“CORRELATION OF THYROID HORMONE PROFILE WITH APACHE II SCORE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT - A ONE YEAR CROSS - SECTIONAL STUDY AT KLES DR PRABHKAR KORE HOSPITAL, BELAGAVI”

REG NO. BG0114009

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"CORRELATION OF THYROID HORMONE PROFILE WITH APACHE II SCORE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT - A ONE YEAR CROSS -SECTIONAL STUDY AT KLES DR PRABHKAR KORE HOSPITAL, BELAGAVI"** is a bonafide research work done by **CANDIDATE REG NO. BG0114009**.

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LIST OF ABBREVIATIONS USED

ρ	-	Spearman's correlation co-efficient
/ 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
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
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

The metabolic responses to sepsis involve every organ and tissue of the body. This study was designed to find correlation of sepsis and thyroid profile and to associate thyroid profile with APACHE II score.

Methodology

The present one year hospital based cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 100 patients with sepsis from January 2015 to December 2015 were studied. All the patients were investigated for thyroid profile.

Results

Out of 100 patients, 57% of the patients were males and 43% were females and male to female ratio was 1.32:1. 18 to 30 years was the most common age group comprised of 23% of the patients. The mean age was 48.55±18.09 years. Type 2 diabetes mellitus was the most common comorbid condition (29%). Most of the patients (18%) had APACHE II scores between 15 to 19. The mean APACHE II scores were 21.26±10.07. Thyroid profile assessment revealed low fT3 levels in 94% of the patients, low fT4 levels in 11% and low TSH levels in 18% of the patients. Most of the patients (68%) of the patients improved and discharged While mortality was noted in 32% of the patients. Pneumonia was the primary diagnosis noted in 31% of the patients followed by pyelonephritis (20%). Statistically significant association was found

between APACHE II scores and outcome ($p<0.001$). There was moderate negative correlation between APACHE II scores and fT3 ($\rho=-0.345$; $p<0.001$) and weak negative correlation between APACHE II scores and fT4 ($\rho=-0.019$; $p<0.848$), and weak APACHE II scores with TSH ($\rho=-0.061$; $p<0.545$).

Conclusion and Interpretation

In ICU patients with sepsis, Thyroid profile in combination with the APACHE II score predicts outcome more accurately than the APACHE II scores alone. There is inverse relationship between APACHE II scores and fT3.

Keywords

APACHE II Score; fT3, fT4, Thyroid stimulating hormone; Sepsis; Septic shock.

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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 inappropriate response to pathogenic microbes, resulting in organ dysfunction, tissue hypoperfusion and hypoxia, 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 has been 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] So far no definitive data on the incidence of sepsis in India is available.[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 hypoxia, which is 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 later 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 leading to 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 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.

The metabolic responses to sepsis involve every organ and tissue of the body and yet, surprisingly, little is known about the underlying mechanisms. During sepsis and other critical illnesses, the state of stress results in hypermetabolism, increased energy expenditure, hyperglycemia and muscle loss.[1,2] It is anticipated that appropriate metabolic support could improve the outcome in these patients.

Stressful situations especially sepsis affect all endocrine axes.[13] Hormonal changes can be seen within the first hours of critical illness and these changes correlate with final outcomes.[14]

Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease.[15-17] Euthyroid Sick Syndrome (ESS) is the commonest endocrine change seen in critically ill patients.[18]

Euthyroid sick syndrome (ESS) is considered when patients with non-thyroidal illness (NTI) demonstrate abnormal thyroid function. Among intensive care unit (ICU) patients, ESS or low-T3 syndrome is more common than true hypothyroidism. A variety of changes in critically ill patients have been observed, including low T3 levels, followed by low T4 and lastly low TSH levels.[19]

In line with the foregoing is the inability of the classical scoring systems for severity of illness, such as APACHE II,[20] to predict mortality in sepsis patients. This enigma reflects lack of understanding of the pathophysiologic mechanisms

underlying onset of recovery or, conversely, the failure to recover from prolonged critically illness. Further, the acute and chronic phases of critical illness are associated with distinct endocrine alterations.[21,22]

Also, whether thyroid hormone indicators can predict ICU mortality independently is unclear. These variables' performance in predicting ICU mortality has not yet been compared. Furthermore, data on the beneficial effect of thyroid hormone treatment on outcome in sepsis patients is so far controversial. And surprisingly no data from India exists regarding the metabolic parameter in sepsis patients and its correlation with APACHE II score.[13] Hence this study was designed to find correlation of sepsis and thyroid profile and to associate thyroid profile with APACHE II score.

OBJECTIVES

The objectives of this study were;

- Correlation of sepsis and thyroid profile.
- To associate thyroid profile with APACHE II score.

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.[23]

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.[24]

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".[24]

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.[24]

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.[25]

<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.

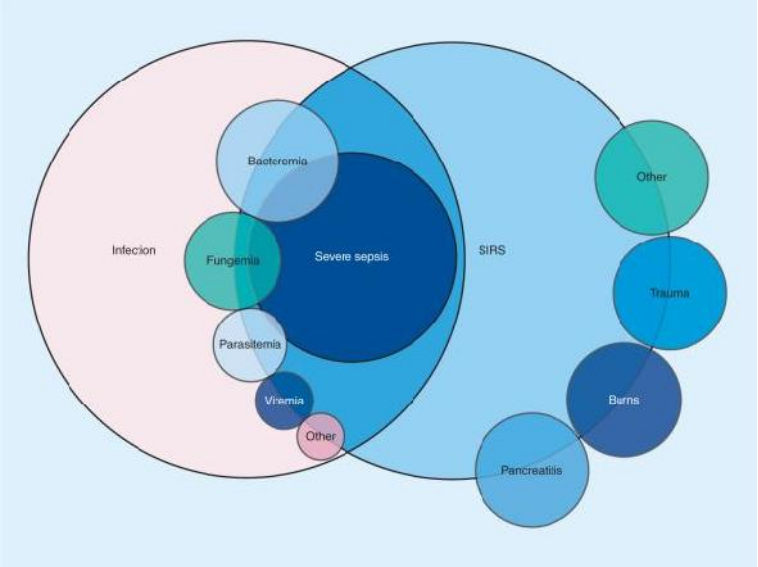


Figure 1. SIRS: Systemic inflammatory response syndrome[23]

These are among the most frequently cited definitions in critical care 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.[23]

Since these consensus definitions had limitations in clinical use, they were revisited in 2001.[3,23]

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.[26]

In view of the above, recently Singer M. et al.[27] in Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) towards a better understanding of the underlying pathobiology by the recognition that many existing terms (e.g., sepsis, severe sepsis) which are used interchangeably, whereas others are redundant (e.g., sepsis syndrome) or overly narrow (e.g., septicemia). Inconsistent strategies in selecting International Classification of Diseases, Ninth Revision (ICD-9), and ICD-10 codes have compounded the problem.[27]

The task force sought to differentiate sepsis from uncomplicated infection and to update definitions of sepsis and septic shock to be consistent with improved understanding of the pathobiology. A definition of sepsis should describe what sepsis "is." This chosen approach allowed discussion of biological concepts that are currently incompletely understood, such as genetic influences and cellular abnormalities. The sepsis illness concept is predicated on infection as its trigger, acknowledging the current challenges in the microbiological identification of infection. It was not, however, within the task force brief to examine definitions of infection.[27]

Sepsis

The current use of 2 or more SIRS criteria to identify sepsis was unanimously considered by the task force to be unhelpful. Changes in white blood cell count, temperature, and heart rate reflect inflammation, the host response to "danger" in the form of infection or other insults. The SIRS criteria do not necessarily indicate a dysregulated, life-threatening response. SIRS criteria are present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes (poor discriminant validity).[28] In addition, 1 in 8 patients admitted to critical care units in Australia and New Zealand with infection and new organ failure did not have the requisite minimum of 2 SIRS criteria to fulfill the definition of sepsis (poor concurrent validity) yet had protracted courses with significant morbidity and mortality.[29] Discriminant validity and convergent validity constitute the 2 domains of construct validity; the SIRS criteria thus perform poorly on both counts.[27]

Organ Dysfunction or Failure

Severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions. Differences in these scoring systems have also led to inconsistency in reporting. The predominant score in current use is the Sequential Organ Failure Assessment (SOFA) (originally the Sepsis-related Organ Failure Assessment[30]).[31] A higher SOFA score is associated with an increased probability of mortality.[31]

The score grades abnormality by organ system and accounts for clinical interventions. However, laboratory variables, namely, PaO2, platelet count, creatinine level, and bilirubin level, are needed for full computation. Furthermore, selection of variables and cutoff values were developed by consensus, and SOFA is not well known outside the critical care community. Other organ failure scoring systems exist, including systems built from statistical models, but none are in common use.[27]

Septic Shock

Multiple definitions for septic shock are currently in use. Further details are provided in an accompanying article by Shankar-Hari et al.[32] A systematic review of the operationalization of current definitions highlights significant heterogeneity in reported mortality. This heterogeneity resulted from differences in the clinical variables chosen (varying cutoffs for systolic or mean blood pressure ± diverse levels of hyperlactatemia ± vasopressor use ± concurrent new organ dysfunction ± defined fluid resuscitation volume/ targets), the data source and coding methods, and enrollment dates.[27]

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.[33]

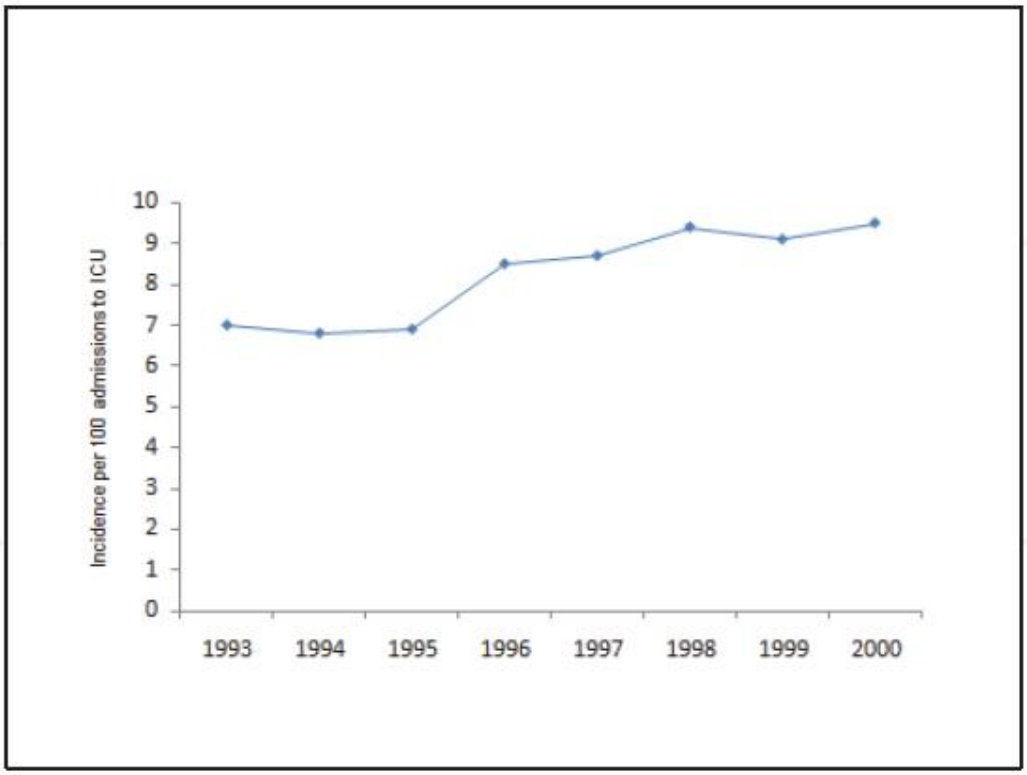


Figure 2. Incidence of septic shock. Data collected over an 8-year period from 22 hospitals[33]

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

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).[34]

The incidences of sepsis, severe sepsis and septic shock are less well-described in the developing world.[35]

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.[23]

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.[23]

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.[36]

Indian scenario

No definitive data on the incidence of sepsis in India is available.[7] However, a multicentric, 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.[37]

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 non-cardiac origin.[38,39] 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.[40]

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.[38]

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 anti-inflammatory response syndrome." However, it has become apparent that infection triggers a much more complex, variable, and prolonged host response, in which both pro-inflammatory and anti-inflammatory mechanisms can contribute to clearance of infection and tissue recovery on the one hand and organ injury and secondary infections on the other.[41]

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, pro-inflammatory reactions (directed at eliminating invading pathogens) are thought to be responsible for collateral tissue damage in severe sepsis, whereas anti-inflammatory responses (important for limiting local and systemic tissue injury) are implicated in the enhanced susceptibility to secondary infections.

