"ESTIMATION OF SERUM PROCALCITONIN LEVELS IN PATIENTS WITH SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS - A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled **"ESTIMATION OF SERUM PROCALCITONIN LEVELS IN PATIENTS WITH SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS - A ONE YEAR HOSPITAL BASED CROSS SECTIONAL STUDY"** is a bonafide research work done by **REG NO. BG0111011.**

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LIST OF ABBREVIATIONS USED

- ACCP : American College of Chest Physicians
- A :G ratio : Albumin –Globulin ratio
- APACHE: Acute Physiology and Chronic Health Evaluation
- COPD: Chronic Obstructive Pulmonary Disease
- CRP : C-Reactive Protein
- CT : Calcitonin
- DNA: Deoxy Ribose Nucleic Acid
- EGDT : Early Goal Directed Therapy
- IL : Interleukin
- LPS : Lipopolysaccharide
- mRNA : Messenger Ribonucleic acid
- NHDS : National Hospital Discharge Survey
- PCT : Procalcitonin
- SCCM : Scociety of Critical Care Medicine
- SIRS : Systemic Inflammatory Response Syndrome
- SOFA : Sequential Organ Failure Assesment
- TNF : Tumour Necrosis Factor
- VAP : Ventilator Associated Pneumonia
- WBC : White Blood Cell.

ABSTRACT

Background and objectives

The present study was undertaken to estimate the levels of serum Procalcitonin in patients with Systemic Inflammatory Response Syndrome and Sepsis and correlate the severity of sepsis with the increase in serum PCT values.

Methodology

This one year cross sectional study was carried out on a total of 50 consecutive patients with SIRS or Sepsis admitted in Medical ICU from January 2012 to December 2012 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Results

Out of 50 patients, males were 31 (62%) and females were 19 (38%). Most number of patients were seen in age group of 18-30 years (36%), followed by those between 51-60 years (24%). SIRS was seen in 23 (46%) of cases, sepsis was observed in 13 (26%) of cases, Severe Sepsis in 7 (14%) cases and septic shock was observed in 7 (14%). Regards to source of sepsis, 11 (22%) had respiratory system involvement, 9 (18%) had Genitourinary involvement, 9 (18%) had gastrointestinal tract related problems, 7 (14%) had CNS related problems, 4 (8%) had skin and soft-tissue infections, while 14 (28%) had other focus of sepsis or SIRS.

Procalcitonin (cut-off ≥2ng/ml) was positive in 25 (50%). CRP was positive in 37 (74%) and negative in 13 (26%). 7 (14%) of cases had blood culture positive and Escherichia coli was the commonest organism isolated (6%). Total count was <4000 in 6 (12%) patients and, >11,000 was noted in 27(54%) of patients and in the remaining 17 (34%) WBC count was normal. Procalcitonin (≥2ng/ml) in comparison

with CRP, had a sensitivity of 85.2%, specificity was 95.8%, PPV was 95.6%, and NPV was 88%.

CRP in comparison with Procalcitonin, sensitivity was 81.5%, specificity was 34.8%, PPV was 59.5%, and NPV was 61.5%. Serum Procalcitonin showed an increase in patients with sepsis (3.42ng/ml) compared to those with SIRS (0.48ng/ml, $p<0.01$). Also, the elevation of PCT in patients with Septic shock (4.94ng/ml) was significantly more than in patients with Sepsis (2.74ng/ml)

Conclusion and interpretation

In our study, increase in serum Procalcitonin was elevated more in patients with sepsis and was found to be a better predictor for differentiating SIRS from Sepsis, compared to CRP, WBC count and other routine markers. There is also a relationship between increasing PCT values and the increasing severity of sepsis, with Septic shock patients having much higher increase in PCT values compared to those with Sepsis and SIRS.

Keywords

SIRS, Sepsis, Severe sepsis, Septic shock, Procalcitonin, CRP, Biomarkers.

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INTRODUCTION

The term ‘sepsis’ is used to define the systemic inflammatory response to an infectious agent (i.e. bacterial, viral, fungal or parasitic). Despite the use of new treatment modalities, improvements in technology and increased experience, bacterial sepsis is a leading cause of morbidity and death among critically ill patients.[1,2] Approximately, 25-35%of patients with severe sepsis and 40-55% of patients with septic shock die within 30 days.[3]

In cases in which non-infectious insults are responsible for systemic inflammatory response syndrome or in comatose patients, the diagnosis of sepsis remains difficult.

In 20–30% of patients with sepsis, the infection site is never identified.[4] The established biological markers of inflammation (like WBC count, CRP) may often be influenced by parameters other than infection and may be slowly released during progression of an infection. There is a need for a reliable diagnostic procedure that allows early diagnosis and discrimination between patients suffering from Systemic Inflammatory Response Syndrome and those with Sepsis.

One such measurement, Procalcitonin, has recently become of interest as a possible marker of sepsis. Procalcitonin is the precursor of calcitonin, and is normally produced in the C-cells of the thyroid gland. Procalcitonin levels are undetectable in healthy individuals (<0.1ng/mL). During systemic and severe infections, procalcitonin is also produced in various extra-thyroidal neuroendocrine tissues, and serum procalcitonin concentrations increase to very high levels. Procalcitonin is more

specific for detecting bacterial infection, because viral infections, autoimmune and allergic disorders do not induce procalcitonin production.

Systemic PCT secretion is a component of the inflammatory response that appears to be relatively specific to systemic bacterial infections. Bacteremic infections appear to cause the highest rises in PCT with lower or negligible rises in localized, viral and intracellular bacterial (e.g. Mycoplasma pneumoniae) infections.[5,6] There is evidence that Gram-negative bacteremias cause higher PCT rises than Gram positive bacteremias.[7]

Importantly, PCT levels in response to sepsis do not appear to be significantly affected by the use of steroids.[8] Also, in bacterial infections, serum PCT levels start to rise at 4 h after the onset of systemic infection, and peak at between 8 and 24 h, making it a good bio-marker for sepsis.

Prompt diagnosis and treatment with appropriate antimicrobial chemotherapy is of the utmost importance in reducing the morbidity and mortality associated with sepsis.[9] The lack of specific early markers of infection may be responsible in part for withholding of, delaying or use of unnecessary antimicrobial treatment in critically ill patients. Thus, there is an unmet need for clinical or laboratory tools that can identify early as well as distinguish between Systemic Inflammatory Response Syndrome and Sepsis.

OBJECTIVES

The objectives of the present study were:

- To estimate the levels of serum Procalcitonin in patients with Systemic Inflammatory Response Syndrome and Sepsis.
- To correlate the serum PCT values with increasing severity of Sepsis
- To evaluate the usefulness of serum PCT in comparison with few other routinely available sepsis markers in differentiating Sepsis from SIRS.

REVIEW OF LITERATURE

Sepsis is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation therapies. It is now widely accepted that starting effective antibiotic therapy early in the course of an infection decreases morbidity and mortality in this cohort of patients.[10] The mortality rate among patients with severe sepsis has been reported at 20% to 50%, and sepsis incidence is increasing at an estimated annual rate of 1.5%.[11,12] In addition, the growing numbers of sepsis patients who have organ dysfunction indicate that sepsis severity is also increasing.[12] A study of National Hospital Discharge Survey (NHDS) data identified organ failure in 19.1% of sepsis patients from 1979 to 1989 and 30.2% from 1990 to 2000.[12] Comparing data from the 5-year time frame between 1979 and 1984 with the span from 1995 to 2000, the number of patients who had dysfunctional organs more than doubled (2.7% to 7.1%), and the number of patients who had at least three dysfunctional organs more than tripled (0.5% to 1.9%).[12]

Evidence supports early intervention and diagnosis in sepsis and that the failure to intervene results in significant morbidity and mortality[13]. The challenges of diagnosing and treating sepsis only seem more daunting as incidence increases, patients become older and sicker, and pathogenic organisms evolve[14]. New understanding of inflammatory mediators and pathways, immunity, and genetic variability in this disease state suggests that the current definitions of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock are oversimplified.[15]

Definitions for the terms of "SIRS", "sepsis", "severe sepsis" or "septic shock" have been proposed by the ACCP/SCCM consensus conference in 1992, and are now widely used:

SIRS (Systemic Inflammatory Response Syndrome): 2 or more of the following criteria:

• Temperature > 38 °C or < 36 °C

• Heart rate > 90 beats/min

• Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg (< 4.3 kPa)

•WBC > 12000 cells/mm3, < 4000 cells/mm3, or > 10% immature (band) forms

Sepsis: Documented infection together with 2 or more SIRS criteria.

Severe Sepsis: Sepsis associated with organ dysfunction, including, but not limited to, lactic acidosis, oliguria, hypoxemia, coagulation disorders, or an acute alteration in mental status.

Septic shock: Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are detected.

The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities.[16,17] The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms of sepsis.[18] Microbiological cultures require time, do not reflect the host response of systemic inflammation nor the onset of organ dysfunction, and may not be positive in

sepsis patients for a number of reasons.

However, the early diagnosis and stratification of the severity of sepsis is very important, increasing the possibility of starting timely and specific treatment.[19,20] Several lines of evidence indicate that early identification and treatment of severe sepsis and septic shock improve outcomes. Early initiation of hemodynamic resuscitation with early goal-directed therapy (EGDT), consistently has improved mortality rates in numerous clinical trials.[21]

These complexities have led to the search for the ‘‘troponin’’ of sepsis, a biomarker or set of biomarkers with compelling sensitivity and specificity for effectively identifying the disease, patients at risk for untoward outcomes, and reliably guiding treatment.

Biomarkers are an appealing addition to the care of patients who have sepsis because they are noninvasive, ideally rapidly available, and may be followed over a patient’s course. They may ultimately serve as potential targets for therapy and large-scale randomized control trials. Assay reliability, the establishment of cut-offs, and timely, affordable processing must be considered and addressed before the widespread adoption of a given marker.

A biomarker is defined as ‘‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.’’[22]

Before the widespread use of a marker of interest, it must endure validation (ie, have known characteristics, be well standardized, and be accurate) and qualification (ie, be integral to the disease process and clinical end points).[23] Depending on the

intended use, the validation and qualification process may be more or less rigorous (known as the ‘‘fit-for-purpose’’ paradigm in drug development)[9].

It remains difficult to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome, and there is a continuous search for better biomarkers of sepsis.[25] Biomarkers can have an important place in this process because they can indicate the presence or absence or severity of sepsis[26], and can differentiate bacterial from viral and fungal infection, and systemic sepsis from local infection. Other potential uses of biomarkers include roles in prognostication, evaluating the response to therapy and recovery from sepsis, differentiating Gram-positive from Gram- negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction). However, the exact role of biomarkers in the management of septic patients remains undefined.[27]

A multitude of biomarkers has been proposed in the field of sepsis, many more than in other disease processes; for example, procalcitonin (PCT), various interleukins (IL-2, IL-6, IL-8 and TNF-α),[28] a study of patients with myocardial infarction revealed 14 biomarkers suitable for diagnosis and determination of prognosis and in patients with Alzheimer’s disease, just 8 biomarkers were identified[29].

This large difference in the numbers of biomarkers for sepsis is likely to be related to the very complex pathophysiology of sepsis, which involves many mediators of inflammation[30], but also other pathophysiological mechanisms. Coagulation, complement, contact system activation, inflammation, and apoptosis are all involved in the sepsis process, and separate markers for each (part of each) system have been proposed. Additionally, the systemic nature of sepsis and the large numbers

of cell types, tissues and organs involved expand the number of potential biomarker candidates, compared with disease processes that involve individual organs or are more localized. It is interesting to note that most of the biomarkers identified have been tested clinically and not experimentally.

