%) developed septic shock while only 4 (6.15%) developed sepsis and SIRS was present in 6 (9.23%) patients. In a study by Basu S. et al.,[14] of the 94 patients, 32% of the patients belonged to sepsis group out of which 24.46% of the

patients had sepsis, 2.12% had severe sepsis and 5.31% had septic shock while 68% of the patients comprised of non-sepsis group (12.76% of the patients without SIRS, 55.31% with SIRS). Similarly Bhadade RR et al.[13] in their study on 125 patients reported 69.6% of the patients with sepsis group and 30.4% of the patients belonged to non-sepsis group. In the present study the frequency of sepsis was very high (90.77%) compared to the studies by Basu S. et al.[14] and Bhadade RR et al.[13]

In this study UACR was raised (>0.20) in 92.31% of the patients at admission which persisted in 87.69% of the patients at 24 hours after admission. These findings differed when compared to a study by Basu S. et al.[14] who encountered 78% of the patients with microalbuminuria within 6 hours of admission with a median ACR value of 125.6 (IQR 37.4 - 229.7) mg/g and at 24 hours of admission, microalbuminuria persisted in 67% of the patients.

In the present study out of 65 patients 90.77% had sepsis and 9.23% had SIRS. UACR was >0.20 at admission in all the 59 (98.33%) patients who had sepsis ($p<0.001$). The UACR of >0.20 at admission was 100% sensitive in predicting sepsis and 83.33% specific with 98.33% positive predictive value and 100% negative predictive value with positive likelihood ratio of 6. Further of the 57 patients with UACR of >0.20 at 24 hours after admission, 98.25% had sepsis ($p<0.001$). The UACR of >0.20 at 24 hours after admission showed 94.92% sensitivity, 83.33% specificity, 98.25% PPV and 62.5 NPV with positive likelihood ratio of 5.69. Also the mean UACR at admission in patients with sepsis was significantly high at admission (0.98 ± 0.54 vs 0.27 ± 0.28; $p=0.003$) as well as at 24 hours after admission (1.17 ± 0.66 vs 0.40 ± 0.06; $p=0.008$). These findings suggest

that UACR of > 0.20 at admission had excellent discriminating power in predicting sepsis among patients with SIRS

A similar study by Basu S. et al.[14] suggested that ACR may not have a good discriminant value for the diagnosis of sepsis (PPV of 51%), its appeal lies in it being a noninvasive, inexpensive and ready-to-use bedside screening test to identify the patients with SIRS who do not have sepsis (NPV 87%). Furthermore, the findings of 80% sensitivity and 64% specificity of 6 hours ACR appears comparable to the reported mean percentage sensitivity of 85% and specificity of 83% of PCT, and 69% and 61%, respectively, of CRP,[85] in differentiating infected individuals from uninfected controls. The ACR test is a simple test regularly done in hospital laboratory and results can be made available as early as 30 minutes. The ACR can also be estimated by the ICU nurses themselves, as a point-of-care test, within 15 min, as shown in Gosling et al's study.[86]

Bhadade RR et al.[13] in their study reported the median levels for UACR at admission as 152.70 mg/g {IQR (interquartile range) 108.71 to 194.92} and 44.48 mg/g (IQR 26.80 to 108.41) for the sepsis and non-sepsis groups, respectively. The levels of microalbuminuria were significantly high among the patients with sepsis at admission as compared to those without sepsis. The microalbuminuria levels after 24 hours were found to decrease significantly among the patients with sepsis as compared to the patients without sepsis. The sensitivity, specificity, PPV and NPV in predicting sepsis were found to be 93.1%, 71.05%, 88.04% and 81.81% at admission with UACR cut-off value of > 62.62 respectively. At 24 hours the cut-off value of 63.22 for UACR yielded sensitivity of 78.16%, specificity of 65.79%, PPV of 83.95% and NPV of 56.81%.

The sensitivities observed by Basu S. et al.[14] and Bhadede RR et al.[13] were low compared to the present study. However, the findings of the present study are consistent with observations made by Basu S. et al.[14] and Bhadade RR et al.[13] On the basis of observations noted in the present study as well as in other studies by Basu S. et al.[14] and Bhadade RR et al.,[13] it could be said that microalbuminuria has a discriminatory role in the diagnosis of sepsis.

In this study mortality was noted in 56.92% of the patients which was high compared to a study by Basu S. et al.[13] who reported mortality in 14% and Bhadade RR et al.[14] reported mortality in 29.6% of the patients. The higher mortality rate observed in the present study may be explained by the higher frequency of sepsis patients in the present study.