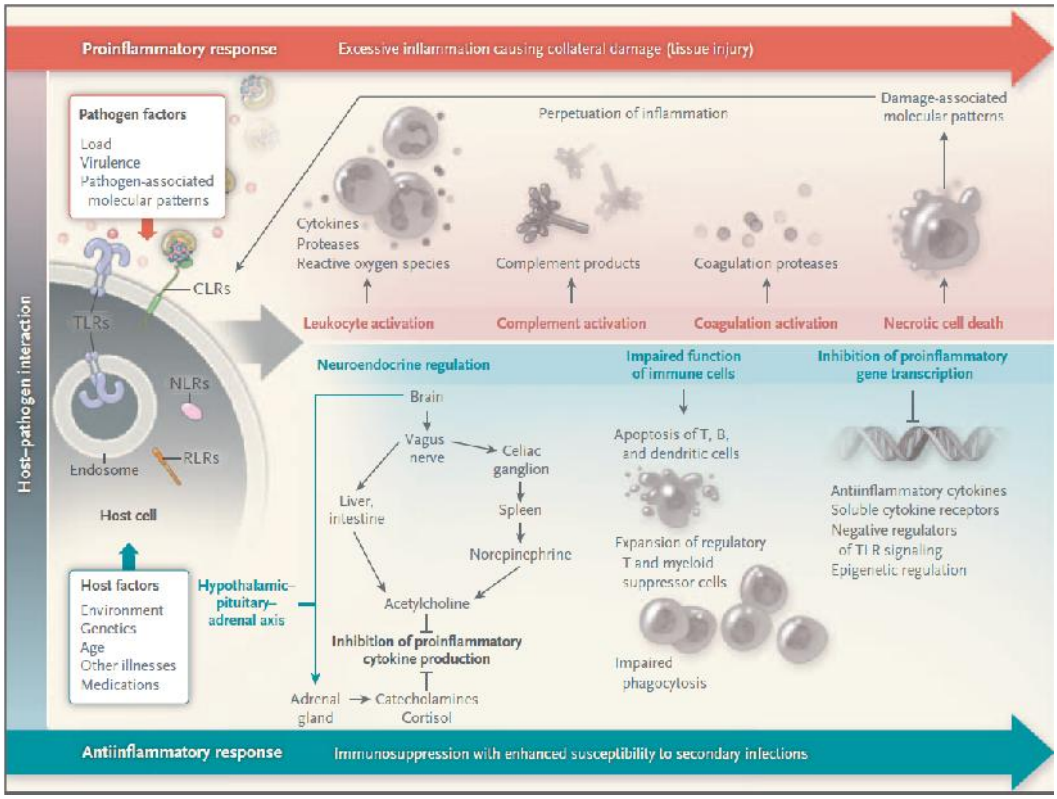


Figure 3. The Host Response in Severe Sepsis[42]

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.[43]

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. This 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.[44]

Coagulation Abnormalities

Severe sepsis is almost invariably associated with altered coagulation, frequently leading to disseminated intravascular coagulation.[45] 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.

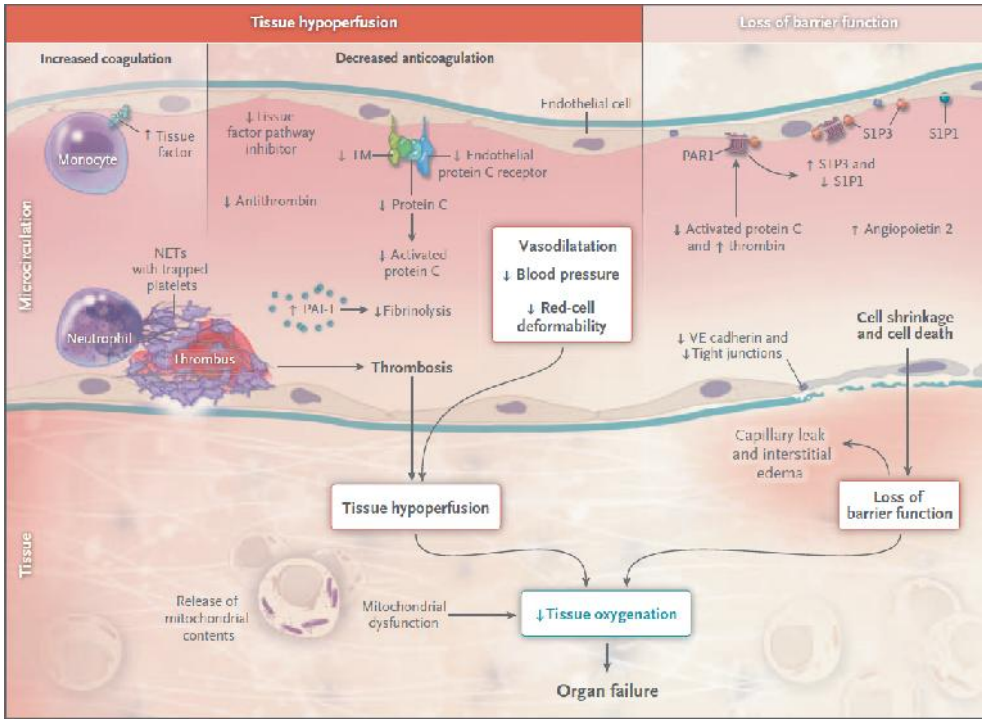


Figure 4. Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria[45]

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.[45] 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.[46]

Anti-inflammatory Mechanisms and Immunosuppression

The immune system harbors humoral, cellular, and neural mechanisms that attenuate the potentially harmful effects of the pro-inflammatory response.[41] Phagocytes can switch to an anti-inflammatory phenotype that promotes tissue repair, and regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. In addition, neural mechanisms can inhibit inflammation.[47]

In the so-called neuro-inflammatory 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 pro-inflammatory cytokines.[48]

In animal models of sepsis,[47] 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.

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.[38]

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.[38]

Evolution of pathogens

This 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.[34]

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.

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.[34] 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,

Sepsis tends to occur from specific and consistent sources. Respiratory infections are invariably the most common cause of sepsis, severe sepsis and septic shock.[23]

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.[23]

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 mortality. Especially critical for septic shock, the risk of dying increases by approximately 10% for every hour of delay in receiving antibiotics.[23]

The other important component of antimicrobial therapy is appropriateness of the antimicrobial regimen. A variety of studies of infected and septic patients show that inappropriate antimicrobial therapy is a consistent predictor of poor outcomes.[23]

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.[49]

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.[23]

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[40]

Element of Care Grade

Resuscitation

- Resuscitation during first 6 hr after recognition.
- Begin initial fluid resuscitation with crystalloid and consider later for albumin. when substantial amounts of crystalloid are required to maintain adequate arterial pressure.
- Avoid hetastarch formulations.
- Initial fluid challenge in patients 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 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.

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.[40]

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).[38]

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.[50]

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.[51]

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.[40] This recommendation is supported by a meta-analysis,[52] but the two largest studies had conflicting results,[53,54] and other clinical trials are ongoing.[55,56]

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.[57]

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 last 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%.[34]

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.

Endocrine dysfunction in sepsis

The pathogenesis of severe sepsis and septic shock has been explained by the excessive production of cytokines, endothelial activation and microvascular thrombosis.[58,59] The host response to infection involves a complex, organized and coherent interaction between immune, autonomic, neuroendocrine and behavioral systems.[60] Recent data have confirmed that disturbances of the autonomic nervous and neuroendocrine systems could contribute to sepsis-induced organ dysfunction,

and several studies have correlated the degree of neuroendocrine dysfunction with severity of illness.[60,61] The clinical features of the endocrine disorder in sepsis are variable, making it difficult to distinguish between a beneficial and a deleterious response to the aggression of pathogens.[61] Moreover, the accuracy of laboratory diagnosis has several limitations[61] related to circadian secretion and pharmacokinetic properties of different hormones as well as specific requirements of sampling, processing and storing blood specimens.[58]

Interrelation between the central nervous system and the immune system during sepsis

The central nervous system (CNS) recognizes macroscopic threats to survival and activates physiologic responses.[59] The innate immune system identifies the microscopic aggressors, such as pathogenic microorganisms, and activates cellular and humoral mechanisms to counteract the germs invasion.[59] Reciprocal interactions between the CNS and the immune system are considered essential parts of the host response during septic shock.[60] The immune system could be regarded as a "diffuse sensory organ" that signals the presence of pathogens to the brain through different pathways, such as the vagus nerve, endothelial activation/dysfunction which leads to release or passive diffusions of cytokines and neurotoxic mediators, and the circumventricular organs, especially the neurohypophysis.[60] These afferent signals trigger efferent CNS responses leading to the activation of the autonomic nervous system and, most importantly, the hypothalamic-pituitary-adrenal (HPA) axis. The hormonal cascade involves the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamic paraventricular and supra-optic nuclei.[60,62] It is suggested that AVP potentiates the action of CRH at the

level of the pituitary gland. Thus, both AVP and CRH stimulate the release of adrenocorticotropic hormone (ACTH), which in turn is responsible for the secretion of cortisol from the adrenal cortex.[62]

The neuroendocrine response is heterogeneous due to the various factors, such as the type of stressor, the known or unknown threat, short or persistent exposure and the characteristics of the host (the most relevant being age and health status).[62]

Hypothalamic-pituitary-adrenal axis in sepsis

The HPA axis is the main neuroendocrine structure involved in modulating the adaptive response to different stressors. It works through the interconnection of the sympathoadrenal and neurohypophyseal systems, which in turn are responsible for catecholamine secretion, cytokines activation and vasopressin release, respectively.[61]

The final step of the HPA axis activation is characterized by an increase in cortisol secretion from the adrenal cortex, usually proportional to the severity of stress.[63] Two different patterns of anterior pituitary gland response have been observed during severe sepsis. Initially, an acute, adaptive and presumed beneficial response is generated, probably explained by the release of hormones from storages. Subsequently, due to the persistence of microbial aggression, a chronic response is elicited, which ultimately leads to the exhaustion of the neuroendocrine system, which could have a deleterious effect on the host.[64] A prolonged septic condition causes a blunting of HPA axis activation, leading to transient or permanent adrenal insufficiency in critically ill patients.[65] Recently, the term “critical illness-related

corticosteroid insufficiency" (CIRCI) has been adopted, to replace absolute or relative adrenal deficiency.[63] The definition of CIRCI comprises the discrepancy between the low level of corticosteroid activity compared to the severity of illness.[61] In field literature, the observed incidence of CIRCI varies from one study to another, between 10% and 70% in patients with severe sepsis.[61] The laboratory diagnosis of CIRCI is reflected by the increase of the cortisol level less than 9 µg/dL at 30–60 minutes after stimulation test with a lower dose of ACTH (1 µg) instead of the high classical dose (250 µg).[58,61]

To assess the integrity of the HPA axis, an ideal approach is based on CRH, AVP and cortisol measurements, but the accuracy of the results is questionable because of confounding factors. Both CRH and AVP are released in a pulsatile pattern, are unstable especially at room temperature, and they have a very short plasmatic half time.[62]

Vasopressin

One of the major hypothalamic stress hormones, which is stimulated by different stressors, is AVP.[62] AVP, a nanopeptide, also known as antidiuretic hormone, derives from a larger 164-amino acid precursor peptide (preprovasopressin) consisting of a signal peptide, AVP, neurophysin II and copeptin.[58]

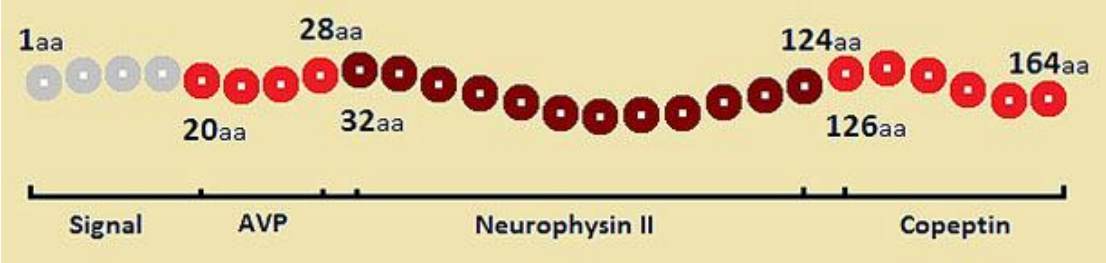


Figure 5: The structure of the preprovasopressin with the main constituent domains: Signal peptide, AVP, neurophysin II and copeptin (aa, aminoacid position; AVP, arginine vasopressin)[58]

AVP synthesis comprises several steps of enzymatic cleavage of the precursor preprovasopressin synthetized in the magnocellular neurons of the hypothalamus. The process starts with the removal of the signal peptide resulting provasopressin, which in turn is packaged into neurosecretory vesicles and the enzymatic cleavage continues during axonal transport to the posterior pituitary. This process usually completed at the level of the neurohypophysis, and it occurs in two steps: a first cleavage splits off AVP, and a second cleavage separates neurophysin II from copeptin.[58]

Once released into the circulation, AVP exerts its peripheral effects through three different receptors: V1a, V1b and V2.[58] V1a receptor is responsible for arteriolar vasoconstriction and is expressed on vascular smooth muscle, hepatocytes and platelets.[66] V1b receptor, mainly central, is expressed in the anterior pituitary gland and hippocampus, and its activation by AVP releases ACTH. Thereby, AVP interacts with the corticosteroid axis in response to different stressors.[66] V2 receptor,

expressed in the renal collecting duct, mediates AVP's antidiuretic effect by increasing water retention through aquaporin-2 water channels.[58,66]