This is likely to be in part related to difficulties creating an experimental model that accurately reflects all aspects of human sepsis, problems with species differences, and problems in determining end-points in animal studies. Additionally, as the sepsis response varies with time, the exact time period during which any specific biomarker may be useful varies, and this is difficult to assess reliably in experimental models. Moreover, as there is no 'gold standard' for the diagnosis of sepsis, the effectiveness of a biomarker needs to be compared with current methods used to diagnose and monitor sepsis in everyday clinical practice, i.e., by the combination of clinical signs and available laboratory variables[31]; experimental models cannot be used for this purpose. Of these and others, PCT has been the most studied and, in some countries, is now being included in routine clinical practice and guideline recommendations.[32]

Procalcitonin (PCT)

Procalcitonin (PCT) is the precursor of Calcitonin. Site of formation is the CALC-1 gene on chromosome 11 of the human genome. After translation from CT-DNA into mRNA the first translation product is Pre-procalcitonin, which then changes by different modification steps into PCT. PCT is a peptide, consisting of 116 amino acids. PCT is enzymatically degraded into lower molecular weight peptides. The final product consists of 32 aminoacids and is named Calcitonin. PCT is a propeptide of calcitonin that is ubiquitously expressed as part of the host's inflammatory response to a variety of insults.[33,34]

In normal physiological conditions, PCT levels in the serum are low (<0.1 ng/mL). However, in bacterial infection PCT is synthesized in various extra-thyroidal neuroendocrine tissues. Systemic PCT secretion is a component of the inflammatory response that appears to be relatively specific to systemic bacterial infections. Bacteremic infections appear to cause the highest rises in PCT with lower or negligible rises in localized, viral and intracellular bacterial (e.g. Mycoplasma pneumoniae) infections.[5,6] There is evidence that Gram-negative bacteremias cause higher PCT rises than Gram positive bacteremias.[7]

Importantly, PCT levels in response to sepsis do not appear to be significantly affected by the use of steroids[8], although at least one study has shown elevated PCT levels at 24 h in volunteers given ibuprofen at the time of endotoxin challenge compared with control volunteers given endotoxin and placebo.[35]

To be a useful diagnostic biomarker in bacterial sepsis, the substance being measured must rise above normal levels early in the course of the infectious process. In bacterial infections, serum PCT levels start to rise at 4 h after the onset of systemic infection, and peak at between 8 and 24 h. In contrast, CRP, which with the exception of the White Blood Cell count (WBC Count) is the most commonly used biomarker of infection, rises slowly and peaks 36 h after an endotoxin challenge.[6,36] PCT can also be elevated in renal impairment in the absence of infection.[37] In surgical patients the picture is less clear, as PCT can increase after trauma or surgery, particularly major abdominal surgery, and in pancreatitis. However, some authors have found that PCT levels only transiently increase for 12–24 h after surgery before, in the absence of infection, falling back to normal levels.[38] Again, this is in contrast to both CRP and WBC count, which can stay elevated for a number of days after surgery without there

being underlying infection. PCT has a half-life of about 24 h, so a sample can be collected and sent to the laboratory as with other routine biochemical blood tests.[6] Laboratory turn-around times will vary depending on local circumstances and the PCT testing kit used, but an average turn-around time appears to be approximately3 h.

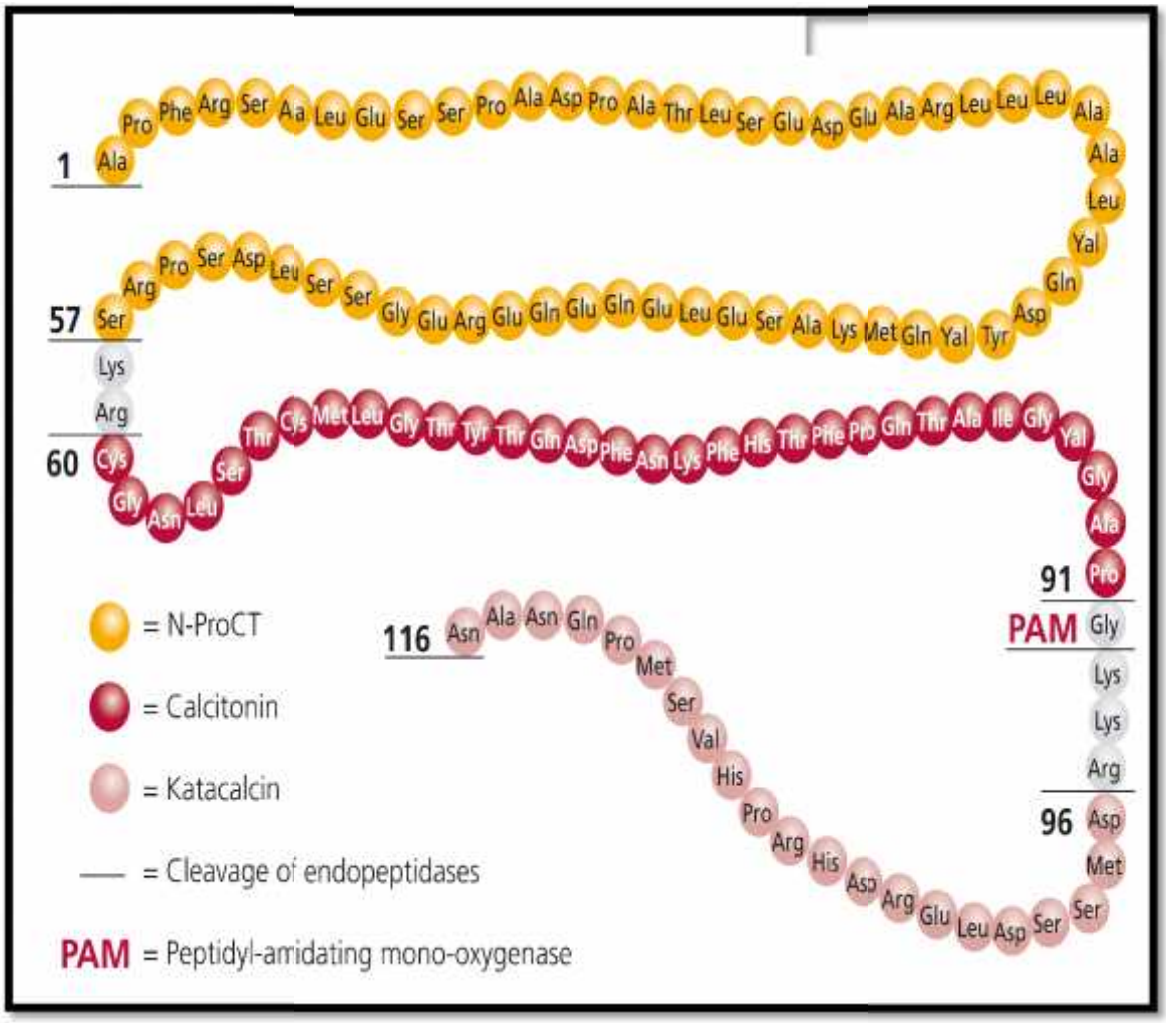


Fig 1: Structure of Procalcitonin

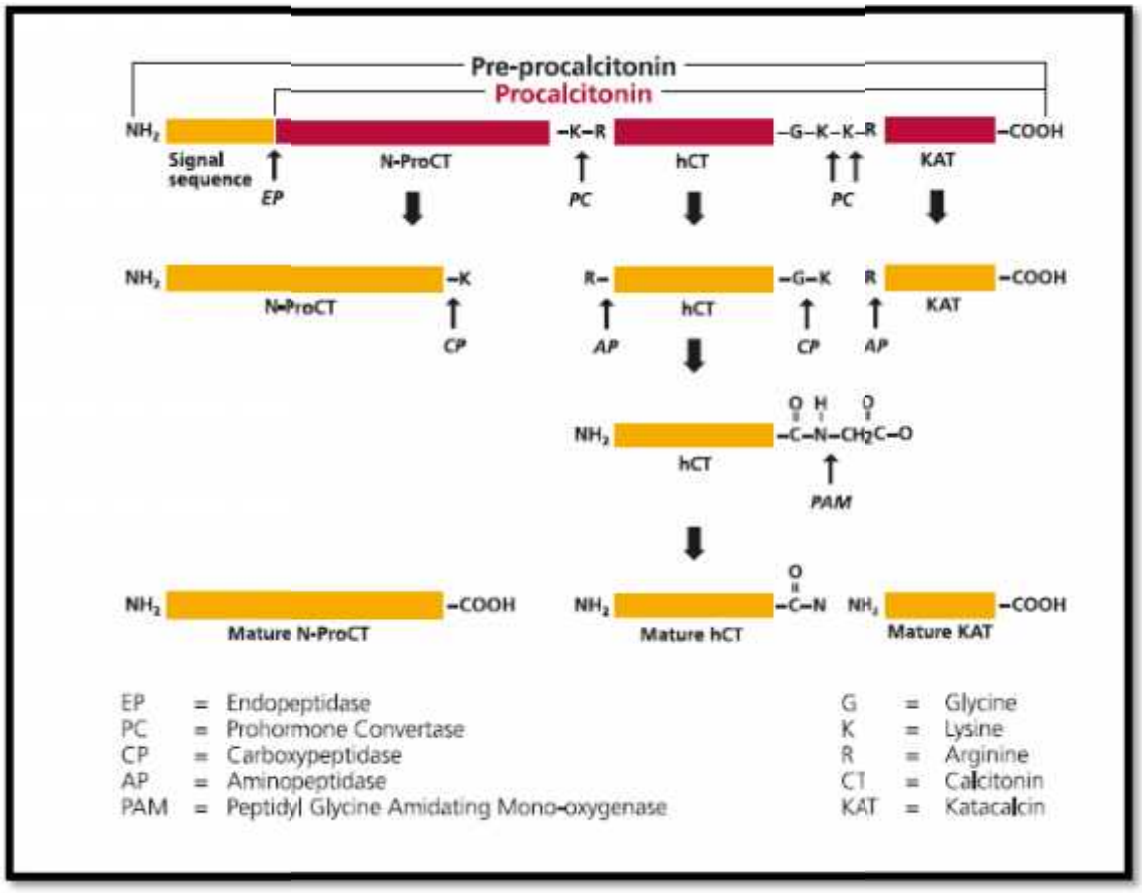


Figure 2: Postranslational modification of Calcitonin Precursors

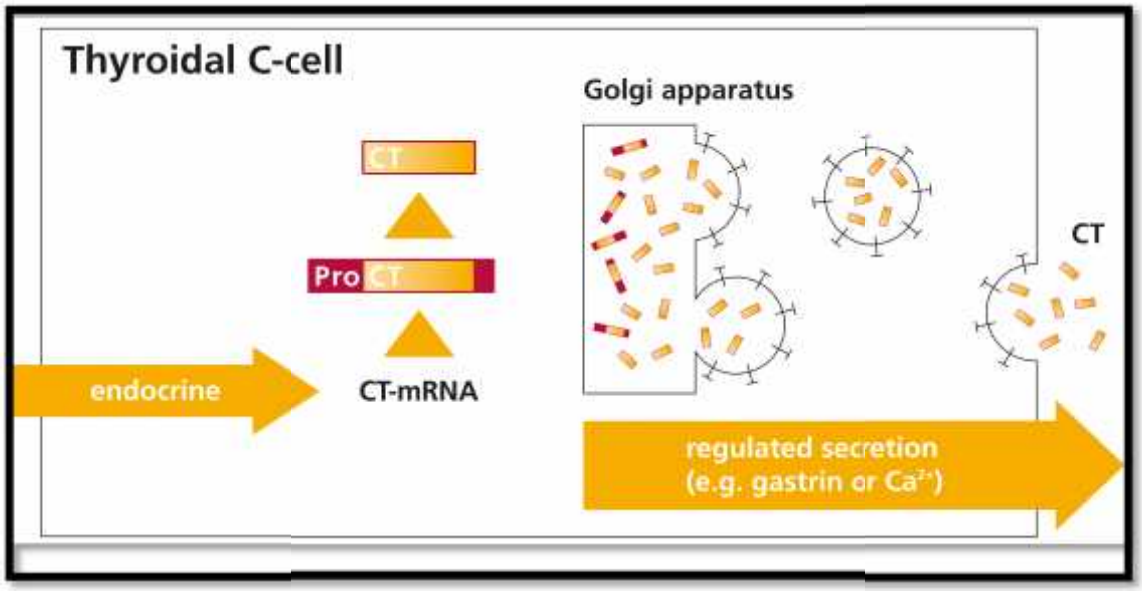


Fig.3: The Classic Neuroendocrine Pathway

The classic neuroendocrine pathway

Site of synthesis for PCT in healthy persons are the C-cells of the thyroid. Expression of CT-mRNA takes place only in the neuroendocrine cells. Release occurs in form of posttranslational processed hormone Calcitonin enclosed in Golgi vesicles (Fig. 3). This hormone plays an important role in the pathway and regulation of calcium and phosphate in the bone metabolism.

