A DISSERTATION ON

"A PROSPECTIVE STUDY ON PROCALCITONIN AS AN USEFUL BIOMARKER FOR PROGNOSIS OF SEPSIS AND GUIDE FOR ANTIBIOTIC THERAPY IN SICU PATIENTS"

Submitted to

THE TAMIL NADU DR.MGR MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfillment of the regulations

For the awards of the degree of

M.S. DEGREE - GENERAL SURGERY

BRANCH – I

GOVERNMENT MOHAN KUMARAMANGALAM

MEDICAL COLLEGE , SALEM

MAY 2020

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SALEM

DECLARATION BY THE CANDIDATE

I solemnly declare that this dissertation **"A PROSPECTIVE STUDY ON PROCALCITONIN AS AN USEFUL BIOMARKER FOR PROGNOSIS OF SEPSIS AND GUIDE FOR ANTIBIOTIC THERAPY IN SICU PATIENTS"** was prepared by me at Government Mohan Kumaramangalam Medical College and Hospital , Salem under the guidance and supervision of **Prof. Dr. K. KESAVALINGAM, M.S.,** Professor of General Surgery, Govt. Mohan Kumaramangalam Medical College and Hospital, Salem. This dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University ,Chennai- 38 in fulfilment of the University regulations for the award of the degree of M.S. General Surgery (Branch I).

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Guide/Principal Investigator	DR. K. KESAVALINGAM, MS., Associate Professor of General Surgery, GMKMC, Salem-30.
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LIST OF ABBREVIATIONS USED

MODS-MULTI ORGAN DYSFUNCTION SYNDROME

SIRS - SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

WBC- WHITE BLOOD CELLS

CRP- C-REACTIVE PROTIEN

IL- INTERLEUKIN

TNF- TUMOR NECROSIS FACTOR

PCT- PROCALCITONIN

ICU- INTENSIVE CARE UNIT

DIC- DISSEMINATED INTRAVASCULAR COAGULATION

CCP- CARBOXY TERMINUS PEPTIDE.

ABSTRACT

Sepsis is most common cause of death in surgical ICU patients .Early diagnosis and appropriate antibiotics plays the major role in saving the patients. Procalcitonin helpful in early detection as well as to monitor the anti microbial therapy.

AIMS AND OBJECTIVES:

To study on effectiveness of procalcitonin as an useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients.

MATERIAL AND METHODS:

Cases admitted to GMKMC hospital Salem with signs of sepsis in SICU patients will be closely monitored from the day of admisssion to the day of discharge. On an average of 100 cases with signs of sepsis in ICU patients admitted between 2017 to 2019.

RESULTS:

A prospective study on Procalcitonin as a useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients revealed the following findings.The mean age is 57.06 years with a standard deviation of 9.39 years. The median age is 56 years ranging between 38 years and 74 years. The majority of the

participants were males (n=56, 56%) while the rest were females. Out of the 100 patients, 76 of them (76%) were blood culture positive while the remaining 24% were blood culture negative. Out of the 100 patients, 68 of them (68%) were pus culture positive while the remaining 32% were pus culture negative. Out of the 100 patients, 80 of them (80%) were urine culture positive while the remaining 20% were urine culture negative. Out of the 100 patients, 66 of them (66%) were wound swab positive while the remaining 34% were wound swab negative. Out of the 100 patients, 42 of them (42%) were Klebsiella positive while 34 of them (34%) were E.coli positive. Pseudomonas was positive in 14% (n=14) of them while Proteus was present in 8% (n=8) of them.The organisms were sensitive to Piptaz (n=50, 50%) and Cefaperazone (n=48, 48%).CRP was positive in 47% of the cases and negative in 53% of the cases. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU.

CONCLUSION:

CRP was positive in 47% of the cases and negative in 53% of the cases. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU. The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis.

KEY WORDS: Sepsis, Procalcitonin, CRP.

INTRODUCTION

Introduction

A systemic infection evokes a strong response from the immune system which is called as sepsis. In around one-third of the cases, the etiology of the infection is unknown[1]. Evolution has handed the human race a great gift of mounting an immune response to an infection, which is otherwise called as host responses. The defence mechanisms are complex and respond in different ways to various invasive pathogenic organisms. One of the earliest responses to an microbial infection is the development of the inflammatory response that happens like a cascade involving a huge number of biochemical messengers[2].

Increased microbial load is correlated with increased mortality[3]. The severity is determined by the number of the microbes which is referred to the microbial load and also if there are more than one type of microorganism, then severity proportionately increases leading to increased morbidity and mortality[3-6].

The source of infections are very important to note as they may dictate the severity of the illness, the morbidity. pharmacological protocol, management decisions, prognosis, outcome and mortality. Following sources are generally associated with sepsis;

a) Acquired from community

b) Hopsitals

c) Other healthcare facilities

Around 18 million new cases of sepsis are reported each year. The global mortality rate is between 30% and 50%[7].

A study on the pattern of the intensive care cases found that the prevalence of sepsis is India is not infrequent. Around 28.3% of the patients admitted in the intensive care unit acquire sepsis, out of which, there is a mortality rate of 34%[8].

Though sepsis can be caused by any of the microbes namely; bacteria, virus, parasites and fungi, yet bacteria is the most common etiologic agent for the infection and development into a full blown sepsis[9-11].

The infection can start from anywhere in the body and the microorganisms enter the blood. They start multiplying in the blood and start releasing factors of virulence into the blood[12]. The blood houses monocytes, macrophages, neutrophils, endothelial cells and plasma cell precursors which get stimulated by these virulent factors. They release the mediators of sepsis that are endogenous in origin[13].

The entry of the microorganisms stimulates the endogenous mediators that acts on the immune system. The immune system in turn elaborates a response in defence to neutralise the pathogens. This leads to the secretion of inflammatory proteins that can damage the tissues and organs of the host[14,15].

The clinical symptoms of sepsis are namely;

1) Tachycardia

2) Tachypnea

3) Elevated temperature

4) Leucocytosis

When the sepsis is severe, there is hypoperfusion and damage of atleast one organ. If this progresses, it leads to shock. Sometimes, multiple organs are involved known as MODS (Multiple Organ Dysfunction Syndrome). If this is associated with hypotension, it is known as septic shock[16].

Sepsis is a very serious and challenging disease in critical care medicine that can be of graded variety namely; from sepsis to severe sepsis and septic shock. The challenges arise from the heterogeneity of the presentation in terms of incidence and symptomatology. This leads to diagnostic confusion in designing the diagnostic and treatment algorithm. Also, the variance in etiology and severity adds constraints to the existing framework. So, developing an universal algorith for the diagnosis and management of sepsis is a challenge. This explains why it is not possible to do randomised control trials for studying sepsis. Multicentric trials have contraindicated the findings of previous studies[33]. Sepsis is multifactorial in origion requiring multidisciplinary approach to management. Economic issues

form a separate facet of this illness. Early identification, diagnosis and treatment is necessary for survival and good prognosis. The task of management starts right from outside the hospital and follows into the emergency departments and then later on into the wards. Any amount of intensive case management is useless without the initial management. In spite of the lack of well designed randomised trials for sepsis, the sporadic studies have given great insight into the incidence, epidemiology and the pathophysiology of the illness. The immunological background of the illness is essential for diagnosis, managment and prognosis.

The outcome of the illness largely depends on the time of diagnosis and initiation of prompt treatment. When the diagnosis or treatment is delayed due to any reason, the outcome and prognosis is very poor and may affect all the organs, a condition called as the Systemic Inflammatory Response Syndrome (SIRS). Early initiation on antimicrobial therapy is crucial in getting a better outcome.

Since the emphasis lies on early diagnosis, there are various attempts to understand if there is a way to find out the onset of sepsis before the clinical signs become evident. Following host responses are widely studied to find if there is a marker that might help in early diagnosis of sepsis;

a) Cytokine

b) Cell marker

c) Receptor Biomarkers

d) Coagulations

e) Vascular Endothelial Damage

f) Vasodilation

g) Organ failure

The recent advancements in the field of molecular biology may aid in screening the biomarkers during the acute phase of sepsis[17].

The conventional markers for the diagnosis and management of sepsis are;

1) WBC

2) CRP (C-reactive protein)

3) IL-1 (Interleukin-1)

Other biomarkers that are elevated during sepsiis are; TNF-α and IL-6. But these biomakers lack sensitivity and specificity. They have low positive and negative predictive values[18].

Procalcitonin have aid better in diagnosis and help in prognosis than CRP. Also, it will help differentiate between bacterial and viral meningitis[19]. The gold standard for the confirmation of bacterial infection in sepsis is through blood culture. But

the time taken for a bacterial culture is too long to delay treatment. This may lead to a loss of golden time[20].

Sepsis leads to excessive catabolism, loss of lean body mass and hyper metabolism that may range between months to years. The early management of sepsis focusses on correcting nutritional deficiencies and maintain the energy requirements. The next phase aims to recover the homeostasis of the body and lower the loss of lean body mass.

Screening of malnutrition is essential and continuous monitoring is required post discharge to aid functional recovery. Sepsis is reported in 2% of all hospitalisations globally[21].

Mortality rate continues to be high despite the latest advancements in healthcare sector. The reduction of morbidity and mortality depends on the early recognition and treatment of sepsis. The diagnostic uncertainty of sepsis proves to be challenging even today though clinical signs are evident. This mandates the presence of serum biomarkers like Procalcitonin that may help in early diagnosis and management.

Procalcitonin is a hormokine (it is so called due to the hormonal origin of the mature protein) which is a propeptide[22]. The production of this hormokine follows one of the two pathways; classical hormonal expression or, alternatively,

a cytokine-like expression pathway. Sometimes, it may be due to a cell mediated host response[23]. It has a long half-life of 25-30 hours[24].

Since 1990s, PCT has been seen as a potential biomarker[25]. In 2003, elevated plasma PCT was included in the updated definition of sepsis[26]. Infection leads to elevated PCT as a part of the complex response of the innate immune system[27]. Increasing serum PCT levels is associated with poor prognosis and decreasing levels is seen as a sign of recovery[28]. PCT levels are diagnostic of systemic bacterial disease[29]. The PCT levels are diagnostic in critically ill patients too[30,31].

There are previous studies that have reported the advantages of using the precursor molecule of calcitonin as a biomarker in sepsis. The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis[32].

Therefore, PCT may be a suitable as a stanndalone biomarker or in combination with other biomarkers for the following;

a) Prediction of sepsis

b) Etiology

c) Diagnosis

d) Progression

e) Response to treatment

f) Regression

g) Outcomes

h) Prognosis

i) Mortality

REVIEW OF LITERATURE

Review of Literature

An Overview

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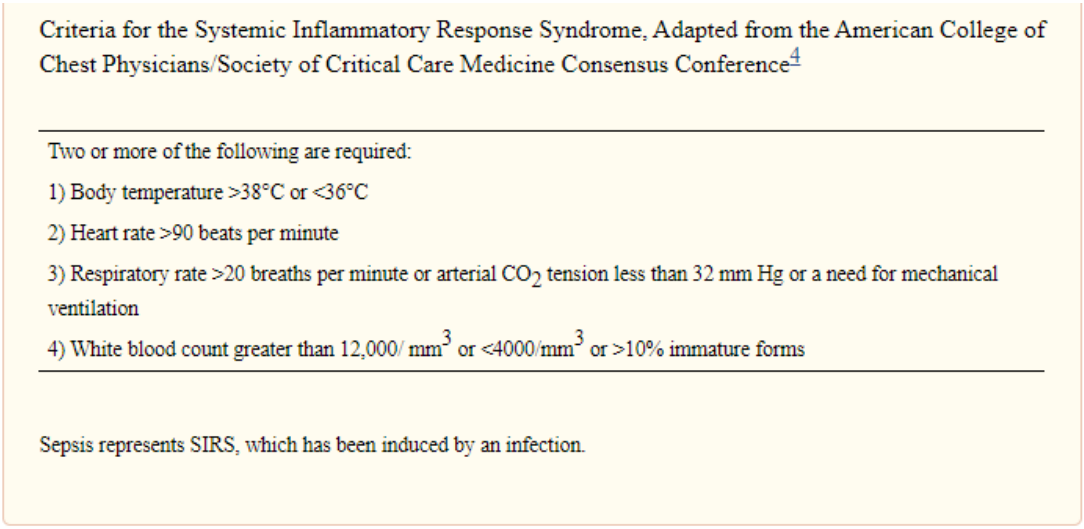
Sepsis- an indefinite disease

The traditional medical school approach of presenting with conclusive signs and symptoms by patients and the physician arriving at a diagnosis using the various clinical and laboratory parameters that dictates management does not apply for sepsis. Unlike stroke or myocardial infarction where diagnostic and treatment protocols are standardised across the world. But, defining sepsis is more complicated than all this. The nomenclature alone took several decades to be framed that was finally christened in Las Vegas in a hotel room in 1980. The term was "Sepsis Syndrome" which had to be framed while drafting a protocol for the one of the earliest prospective randomized trials in sepsis. This was done by late Roger Bone[34,35]. The same group of scientists released the name in the statement paper called “Sepsis Syndrome: A Valid Clinical Entity”.

They presented the classical signs of sepsis syndrome namely;

1. fever/hypothermia
2. leukocytosis/leukopenia
3. tachycardia
4. hypotension

As expected, these signs were not specific for sepsis but was a presenting spectrum of symptoms and signs for a number of illnesses which led to the inclusions of large cohorts with lot of false positive cases. This led to the formulation of the "consensus criteria" of sepsis during the consensus conference[36]. The following image shows the consensus criteria of sepsis.



Criteria for the Systemic Inflammatory Response Syndrome, Adapted from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference[4]

Two or more of the following are required:

1) Body temperature >38°C or <36°C

2) Heart rate >90 beats per minute

3) Respiratory rate >20 breaths per minute or arterial CO_2 tension less than 32 mm Hg or a need for mechanical ventilation

4) White blood count greater than 12,000/ mm^3 or <4000/mm^3 or >10% immature forms

Sepsis represents SIRS, which has been induced by an infection.