It has been noted that in the early stages of sepsis (within 15 minutes of initiation of sepsis) a massive release of AVP, to supraphysiologic levels, occurs. Following the early release of AVP in septic shock, the serum levels of AVP become inadequate compared to the illness severity due to the depletion of deposits along with the sustained decreasing of AVP synthesis.[58,66] In sepsis, one of the main patterns of endocrine response is defined by the rapidity of activation followed by the exhaustion with the same rapidity.[58]

The detection of endogenous AVP deficiency is limited by the fact that the mature hormone is unstable in isolated plasma and serum, it has a short half-life (24 minutes in vivo) and more than 90% of AVP circulates attached to platelets.[58,63] There are currently no recommendations for routine testing for endogenous AVP levels in the setting of sepsis. [58,63]

The current guidelines for sepsis make clear recommendations regarding the use of AVP: it should be used in combination with NE in order to raise the MAP or to reduce the NE dosage; low doses of AVP should not be used as the single initial vasopressor for treatment of hypotension; higher doses, over 0.03–0.04 units/minute, should be reserved for salvage therapy.[40]

Copeptin

Copeptin, a 39-amino-acid glycopeptide, represents the C-terminal fragment of the provasopressin peptide (CTproAVP). Copeptin is released in an equimolar ratio to AVP and is more stable in the blood and easy to determine. The exact role of

copeptin has not been clear yet. However, it has been suggested that copeptin may play a role in the process of AVP precursor production. There are some advantages of copeptin, as it reliably mirrors the production of AVP, it is extremely stable in plasma or serum ex vivo. Due to the positive association of copeptin with the severity of illness and outcome, copeptin has been proposed as a more sensitive and potential prognostic biomarker in sepsis. The role of copeptin as a prognostic biomarker has been investigated in various infectious conditions, such as sepsis, pneumonia, lower respiratory tract infections, and it was found to accurately discriminate between patients with favorable and unfavorable outcomes.[40,58]

In patients with sepsis, copeptin concentration increases in parallel with the severity of the disease, reaching levels more than 30-fold higher in septic shock than in healthy individuals.[67]

However, there are some limitations of copeptin use as a single biomarker. Copeptin levels may be decreased by exogenous corticosteroid usage in a dose-dependent way, and, on the other hand copeptin levels are higher in patients with renal insufficiency.[58,62]

Cortisol

The normal response of the HPA axis to septic aggression consists in the release of cortisol from the adrenal cortex.[58,61]

Cortisol is important in maintaining vascular reactivity to circulating catecholamines through up-regulation of adrenergic receptors and inhibition of nitric oxide synthase, prostaglandin E1 and prostacyclin, thus preserving perfusion of vital organs.[58,62] It is known that, in sepsis, adrenal insufficiency is partly responsible for

reduction of vascular reactivity to vasopressors and is associated with an increased risk of death. It is well known that existing commercially assays are able to quantify only the total level of serum cortisol. On the other hand, the serum cortisol is largely (90%) bound to albumin and cortisol-binding globulin, underscoring the difficulties of interpreting the results especially in hypoalbuminemic patients. As adrenal insufficiency can occur in severe sepsis, there are some expectations related to steroid use in this setting such as attenuation of the systemic inflammation and cytokine activation and improvement of the hemodynamic function. The main issues of the exogenous steroids usage in sepsis are related to an increased risk of morbidity secondary to superinfection, myopathy, hyperglycemia and hypernatremia. More data support the role of corticosteroids in reversing shock and decreasing mortality mainly in patients with sepsis-induced hypotension refractory to fluid replacement and vasopressor therapy.[40,52] The 2012 Surviving Sepsis Campaign recommended administration of intravenous hydrocortisone alone at a dose of 200 mg/day as a treatment of adult septic shock patients only if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability.[40] The response of septic shock patients to fluid and vasopressor therapy seems to be an important factor in selection of patients for optional hydrocortisone therapy.[40] Although the clinical impact is not clear.[58]

Hypothalamo-pituitary-thyroid axis in sepsis

Critical illness, such as sepsis, is often associated with thyroid hormone abnormalities. It is believed that the thyroid dysfunction observed during sepsis constitutes part of an adaptive metabolic response in an attempt to increase resistance to different stressors by lowering the cellular metabolic activity. The

prevalence of thyroid abnormalities in the general population varies between 1% and 10%, which could explain the presence of various forms of thyroid dysfunction in some patients with sepsis. The initial abnormality is a decrease in total T3 concentration secondary to a decrease of peripheral conversion of thyroxine (T4) to T3 by reducing 5′-deiodinase activity. Typically, an initially low level of total T3 is followed by a decline in total T4 caused by a decrease in thyroxin-binding globulin as well as a reduction in its binding affinity. The hypothalamic-pituitary-thyroid axis malfunction could be attributed to various cytokines. Several inflammatory cytokines (IL-1β, IL-6, and TNF-α) can directly or indirectly suppress thyroid function at different levels, leading to a reduction in thyrotropin-releasing hormone (TRH) secretion at the level of the hypothalamus or a direct suppression of TSH release.[58]

The majority of existing data suggest a correlation between lower levels of baseline T3 or T4 and worse outcome.[68,69] There is little evidence regarding thyroid hormone substitution in human critical illness.[69] Some studies have shown that T4 substitution can result in reduction in the need for vasopressors in circulatory shock.[70] Follow-up thyroid function tests are recommended if abnormal levels are detected during sepsis, as usually most of these abnormalities are transient and do not represent a true underlying thyroid disease.[58,69]

THYROID HORMONES IN CRITICAL ILLNESS

Triiodothyronine (T3)

T3 is the biologically active thyroid hormone and its low serum levels in critical illness reflect altered thyroid homeostasis and a mechanism of adaptation.

Normally most (80%-90%) of T3 is produced by monodeiodination of 40% of circulating T4, a reaction catalyzed by 5'-monodeiodinases in organs such as the liver and kidney (Figure 1). The remaining (10%-20%) is directly secreted by the thyroid gland. Inhibition of the enzyme 5'-deiodinase that catalyzes the conversion of T4 to T3 has been considered a possible mechanism responsible for the sick euthyroid syndrome.[71-73]

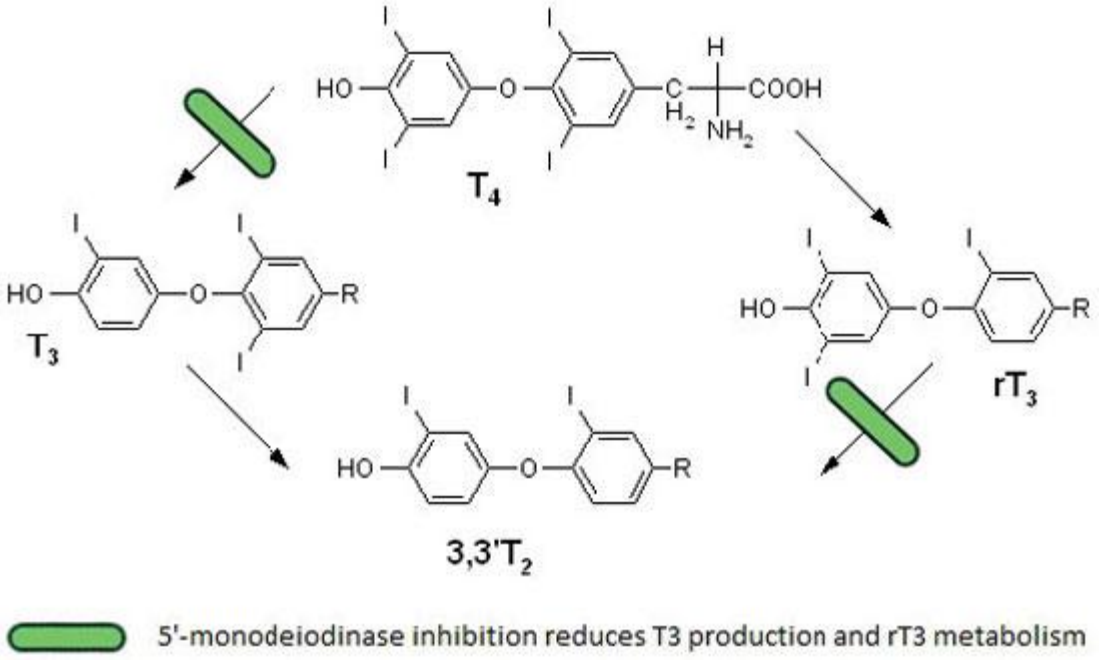


Figure 6: Thyroxine Metabolism

The majority of critically ill patients have low serum T3 concentrations, as do some outpatients during illness.[71]

Several mechanisms can contribute to the inhibition of 5'-monodeiodination and therefore to the low serum T3 concentrations in critically ill patients with nonthyroidal illness:[71]

A. Exogenous glucocorticoid therapy.[74]

B. Circulating inhibitors of deiodinase activity, such as free (non-esterified) fatty acids.[75]

C. Treatment with drugs that inhibit 5'-monodeiodinase activity, such as amiodarone and high doses of propranolol.

D. Cytokines (such as tumor necrosis factor, interferon-alpha, NF-kB and interleukin-6).[76-78]

Reverse triiodothyronine (rT3)

The initial and most common abnormality observed in any person who has a significant acute illness is a fall in total T3 concentrations accompanied by an increase in rT3 levels. T4 conversion to rT3 by 5'-deiodinase is called the "inactivating pathway".[71]

The conversion of reverse T3 to diiodothyronine (T2) is reduced in nonthyroidal illness because of inhibition of the 5'-monodeiodinase activity.[79] This constitutes an additional mechanism of high serum rT3 values in patients with nonthyroidal illnesses, except in those with renal failure and some patients with AIDS.[80,81]

Thyroxine (T4)

Serum T4 in nonthyroid illness can be reduced within 24 to 48 hrs. The initial decline is predominantly due to decreased binding to carrier proteins, such as thyroid hormone binding globulin (TBG), transthyretin (TTR), or thyroxine-binding prealbumin [TBPA]) and albumin. Many drugs, including salicylates, phenyntoin, carbamazepine, furosemide, compete with thyroid hormone for binding to TBG.

The presence of circulating inhibitors of T4 binding, such as high concentrations of fatty acid, disordered iodine uptake by the thyroid or abnormal peripheral metabolism, are also possibly implicated in the low total and/or free T4 levels.[82-85] Some drugs including phenytoin, carbamazepine, rifampin, phenobarbital, may also contribute to low total T4 concentration by accelerating its clearance.[71]

Hyperthyroidism						
Drugs	iodine amiodarone			interferon-alpha interleukin-2		
Mechanism	Stimulation of thyroid hormone synthesis and/or release			Immuno-dysregulation		
Drugs causing abnormal thyroid function tests without thyroid dysfunction						
Drugs	androgens, danazol, glucocorticoids, nicotinic acid l-asparaginase	estrogens, tamoxifen, raloxifene, methadone, 5-fluouracil, clofibrate, heroin, mitotane	salicylates salsalate furosemide heparin NSAIDs	phenytoin, carbamazepine, rifampin, phenobarbital	dobutamine, glucocorticoids, octreotide	amiodarone glucocorticoids, contrast agents (e.g., iopanoic acid), propylthiouracil, propanolol
Mechanism	Low serum TBG	High serum TBG	Decreased T4 binding to TBG	Increased T4 clearance	Suppression of TSH secretion	Impaired conversion of T4 to T3

Hypothyroidism						
Drugs	thionamides, lithium, perchlorate, aminoglutethimide, thalidomide iodine and iodine-containing drugs • amiodarone, • radiographic agents, • expectorants • potassium iodine solutions • Betadine douches • topical antiseptics	cholestyramine colestipol, aluminum hydroxide, calcium carbonate, sucralfate, iron sulfate, raloxifene, omeprazole, lansoprazole sevelamer lanthanum carbonate	interferon-alpha interleukin-2	dopamine	sunitinib	bexarotene
Mechanism	Inhibition of thyroid hormone synthesis and/or release	Decreased absorption of T4	Immuno-dysregulation	Suppression of TSH	Possible destructive thyroiditis	Increased T4 clearance and suppression of TSH

Figure 7. Drugs causing alterations in thyroid function and mechanisms involved.[71]

Free T4

Despite low total T4 in critical illness, serum concentrations of free T4 remain in the normal range in most patients unless the illness is severe and

protracted.[86] However, hypothalamic-pituitary suppression, usually present in prolonged critically illness, leads to decreased secretion of TSH, decreased T4 production by the thyroid gland and a subsequent decline of free T4 levels in the circulation, a sign of severity of the disease and a predictor of poor outcome.[87]

Thyrotropin (TSH)

Under normal conditions, TSH synthesis is relatively stable and is controlled by thyroid hormones, neuropeptides and neurotransmitters. Hypothalamic thyrotropine-releasing hormone (TRH) is the main stimulating factor of TSH synthesis and its effect is enhanced by catecholamines.. In euthyroid sick syndrome, TSH levels are commonly within the normal range and only in prolonged illness may be low.[71]