The alternative pathway in sepsis and inflammation

In contrast to the role of PCT in the framework of the endocrine processes there are alternative possibilities of synthesis in connection with microbial infections.

Inductors for the synthesis are inflammatory cytokines like IL-1β and TNF-α but also elements of membranes or cell wall of the microbes like LPS or peptidoglycanes (Fig. 4).

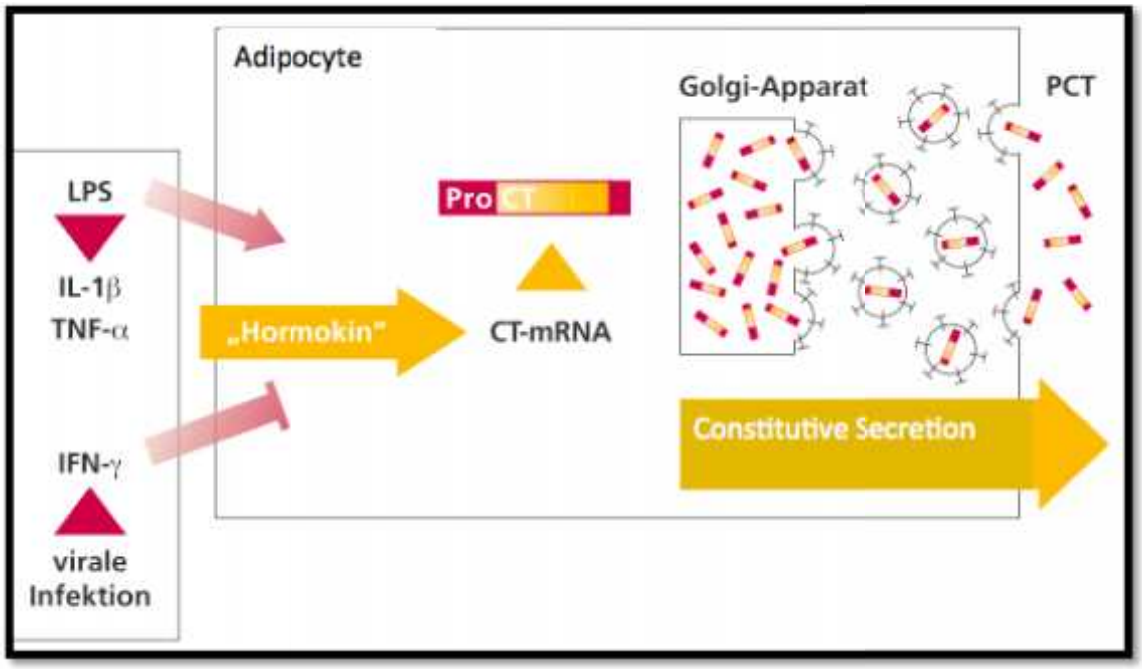


Fig. 4: Alternative synthesis of PCT

After induction of sepsis it was possible to detect mRNA for PCT in all investigated tissues (Fig.5). In septic patients only the 3-116 fragment is detectable, not the complete PCT molecule.

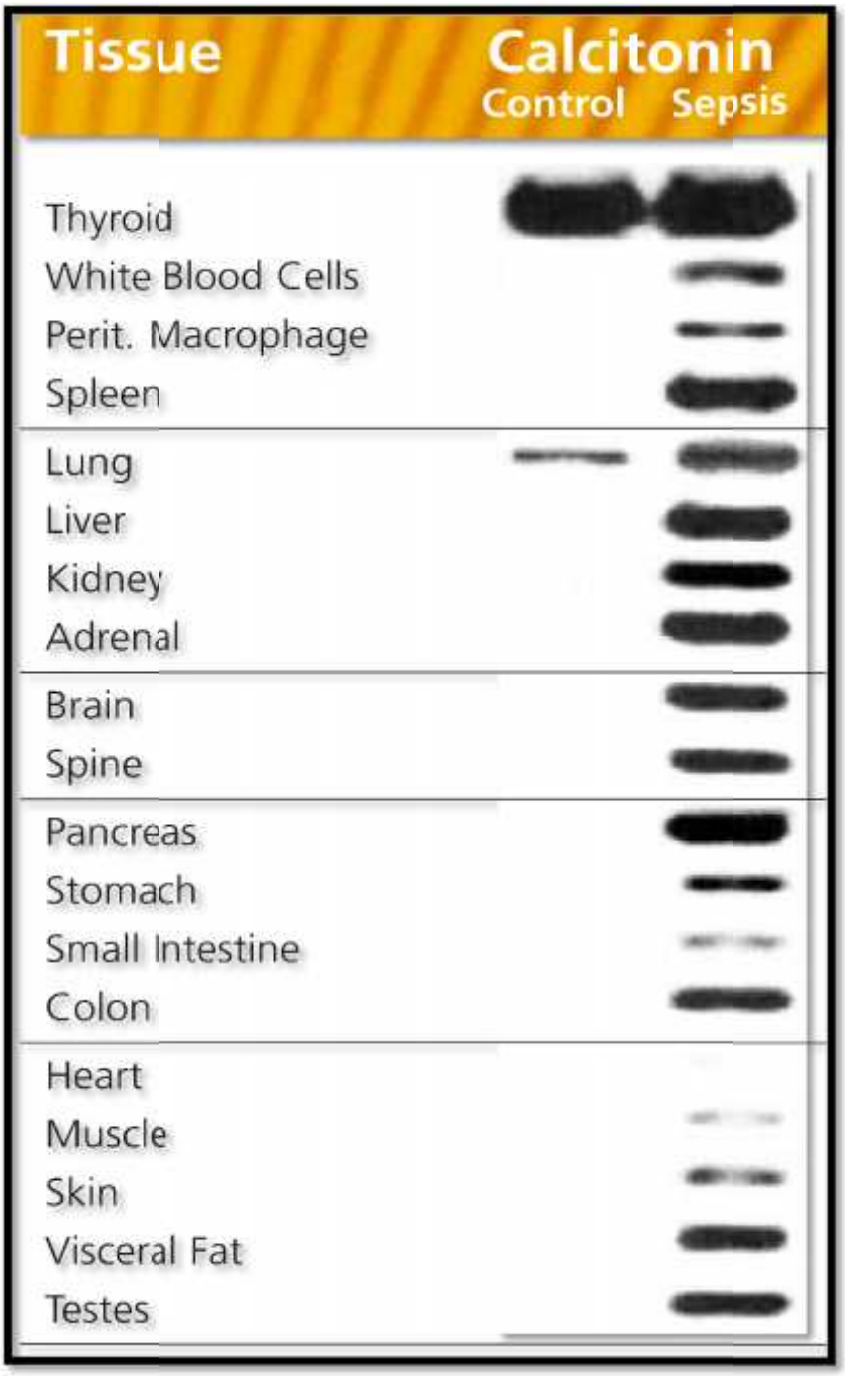


Fig 5: Detection of PCT-mRNA-synthesis in different types of tissue after LPS-stimulation

Although calcitonin is a neurohormone classically produced in the thyroid and involved in calcium homeostasis, PCT is one of several calcitonin precursors involved in the immune response, acting as a so- called ‘‘hormokine’’[34] in a variety of inflammatory states, including cardiogenic shock[39], trauma[40], necrotizing pancreatitis[41], burns[42], surgery[43], and infection.

A growing body of literature suggests that PCT is a specific marker for severe bacterial infection[44-50] and, in clinical context, may distinguish patients who have sepsis from patients who have SIRS. Higher absolute concentrations[45] and, perhaps more important clinically, persistent elevations in PCT after ICU admission have been associated with poor outcomes, distinguishing survivors from nonsurvivors.[51-54]

a. Procalcitonin in Sepsis

There have been a number of studies looking at the diagnostic ability of PCT in critically ill patients and, more specifically, its ability to differentiate between SIRS and bacterial sepsis. The results are conflicting, making it difficult to draw any firm conclusions. There have been two meta-analyses performed within the last 5 years, however, that have attempted to clarify the situation.[55,56]

In the 25 studies that looked at PCT, the sensitivities ranged from 42% to 100% and the specificities from 48% to 100%. The sensitivities and specificities for CRP ranged from 35% to 100% and from 18% to 84%, respectively. The results of the meta-analysis found a global diagnostic accuracy odds ratio for PCT of 15.7 and of 5.4 for CRP. Interestingly, the larger studies included in these reviews tended to find lower estimates of PCT sensitivity and specificity than smaller studies.

Despite these limitations, Uzzan et al.[55] concluded that 'PCT represents a good biological diagnostic marker for sepsis, severe sepsis and septic shock' and 'should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units'. Ruiz-Alvarez et al.[57] found that PCT and the sequential organ failure assessment (SOFA) score, but not CRP, were the only independent predictors of infection in 103 intensive care patients with suspected sepsis. Based on these studies, PCT appears to be a genuine advance on CRP in the diagnosis of sepsis.[58]

Reflecting this, the American College of Critical Care Medicine and the Infectious Diseases Society of America have recently recommended, graded as Level 2 evidence, that serum PCT can be used as 'an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations' in their guidelines for the evaluation of new fever in critically ill adults.

Given that PCT can be elevated in certain non-infective conditions[59], it is probably better used to rule out than rule in systemic bacterial infection. However, false-negative results can occur if samples are taken too early in the course of infection and few physicians will be persuaded not to prescribe antibiotics on the basis of a single low PCT value performed on or shortly after admission to hospital for a critically ill patient without a clear diagnosis; a repeat test should be performed at 6–12 h[58,60]. However, if all microbiological cultures are negative and a clear source of infection

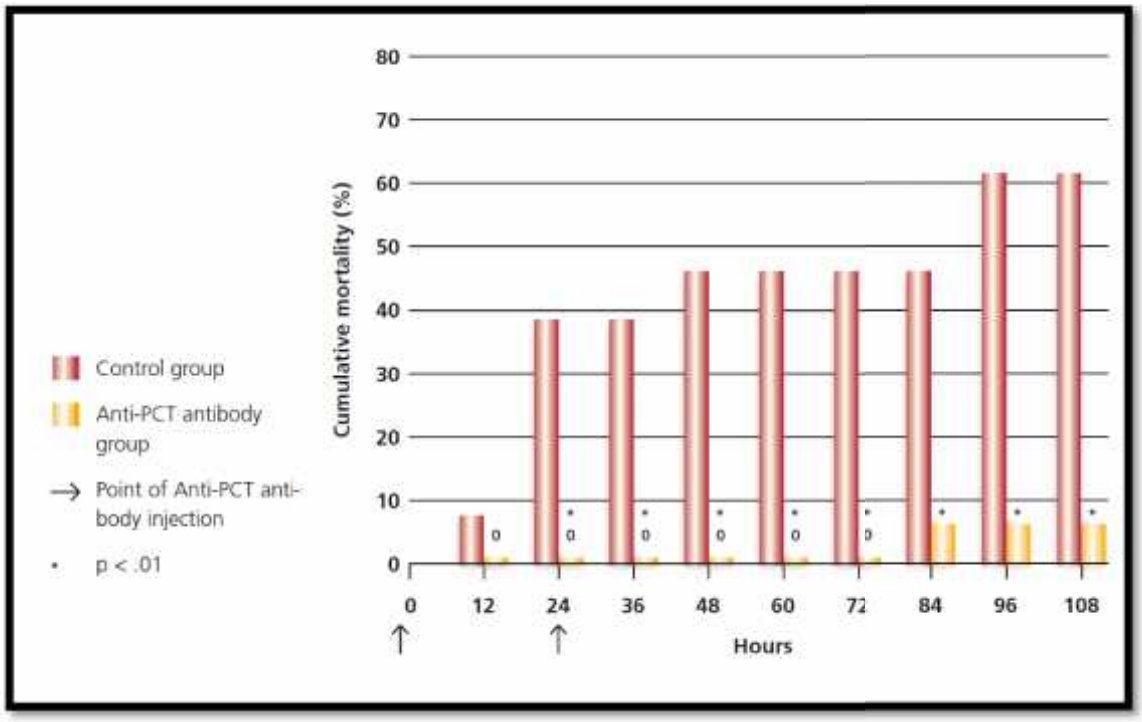


Figure 6: Role of PCT in experimental sepsis

Has not declared itself by 24 h, a repeat low PCT, combined with clinical judgement, provides a strong argument for discontinuing antimicrobial therapy and searching for an alternative diagnosis. Such an approach is likely to avoid ≥3–4 days of broad-spectrum antibiotic therapy per patient.