Image 1: Consensus Criteria for Sepsis

This is widely criticised and questioned by the present day experts on the subject[37]. The need for the change of definition parallels the advancements in the field of

medicine including immunology and biochemistry. In order to save the older concepts, the newer definitions are more detailed over the previous one[38]. The changing diagnosis and the subsequent challenges can be attributed to the changing information on the pathophysiology of the illness which is discussed in detail later.

International societies that study sepsis have therefore come up with the international task force for drafting the definition of sepsis which is based on pathophysiology. Since, there are no conclusive radiological or laboratory investigations, sepsis is difficult to diagnose.

Diagnostic insufficiencies can explain the morbidity and mortality due to sepsis even when technology is constantly improving day by day. Another way of looking at it is that sepsis per se is not a disease rather a confluence of plethora of features that might surface as a result of failure of any system. Different organs and systems are involved in the disease process with a large of combinations of derangements clouding the pciture of individual contributions in the process. One thing that is certain is that patients with sepsis have serious alterations of their coagulation system. Activated protein C is therefore used today as a component of pharmacological treatment in sepsis. Older schools of thought saw sepsis as a hyperinflammatory and exaggerated response to an underlying inflammation of the organ. But not all responses are due to hyperinflammatory response as some are even due to the suppression of the immune system. This immuno-stimulation

and immuno-suppression confusion continues even today. Sometimes, there is an increasing destruction of the cells like lymphocyte apoptosis. Another aspect of sepsis is the incidence of the metabolic changes. The present literature suggests that there are no single etiologic agent, pathogen, system, pathway or mediator for sepsis which makes it all the more difficult.

The evolution of bacteria precedes that of man which suggests that sepsis has been affecting men since the beginning of time. Sepsis has been causative in the global mortality rates. A review in 1995 for sepsis in the US showed that the incidence was 751,000 cases including the 215,000 deaths[40]. The actual number of deaths due to sepsis is increasing according to a recent report[41]. This is expected to continue with the aging population. The mortality rate for sepsis is based on 28-day survival as against the traditional mortality rates that are calculated on 5-year survival. Apart from the mortality rate, the disease is also known to affect the quality of life and leads to a significant number of the lost years of life.

The definition of sepsis has been attempted by two major consensus conferences. In 1992, the first consensus suggested SIRS (Systemic Inflammatory Response Syndrome). This consensus said that sepsis can be present even without overt microbial presence in the blood confirmed by blood cultures. Subsequently, the following definitions are considered;

- When SIRS is initiated by infection, it is called sepsis[42].

- When sepsis is accompanied by dysfuctions of an organ or an organ system, then it is called severe sepsis

- When severe sepsis presents with hypotension, then it is called septic shock in 2001, another conference on the International Sepsis Definitions altered the model of SIRS. They expanded the view after a systematic review of the literature[43]. An acronym PIRO was used for developing the staging system of sepsis.

P- predisposition, any pre-existing co-morbid conditions
I- insult or infection
R- response
O-organ dysfunction and organ failure

The symptoms, signs and etiology of sepsis is a conundrum as they are non-specific. Any specific test would be a good candidate for utilising in the management of sepsis. The true reason behind this confusion is that any organism can cause sepsis and it is multifactorial. Gram-positive organism are known to cause more sepsis than gram-negative[44].

The interactions between pathogens and the Toll-like receptors have been implicated in sepsis. But animal testing has shown that absence of TLR does not necessary prevent sepsis[45].

. Epidemiology

Reported epidemiological studies state that more patients are being affected by sepsis today than before[46]. One of the recent data from the United States shows that sepsis is one of the most expensive reasons for current hospitalisations with a mortality rates between 20% and 50%[47,48]. But this reported mortality is different across the globe. In New Zealand and Australia, these mortality rates have decreased though the incidence of sepsis has increased[49]. A trial called PROCESS in the United States showed a mortality rate around 20%[50]. The study also showed that the outcome has improved over the years.

But a study from Europe was contradictory with and increased mortality between 45% and 55%. This was also accompanied by longer hospital stay and admission in the ICU[51,52].

What causes these differences? Is it because the care and support is better than other countries or is it an independent finding. Also, the lack of data in various aspects like the definition, diagnosis and treatment, it is difficult to really understand the global burden of the problem and how it varies geographically. This

is the same with the mortality rates. What were the cases that constituted the cohort? What were the cases taken for calculating mortality rates, etc? For instance, in septic shock cohort, the mortality rate is high which cannot be considered as the true reflection of the disease. Existing comorbidities also affect the true picture including diagnosis, treatment and prognosis. Intrinsic factors of the patient like the host's response also affect the outcome. Following image shows how the incidence and epidemiology of sepsis is multifactorial.

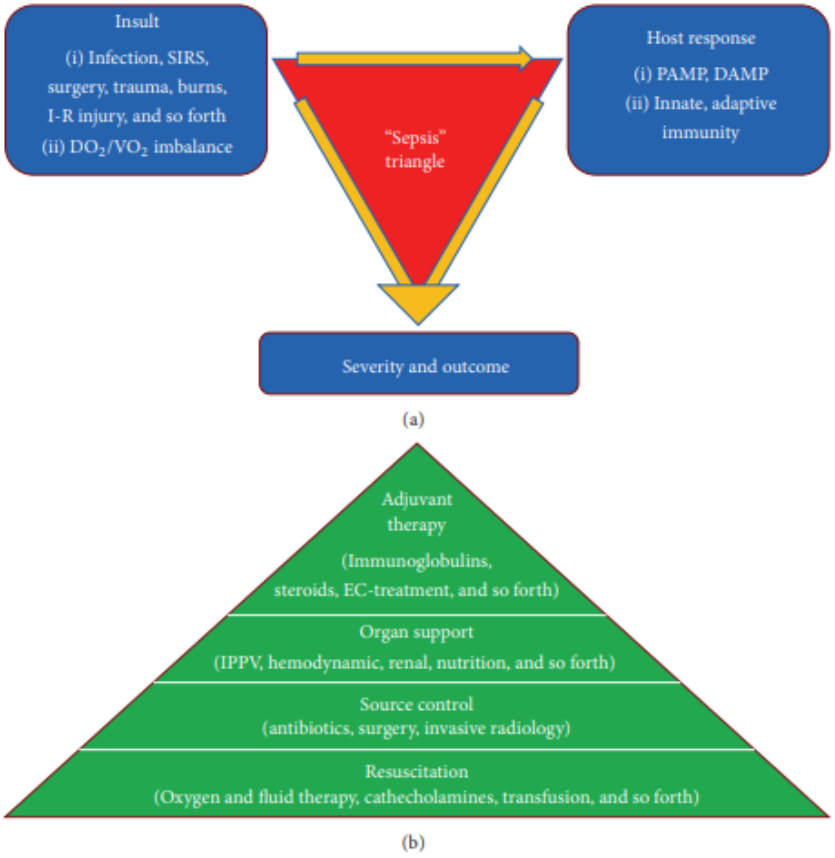


FIGURE 1: The "sepsis-triangles": pathomechanism and treatment. SIRS: systemic inflammatory response syndrome, I-R: ischemia-reperfusion, DO_2: oxygen delivery, VO_2: oxygen consumption, PAMP: pathogen-associated molecular patterns, DAMP: damage-associated molecular patterns, EC: extra corporeal, and IPPV: intermittent positive pressure ventilation.

Image 2: Multifactorial Pathophysiology

Pathophysiology; *Dysregulated coagulation pathways*

When a person gets injured, the coagulation pathways gets activated whereas in normal conditions, the fluidity of the blood is maintained. The equilibrium between clotting and not clotting is complex under normal conditions[53]. But this equilibrium is disturbed when there is an injury. The initiating event can be any etiologic factor that causes the initiation and the maintenance of the coagulation pathways from factors released by the system and the cells of the system[54]. Patients with sepsis show disseminated intravascular coagulation (DIC) where there is a loss of platelets and thereby prolonging the coagulation time of the patients. Alternatively, blood starts clotting when there is no need for the same. These two events can be triggered by any etiologic agent and differs widely. In addition, the liver manufactures the factors of the coagulation system in a fixed quantity and the bone marrow releases limited number of cells. Any event causes an local effect that enlarges to a systemic response. In spite of the systemic coagulopathy, bleeding occurs only in select sites. This may be because of the interaction of the following;

- clotting system
- circulating white blood cells
- platelets
- endothelium

The following image shows the pathways how they interact;

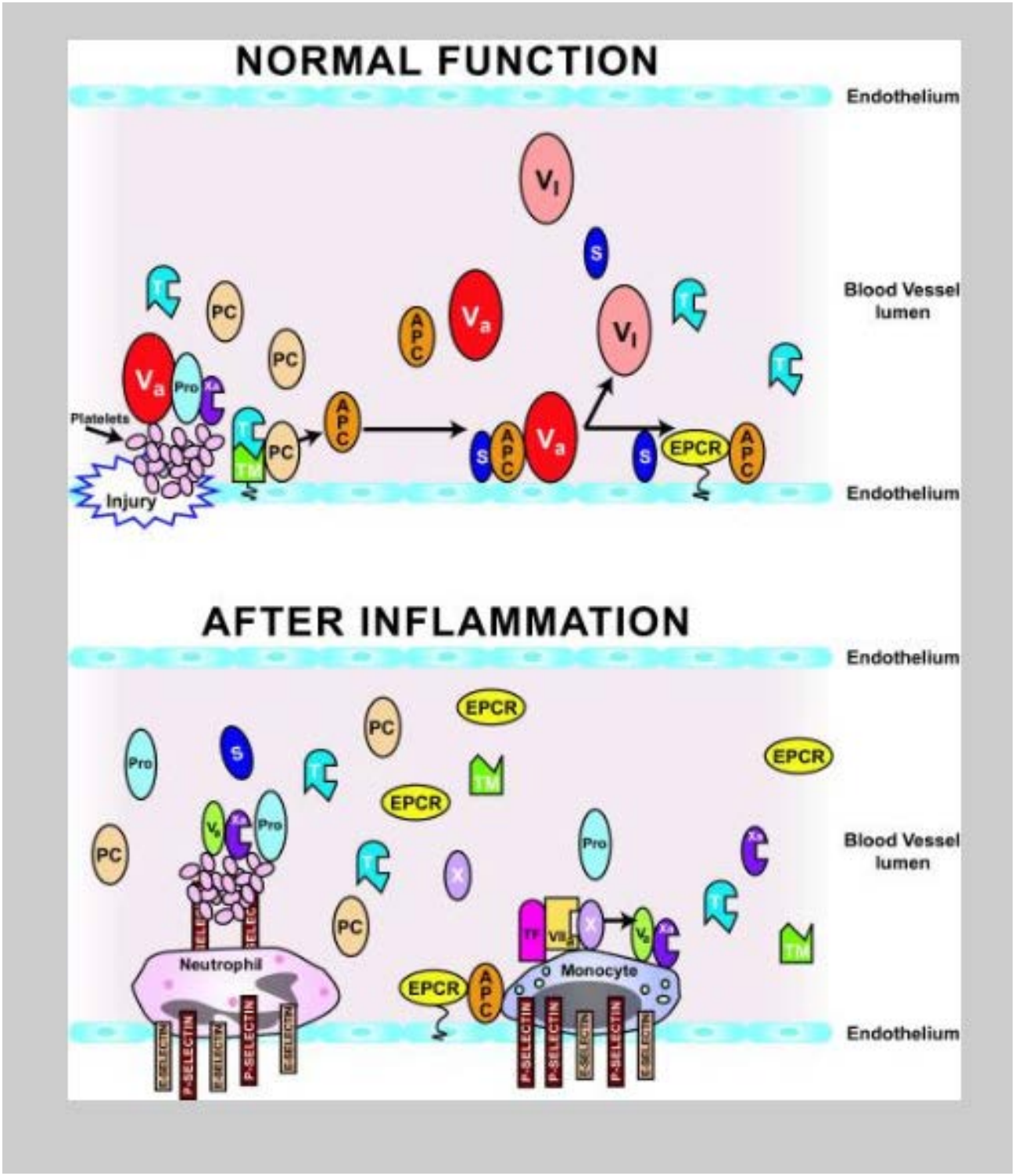


Image 3: Coagulation before and after inflammation

Systemic illnesses may be instrumental in creating the abnormalities of the coagulation system. Virchow's triad of endothelial cell injury, coagulability, and abnormal blood flow is typically present in the illness and leads to reduced blood flow to the organs leading to dysfunction of the system. Cytopathic hypoxia is commonly seen is patients who have been tried on oxygen[55]. In spite of these ongoing studies, not much information is available regarding the actual pathophysiology of sepsis.