Assessment of thyroid function in ICU

Thyroid function abnormalities observed during critical illness are transient and do not represent an underlying thyroid disease.[86,88] Still, certain data suggest that the magnitude of thyroid hormone alterations in patients admitted to the intensive care unit (ICU) due to various causes is associated adversely with the patient outcome.[88]

Association of thyroid hormones at baseline with outcome

A review reported that, Specifically, six of the nine studies included by univariate analysis, showed that among patients with sepsis or septic shock those with an unfavorable outcome had lower baseline serum levels of, either total or free, T3 or T4, than those with a favorable outcome.[88] In two other studies that involved

children and adults, who in both studies were admitted in the ICU due to septic shock, there was no difference in baseline T3 or T4 between non-survivors and survivors.[89,90] In the remaining study, which evaluated children with meningococcal sepsis admitted to the PICU, those who did not survive had higher baseline serum levels of T3 than those who survived, while no difference was detected in the total and free T4 levels.[91] In this study, non-survivors also had higher baseline levels of TSH.[91]

One study showed lower baseline TSH was associated with higher mortality in a study that evaluated septic neonates admitted in the ICU;[92] this was also accompanied with lower T3 and T4. The baseline TSH levels in the remaining six studies did not differ between patients with an unfavorable outcome compared with those with a favorable outcome. In addition, a lower rT3 value and a higher T3/rT3 ratio were associated with an adverse outcome in two studies,[91,93] whereas non-significant findings were observed in the other two studies that assessed the same parameters.[94,95] Three of the included studies further evaluated the above-described associations in multivariate analysis. One of these studies showed that in pediatric patients who survived meningococcal septic shock, lower baseline serum T4 was an independent predictor of an unfavorable outcome, specifically prolonged ICU stay.[94] The baseline interleukin 6 (IL6) level was also independently associated with this outcome. The second study that included pediatric ICU patients with meningococcal sepsis or septic shock showed that the effect of the thyroid function tests on mortality lost significance in the multivariate analysis, and that IL6 was the only independent predictor of this outcome.[93] In the remaining study, which was performed on newborns admitted to the ICU with bacterial sepsis, the presence of

euthyroid sick syndrome was independently associated with mortality.[92] The correlation of thyroid function tests at baseline with various sepsis prognostic scores. Such associations were reported in three of the nine included studies, which all evaluated children with meningococcal sepsis or septic shock admitted to the PICU.[88] In one of these studies, both the pediatric risk of mortality (PRISM) score and the sequential organ failure assessment score had a moderate negative correlation with the baseline T4 value.[93] In another study, the PRISM score had a rather weak positive correlation with baseline TSH.[91] In the remaining study, no significant relevant associations were observed.[94]

The endocrine milieu of patients hospitalized in intensive care units (ICU) and/or in critical condition has been assessed in many studies and differences have been found between survivors and non- survivors.[96]

A study conducted in India concluded that low T3 is an important marker of mortality in critically ill patients. Non-survivors had low T3 as compared to survivors (49.1 ± 32.7 vs 66.2 ± 30.1).[13]

In a recent study of 206 patients, a logistic regression model incorporating a well-established clinical measure of ICU patients evaluation - the Acute Physiology and Chronic Health Evaluation II; APACHE II score (11.50 vs 15.82, $P < 0.0005$), free triiodothyronine (fT3 – 2.18 vs 1.72 pg/ml, $P = 0.002$) and thyrotropin(TSH) values was shown to add to the prognostic value of APACHE II in patients with acute respiratory distress syndrome (ARDS) in survivors vs non-survivors.[97]

In another recent study of 113 ICU patients with only 4 of them admitted because of trauma had an area under the receiver operating characteristic curve of

0.88, significantly higher than the APACHE score alone with 0.75 which showed that the addition of TSH and total T3 improved the prognostic value of the APACHE II score.[98]

Thus, in patients admitted to ICU with sepsis, thyroid profile in combination with the APACHE II score,[20] may predict outcome more accurately than the APACHE II score[20] alone.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015.

Study design and duration

The study design was a hospital based cross-sectional study.

Study period

The present study was done for the period of one year from January 2015 to December 2015.

Place

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

Source of Data

Patients presenting with sepsis in the Department of General Medicine, KLES Dr Prabhakar Kore Hospital and MRC, Belagavi.

Sample size

A total of 100 patients with sepsis were studied.

Sampling procedure

The sample size was calculated using the following formula as below.

Sample Size (n) = $4PQ/D^2$

Where,

N = Sample size

P = Prevalence of the disease (50%)

Q = 100- P

D = Absolute error considered as 10%

Therefore, $n = 4 \times 50 \times (100 - 50) / 10^2$

$n = 100$

Hence the sample size of 100 was considered for this study.

Sample Method

All consecutive patients fulfilling the selection criteria.

Selection criteria

Inclusion Criteria

- Patients aged 18 and above.
- Patients fulfilling sepsis criteria (fever or hypothermia, leukocytosis or leukopenia, tachypnea or tachycardia i.e. systemic inflammatory response

(SIRS), if infection proven or suspected in SIRS patients then its called as SEPSIS).

Exclusion Criteria

- Known case of thyroid disease, adrenal insufficiency.
- Patients not fulfilling criteria predefined for sepsis.

Ethical clearance

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

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

The selected patients were interviewed for the history of presenting illness and other comorbid conditions and the demographic data. 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.
- Pulse rate was measured by palpatory method.
- Respiratory rate.
- Glasgow coma scale.

- Apache II score

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

Investigations

Blood samples (10ml venous and 2ml Arterial) were collected immediately on admission to intensive care unit from the selected patients and were subjected following investigations.

- Arterial blood gas analysis was done (2ml arterial blood).
- Thyroid profile (fT3, fT4 and TSH)
- Complete blood count
- Liver function test
- Renal function test
- Chest x-ray
- Ultrasonography

Outcome variables

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

Clinical severity

The clinical severity as well as the prediction of outcome was assessed by APACHE II scores. APACHE II ("Acute Physiology and Chronic Health Evaluation II") is a severity-of-disease classification system[20,99] one of several ICU scoring

systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. APACHE II score was calculated for each patient at admission to medical ICU.

Physiologic Variable	**High Abnormal Range**					**Low Abnormal Range**				
	+4	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**	**Points**
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO2 **or** PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Figure 8. Acute Physiology and Chronic Health Evaluation II scoring system

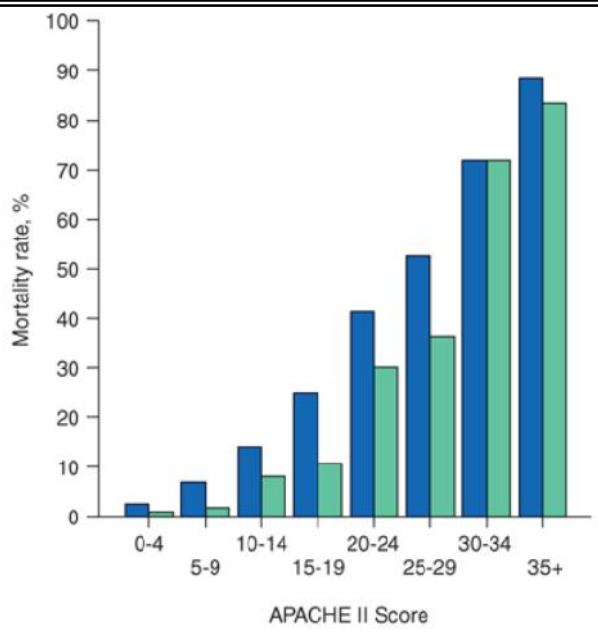


Figure 9. Interpretation of severity based on APACHE II scoring system[100]

Outcome:

The outcome was considered as survival or mortality.

Thyroid profile

The thyroid profile was assessed by withdrawing venous blood under aseptic precautions and estimation of TSH, FT3 and FT4 was done using a fully automated immunoflorescence immunoassay analyzer (Make: Abott Axsym) was used to estimate TSH, fT3 and fT4. The results obtained were interpreted as below ;[101,102]

Thyroid stimulating hormone

- Normal range – 0.55 to 4.78 µIU/mL.
- Abnormal - < 0.55 or > 4.78 µIU/mL.

Free Triiodothyronine

- Normal range – 2.30 to 4.20pg/mL.
- Abnormal - < 2.30or > 4.20 pg/mL.

Free thyroxine

- Normal range – 0.89to 1.76 ng/dL.
- Abnormal - < 0.89 or > 1.76 ng/dL.

Statistical methods

The data obtained was coded and entered into Microsoft excel spreadsheet and data was analyzed using SPSS version 21. 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 correlation of free T3, free T4 and TSH with APACHE II score was done using spearman's correlation co-efficient. At 95% confidence interval, a probability (p) value of ≤ 0.050 was considered as statistically significant.

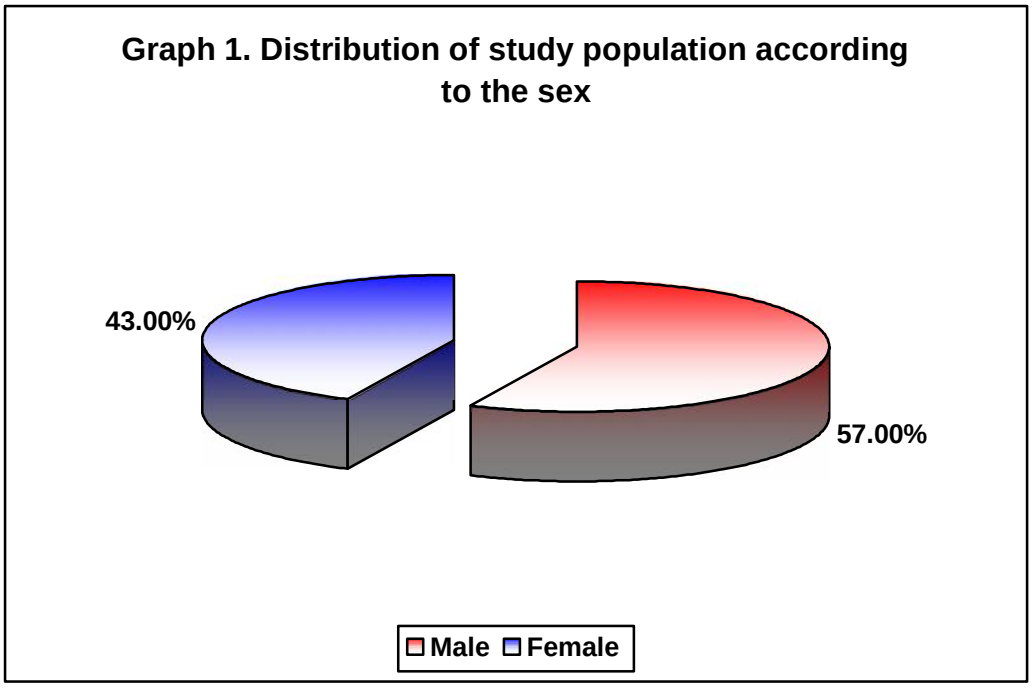
RESULTS

The hospital based cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 100 patients with sepsis were studied.

The data obtained was analyzed and the final results and observations were tabulated as below.

Table 1. Distribution of study population according to the sex

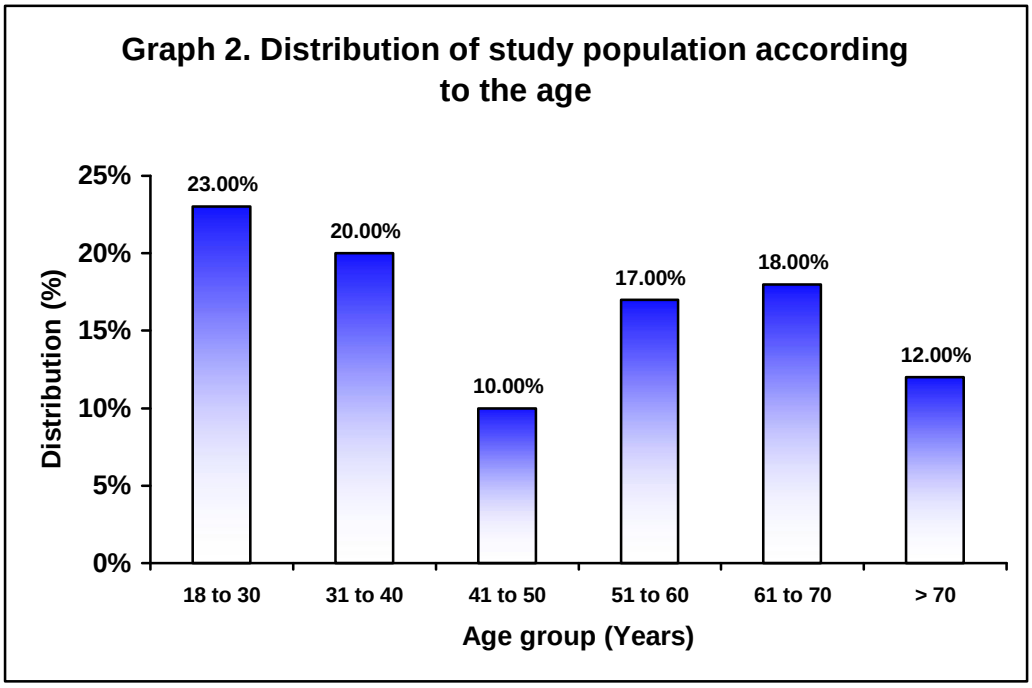
Sex	Distribution (n=100)	
	Number	**Percentage**
Male	57	57.00
Female	43	43.00
Total	**100**	**100.00**



In the present study 57% of the patients were males and 43% were females. The male to female ratio was 1.32:1.

