"PREDICTION OF OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK USING SHOCK INDEX AND OTHER PARAMETERS-A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled **"PREDICTION OF OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK USING SHOCK INDEX AND OTHER PARAMETERS-A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0113011.**

Dr. Rekha S. Patil **MD**
Professor and Head,
Department of Medicine,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. N. S. Mahantshetti **MD**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

/Cumm	-	Per cubic millimeter
/mcl	-	Per micro liter
°C	-	Degree Centigrade
°F	-	Degree Fahrenheit
ACCP	-	American College of Chest Physicians
APACHE II	-	Acute Physiology and Chronic Health Evaluation II
aPTT	-	Activated prothrombin time
ARDS	-	Acute respiratory distress syndrome
AUC	-	Area under curve
BC	-	Before Christ
CI	-	Confidence interval
CNS	-	Central nervous system
CO	-	Cardiac output
COPD	-	Chronic obstructive pulmonary disease
CRP	-	C-Reactive Protein
CVL	-	Central venous line
CVP	-	Central venous pressure
DBP	-	Diastolic blood pressure
DIC	-	Disseminated intravascular coagulation
DNA	-	Deoxyribonucleic acid
e.g.	-	For example
ED	-	Emergency Department
F	-	Female
FiO2	-	Fraction of inspired oxygen

g/dl	-	Gram per deciliter
GCS	-	Glasgow coma scale
HIV	-	Human Immunodeficiency Virus
HR	-	Heart rate
hr	-	Hour
I. P. No.	-	In patient number
i.e.	-	That is
ICU	-	Intensive Care Unit
IL	-	Interleukin
ITUs	-	Intensive Therapy Units
IUD	-	Intrauterine death
kPa	-	Kilopascal
L	-	Liter
LSCS	-	Lower segment caesarean section
M	-	Male
mg/dL	-	Milligrams per deciliter
min	-	Minutes
ml	-	Milli liters
mm^3	-	Cubic millimeter
mmHg	-	Millimeters of mercury
mmol	-	Millimole
MPM	-	Mortality Prediction Model
MRSA	-	Methicillin resistant staphylococcus aureus
n	-	Total number
NPV	-	Negative predictive value

O.P. No.	-	Out patient number
OSF	-	Organ System Failure
p	-	Probability
PaO2	-	Partial pressure of arterial oxygen
PAR	-	Protease-activated receptor
PCT	-	Procalcitonin
PIRO	-	Predisposition, Infection, Response and Organ
PPV	-	Positive predictive value
PT	-	Prothrombin time
r	-	Pearson’s correlation coefficient
RNA	-	Ribonucleic acid
ROC	-	Receiver operating characteristic
SAPS	-	Simplified Acute Physiology Score
SBP	-	Systolic blood pressure
SCCM	-	Society of Critical Care Medicine
SD	-	Standard deviation
SE	-	Standard error
SI	-	Shock Index
SIRS	-	Systemic inflammatory response syndrome
SOFA	-	Sequential Organ Failure Assessment
SpO2	-	Peripheral capillary oxygen saturation
SSC	-	Surviving Sepsis Campaign
SvO2	-	Mixed venous oxygen saturation
TLR	-	Toll-like receptor
TNF	-	Tumor necrosis factor

UK	-	United Kingdom
US	-	United States
USA	-	United States of America
vs	-	Versus
WBC	-	White blood cell
µmol/L	-	Micromole per litre

ABSTRACT

Background and Objectives

Shock Index is a simple bedside measurement tool that can predict prognosis in patients admitted to the emergency department. The present study was aimed to evaluate the value of shock index in prognosticating short-term outcome for patients with severe sepsis and septic shock at admission and after half an hour of initial resuscitation.

Methodology

The present one year hospital based observational study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients admitted with severe sepsis or septic shock in the Emergency Department from January 2014 to December 2014 were studied. Shock Index, calculated as heart rate divided by the systolic blood pressure was assessed at admission and after half an hour of initial resuscitation in emergency department.

Results

Of the 100 patients studied, 62% of the patients had severe sepsis and 38% had septic shock. Most of the patients were males (62%) and the male to female ratio was 1.63:1. The commonest age group was 41 to 50 years (21%) and the mean age was 49.8 ± 16.5 years. Shock index of > 0.7 was noted in majority of the patients at admission (99%) and at 30 minutes after admission (94%). Mortality was noted in 62% of the patients. Significantly higher mortality was noted in patients with a higher shock index at 30 minutes after admission

($p<0.001$). The mean shock index at 30 minutes after admission was significantly higher in patients who expired ($p<0.001$). Using a cut-off value of shock index as 1.15 (AUC=0.949; $p<0.001$) after initial resuscitation of 30 minutes from admission, yielded higher accuracy in predicting mortality (sensitivity 87.1% and specificity 92.11%).

Conclusion and Interpretation

Shock index not only helps in risk stratification of patients with septic shock and severe sepsis but helps in prognosticating mortality when evaluated after initial resuscitation of 30 minutes.

Keywords

Sepsis; Septic shock; Severe sepsis; Shock Index

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INTRODUCTION

Sepsis is a syndrome clinically defined as the body's systemic inflammatory response to infection.[1] Severe sepsis and septic shock are the end results of the body's maladaptive and inappropriate response to pathogenic microbes, resulting in organ dysfunction, tissue hypoperfusion and dysoxia, and ultimately death.[2] In 1992, the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference outlined definitions of Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis and septic shock in an effort to standardize the classification of host responses to infection.[3]

Despite continued advances in medicine and technology, the incidence of sepsis is increasing. From 2000 to 2008, hospitalizations for sepsis more than doubled from 326,000 to 727,000, according to the Center for Disease Control report examining hospital admission data from the National Hospital Discharge Survey.[4,5] Annual incidence of sepsis is reported to be 20-300/100,000 population.[6,7] No definitive data on the incidence of sepsis in India is available, but it could be well above this.[7]

The incidence of sepsis is greatest at the extremes of age, occurring in 5.3/1000 patients under 12 months of age and 26.2/1000 patients aged 65 years or older.[8] Age-related alterations in the host immune system affect an individuals response to an infectious challenge.[5] Older individuals have been found to exhibit dysregulation in Toll-like receptor (TLR) trafficking, deficits in dendritic cell function secondary to decreased numbers and/or decreased receptor signaling, an increased proportion of naive B cells, signaling deficits in the T-cell receptor CD3

complex, increased numbers of inhibitory receptors and changes in cytokine signaling.[9]

Tissue dysoxia, defined as limited metabolic energy production due to a lack of oxygen supply or utilization, clinically manifests as shock.[10] In the presence of sepsis, this form of shock is typically distributive in nature, resulting in a relative hypovolemia due to systemic vascular dilation and increased capillary permeability and leakage. This can lead to a decrease in oxygen uptake and utilization and result in organ failure, lactic acidosis, and tissue necrosis.[11] Oxygen uptake into the tissue (VO2) can be affected by alterations in cardiac output (CO), oxygen carrying capacity (i.e.: anemia), and oxyhemoglobin saturation (i.e.: hypoxemia).[12]

Sepsis is a complex syndrome that is difficult to define, diagnose and treat. It produces a range of clinical conditions caused by the body's systemic response to an infection, which causes rapid deterioration into severe sepsis. This in turn, accompanied by single or multiple organ dysfunction or failure, often leads to death if poorly treated or recognized. This makes sepsis as a major cause of mortality and morbidity throughout the world. Mortality rates with severe sepsis and septic shock range from 25% to over 75%, with higher rates of death in patients with multi–organ dysfunction and prolonged hypoperfusion.[1] Severe sepsis and septic shock account for greater than 17% of all in hospital deaths and is the eleventh leading cause of death in the United States.[4]

The management of sepsis is closely related to the availability of relevant equipment and efficacy of clinical and serological indices, which is used as a guide for the prognostication and effective treatment goals. The development of cost

effective and easily attainable clinical parameters that would effectively prognosticate the outcome of sepsis patients would be invaluable within an emergency department setting. Availability of such parameters would result in optimized triaging, risk stratification and also contribute to accurate identification of intensive care unit candidates amongst severely ill patients, at a fraction of the cost.

Many prognostic and severity parameters of sepsis have been suggested in the past such as serum lactate levels, plasma diffused arterial oxygen saturations (PaO2), percutaneous haemoglobin oxygen saturations (SpO2), central venous oxygen saturations (SvO2), severity of metabolic acidosis, C-Reactive Protein (CRP) levels, total white cell count, and hematocrit. These parameters have been well studied and documented for their role in the management of sepsis patients. These indices require high cost investments and the availability of certain specialized equipments in calculating or generating its values.[8,13,14]

Being able to generate a cost effective, easily attainable parameter would greatly assist in the effective management of sepsis patients, especially in emergency departments that are sub-optimally equipped.[14]

In developing countries emergency departments in the peripherals / districts are not readily equipped with hematological stat laboratory equipments and arterial blood gas machines due to their high cost. The results of various blood parameters may not be immediately available upon request, potentially compromising accurate risk stratification and delaying the management of these patients. Certain procedures such as the placement of central venous line (CVL) catheters also require time, trained personnel and additional cost which may not be easily available within the

setting of smaller sub-urban hospitals. The parameters that could be gathered from insertion of a CVL and central venous blood aspiration (ie. Central venous pressure reading, severity of metabolic acidosis, central venous oxygen saturation, and hematocrit concentration) is clearly vital and plays a prognosticating role for determining survival outcome in management of patients with SIRS-sepsis spectrum.[15]

Shock Index (SI), which is the heart rate divided by the systolic blood pressure, is a measurement that could be readily and affordably attained. It is an easily accessible, non-invasive, and non-costly risk stratification tool in prognosticating short-term survival to discharge for patients presenting with sepsis. Majority of previous studies investigated the value of SI in the management and early detection of clinical shock for patients presenting with hemorrhage from various etiologies.[16-19] The outcome of these previous studies has proven that SI plays a role in early detection of hemorrhagic shock requiring early surgical intervention and can be reliably used as a risk-stratifying indicator for these groups of patients. As compared to visualizing the conventional vital signs (HR, SBP, DBP) on its own, SI combines these variables into a single ratio making it a comprehensive physiological variable. The critically ill patient demonstrates a physiological compensatory mechanism, keeping the blood pressure from falling despite the presence of decreased circulating blood volume, stroke volume, and cardiac output. In such events, SI would serve well as an early warning indicator as compared to the conventional vital sign.[14] This prompted us to study the value of shock index in prognosticating short-term outcome for patients with the end spectrum of SIRS-sepsis band, that is, severe sepsis and septic shock on patients

arrival in the emergency department and after half an hour of initial resuscitation, for prognosticating short term outcome.

OBJECTIVES

The objective of the present study was to predict the outcome in patients with severe sepsis and septic shock using shock index and other parameters, that is, to identify the best parameter that could prognosticate mortality namely, age, gender, temperature, heart rate, respiratory rate and shock index.

REVIEW OF LITERATURE

Historical note

Historically, sepsis has been a condition which is difficult to identify and diagnose. As far back as 100 BC, Marcus Terentius Varro the ancient Roman scholar and writer (116 BC–27 BC), was quoted as noting that small creatures, invisible to the eye, fill the atmosphere and when breathed through the nose cause dangerous diseases. Perhaps the most prescient description of sepsis was by the historian, philosopher, humanist and Renaissance author Niccolo Machiavelli (1469–1527), as reported in his treatise, *The Prince*, in 1513. Early in the book, he very eloquently stated that, "hectic fever, at its inception, is difficult to recognize but easy to treat; left unattended it becomes easy to recognize and difficult to treat." Although hectic fever is not the name by which we know sepsis now, the description of a disease that is difficult to recognize in its early stages, at a time when the condition may be amenable to treatment, and more difficult to treat in its later more obvious stages is a clear description of the more severe forms of sepsis.[20]

In an attempt to better clinically understand sepsis, in the past century, a variety of definitions have been developed. Among the earliest concepts was to consider sepsis as a systemic host response to an infection.[21]

In fact, it was classically described by the eminent American physician William Osler (1849–1919) in his seminal observation that the patient appears to die from the body's response to an infection rather than from the infection itself. Closer

to the modern era, in 1972 this concept was reinforced in a medical review, noting that "it is our response that makes the disease".[21]

The general concept has long been considered a form of poisoning, often considered as blood poisoning, but more practically representing the presence of pathogenic organisms or their toxins in the blood or tissues. It was the failure of these medical definitions, and myriad attempts at developing diagnostic tools and assays to identify sepsis, that led to a consensus conference focusing on a way to clinically define sepsis.[21]

Definition

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) jointly published the consensus definitions of sepsis.[3] In 2001, an International Sepsis Definition Conference[17] 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.[3] Based on this conference a consensus document was developed, concluding that there was not enough evidence to support a change to the previous definitions.[17]

<u>Systemic inflammatory response syndrome</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.

Sepsis

- SIRS that has a proven or suspected microbial etiology

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
    - Platelet count <80,000/L or 50% decrease in platelet count from highest value recorded over previous 3 days
  - 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.

MODS

- Dysfunction of more than one organ, requiring intervention to maintain homeostasis.

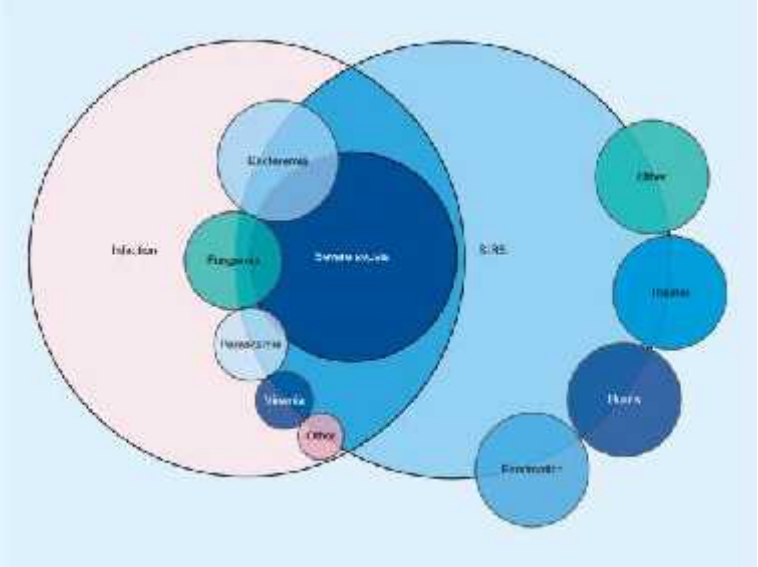


Figure 1. SIRS: Systemic inflammatory response syndrome[20]

These are among the most frequently cited definitions in critical care and they have become second nature to many critical care physicians (intensivists) and other intensive care providers throughout the world. Their novel description of the SIRS criteria and specific definitions for sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome were all critical developments in the field of sepsis.[20]

Since these consensus definitions had limitations in clinical use, they were revisited in 2001.[3,20]

Although there were many limitations recognized of the current definitions, there was no superior alternative identified. There was significant consideration to expanding the foundational `systemic inflammatory response syndrome' criteria to include other parameters that may be associated with sepsis. However, these represented a broadening of the potential diagnostic criteria that would, if anything, make the sepsis definition less specific than it was previously. In addition, some of the criteria overlapped with the definitions developed for identifying organ dysfunction, which is a critical component of distinguishing severe sepsis and septic shock. Perhaps the most important result from the 2001 Consensus Conference was the proposal for a `Predisposition, Infection, Response and Organ dysfunction' (PIRO) system for staging sepsis. The concept of PIRO was analogous to staging cancer or other medical conditions, and it appears that these criteria do allow for differentiating groups of patients with sepsis.[23]

Epidemiology

Worldwide

The worldwide reported prevalence of severe sepsis in hospital per 100 admissions during the last decade was between 2.6 to 12.4. The prevalence of severe sepsis in ICUs per 100 ICU admissions ranges between 11 to as high as 30.[24]

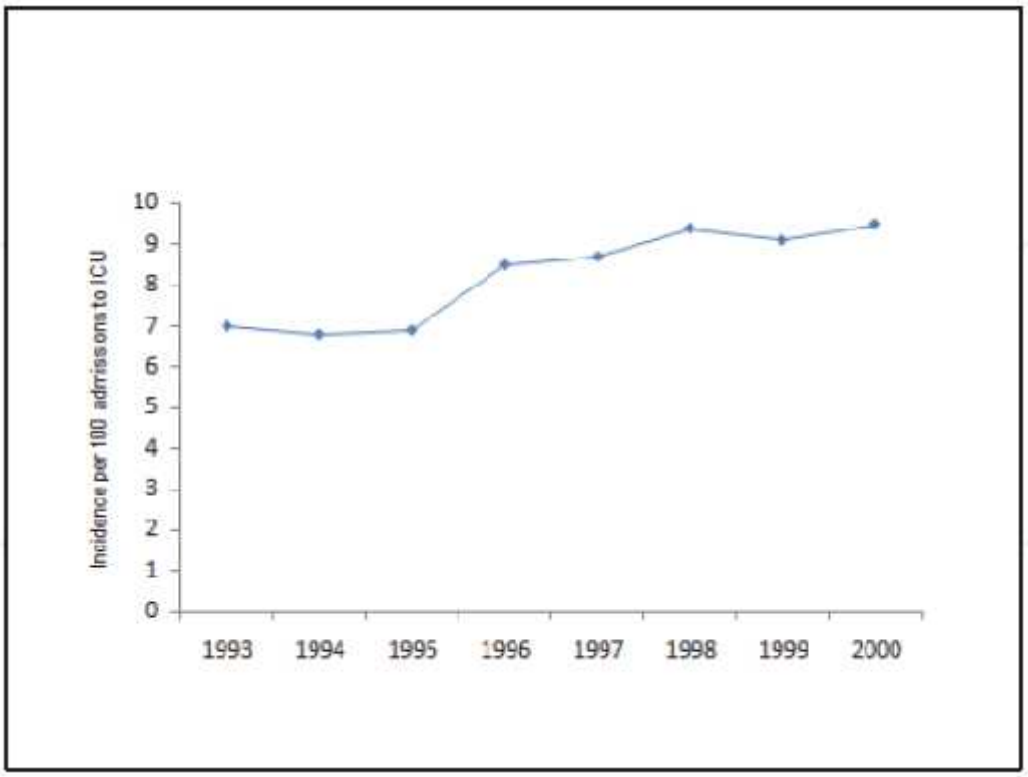


Figure 2. Incidence of septic shock. Data collected over an 8-year period from 22 hospitals[25]

Annual incidence of sepsis is reported to be 20-300/100,000 population with a mortality rate ranging between 30% and 80%.[6,7]

In general, sepsis occurs in approximately 2% of all hospitalizations in developed countries. Sepsis may occur in between 6% and 30% of all intensive care unit (ICU) patients, with substantial variation due to the heterogeneity between ICUs.[26]

Overall, the incidence of sepsis is three to four-times higher, reflecting the relative percentage of patients who develop organ dysfunction and thus meet more severe definitions (severe sepsis or septic shock).[27]

A two-decade study of US hospitalizations identified an increase in the incidence of sepsis among hospitalized patients by 8.7% per year.[27] At present, it is estimated that there are more than 1,000,000 cases of sepsis among hospitalized patients each year in the USA. Numerous reports have shown the incidence of sepsis and severe sepsis increasing in excess of the growth of the population. Similar reports exist from the UK, Australia and from Croatia.[20]

The incidences of sepsis, severe sepsis and septic shock are less well-described in the developing world.[28] There are more data available on the incidence of infectious diseases, which remains a constant battle for which there are many high incidence conditions. As infectious diseases are inevitably the cause of sepsis, sepsis presumably is of similar or even greater importance in these areas of the world than in the most developed nations. The responsible organisms for sepsis are more likely to be Gram-negative enteric pathogens and atypical pathogens.[29]

The incidence of sepsis is affected by a variety of patient-specific factors. It has been long recognized that age is an important component of someone's risk for developing sepsis. The incidence of sepsis is greatest at the extremes of age, occurring in 5.3/1000 patients under 12 months of age and 26.2/1000 patients aged 65 years or older.[8]

More recently it has been recognized that race, ethnicity and gender may also contribute to the differential risk for developing sepsis.[20]

In general, males have a higher risk for developing sepsis than females, regardless of age. The mechanisms behind differential incidence based on race and

ethnicity are less clear, but in general non-Caucasian races are at higher risk for developing sepsis compared with Caucasians.[20]

The risk factors also include variety of comorbid medical conditions. Most obvious are conditions like HIV, cancer, diabetes and in patients on steroids, each of which may alter the immune system. These conditions result in a significantly elevated risk for developing sepsis, and may also increase the risk of nosocomial sepsis given these individuals frequent interactions with healthcare systems.[30]

Indian scenario

No definitive data on the incidence of sepsis in India is available.[7] However, a multicentre, prospective, observational study was conducted in four intensive therapy units (ITUs) in India from June 2006 to June 2009 to determine the incidence of severe sepsis among 5,478 ITU admissions. SIRS with organ dysfunction was found in 1,385 (25%) patients, of which 731 (52.77%) were due to sepsis. The incidence of severe sepsis was 16.45% of all admissions. Mean age of the study population was 58.17 years (SD 18.66), of which 57.71% were male.[31]

Clinical features

The clinical manifestations of sepsis are highly variable, depending on the initial site of infection, the causative organism, the pattern of acute organ dysfunction, the underlying health status of the patient, and the interval before initiation of treatment. The signs of both infection and organ dysfunction may be subtle, and thus the most recent international consensus guidelines provide a long list of warning signs of incipient sepsis.

Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically manifested as the acute respiratory distress syndrome (ARDS), which is defined as hypoxemia with bilateral infiltrates of noncardiac origin.[32,33] Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors.[34]

The brain and kidneys are also often affected. Central nervous system dysfunction is typically manifested as obtundation or delirium. Imaging studies generally show no focal lesions, and findings on electroencephalography are usually consistent with nonfocal encephalopathy. Critical illness polyneuropathy and myopathy are also common, especially in patients with a prolonged ICU stay. Acute kidney injury is manifested as decreasing urine output and an increasing serum creatinine level and frequently requires treatment with renal-replacement therapy. Paralytic ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and the euthyroid sick syndrome are all common in patients with severe sepsis.[32]

Pathophysiology

Host Response

As the concept of the host theory emerged, it was first assumed that the clinical features of sepsis were the result of overly exuberant inflammation. Later, Bone et al.[35] advanced the idea that the initial inflammatory response gave way to a subsequent "compensatory antiinflammatory response syndrome." However, it has

become apparent that infection triggers a much more complex, variable, and prolonged host response, in which both proinflammatory and antiinflammatory mechanisms can contribute to clearance of infection and tissue recovery on the one hand and organ injury and secondary infections on the other.[36]

The specific response in any patient depends on the causative pathogen (load and virulence) and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels. The composition and direction of the host response probably change over time in parallel with the clinical course. In general, proinflammatory reactions (directed at eliminating invading pathogens) are thought to be responsible for collateral tissue damage in severe sepsis, whereas antiinflammatory responses (important for limiting local and systemic tissue injury) are implicated in the enhanced susceptibility to secondary infections.

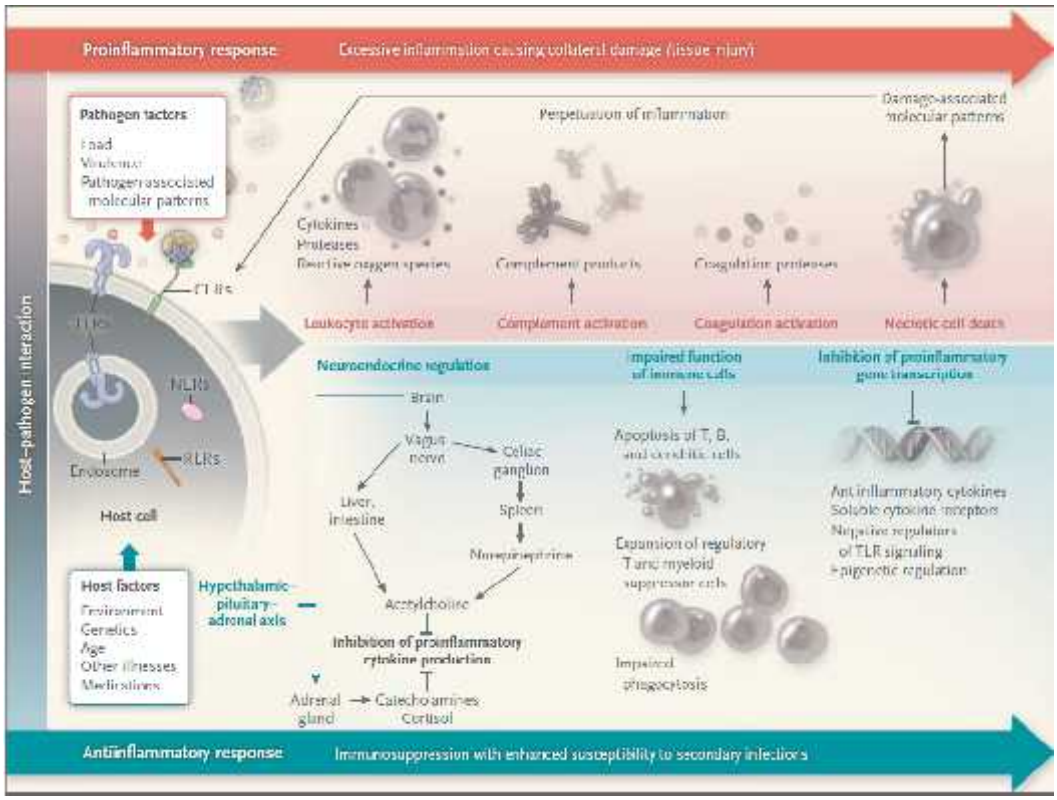


Figure 3. The Host Response in Severe Sepsis[32]

Innate Immunity

Knowledge of pathogen recognition has increased tremendously in the past decade. Pathogens activate immune cells through an interaction with pattern-recognition receptors, of which four main classes — toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors — have been identified, with the last group partially acting in protein complexes called inflammasomes.[37]

These receptors recognize structures that are conserved among microbial species, so-called pathogen-associated molecular patterns, resulting in the up-regulation of inflammatory gene transcription and initiation of innate immunity. The same receptors also sense endogenous molecules released from injured cells, so-called damage-associated molecular patterns, or alarmins, such as high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones. Alarmins are also released during sterile injury such as trauma, giving rise to the concept that the pathogenesis of multiple organ failure in sepsis is not fundamentally different from that in noninfectious critical illness.[38]

Coagulation Abnormalities

Severe sepsis is almost invariably associated with altered coagulation, frequently leading to disseminated intravascular coagulation.[39] Excess fibrin deposition is driven by coagulation through the action of tissue factor, a transmembrane glycoprotein expressed by various cell types, by impaired anticoagulant mechanisms, including the protein C system and antithrombin and by compromised fibrin removal owing to depression of the fibrinolytic system.

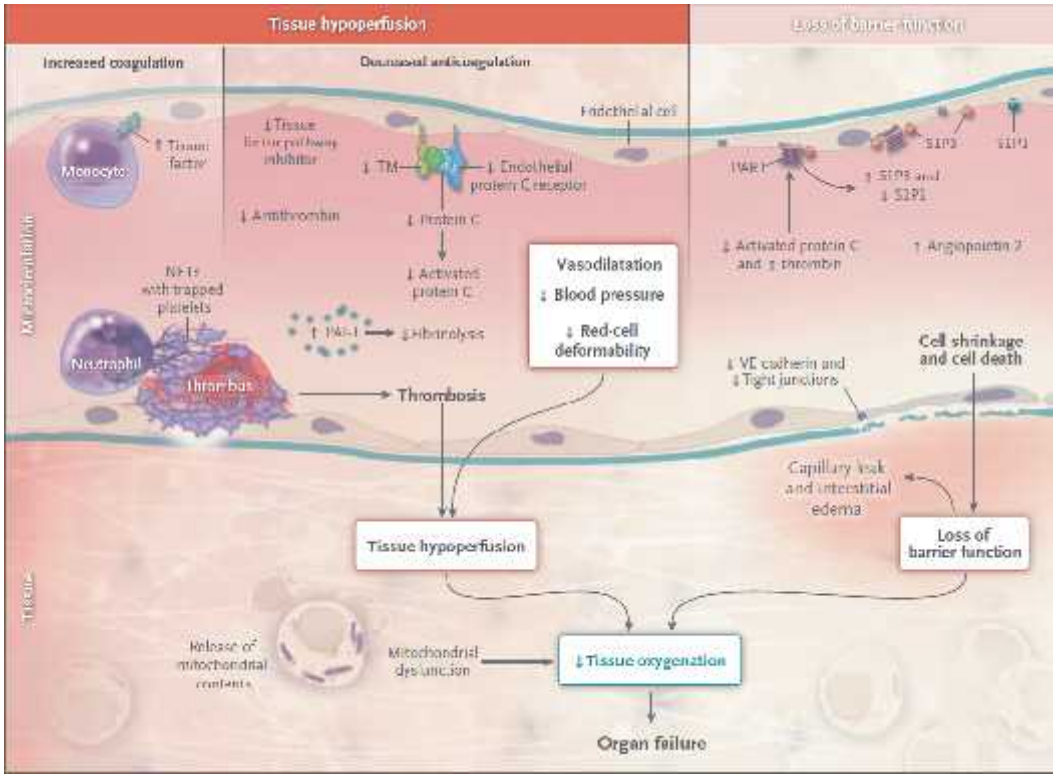


Figure 4. Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria[39]

Protease-activated receptors (PARs) form the molecular link between coagulation and inflammation. Among the four subtypes that have been identified, PAR1 in particular is implicated in sepsis.[39] PAR1 exerts cytoprotective effects when stimulated by activated protein C or low-dose thrombin but exerts disruptive effects on endothelial-cell barrier function when activated by high-dose thrombin. The protective effect of activated protein C in animal models of sepsis is dependent on its capacity to activate PAR1 and not on its anticoagulant properties.[40]

Antiinflammatory Mechanisms and Immunosuppression

The immune system harbors humoral, cellular, and neural mechanisms that attenuate the potentially harmful effects of the proinflammatory response.[36]

Phagocytes can switch to an antiinflammatory phenotype that promotes tissue repair, and regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. In addition, neural mechanisms can inhibit inflammation.[41]

In the so-called neuroinflammatory reflex, sensory input is relayed through the afferent vagus nerve to the brain stem, from which the efferent vagus nerve activates the splenic nerve in the celiac plexus, resulting in norepinephrine release in the spleen and acetylcholine secretion by a subset of CD4+ T cells. The acetylcholine release targets α7 cholinergic receptors on macrophages, suppressing the release of proinflammatory cytokines.[42]

In animal models of sepsis,[41] disruption of this neural-based system by vagotomy increases susceptibility to endotoxin shock, whereas stimulation of the efferent vagus nerve or α7 cholinergic receptors attenuates systemic inflammation.

Patients who survive early sepsis but remain dependent on intensive care have evidence of immunosuppression, in part reflected by reduced expression of HLA-DR on myeloid cells. These patients frequently have ongoing infectious foci, despite antimicrobial therapy, or reactivation of latent viral infection.[32]

Multiple studies have documented reduced responsiveness of blood leukocytes to pathogens in patients with sepsis,[36] findings that were recently corroborated by postmortem studies revealing strong functional impairments of splenocytes obtained from patients who had died of sepsis in the ICU. Besides the spleen, the lungs also showed evidence of immunosuppression; both organs had enhanced expression of ligands for T-cell inhibitory receptors on parenchymal cells.[43] Enhanced apoptosis, especially of B cells, CD4+ T cells, and follicular

dendritic cells, has been implicated in sepsis-associated immunosuppression and death. Epigenetic regulation of gene expression may also contribute to sepsis-associated immunosuppression.[32]

Organ Dysfunction

Although the mechanisms that underlie organ failure in sepsis have been only partially elucidated, impaired tissue oxygenation plays a key role. Several factors — including hypotension, reduced red-cell deformability, and microvascular thrombosis — contribute to diminished oxygen delivery in septic shock. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema. In addition, mitochondrial damage caused by oxidative stress and other mechanisms impairs cellular oxygen use. Moreover, injured mitochondria release alarmins into the extracellular environment, including mitochondrial DNA and formyl peptides, which can activate neutrophils and cause further tissue injury.[32]

Evolution of pathogens

The causative organisms for sepsis have evolved over many years. Originally sepsis was described, and strongly considered to be, a disease specifically related to Gram-negative bacteria.[44] This is because sepsis was considered to be a response to endotoxin – a molecule that was thought to be relatively specific for Gram-negative bacteria. In fact, some of the original studies of sepsis bore out that Gram-negative bacteria were among the most common causes of sepsis.[45]

This resulted in a number of trials that focused on Gram-negative therapies, and even highly specific therapies for endotoxin, which were felt to be potentially

useful treatments for sepsis. We now recognize that sepsis may occur from any bacteria, as well as from fungal and viral organisms. More recent epidemiology studies reveal that Gram-positive bacteria have become the most common cause of sepsis in the past 25 years.[27]

Large epidemiologic studies show Gram-positive organisms superceding Gram-negatives in the early- to mid-1980s as the most common cause of sepsis in the USA. According to the most recent estimates in sepsis, there are approximately 200,000 cases of Gram-positive sepsis each year, compared with approximately 150,000 cases of Gram-negative sepsis.[27]

While bacterial causes of sepsis have increased with the general increases in incidence, fungal causes of sepsis have grown at an even more rapid pace.[27] This may represent a general increase in nosocomial cases of sepsis, or it may reflect our effective treatment of bacterial infections, thus promoting fungal infections to a more leading role. While there has been an overall increase in the number of fungal nosocomial infections, we have also observed shifts away from the most common *Candida albicans* organism to the more recalcitrant *torulopsis, glabrata* and *krusei* subspecies.[20]

Sepsis tends to occur from specific and consistent sources. Respiratory infections are invariably the most common cause of sepsis, severe sepsis and septic shock.[20]

Overall, respiratory infections account for approximately half of all cases of sepsis. The next most common causes are genitourinary and abdominal sources of infection with primary bacteremia and unknown sources being the next most

common causes. The occurrence of acute organ dysfunction (i.e., severe sepsis) is related to the source of infection, as in patients with respiratory infections who are at higher risk for developing respiratory organ dysfunction.[20]

Regardless of the era and the organisms, the treatment of infection is the cornerstone of antisepsis therapy. There are two particular components of antimicrobial therapy that are important. The first is early antimicrobial therapy, with initiation of antibiotics in an appropriate time interval depending on the location of the patient. There are particular data from patients with pneumonia, and from those with septic shock, that show that delays in antimicrobial therapy lead to a significantly increased risk of dying. Especially critical for septic shock, the risk of dying increases by approximately 10% for every hour of delay in receiving antibiotics.[20]

The other important component of antimicrobial therapy is appropriateness of the antimicrobial regimen. It may be intuitive that coverage of the appropriate organisms is critical, as failure to cover the appropriate organisms is synonymous with delays of antimicrobial therapy. A variety of studies of infected and septic patients show that inappropriate antimicrobial therapy is a consistent predictor of poor outcomes.[20]

From a clinical perspective this means that the antimicrobial therapy must almost always be empiric. The choice of antibiotics, and the timing of their administration, cannot wait for isolation and identification of the causative organism and determination of the organism's sensitivity to various antibiotics. These

principles underlie the observation that combination antimicrobial therapy may be superior to monotherapy.[46]

In addition, in certain circumstances antibiotic therapy alone is not sufficient to treat the infection causing sepsis, in which case source control is also necessary to eradicate the infection.[20]

Treatment

The Surviving Sepsis Campaign, an international consortium of professional societies involved in critical care, treatment of infectious diseases, and emergency medicine, recently issued the third iteration of clinical guidelines for the management of severe sepsis and septic shock.

Guidelines for the Treatment of Severe Sepsis and Septic Shock from the Surviving Sepsis Campaign.[34]

Element of Care Grade

Resuscitation

- Begin goal-directed resuscitation during first 6 hr after recognition.
- Begin initial fluid resuscitation with crystalloid and consider the addition of albumin.
- Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure.
- Avoid hetastarch formulations.

- Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 ml of crystalloids per kilogram of body weight.

- Continue fluid-challenge technique as long as there is hemodynamic improvement.

- Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mm Hg.

- Use epinephrine when an additional agent is needed to maintain adequate blood pressure.

- Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated.

- Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate).

- Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure.

- Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day.

- Target a hemoglobin level of 7 to 9 g/dl in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage.

Infection control

- Obtain blood cultures before antibiotic therapy is administered.
- Perform imaging studies promptly to confirm source of infection.
- Administer broad-spectrum antibiotic therapy within 1 hr after diagnosis of either severe sepsis or septic shock.
- Reassess antibiotic therapy daily for de-escalation when appropriate.
- Perform source control with attention to risks and benefits of the chosen method within 12 hr after diagnosis.

Respiratory support

- Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS.
- Apply a minimal amount of positive end-expiratory pressure in ARDS.
- Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS.
- Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS.

- Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice.

- Elevate the head end of the bed in patients undergoing mechanical ventilation, unless contraindicated.

- Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion.

- Use weaning protocols.

Central nervous system support

- Use sedation protocols, targeting specific dose-escalation end points.

- Avoid neuromuscular blockers if possible in patients without ARDS.

- Administer a short course of a neuromuscular blocker (<48 hr) for patients with early, severe ARDS.

General supportive care

- Use a protocol-specified approach to blood glucose management, with the initiation of insulin after two consecutive blood glucose levels of >180 mg/dl (10 mmol/ liter), targeting a blood glucose level of <180 mg/dl.

- Use the equivalent of continuous venovenous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload.

- Administer prophylaxis for deep-vein thrombosis.

- Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding.

- Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hr after a diagnosis of severe sepsis or septic shock.

- Address goals of care, including treatment plans and end-of-life planning as appropriate.

The most important elements of the guidelines are organized into two "bundles" of care: an initial management bundle to be accomplished within 6 hours after the patient's presentation and a management bundle to be accomplished in the ICU.[34] Implementation of the bundles is associated with an improved outcome.[32]

The principles of the initial management bundle are to provide cardiorespiratory resuscitation and mitigate the immediate threats of uncontrolled infection. Resuscitation requires the use of intravenous fluids and vasopressors, with oxygen therapy and mechanical ventilation provided as necessary. The exact components required to optimize resuscitation, such as the choice and amount of fluids, appropriate type and intensity of hemodynamic monitoring, and role of adjunctive vasoactive agents, all remain the subject of ongoing debate and clinical trials; many of these issues will be covered in this series. Nonetheless, some form of resuscitation is considered essential, and a standardized approach has been advocated to ensure prompt, effective management.[34]

The initial management of infection requires forming a probable diagnosis, obtaining cultures, and initiating appropriate and timely empirical antimicrobial therapy and source control (i.e., draining pus, if appropriate).[32]

The choice of empirical therapy depends on the suspected site of infection, the setting in which the infection developed (i.e., home, nursing home, or hospital), medical history, and local microbial-susceptibility patterns. Inappropriate or delayed antibiotic treatment is associated with increased mortality. Thus, intravenous antibiotic therapy should be started as early as possible and should cover all likely pathogens. It has not been determined whether combination antimicrobial therapy produces better outcomes than adequate single-agent antibiotic therapy in patients with severe sepsis.[32] Current guidelines recommend combination antimicrobial therapy only for neutropenic sepsis and sepsis caused by pseudomonas species. Empirical antifungal therapy should be used only in patients at high risk for invasive candidiasis.[47]

The patient should also be moved to an appropriate setting, such as an ICU, for ongoing care. After the first 6 hours, attention focuses on monitoring and support of organ function, avoidance of complications, and de-escalation of care when possible. De-escalation of initial broad-spectrum therapy may prevent the emergence of resistant organisms, minimize the risk of drug toxicity, and reduce costs, and evidence from observational studies indicates that such an approach is safe.[48]

The only immunomodulatory therapy that is currently advocated is a short course of hydrocortisone (200 to 300 mg per day for up to 7 days or until vasopressor support is no longer required) for patients with refractory septic shock.[34]

This recommendation is supported by a meta-analysis,[49] but the two largest studies had conflicting results,[50,51] and other clinical trials are ongoing.[52,53]

Clinical outcomes

Patients with sepsis are classically considered to be patients who have a high risk of morbid complications and death. This is in large part owing to the organ dysfunction caused by sepsis, and the attendant complications of treating the organ dysfunction. Septic patients tend to be high resource consumers in the hospital and in the ICUs, and their presence affects the outcomes of those ICUs overall. For example, ICUs with a higher percentage of patients with sepsis also inevitably have higher average mortality rates.[26]

In addition, the costs of sepsis are quite substantial. There are estimates from around the world that consistently report cases of sepsis to cost from US$25,000 to $50,000 per episode.[20]

There are many different ways to predict the risk of dying for patients with sepsis. The most facile approach may be to accurately classify the patient according to their stage of sepsis. Applying the consensus conference definition, rough estimates of fatality rates (the percentage of patients who die) are as follows:

- Sepsis: 10–20%
- Severe sepsis: 20–50%
- Septic shock: 40–80%

The PIRO system is attractive for its potential ability to group sepsis patients according to specific factors that may produce more homogeneous groups, such as

comorbidities, type or source of infection and dysfunctional organ systems, among others. To date, whether PIRO staging is additive to this simple prediction schema remains to be determined.

Perhaps more important than these crude mortality estimates is that the risk of dying with sepsis has been falling over the past three decades. From data extending back to 1979, the risk of dying with sepsis was near 30% in the early years, and since the year 2000 the risk has been under 20%.[27] Similar results have also been observed when analyzing temporal changes in mortality from clinical trials of sepsis therapies.[54]

Unfortunately, despite an apparent reduction in patients risk of dying, owing to the increasing incidence of sepsis, the total number of people dying with the condition each year continues to rise. In fact, the number of people dying from sepsis each year (estimated to exceed 200,000) is similar to the number of people dying with acute myocardial infarction, and far exceeds those who die from HIV, breast cancer or stroke. In the USA, sepsis is the tenth leading cause of death overall.[20]

Markers for prediction of mortality

Sepsis is diagnosed by history and physical findings, corroborated by laboratory data such as circulating leukocyte count, body fluid examination and culture.