Apart from dysfunctional coagulopathy, the following factors are also seen in sepsis;

1) Aberrant Mediator Production

a. Hyperinflammatory Response

b. Blunted Inflammatory Response

c. Unknown Inflammatory Response

2) Cellular Dysfunction

a. Lymphocyte Apoptosis

b. Neutrophil Hyperactivity

c. Endothelial Cell Failure and Apoptosis in Other Cells

3) Metabolic Alterations

a. Glycemic Control

b. Low-Dose Steroids

c. Early Goal-Directed Therapy

The following image shows how the blood picture varies between sepsis and normal state;

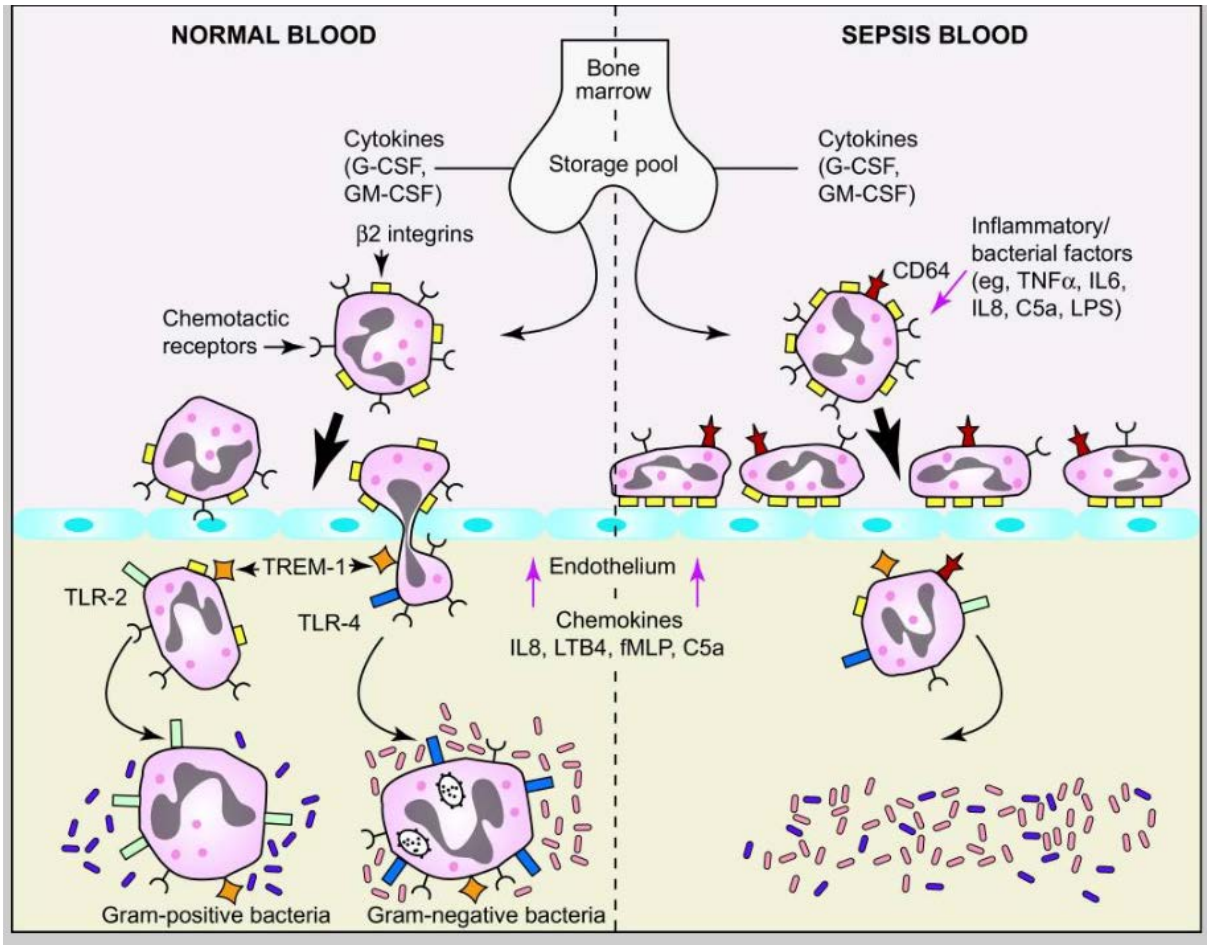


Image 4: Blood picture between sepsis and normal state

The mortality and morbidity in sepsis is very varied and leaves with the following crucial questions even today;

1) How does coagulopathy affect organ injury and mortality of sepsis?

2) Is sepsis a state of immuno-suppression or immuno-expression?

3) Is there a way to improve the survival rate of the patients?

4) What leads to cellular response in sepsis?

5) What is the best management for sepsis?

This understanding of the pathophysiology is essential for planning treatment[56].

Procalcitonin

An overview

Procalcitonin is a hormokine (it is so called due to the hormonal origin of the mature protein) which is a propeptide[22]. The production of this hormokine follows one of the two pathways; classical hormonal expression or, alternatively,a cytokine-like expression pathway. Sometimes, it may be due to a cell mediated host response[23]. It has a long half-life of 25-30 hours[24]. Since 1990s, PCT has been seen as a potential biomarker[25]. In 2003, elevated plasma PCT was included in the updated definition of sepsis[26]. Infection leads to elevated PCT as a part of the complex response of the innate immune system[27]. Increasing serum PCT levels is associated with poor prognosis and decreasing levels is seen as a sign of recovery[28]. PCT levels are diagnostic of systemic bacterial disease[29]. The PCT levels are diagnostic in critically ill patients too[30,31].

There are previous studies that have reported the advantages of using the precursor molecule of calcitonin as a biomarker in sepsis. The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect

sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis[32].

Therefore, PCT may be a suitable as a stanndalone biomarker or in combination with other biomarkers for the following;a) Prediction of sepsis; b) Etiology ; c) Diagnosis; d) Progression; e) Response to treatment; f) Regression

g) Outcomes; h) Prognosis and i) Mortality

Here are the salient features of procalcitonin;

a) It is the peptide precursor for the hormone called calcitonin.

b) Calcitonin is the hormone involved in homeostasis

c) It is an 116-amino acid prohormone

d) It is composed of three peptides[57];

1) 57-amino acid sequence at the amino terminus (NProCT)

2) The centrally positioned immature CT that contains a terminal glycine

3) A 21-amino acid CT carboxyterminus peptide I (CCP-I)

e) These peptides are present in normal persons in their serum

f) Calcitonin has a short half-life of 10 minutes

g) Procalcitonin has a long hald life of 25 to 30 hours[58]

Genetics and Production of Procalcitonin

Parafollicular cells of thyroid produces procalcitonin. Additionally, the neuroendocrine cells of the intestine and lungs also secrete the petide precursor. The gene responsible for the generation of procalcitonin is the (CALC-1) gene on chromosome 11. During an episode of bacterial infection, the additional extrathyroidal tissues of the body starts producing procalcitonin through the increased expression of the PCT-producing calcitonin 1 (CALC-1) gene. The expression of this extrathyroidal PCT-producing calcitonin 1 (CALC-1) gene is suppressed in the absence of infection[59,60]. The PCT that is found in plasma during an infection is mainly produced by the extrathyroidal tissues of the body. The PCT becomes detectable between 2 and 4 hours and peaks in 12 to 24 hours. After the peak levels, it starts declining with a half-life of 1-1½ days[61]. The inflammation related functions of the propeptides are also reduced[62].

. *Procalcitonin and Pathogenesis of Sepsis*

The pathogenesis of sepsis is regulated by ctyokines. The macrophages in the body phagocytose bacteria and lead to the release of a huge number of proinflammatory cytokines. These cytokines stimulates the innate immune system of the body namely;

a. Interleukin (IL)-1β

b. Tumor necrosis factor (TNF)

c. IL-6

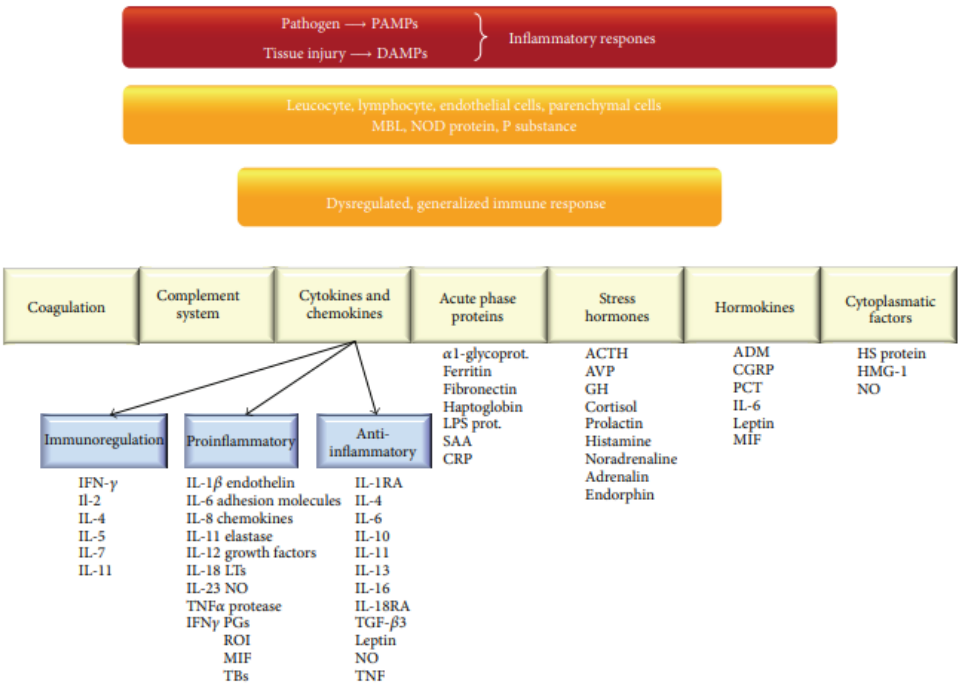


FIGURE 2: The main pillars of systemic inflammatory response. PAMPs: pathogen-associated molecular pattern, DAMPs: damage-associated molecular pattern molecules, MBL: mannose-binding lectin, NOD protein: nucleotide-binding oligomerization domain protein, and NALP: a type a NOD like receptors. For explanation, see text.

Image 5: Systemic Inflammatory Response

These cytokines are biochemically visible and are known to cause sepsis[63].

a. The usefulness of these cytokines have been studied from time to time for their effectiveness in the diagnosis and treatment of sepsis[64].

b. Following biomarkers have been widely studied; Interleukin (IL)-1β, Tumor necrosis factor (TNF), CRP and IL-6

This led to the addition of procalcitonin for the diagnosis of sepsis in 2003 for the updated definition[65]. PCT forms an important component in the pathogenesis of sepsis[66]. The following figure shows the comparison of CRP and PCT.

	CRP	PCT
Differentiating bacterial infection from SIRS	− [27]	Specific for bacteria [28, 29]
Response to infection	Slower (days) [27]	2–6 hours [30]
Peak response after infection	2-3 days [27]	12–48 hours [27]
Half-life	Several days [27]	20–35 hours [31]
Plasma kinetic	Slow [27]	Rapid [27]
Price	+	++++
Correlating disease severity and progression	Slightly [27]	+++ [32]
Correlating effective therapy	+	+++ [33, 34]
Prognostic factor for mortality	Weak or nonexistent [27]	Good predictor [31, 32]
Differentiating G+ from G−	− [35]	++ [35]
Response to other factors	Virus, autoimmune diseases, local infections, surgery, trauma [27]	Surgery, trauma, burn, cardiogenic shock, liver cirrhosis [36–38]
Fungal infection	same as bacterial [35]	Slightly elevated [35]
Immunosuppression	Formation can be changed [27]	The induction is reduced [27]
Biological effect	Opsonin for phagocytosis [27]	Chemokine [27]
Sensitivity/specificity	Sensitive but nonspecific [27]	Sensitive and specific [27, 39]
General use	Outpatient care [27]	In intensive care [27]

Image 6: Comparison between CRP and PCT

Increased PCT is seen in the initial stages of the disease, peaks during admission and gradually declines. Interestingly, the PCT levels tend to resurge if the infection is persisting or the condition is not improving. Also, the PCT reduces when the condition improves giving a better picture of the prognosis. During an episode of bacterial infection, the additional extrathyroidal tissues of the body starts producing procalcitonin through the increased expression of the PCT-producing calcitonin 1 (CALC-1) gene. The PCT that is found in plasma during an infection is mainly produced by the extrathyroidal tissues of the body.

The following image shows how PCT levels vary during infection;

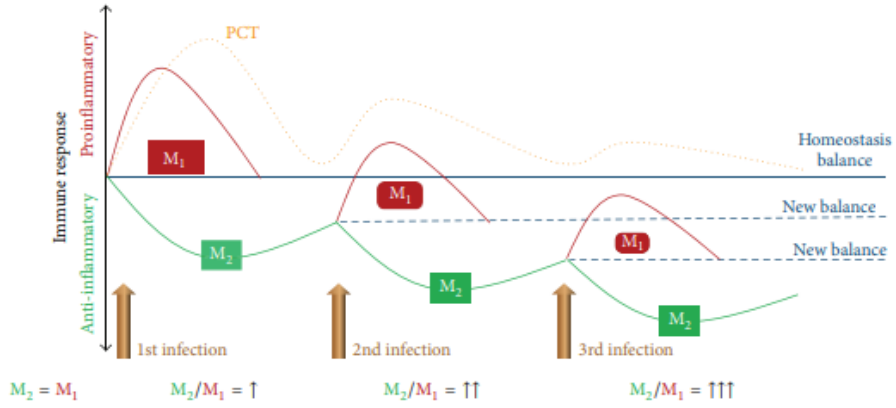


FIGURE 3: Procalcitonin response to consequent infectious insults. During regulated inflammatory response the two phenotypes of macrophages, (M) the proinflammatory (M_1) and anti-inflammatory (M_2), are balanced. As time goes by due to a dysregulated response patients become immunoparalyzed; in other words, M_2 overwhelms M_1; hence, forces are shifted towards "new balance." This is reflected by lower PCT peak levels after each new infectious insult, which can be of the same gravity clinically. For further explanation see text.

Image 7: Variation of PCT levels during infection

The challenge of understanding the role of PCT in sepsis though still remains[67]. PCT is known to amplify the inflammatory cascade which means that it is positively correlated to the severity of infection as well. For instance, if the infection increases, the levels of PCT also increases and decreases when the inflammation subsides[68]. The present literature is devoid of weel designed trials for understanding the role of PCT in sepsis though the usage of PCT in sepsis is increasing. It is being studied if the levels of procalcitonin may point to the risk of developing sepsis.

Procalcitonin as a Diagnosis Marker for Sepsis

The diagnosis of sepsis multipronged with a battery of tests including CRP levels, cytokines (TNF-α, IL-1β, or IL-6) and leukocyte cell count. But these tests are not specific for sepsis which has led to the conquest of looking for a more specific tests.