In the present study UACR of >0.20 was noted in 60 at admission and of these 37 (61.67%) patients expired (p=0.012). The sensitivity of > 0.20 UACR at admission in predicting mortality was 100% with 17.86% specificity, 61.67% PPV and 100% NPV and the positive likelihood ratio was 1.22. At 24 hours after admission, out of 57 patients with UACR of >0.20, 37 (64.91%) patients expired (p=0.001) and the sensitivity of UACR was 100% but specificity was low i.e., 28.57% with high PPV (64.91%) and NPV (100%). The positive likelihood ratio was 1.40. Also the mean UACR value at admission (1.15 ± 0.52 vs 0.58 ± 0.42; p<0.001) and at 24 hours (1.58 ± 0.40 vs 0.46 ± 0.42; p<0.001) was significantly high in non survivors compared to survivors. These findings indicate strong association of UACR measured at admission and at 24 hours with mortality but lacks discrimination for mortality due to low specificity (17.86% at admission and 28.57% after 24 hours of admission).

In contrast to the findings of the present study, other studies done by Gosling,[63] Thorevska,[64] Gopal,[79] found microalbuminuria as a good marker in the prediction of mortality. In a study by Basu S. et al.[14] for the entire population, the area under the ROC curves for prediction of mortality was highest for UACR after 24 hours of admission. To estimate the diagnostic accuracy of the urine albumin-creatinine ratio in the prediction of ICU mortality, the sensitivity and specificity were determined for an optimum cut-off level of UACR at 99.6 mg/g after 24 hours of admission. At this value, UACR had a sensitivity of 85%, specificity of 68% with a NPV of 97% and PPV of 30% for the prediction of death. The lack of diagnostic accuracy in the present study for predicting outcome can be attributed to higher mortality rate and greater subset of patients with sepsis.

In the present study among 41.54% of the patients length of hospital stay was between 4 to 7 days and it was between 8 to 14 days in 30.77% of the patients. Also no association was found between length of hospital stay and UACR assessed at admission (p=0.495) as well as at 24 hours after admission (p=1.000). These findings suggest that, UACR at admission as well as at 24 hours after admission fail to predict the length of hospital stay.

Overall the present study showed that, UACR is significantly higher in the sepsis cohort in comparison to other systemic inflammatory diseases that probably indicates a distinct yet unknown pathophysiology. Further it has excellent discriminator in predicting sepsis among the patients with SIRS irrespective of time interval that is at admission or 24 hours after admission. However microalbuminuria

showed poor discrimination in predicting mortality among the patients with SIRS and sepsis band.

CONCLUSION

Based on the findings of this study it may be concluded that, microalbuminuria as determined by raised UACR seems to be reliable biomarker of sepsis at admission as well as 24 hours after admission in patients admitted with SIRS.

UACR is sensitive in predicting ICU mortality among the patients with SIRS. However, lack of specificity and high NPV limits its ability to predict mortality and needs further evaluation.

SUMMARY

Despite extensive research during the past two decades no single biomarker can serve as the lone diagnostic parameter for the diagnosis of sepsis in patients with SIRS. This study explored the feasibility of microalbuminuria as a biomarker of sepsis and evaluated the feasibility of microalbuminuria to predict ICU mortality.

This one year cross sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 65 patients who presented with the diagnosis of SIRS as defined by ACCP and SCCM were studied. All the patients were evaluated for the presence of microalbuminuria at admission and 24 hours after admission.

Most of the patients were males (63.08%) and male to female ratio was 1.70:1. The commonest age group was between 41 to 50 years (27.69%) and the mean age was 51.12 ± 15.87 years. Fever was the common clinical presentation (95.38%). History of smoking and alcohol consumption were in 40% and 36.92% of the patients. All the patients (100%) had pulse rate of >90 /minute, 56.92% of the patients had temperature of ≥ 100.4 ^{0}F. Majority (72.31%) of the patients had respiratory rate of ≥ 20 per minute. The blood culture was positive in 26.15% of the patients and commonest organism isolated was staphylococcus epidermidis (58.82%) while urine culture was positive in 3.08% of the patients and 1 each had escherachia coli (50%) and enterococcus (50%). UACR at admission was >0.20 in 92.31% of the patients and at 24 hours after admission it was >0.20 in 87.69% of the patients. Diagnosis of severe sepsis was noted in 58.46% of the patients and

commonest etiological diagnosis was pneumonia (36.92%). 56.92% of the patients expired and length of hospital stay between 4 to 7 days in most of the patients (41.54%). Out of 60 patients with UACR of >0.20 at admission, 98.33% had sepsis ($p<0.001$) and it was 100% sensitivity in predicting sepsis (83.33% specificity, 98.33% PPV, 100% NPV with positive likelihood ratio of 6) and similar sensitivity pattern was noted with regard to 24 hours UACR. The mean UACR at admission in patients with sepsis was significantly high at admission (0.98 ± 0.54 vs 0.27 ± 0.28; $p=0.003$) as well as at 24 hours after admission (1.17 ± 0.66 vs 0.40 ± 0.06; $p=0.008$). Out of 60 patients with UACR of >0.20 at admission, 61.67% of the patients expired ($p=0.012$) and sensitivity of > 0.20 UACR at admission in predicting mortality was 100% with 17.86% specificity, 61.67% PPV and 100% NPV and the positive likelihood ratio was 1.22 which was nearly same for values of UACR at 24 hours after admission. No association was found between length of hospital stay and UACR assessed at admission ($p=0.495$) as well as at 24 hours after admission ($p=1.000$). Significantly higher mean UACR value was noted at admission in patients who expired (1.15 ± 0.52 vs 0.58 ± 0.42; $p<0.001$) and at 24 hours after admission (1.58 ± 0.40 vs 0.46 ± 0.42; $p<0.001$) compared to those who improved.