Detecting the syndrome in hospitalized patients is particularly important, as nosocomial sepsis is associated with longer lengths of stay and higher mortality rates compared with community-acquired sepsis.[55,56] Most patients will meet at least three

SIRS criteria at intensive care unit (ICU) admission.[57] Fever occurs in approximately 60% of patients at admission but may be suppressed in those with advanced age, renal failure or patients taking anti-inflammatory medications. Hypothermia, although uncommon, is an ominous finding associated with mortality rates of up to 60%. The lethality of hypothermia likely is not a consequence of the temperature itself but rather the relationship of hypothermia with underlying chronic diseases, shock and an exaggerated inflammatory response. Tachypnea is present in up to 80% of ICU patients. Although possible, the diagnosis should be questioned in patients lacking tachypnea or gas exchange abnormalities. Hypoxia is common in septic patients; more than 90% of patients will develop sufficient hypoxemia that requires supplemental oxygen, generally correlating with a PaO2/FiO2 ratio less than 300. Tachycardia is a cardinal sign of sepsis, unless patients have intrinsic cardiac disease or is taking nodal blocking medications, tachycardia is nearly universal. Abnormalities in circulating leukocyte count (more than 12,000 cells/mm3 or fewer than 4000 cells/mm3) are frequent enough to be considered important diagnostic criteria.[55]

Several serum biomarkers are purported to have diagnostic and/or prognostic value, but none have demonstrated acceptable sensitivity and specificity for routine clinical use.

The serum lactate level is suggested to be a marker of global hypo-perfusion and tissue hypoxia in sepsis. According to the theory, even before patients develop frank hypotension, tissue perfusion is impaired by myocardial depression, relative hypovolemia from a leaky endothelium, increased metabolic demands and impaired vasoregulatory mechanisms. Consequently, oxygen demand exceeds supply and

anaerobic production of lactate ensues. Not all agreed that lactate production was a reliable marker of global hypoxia in sepsis.[58]

Animal models of polymicrobial sepsis suggested that certain organs, particularly the liver and small intestine, may be more sensitive to impaired oxygen delivery. Regardless of its exact mechanism of production, patients admitted with a sepsis-related diagnosis and elevated serum lactate levels (greater than 4 mmol/L) had an increased mortality rate. Furthermore, mortality rates have decreased in septic patients with higher lactate clearance rates after 6 hours of therapy. Serum lactate is a component of prognostic models in severe sepsis and septic shock and concentrations increased in these patients.[55]

Procalcitonin and C-reactive protein (CRP), both markers of inflammation, have been studied as potential diagnostic tests in sepsis. The reported sensitivities and specificities of these tests vary, hence neither has achieved widespread acceptance.[55]

Most prognostic models evaluate survival using data collected at admission or within the first 24 hours in ED. There are two types including general models and disease-specific models.[55]

The main categories of general prognostic models include the models for evaluating the severity of illness that is, APACHE II and III, Simplified Acute Physiology Score (SAPS) II, Mortality Prediction Model (MPM) II and the models for quantifying organ dysfunction and failure that is, Logistic Organ Dysfunction System, Multiple Organ Dysfunction Score, Organ System Failure (OSF), Sequential Organ Failure Assessment (SOFA).[55]

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease.

A 3000-parient ED-based study demonstrated that organ dysfunction with septic shock portended increasingly worse outcomes. Patients with suspected infection alone had a mortality rate of 2.1%, while the presence of SIRS criteria and suspected infection had a mortality rate of only 1.3%.[59] However, the mortality rate was 9% for those patients with severe sepsis (sepsis plus organ dysfunction) and 28% for those with septic shock.[60]

The cardiovascular insufficiency is the most important events in severe sepsis leading to morbidity and mortality characterized by global tissue hypoxia, decreased contractility and ventricular dilatation.[55]

Echocardiographic findings demonstrated that in 40-50% of patients with severe sepsis developed myocardial depression and changes in cardiac performances. The responsible mechanisms for this organ dysfunction are probably mitochondrial dysfunction, myocardial cell death; however, the cardiac function is fully reversible in the survived patients.[55]

Hematologic manifestation of organ dysfunction is well-recognized in severe sepsis. The most common abnormalities include leukocytosis, anemia, thrombocytopenia, abnormal PT and aPTT and DIC.[55]

Patients with sepsis often display neurologic impairments manifested by altered mental status and lethargy, commonly referred as septic encephalopathy. The incidence has been reported between 10 and 70%. The mortality rate in patients with

septic encephalopathy is higher than that in septic patients without significant neurologic involvement.[55]

The lung is an early victim of the inflammatory response to sepsis. These effects are apparent irrespective of the primary infection that causes sepsis. Significant right-to-left shunting, arterial hypoxemia and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths. Sepsis produces a highly catabolic state and places significant demands on the respiratory system. At the same time, airway resistance increases and muscle function is impaired. Irrespective of whether pneumonia is the cause of sepsis, the common pulmonary endpoint is acute respiratory distress syndrome (ARDS). The development of ARDS occurs 4 to 24 hours after radiographic abnormalities develop.[55]

An absolute or relative adrenal insufficiency is common in sepsis. Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. Interleukin (IL) 1 and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF-α and corticostatin depress pituitary function. Other factors contributed to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary function and pituitary secretion of adrenocorticotropic hormone due to severe stress.[55]

However, despite the limitless resources available patient with septic shock have a high mortality, as yet there is no predictive scoring system which gives accurate predictions of outcome for individual patient. Survival from an episode of septic shock is dependent on patient's age, number of failed organs, previous health

and the time delay before the onset of medial intervention, as well as the appropriateness and quality of medical care.[61]

The time required to order, draw, analyze, and report laboratory tests is substantial, particularly when these are used to fulfill criteria for diagnosis or to make clinical decisions. On the one hand, protocol-driven laboratory draws, screen low-risk patients, potentially generating many false positives. On the other hand, relying on laboratory information to define treatment strategies causes delays in care. Hence non-laboratory immediate bedside "red flags" for sepsis may alert providers to initial assessment of those at risk for severe sepsis, like shock index. Congruently, a clinical basis to re-prioritize those with more benign parameters on presentation would direct resources appropriately.

Shock index

The SI was first described in the 1960s as the ratio of heart rate to systolic blood pressure.[62,63] While it was originally designed to identify apparently stable yet critically ill trauma patients, the SI has since been shown to be a simple, non-invasive risk stratification tool useful for detecting changes in cardiovascular performance before the onset of systemic hypotension and cardiorespiratory collapse.[64] Since its original description, the SI has been evaluated for this purpose in patients with cardiogenic shock, sepsis, ectopic pregnancy, gastro-intestinal hemorrhage, and pulmonary embolism.[63]

The shock index (SI) is a bedside assessment defined as heart rate divided by systolic blood pressure, with a normal range of 0.5 to 0.7 in healthy adults. Allgöwer and Buri[13] first introduced the concept in 1967 as a simple and effective means of

gauging the degree of hypovolemia in hemorrhagic and infectious shock states. Experimental and clinical studies have shown that SI is linearly inversely related to physiologic parameters, such as cardiac index, stroke volume, left ventricular stroke work, and mean arterial pressure.[65]

What is considered an abnormal SI elevation? The reported range in the literature is between 0.8 to 1.0.[66-68] One study from Mexico showed an improvement in sensitivity to 95% when using a SI of 0.8, although their population evaluated surgical patients and did not focus specifically on sepsis.[66] Given the variable definition of an elevated SI, there is no established cut-off for an elevated SI above normal (0.5–0.7) that has been routinely applied to critical care literature.[63]

A SI ≥ 1.0 has been associated with significantly poorer outcomes in patients with acute circulatory failure.[65] Furthermore, SI was also shown to indicate persistent failure of left ventricular function during aggressive therapy of shock patients in the ED.[69]

In a precursor study, Rady et al.[67] looked at patients with apparently stable vital signs and divided them into 2 groups based on whether the patient had a SI elevation. The study associated an elevated SI with higher admission rates to hospital floor beds and to ICUs, as well as poorer outcomes. Authors concluded that when used alone, an elevated SI was more sensitive than using heart rate or systolic blood pressure alone to predict the severity of illness, and had a higher specificity.

In 1994, Rady et al.[68] found that a SI ≥ 0.9 predicted higher illness priority at triage, higher hospital admission rates, as well as intensive therapy on admission than pulse or blood pressure alone. This suggests that SI may be a valuable tool for

the early recognition and evaluation of critical illness in the ED, as well as a means to track progress of resuscitation.[69]

As an adjunct to established methods, SI may identify and risk-stratify septic patients early in the ED course. One of these established markers for sepsis severity – hyperlactemia (serum lactate ≥ 4.0 mmol/L) - is an entry criterion for EGDT protocols and is associated with significant short-term mortality risk.[63] The shock state causes cellular hypoxia, leading to anaerobic metabolism and increased lactate production, as well as decreased clearance, even before vital signs are compromised.[68] Persistently high lactate levels are associated with under-resuscitation and have been shown to down-trend with successful resuscitation.[69] SI emphasizes current physiologic dynamics, rather than static criteria.[63]

A normal shock index may serve as an adjunct to triage the patients out of all the critically ill patients in emergency department. Thus we can report that this no-cost bedside triage tool (SI) which predicts critical illness, in absence of a reliable marker of severe sepsis (lactate), would suggest that low-risk patients with a normal SI may forgo (or not urgently need) routine triage laboratory screening for sepsis, especially from triage and before full evaluation. Additionally, using SI for triage decisions regarding severe sepsis screening can be made without waiting for results of the WBC. This has corresponding implications for efficiency and cost-effectiveness in ED protocols.[70]

The shock index is an effective, no-cost modality in the initial assessment of patients at risk for sepsis. Patients presenting with a presumed infection and a normal SI were found to be at very low risk (high NPV) for occult severe sepsis on

presentation (as defined by a surrogate marker for morbidity, hyperlactatemia). SI may be used as an additional bedside assessment tool – a "red flag" for severe disease; this is particularly useful when traditional vital signs are seemingly relatively benign. Multisite prospective work is needed to clarify its role in resource utilization, risk stratification of patients with sepsis, and in tracking resuscitation progress.[70]

Furthermore, a sustained SI elevation may be a promising simple, cost-efficient, and non-invasive measurement to help risk stratify patients who present to the ED with severe sepsis, and may complement other predictors of disease progression. A sustained SI elevation may be a useful modality to identify patients with severe sepsis at risk for disease progression.[14,63,70]

In a study done in Kuala Lumpur, Malaysia involving 50 patients admitted to the University of Malaya Medical Centre between June 2009 and June 2010 with either severe sepsis or septic shock, of all the parameters analysed, (shock index, heart rate, respiratory rate, body temperature, age, gender) shock index was found to the best predictor of mortality in emergency department. Shock Index-2 (Evaluated after two hours after admission) was the best predictor for death with a sensitivity of 80.8%, specificity of 79.2% at a cut-off point of ≥1.0.[14]

In another retrospective study on a cohort of adult emergency department patients at an academic community trauma center from February 1st, 2007 to May 28th, 2008 it was shown that patients with abnormal shock index of 0.7 or more were three times more likely to present with hyperlactatemia (15.8% vs 4.9%).

Shock index was the most sensitive screening test for hyperlactatemia and 28-days mortality.[168]

Another study at Department of Emergency Medicine, Henry Ford Hospital, Detroit, was conducted on 275 adults who presented to the emergency department. Group 1 (41) had an SI of more than 0.9, and group 2 (234) had an SI of less than 0.9 on arrival in the emergency department. Of both the groups, patients of group 1 were identified to have priority and were treated with immediate care and in intensive unit. The study showed that shock index may be a useful parameter to evaluate acute critical illness in the emergency department.[68]

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014.

Study design and duration

The study design was a hospital based observational study.

Study period

The present study was done for the period of one year from January 2014 to December 2014.

Place

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

Source of Data

Patients presenting with severe sepsis or septic shock in the Emergency Department at KLES Dr Prabhakar Kore Hospital and MRC, Belgaum

Sample size

A total of 100 patients with severe sepsis or septic shock were included in the study.

Sampling procedure

To demonstrate Sensitivity of Shock Index of 80.8%[14] with 5% error and mortality rate of 9.2%[71] with 95% confidence level sample size was calculated using the formula as below.

Sample Size (n) = 4 x sensitivity x (100–sensitivity)/(10% of sensitivity)^2

Therefore, $n = 4 \times 80.8^{14} \times (100 - 80.8) / (0.1 \times 80)^2$

$n = 96.96 \approx 97$

Hence the sample size of 100 (round off) was considered for this study.

Selection criteria

Inclusion Criteria

- Patients aged 18 and above.
- Patients who are in severe sepsis or septic shock as defined by American College of Chest Physicians and Society of Critical Care Medicine.[3]

Systemic inflammatory response syndrome

- 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; or
        - Platelet count <80,000/L.
    - 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.

Exclusion Criteria

- Patients aged < 18 years old.

- Patients with internal pacemakers.
- Patients with acute coronary syndrome.
- Patients with atrial fibrillation.
- Patients taking medications that have significant atria-ventricular blockage effect.
- Patients presenting with complaints of hematemesis.
- Patients on immunosuppressant drug therapy (oral or parentral).
- Patients who were started immediately on inotropic drugs
- Patients with end-stage malignancies
- Patients with inborn errors of lactate metabolism.
- Patients with HIV.

Ethical clearance

Prior to the beginning, the study was approved by the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed consent

The patients who fulfilled the selection criteria were informed about the nature of study and a written informed consent was obtained (Annexure–I).

Data collection

At the Emergency Department, the demographic data of the patients was noted along with the history of presenting illness and other comorbid conditions. Further these patients underwent clinical examination followed by systemic examination. Patients were evaluated for the following parameters on admission.

- Body temperature was measured by a medical thermometer.
- Blood pressure was measured by a sphygmomanometer on left upper arm first at arrival at the emergency department and then after 30 minutes.
- Heart rate was measured by palpatory method, first at arrival at emergency department and then after 30 min.
- Respiratory rate.
- Glasgow coma scale.
- Shock Index.

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

Investigations

Patients were subjected to following investigations.

- Complete blood count
- Platelet count
- White blood cell count
- Differential cell count
- Random blood sugar levels
- Serum electrolytes
- Serum lactate levels
- Serum urea levels
- Serum creatinine levels
- Liver function test

- Chest X-ray
- Arterial blood gas study
- Blood culture and sensitivity

Outcome variables

Based on clinical presentation, examination and investigations, patients were evaluated for;

- Symptom profile
- Risk factors
- Clinical signs
- Lipid abnormalities
- Haematological and biochemical variations
- Complications
- Etiology
- Stroke risk assessment, and antithrombotic therapy
- Creatinine clearance

Study variables

- Shock index: Shock Index was calculated as, heart rate divided by systolic blood pressure. The shock index was determined first immediately at arrival to the emergency department (S1) and then after 30 minutes (S2). The values of shock index were interpreted as raised (> 0.7) and normal shock index (0.5-0.7).[14]

- Outcome: The outcome was considered as survival or mortality.

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

Shock Index was compared with clinical parameters to identify the best parameter that could prognosticate mortality namely, age, gender, temperature, heart rate and respiratory rate. Two different values of shock index were compared to each other for the prediction of mortality in selected patients, one is at admission and other is after 30 min of initial resuscitation and stabilization.

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 discrimination between survivors and non survivors was made using the receiver operating characteristic curve (ROC curve). The accuracy of shock index in discriminating the survival at admission and after 30 minutes of admission was expressed in terms of sensitivity, specificity, positive predictive value, negative predictive value and positive likelihood ratio. The correlation of shock index with serum lactate levels and CVP was done using Pearson's correlation co-efficient. At 95% confidence interval, a probability (p) value of ≤ 0.050 was considered as statistically significant.

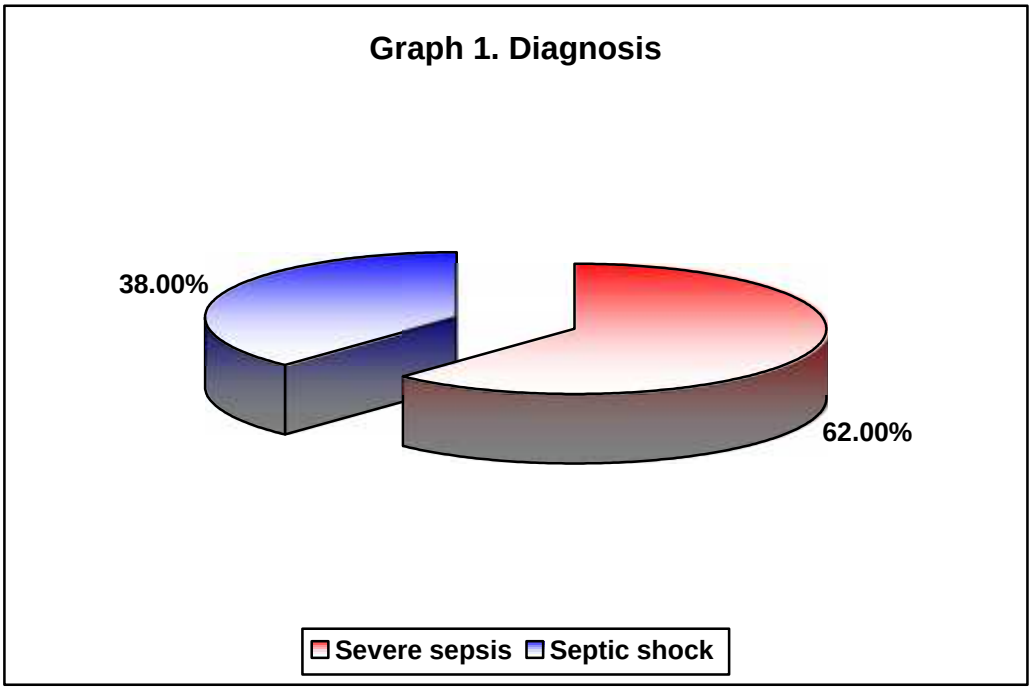
RESULTS

This one year hospital based observational study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2014 to December 2014. A total of 100 patients admitted with severe sepsis or septic shock in the Emergency Department were studied.

The data obtained was coded and entered into the excel spreadsheet. The data was analysed and the final results and observations were tabulated as below.

Table 1. Diagnosis

Diagnosis	Distribution (n=100)	
	Number	**Percentage**
Severe sepsis	62	62.00
Septic shock	38	38.00
Total	**100**	**100.00**

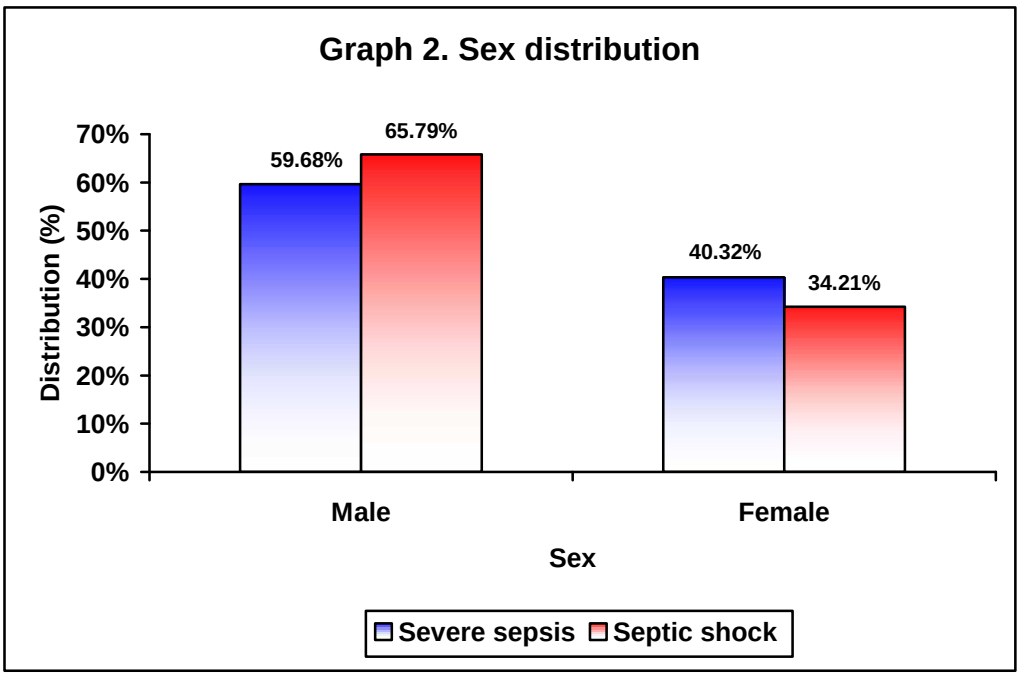


In the present study 62% of the patients had severe sepsis and 38% has septic shock.