Here are a number of things that makes PCT as a diagnostic marker;

a. It can differentiate sepsis from infectious and non-infectious causes
b. It is approved by the US FDA for usage in concurrence with other tests
c. It can predict the course of illness
d. PCT can indicate if the patient is going towards septic shock
e. PCT is elevated only in bacterial infections making it ideal for systemic bacterial infections[69]
f. It may show the severity of the illness

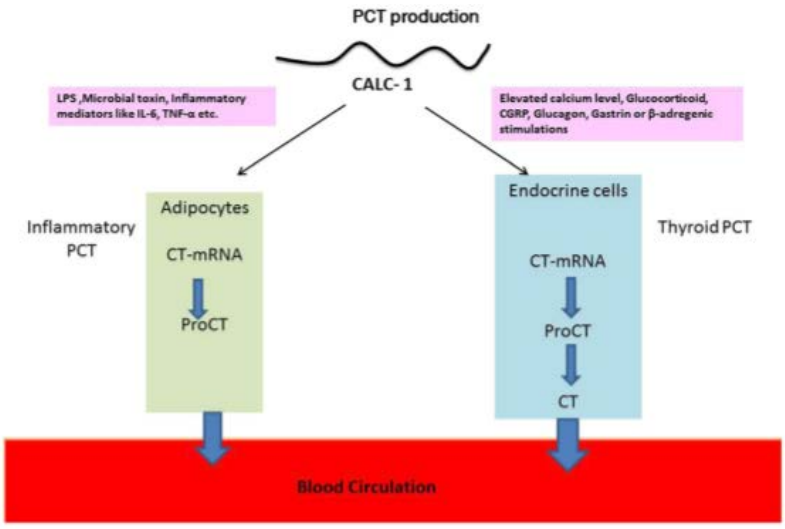


Image 8: PCT in Normal conditions and Sepsis

The reference values are;

Normal reference value= < or =0.15 ng/mL

Values between 0.15 and 2.0 ng/mL may be suggestive of localised infections

Values> 2.0 ng/mL are highly correlated with systemic bacterial infection/sepsis or severe localized bacterial infection[70].

Daily estimations may be an important tool for follow-up[71,72].

Another meta-analysis and systemic review on 30 studies in 2013[73] showed that -

PCT has a mean sensitivity of 0.77 (95% CI 0.72-0.81)

-PCT has a specificity of 0.79 (95% CI 0.74-0.84)

PCT alone is not an effective tool but in collaboration with clinical and laboratory parameters, it appreas to be an effective tool for the diagnosis, management and prognosis of sepsis.

Antibiotic Use

The following image shows the algorithm for treatment based on PCT levels though studies are not adequate to prove the effectiveness of the test.

Image 9: Algorithm for treatment

Need for the study

The recent advancements in the field of molecular biology may aid in screening the biomarkers during the acute phase of sepsis[17]. But these biomakers lack sensitivity and specificity. They have low positive and negative predictive values.

Procalcitonin have aid better in diagnosis and help in prognosis than CRP. Also, it will help differentiate between bacterial and viral meningitis. The gold standard for the confirmation of bacterial infection in sepsis is through blood culture. But the time taken for a bacterial culture is too long to delay treatment. This may lead to a loss of golden time.

Infection leads to elevated PCT as a part of the complex response of the innate immune system[27]. Increasing serum PCT levels is associated with poor prognosis and decreasing levels is seen as a sign of recovery. PCT levels are diagnostic of systemic bacterial disease. The PCT levels are diagnostic in critically ill patients too.

There are previous studies that have reported the advantages of using the precursor molecule of calcitonin as a biomarker in sepsis. The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect

sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis.

The present study aims to study the effectiveness of procalcitonin as an useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients.

MATERIALS AND METHODS

Materials and Methods

Aims and objectives of the study:

To study the effectiveness of procalcitonin as an useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients.

Study design

Prospective Single Center Study

Place of study

GMKMC hospital

Study period

July 2017 to June 2019

Study population & Sampling Methodology

- Cases admitted to GMKMC hospital Salem with signs of sepsis in SICU patients will be closely monitored from the day of admission to the day of discharge.
- The patients with signs of sepsis admitted in SICU between 2017-2019 were chosen.
- This study includes 100 patients presenting with signs of sepsis.

Inclusion criteria:

- All the patients with signs of sepsis admitted in SICU.

Exclusion criteria:

- Patients not Willing For Study
- Patients with known comorbid conditions at the time of admission (PLHIV, on ATT drugs, Carcinoma)

Methodology

The following data was collected using a structured questionnaire: age,demographic characteristics, socio economic status, patients complaints and duration of complaints. A detailed general examination was done. Systemic examination and basic investigations were done.

Investigations

Following specific investigations were done;

a) Serum Procalcitonin at the time of;

- Diagnosis of sepsis

- On day 5

- On day 10

- and more if required

Laboratory Methods

Serum Procalcitonin level detection by ELISA:

All the 100 samples were tested for Procalcitonin using ELISA with the help of HUMAN PROCALCITOIN ELISA KIT (SINCERE BIOTECH, Beijing, China).

Statistical Analysis

Data were analyzed according to history, clinical examination and investigation. Data were entered in excel sheet and analyzed using SPSS v23. Frequencies and percentage analysis were done. Cross tabulation and Chi-square analyses were done to find the relationship and association between various variables.

RESULTS

RESULTS

A prospective study on Procalcitonin as a useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients revealed the following findings.The mean age is 57.06 years with a standard deviation of 9.39 years. The median age is 56 years ranging between 38 years and 74 years. The majority of the participants were males (n=56, 56%) while the rest were females. Out of the 100 patients, 76 of them (76%) were blood culture positive while the remaining 24% were blood culture negative. Out of the 100 patients, 68 of them (68%) were pus culture positive while the remaining 32% were pus culture negative. Out of the 100 patients, 80 of them (80%) were urine culture positive while the remaining 20% were urine culture negative. Out of the 100 patients, 66 of them (66%) were wound swab positive while the remaining 34% were wound swab negative. Out of the 100 patients, 42 of them (42%) were Klebsiella positive while 34 of them (34%) were E.coli positive. Pseudomonas was positive in 14% (n=14) of them while Proteus was present in 8% (n=8) of them.The organisms were sensitive to Piptaz (n=50, 50%) and Cefaperazone (n=48, 48%).CRP was positive in 47% of the cases and negative in 53% of the cases. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU.

Age

The following table and figure shows the age distribution of the participants. The mean age is 57.06 years with a standard deviation of 9.39 years. The median age is 56 years ranging between 38 years to 74 years.

Characteristics	Age (years)
Mean	57.06
Median	56
Mode	47
Standard Deviation	9.39
Minimum	38
Maximum	74

Table 1: Age distribution of the participants

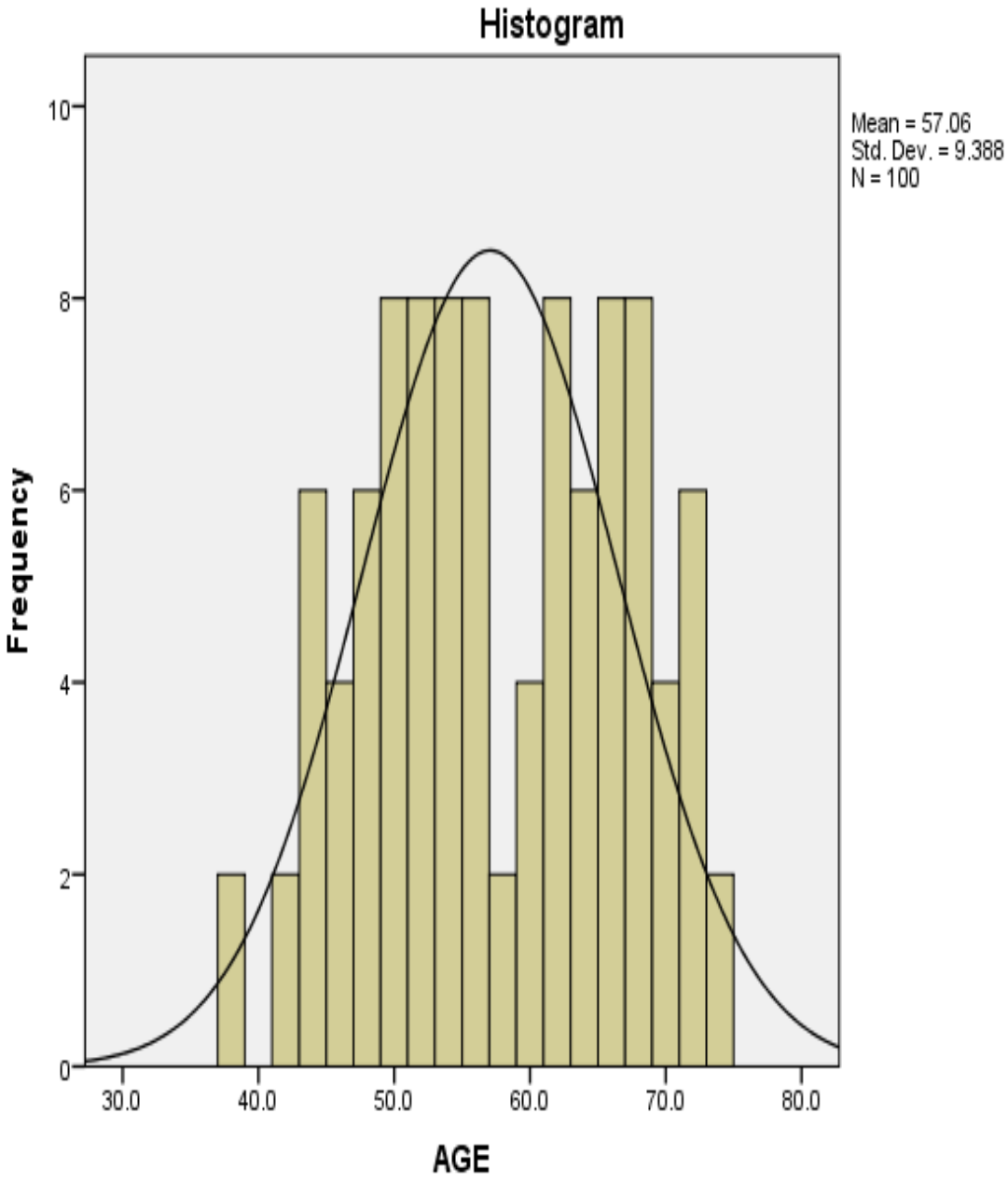


Figure 1: Age distribution of the participants

Gender

The majority of the participants were males (n=56, 56%) while the rest were females. The following table and figure shows the gender distribution of the patients.

Gender	Frequency	Percentage
Male	56	56
Female	44	44

Table 2: Gender distribution of the participants

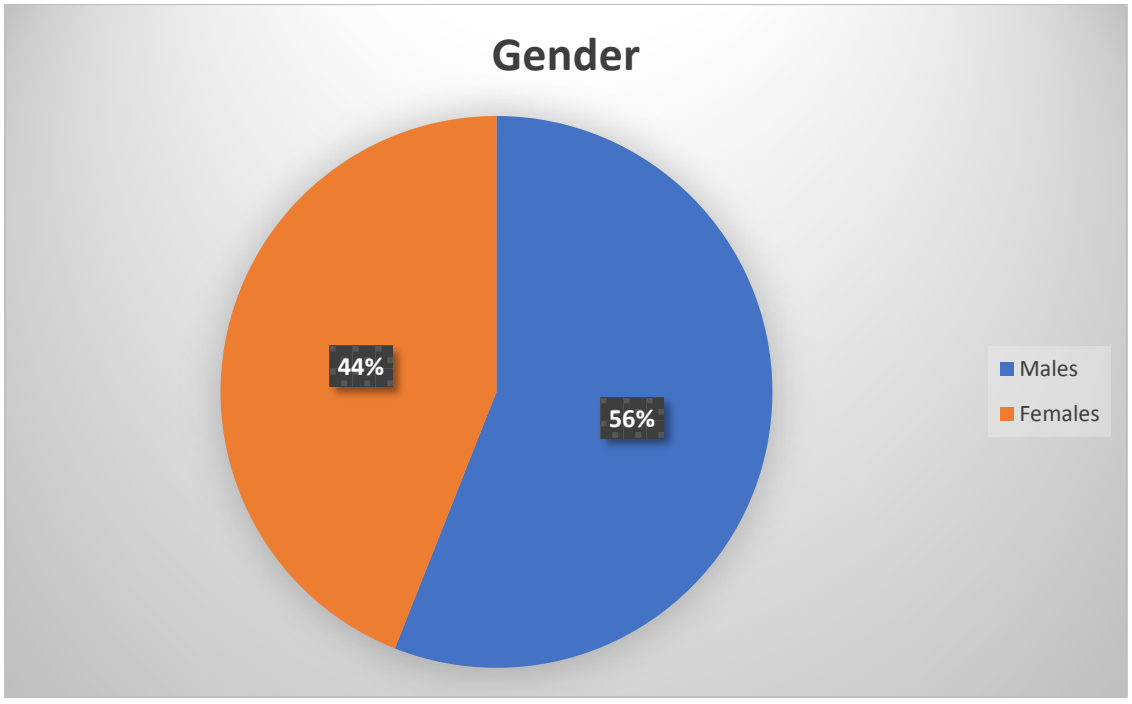


Figure 2: Gender distribution of the patients

Blood culture sensitivity

Out of the 100 patients, 76 of them (76%) were blood culture positive while the remaining 24% were blood culture negative. The following table and figure shows blood culture and sensitivity.

Blood Culture and Sensitivity	Frequency	Percentage
Positive	76	76
Negative	24	24

Table 3: Blood Culture Sensitivity

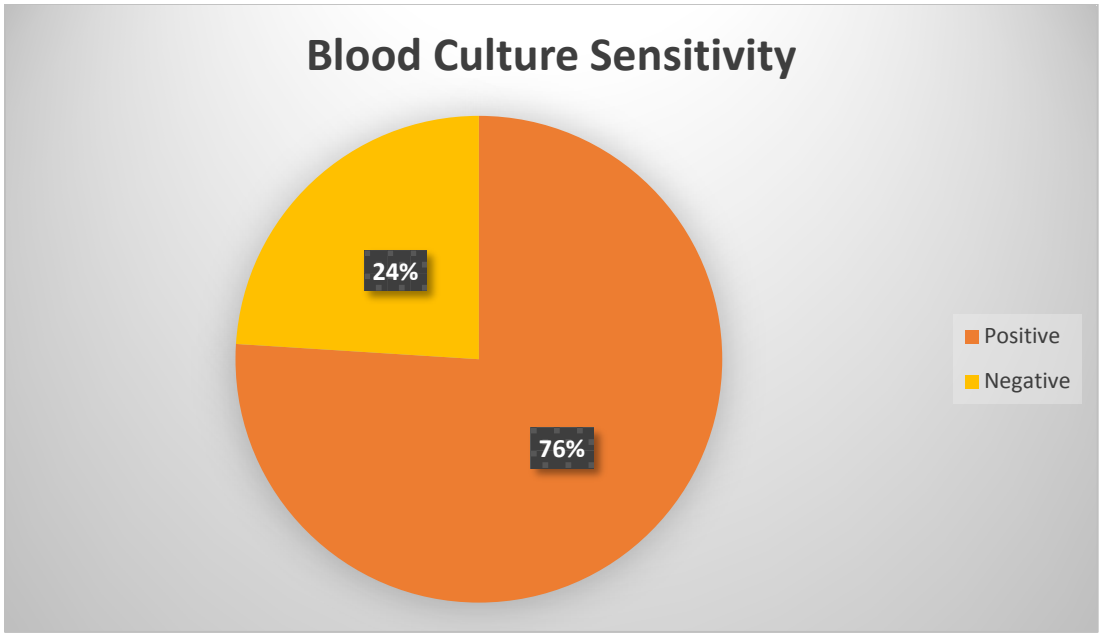


Figure 3: Blood Culture Sensitivity

Pus culture sensitivity

Out of the 100 patients, 68 of them (68%) were pus culture positive while the remaining 32% were pus culture negative. The following table and figure shows pus culture and sensitivity.