However, PCT tests are currently more expensive than CRP and although this approach is attractive, it is yet to be subjected to robust cost-effectiveness analyses.

b.<u>Role in Nosocomial Infections</u>

PCT is also potentially useful diagnostically in critically ill patients who deteriorate during their admission when intercurrent bacterial infection is in the differential diagnosis as the cause for the deterioration. Ventilator-associated pneumonia (VAP) is one of the more common problems, the diagnosis of which is particularly challenging because clinical signs are often non-specific and there is no

gold-standard diagnostic test. In addition, microbiological tests, often endotracheal aspirates, can be difficult to interpret because of microbial colonization of the respiratory tract. This uncertainty can lead to the delayed diagnosis and treatment of VAP and poorer clinical outcomes, but it is also widely acknowledged that VAP is over-diagnosed and, even when a clear diagnosis can be made, patients are often treated for too long.

A diagnostic test that indicates the early presence of bacterial respiratory tract infection with some certainty in ventilated patients would clearly represent an important clinical advance. Most of the studies performed in this area have been small and observational in nature. The results of two recently published studies, however, provide useful insights. The first, by Charles et al.[61] looked at consecutive patients with either suspected VAP or confirmed bacteraemia. PCT results in the patients were compared on the first day of fever (day 0) as well as the difference between PCT levels taken 1, 2 or 3 days before day 0. The day 0 PCT levels were significantly higher in cases of proven infection than in those without (5.5 versus 0.7 ng/mL, P=0.018). The absolute difference between the day 0 result and that on any of the preceding days was also significantly different between cases and controls (+5.8 versus 20.5, P=0.035 for day 0 to day 1). The sensitivity and specificity for the ability of PCT to diagnose VAP on day 0 (cut-off 0.44ng/mL) were 65.2% and 83%, respectively.

Tsangaris et al.[62] also looked at the diagnostic ability of PCT compared with CRP and WBC count in 27 patients who had been in an intensive care unit for 10 days and had developed proven infection (bacteraemia, respiratory or abdominal) compared with 23 patients without infection. The sensitivity and specificity for a PCT

cut-off of 1.0 ng/mL were 70% and 91%, respectively. Importantly, they also found that the difference in the PCT values from day 0 and any of the values for the 10 days before day 0 was significantly different in both cases and controls.

The sequential measurement of PCT in identifying healthcare-associated infection is undoubtedly attractive, and there is some evidence that PCT measured twice or thrice weekly and on the day infection is suspected for the first time might be sufficient and clinically useful. PCT used in this way may also reduce unnecessary antibiotic prescribing in patients who deteriorate for non-infection reasons, but it will also add to critical care admission costs. The cost-effectiveness of such an approach needs to be evaluated, including against strategies that aim to prevent healthcare-associated infections in the first place.

The results of The Procalcitonin and Survival Study (PASS), a randomized trial of a PCT-guided treatment strategy in 1200 critically ill patients (NCT00271752), may provide important insights and is therefore eagerly awaited.[63]

c. <u>Prognostic Role:</u>

Serum PCT levels have also been noted to increase with increasing severity of sepsis and organ dysfunction. This was demonstrated by Giamarellos-Bourboulis et al.[64] This has led to interest in using PCT as a prognostic indicator in critical care patients and a number of studies have now been performed.

One of the largest studies was performed by Jensen et al.[65] This study prospectively looked at daily PCT measurements in 472 critical care patients and correlated the results with all-cause mortality in a 90 day study period. They found that a high maximum PCT and an increase of PCT value following the first reading

>1.0 ng/mL were both independent predictors of 90 day mortality. The relative risk for mortality increased with every day the PCT value continued to rise after the first reading >1.0 ng/mL: 1.8 for 1 day; 2.2 for 2 days; and 2.8 for 3 days.

In contrast, levels of CRP and WBC count were not found to be predictive of mortality. In a smaller study by Pettila et al.[66] there was a significant difference in PCT values between survivors and non-survivors on day 1 and day 2 after admission to intensive care. However, there were similar statistically significant differences for IL-6 levels, and Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA scores. The evidence for using PCT to predict mortality in patients after surgery is more complicated to interpret, not least because studies have found markedly different cut-off points.

Schneider et al.[67] found an optimum cut-off point of 1.44 ng/mL in their study of 220 unselected post-surgery patients requiring postoperative critical care. Using this cut-off for a serum PCT measured on the day after surgery, the ROC curve for combined mortality and morbidity was 0.75 (95% CI 0.66–0.85) and for the APACHE II score was 0.69 (95% CI 0.59–0.78). In contrast, in a study of post-elective coronary bypass patients, Fritz et al.[68] found a cut-off for mortality prediction at 2.5 ng/mL, whereas Rau et al.[69] found a cut-off of 16 ng/mL in patients who had undergone surgery for peritonitis.

The requirement to use markedly different cut-off points for subgroups of surgical patients would certainly complicate clinical decision-making and reduce the clinical usefulness of PCT for prognostic assessment in critical care.

So, based on the above, does PCT add anything to the already established

clinical methods of prognostic assessment in critical care? APACHE II and SOFA scores have been validated for mortality risk stratification, but are clinically unwieldy and tend to be used more for audit and research than clinical decision making. A rapidly available biochemical test that provides similar prognostic information could therefore be useful, e.g. to help discussions about prognosis with patients' relatives and decisions regarding earlier interventions. It seems doubtful that such a test, unless highly prognostic, will heavily influence day-to-day clinical decision-making for the latter; although, as suggested by Giamarellos-Bourboulis et al.,[64] a rising PCT level might be used as an indicator that an infectious process is not under control and that better source control is required.

d.Role in Antibiotic Stewardship:

The use of PCT as an antimicrobial stewardship tool is extremely attractive in the current climate of increasingly antibiotic resistant microbes. The theory is that with daily or serial PCT measurements, antibiotics can be safely stopped once the PCT level declines below a certain cut-off point or reduces to a certain percentage of its initial value. The use of PCT in the avoidance of antibiotic initiation and in reducing antibiotic course length has been extensively studied outside of the critical care environment.

It is shown that the PCT kinetic within the first 48 hours of management of sepsis could be significantly different according to the appropriateness of the first-line empirical antibiotic therapy. Actually, PCT variations between Day 2 and Day 3 were shown to be critical since a significantly greater PCT decline within this period was expected in the patients with appropriate empirical antibiotic therapy. In addition, a trend toward a greater rise in PCT between Day 1 and Day 2 was observed in patients

with inappropriate antibiotics as compared with those with appropriate therapy. As a result, it was suggested that patient management might be reassessed if PCT does not decrease by 30% between Day 2 and Day 3.[70] In such cases, empirical antibiotic therapy modification towards a broader spectrum should be considered while the microbiological findings, if any, are still pending.

Several large, high-quality randomized controlled trials have demonstrated significant decreases in antibiotic use without any apparent increase in harm in lower respiratory tract infection,[71] exacerbations of chronic obstructive pulmonary disease[72] and community-acquired pneumonia.[73] There have now been a number of studies using the same principles in critically ill patients. The results showed a significant reduction in antibiotic duration in patients who were strictly treated by PCT guidance. There was no difference in mortality and infection recurrence in the two groups, but intensive care unit stay was shortened in the PCT cohort. In patients with VAP, PCT use significantly increased the number of antibiotic-free days alive with an overall reduction in antibiotic exposure.

The PRORATA trial is the largest randomized PCT trial to date.[60] The study was performed in eight French intensive care units, was open-label and compared PCT-guided antibiotic therapy (307 patients) to usual care (314 patients) for predominantly nonsurgical patients (10% were surgical) with suspected bacterial sepsis on either entry to intensive care or during their admission. Of the 307 patients randomized to the PCT group, recommendations were not followed in 219 patients (71%); of these, the algorithm was overruled at inclusion or during follow-up in 57 patients (19%). On admission, a high and similar proportion of patients in both cohorts were prescribed antibiotics, but, overall, PCT patients had significantly more

days without antibiotic exposure than control patients [14.3 days versus 11.6 days] and received significantly fewer days of antibiotics. There was no difference in the proportion of patients with emerging multidrug-resistant bacteria; a cost-effectiveness analysis was not performed.

In contrast, but in a smaller observational study,[74] it was found that in critically ill patients with culture positive sepsis, the mean PCT level remained elevated throughout the course of antibiotics, only falling to <1.0 ng/mL on day 10 and to <0.5 ng/mL on day 14. The mean PCT levels of patients in the culture-negative sepsis group were generally lower, and went to <1.0 ng/mL by day 7 and to<0.5 ng/mL by day 10. On the basis of these results, the authors concluded that 'due to significant overlap in PCT levels it was not possible to define a cut-off point for PCT under which it was safe to discontinue antibiotics'. They suggested a number of potential reasons for their results, including that PCT may have been raised in the presence of organ dysfunction, irrespective of its aetiology, and that improvement in PCT levels may reflect improvement in the underlying inflammatory response rather than eradication of infection.

The studies that have demonstrated a significant reduction in antibiotic duration are mostly studies in which the length of a course of 'usual care' antibiotic therapy appears to be about 10–14 days. Therefore, while the use of PCT has had a significant impact within clinical trials, its impact in real life is likely to be dependent on the baseline length of a 'usual care' antibiotic course within the intended environment of use. This is known to vary considerably from country to country and between hospitals within countries. In units that usually use antibiotic courses in the region of 10–14 days or more for infections such as VAP, PCT may well be a highly cost-

effective strategy to provide the necessary confidence to clinicians in stopping antibiotics earlier.

C-reactive protein (CRP)

CRP was first described in 1930, when Tillet and Francis[75] reported that serum from individuals acutely ill with lobar pneumonia was able to precipitate a substance derived from the C polysaccharide of Streptococcus pneumoniae, which they called fraction C. Importantly, they noted that when serum was taken from patients when they were acutely ill there was a strong precipitation reaction but the strength of the reaction decreased as the patients recovered. This observation suggested that this reaction could be used as a marker of disease. The investigators also reported that this precipitation reaction was not specific to pneumococcal infection but was also present in patients with bacterial endocarditis and acute rheumatic fever, and Ash[76] noted its presence in patients with gram-negative infections, which was later determined that the reactive substance being precipitated by fraction C was a protein. The investigators commented that because this substance was present in many different infections, it could not be derived from the bacteria per se, but from the host "as a result of pathologic changes induced by or associated with acute infection."[77] CRP was the first so-called acute phase protein to be described.