Table 2. Distribution of study population according to the age

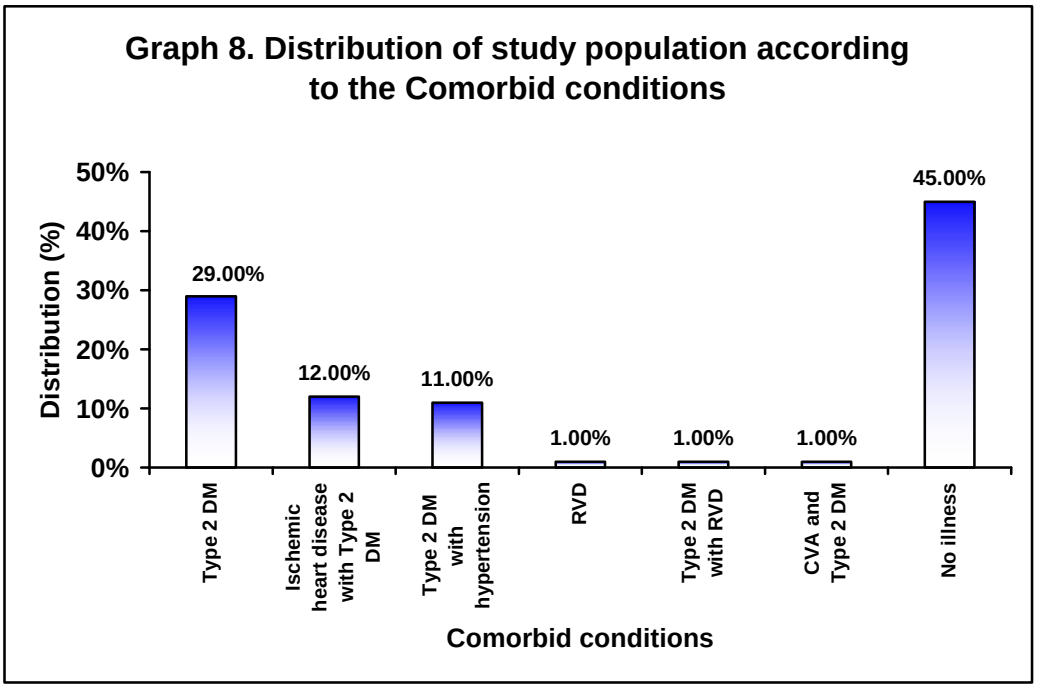
Age group (Years)	Distribution (n=100)	
	Number	**Percentage**
18 to 30	23	23.00
31 to 40	20	20.00
41 to 50	10	10.00
51 to 60	17	17.00
61 to 70	18	18.00
> 70	12	12.00
Total	**100**	**100.00**



In this study most of the patients were aged between 18 to 30 years (23%). The mean age was 48.55 ± 18.09 year and median age was 45 years with range 18 being minimum and 92 being maximum.

Table No 3. Distribution of study population according to the comorbid conditions

Comorbid conditions	Distribution (n=100)	
	Number	Percentage
Type 2 DM	29	29.00
Ischaemic heart disease with Type 2 DM	12	12.00
Type 2 DM with hypertension	11	11.00
RVD	1	1.00
Type 2 DM and RVD	1	1.00
CVA and Type 2 DM	1	1.00
No illness	45	45.00
Total	**100**	**100.00**



In the present study type 2 diabetes mellitus was the most common comorbid condition noted in 29% of the patients.

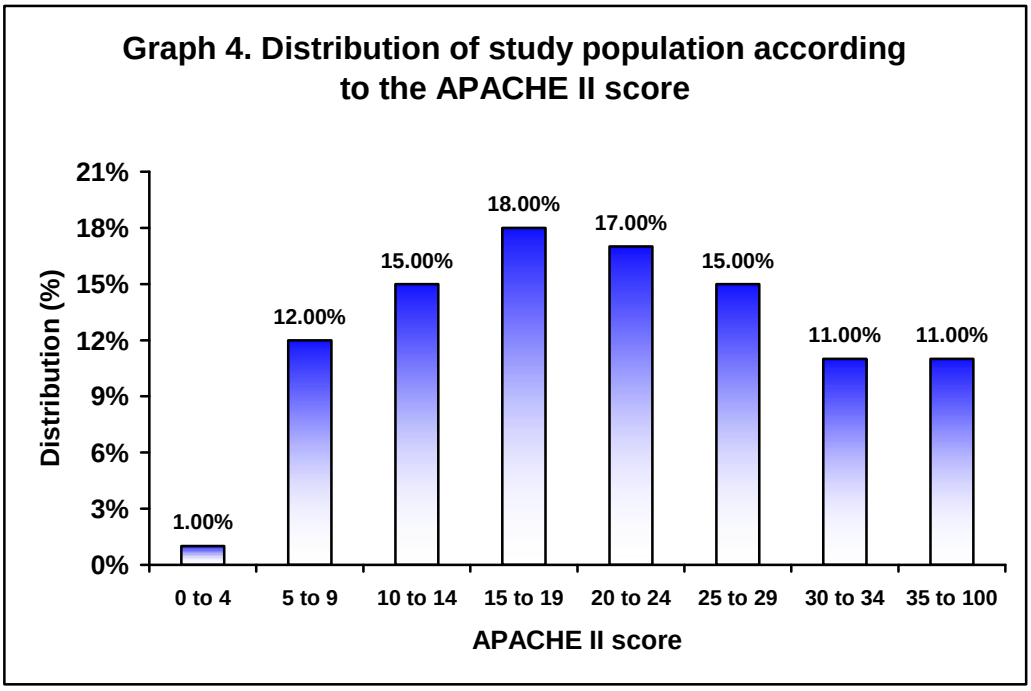
Table 4. Clinical profile of study population

Parameters	Mean (n=100)		Median	Range	
	Mean	SD		Min	Max
Pulse rate (/Minute)	118.14	10.87	120	100	150
Respiratory rate (/Minute)	37.35	7.44	36	24	66
Systolic BP (mm Hg)	79.9	11.76	80	40	100
Diastolic BP (mm Hg)	59.56	9.01	60	40	70
Temperature (^{0}F)	101.35	0.80	101	99	103
Mean BP (mm Hg)	62.85	14.59	66.6	16	80
pH arterial	7.18	0.15	7.2	6.8	7.45
Oxygenation (%)	81.14	15.93	84	9	100
Serum sodium (mmol/L)	136.15	6.40	137	108	157
Serum Potassium (mmol/L)	4.15	0.94	4.05	2.22	7.13
Serum creatinine (mg/dL)	3.52	12.87	1.6	0.51	129
Haemocrit (%)	33.35	8.79	33	9	54
WBC (/Cumm)	19072	8590.68	18000	1200	58400
Glassgow coma score	11.93	2.73	12	4	15
APACHE II score	21.26	10.07	21	2	46
Free T3 (ng/dL)	1.81	0.68	1.9	0.08	3.17
Free T4 (ng/dL)	1.76	1.65	1.33	0.55	10.3
TSH (mIU/L)	1.79	1.51	1.45	0.1	10.8
Hospital stay (Days)	7.05	3.98	6	1	20

The clinical profile of the study population is as shown in table 4.

Table 5. Distribution of study population according to the APACHE II score

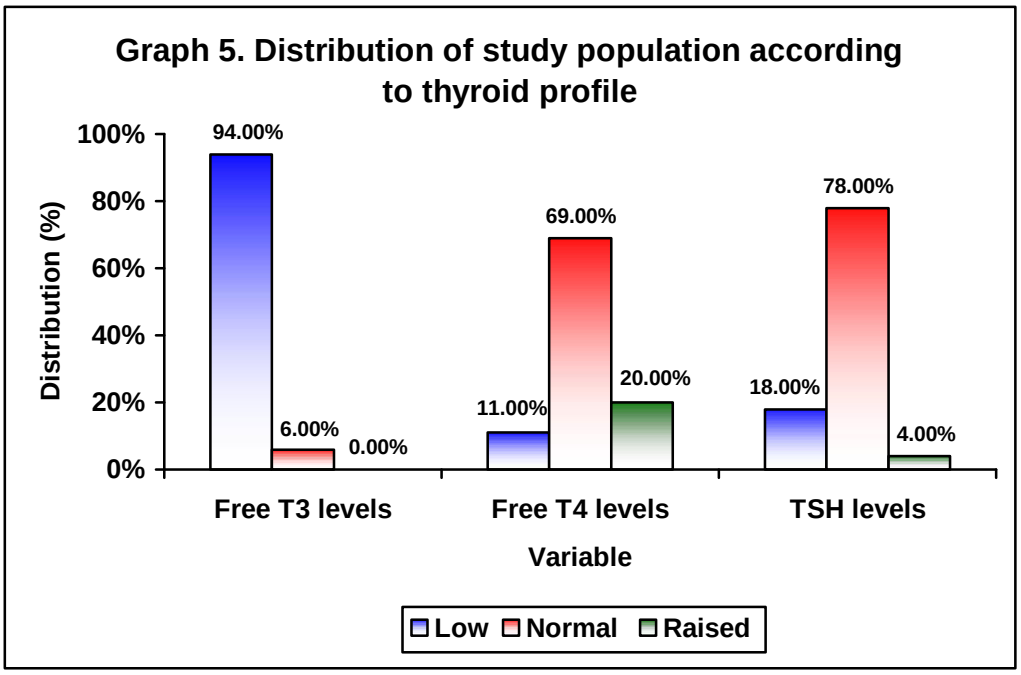
APACHE II score	Distribution (n=100)	
	Number	Percentage
0 to 4	1	1.00
5 to 9	12	12.00
10 to 14	15	15.00
15 to 19	18	18.00
20 to 24	17	17.00
25 to 29	15	15.00
30 to 34	11	11.00
35 to 100	11	11.00
Total	**100**	**100.00**



In the present study 18% of the patients had APACHE II score between 15 to 19. The mean APACHE II scores were 21.26 ± 10.07 and median scores were 21 with range 2 being minimum and 46 being maximum.

Table 6. Distribution of study population according to thyroid profile

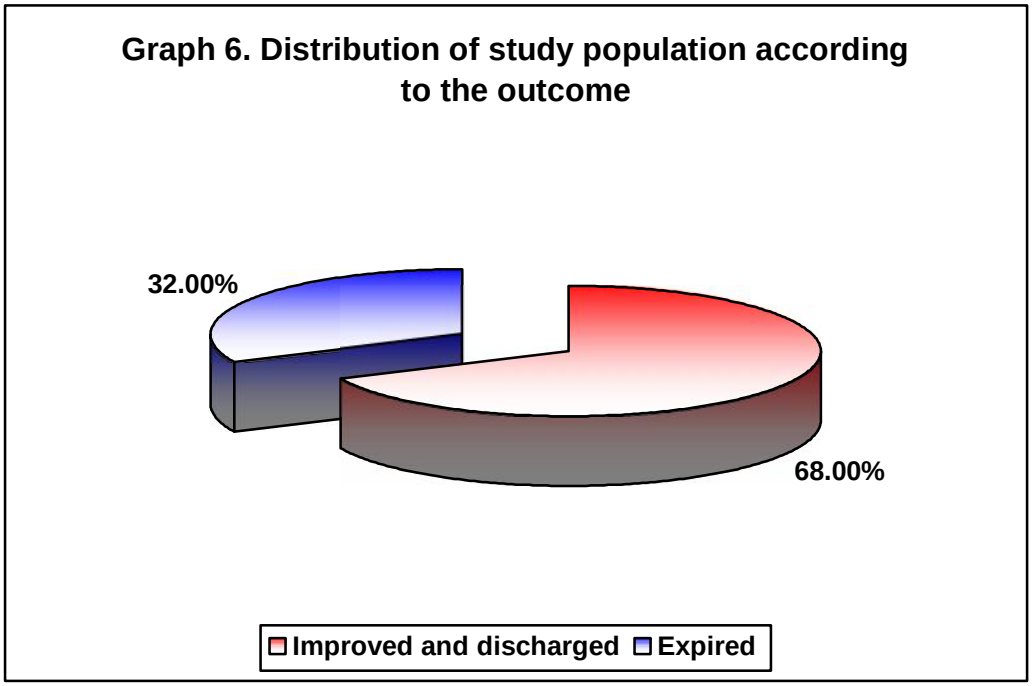
Variable	Findings	Number	Percentage
Free T3 levels	Low (< 2.3)	94	94.00
	Normal (2.3 to 4.2)	6	6.00
	Total	**100**	**100.00**
Free T4 levels	Low (<0.89)	11	11.00
	Normal (0.89-1.76)	69	69.00
	Raised (>1.76)	20	20.00
	Total	**100**	**100.00**
TSH levels	Low (<0.55)	18	18.00
	Normal (0.55 to 4.76)	78	78.00
	Raised (> 4.76)	4	4.00
	Total	**100**	**100.00**



In this study, thyroid profile revealed low fT3 levels in majority of the patients (94%) while low fT4 in 11% of the patients and low TSH was noted in 18% of the patients.