Table 2. Sex distribution

Sex	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
Male	37	59.68	25	65.79	62	62.00
Female	25	40.32	13	34.21	38	38.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.541

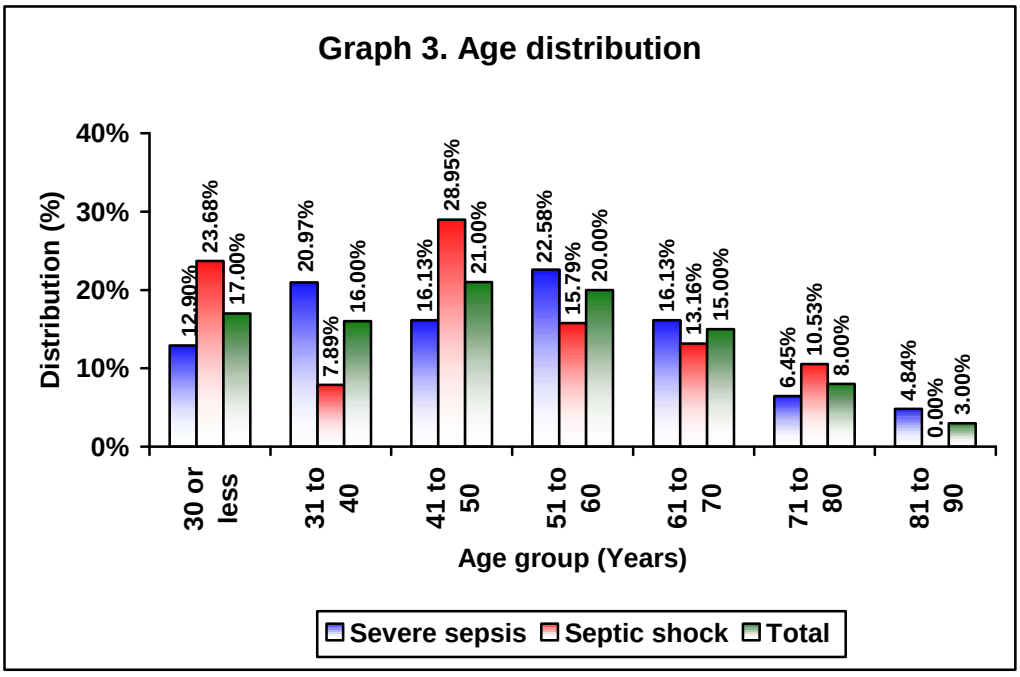


In this study most of the patients were males (62%) and the male to female ratio was 1.63:1. The male to female ratio in patients with severe sepsis and septic shock was noted as 1.48:1 and 1.92:1 respectively.

Table 3. Age distribution

Age group (Years)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
30 or less	8	12.90	9	23.68	17	17.00
31 to 40	13	20.97	3	7.89	16	16.00
41 to 50	10	16.13	11	28.95	21	21.00
51 to 60	14	22.58	6	15.79	20	20.00
61 to 70	10	16.13	5	13.16	15	15.00
71 to 80	4	6.45	4	10.53	8	8.00
81 to 90	3	4.84	0	0.00	3	3.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

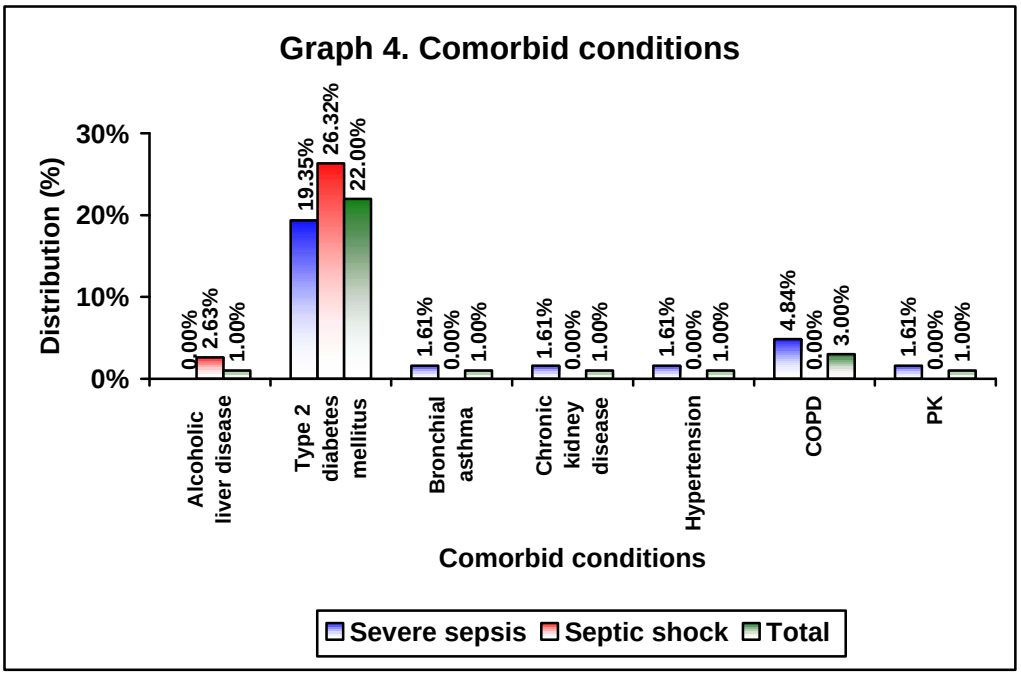
p = 0.191



In the present study most of the patients were aged between 41 to 50 years (21%). The severe sepsis was common in the age group between 51 to 60 years (22.58%) while septic shock was common in patients who were aged between 41 to 50 years (28.95%).

Table 4. Comorbid conditions

Comorbid conditions	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
Alcoholic liver disease	0	0.00	1	2.63	1	1.00
Type 2 diabetes mellitus	12	19.35	10	26.32	22	22.00
Bronchial asthma	1	1.61	0	0.00	1	1.00
Chronic kidney disease	1	1.61	0	0.00	1	1.00
Hypertension	1	1.61	0	0.00	1	1.00
COPD	3	4.84	0	0.00	3	3.00
PK	1	1.61	0	0.00	1	1.00

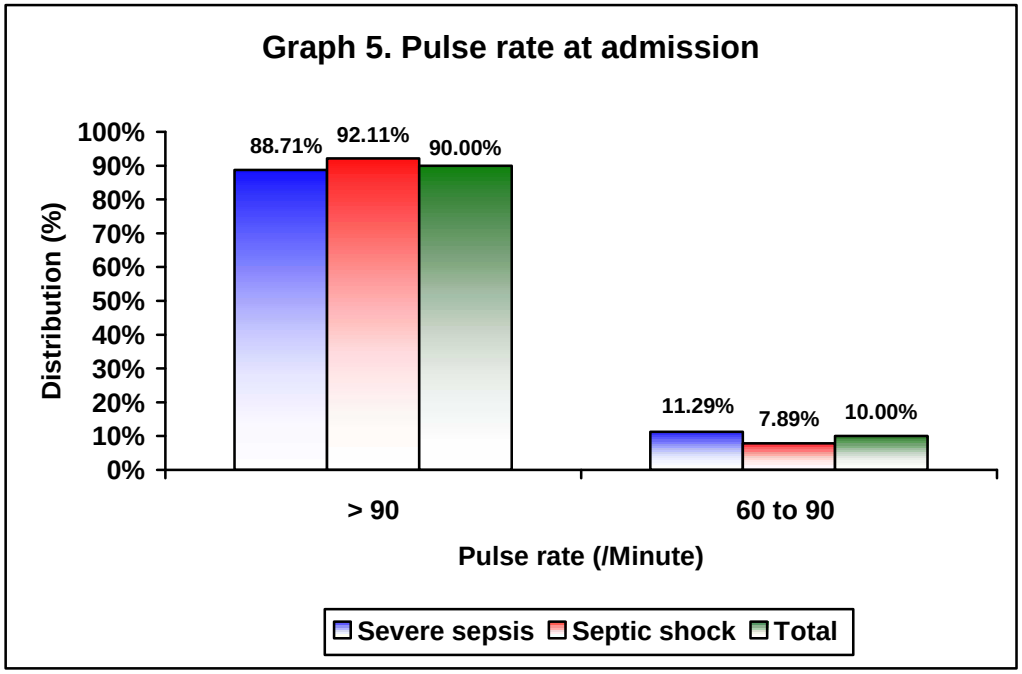


In this study the commonest comorbid condition was type 2 diabetes mellitus present in 22% of the patients. In patients with severe sepsis and septic shock type 2 diabetes mellitus was present in 19.35% and 26.32% respectively.

Table 5. Pulse rate at admission

Findings (/Minute)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
> 90	55	88.71	35	92.11	90	90.00
60 to 90	7	11.29	3	7.89	10	10.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.428

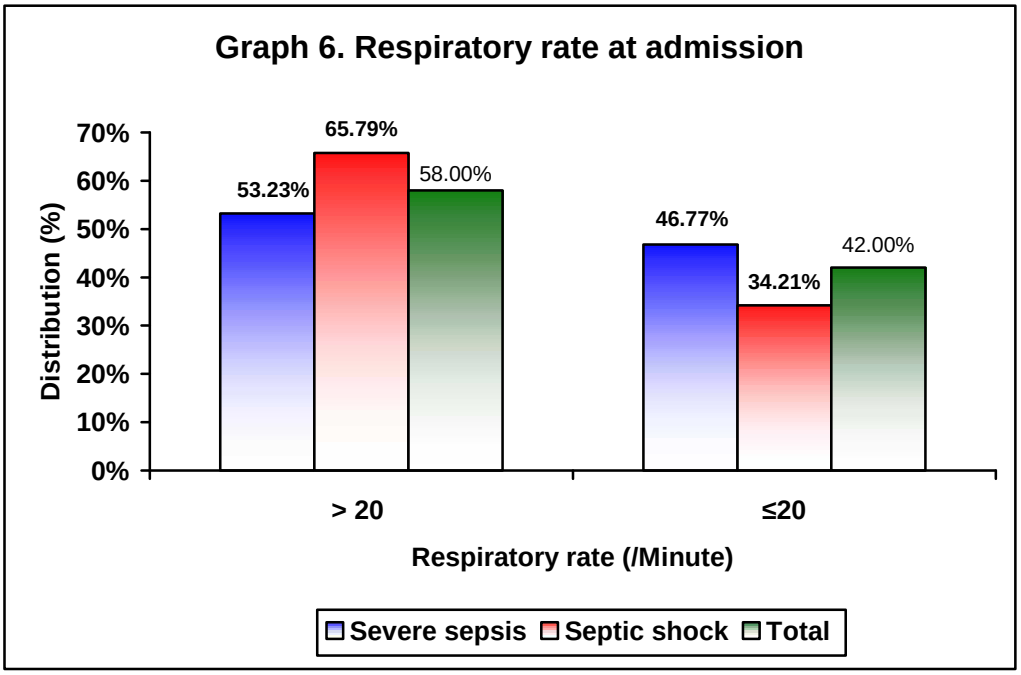


In the present study 90% of the patients had pulse rate of > 90 per minute at admission. Further, pulse rate of > 90 per minute was noted in 88.71% of the patients with severe sepsis and 92.11% of the patients with septic shock.

Table 6. Respiratory rate at admission

Findings (/Minute)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
>20	33	53.23	25	65.79	58	58.00
≤20	29	46.77	13	34.21	42	42.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.217

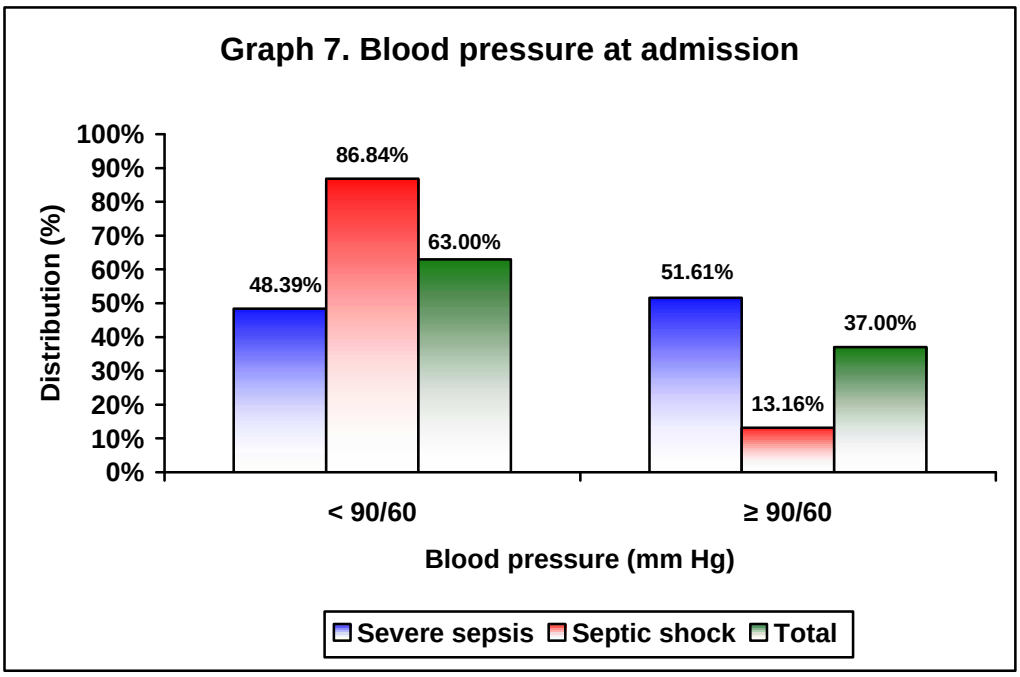


In this study the respiratory rate at admission was > 20 /minute in 53.23% of the patients with severe sepsis and 65.79% in patients with septic shock. Overall the respiratory rate was > 20 /minute in 58% of the patients.

Table 7. Blood pressure at admission

Blood pressure (mm Hg)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
< 90/60	30	48.39	33	86.84	63	63.00
≥ 90/60	32	51.61	5	13.16	37	37.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p < 0.001

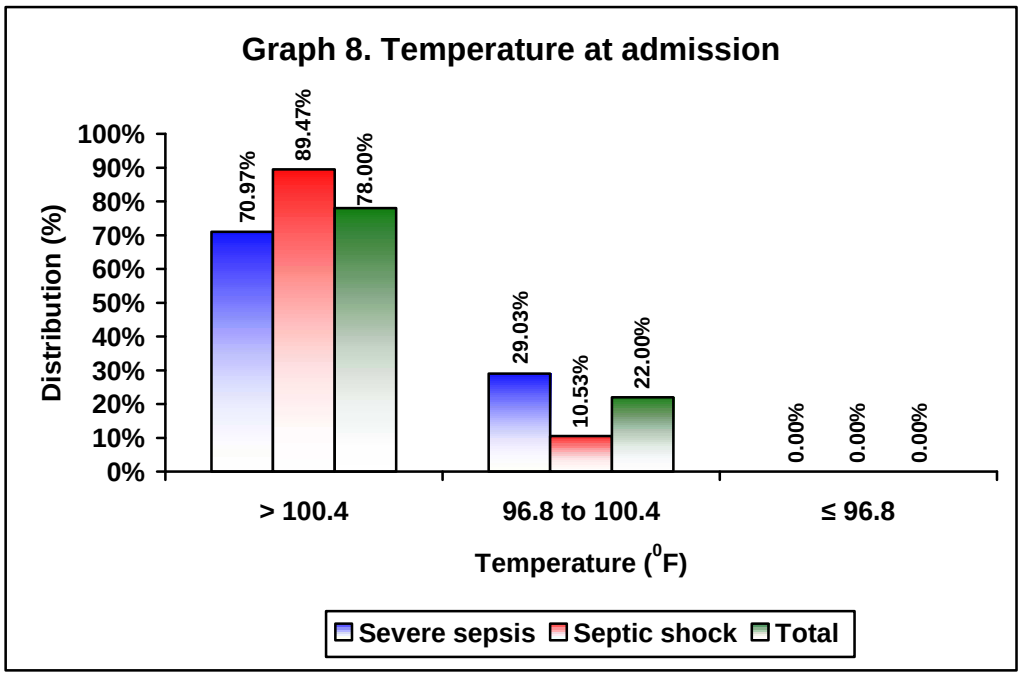


In the present study blood pressure at admission was < 90/60 mm Hg in 63% of the patients. The blood pressure of < 90/60 mm Hg was noted in 48.39% of the patients with severe sepsis and 86.84% of the patients with septic shock.

Table 8. Temperature at admission

Temperature (^{0}F)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
>100.4	44	70.97	34	89.47	78	78.00
96.8 to 100.4	18	29.03	4	10.53	22	22.00
≤ 96.8	0	0.00	0	0.00	0	0.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.030

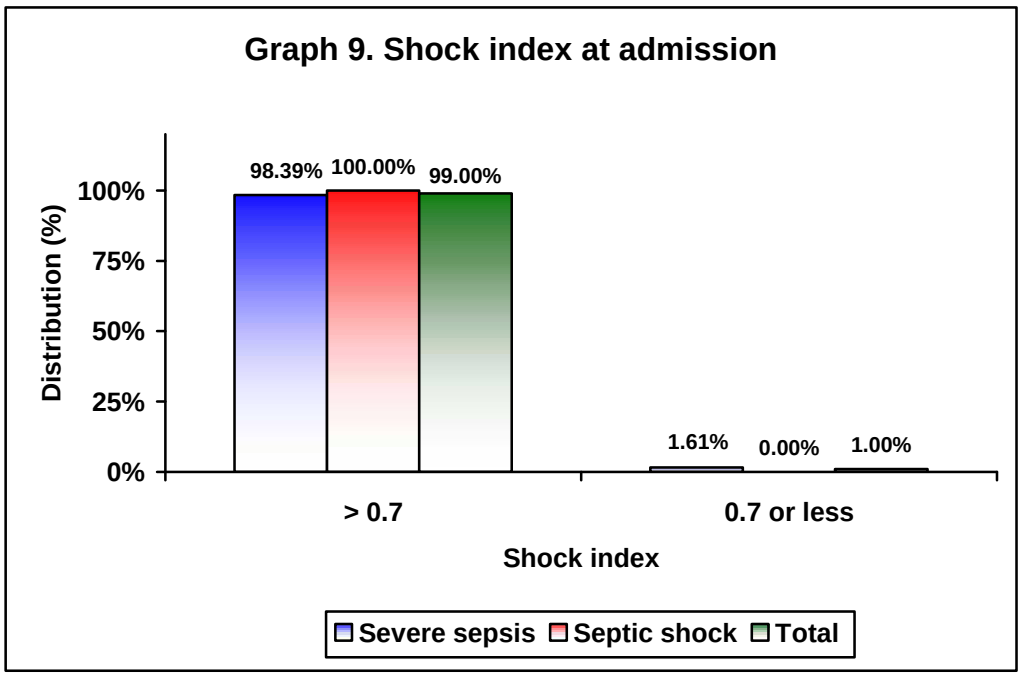


In this study majority of the patients (78%) presented with temperature > 100.4 ^{o}F and in patients with severe sepsis and septic shock 70.97% and 89.47% had temperature of > 100.4 ^{o}F respectively.

Table 9. Shock index at admission

Shock index	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
> 0.7	61	98.39	38	100.00	99	99.00
0.7 or less	1	1.61	0	0.00	1	1.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.620

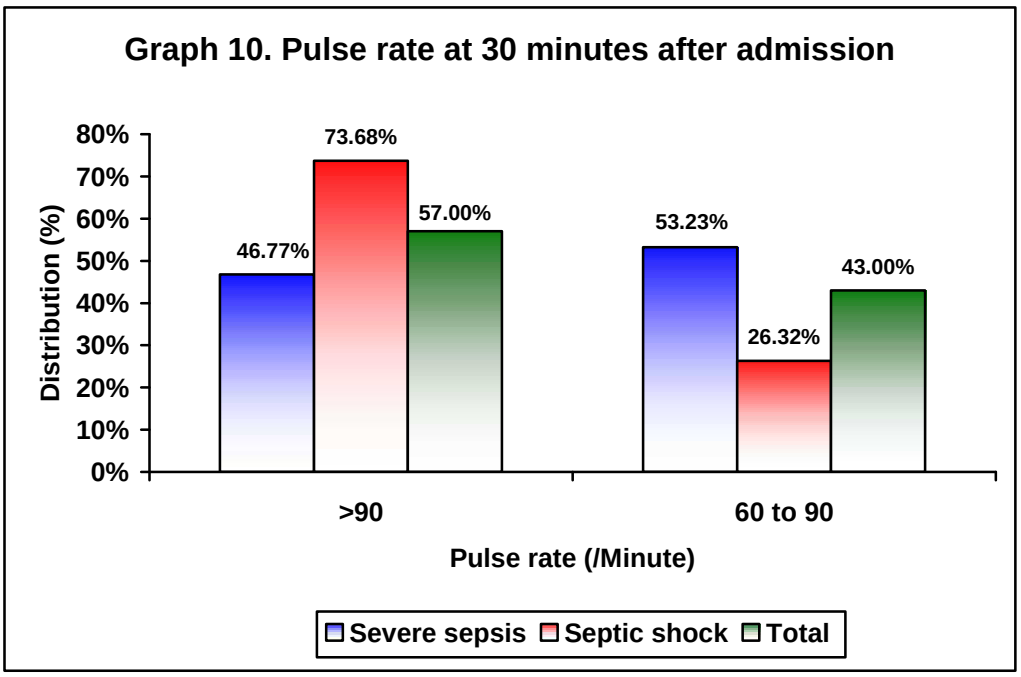


In the present study majority of the patients (99%) had shock index of > 0.7 at admission.