It is now known that CRP is a member of the pentraxin family of calcium-dependent ligand-binding plasma proteins. The other member of this family present in humans is serum amyloid P component. The human CRP molecule is composed of 5 identical nonglycosylated polypeptide subunits, each containing 206 amino acid residues, forming an annular configuration.[78] CRP is synthesized principally by hepatocytes in response to stimulation by cytokines, notably interleukin (IL) 6. The

plasma half-life of CRP is about 19 hours. In healthy young adults, the normal plasma concentration of CRP is about 0.8 mg/L.[79,80] During infection or acute inflammation, these values can increase by some 10,000-fold.[81] The plasma clearance of CRP is similar in healthy individuals and in those with disease, and the synthesis rate is the only significant determinant of its plasma level, making measurement of CRP levels a useful objective index of the acute phase response.[82]

a. Physiologic activities:

The pentraxin family is highly conserved in evolution, suggesting that members have an important physiologic role. This theory is supported by the fact that there are no known deficiencies of CRP in humans. It has been suggested that CRP may act in a pro-inflammatory or in an anti-inflammatory capacity to aid host defense. In vitro, CRP has been shown to increase release of the anti-inflammatory cytokine IL-10 and decrease synthesis of several proinflammatory cytokines including IL-12, tumor necrosis factor and interferon-g.[83,84] CRP also activates complement, enhances phagocytosis, inhibits activated neutrophils, increases nitric oxide synthesis, and induces tissue factor and adhesion molecule expressions.[85-90] Several in vivo models support an effect on host defense. For example, CRP transgenic mice infected with Streptococcus pneumoniae1 or Salmonella enterica ser Typhimurium have increased survival rates when compared with wild-type mice. In critically ill patients, the studies have shown a significant correlation between plasma fibrinolytic capacity and serum CRP levels, again supporting a link between CRP and the inflammatory response.[91] Nevertheless, the precise biologic properties of CRP remain somewhat controversial and the variations in form and function among species make it difficult to extrapolate data from animal studies to humans.

b.CRP as a biomarker of disease:

CRP is an acute phase protein and as such plasma levels are increased in most forms of acute and chronic inflammatory diseases. CRP is a recognized and widely used marker in rheumatology, with levels elevated in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, polymyalgia rheumatica, to mention just a few. In such patients, CRP levels, especially when using new high-sensitivity CRP assays, can be used to assess the effectiveness of treatment and to monitor periods of disease exacerbation.[92,93] Similarly, CRP is used in gastroenterology, with high levels present in patients with acute relapses of Crohn disease. Increased serum CRP concentrations are also considered a severity marker in pancreatitis.[94] CRP has been suggested as a potential marker of severity of asthma[95] and of development of chronic obstructive pulmonary disease (COPD) and may be useful for guiding antibiotic therapy in patients with acute exacerbations of respiratory disease.[96]

c. CRP as a biomarker of infection:

A useful biomarker of infection, or rather the host response to infection, should provide additional information to the clinical picture in the fields of diagnosis, disease severity stratification and prognosis, and therapeutic guidance.[97] CRP has been investigated in all these 3 areas.

For Diagnosis:

CRP is perhaps the most widely used biomarker of infection in critically ill patients and has been studied in adults and children. In 190 adult patients in the ICU, Ugarte and colleagues[98] reported a sensitivity of 67.6% and specificity of 61.3% for diagnosis of infection using a cutoff value of 7.9 mg/dL. In 112 patients in the ICU,

Povoa and colleagues[99] reported that a serum CRP concentration greater than 8.7 mg/dL was associated with a diagnosis of infection with a sensitivity of 93.4% and a specificity of 86.1%. The combination of CRP concentration greater than 8.7 mg/dL and temperature greater than 38.2ºC increased the specificity for infection diagnosis to 100%.

Sierra and colleagues[100] reported a sensitivity of 94.3% and specificity of 87.3% using a cut-off of 8 mg/dL and noted that median CRP levels were significantly higher in patients with sepsis (18.9 mg/dL; 95% confidence interval [CI], 17.1–21.8) than in healthy subjects (0.21 mg/dL; 95% CI, 0.21–0.4), in patients with acute myocardial infarction (2.2 mg/dL; 95% CI, 2.1–4.9), and in non-infected patients with systemic inflammatory response syndrome (1.7 mg/dL; 95% CI, 2.4–5.5). Peres Bota and colleagues[101] suggested that the combination of several signs of sepsis (temperature, heart rate, respiratory rate, white blood cell count) with the CRP concentration and the Sequential Organ Failure Assessment (SOFA) score could provide a useful score to indicate the likelihood of infection. A score less than 14 was associated with a less than10% chance of having an infection. This infection probability score was shown to be higher in patients with definite or probable infection than in those with unlikely or no infection and had a positive predictive value of 80% and a negative predictive value of 86% for infection.

Importantly, absolute CRP values are in general not helpful. There is a large overlap in CRP levels between infected and non-infected patients, perhaps particularly in patients in the ICU in whom other causes of inflammation may be present. In addition, many patients, perhaps particularly the more elderly, will already have elevated baseline CRP levels before ICU admission because of the presence of

co-morbidities associated with inflammatory processes. Therefore, although a single high CRP level adds evidence to a strong clinical suspicion of infection, following the pattern of CRP levels over time may provide a clearer picture, with an increasing CRP level suggesting that infection is developing or worsening.

In an observational cohort study in which CRP levels were measured daily in patients in the ICU, Povoa and colleagues[102] noted that a maximum daily CRP variation greater than 4.1 mg/dL was a good marker for the prediction of nosocomial infection (sensitivity 92.1%, specificity 71.4%) and that in combination with a CRP concentration greater than 8.7 mg/dL, the discriminative power increased even further (sensitivity 92.1%, specificity 82.1%).

Importantly, although CRP levels are still useful indicators of sepsis in patients with cirrhosis, in patients with fulminant liver failure, CRP levels do not always increase in the presence of sepsis. Therefore, CRP should not be used as a marker of infection in such patients.

In addition to aiding with diagnosis of infection versus other causes of inflammation, attempts have been made to use biomarker levels to distinguish between different types of infection. However, although serum CRP concentrations are generally higher in bacterial infections than in infections of other causes,[103-106] it is unclear whether this is a reliable means of clearly distinguishing among bacterial, fungal, or viral infections in clinical practice.

In children hospitalized with community-acquired pneumonia, the CRP level in patients with bacterial infection was higher than that in patients with viral infection (median 9.6 vs 5.4 mg/dL, P 5 .008), but the investigators commented that there was

considerable overlapping of values in the 2 groups.[107] In a retrospective study of patients with nosocomial bacteremia, serum CRP levels were reported as being substantially higher in patients with gram-negative bacteremia than in those with gram-positive bacteremia.[107] Gram-negative bacteremia was associated with an increase in CRP concentrations from 2 days before diagnosis to 1 day after diagnosis, whereas CRP levels remained unchanged in patients with gram-positive bacteremia.

For Prognosis:

As for diagnosis, single CRP values are of less use for prognostication than trends in CRP over time. In 158 patients with sepsis, Silvestre and colleagues[108] reported no correlation between concentrations of CRP measured on the day of sepsis diagnosis and severity of sepsis.

However, in a prospective cohort study, Lobo and colleagues[109] reported that at ICU admission patients with serum CRP levels greater than 10 mg/dL when compared with patients with CRP levels less than 1 mg/dL had a significantly higher incidence of respiratory (65% vs 28.8%, P<.05), renal (16.6% vs 3.6%, P<.05), and coagulation (6.4% vs 0.9%, P<.05) failures and higher mortality rates (36% vs 21%, P<.05). Moreover, patients who had a CRP concentration greater than 10 mg/dL at ICU admission and in whom the CRP level decreased after 48 hours had mortality rates of 15%, whereas those in whom the CRP level increased had mortality rates of 61% (relative risk, 0.25; 95% CI, 0.07–0.91; P<.05).

For Therapeutic Guidance:

The rationale for using CRP levels to guide antibiotic therapy is supported by several studies suggesting that CRP levels decrease as sepsis resolves. In a

retrospective analysis, a decrease in CRP by 25% or more from the previous day's level was reported to be a good indicator of resolution of sepsis, with a sensitivity of 97%, specificity of 95%, and predictive value of 97%.64 However, data actually linking CRP levels to antibiotic therapy are limited and are mainly from studies in the neonates. Schmit and Vincent[110] reported that CRP concentrations decreased more rapidly and more markedly in those with a favorable response to empirical antibiotics than in those who required a change in antibiotic therapy. An increase in CRP of at least 2.2 mg/dL in the first 48 hours was associated with ineffective initial antibiotic therapy with a sensitivity of 77% and a specificity of 67%.67 In patients with ventilator-acquired pneumonia, mean serum CRP levels 96 hours after diagnosis were significantly lower in patients with appropriate antibiotic treatment than in those with inappropriate empirical treatment (10.3 ± 10 mg/dL vs 19.2 ± 14 mg/dL, P<.05). A CRP ratio of 0.8 at 96 hours was a useful indicator of appropriateness of antibiotic therapy (sensitivity 77%, specificity 87%).

CRP versus Procalcitonin:

Several studies have suggested that procalcitonin (PCT) is a more reliable marker of sepsis than CRP,[111,112] but not all studies support this.113-115 Luzzani and colleagues[112] reported that PCT levels predicted infection and severity of disease more reliably than CRP levels in 70 critically ill patients, and 2 meta-analyses concluded that PCT was a better diagnostic indicator than CRP. However, in patients with acute exacerbations of COPD, Daniels and colleagues[96] reported that CRP levels were higher in patients with sputum positive for bacteria than in those without, whereas PCT levels were the same in the 2 groups. Also, in patients with suspected community-acquired pneumonia and sepsis, Gaini and colleagues[114] reported that CRP was better than PCT as a diagnostic marker for infection and sepsis, whereas

PCT was a better severity marker. A literature review of 18 studies in critically ill patients also concluded that PCT could not reliably differentiate sepsis from other inflammatory conditions.[115]

Eosinopenia

Eosinopenia is an attractive potential biomarker in sepsis, as the eosinophil count is already serially measured in routine clinical practice and the additional costs would therefore be minimal.[116] A study found an AUROC of 0.89 for an eosinophil count cut-off of 50 cells/mm3, performed on admission, in differentiating between non-infected and infected patients in a medical intensive care unit in Morocco. Although this is promising, other studies have found that CRP (cut-off 70 mg/L) and PCT (cut-off 1.5 ng/mL) outperformed eosinopenia as a marker of sepsis (negative predictive value 94%, 87% and 80%, respectively).[117]

Serum Lactate:

Increased blood lactate levels in critically ill patients are generally associated with increased morbidity and mortality.[118,119] Even haemodynamically stable patients with raised lactate levels, a condition referred to as compensated shock, are at increased risk of dying. This not only applies to patients admitted to the intensive care unit; also early in the course of illness, increased blood lactate levels are related to increased morbidity and mortality.

The venous lactate levels can predict 28-day in-hospital mortality. The predictive power of the lactate level is independent of blood pressure and co-variates. In patients with normal blood pressure, increased blood lactate levels (>4.0 mmol/l) are associated with a ten times higher mortality rate than normal lactate levels

(mortality 26.5%).[120] Few studies show that an increased lactate level (> 2.0 mmol/l) s a better predictor of morbidity and mortality than physiological triage criteria (composed of heart rate, blood pressure, Glasgow coma scale and respiratory rate).[121,122]

A systemic imbalance between oxygen delivery (DO_2) and demand causes lactate levels to sharply rise, both in various experimental and in clinical[123] conditions. Increased lactate levels have thus long been used to reflect the presence of tissue hypoxia. Hypoxia results in cell death and thus, if not resolved, leads to organ failure. Increased lactate levels and the duration of hyperlactataemia have indeed been associated with the level of organ failure in patients with septic shock. However, besides this anaerobic mechanism, aerobic processes are also known to raise lactate levels in critically ill patients. First, increased aerobic glycolysis by cytokine-mediated cellular uptake of glucose or by catecholamine-stimulated Na-K pump hyperactivity[124] can result in increased pyruvate production that exceeds the capacity of the pyruvate dehydrogenase enzyme complex (PDH) and thus results in increased lactate levels by mass effect. Second, in sepsis, PDH dysfunction has been reported[125]. Third, the lung is known to produce lactate, probably marking metabolic adaptations in response to inflammatory mediators rather than tissue hypoxia.[126] Finally, reduced clearance of lactate will result in increased levels even when lactate production is not increased. In hemodynamically stable patients with sepsis, impaired clearance has been associated with increased lactate levels.

Lactate clearance can be defined as the percentage lactate decrease over the initial six hour evaluation and treatment period. It is shown that, the higher the lactate clearance, the lower the mortality. In fact, mortality was reduced approximately 11%

for each 10% increase in lactate clearance. Patients with a lactate clearance >10% had a greater improvement in Acute Physiology And Chronic Health Evaluation (APACHE) II scores and lower 60-day mortality.[127]

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with Sepsis and Systemic Inflammatory Response Syndrome (SIRS) during the period of January 2012 to December 2012.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2012 to December 2012.