Pus Culture and Sensitivity	Frequency	Percentage
Positive	68	68
Negative	32	32

Table 4: Pus Culture Sensitivity

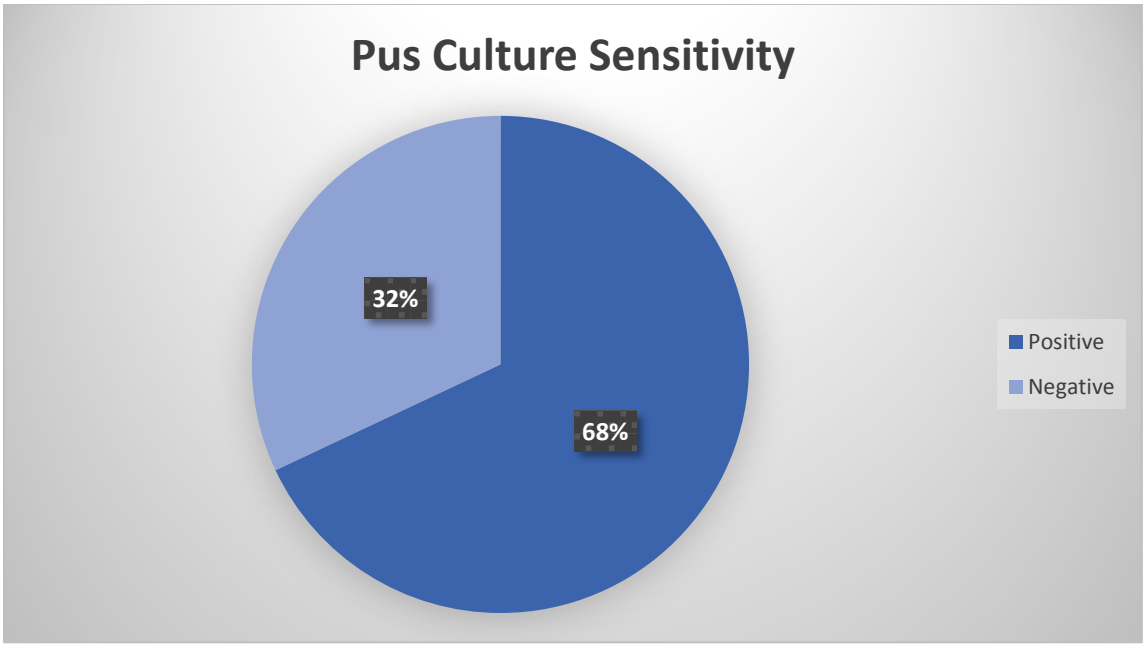


Figure 4: Pus Culture Sensitivity

Urine culture sensitivity

Out of the 100 patients, 80 of them (80%) were urine culture positive while the remaining 20% were urine culture negative. The following table and figure shows urine culture and sensitivity.

Urine Culture and Sensitivity	Frequency	Percentage
Positive	80	80
Negative	20	20

Table 5: Urine Culture Sensitivity

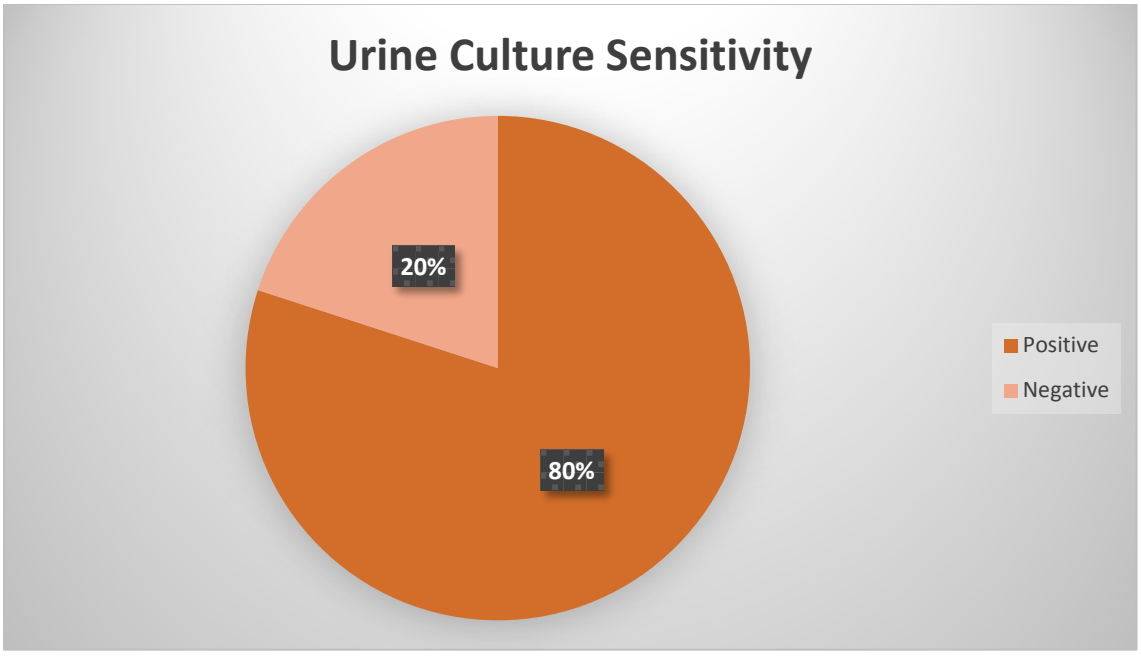


Figure 5: Urine Culture Sensitivity

Wound Swab

Out of the 100 patients, 66 of them (66%) were wound swab positive while the remaining 34% were wound swab negative. The following table and figure shows wound swab results.

Wound Swab	Frequency	Percentage
Positive	66	66
Negative	34	34

Table 6: Wound Swab

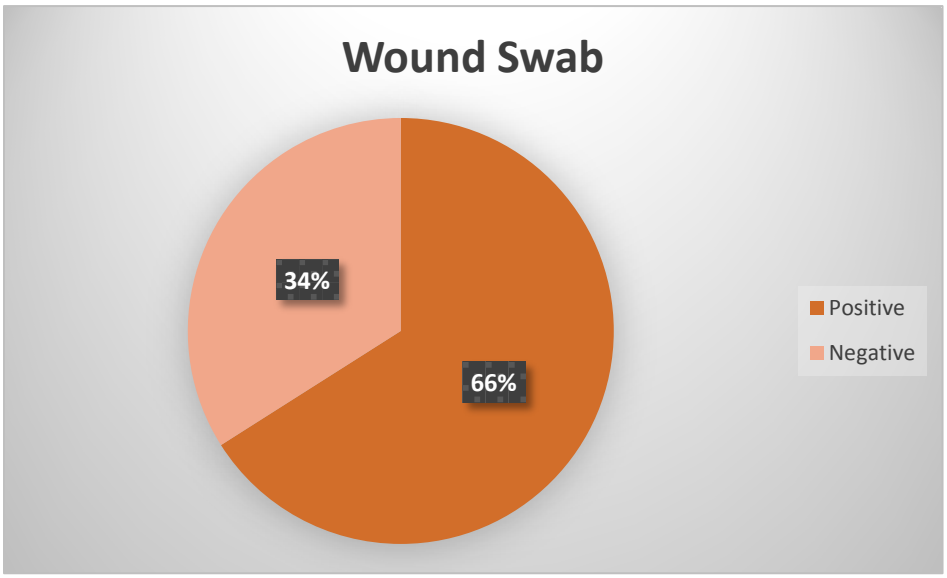


Figure 6: Wound Swab

Organism

Out of the 100 patients, 42 of them (42%) were Klebsiella positive while 34 of them (34%) were E.coli positive. Pseudomonas was positive in 14% (n=14) of them while Proteus was present in 8% (n=8) of them. The following table and figure shows the organism identified in the cultures.

Organism	Frequency	Percentage
ACINETOBACTER	2	2
E.COLI	34	34
KLEBSIELLA	42	42
PROTEUS	8	8
PSEUDOMONAS	14	14

Table 7: Organism isolated from the cultures

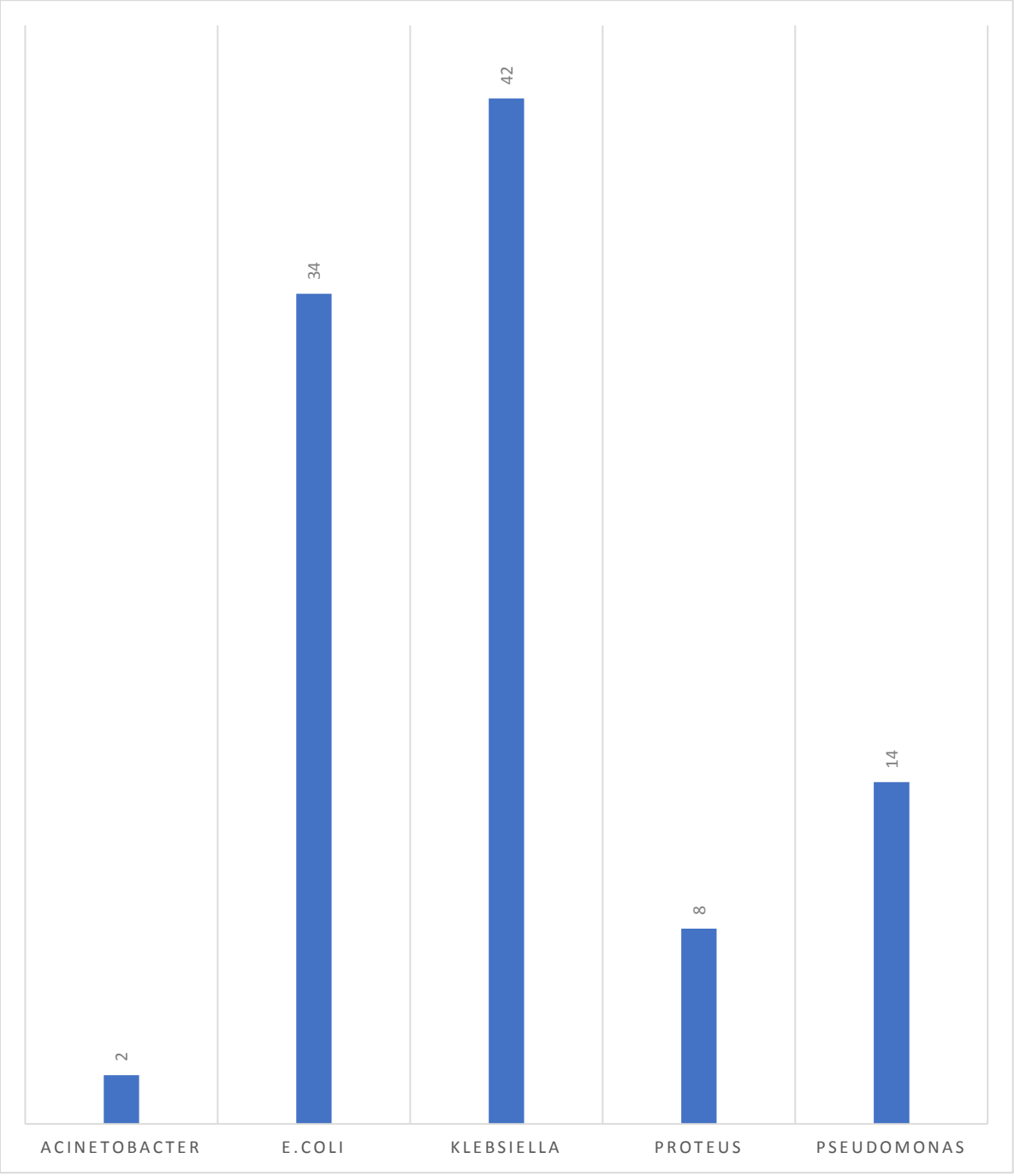


Figure 7: Organism isolated from the cultures

Antibiotic Sensitivity

The organisms were sensitive to Piptaz (n=50,50%) and Cefaperazone (n=48, 48%). The following table figure shows the antibiotic sensitivity.