Table 10. Pulse rate at 30 minutes after admission

Pulse rate (/Minute)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
> 90	29	46.77	28	73.68	57	57.00
60 to 90	33	53.23	10	26.32	43	43.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.008

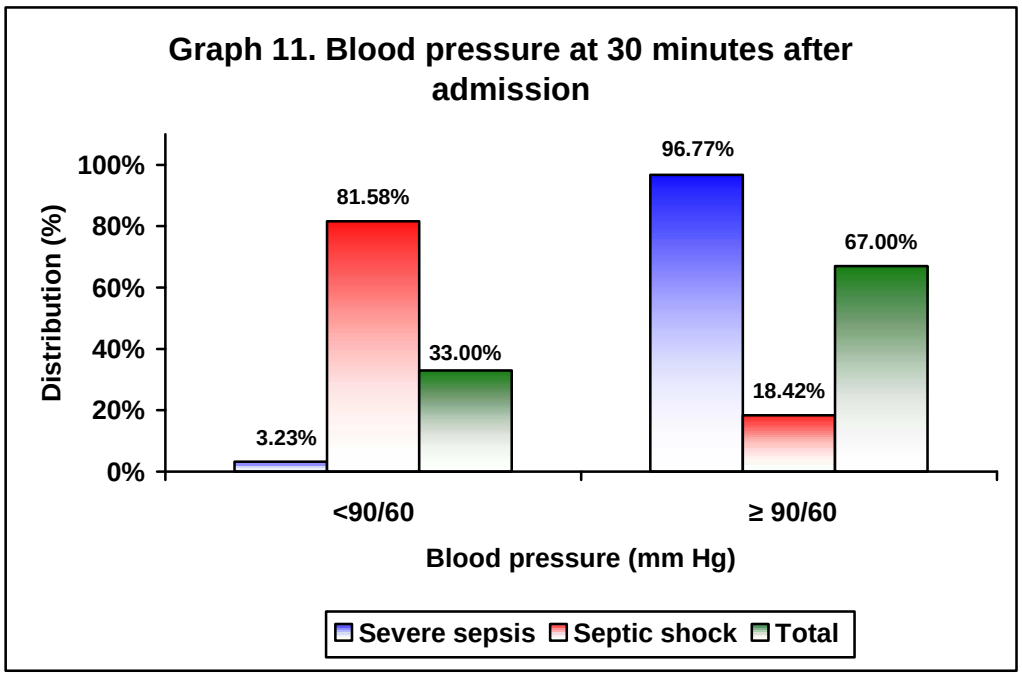


In the present study the pulse rate after 30 minutes of admission was > 90 per minute in 57% of the patients. The pulse rate was > 90 per minute in 46.77% of the patients with severe sepsis and 73.68% of the patients with septic shock.

Table 11. Blood pressure at 30 minutes after admission

Blood pressure (mm Hg)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
< 90/60	2	3.23	31	81.58	33	33.00
≥ 90/60	60	96.77	7	18.42	67	67.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p<0.001

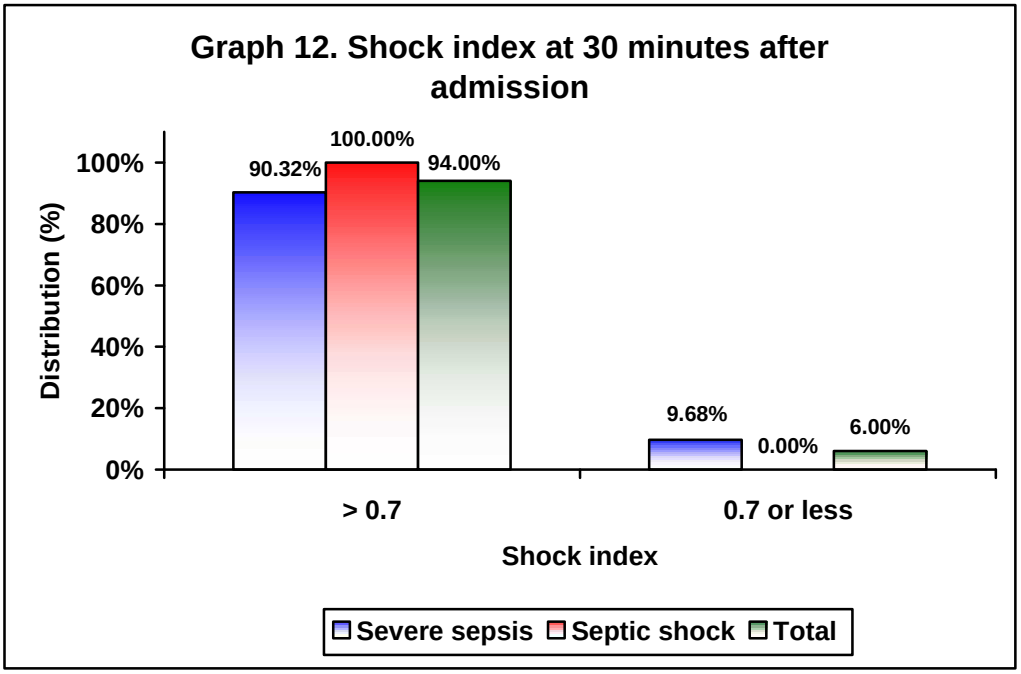


In the present study blood pressure at 30 minutes after admission was noted as < 90/60 mm Hg in 33% of the patients. In patients with severe sepsis 3.23% of the patients had blood pressure levels of < 90/60 mm Hg compared to 81.58% in septic shock.

Table 12. Shock index at 30 minutes after admission

Shock index	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
> 0.7	56	90.32	38	100.00	94	94.00
0.7 or less	6	9.68	0	0.00	6	6.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.052

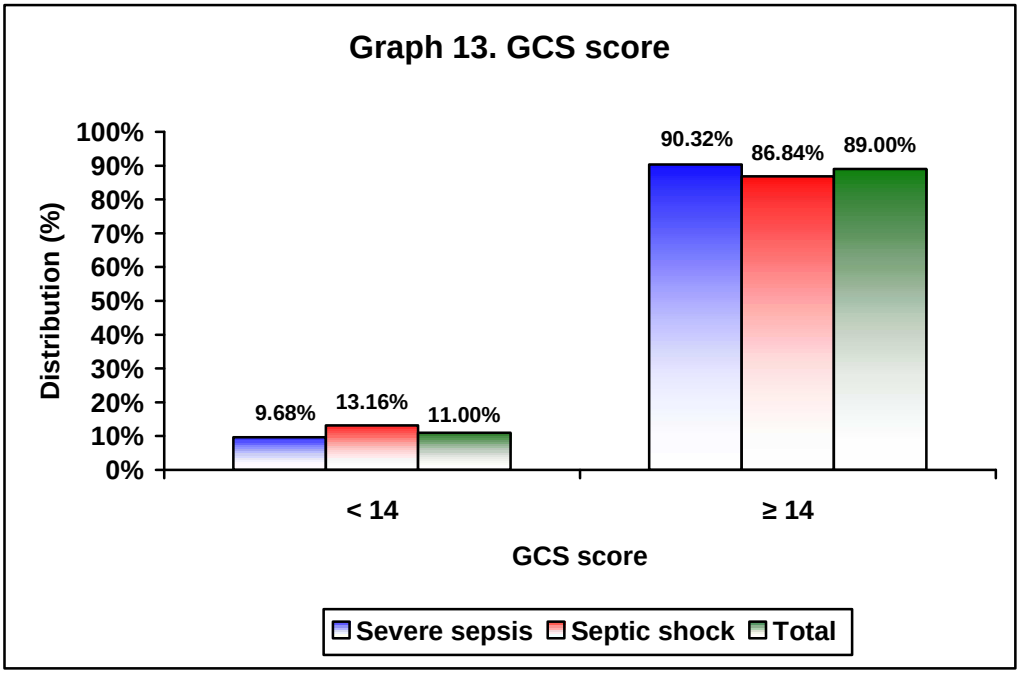


In this study the shock index at 30 minutes after admission was > 0.7 in 94% of the patients.

Table 13. GCS score

GCS score	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
< 14	6	9.68	5	13.16	11	11.00
≥ 14	56	90.32	33	86.84	89	89.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.409

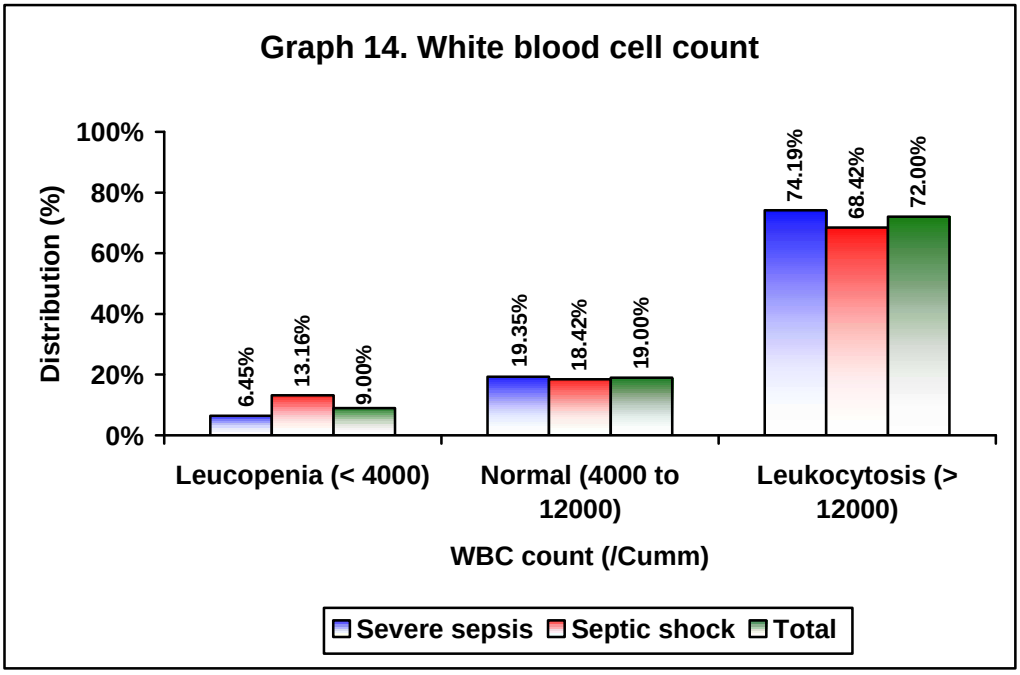


In this study GCS score was < 14 in 11% of the patients.

Table 14. White blood cell count

WBC count (/Cumm)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
Leukopenia (< 4000)	4	6.45	5	13.16	9	9.00
Normal (4000 to 12000)	12	19.35	7	18.42	19	19.00
Leukocytosis (>12000)	46	74.19	26	68.42	72	72.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.558

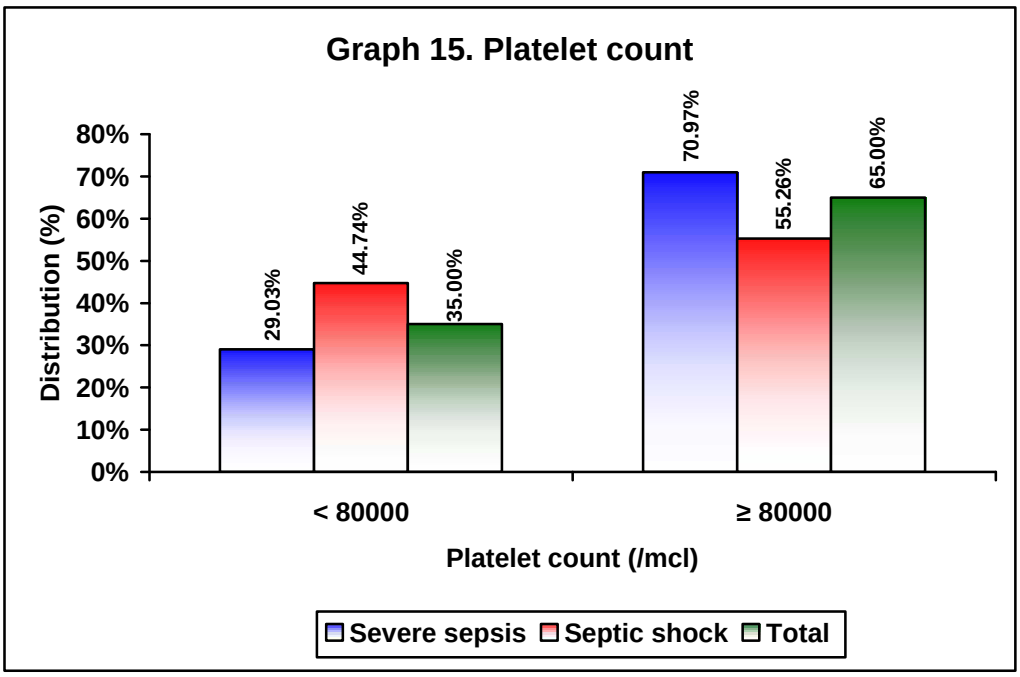


In the present study leukocytotis was noted in 72% of the patients and leukopenia was noted in 9%.

Table 15. Platelet count

Platelet count (/mcl)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
<80000	18	29.03	17	44.74	35	35.00
≥ 80000	44	70.97	21	55.26	65	65.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.084

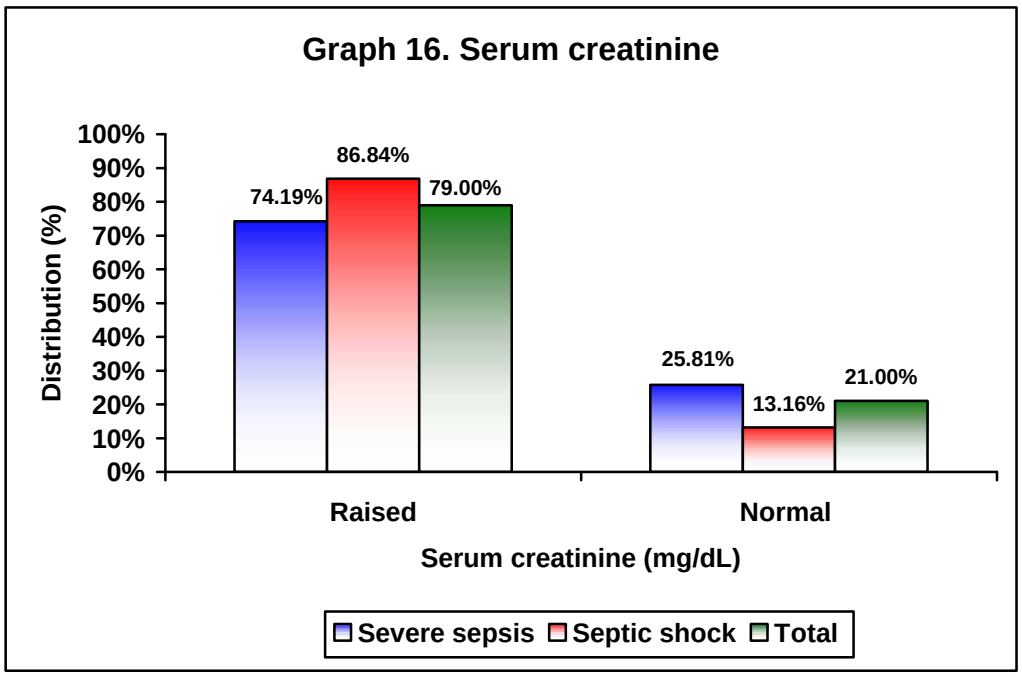


In this study platelet count was < 80000 /mcl in 35% of the patients.

Table 16. Serum creatinine

Serum creatinine (mg/dL)	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Raised (M>1.20; F>1.0)	46	74.19	33	86.84	79	79.00
Normal (M 0.7-1.2; F 0.5-1.0)	16	25.81	5	13.16	21	21.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.132

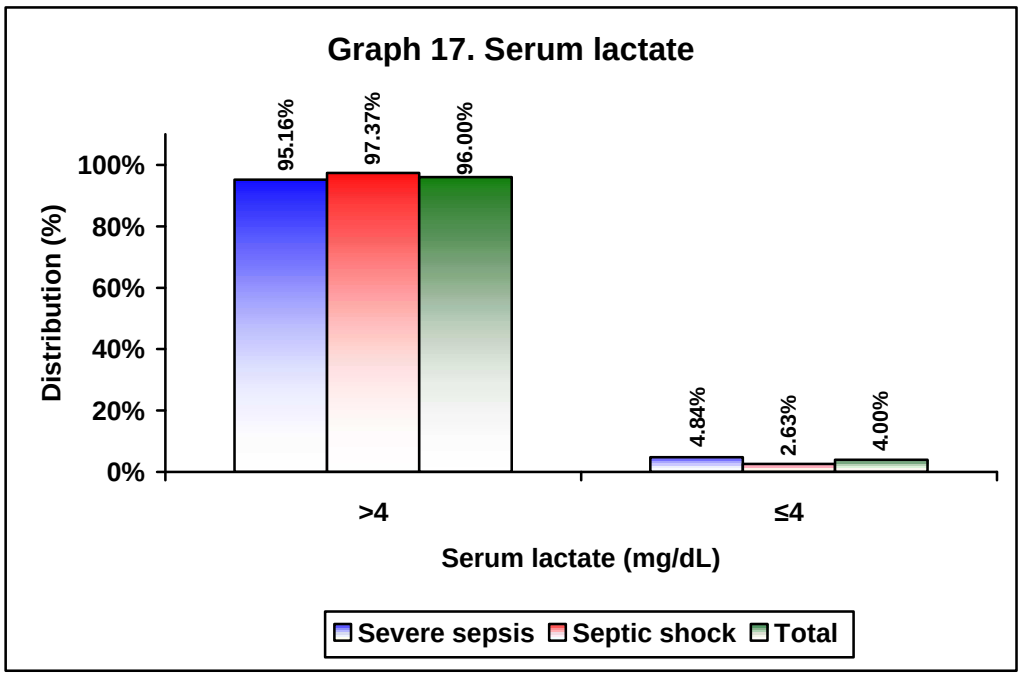


In the present study raised serum creatinine levels were noted in 79% of the patients. The serum creatinine levels were raised in 74.19% and 86.84% of the patients with severe sepsis and septic shock respectively.

Table 17. Serum lactate

Serum lactate (mg/dL)	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Hyperlactataemia (>4)	59	95.16	37	97.37	96	96.00
Normal (≤ 4)	3	4.84	1	2.63	4	4.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.509

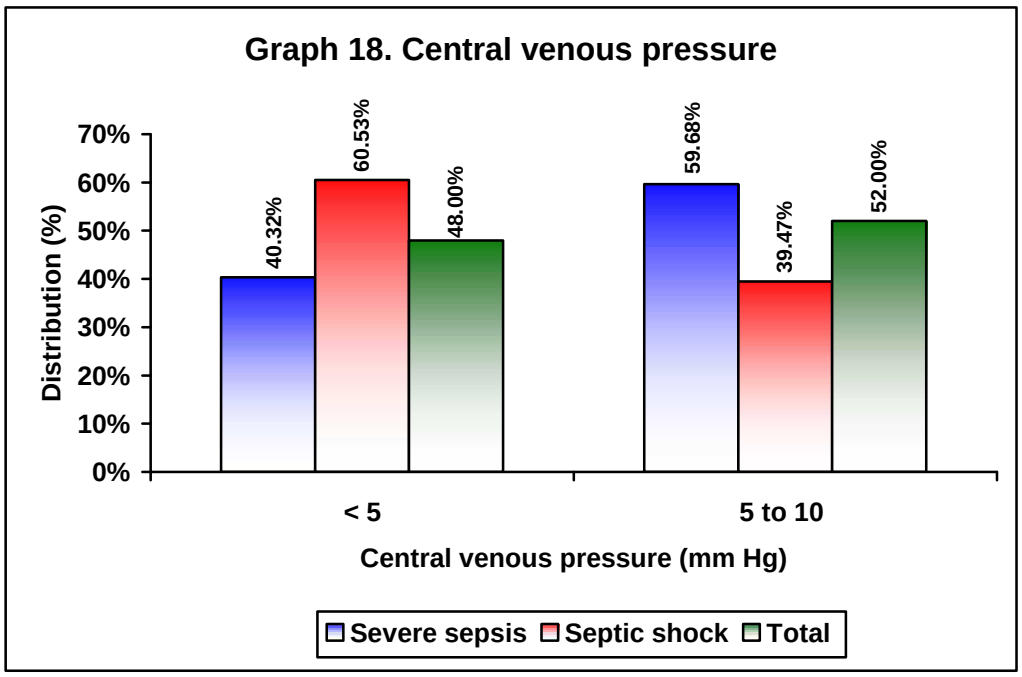


In the present study serum lactate levels were > 4 mg/dL in 96% of the patients.