Table 7. Distribution of study population according to the outcome

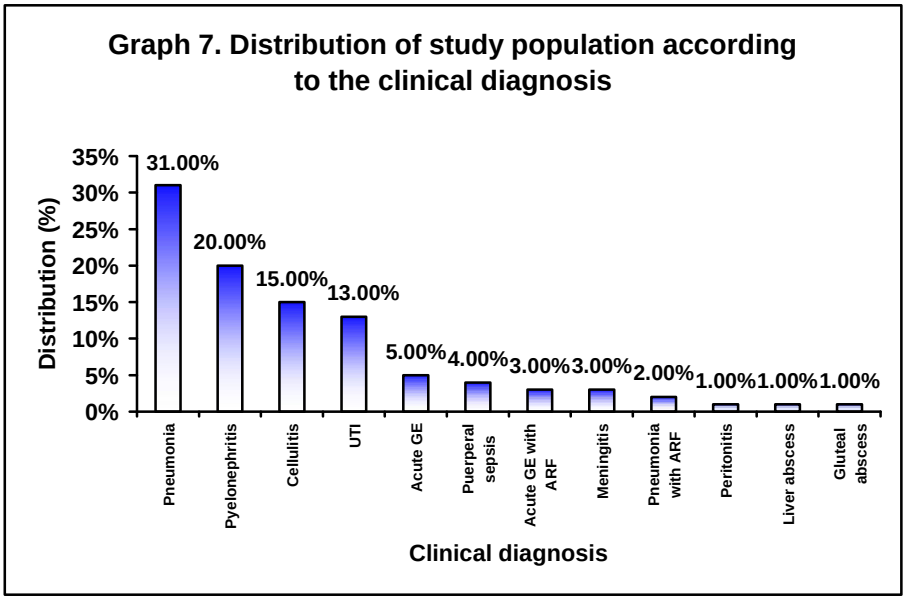
Outcome	Distribution (n=100)	
	Number	**Percentage**
Improved and discharged	68	68.00
Expired	32	32.00
Total	**100**	**100.00**



In the present study 68% of the patients improved and discharged while mortality was noted in 32% of the patients.

Table 8. Distribution of study population according to the clinical diagnosis

Clinical diagnosis	Distribution (n=100)	
	Number	**Percentage**
Pneumonia	32	31.00
Pyelonephritis	20	20.00
Cellulitis	15	15.00
UTI	13	13.00
Acute GE	5	5.00
Puerperal Sepsis	4	4.00
Acute GE with ARF	3	3.00
Meningitis	3	3.00
Pneumonia with ARF	2	2.00
Peritonitis	1	1.00
Liver abscess	1	1.00
Gluteal abscess	1	1.00
Total	**100**	**100.00**



In this study pneumonia was the primary diagnosis in 31% of the patients while pyelonephritis was noted in 20% of the patients and cellulites in 15% of the patients. The other diagnoses are as shown in table 8 and graph 7.

Table 9. Association of outcome with APACHE II score

APACHE II Score	Outcome				Total (n=100)	
	Non- Survivors		Survivors			
	No	%	No	%	No	%
0 to 4	0	0.00	1	100.00	1	100.00
5 to 9	0	0.00	12	100.00	12	100.00
10 to 14	1	6.67	14	93.33	15	100.00
15 to 19	0	0.00	18	100.00	18	100.00
20 to 24	6	35.29	11	64.71	17	100.00
25 to 29	9	60.00	6	40.00	15	100.00
30 to 34	7	63.64	4	36.36	11	100.00
35 to 100	9	81.82	2	18.18	11	100.00
Total	**32**	**32.00**	**68**	**68.00**	**100**	**100.00**

$p < 0.001$

In this study statistically significant association was found between APACHE II scores and outcome as APACHE II scores between 35 to 100 were noted in 11 patients out of which majority (81.82%) expired. ($p<0.001$)

Table 10. Association of outcome with thyroid profile

Thyroid profile	Findings	Outcome				p value
		Non- Survivors		Survivors		
		No	%	No	%	
Free T3	< 2.3	31	32.98	63	67.02	**0.705**
	2.3 to 4.2	1	16.67	5	83.33	
	Total	**32**	**32.00**	**68**	**68.00**	
Free T4	<0.89	4	36.36	7	63.64	**0.880**
	0.89-1.76	21	30.43	48	69.57	
	>1.76	7	35.00	13	65.00	
	Total	**32**	**32.00**	**68**	**68.00**	
TSH	<0.55	3	16.67	15	83.33	**0.110**
	0.55 to 4.76	29	37.18	49	62.82	
	> 4.76	0	0.00	4	100.00	
	Total	**32**	**32.00**	**68**	**68.00**	

In the present study no statistically significant association was noted between outcome and fT3, fT4 and TSH ($p>0.05$).

Table 11. Association of APACHE II score with Free T3

APACHE II scores	Free T3					
	<2.3		2.3-4.2		Total	
	No	%	No	%	No	%
0 to 4	1	100.00	0	0.00	1	100.00
5 to 9	7	58.33	5	41.67	12	100.00
10 to 14	13	86.67	2	13.33	15	100.00
15 to 19	13	72.22	5	27.78	18	100.00
20 to 24	14	82.35	3	17.65	17	100.00
25 to 29	12	80.00	3	20.00	15	100.00
30 to 34	10	90.91	1	9.09	11	100.00
35 to 100	11	100.00	0	0.00	11	100.00
Total	**81**	**81.00**	**19**	**19.00**	**100**	**100.00**

p=0.293

In the present study no association was noted between outcome and free T3. (p=0.293)

Table 12. Association of APACHE II score with free T4

APACHE II scores	Free T4						Total	
	< 0.89		0.89-1.76		>1.76			
	No	%	No	%	No	%	No	%
0 to 4	1	100.00	0	0.00	0	0.00	1	100.00
5 to 9	0	0.00	9	75.00	3	25.00	12	100.00
10 to 14	3	20.00	11	73.33	1	6.67	15	100.00
15 to 19	0	0.00	14	77.78	4	22.22	18	100.00
20 to 24	1	5.88	11	64.71	5	29.41	17	100.00
25 to 29	3	20.00	9	60.00	3	20.00	15	100.00
30 to 34	1	9.09	7	63.64	3	27.27	11	100.00
35 to 100	2	18.18	8	72.73	1	9.09	11	100.00
Total	**11**	**11.00**	**69**	**69.00**	**20**	**20.00**	**100**	**100.00**

p = 0.318

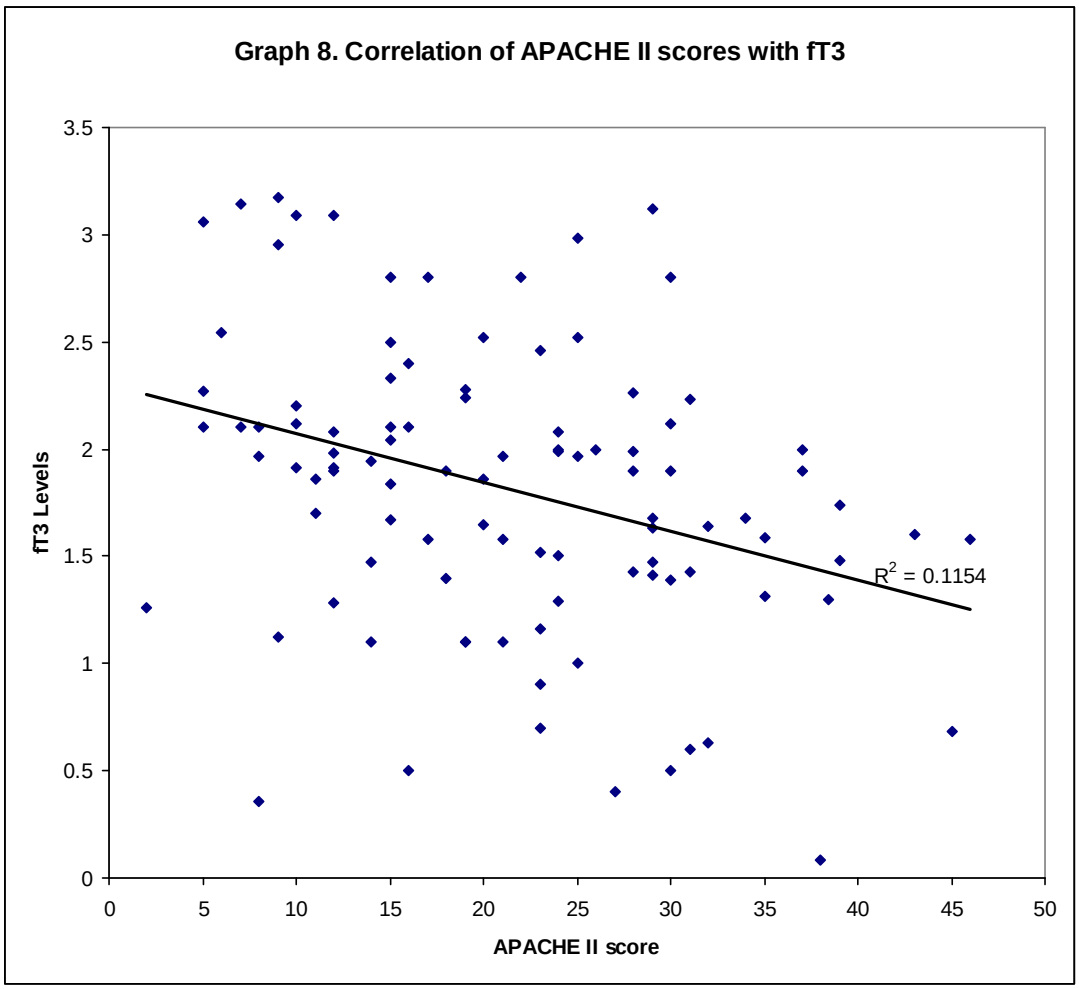
In the present study no association was found between APACHE II scores with free T4 (p=0.318).

Table 13. Association of APACHE II score with TSH

APACHE II scores	TSH						Total	
	<0.55		0.55-4.76		>4.76			
	No	**%**	**No**	**%**	**No**	**%**	**No**	**%**
0 to 4	1	100.00	0	0.00	0	0.00	1	100.00
5 to 9	1	8.33	10	83.33	1	8.33	12	100.00
10 to 14	5	33.33	9	60.00	1	6.67	15	100.00
15 to 19	5	27.78	12	66.67	1	5.56	18	100.00
20 to 24	1	6.25	15	93.75	1	5.90	17	100.00
25 to 29	3	20.00	12	80.00	0	0.00	15	100.00
30 to 34	0	0.00	11	100.00	0	0.00	11	100.00
35 to 100	2	18.18	9	81.82	0	0.00	11	100.00
Total	**18**	**18.00**	**78**	**78.00**	**4**	**4.00**	**100**	**100.00**

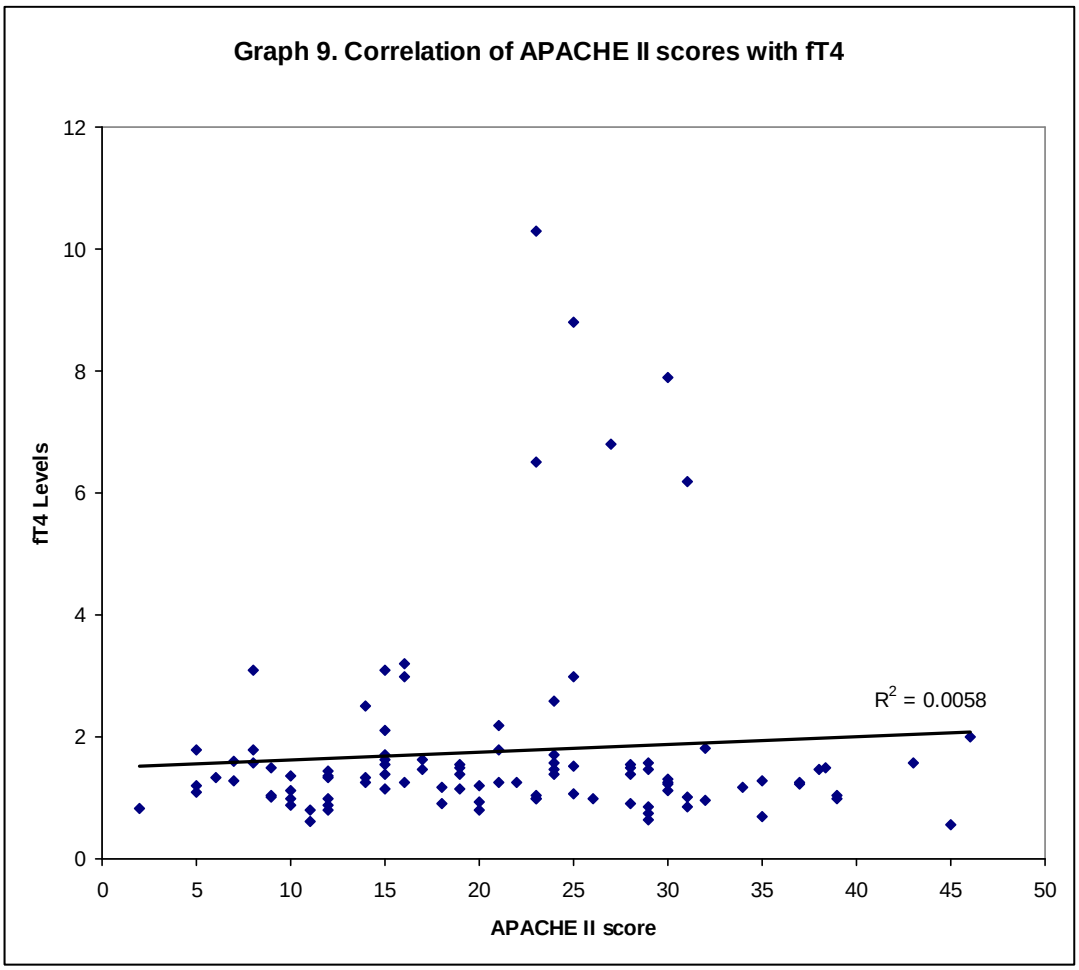
p = 0.290

In this study no association was found between APACHE II scores and TSH (p=0.290).