Antibiotic Sensitivity	Frequency	Percentage
CEFAPERAZONE	48	48
MEROPENEM	2	2
PIPTAZ	50	50

Table 8: Antibiotic Sensitivity

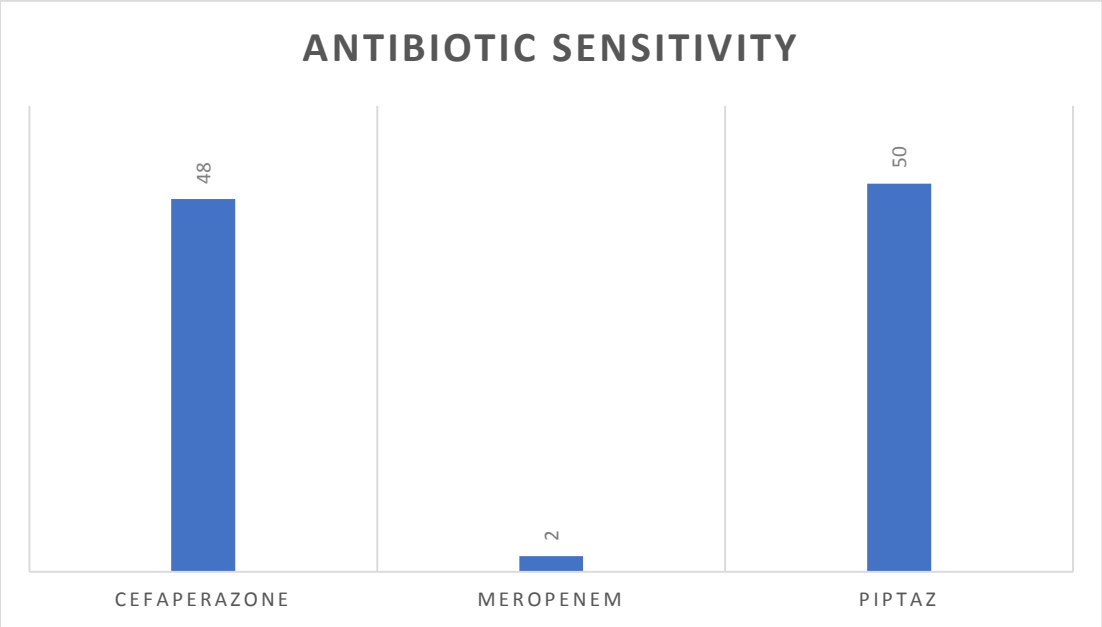


Figure 8: Antibiotic Sensitivity

Antibiotic Course

The duration of antibiotics is mean=5.45 days (S.D=1.28 days). Median is five days range between 5 and 11 days. Following table and figure shows the duration of antibiotics.

Characteristics	Antibiotic Course (Days)
Mean	5.45
Median	5
Mode	5
Standard Deviation	1.28
Minimum	5
Maximum	11

Table 9: Duration of antibiotics

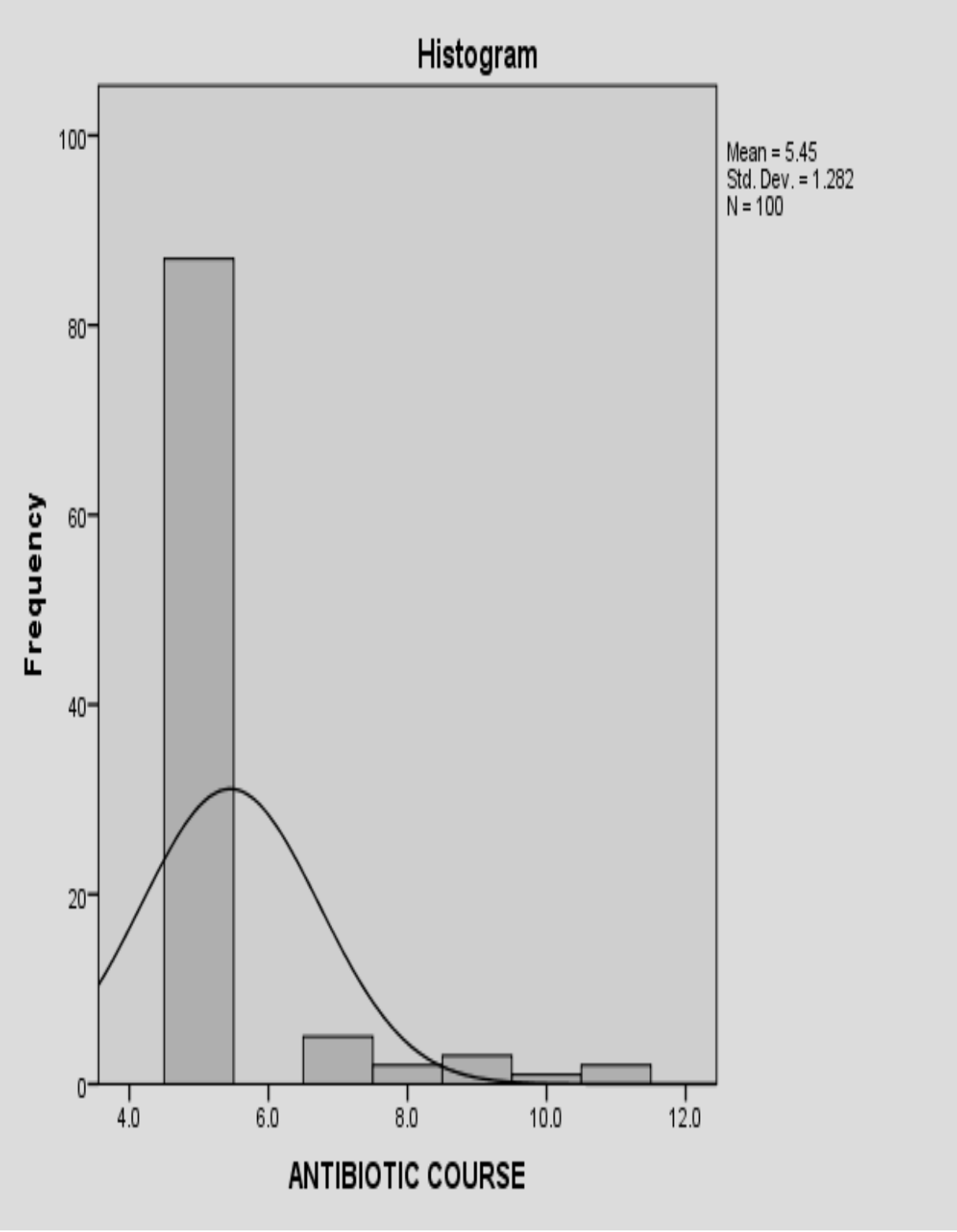


Figure 9: Duration of antibiotics

C-Reactive Protein

CRP was positive in 47% of the cases and negative in 53% of the cases. The following table figure shows the CRP in patients.

CRP	Frequency	Percentage
Positive	47	47
Negative	53	53

Table 10: C-Reactive Protein

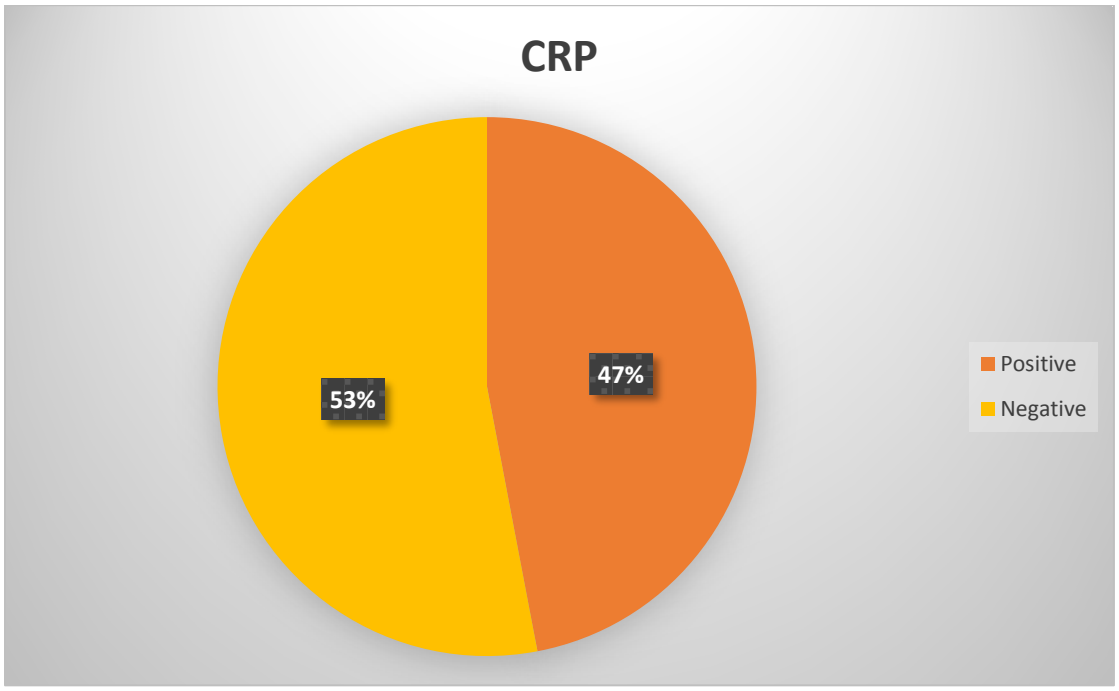


Figure 10: C-Reactive Protein

Procalcitonin on day 0 and 5

The Procalcitonin levels were elevated in all patients in Day 0 and decreased to 13% on Day 5. The following figure shows the Procalcitonin.

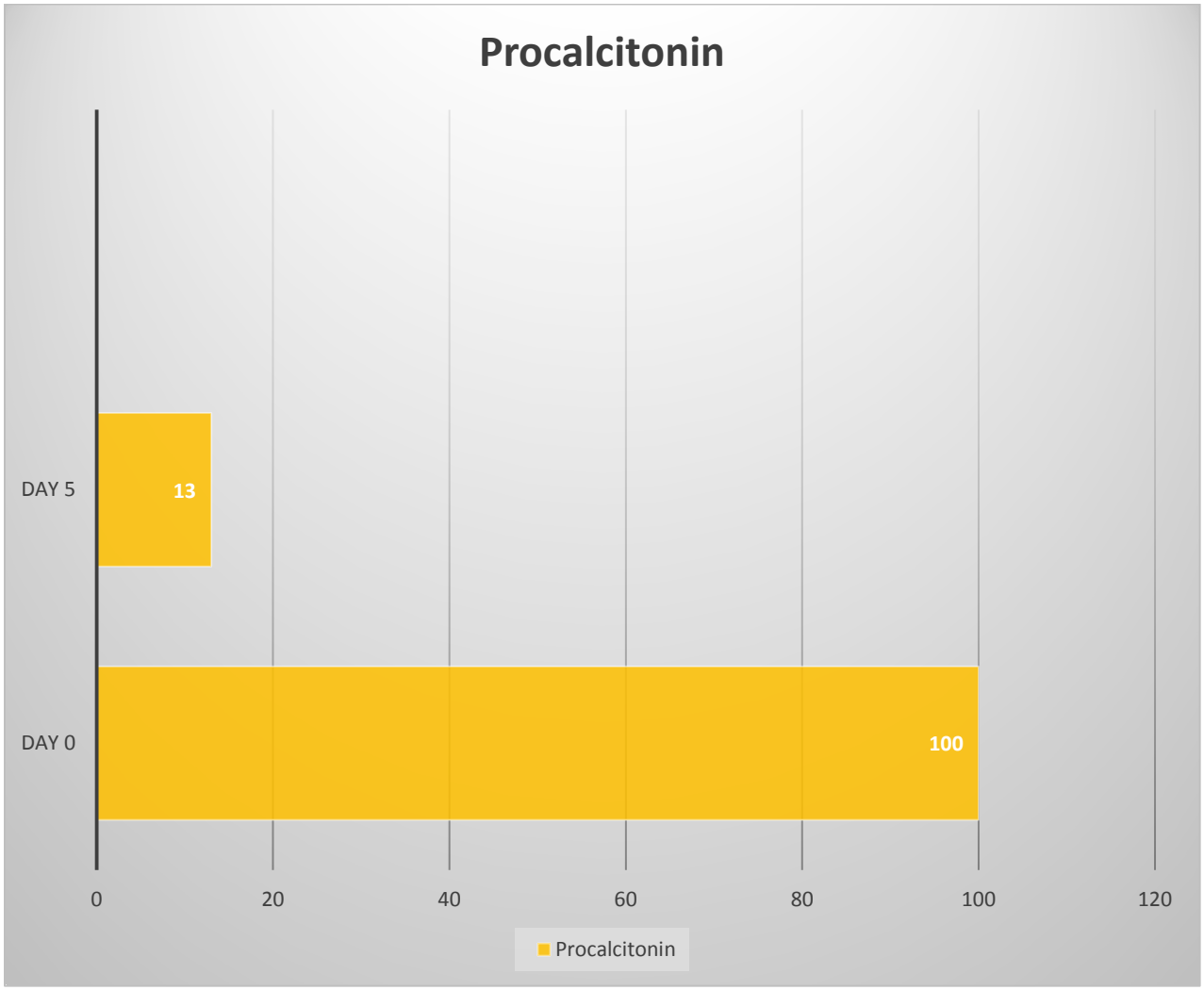


Figure 11: Procalcitonin levels on day 0 and 5

Duration of stay in the hospital

The mean duration of stay in the hospital is six days with a standard deviation of 1.15 days ranging between 5 and 11 days. The following figure shows the duration of stay in the hospital.