Table 18. Central venous pressure

Central venous pressure (mm Hg)	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
< 5	25	40.32	23	60.53	48	48.00
5 to 10	37	59.68	15	39.47	52	52.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.039

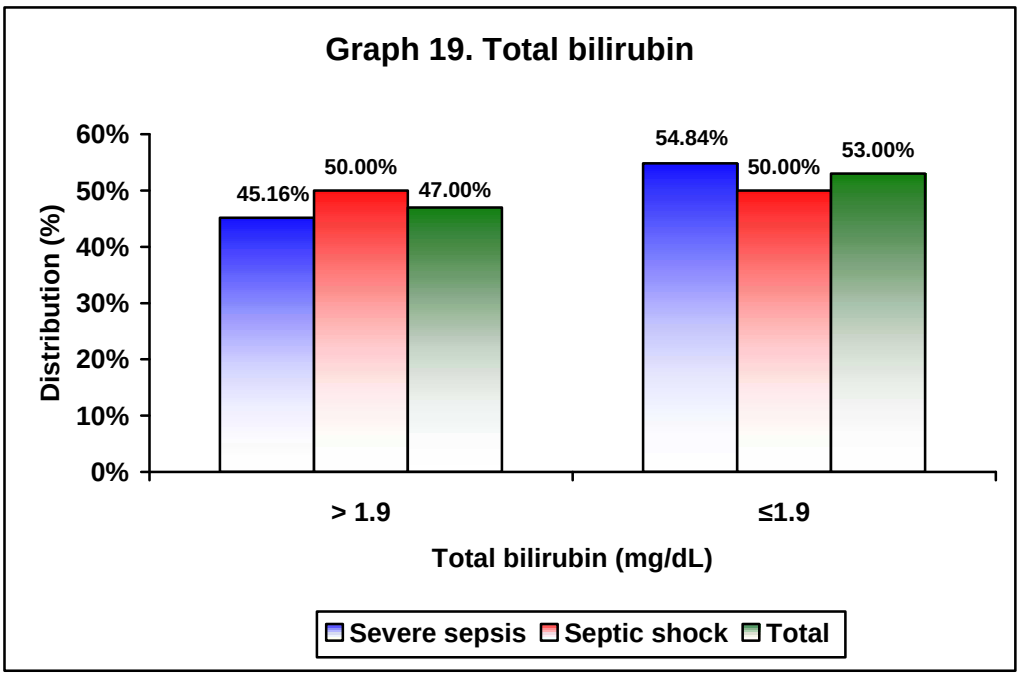


In this study central venous pressure was < 5 mm Hg in 48% of the patients. In patients with severe sepsis CVP was < 5 mm Hg in 40.32% while in patients with septic shock CVP was < 5 mm Hg in 60.53% of the patients.

Table 19. Total bilirubin

Total bilirubin (mg/dL)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
>1.9	28	45.16	19	50.00	47	47.00
≤ 1.9	34	54.84	19	50.00	53	53.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.396

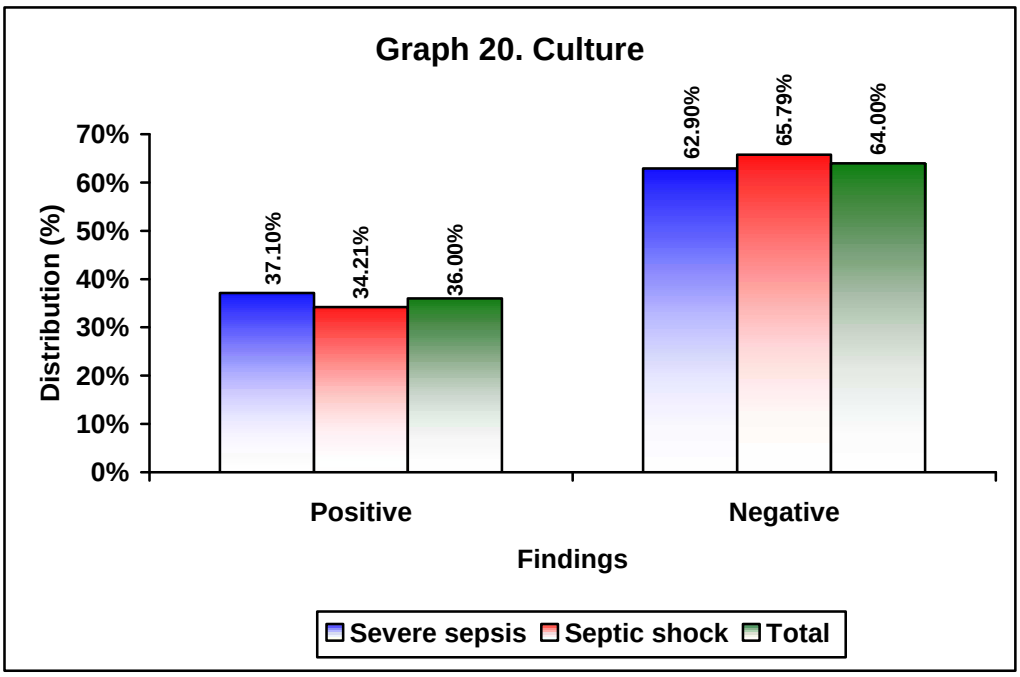


In this study bilirubin levels were > 1.90 in 47% of the patients.

Table 20. Culture

Findings	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Positive	23	37.10	13	34.21	36	36.00
Negative	39	62.90	25	65.79	64	64.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.770



In the present study only 36% of the patients had positive blood culture.

Table 21. Organisms

Organisms	Severe sepsis		Septic shock		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Escherichia coli	5	8.06	4	10.53	9	9.00
Coagulase negative staph aureus	4	6.45	3	7.89	7	7.00
Staphylococcus hemolyticus	5	8.06	1	2.63	6	6.00
Klebsiella pneumoniae	3	4.84	1	2.63	4	4.00
Staphylococcus epidermis	1	1.61	2	5.26	3	3.00
Acitinobacter	2	3.23	0	0.00	2	2.00
Staph aureus	1	1.61	1	2.63	2	2.00
MRSA	2	3.23	0	0.00	2	2.00
Pseudomonas	0	0.00	1	2.63	1	1.00
Negative	39	62.90	25	65.79	64	64.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

Table 21 shows the organisms isolated in patients with severe sepsis and septic shock. It was observed that, *Escherichia coli* was the commonest organism involved in patients with severe sepsis (8.06%) and septic shock (10.53%).

Table 22. Involvement of the system

System involved	Distribution (n=100)	
	Number	**Percentage**
Respiratory system	31	31.00
Systemic	29	29.00
Genitourinary	21	21.00
Gastrointestinal system	16	16.00
CNS	3	3.00
Total	**100**	**100.00**

In the present study most of the patients had involvement of respiratory system (31%) followed by systemic involvement (29%), genitourinary system (21%), gastrointestinal system (16%) and CNS (3%).

Table 23. Diagnosis

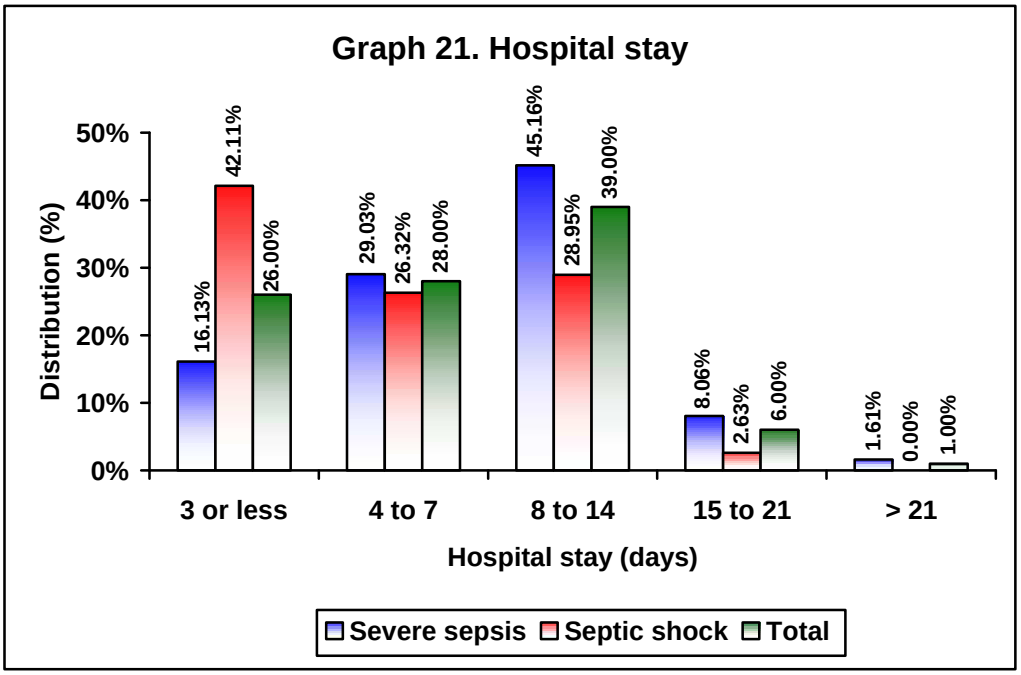
Diagnosis	Distribution (n=100)	
	Number	**Percentage**
Pneumonia	21	21.00
Urosepsis	20	20.00
Cellulitis	13	13.00
Viral fever	8	8.00
Acute gastroenteritis	8	8.00
COPD	6	6.00
Acute pancreatitis	5	5.00
Acute bacterial meningitis	2	2.00
Bacterial encephalitis	1	1.00
Acute bacterial peritonitis	1	1.00
Acute bronchitis	1	1.00
IUD	1	1.00
Pharyngitis	1	1.00
Liver abscess	1	1.00
Post LSCS wound infection	1	1.00
Pulmonary Koch's	1	1.00
Oral mucor mycosis	1	1.00
Peritoneal abscess	1	1.00
Not identified	7	7.00
Total	**100**	**100.00**

In the present study commonest diagnosis was pneumonia (21%) followed by urosepsis (20%) and cellulitis (13%).

Table 24. Hospital stay

Hospital stay (days)	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
3 or less	10	16.13	16	42.11	26	26.00
4 to 7	18	29.03	10	26.32	28	28.00
8 to 14	28	45.16	11	28.95	39	39.00
15 to 21	5	8.06	1	2.63	6	6.00
> 21	1	1.61	0	0.00	1	1.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.040

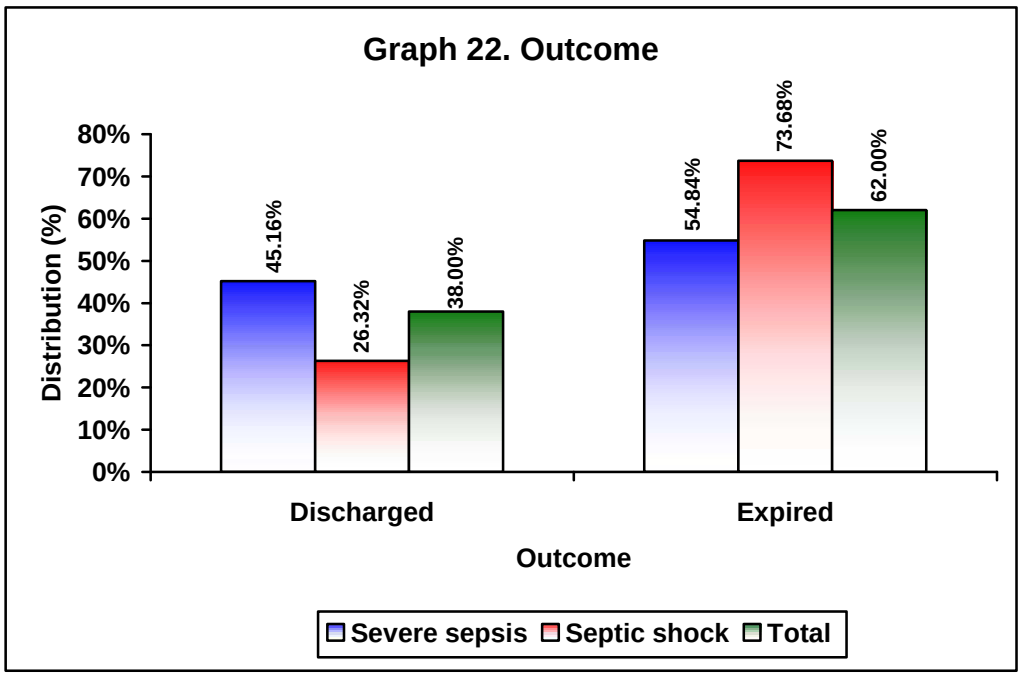


In the present study hospital stay of 8 to 14 days was noted in 39% of the patients.

Table 25. Outcome

Outcome	Severe sepsis		Septic shock		Total	
	No.	%	No.	%	No.	%
Discharged	28	45.16	10	26.32	38	38.00
Expired	34	54.84	28	73.68	62	62.00
Total	**62**	**100.00**	**38**	**100.00**	**100**	**100.00**

p = 0.050



In this study 62% of the patients expired. In patients with severe sepsis and septic shock 54 .84% and 73.68% of the patients, expired respectively.

Table 26. Association of outcome with shock index at admission

Shock index	Outcome				Total	
	Improved		Expired			
	No.	%	No.	%	No.	%
0.5-0.7	1	100.00	0	0.00	1	100.00
0.8-1.0	5	71.43	2	28.57	7	100.00
1.1-1.3	17	43.59	22	56.41	39	100.00
1.4-1.7	10	27.03	27	72.97	37	100.00
1.8-2.0	2	28.57	5	71.43	7	100.00
>2.0	3	33.33	6	66.67	9	100.00
Total	**38**	**38.00**	**62**	**62.00**	**100**	**100.00**

p = 0.165

In the present study no association was found between shock index at admission and mortality (p=0.165)

Table 27. Association of outcome with shock index at 30 minutes from admission

Shock index	Outcome				Total	
	Improved		Expired			
	No.	%	No.	%	No.	%
0.5-0.7	6	100.00	0	0.00	6	100.00
0.8-1.0	27	81.82	6	18.18	33	100.00
1.1-1.3	4	14.29	24	85.71	28	100.00
1.4-1.7	1	3.85	25	96.15	26	100.00
1.8-2.0	0	0.00	3	100.00	3	100.00
>2.0	0	0.00	4	100.00	4	100.00
Total	**38**	**38.00**	**62**	**62.00**	**100**	**100.00**

$p < 0.001$

In this study as the shock index at 30 minutes raised mortality increased significantly ($p<0.001$) that is, none of the patient with shock index between 0.5 to 0.7 expired while maximum mortality was noted among the patients with shock index ≥ 1.8 (100%).

Table 28. Association of outcome with difference in shock index at admission to shock index at 30 minutes of admission

Difference in shock index	Outcome				Total	
	Improved		Expired			
	No.	%	No.	%	No.	%
Minus 0.3 to Minus 0.6	0	0.00	5	100.00	5	100.00
0.0 to Minus 0.2	2	18.18	9	81.82	11	100.00
0.1 to 0.3	10	19.61	41	80.39	51	100.00
0.4 to 0.6	19	79.17	5	20.83	24	100.00
0.7 to 0.9	5	83.33	1	16.67	6	100.00
1.0 to 1.2	1	50.00	1	50.00	2	100.00
> 1.2	1	100.00	0	0.00	1	100.00
Total	**38**	**38.00**	**62**	**62.00**	**100**	**100.00**

p < 0.001

In the present study, as the difference in shock index at admission to shock index at 30 minutes of admission increased significantly higher number of patients improved ($p<0.001$). In patients with difference in shock index at admission and shock index at 30 minutes of admission of Minus 0.3 to Minus 0.6, none of the patient improved, while majority of the patients with difference in shock index at admission to 30 minutes between 0.4 to 0.6 (79.17%), 0.7 to 0.9 (83.33%) improved.

Table 29. Association of length of hospital stay with shock index at admission

Length of hospital stay (Days)	Shock index at admission				Total	
	> 0.7		0.5-0.7			
	No.	%	No.	%	No.	%
3 or less	26	100.00	0	0.00	26	100.00
4 to 7	28	100.00	0	0.00	28	100.00
8 to 14	39	100.00	0	0.00	39	100.00
15 to 21	6	100.00	0	0.00	6	100.00
>21	0	0.00	1	100.00	1	100.00
Total	**99**	**99.00**	**1**	**1.00**	**100**	**100.00**

p = 0.010

In this study positive association was noted between higher shock index at admission and duration of hospital stay (p=0.010).

Table 30. Association of length of hospital stay with shock index at 30 minutes after admission

Length of hospital stay (Days)	Shock index at 30 minutes after admission				Total	
	> 0.7		0.5-0.7			
	No.	%	No.	%	No.	%
3 or less	26	100.00	0	0.00	26	100.00
4 to 7	28	100.00	0	0.00	28	100.00
8 to 14	37	94.87	2	5.13	39	100.00
15 to 21	2	33.33	4	66.67	6	100.00
>21	1	100.00	0	0.00	1	100.00
Total	**94**	**94.00**	**6**	**6.00**	**100**	**100.00**

p < 0.001

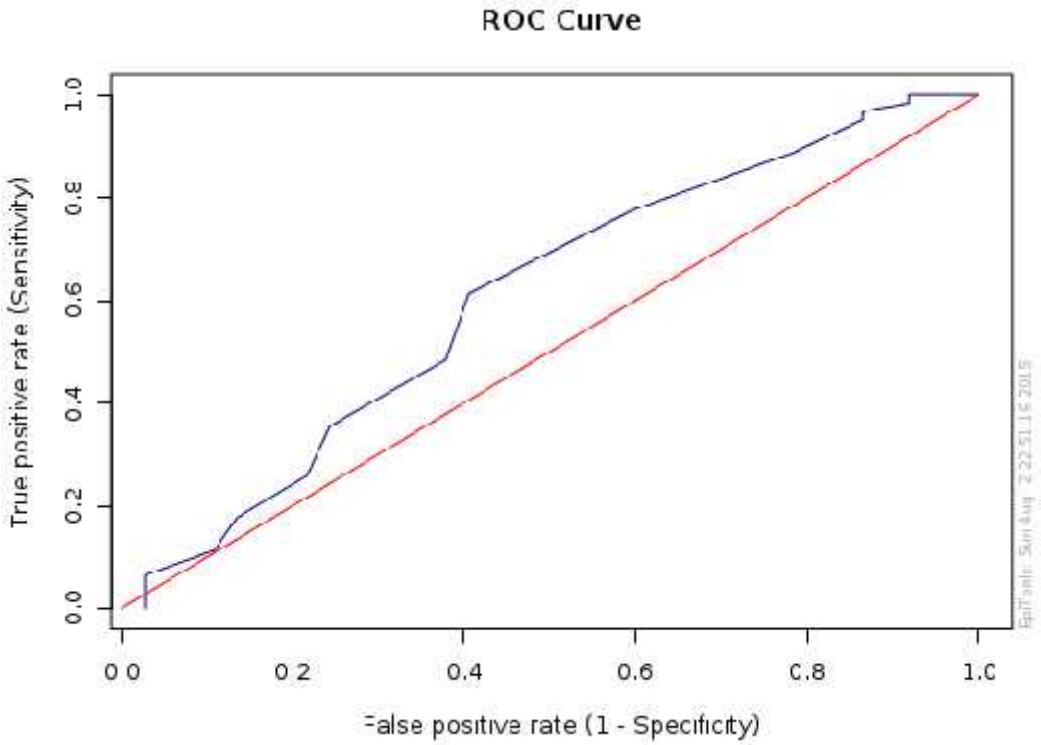
In the present study length of hospital stay was significantly high in patients with higher shock index at 30 minutes after admission (p<0.001)

Table 31. Mean shock index and outcome

Shock index	Outcome				p value
	Improved		Expired		
	Mean	SD	Mean	SD	
Shock index at admission	1.37	0.40	1.50	0.34	0.111
Shock index at 30 minutes	0.90	0.16	1.41	0.32	**<0.001**
Difference in shock index	0.47	0.30	0.08	0.28	**<0.001**

In this study the mean shock index at 30 minutes after admission was significantly high in patients who expired (1.41 ± 0.32) compared to those patients who improved (0.90 ± 0.16) ($p<0.001$). Further the difference in shock index from admission to 30 minutes after admission was significantly high in patients who improved (0.47 ± 0.30) compared to those who expired (0.08 ± 0.28) ($p<0.001$).