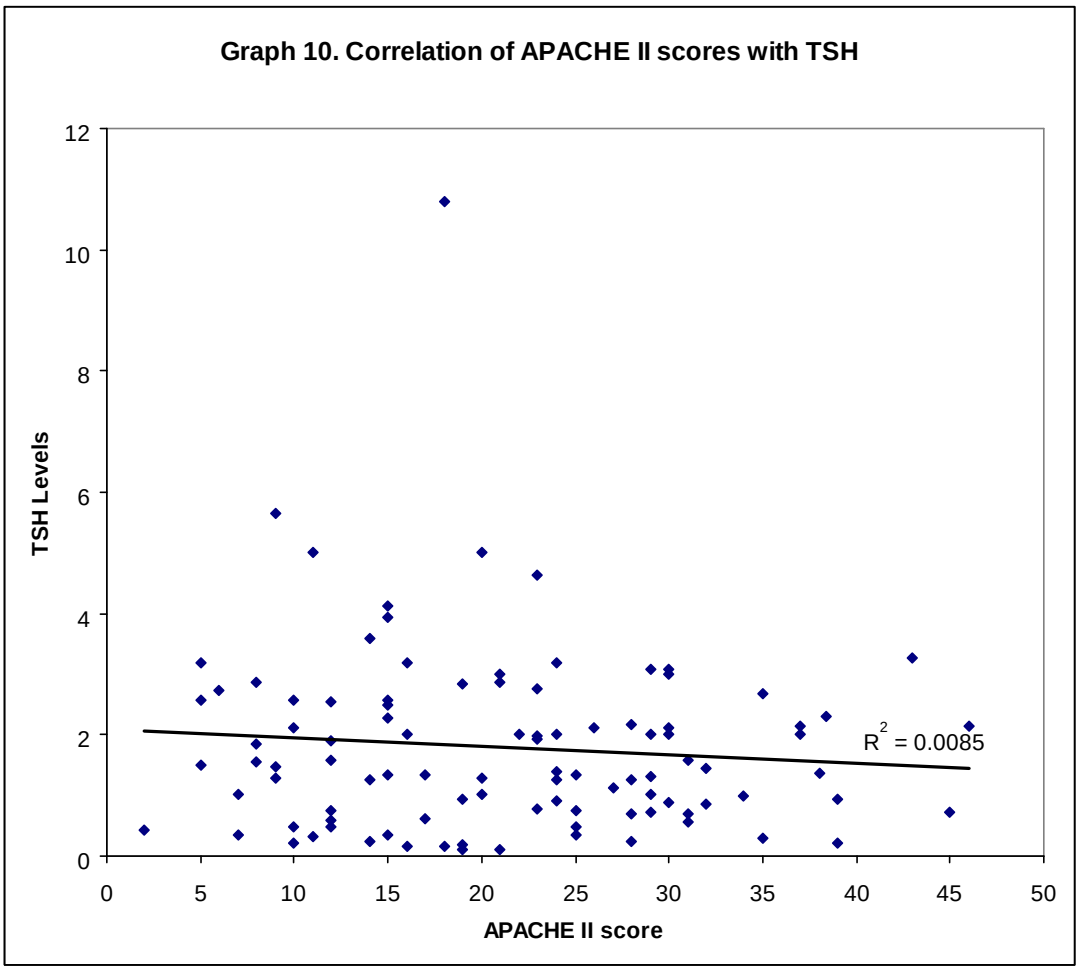
ρ=-0.345; p<0.001

The correlation of APACHE II scores with fT3 is as shown in figure. There was moderate negative correlation between APACHE II scores and fT3 (ρ=-0.345; p<0.001).



ρ= -0.019; p<0.848

The correlation of APACHE II scores with fT4 is as shown in figure. There was weak negative correlation between APACHE II scores and fT4 (ρ=-0.019; p<0.848).



ρ= -0.061; p<0.545

The correlation of APACHE II scores with TSH is as shown in figure. There was weak negative correlation between APACHE II scores and TSH (ρ=-0.061; p<0.545).

DISCUSSION

The evaluation of altered thyroid function parameters in systemic illness and stress remains a complex issue and presents many diagnostic problems because changes occur at all levels of the hypothalamic-pituitary-thyroid axis. Unique changes in thyroid function parameters are observed in various relevant clinical states, including starvation and fasting, cardiac disease, renal disease, hepatic disease and infection. Many pharmacologic agents also cause changes in thyroid economy that can complicate the interpretation of thyroid function parameters in systemic illness. Whether alterations in thyroid parameters during critical illness represent adaptive changes to conserve energy expenditure by reducing metabolic activity is still debatable. According to current data thyroid hormone replacement therapy has not been shown to be of benefit in the vast majority of these patients. LT3, however, appears to slightly improve hemodynamic and neurohumoral variables in patients with congestive heart failure, these benefits possibly representing a pharmacologic effect of T3 rather than a physiologic hormonal replacement effect.[71]

The metabolic responses to sepsis involve every organ and tissue of the body and yet, surprisingly, little is known about the underlying mechanisms. During sepsis and other critical illnesses, the state of stress results in hypermetabolism, increased energy expenditure, hyperglycemia and muscle loss[103,104] It is anticipated that appropriate metabolic support could improve the outcome in these patients, but considerable controversy remains regarding the indicated therapeutic approach.[71]

Critical illness is often associated with alterations in thyroid hormone concentrations in patients with no previous intrinsic thyroid disease.[71] Changes in parameters of thyroid function are very common but rarely isolated. They are often associated with alterations in other endocrine axes (reductions in serum gonadotropin and sex hormone concentrations and increases in serum adrenocorticotropic hormone and free cortisol levels)[105,106.] Whether thyroid hormone indicators can predict ICU mortality independently of both predictors is unclear. These variables' performance in predicting ICU mortality has not yet been compared.[71]

Few studies have reported that the low thyroid hormones are independent predictors of mortality in patients admitted to intensive care units (ICU), suggesting the inclusion of the thyroid profile in these scoring systems[13,107-110] There appears a continuum of changes in critically ill patients, starting with low triiodothyronine (T3) followed by low thyroxine (T4) and lastly low thyroid stimulating hormone (TSH).[111]

Furthermore, data on the beneficial effect of thyroid hormone treatment on outcome in sepsis patients is so far controversial. And surprisingly no data from India exists regarding the endocrinological parameter in sepsis patients and its correlation with APACHE II score.[13] Hence this study was designed to find correlation of sepsis and thyroid profile and to associate thyroid profile with APACHE II score.

Stressful situations affect all endocrine axes and differ in the response during acute and chronic phases of stress.

Triiodothyronine (T3**)** is the biologically active thyroid hormone and its low serum levels in critical illness reflect altered thyroid homeostasis and a mechanism of adaptation. Normally most (80%-90%) of T3 is produced by monodeiodination of 40% of circulating T4, a reaction catalyzed by 5'-monodeiodinases in organs such as the liver and kidney. The remaining (10%-20%) is directly secreted by the thyroid gland. The majority of critically ill patients have low serum T3 concentrations, as do some outpatients during illness. Moreover, patients with fatal illness have low tissue T4 and T3 concentrations[74,112.] Circulating inhibitors of deiodinase activity, such as free (non-esterified) fatty acids[75] and treatment with drugs that inhibit 5'-monodeiodinase activity, such as amiodarone and high doses of propranolol and cytokines (such as tumor necrosis factor, interferon-alpha, NF-kB and interleukin-6).[76-78] The majority of critically ill patients have low serum T3 concentrations, as do some outpatients during illness.

Serum Thyroxine (T4) in nonthyroid illness can be reduced within 24 to 48 hrs. The initial decline is predominantly due to decreased binding to carrier proteins, such as thyroid hormone binding globulin (TBG), transthyretin (TTR), or thyroxine-binding pre-albumin [TBPA]) and albumin.[113]

Many drugs, including salicylates, phenytoin, carbamazepine, furosemide, compete with thyroid hormone for binding to TBG, resulting in an acute increase in free T4 and a decrease in total T4 concentrations.

Under normal conditions, Thyrotropin (TSH) synthesis is relatively stable and is controlled by thyroid hormones, neuropeptides and neurotransmitters. Hypothalamic thyrotropine-releasing hormone (TRH) is the main stimulating factor

of TSH synthesis and its effect is enhanced by catecholamines. Somatostatin and dopamine are the main inhibitory factors of TSH synthesis. In euthyroid sick syndrome, TSH levels are commonly within the normal range and only in prolonged illness may be low. Most ICU patients suffer from sepsis. It is supposed that early alterations in the regulation of thyroid hormones economy during sepsis involve mainly peripheral mechanisms, such as impaired peripheral deiodination and reduced thyroid hormone secretion. The late phase of sepsis is associated with centrally induced hypothyroidism as suggested by restoration of T3 and T4.[114] In addition, postmortem examination showed diminished thyroid gland weight and follicular size,[115] low expression of TRH messenger RNA in the hypothalamic paraventricular nuclei and low concentrations of tissue T3 in patients who died while in the late phase of sepsis. Common late alteration in thyroid metabolism is a decrease in the pituitary secretion of TSH that typically occurs in parallel with the decline in serum T4 concentrations. The causes are multifactorial and attributed to effects of the illness per se, malnutrition and the suppressive effects of cytokines and by medications such as corticosteroids and dopamine. If the illness persists, reduced TSH secretion likely contributes to low total and eventually low free T4 concentrations. Such changes may be a self-protective adaptation to illness, as the body attempts to conserve energy. This state is usually transient, resolving once the patient shows signs of improvement. The recovery of the thyroidal axis begins with a rise in serum TSH and is eventually followed by normalization in T4 concentrations.[38] Because of the difference in half-lives of T4 (days) and TSH (hours), the normalization of T4 lags behind the increase in TSH. As a result, the picture during the resolution of euthyroid sick syndrome may suggest primary hypothyroidism.[71]

It remains controversial whether development of the aforementioned changes in thyroid metabolism reflects a protective mechanism or a maladaptive process during illness.[71]

If these changes constitute an adaptation mechanism, then treatment to restore thyroid hormone levels to the normal range could have deleterious effects. In contrast, if these changes are pathologic, treatment may improve an otherwise poor clinical outcome.[71]

The presence of euthyroid sick syndrome is associated with increased mortality among critically ill patients. Low serum T4 or low T3 levels seem to be a poor prognostic indicator in hospitalized cardiac patients or in patients after bone marrow transplantation. Whether this low hormone state could be related to recovery delay indicating therapeutic intervention has not been fully elucidated.[71]

Only a few studies have examined the use of supplemental thyroid hormone therapy in critically ill general medical patients. Brent and Hershman[116] examined the effect of thyroid hormone therapy in medical intensive care unit patients. The patients included in the study had serum T4 levels <5 µg/dL with no evidence of intrinsic thyroid dysfunction and were given either T4 or placebo intravenously on a daily basis. There was no significant difference in mortality between the two groups and the T4 replacement was detrimental to the restoration of normal pituitary-thyroid regulation. In organ donors exogenous thyroid hormones stabilizes the function of the cardiovascular system. There have been other trials in patients who suffered acute renal failure or underwent renal transplantation that also failed to show any benefit.[71]

One could argue that levothyroxine therapy applied for the management of the euthyroid sick syndrome is not expected to have any effect because of the pronounced inhibition of conversion of T4 to T3 in these patients. It is interesting that hepatic deiodinase is a selenoprotein and selenium deficiency is commonly seen in septic ICU patients. Thus, one could conclude that supplementation with selenium may result in a quicker normalization of T4 and rT3. Becker et al.[117] examined the effect of treatment with T3 in 36 patients with acute burn injuries. Treatment with liothyronine (LT3) normalized serum T3 concentrations but resulted in no change in either mortality or basal metabolic rate. Since it is easier to diagnose sick euthyroid syndrome than to treat it properly, avoidance of thyroid hormone substitution seems a reasonable option at present.[71]

The goal of TFTs in the ICU should mainly be the identification of previously unrecognized thyroid dysfunction that would require therapeutic intervention. When hypothyroidism is suspected clinically in an ICU patient (e.g. hypothermia, bradycardia, respiratory acidosis, pleural effusions, failure to wean), and the evaluation suggests central hypothyroidism, one should consider, that the probability of euthyroid sick syndrome is much higher than the pituitary or hypothalamic disease. If hyperthyroidism is suspected (e.g. tachyarrhythmias, widened pulse pressure, respiratory alkalosis, high-output heart failure) and low TSH is detected, TSH is suppressed fully and the free T4 is elevated or at least in the upper limits of the normal range. If the free T4 is low or low-normal, the patient is probably not hyperthyroid. however, repeating the free T4 is advised before firmly establishing the diagnosis, especially if clinical suspicion persists.[71]

This hospital based one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015. A total of 100 patients with sepsis were subjected to the assessment of thyroid profile.