Characteristics	Duration of stay (days)
Mean	6.06
Median	6
Mode	6
Standard Deviation	1.15
Minimum	5
Maximum	11

Table 11: Duration of stay in the hospital

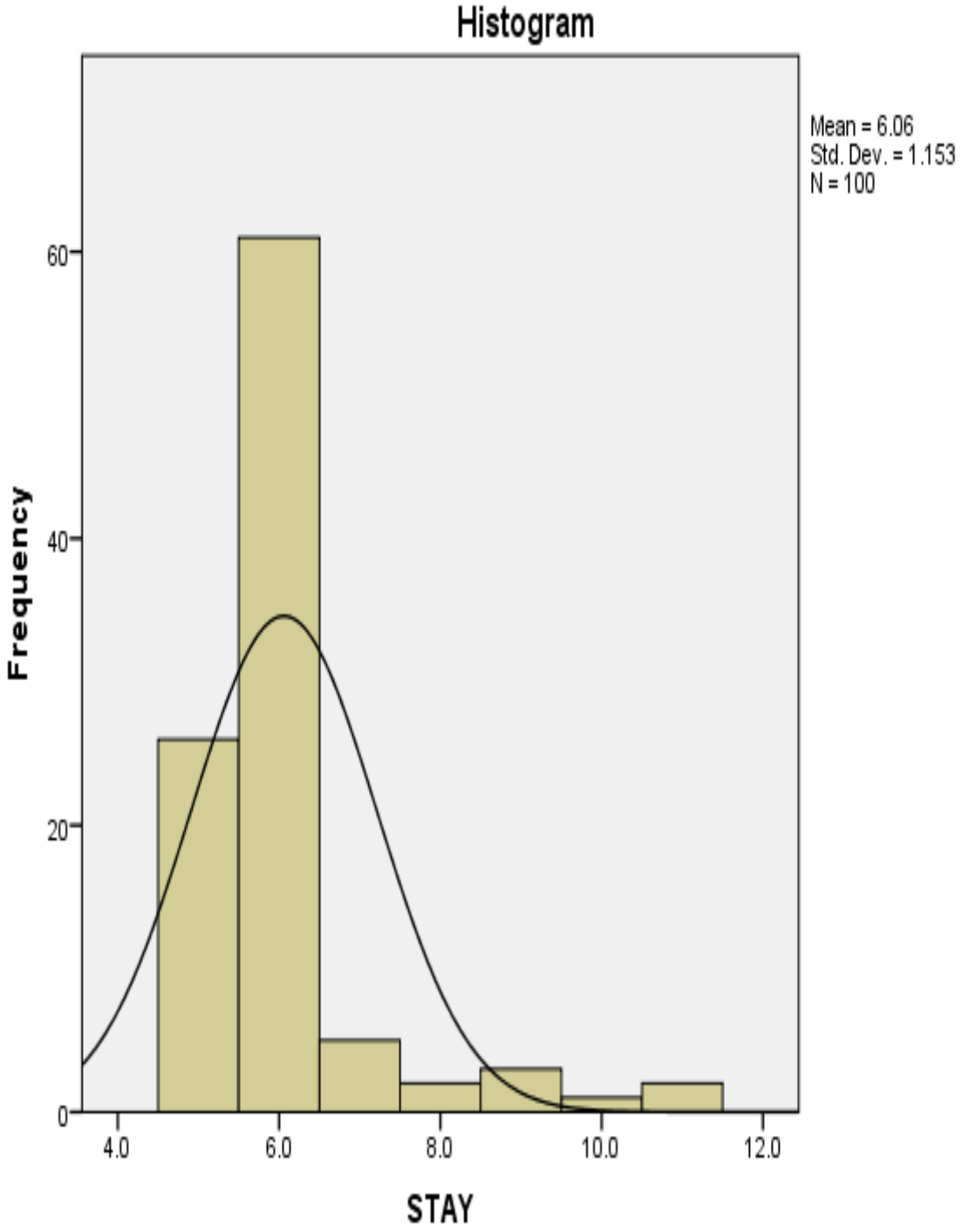


Figure 12: Duration of stay in the hospital

Outcome of the illness

Out of 100 patients, 87 were cured and 13 of them expired. Following figure shows the outcome of the illness.

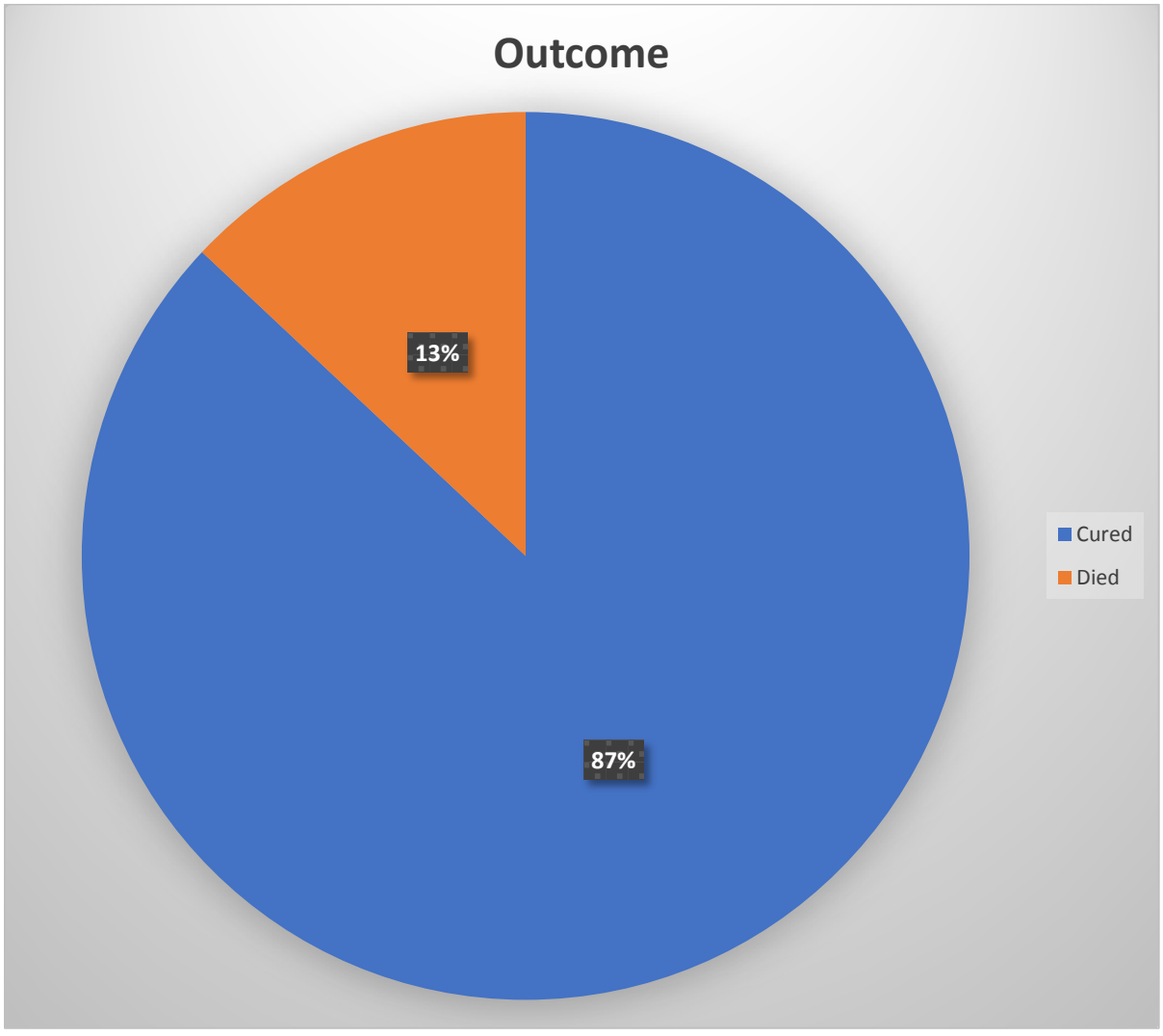


Figure 13: Outcome of the illness

Sensitivity and Specificity of Procalcitonin test

The following table shows the sensitivity and specificity of Procalcitonin in predicting the prognosis in patients of surgical ICU. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU.

Sensitivity and Specificity of Procalcitonin	Frequency/ Percentage
No. of true-positive findings	13
No. of true-negative findings	87
No. of false-positive findings	0
No. of false-negative findings	0
Sensitivity (%)	100
Specificity (%)	100
Accuracy (%)	100
Positive predictive value (%)	100
Negative predictive value (%)	100

Table 12: Sensitivity and Specificity of Procalcitonin test

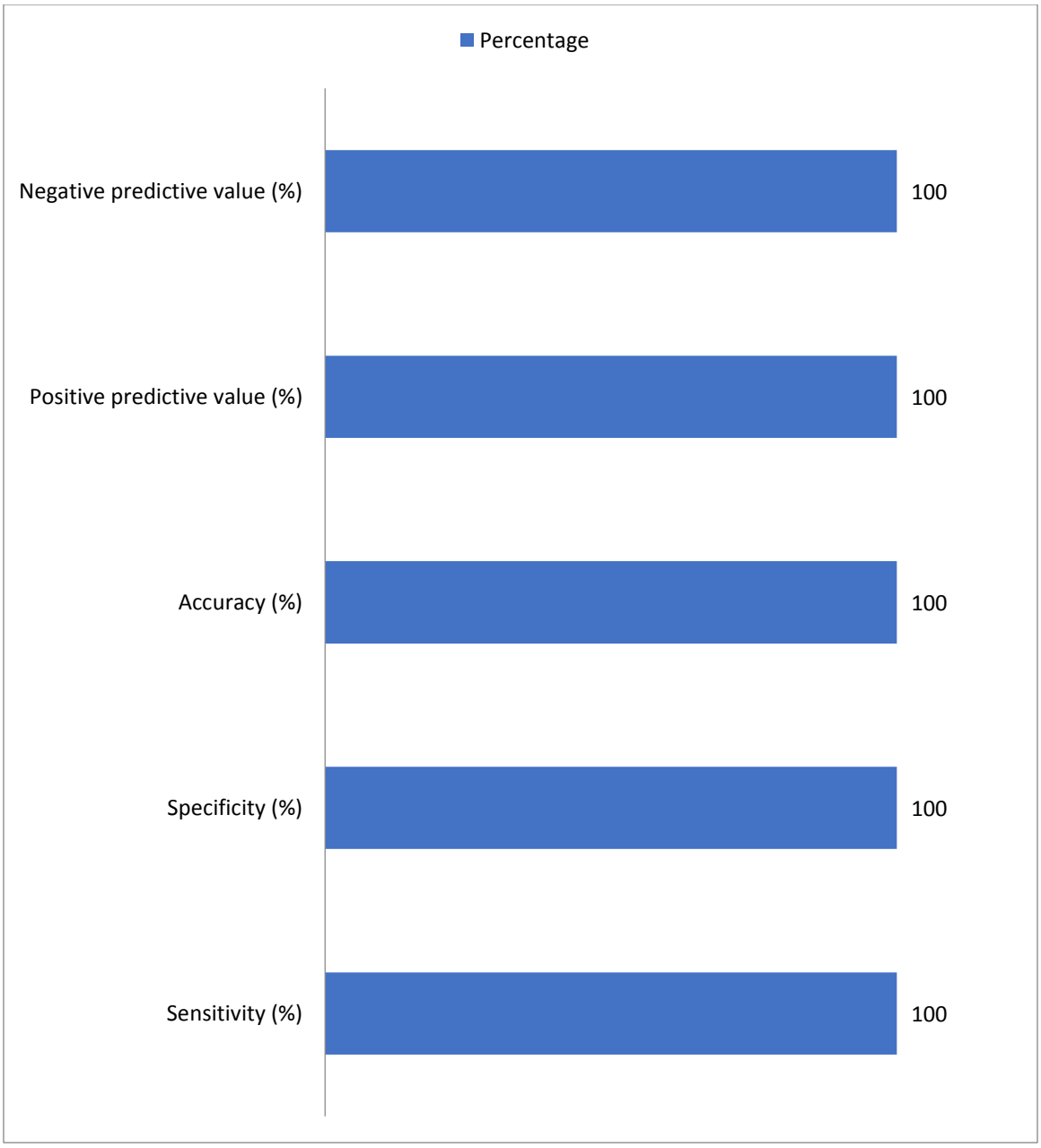


Figure 14: Sensitivity and Specificity of Procalcitonin test

DISCUSSION

Discussion

A prospective study on Procalcitonin as a useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients revealed the following findings.The mean age is 57.06 years with a standard deviation of 9.39 years. The median age is 56 years ranging between 38 years and 74 years. The majority of the participants were males (n=56, 56%) while the rest were females. Out of the 100 patients, 76 of them (76%) were blood culture positive while the remaining 24% were blood culture negative. Out of the 100 patients, 68 of them (68%) were pus culture positive while the remaining 32% were pus culture negative. Out of the 100 patients, 80 of them (80%) were urine culture positive while the remaining 20% were urine culture negative. Out of the 100 patients, 66 of them (66%) were wound swab positive while the remaining 34% were wound swab negative. Out of the 100 patients, 42 of them (42%) were Klebsiella positive while 34 of them (34%) were E.coli positive. Pseudomonas was positive in 14% (n=14) of them while Proteus was present in 8% (n=8) of them.The organisms were sensitive to Piptaz (n=50, 50%) and Cefaperazone (n=48, 48%).CRP was positive in 47% of the cases and negative in 53% of the cases. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU.

Sepsis is a very serious and challenging disease in critical care medicine that can be of graded variety namely; from sepsis to severe sepsis and septic shock. The

challenges arise from the heterogeneity of the presentation in terms of incidence and symptomatology. This leads to diagnostic confusion in designing the diagnostic and treatment algorithm. Also, the variance in etiology and severity adds constraints to the existing framework. So, developing an universal algorith for the diagnosis and management of sepsis is a challenge. This explains why it is not possible to do randomised control trials for studying sepsis. Multicentric trials have contraindicated the findings of previous studies[33]. Sepsis is multifactorial in origion requiring multidisciplinary approach to management. Economic issues form a separate facet of this illness. Early identification, diagnosis and treatment is necessary for survival and good prognosis. The task of management starts right from outside the hospital and follows into the emergency departments and then later on into the wards. Any amount of intensive case management is useless without the initial management. In spite of the lack of well designed randomised trials for sepsis, the sporadic studies have given great insight into the incidence, epidemiology and the pathophysiology of the illness. The immunological background of the illness is essential for diagnosis, managment and prognosis.

A systemic infection evokes a strong response from the immune system which is called as sepsis. In around one-third of the cases, the etiology of the infection is unknown. Evolution has handed the human race a great gift of mounting an immune response to an infection, which is otherwise called as host responses. The

defence mechanisms are complex and respond in different ways to various invasive pathogenic organisms. One of the earliest responses to an microbial infection is the development of the inflammatory response that happens like a cascade involving a huge number of biochemical messengers. Increased microbial load is correlated with increased mortality. The severity is determined by the number of the microbes which is referred to the microbial load and also if there are more than one type of microorganism, then severity proportionately increases leading to increased morbidity and mortality.

The source of infections are very important to note as they may dictate the severity of the illness, the morbidity. pharmacological protocol, management decisions, prognosis, outcome and mortality. Following sources are generally associated with sepsis;Acquired from community, Hopsitals and Other healthcare facilities.

Around 18 million new cases of sepsis are reported each year. The global mortality rate is between 30% and 50%[7].A study on the pattern of the intensive care cases found that the prevalence of sepsis is India is not infrequent. Around 28.3% of the patients admitted in the intensive care unit acquire sepsis, out of which, there is a mortality rate of 34%[8]. Though sepsis can be caused by any of the microbes namely; bacteria, virus, parasites and fungi, yet bacteria is the most common etiologic agent for the infection and development into a full blown sepsis. The infection can start from anywhere in the body and the microorganisms enter the

blood. They start multiplying in the blood and start releasing factors of virulence into the blood[12]. The blood houses monocytes, macrophages, neutrophils, endothelial cells and plasma cell precursors which get stimulated by these virulent factors. They release the mediators of sepsis that are endogenous in origin.