Method of collection of data

Source of Data

This study was conducted on patients admitted with Sepsis or SIRS in Medical Intensive Care Unit (MICU) at KLES Dr Prabhakar Kore Hospital and Medical Researcgh Centre, Belgaum. The MICU is equipped with a split level air conditioning system having nurse patient ratio of 1:3 for ventilated patients. It has facilities for conventional ventilatory support and rigorous monitoring of all critically ill patients.

Sample size and sampling method

A total of 50 patients admitted with Sepsis or SIRS during the study period at MICU, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belgaum were included in the study.

Selection criteria

Inclusion Criteria

- All MICU patients above the age of 18 years of either gender admitted with SIRS or Sepsis were included in the study.

Exclusion Criteria

- Major trauma, burns, surgery
- Patients who had received massive blood transfusion;
- Chronic infection necessitating antibiotic use
- Immunosuppression

Sepsis and SIRS were diagnosed as per the American College of Chest Physicians/Society of Critical Care Medicine Consensus criteria:

Systemic Inflammatory Response Syndrome (SIRS): defined as the presence of at least two of the following:

1. Body Temperature >38^{o}C or <36^{o}C
2. Heart Rate > 90/min
3. Respiratory Rate >20/min or PaCO2 <32mm Hg
4. White Blood Cell Count >12.0 x 10^{9}/L or <4.0 x 10^{9}/L or >10% immature band forms.

Sepsis:

It is defined as, Systemic Inflammatory Response Syndrome plus clinical or laboratory evidence of infection.

Severe Sepsis:

It is defined as Sepsis associated with organ dysfunction, systemic hypoperfusion or hypotension.

Septic shock:

It is defined as Sepsis with hypotension despite adequate fluid replacement.

Procedure

The study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Belgaum. Patients Admitted in MICU under the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were evaluated based on diagnostic criteria for SIRS or Sepsis based on American College of Chest Physicians/Society of Critical Care Medicine Consensus criteria. The selected patients were briefed about the nature of the study and a written informed consent was obtained (Annexure–I).

Demographic data like gender and age were collected along with relevant history and recorded on predesigned and pretested proforma (Annexure-II). A thorough clinical examination was conducted and the findings were also recorded.

All relevant data from patient's medical records, bed-side flow sheets including gender, age, admission diagnosis were noted. History of preexisting diseases like Diabetes Mellitus, Hypertension, Stroke, Ischaemic Heart Disease, and previous admission to hospital and present symptomatology was listed and detailed physical examination was done. Details of medical interventions were recorded.

Blood sample will be collected for Complete Blood Count, Liver function tests, Renal function tests, HIV ELISA, and Serum Procalcitonin, within 24 hours of

admission. Appropiate cultures will be taken. Chest X-ray and other imaging modalities will be done as required.

SAMPLE COLLECTION

Approximately, 20ml of blood was collected from the peripheral venous site.

The venepuncture site was disinfected with surgical spirit (70% alcohol) rubbing vigorously and allowed to dry. This was followed by application of Povidone iodine in concentric circles over the site and allowed to dry for at least I minute. About 20 ml of blood was collected, out of which 15ml was inoculated aseptically into blood culture bottle, 2ml was collected in sterile bottle to separate serum for Procalcitonin and CRP, 1ml of blood was collected in a sterile bottle containing the anticoagulant EDTA for estimation of complete blood count, and 2ml for renal and liver function tests.

Blood culture

About 15ml of blood was drawn aseptically and inoculated into a blood culture bottle. After inoculation, the blood culture bottles were incubated at 37 degree centigrade under aerobic conditions in the incubator for 7 days. The first subculture was done after 24 hours of incubation, the second on the third day and final on the seventh day.

Subcultures were done on to chocolate agar, 5% sheep blood agar and Mac Conkey agar plates. The inoculated plates were incubated aerobically in the incubator for 37 degree centigrade and the plates were observed for growth. The growth was identified by colony characteristics, grams stain and biochemical tests.

Cultures which did not yield any growth following three subcultures were reported negative at the end of 7 days.

PROCALCITONIN

Procalcitonin level analysis was done using enzyme linked immunoflourescence assay by using VIDAS BRAHMS PCT KIT manufactured by BIOMERIUX INDIA (P) LTD.

CRP:

CRP analysis was done using LATEX AGGLUTINATION METHOD which is a qualtitative method of analyzing CRP level.

Other hematological tests

A drop of EDTA blood was taken on a clean dry slide and a thin tongue shaped smear was made, air dried and stained with Leishman stain. The Total count, absolute neutrophil count and band cell ratio were calculated as per standard hematological methods. Other tests were performed as and when required using standardized methods.

Statistical analysis

The data obtained was tabulated on Excel spread sheet (Annexure IV). The data was expressed as rates, ratios and percentages. The continuous variables were expressed as mean and standard deviation (SD). The data will be compared using unpaired‘t’ test. A probability value (p value) of less than or equal to 0.05 was considered as statistically significant.

The Statistical software namely **SPSS 15.0,** was used for the analysis of the data and Microsoft Word and Excel have been used to generate graphs, tables etc**.** Significance is assessed at 5% level of significance.

Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups.

Diagnostic statistics viz. Sensitivity, Specificity, PPV, NPV, was computed and 90% confidence interval computed in the study.

RESULTS

This cross sectional study was conducted in Medical ICU, KLE's Dr. Prabhakar Kore Hospital and Research Centre over a period of one year from January 2012 to December 2012. The blood samples from 50 patients meeting the inclusion and exclusion criteria constituted the material for study.

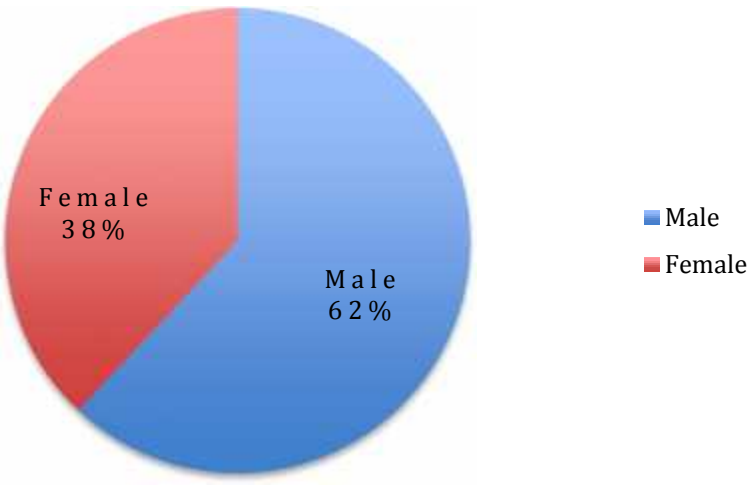
Distribution of cases according to sex (n=50)

Among the 50 patients, there were 31 (62%) males, and 19 (38%) females.

Table 1: Distribution of cases according to sex (n=50)

Sex	No.	Percent
Male	31	62
Female	19	38
Total	50	100

Fig.7: Distribution of cases according to sex

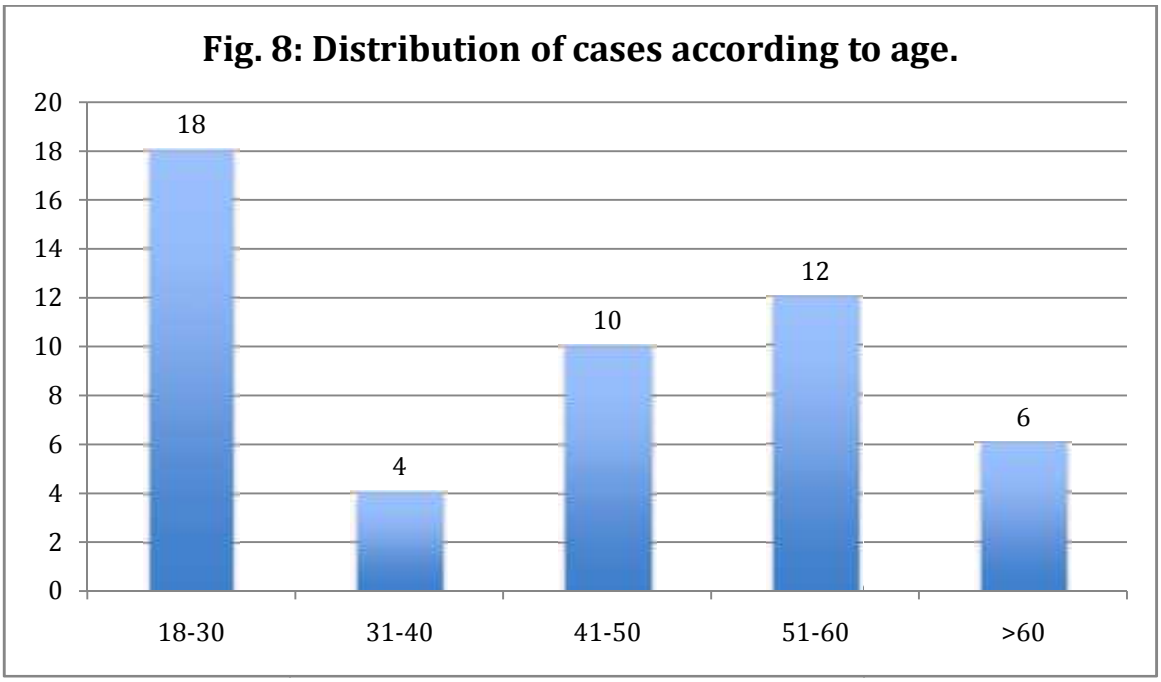


Distribution of cases according to age (n=50)

Among the 50 patients, most number of patients were seen in age group of 18-30 years (36%), followed by those between 51-60 years (24%)

Table 2: Distribution of cases according to age (n=50)

Age (in years)	No.	Percentage
18-30	18	36
31-40	4	8
41-50	10	20
51-60	12	24
>60	6	12
Total	50	100

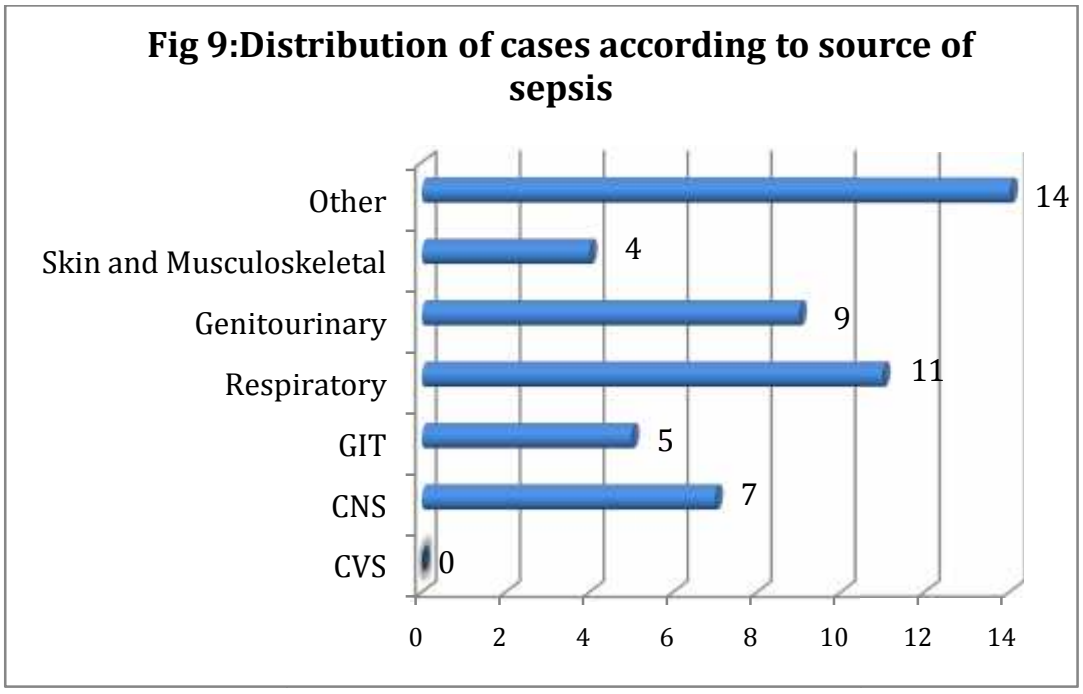


Distribution of cases according to source of sepsis

Among 50 patients who developed signs of sepsis, 22% had respiratory problems, followed in frequency by Genitourinary (18%) and Neurological (14%) diseases.