Microalbuminuria is a reliable biomarker in determination of development of sepsis among the patients admitted with SIRS as measured by UACR at admission and 24 hours after admission but has limited ability in predicting ICU mortality.

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ANNEXURE I – CONSENT FORM

TITLE OF RESEARCH STUDY: "MICROALBUMINURIA AS A BIOMRKER OF SEPSIS AND ITS PROGNOSTIC SIGNIFICANCE IN CRITICALLY ILL PATIENTS-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

Principal Investigator
Dr. *** ******
Post Graduate Student,
Department of General Medicine,
Jawaharlal Nehru Medical College,
Belgaum -590 010.

Introduction

This study is being done to evaluate microalbuminuria as a biomarker of sepsis and its prognostic significance in critically ill patient.

Procedure

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) all the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for your condition.

Privacy and Confidentiality

All information collected about your during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts / incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

In case of the queries during study or in future you may contact following persons,

1. Dr. ***** ******,
Jawaharlal Nehru Medical
College,
Ethical Committee for
Human Research,
Phone No.: ****** *****.

2. Dr. ***** ******,
Professor & Head of Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum - 590 010.
Phone No.: ***** ******, Extn: *****

3. Dr. ***** ******,
Professor and Head of Unit,
Department of General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010
Phone No: ***** ******,

4. Dr. ***** ******,
Investigator,
Post Graduate in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010.
Phone No.: ***** ******,

CONSENT FORM

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of consent form.

Signature / Left Thumb print of the Participant or legally authorized representative.

Participant's Name :----------

Signature / Left Thumb
Impression of the participant's :----------

Name of the legally
Authorized representative / Guardian :----------

Signature / Left Thumb Impression. :----------

Witness's Name :----------

Signature / Left Thumb Impression. :----------

Investigators name and Signature :----------

Date:

Place:

Dr. ***** ******,
Professor and Head of Unit,
Department of General Medicine
Jawaharlal Nehru Medical College,
Blegaum – 590 010.
Phone No.: ***** ******,

Dr. ***** ******,
Investigator,
Post Graduate in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010.

ANNEXURE II – PROFORMA

TITLE OF RESEARCH STUDY: "MICROALBUMINURIA AS A BIOMRKER OF SEPSIS AND ITS PROGNOSTIC SIGNIFICANCE IN CRITICALLY ILL PATIENTS-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

Patient Name:	In Patient Number:
Age:	Sex:
Address:	Occupation:
Date of admission:	Date of discharge:

Symptoms

1. Fever Yes / No
2. Cough with expectoration Yes / No
3. Breathlessness Yes / No
4. Burning micturition Yes / No
5. Headcahe Yes / No
6. Vomiting Yes / No
7. Altered consciousness Yes / No
8. Abdominal Pain Yes / No
9. Decreased urine out put Yes / No
10. Bleeding Diathesis Yes / No

Past History

1. Blood transfusion Yes / No
2. Trauma, Burns, Surgery Yes / No
3. History of HIV infection Yes / No

Treatment History

Immunosuppressant therapy	Yes / No
Chronic Antibiotic use	Yes / No

Personal History

Habits: h /o smoking	Yes / No
H/o Alcohol consumption	Yes / No

Physicla Examination

VITALS

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Systemic Examination

Respiratory system:

Cardiovascular system:

Per Abdomen:

Central Nervous System:

Laboratory investigations

Comple Blood Count:

Renal Function Tests:

Liver Function Tests:

Chest X-ray:

HIV Elisa:

C- Reactive Protein:

Appropriate cultures:

Albumin creatinine ratio:

Diagnosis

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
/Cumm	-	Per cubic millimeter
/Minute	-	Per minute
+	-	Present
ARDS	-	Acute respiratory distress syndrome
B/L	-	Bilateral
BP	-	Blood Pressure
COPD	-	Chronic obstructive pulmonary disease
Crep	-	Crepitations
DC	-	Discharged
DR	-	Drowsy
E COLI	-	Escherichia coli
EX	-	Expired
F	-	Female
gm%	-	Gram in percentage
HEP	-	Hepatomegaly
HIV	-	Human immunodeficiency virus
K.pneumoniae	-	Klebsiella pneumoniae
M	-	Male
mEq/L	-	Milliequivalents per liter
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
MODS	-	Multiple organ dysfunction syndrome

N	-	Normal
Sep sh	-	Septic shock
Sep	-	Sepsis
SF	-	Soft
SIRS	-	Systemic inflammatory response syndrome
SS	-	Severe sepsis
Staph hemo	-	Staphylococcus haemolyticus
Staphylo	-	Staphalycoccus aureus
T	-	Tender
UACR	-	Urine albumin creatinine ratio