Graph 23. Receiver operating characteristic curve for shock index at admission as a predictor of mortality

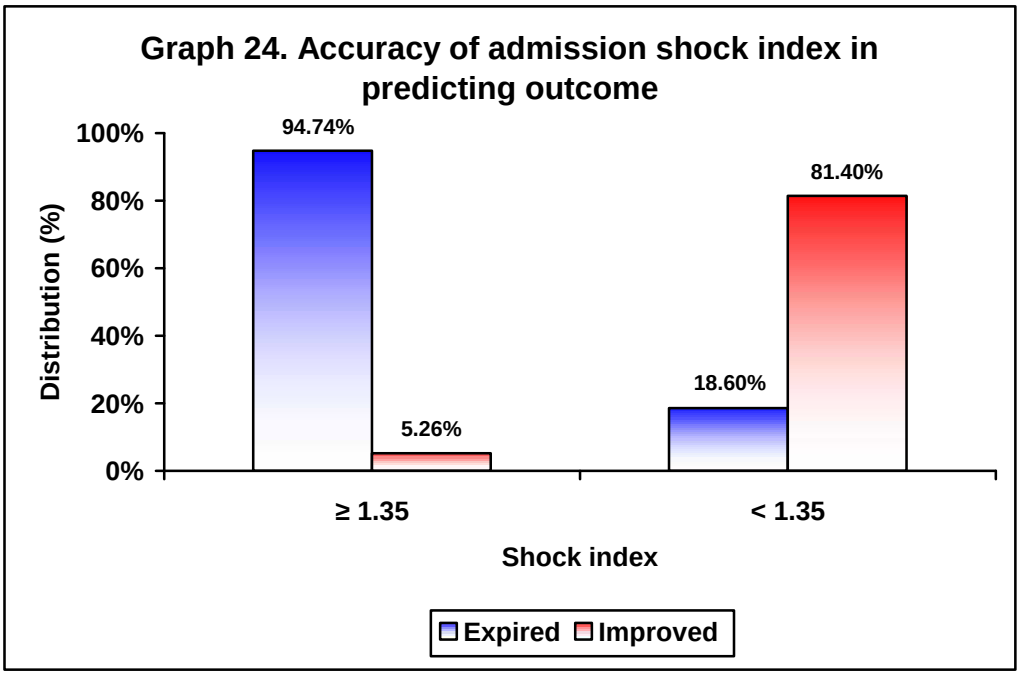


In the present study ROC curve for shock index at admission as a predictor of mortality showed maximum sensitivity and specificity at a cut off value of 1.35 with AUC of 0.616 (95% CI - 0.498 to 0.733 SE = 0.060 p=0.053).

Table 32. Accuracy of admission shock index in predicting outcome

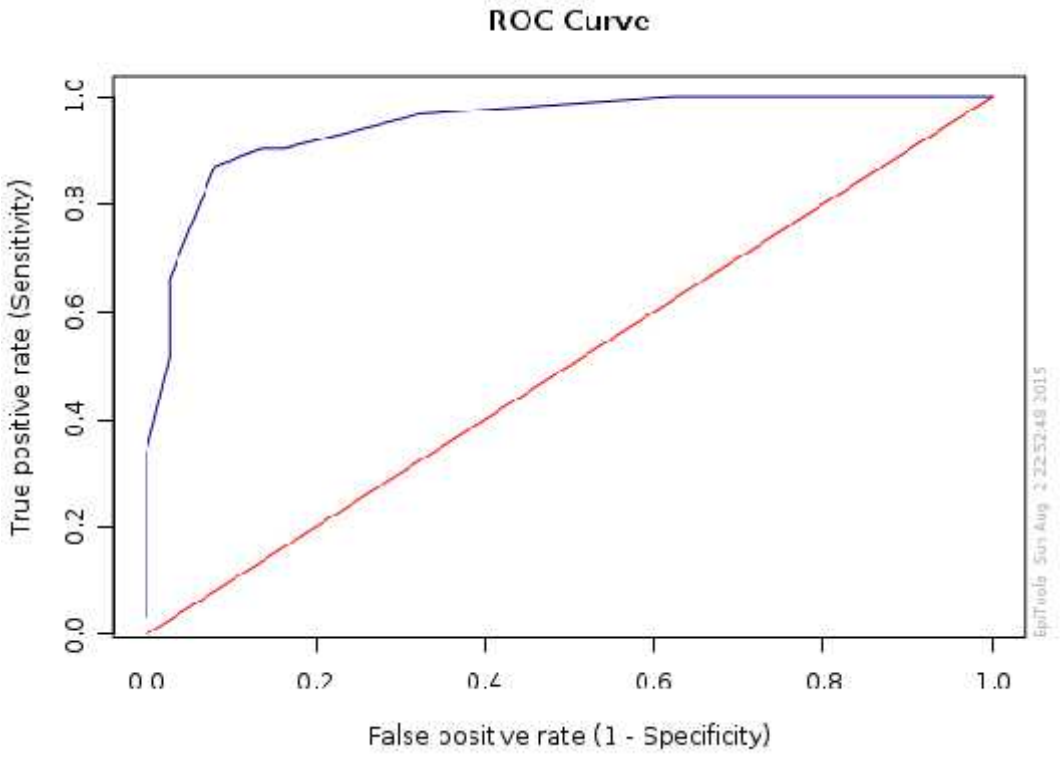
Shock index	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
≥ 1.35	54	94.74	3	5.26	57	100.00
< 1.35	8	18.60	35	81.40	43	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p < 0.001



In this study using a cut-off value of 1.35 for shock index at admission the sensitivity of shock index in predicting mortality was 61.29% with a specificity of 60.53%, PPV of 71.7% and NPV of 48.94% and positive likelihood ratio was 1.55.

Graph 25. Receiver operating characteristic curve for shock index at 30 minutes after admission as a predictor of mortality

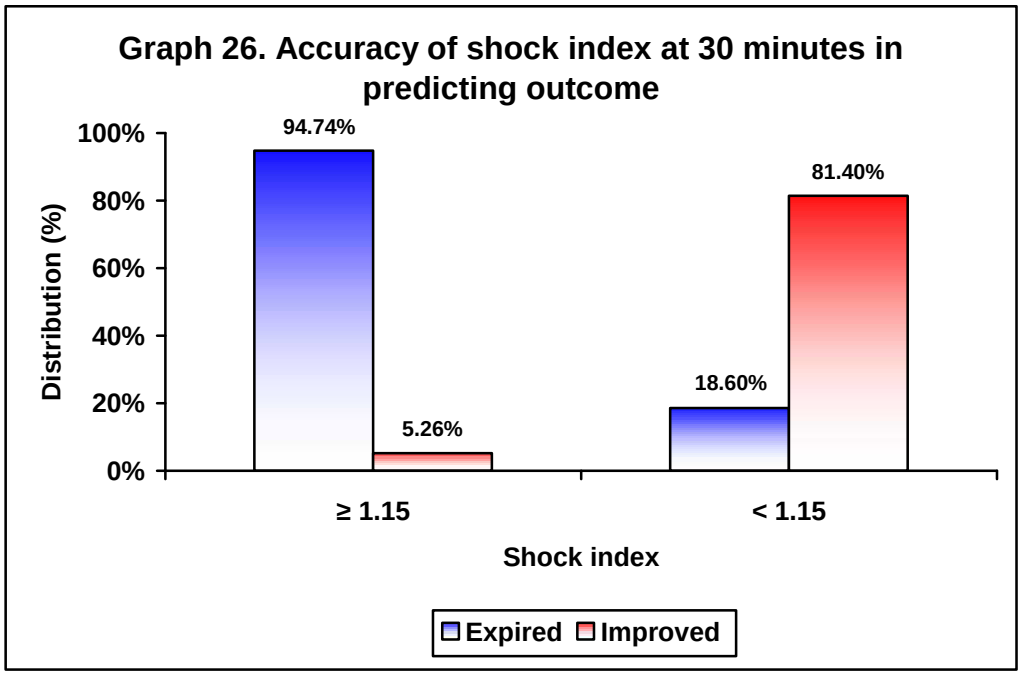


In the present study for shock index at 30 minutes from admission showed AUC of 0.949 in predicting mortality with a cut off value of 1.15 with (95% CI - 0.908 to 0.0.991 SE = 0.021 p<0.001).

Table 33. Accuracy of shock index at 30 minutes in predicting outcome

Shock index	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
≥ 1.15	54	94.74	3	5.26	57	100.00
< 1.15	8	18.60	35	81.40	43	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p<0.001

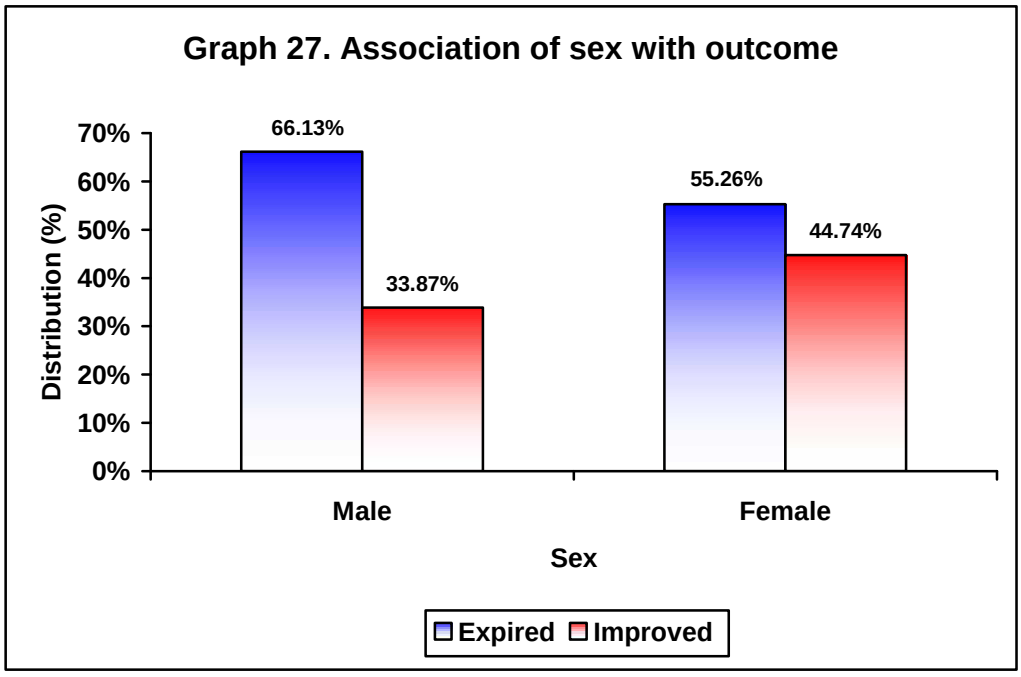


In this study with a cut-off value of 1.15 for shock index at 30 minutes after admission showed sensitivity of 87.1%, specificity of 92.11%, NPV of 94.74% and PPV of 81.40 in predicting mortality and high positive likelihood ratio (11.03) were noted.

Table 34. Association of sex with outcome

Sex	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
Male	41	66.13	21	33.87	62	100.00
Female	21	55.26	17	44.74	38	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p = 0.277



In the present study no association was noted between sex and outcome (p=0.277)

Table 35. Association of age with outcome

Age group (Years)	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
30 or less	9	52.94	8	47.06	17	100.00
31 to 40	5	31.25	11	68.75	16	100.00
41 to 50	12	57.14	9	42.86	21	100.00
51 to 60	15	75.00	5	25.00	20	100.00
61 to 70	12	80.00	3	20.00	15	100.00
71 to 80	7	87.50	1	12.50	8	100.00
81 to 90	2	66.67	1	33.33	3	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p = 0.041

In this study significantly higher number of patients expired who were aged 71 to 80 years (87.5%), 51 to 60 years (75%), 61 to 70 years (80%) and 81 to 90 years (66.67%) (p=0.041).

Table 36. Association of temperature with outcome

Temperature	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
≥ 99.9	49	62.82	29	37.18	78	100.00
< 99.9	13	59.09	9	40.91	22	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p = 0.750

In the present study no association was found between temperature and outcome (p=0.750).

Table 37. Association of respiratory rate with outcome

Respiratory rate (/minute)	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
< 16	6	27.27	16	72.73	22	100.00
16 to 20	14	70.00	6	30.00	20	100.00
> 20	42	72.41	16	27.59	58	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p=0.001

In this study significantly higher number of patients with respiratory rate of > 20 expired (72.41%, p=0.001).

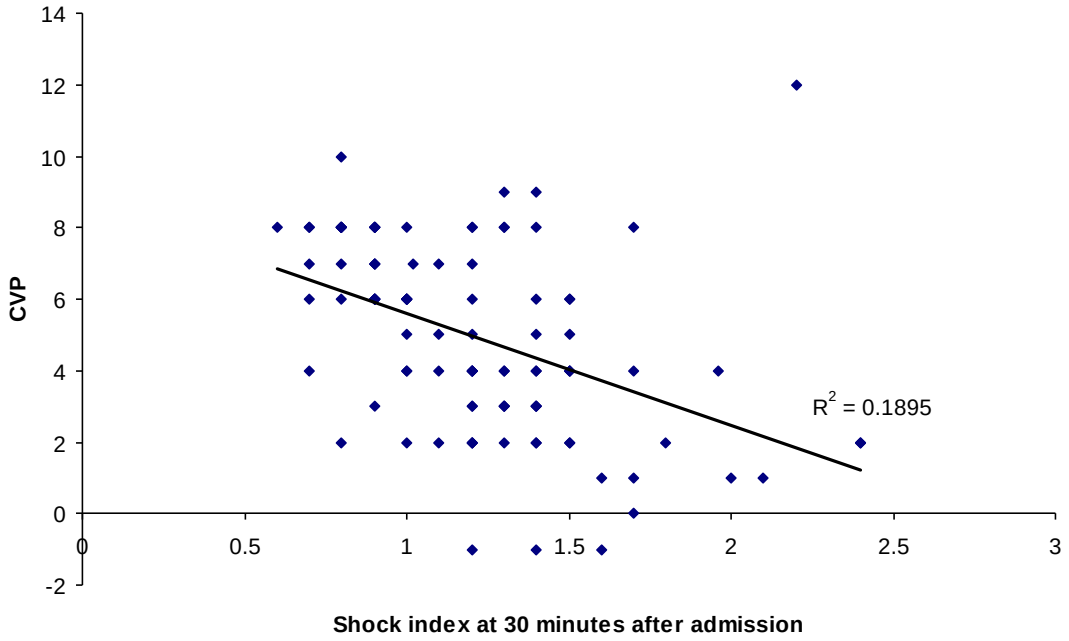
Table 38. Association of pulse rate with outcome

Pulse rate (/minute)	Outcome				Total	
	Expired		Improved			
	No.	%	No.	%	No.	%
60 to 90	6	60.00	4	40.00	10	100.00
> 90	56	62.22	34	37.78	90	100.00
Total	**62**	**62.00**	**38**	**38.00**	**100**	**100.00**

p = 0.572

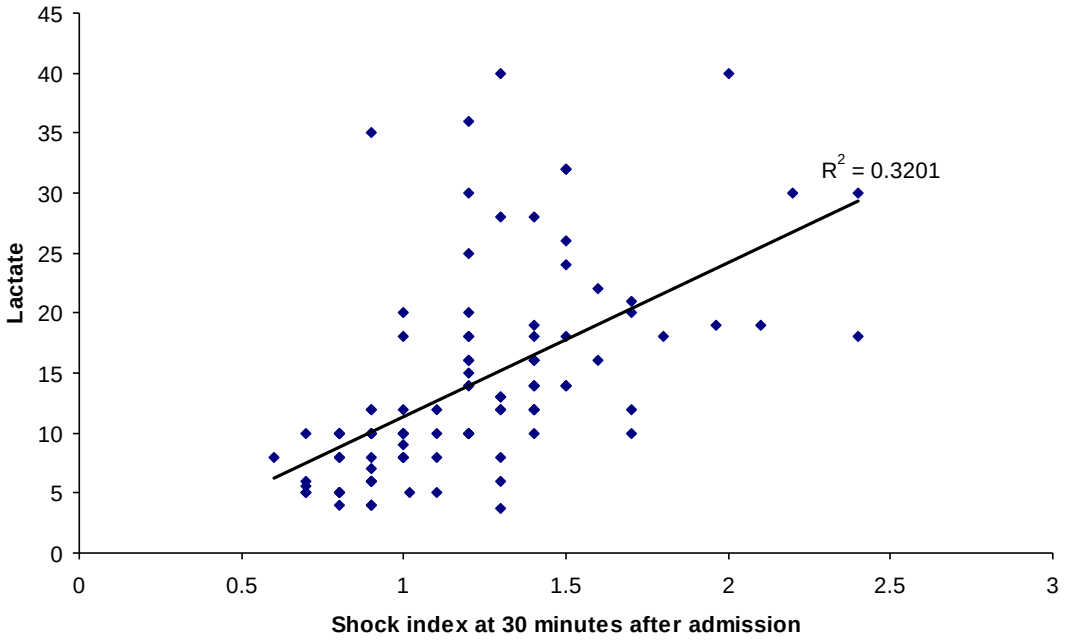
In the present study no statistically significant association was found between pulse rate and outcome (p=0.572).

Graph 28. Correlation of shock index at 30 minutes after admission with CVP



The correlation of CVP with shock index at 30 minutes after admission is as shown in figure above. There was moderate negative correlation between CVP and shock index at 30 minutes after admission ($r=-0.435$; $R^2=0.189$; $p<0.001$).

Graph 29. Correlation of shock index at 30 minutes after admission with lactate



The above figure shows correlation of serum lactate levels with shock index at 30 minutes after admission. There was strong positive correlation between serum lactate levels and shock index at 30 minutes after admission ($r=0.565$; $R^2=0.320$; $p<0.001$).

DISCUSSION

Sepsis and its spectrum of clinical entities remain one of the common critical illnesses, encountered in the emergency department, with an estimated mortality rate of 20 to 30% in population-based studies. The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis. However, the early diagnosis and stratification of the severity of sepsis is very important which increases the possibility of starting timely and specific treatment which is essential for improved outcomes among these patients. Unfortunately, the severity of the condition may not be apparent at admission, which makes it more challenging in an evolving ED practice, where care is increasingly being delivered in overcrowded situations with limited resources particularly in urban settings with a heavy workload.[72]

Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis, and can differentiate bacterial from viral and fungal infection, and systemic sepsis from local infection. Other potential uses of biomarkers include roles in prognostication, guiding antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from Gram-negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction). However, the exact role of biomarkers in the management of septic patients remains undefined. C-reactive protein (CRP) has been used for many years but its specificity has been challenged. Procalcitonin (PCT) has been proposed as a more specific and better prognostic marker than CRP,

although its value has also been challenged . Moreover, all these parameters require long time for estimation and/or can not predict immediate mortality and they need high investment and immediate availability of specialized instruments.[72]

This prompts a cost effective and easily attainable clinical parameter that would effectively prognosticate the outcome of sepsis patients in ED and would help in optimized triaging, risk stratification and accurate identification of ICU candidates amongst severely ill patient. Shock index which is a measurement that could be easily and affordably attained, can be used as a predictor for severity of sepsis in ED.[14] However, to-date, little is known about the value of shock index in prognosticating severity and mortality of the patients in sepsis.[14] Majority of studies have evaluated the value of shock index in haemorrhagic shock but only few studies are available on value of shock index in septic shock.[63-71] The present study was an attempt to predict outcome in patients with severe sepsis and septic shock using shock index.

The present one year hospital based observational study was done from January 2014 to December 2014. A total of 100 patients admitted with severe sepsis or septic shock in the Emergency Department under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied. Shock index was calculated and the patients were monitored for outcome.

In the present study of the 100 patients studied, 62% had severe sepsis and 38% had septic shock. The sex distribution pattern revealed male preponderance, as 62% of the patients were males and 38% were females, with male to female ratio of 1.63:1. The sepsis pattern noted in the present study was sharply in agreement with a

similar study by Mohd Yussof SJ. et al.[14] from Malaysia where the number of severe sepsis and septic shock cases were 62%, and 38% respectively whereas the same study reported female preponderance that is 62% females and 38% males.

It has been long recognized that age is an important component for developing sepsis. The incidence of sepsis is greatest at the extremes of age, occurring in 5.3/1000 patients under 12 months of age and 26.2/1000 patients aged 65 years or older. In the present study age ranged from 19-83 years. Most of the patients (21%) were aged between 41-50 years followed by 51-60 years (20%), ≤ 30 years (17%), 31-40 years (16%) and 61-70 years (15%). The mean age was 49.8 ± 16.5 years. The mean age observed in the present study was comparable to the study by Mohd Yussof SJ. et al.[14] which reported median age as 54 years with range from 17-84 years. In contrast a study by Myint PK. et al.[73] to assess the association of shock index in patients with community-acquired pneumonia reported median age of 76 years.

In the present study, with regards to source of sepsis, 31% had respiratory system involved, 21% had genitourinary system and 16% had gastrointestinal system involved while 29% of the patients had other focus of sepsis. The commonest organism was Escherachia coli in 8.06% of the patients with severe sepsis and 10.53% of the patients with septic shock.

In this study, at admission, almost all the patients (99%) had shock index of >0.7 whereas at 30 minutes after admission, shock index of >0.7 was noted in 94% of the patients.