Table 3: Distribution of cases according to source of sepsis/SIRS

Source of sepsis	No.	Percentage (%)
Respiratory system	**11**	**22**
Cardiovascular system	**0**	**0**
Gastrointestinal	**5**	**10**
Genitourinary	**9**	**18**
CNS	**7**	**14**
Other	**14**	**28**
Skin & Musculoskeletal system	**4**	**8**
Total	**50**	**100**



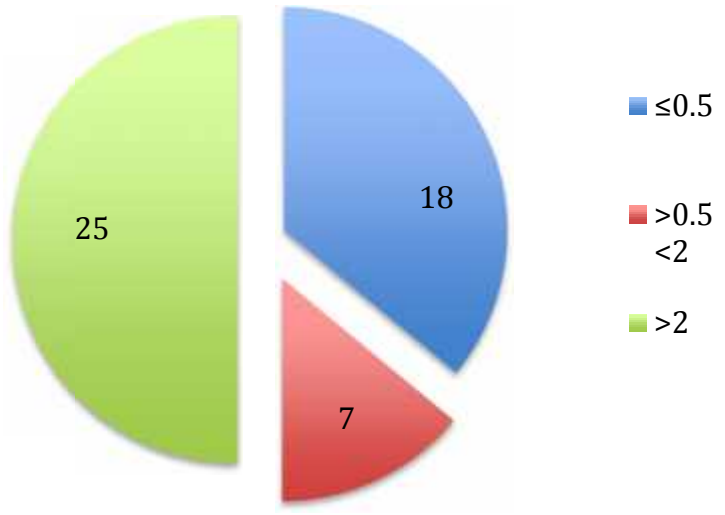
Frequency distribution of Procalcitonin

Among 50 patients, Procalcitonin was ≤0.5ng/ml in 18 (36%), >0.5 and <2 in 7 (14%) and ≥2 in 25 (50%) patients.

Table 4: Frquency distribution of Procalcitonin

Procalcitonin (ng/ml)	Number	Percent
≤0.5	18	36
>0.5 - <2	7	14
≥2	25	50
Total	**50**	**100**

Fig.10:Frequency distribution of Procalcitonin

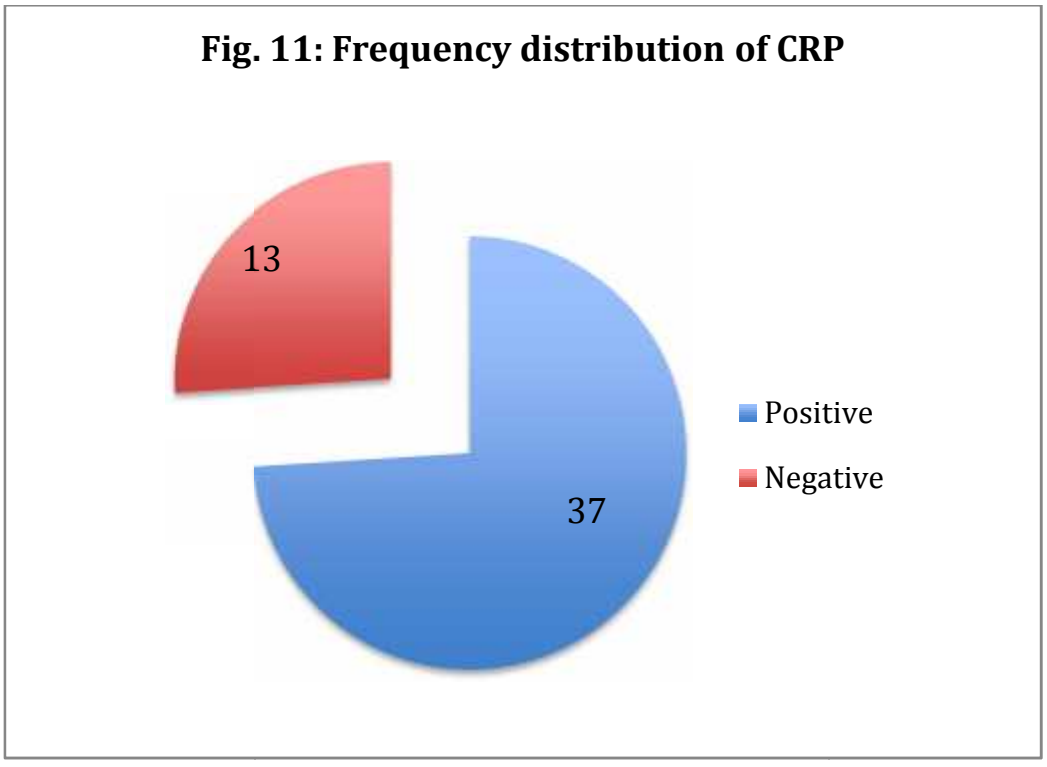


Frequency distribution of CRP

Among 50 cases, CRP was positive in 37 (74%) and negative in 13 (26%) patients.

Table 5: Frequency distribution of CRP

CRP	Number	Percent
Positive	18	36
Negative	7	14
Total	**50**	**100**

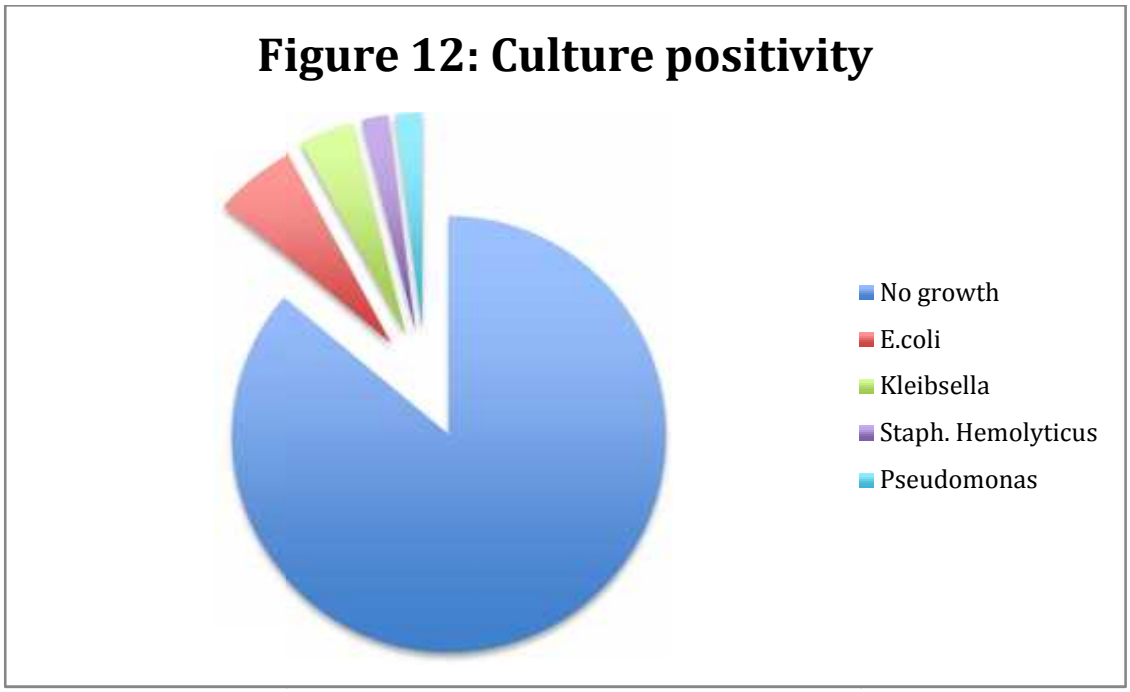


Distribution of Blood culture cases

Of total 50 cases, 43 (88%) had blood culture negative, and 7 cases were positive, of which 2 (4%) had Klebsiella positive, 3 (6%) cases had E. coli growth, and 1 (2%) each had Coagulase negative staphylococcus and Pseudomonas aeruginosa.

Table 6: Frequency of Organisms isolated

	No.	Percentage (%)
No Growth	43	86
Escherichia coli	3	6
Kleibsella pneumonia	2	4
Staphylococcus hemolyticus	1	2
Pseudomonas aeruginosa	1	2

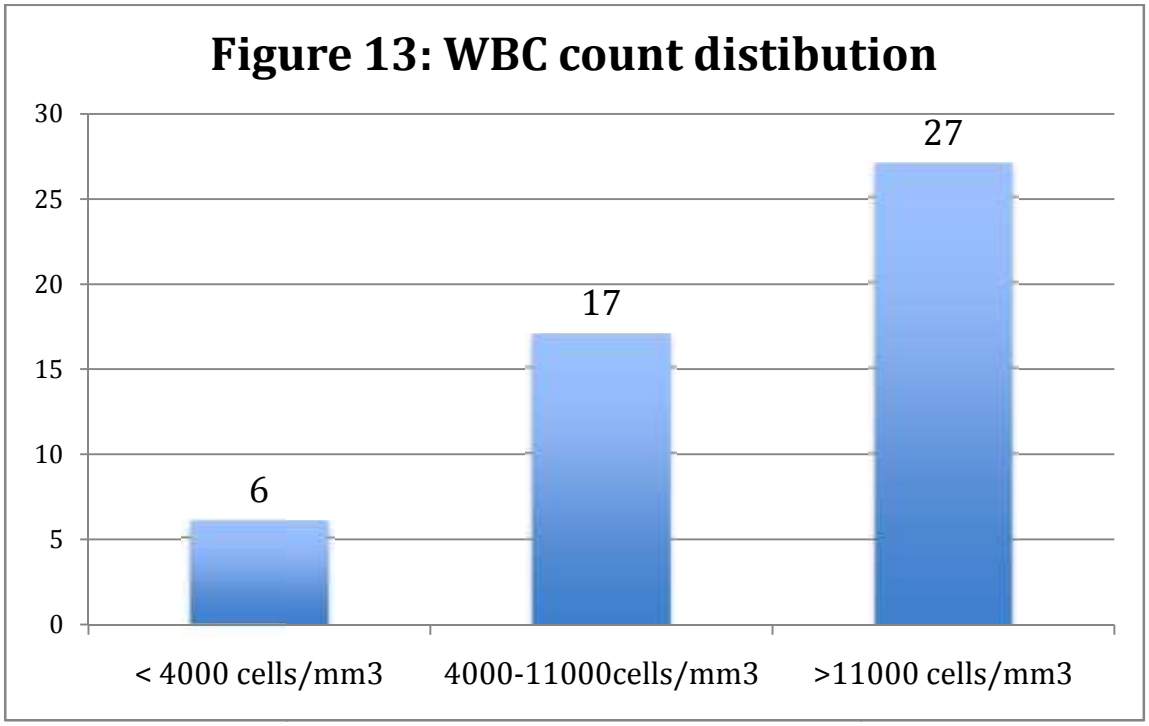


Distribution of cases according to Total blood count

Among the 50 patients, Total count was < 4000 in 6 (12%) patients, and 4000-11000 in 17 (34%) patients, and >11000 in 27 (54%) patients

Table 7: WBC count distribution

WBC count (cells/mm3)	Number	Percent
<4000	6	12
4000-11000	17	34
>11000	27	54
Total	**50**	**100**



Distribution of cases according to final diagnosis

Among the 20 cases, sepsis was observed in 27 (54%) of cases, and SIRS was observed in 23 (46%) of cases.