In the present study slight male preponderance was noted as 57% of the patients were males and 43% were females with the male to female ratio of 1.32:1. The sex distribution pattern observed in this study was consistent with a single centre, prospective, observational study by Hari Kumar KVS et al.[13] to evaluate the thyroid hormone profile, prolactin and, glycosylated hemoglobin (HbA1c) at admission and analyze their correlation with mortality where 52% of the patients were males and 48% were females.

In the present study the age of the patients in this study ranged between 18 to 92 years while, most of the patients were aged between 18 to 30 years (23%). But, the mean age was 48.55 ± 18.09 year and median age was 45 years. Hari Kumar KVS et al.[13] in their single centre, prospective, observational study to evaluate the thyroid hormone profile, prolactin and, glycosylated hemoglobin (HbA1c) at admission and analyze their correlation with mortality reported mean age as 58.7 ± 16.9 years (range, 16–94 years).

In the present study type 2 diabetes mellitus was the most common comorbid condition (29%). In this study pneumonia was the most common primary diagnosis noted in (31%) of the patients followed by pyelonephritis (20%) and cellulitis (15%).

Most of the patients of the patients had APACHE II scores between 15 to 19 (18%). The mean APACHE II scores were 21.26 ± 10.07 and median scores were 21 with range 2 being minimum and 46 being maximum.

In this study thyroid profile revealed majority of the patients with low Ft3 levels (94%) but, low fT4 levels in11% of the patients and TSH levels were low in 18% of the patients.

Hari Kumar KVS et al.[13] in their single centre, prospective, observational study to evaluate the thyroid hormone profile, prolactin and, glycosylated hemoglobin (HbA1c) at admission and analyze their correlation with mortality reported low T3 (61%) as the commonest abnormality followed by lowT4 (14%) and low TSH (7%). Previous data from pediatric ICU patients from Mumbai showed low T3 in 80%, low T4 in 50%, and low TSH in 6.7% patients, and it was conducted in 30 critically ill children and controls of less than 12 years age admitted in pediatric ICU. Two samples were collected from all patients, first at admission and second sample at the time of discharge from ICU or death.

In the present study most of the patients (68%) improved and discharged while mortality was noted in 32% of the patients.

In this study, 11 patients each has APACHE II scores between 35 to 100 and 30 to 34. among them significantly higher number of patients expired that is, 63.64% and 81.82%. Also majority of the patients with APACHE II scores of < 19 improved (97.83) ($p<0.001$) showing strong association between APACHE II scores and outcome as ($p<0.001$). Hence the present study confirms outcome is hypothesized to be worst in patients with higher APACHE II scores.

In the present study outcome was comparable in patients with normal (32.98%) and abnormal fT3 (16.67%) (p=0.705). Similarly, in patients with low fT4 (<0.89) (36.36%), normal (0.89-1.76) (30.43%), and raised fT4 levels (>1.76) (30.43%) the outcome was comparable (p=0.880) Also in patients with (<0.55) (16.67%), normal TSH levels (0.55 to 4.76) (37.18%) and raised TSH levels (0%) the outcome was comparable (p>0.050). suggesting lack of association between thyroid hormones viz. fT3, fT4 and TSH and outcome (p>0.05).

Surprisingly the correlation of APACHE II scores with fT3 showed statistically significant moderate negative correlation (ρ=-0.345; p<0.001). However, there was weak negative correlation was between APACHE II scores with fT4 (ρ=-0.019; p<0.848). Similarly, weak negative correlation was noted between APACHE II scores with TSH (ρ=-0.061; p<0.545). These findings suggest that, there is Inverse relationship between APACHE II scores and fT3 posing strong relationship between lower fT3 levels with high APACHE II scores there by high chances of mortality as higher APACHE II scores were significantly associated with significantly higher mortality rate. These findings were consistent with other studies by Hari Kumar KVS et al., Ture M, et al. Peters RP et al. in the literature. However, Hari Kumar KVS et al. and Ture M. et al. did not comment on APACHE II scores.

Euthyroid sick syndrome is the term used to describe thyroid hormonal changes in critically ill patients due to nonthyroidal illness. Low T3 is the earliest manifestation followed by low T4 and finally low TSH, indicating a continuum of changes in the spectrum.[89] A similar study by Suvarna JC et al.[118] involving pediatric ICU patients showed that low T3 is a good predictor of mortality, and the risk is increased by 30 times when it is associated with low T4.[89] However, that

trend was not observed in our study, and this could be due to difference in age and number of study population and performing a single sample estimation instead of serial monitoring in our study.

Hari Kumar KVS et al.[13] from Lucknow, India also concluded that, low T3 is an important marker of mortality in critically ill patients. Low T4 and TSH did not increase the predictability. Admission HbA1c and prolactin did not vary between survivors and nonsurvivors.

Ture M. et al. in a prospective, observational study analyzed and compared the prognostic accuracy of free tri-iodothyronine (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH), along with the APACHE II and SOFA scoring systems in predicting intensive care unit (ICU) mortality in critically ill patients. They concluded that, in critically ill patients, serum fT3 concentrations markedly decreased after ICU admission among non-survivors. According to the findings, fT3 levels might have additive discriminatory power to age, SOFA and APACHE II scores in predicting short-term mortality in ARDS patients admitted to ICU.

In another study by Chinga-Alayo E et al.[98] investigated whether mortality prediction based on the Acute Physiology and Chronic Health Evaluation (APACHE) is improved by combining this score with hormone measurements. of 113 ICU patients (with only 4 of them admitted because of trauma), This model had an area under the receiver operating characteristic curve of 0.88, significantly higher than the APACHE score alone with 0.75 which showed that the addition of TSH and total T3 improved the prognostic value of the APACHE II score.

Overall, from the above observations and the other study reports it is evident that, in critically ill patients, thyroid profile on admission to the ICU, in combination with the APACHE II score, predicts outcome more accurately than the APACHE II scores alone. However, this study had several limitations that is, smaller sample size involved patients from single centre. Further studies involving a large number of patients with multicentric design are required to unravel the mystery of thyroid hormones in patients with sepsis.

CONCLUSION

The present study showed that,

- There is strong inverse relationship between lower fT3 levels with high APACHE II scores thereby high chances of mortality as higher APACHE II scores were significantly associated with significantly higher mortality rate.

- In sepsis patients, thyroid profile in combination with the APACHE II score in ICU patients, predicts outcome more accurately than the APACHE II scores alone.

SUMMARY

.In the present study of 100 patients titled **"CORRELATION OF THYROID HORMONE PROFILE WITH APACHE II SCORE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT"** a one year hospital based cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015 were subjected to the assessment of thyroid profile. This study was designed to find correlation of sepsis and thyroid profile and to associate thyroid profile with APACHE II score.

The salient findings of the study are as summarized below:

- There was slight male preponderance with 57% of the patients being males and 43% being females and male to female ratio of 1.32:1.
- The most common age group was between 18 to 30 years (23%). The mean age was 48.55 ± 18.09 year.
- Type 2 diabetes mellitus was the most common comorbid condition (29%).
- Most of the patients that is, 18% had APACHE II score between 15 to 19. The mean APACHE II scores were 21.26 ± 10.07.
- Thyroid profile assessment revealed low fT3 levels in majority of the patients (94%) while low fT4 in 11% patients and low TSH noted in 18% patients.

- 68% of the patients improved and discharged while mortality was noted in 32% of the patients.

- Pneumonia was the primary diagnosis noted among 31% of the patients followed by pyelonephritis (20%) and cellulitis (15%).

- Statistically significant association was found between APACHE II scores and outcome as APACHE II scores between 35 to 100 were noted in 11 patients out of which majority (81.82%) expired. ($p<0.001$)

- Statistically significant association was found between APACHE II scores and outcome as majority of the patients with APACHE II scores of < 19 improved (97.83) ($p<0.001$).

In critically ill patients, thyroid profile on admission to the ICU, in combination with the APACHE II score, predicts outcome more accurately than the APACHE II scores alone. There is inverse relationship between APACHE II scores and fT3.

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ANNEXURE I - CONSENT FORM

CORRELATION OF THYROID HORMONE PROFILE WITH APACHE II SCORE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT

Objective and purpose of the study

This research is intended to assess **on thyroid hormone role in sepsis patients.** The principal investigator of the study is **Dr. *** ****** under the guidance of **Dr. **** ****** ******

Procedure

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

Risk and Benefits

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

Does not apply to this research

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, Belagavi as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about study you may call:

1. Dr. ** ********
Investigator,
PG General Medicine
Jawaharlal Nehru Medical College
Belagavi – 590 010
Phone No.: **** *****

2. Dr. *** *******
Vice-Principal, Professor,
Department of Medicine,
Jawaharlal Nehru Medical College
Belagavi – 590 010
Phone no. ****** *****
Extn: ****/ ******

If you have any questions about your rights as a participant you may contact

3. DR.** ******* , Chairman,
J.N.M.C Ethical Committee for Human Research,
Professor and Head Department of Pathology,
Jawaharlal Nehru Medical College,
Belagavi – 590 010

CONSENT STATEMENT

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

Date: Place :

ANNEXURE II – PROFORMA

Study Title: CORRELATION OF THYROID HORMONE PROFILE WITH APACHE II SCORE AS A PROGNOSTIC MARKER IN PATIENTS WITH SEPSIS IN INTENSIVE CARE UNIT

HISTORY: (by the patient/ relative)

Patient's Personal Information

Name:

In Patient /Out Patient Number:

Age:

Sex:

Address:

Education:

Occupation:

Religion:

Socio economic status:

Date of admission in ICU:

Relative's personal details

Name:

Age:

Sex:

Relation with patient:

Brief History of present illness:

Chief complaints:

Duration of the disease:

Duration of illness before intensive care admission:

Who diagnosed the disease?

How was it diagnosed?

Past history

History of any Thyroid illness Yes/No

- If yes then specify the type and duration of illness?

- If yes are you on any medication?

Any other chronic disease ?

History of any similar disease in the past and need for any treatment then?

Drug History (if any)

Were you at any other medications at the time of diagnosis? : Are you compliant to the medication?

Treatment History of disease before admission

Were you given any other medication before coming to the hospital? if so then what medication and by whom?

Family History (if similar complains in the family?)

Yes / No?

If yes then specify?

History of Thyroid Disorders in Family

Examination by the investigator

Vitals	:	Pulse	:
Blood pressure	:	Respiratory rate	:

Temperature:

General Physical Examination

Systemic Examination

Respiratory System:

Cardio Vascular System:

Per Abdomen:

Central Nervous System:

Apache II Grading

Age	:	Temperature	:
Mean blood pressure	:	Ph arterial	:
Heart rate	:	Respiratory rate:	
Oxygenation	:	Serum sodium	:
Serum potassium	:	Creatinine	:
Haemocrit	:	WBC count	:

Glassgow Coma Scale

Apache II Score

Investigations

Complete blood count	:	Peripheral smear	:
Renal profile	:	Liver function test	:
Urine routine with culture	:	Chest X-ray	:
Arterial blood gas analysis	:	USG abdomen	:

Thyroid profile

Free T3	:	Free T4	:	TSH	:

Duration of stay

Outcome

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
/Cumm	-	Per cubic millimeter
/Minute	-	Per minute
+	-	Present
^{0}F	-	Degree Fahrenheit
APACHE II	-	Acute Physiology and Chronic Health Evaluation II
ARF	-	Acute renal failure
BP	-	Blood pressure
CVA	-	Cerebrovascular accident
DISCH	-	Discharged
EXP	-	Expired
F	-	Female
fT3	-	Free Triiodothyronine
fT4	-	Free Thyroxine
GE	-	Gastroenteritis
HTN	-	Hypertension
IHD	-	Ischaemic heart disease
M	-	Male
mg/dL	-	Milligrams per deciliter
mIU/L	-	Milli international units per litre
mm Hg	-	Millimeter of mercury
mmol/L	-	Millimole per litre
ng/dL	-	Nanograms per deciliter
RVD	-	Retro viral disease
T2DM	-	Type 2 diabetes mellitus
TSH	-	Thyroid stimulating hormone
UTI	-	Urinary tract infection
WBC	-	White blood cell