Patients with sepsis are classically considered to be patients who have a high risk of morbid complications and death. This is in large part owing to the organ dysfunction caused by sepsis, and the attendant complications of treating the organ dysfunction.[20] In this study the mortality rate was high. Of the 100 patients studied, mortality was noted in 62% of the patients. Further significantly higher mortality was noted in patients with septic shock compared to severe sepsis (73.68% vs 54.84%; p=0.050). The mortality rate observed in the present study was slightly high compared a similar study[14] from Malaysia where authors reported 54% mortality rate.

With the advent of early identification and treatment strategies for sepsis in the context of ever-shrinking resources, fast, reliable screening tools are needed. In the high-acuity and high-uncertainty setting of the ED, the goal is to avoid potentially dangerous under-triage while appropriately assigning higher priority to seriously ill patients.[74] Haas[75] described the ideal triage tool as simple to use, accurate, rapid, reproducible, and discriminative. SI emphasizes current physiologic dynamics, rather than static criteria. We sought to find its usefulness in our emergency department for predicting outcome in patients with sever sepsis and septic shock.

In the present study higher number of the patients expired who had higher shock index. The mortality rate in patients with shock index of > 2.0 was 66.67%, from 1.8 to 2.0 it was 71.43%, from 1.4 to 1.7 it was 72.97% and from 1.1 to 1.3 the mortality rate was 56.41%. However the same was not true statistically (p=0.165).

When shock index was calculated at 30 minutes after admission, it was noted that, higher the shock index higher is the mortality that is, mortality was high in patients with shock index > 2.0 (100%), from 1.8 to 2.0 (100%), 1.4 to 1.7 (96.15%) and 1.1 to 1.3 (85.71%). It was observed that, of the 33 patients with shock index of 0.8 to 1.0 at 30 minutes of admission, maximum patients (81.82%) improved and mortality was noted in few (18.18%). These findings were statistically significant ($p<0.001$).

The further analysis was sought to confirm these findings by calculating the difference in between shock index at admission and shock index at 30 minutes after admission, which showed a statically significant trend of reduction in mortality as the difference between the two increased.

In patients with difference in shock index at admission to 30 minutes of Minus 0.3 to Minus 0.6 all the patients expired and majority of the patients with difference in shock index at admission to 30 minutes between 0.4 to 0.6 (79.17%), 0.7 to 0.9 (83.33%) improved.

Further the mean shock index at 30 minutes after admission showed significantly higher value in patients who expired (1.41 ± 0.32) compared to those who improved (0.90 ± 0.16) ($p<0.001$). However, the mean shock index value at admission was comparable in patients who expired (1.50 ± 0.34) and who improved (1.37 ± 0.40) ($p=0.111$).

These findings indicate not only the usefulness of shock index as a simple bedside measure in risk stratification of patients with sepsis and severe sepsis but

also emphasize that, shock index evaluated at 30 minutes post admission helps the treating physician to determine risk of mortality and effect of resuscitation.

Shock index has a low cost attainable value and is immediately available as compared to other hematological or serological parameters. It is also a noninvasive parameter and does not require blood aspirations, which decreases the risk of biohazard exposure to medical staff. This is especially emphasized if the marker is required to be taken serially. The calculation of the index is simple and can be taught easily to medical support staff. This parameter would prove useful in the setting of peripheral hospitals for early detection of the critically ill patient. Attaining this marker would further assist clinicians in decision making for tertiary referrals. In hospitals, which are sub-equipped with stat laboratory equipments, this marker would prove useful as a tool in early detection of critically ill sepsis patients. The information gained from the shock index would also help to improve effective communication amongst Emergency Physicians and relatives of patients while deciding further management.

These findings were consistent with observations made by Mohd Yussof SJ. et al.[14] from Malaysia who reported that, shock index on arrival to ED (p: 0.009) and at two hours after admission (SI 2) ($p<0.001$). The authors also reported that, the median shock index in patients who survived were significantly low on arrival to ED (1.2 [range – 0.4 to 1.7] vs 1.4 [range – 0.8 to 2.7]; $p=0.009$) as well as two hours after admission (0.9 [range – 0.6 to 1.1] vs 1.1 [range – 0.8 to 1.8]; $p=0.009$) which was similar to present study. However the authors did not comment on the difference between the shock index from admission to two hours, while the present study calculated the difference between the two shock index, which showed

significantly higher difference among the patients who improved compared to those who expired (0.47 ± 0.30 vs 0.08 ± 0.28; p<0.001).

The present study also assessed the usefulness of shock index as a predictor of mortality. Shock index at 30 minutes from admission with cut-off value of 1.15 showed higher accuracy in predicting mortality (sensitivity of 87.1%, specificity of 92.11%, NPV of 94.74%, PPV of 81.40 and high positive likelihood ratio 11.03) with higher AUC (AUC=0.949; 95% CI=0.908 to 0.0.991 SE=0.021; p=<0.001). Whereas, the assessment ROC curve for shock index on admission as a predictor of mortality showed maximum sensitivity and specificity at a cut off value of 1.35 with low AUC of 0.616 (95% CI - 0.498 to 0.733 SE = 0.060 p=0.053). Using this cut-off, shock index at admission was less sensitive that is, 61.29% sensitive and 60.53% specific in predicting mortality with positive likelihood ratio of 1.55 (PPV of 71.7% and NPV of 48.94%). These finding suggest that the shock index estimated at 30 minutes from arrival to ED is more accurate in predicting mortality as compared to the shock index which is calculated at admission.

These findings were consistent with observations made by Mohd Yussof SJ. et al.[14] from Malaysia who showed that, shock index two hours after admission had higher sensitivity, specificity and ROC values that is, 80.8%, 79.2%, 0.8894 [CI95 0.8052, 0.9736] compared to shock index at admission that is, 73.1%, 45.8%, 0.7075 [CI95 0.5642, 0.8508]. The cut-off point for shock index at admission was ≥ 1.2 and at two hours after admission was ≥ 1.0. The cut-off observed in the present study were ≥ 1.35 at admission, and ≥ 1.15 after 30 minutes of admission, it showed slight variation which can be explained by the longer interval and smaller sample size by Mohd Yussof SJ. et al.[14]

Previous research that studied the utility of SI in predicting mortality amongst community acquired pneumonia patients did not include serial SI data but only a single admission SI reading.[73] Similarly a previous study involving mortality in trauma patients only documented a single SI reading for the study purpose.[17]

In the present study, it was observed that, shock index at admission was less accurate compared to shock index at 30 minutes from admission which can be attributed to fact that, rise in physiological parameters (especially heart rate) due to anxiety, fear, fever or pain through resuscitation and administration of initial treatment. Hence shock index at 30 minutes makes a realistic reflection of the patient's current clinical status, making it a reliable predictive index.

This study with the study by Mohd Yussof et al.[14] demonstrates a vast difference in significance and predictive value of SI when taken at two different time point intervals. In this study, thirty minute interval period was considered from arrival to ED so as to allow adequate initial resuscitation to take place, and a physiological response to the resuscitation be evaluated on a second reading. Initial resuscitation would involve the stabilization of the airway, breathing and circulation components. It includes the administration of oxygen, measures of airway maintenance, intravenous fluids administration, antibiotics, antipyretics, necessary initial symptomatic treatment and procedures (eg. central venous catheter placement, placement of continuous bladder drainage catheters and naso-gastric tube insertion).

In the present study there was positive association between hospital stay and shock index at admission ($p=0.010$) as well as at 30 minutes ($p<0.001$)

The present study assessed several other parameters different from shock index (like sex, age, temperature, pulse rate and respiratory rate) that could identify best parameter which may prognosticate the outcome and found that age and respiratory rate were significantly associated with mortality. With regard to age, significantly higher number of patients expired who were aged 71 to 80 years (87.5%), 51 to 60 years (75%), 61 to 70 years (80%) and 81 to 90 years (66.67%) compared to those who were aged ≤ 30 (52.94%), 31 to 40 (31.25%) and 41 to 50 (57.14%) (p=0.041). Also significantly higher number of patients with respiratory rate of >20 expired (72.41%, p=0.001) showing positive association with outcome. However, other variable including sex (p=0.277), temperature (p=0.750) and pulse rate (p=0.572) lacked to show significant association with mortality.

Mohd Yussof SJ. et al.[14] also assessed age, gender, temperature, heart rate and respiratory rate to identify best parameter which may prognosticate the outcome and found that, HR (p=0.749), RR (p=0.335), age (p=0.648), gender (p=0.944), and Temp (p=0.460) failed to predict the outcome.

The present study had few other important implications that is, there was moderate negative correlation between CVP and shock index at 30 minutes after admission (r=0.435; R^2=0.189; p<0.001) while strong positive correlation was noted between serum lactate levels and shock index at 30 minutes after admission (r=0.565; R^2=0.320; p<0.001).

Elevated lactic acid is a marker for the suboptimal supply of oxygen to the tissues and is associated with increased mortality in sepsis. During sepsis, lack of oxygen delivery to the tissues results in decreased cellular metabolism and

ultimately an increase in cellular lactate production and subsequent diffusion into the blood.[76] Rising levels of lactic acid are associated with increased mortality and, conversely, decreasing levels are associated with decreased mortality, in patients with septic shock.[77] This association has been found to be independent of degree of organ dysfunction and shock at presentation.[78]

The most recent SSC guidelines recommend beginning resuscitation immediately in patients with hypotension or elevated serum lactate > 4 mmol/L.[1] In the present study the strong positive correlation was noted between serum lactate levels and shock index at 30 minutes after admission ($r=0.565$; $R^2=0.320$; $p<0.001$) thus it was noted that, patients with higher value of shock index showed higher levels of serum lactate. Hence shock index at 30 minutes after admission can be helpful in determining the risk of mortality in patients with severe sepsis and septic shock.

Central venous pressure has been used for many years as a monitor of central venous blood volume and represents the back-pressure to systemic venous return. It is unclear whether the use of CVP alone as a target of quantitative resuscitation has a mortality benefit, and the validity of CVP measurements in patients with sepsis is widely debated. There is no threshold value of CVP that identifies patients whose cardiac output (CO) will increase in response to fluid resuscitation;[79] however, it is commonly accepted that a very low CVP is indicative of low intravascular volumes. In contrast, an elevated CVP does not always correlate with adequate intravascular volume.[80]

CVP, especially when low, in conjunction with other measurements is often used successfully to assess and guide resuscitation in patients with sepsis.[12] The current SSC guidelines recommend during the initial 6-hour resuscitation period targeting a CVP of 8 to 12 mm Hg.[80] In this study there was moderate negative correlation between CVP and shock index at 30 minutes after admission ($r=0.435$; $R^2=0.189$; $p<0.001$) which indicates that shock index at 30 minutes after admission is useful in the risk stratification of mortality in patients with severe sepsis and septic shock and can be used to monitor effect of resuscitation in the emergency department.

The strength of the study was that, previous studies have proven SI as a sensitive index in identifying severely ill patients[81] and nevertheless there was no evidence to suggest SI as a reliable tool that could be used to monitor the progress or outcome of resuscitation for sepsis patients. In this study, SI was proven to be valuable in prognosticating the outcome of death. Further the study population represented from diverse etiologies and all the age groups (except paediatric population).

The limitation of the study was that, the study was conducted in a tertiary care hospital and it was a single centre study involving relatively smaller sample size which limits us to generalize the observations to the entire population. Further the observational study design limited us to monitor the patients for outcome till their hospital stay and long term outcome remained unknown. Hence large multicentric studies with longitudinal design would focus the precise role of shock index in the management and prognosticating outcome of patients admitted with severe sepsis and septic shock.

CONCLUSION

Based on the results of this study it may be concluded that, shock index assessed at 30 minutes after resuscitation had potential to predict the mortality in patients with severe sepsis and septic shock. Hence shock index at 30 minutes can be a simple, cost effective and reliable tool that could be used to monitor the progress or outcome of the patients with severe sepsis and septic shock. There is positive association of higher age and respiratory rate with mortality, while sex, temperature and pulse rate are not associated with outcome.

SUMMARY

Reliable indicators and markers in prognosticating survival of patients with severe sepsis and septic shock assist in the course of effective dynamic triaging and goal directed management. Shock Index is a simple bedside measurement that could be readily and affordably attained. The present study was aimed to evaluate the value of shock index in prognosticating short-term outcome for patients with severe sepsis and septic shock at admission and after half an hour of initial resuscitation.

The present one year hospital based observational study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients admitted with severe sepsis or septic shock in Emergency Department from January 2014 to December 2014 were studied. Shock Index, calculated as heart rate divided by the systolic blood pressure was assessed at admission and after half an hour of initial resuscitation in emergency department. The salient findings of the study are summarized as below.

- Most of the patients were males (62%) and the male to female ratio was 1.63:1.
- The commonest age group was 41 to 50 years (21%) and the mean age was 49.8 ± 16.5 years.
- Shock index of > 0.7 was noted in majority of the patients at admission (99%) and at 30 minutes after admission (94%).
- Most of the patients had involvement of respiratory system (31%).
- The commonest diagnosis was pneumonia (21%) followed by urosepsis (20%).

- 62% of the patients had severe sepsis and 38% has septic shock.
- Mortality was noted in 62% of the patients.
- Majority of the patients (99%) had shock index of > 0.7 at admission and 94% of the patients had shock index of >0.7 after 30 minutes of admission.
- No association was found between shock index at admission and mortality (p=0.165)
- The ROC curve showed a cut-off value of 1.35 for shock index at admission with sensitivity of shock index as 61.29% with a specificity of 60.53%, PPV of 71.7% and NPV of 48.94% and positive likelihood ratio was 1.55 in predicting mortality.
- Significantly higher mortality was noted in patients with higher shock index at 30 minutes after admission (p<0.001).
- Shock index at 30 minutes from admission, with cut-off value of 1.15, showed higher accuracy in predicting mortality (sensitivity of 87.1%, specificity of 92.11%, NPV of 94.74%, PPV of 81.40 and high positive likelihood ratio 11.03) with higher AUC (AUC=0.949; 95% CI=0.908 to 0.0.991 SE=0.021; p=<0.001).
- The mean shock index at 30 minutes after admission was significantly higher in patients who expired (1.41 ± 0.32) compared to those who improved (0.90 ± 0.16) (p<0.001).
- The difference in shock index from admission, to 30 minutes after admission was significantly high in patients who improved (0.47 ± 0.30) compared to those who expired (0.08 ± 0.28) (p<0.001).

- There was moderate negative correlation between CVP and shock index at 30 minutes after admission ($r=0.435$; $R^2=0.189$; $p<0.001$).
- The correlation of serum lactate levels with shock index at 30 minutes after admission showed strong positive correlation ($r=0.565$; $R^2=0.320$; $p<0.001$).
- Significantly higher number of patients expired who were aged 71 to 80 years (87.5%), 61 to 70 years (80%), 51 to 60 years (75%) and 81 to 90 years (66.67%) ($p=0.041$).
- Significantly higher number of patients with respiratory rate of >20 expired (72.41%, $p=0.001$).
- No association was noted between sex and outcome ($p=0.277$)
- No association was found between temperature and outcome ($p=0.750$).
- No statistically significant association was found between pulse rate and outcome ($p=0.572$).

Shock index is a simple bedside measure in risk stratification of patients with septic shock and severe sepsis. Shock index evaluated at 30 minutes post admission helps in prognosticating mortality.

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ANNEXURE I – CONSENT FORM

Dr. ***** *******,
Post-Graduate,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum-590 010
Ph. No. *****-*****
Ext. *****

TITLE OF RESEARCH STUDY: "PREDICTION OF OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK USING SHOCK INDEX AND OTHER PARAMETERS - A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"

Objective and purpose of the study

This research is intended to evaluate the value of shock index in predicting mortality of patients with severe sepsis and septic shock .The principal investigator of the study is Dr. **** ****** under the guidance of Dr. ***** ******.

Need For Study

This study could be of great use for evaluating the patients with severe sepsis early in the emergency department, and to take necessary quick steps for improving their prognosis.

Procedure

If you agree to be part of the research study you will be asked history and will be subjected to clinical examination and investigations.

Risk and Benefits

There is as if no risk involved in the study except from the only risk and possible discomfort you might get is while taking blood from the arm for the investigations, which is a routine procedure done for all sepsis patients. It may cause swelling, pain, redness, bruising or infection (rarely happens) at 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 my 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 sponsored may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you 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

In the event of injury, related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Medical Research Center, Belgaum. There is no compensation or payment for such medical treatment by law.

Voluntary participation / withdrawal

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

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 the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant and regarding the study you may call

DR. *** *******,**
Investigator,
PG in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum - 590 010
Ph. No.: **** ******

DR. *** ******
Professor and Vice Principal,
Department of General Medicine,
Jawaharlal Nehru Medical College,
Belgaum – 590 010
Ph. No. **** - *******
Ext: **** / ****

DR. **** ******,**
Chairman,
J.N.M.C., Ethical Committee for Human Research,
Professor and Head Department of Pathology,
Jawaharlal Nehru Medical College,
Belgaum – 590 010
Ph. 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 indicates that I have read this entire consent form or it has been read to me, and has been explained to me in my own vernacular language and has all my questions answered. I will be given a copy of this 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 & Vice Principal,
Department of General Medicine,
Jawaharlal Nehru Medical College,
Nehru Nagar, Belgaum - 590 010.
Ph. No. ****-****** Ext. ****

ANNEXURE II – PROFORMA

TITLE: "PREDICTION OF OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK USING SHOCK INDEX AND OTHER PARAMETERS - A ONE YEAR HOSPITAL BASED OBSERVATIONAL STUDY"

Serial Number:	Name:
Age:	Sex:
Occupation:	Religion:
I. P. No. / O.P. No.:	Address:
Date of Admission:	Date of Discharge:

History

Presenting complaints

History of presenting illness

Past history

Coronary artery disease :

Any operations :

Any malignancies :

Any inborn error's of lactate metabolism:

History of any infections:

History of any other diseases:

Treatment history

Drug name :

Dosage :

Frequency :

Duration of treatment :

Other drugs if any :

Significant personal history

Significant family history

General physical examination

Vital signs :

Pulse (at admission) :

Blood pressure (at admission) :

Pulse (after 30 min) :

Blood pressure (after 30 min) :

Respiratory rate :

Temperature :

Glasgow coma outcome score :

S1 :

S2 :

Any significant findings

(Pallor, Icterus) :

Systemic examination

Cardiovascular System :

Respiratory System :

Per Abdomen :

Central Nervous System :

Investigations

Random Blood Sugar :

Complete Blood Count :

Serum electrolytes :

Serum urea levels :

Serum creatinine :

Liver function test :

Serum lactate levels :

Arterial Blood Gas analysis :

Diagnosis and result

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
^{0}C	-	Degree Centigrade
AB	-	Acute bronchitis
ABE	-	Acute bacterial encephalitis
ABP	-	Acute bacterial peritonitis
ABT	-	Acute bacterial meningitis
AGE	-	Acute gastroenteritis
AIO	-	Acute intestinal obstruction
ALD	-	Alcoholic liver disease
ALF	-	Acute liver failure
ANAE	-	Anaemia
AP	-	Acute pancreatitis
ARDS	-	Acute respiratory distress syndrome
ARF	-	Acute renal failure
BCP	-	Bronchopneumia
BLLC	-	Bilateral lower limb cellulitis
BLP	-	Bilateral pneumonia
BLPN	-	Bilateral pyelonephritis
CKD	-	Chronic kidney disease
CN	-	Coagulase negative
COPD	-	Chronic obstructive pulmonary disease
DKAC	-	Diabetic ketoacidosis

DM	-	Diabetes mellitus
EXP	-	Expired
F	-	Female
GA	-	Gluteal abscess
gm	-	Gram
GPS	-	Gram positive septicaemia
H	-	Hepatitis
HB	-	Hepatitis B
H_2O	-	Hydrogen peroxide
HTN	-	Hypertension
IP	-	Intestinal perforation
IUD	-	Intra uterine death
LA	-	Liver abscess
LBCP	-	Left Bronchopneumia
LLLC	-	Left lower limb cellulitis
LLP	-	Left lobar pneumonia
LSCS	-	Lower segment caesarean section
M ACID	-	Metabolic acidosis
M	-	Male
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
MODS	-	Multiple organ dysfunction syndrome
OMM	-	Oralmucormycosis
PK	-	Pulmonary Koch’s
PRB	-	Peritoneal abscess

RA	-	Respiratory acidosis
RLLC	-	Right lower limb cellulitis
RLP	-	Right lobar pneumonia
RPN	-	Right pyelonephritis
RSP	-	Right sided pneumonia
S1	-	Shock index at admission
S2	-	Shock index at 30 minutes
SE	-	Septic Encephalopathy
SMA	-	Severe metabolic acidosis
SPG	-	Severe pharyngitis
SS	-	Severe sepsis
SSK	-	Septic shock
T2DM	-	Type 2 diabetes mellitus
THRP	-	Thrombocytopenia
URS	-	Urosepsis
UTI	-	Urinary tract infection
VF	-	Viral fever
VME	-	Viral meningoencephalitis
WI	-	Wound infection