The entry of the microorganisms stimulates the endogenous mediators that acts on the immune system. The immune system in turn elaborates a response in defence to neutralise the pathogens. This leads to the secretion of inflammatory proteins that can damage the tissues and organs of the host.

The clinical symptoms of sepsis are namely;Tachycardia, Tachypnea, Elevated temperature and Leucocytosis. When the sepsis is severe, there is hypoperfusion and damage of atleast one organ. If this progresses, it leads to shock. Sometimes, multiple organs are involved known as MODS (Multiple Organ Dysfunction Syndrome). If this is associated with hypotension, it is known as septic shock.

The outcome of the illness largely depends on the time of diagnosis and initiation of prompt treatment. When the diagnosis or treatment is delayed due to any reason, the outcome and prognosis is very poor and may affect all the organs, a condition called as the Systemic Inflammatory Response Syndrome (SIRS). Early initiation on antimicrobial therapy is crucial in getting a better outcome.

Since the emphasis lies on early diagnosis, there are various attempts to understand if there is a way to find out the onset of sepsis before the clinical signs become evident.

The recent advancements in the field of molecular biology may aid in screening the biomarkers during the acute phase of sepsis[17]. But these biomakers lack sensitivity and specificity. They have low positive and negative predictive values[18].

Procalcitonin have aid better in diagnosis and help in prognosis than CRP. Also, it will help differentiate between bacterial and viral meningitis[19]. The gold standard for the confirmation of bacterial infection in sepsis is through blood culture. But the time taken for a bacterial culture is too long to delay treatment. This may lead to a loss of golden time[20].

Mortality rate continues to be high despite the latest advancements in healthcare sector. The reduction of morbidity and mortality depends on the early recognition and treatment of sepsis. The diagnostic uncertainty of sepsis proves to be challenging even today though clinical signs are evident. This mandates the presence of serum biomarkers like Procalcitonin that may help in early diagnosis and management.

Procalcitonin is a hormokine (it is so called due to the hormonal origin of the mature protein) which is a propeptide[22]. The production of this hormokine follows

one of the two pathways; classical hormonal expression or, alternatively,a cytokine-like expression pathway. Sometimes, it may be due to a cell mediated host response[23]. It has a long half-life of 25-30 hours[24].

Since 1990s, PCT has been seen as a potential biomarker[25].

Here are a number of things that makes PCT as a diagnostic marker and can be used as a guide for antibiotic therapy;

a. It can differentiate sepsis from infectious and non-infectious causes
b. It is approved by the US FDA for usage in concurrence with other tests
c. It can predict the course of illness
d. PCT can indicate if the patient is going towards septic shock
e. PCT is elevated only in bacterial infections making it ideal for systemic bacterial infections[69]
f. It may show the severity of the illness

Daily estimations may be an important tool for follow-up[71,72].

Another meta-analysis and systemic review on 30 studies in 2013[73] showed that -

PCT has a mean sensitivity of 0.77 (95% CI 0.72-0.81)

-PCT has a specificity of 0.79 (95% CI 0.74-0.84)

Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU in this study.

PCT alone is not an effective tool but in collaboration with clinical and laboratory parameters, it appreas to be an effective tool for the diagnosis, management and prognosis of sepsis.

In 2003, elevated plasma PCT was included in the updated definition of sepsis[26]. Infection leads to elevated PCT as a part of the complex response of the innate immune system[27]. Increasing serum PCT levels is associated with poor prognosis and decreasing levels is seen as a sign of recovery[28]. PCT levels are diagnostic of systemic bacterial disease[29]. The PCT levels are diagnostic in critically ill patients too[30,31].

There are previous studies that have reported the advantages of using the precursor molecule of calcitonin as a biomarker in sepsis. The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis[32].

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

A prospective study on Procalcitonin as a useful biomarker for prognosis of sepsis and guide for antibiotic therapy in SICU patients revealed the following findings.

CRP was positive in 47% of the cases and negative in 53% of the cases. Procalcitonin is 100% sensitive and specific in predicting the prognosis in patients of surgical ICU.

Infection leads to elevated PCT as a part of the complex response of the innate immune system. Increasing serum PCT levels is associated with poor prognosis and decreasing levels is seen as a sign of recovery. PCT levels are diagnostic of systemic bacterial disease. The PCT levels are diagnostic in critically ill patients too.

The levels of procalcitonin in sepsis rises rapidly and tends to peak sooner than CRP. They also return to baseline sooner in response to treatment. Either ways, procalcitonin can be used to detect sepsis and also the response to treatment. This is why, it is an ideal candidate as a biomarker in sepsis.

LIMITATIONS

Limitations

1) The study of biomarkers requires a larger sample size and longer follow-up. The present study has a smaller sample size and a shorter duration of study
2) This is a single center study which limits the generalizability of the results
3) The use of biomarkers is still underrated in clinical research due to lack of resources

FUTURE

RECOMMENDATIONS

Future Recommendations

Following are the recommendations from the study;

1) Use of biomarkers for making clinical decisions should be encouraged. This necessitates adequate amount of data to validate the findings
2) A larger sample size should be studied for generalizability of the results/
3) A multi centric study should be done for validation of the findings
4) Biomarkers are potential diagnostic and prognostic tools for clinical practice and their research must be promoted in regular clinical practice

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ANNEXURES

PATIENT CONSENT FORM

STUDY TITLE:

"PROSPECTIVE STUDY ON PROCALCITONIN AS USEFUL BIOMARKER FOR PROGNOSIS OF BACTERIAL INFECTION AND GUIDE FOR ANTIBIOTIC THERAPY IN SICU PATIENTS"

Department of General surgery, GMKMCH

PARTICIPANT NAME : AGE : SEX: I.P. NO :

I confirm that I have understood the purpose of surgical/invasive procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during and after medical/ surgical procedure. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study for various surgical/invasive procedures and their outcomes.

Time :

Date : Signature / Thumb Impression Of Patient

Place :

Patient's name:

Signature of the investigator: _____

Name of the investigator : _____

“A PROSPECTIVE STUDY ON PROCALCITONIN AS USEFUL BIOMARKER FOR PROGNOSIS OF BACTERIAL INFECTION AND GUIDE FOR ANTIBIOTIC THERAPY IN SICU PATIENTS”

PROFORMA

A.

Name:

Address:

Age/sex:

RELIGION:

O.PNo:

I.P No:

D.O.A:

DATE OF OPERATION:

D.O.D:

B. CHIEF COMPLAINTS:

Duration of symptoms:

C.**PAST HISTORY:**

1. DM : Yes/ No
2. TB : Yes/ No
3. EPILEPSY
4. MALARIA
5. PREVIOUS SURGERY
6. JAUNDICE
7. CIRRHOSIS

D.**PERSONAL HISTORY:**

SMOKER

ALCOHOLIC

E.**INITIAL ASSESSMENT OF PATIENT**

1.Vitals:

PR :

BP :

RR :

Temperature :

2.GENERAL SIGNS:

Pallor

Tongue

Skin

Icterus

Cyanosis

Lymphadenopathy:

K.SYSTEMIC EXAMINATION:

CVS

RS

CNS

Abdomen:

LOCAL EXAMINATION :

CLINICAL DIAGNOSIS

INVESTIGATIONS

A. HB%
B. GROUPING & TYPING
C. BT/CT
D. PC
E. HIV
F. ECG
G. URINE:

Culture

Albumin

Sugar

H. BLOOD:

RBS

BLOOD UREA

SER.CREATININE

CULTURE

I.SERUM PROCALCITONIN

DAY 0:

DAY 5:

DAY 10:

J.PUS CULTURE AND SENSITIVITY

ANESTHESIA:

SURGICAL PROCEDURE:

COMPLICATIONS:

OUTCOME OF TREATMENT:

1.IMPROVEMENT

2.WORSENING OF DISEASE

3.MULTI ORGAN FAILURE

4.DEATH

KEY TO MASTER CHART

M-MALE

F- FEMALE

CRP- C-REACTIVE PROTIEN

C/S- CULTURE AND SENSITIVITY

-VE- NEGATIVE

+VE- POSITIVE

S. NO	AGE	SEX	BLOOD C/S	PUS C/S	URINE C/S	WOUND SWAB	ORGANISM	SENSITIVE ANTIBIOTIC	CRP	PROCALCITONIN ON DAY 0	PROCALCITONIN ON DAY 5	ANTIBIOTIC COURSE	STAY	OUTCOME
1.	45	M	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	-VE	5	6	CURED
2.	56	F	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
3.	64	M	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	- VE	5	6	CURED
4.	66	M	POSTIVE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	- VE	5	5	CURED
5.	62	M	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	- VE	5	6	CURED
6.	54	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	- VE	5	5	CURED
7.	56	F	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	- VE	5	6	CURED
8.	51	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	+ VE	10	10	DEATH
9.	67	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	- VE	5	6	CURED
10.	43	M	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	- VE	5	6	CURED
11.	47	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	+ VE	7	7	DEATH
12	53	M	POSITI VE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
13	66	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+VE	-VE	5	6	CURED
14	72	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
15	71	M	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	5	CURED
16	62	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
17	59	F	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+VE	+VE	8	8	DEATH
18	55	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
19	41	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
20	38	F	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	5	CURED
21	44	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	+VE	7	7	DEATH
22	49	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	-VE	+ VE	- VE	5	6	CURED
23	51	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
24	53	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	- VE	5	6	CURED
25	69	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	- VE	5	5	CURED
26	67	M	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	- VE	5	6	CURED
27	59	F	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	5	CURED
28	62	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	- VE	5	6	CURED
29	67	M	POSTIVE	POSITIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	- VE	5	6	CURED
30	49	M	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
31	52	F	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
32	51	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	5	CURED
33	63	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
34	65	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	5	CURED
35	50	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	6	CURED

S. NO	AGE	SEX	BLOOD C/S	PUS C/S	URINE C/S	WOUND SWAB	ORGANISM	SENSITIVE ANTIBIOTIC	CRP	PROCALCITONIN ON DAY 0	PROCALCITONIN ON DAY 5	ANTIBIOTIC COURSE	STAY	OUTCOME
36	47	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
37	72	M	POSITI VE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
38	64	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+VE	+VE	9	9	DEATH
39	53	F	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	6	CURED
40	47	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	6	CURED
41	70	M	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
42	61	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	+VE	+VE	-VE	5	5	CURED
43	57	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	+VE	7	7	DEATH
44	49	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
45	68	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	- VE	5	6	CURED
46	74	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	6	CURED
47	56	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	- VE	5	5	CURED
48	44	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	+ VE	11	11	DEATH
49	46	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	6	CURED
50	66	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	6	CURED
51	45	M	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
52	56	F	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	-VE	5	5	CURED
53	64	M	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	+VE	9	9	DEATH
54	66	M	POSTIVE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
55	62	M	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	6	CURED
56	54	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
57	56	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	+VE	11	11	DEATH
58	51	M	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+VE	-VE	5	6	CURED
59	67	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+VE	-VE	5	6	CURED
60	43	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	ACINETOBACTER	MEROPENEM	-VE	+VE	-VE	5	6	CURED
61	47	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
62	53	M	POSITI VE	POSITIVE	NEGATIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
63	66	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	+VE	+VE	-VE	5	5	CURED
64	72	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	+VE	7	7	DEATH
65	71	M	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
66	62	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	+VE	+ VE	- VE	5	6	CURED
67	59	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	+VE	+ VE	- VE	5	6	CURED
68	55	M	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	-VE	5	5	CURED
69	41	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
70	38	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+ VE	-VE	5	5	CURED

S. NO	AGE	SEX	BLOOD C/S	PUS C/S	URINE C/S	WOUND SWAB	ORGANISM	SENSITIVE ANTIBIOTIC	CRP	PROCALCITONIN ON DAY 0	PROCALCITONIN ON DAY 5	ANTIBIOTIC COURSE	STAY	OUTCOME
71	44	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	-VE	5	6	CURED
72	49	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
73	51	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	-VE	5	6	CURED
74	53	F	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+ VE	-VE	5	6	CURED
75	69	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	5	CURED
76	67	M	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
77	59	F	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	5	CURED
78	62	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	+VE	8	8	DEATH
79	67	M	POSTIVE	POSITIVE	NEGATIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	6	CURED
80	49	M	POSITIVE	NEGATIVE	NEGATIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
81	52	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
82	51	F	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
83	63	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+VE	- VE	5	6	CURED
84	65	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	+VE	+VE	-VE	5	5	CURED
85	50	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	-VE	+ VE	- VE	5	6	CURED
86	47	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	-VE	+VE	- VE	5	5	CURED
87	72	M	POSITI VE	POSITIVE	NEGATIVE	NEGATIVE	ACINETOBACTER	MEROPENEM	+VE	+ VE	-VE	5	6	CURED
88	64	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	+VE	9	9	DEATH
89	53	F	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
90	47	M	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	PROTEUS	PIPTAZ	-VE	+ VE	-VE	5	6	CURED
91	70	M	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	6	CURED
92	61	F	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	KLEBSIELLA	PIPTAZ	+VE	+ VE	-VE	5	5	CURED
93	57	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	+VE	+ VE	-VE	5	6	CURED
94	49	F	POSITIVE	POSITIVE	POSITIVE	POSITIVE	PSEUDOMONAS	CEFAPERAZONE	+VE	+ VE	-VE	5	5	CURED
95	68	F	POSITIVE	NEGATIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+ VE	-VE	5	6	CURED
96	74	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	E.COLI	CEFAPERAZONE	-VE	+VE	-VE	5	6	CURED
97	56	M	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	PROTEUS	PIPTAZ	+VE	+VE	+VE	7	7	DEATH
98	44	M	POSITIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	+VE	+VE	-VE	5	6	CURED
99	46	F	NEGATIVE	POSITIVE	POSITIVE	POSITIVE	KLEBSIELLA	PIPTAZ	-VE	+VE	-VE	5	5	CURED
100	66	F	POSITIVE	POSITIVE	POSITIVE	NEGATIVE	E.COLI	CEFAPERAZONE	+VE	+VE	-VE	5	6	CURED