Table 8: Distribution of cases according to final diagnosis

Diagnosis	Number	Percent
SIRS	27	54
Sepsis	23	46
Total	**50**	**100**

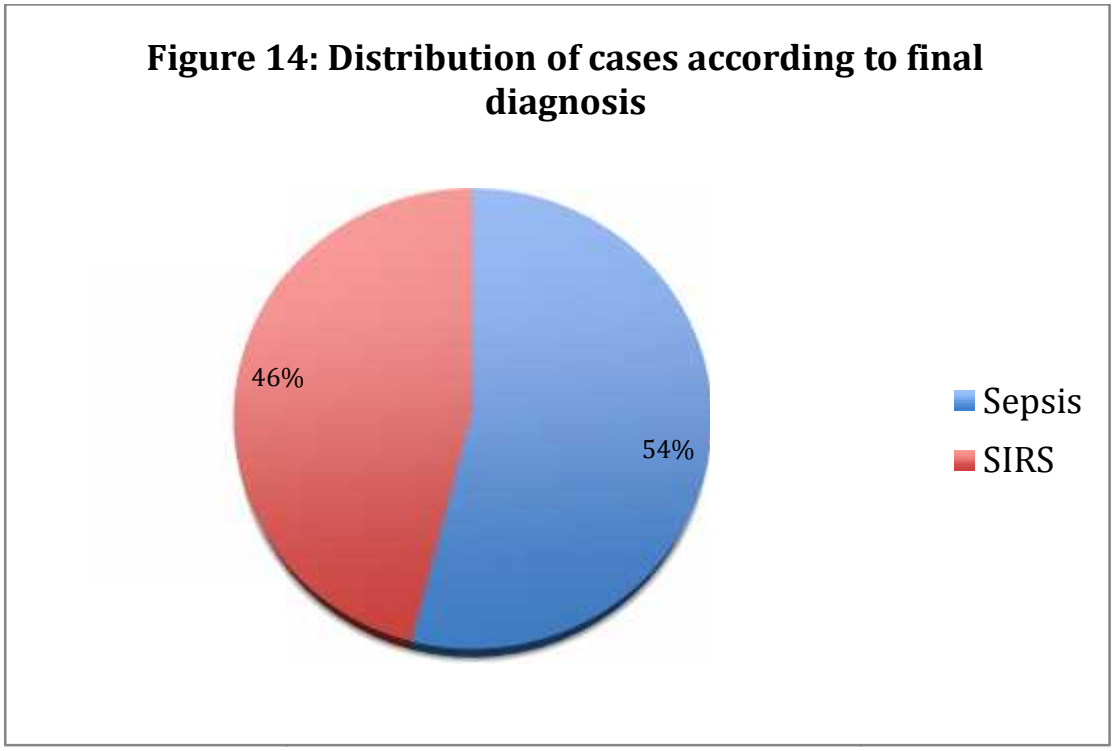


Table 9: Sensitivity, Specificity and Predictive values of Procalcitonin (Cut-off 2ng/ml)

Sepsis/PCT	Positive (≥2ng/ml)	Negative	Total
Present	23	4	27
Absent	1	22	23
Total	24	25	50

X^2=0.375 p=0.54

The Sensitivity of Procalcitonin for diagnosing sepsis at a cut off of ≥2ng/ml was 85.2%, with a Specificity of 95.8%, Positive Predictive value of 95.6%, and a Negative Predictive Value of 88%.

Table 10: Sensitivity, Specificity and Predictive values of Procalcitonin (Cut-off 0.5ng/ml)

Sepsis/PCT	Positive (>0.5ng/ml)	Negative	Total
Present	26	1	27
Absent	6	17	23
Total	32	18	50

X^2 = 2.89 p=0.09

The Sensitivity of Procalcitonin for diagnosing sepsis at a cut off of 0.5ng/ml was 96.3%, with a Specificity of 73.9%, Positive Predictive value of 81.3%, and a Negative Predictive Value of 94.4%.

Table 11: Sensitivity, Specificity and Predictive values of CRP

Sepsis/CRP	Positive	Negative	Total
Present	22	5	27
Absent	15	8	23
Total	37	13	50

The Sensitivity of CRP for diagnosing sepsis was 81.5%, with a Specificity of 34.8%, Positive Predictive value of 59.5%, and a Negative Predictive Value of 61.5%.

Table 12: Sensitivity, Specificity and Predictive values of abnormal WBC count

Sepsis/WBC	Abnormal	Normal	Total
Present	20	7	27
Absent	13	10	23
Total	33	17	50

The Sensitivity of Leucocytosis or Leucopenia for diagnosing sepsis was 74.1%, with a Specificity of 43.5%, Positive Predictive value of 60.6%, and a Negative Predictive Value of 50.8%.

Table 13: Sensitivity, Specificity and Predictive values of Eosinopenia

Sepsis/Eosinopenia	Present	Absent	Total
Present	13	14	27
Absent	13	10	23
Total	26	24	50

The Sensitivity of Eosinopenia for diagnosing sepsis was 48.1%, with a Specificity of 43.5%, Positive Predictive value of 50%, and a Negative Predictive Value of 41.7%.

Table 14: Sensitivity, Specificity and Predictive values of Lactate levels

Sepsis/Lactate	≥2 mmol/L	<2 mmol/L	Total
Present	16	11	27
Absent	12	11	23
Total	28	22	50

The Sensitivity of Hyperlactatemia for diagnosing sepsis was 59.3%, with a Specificity of 47.8%, Positive Predictive value of 57.1%, and a Negative Predictive Value of 50%.

Table 15: Sensitivity, Specificity and Predictive values of A:G ratio

Sepsis/AG ratio	≤ 1	>1	Total
Present	23	4	27
Absent	19	4	23
Total	42	8	50

The Sensitivity of abnormal A:G ratio for diagnosing sepsis was 85.2%, with a Specificity of 17.4%, Positive Predictive value of 54.8%, and a Negative Predictive Value of 50%.

Table 16: Sensitivity, specificity, Positive Predictive Value (PPV) and Negative predictive value (NPV) of laboratory parameters in predicting sepsis

Parameter	Sensitivity	Specificivty	PPV	NPV
Procalcitonin (>0.5ng/ml)	96.3	73.9	81.3	94.4
Procalcitonin (≥2ng/ml)	85.2	95.8	95.6	88
CRP	81.5	34.8	59.5	61.5
WBC count	74.1	43.5	60.6	50.8
Eosinopenia	48.1	43.5	50	41.7
Lactate (>2mmol/L)	59.3	47.8	57.1	50
A:G ratio	85.2	17.4	54.8	50

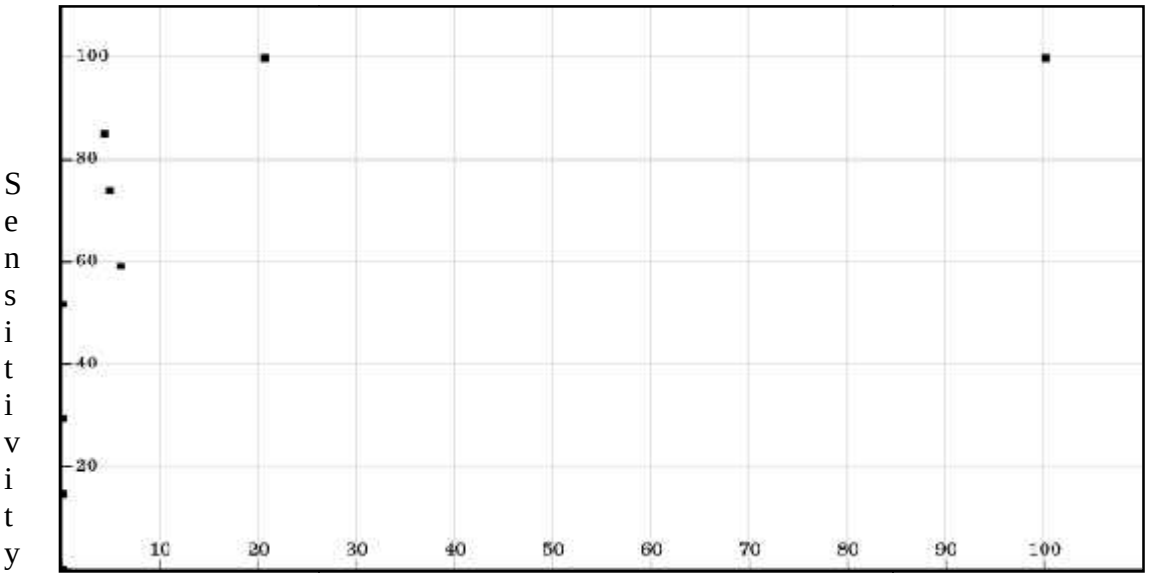
The study shows that Procalcitonin has the highest sensitivity and specifity for diagnosing sepsis. Further, increasing the cut-off of serum procalcitonin from 0.5ng/ml to 2ng/ml increases the specificity from 73.9% to 95.8%, but the sensitivity decreases from 96.3% to 85.2%.

Table 17: Evaluation of Procalcitonin, CRP, serum Lactate, Eosinopenia, WBC count, AG ratio and Culture positivity in patients with SIRS and Sepsis.

Parameter	Total (n=50)	SIRS (n=23)	Sepsis (n=27)	p value
Age	41.2	30.5	51.9	-
Male gender	32	13	19	-
WBC count (cells/mm3)	13914	11817	16011	0.11
Neutrophilia (% of WBC)	73.5	69.1	80.8	0.02
Eosinophil count (cells/mm3)	113.2	115.7	111.1	0.84
CRP positivity (%)	74	65.2	81.5	0.22
Serum Lactate (mmol/L)	2.53	2.51	2.54	0.92
AG ratio	0.75	0.81	0.7	0.14
Serum Procalcitonin (ng/ml)	2.07	0.48	3.42	<0.01
Mortality (%)	20	21.7	18.5	

The study shows that, Serum Procalcitonin is elevated more in cases of Sepsis than SIRS (3.42 v/s 0.48, $p<0.01$), which is statistically significant.

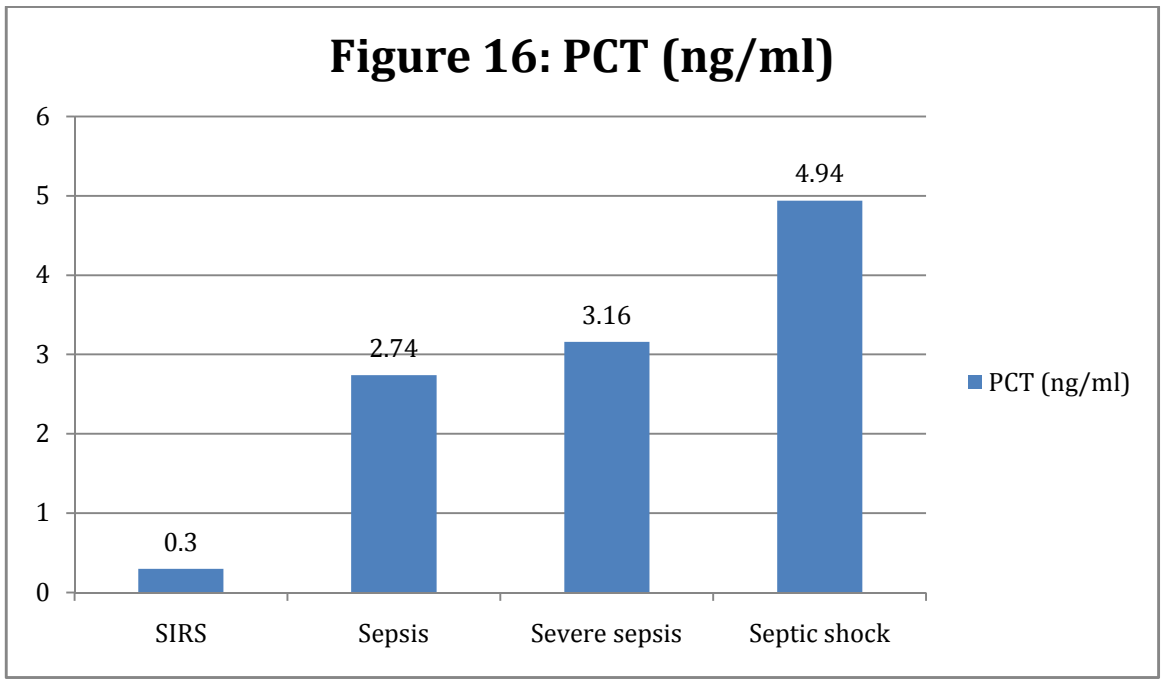
Figure 15: AUROC for PCT



From the above graph for area under receiver operator characteristics, it can be seen that the optimal cut-off value for PCT using Youden index is ≥2 ng/ml, with a sensitivity of 85.2%, and specificity of 95.8%

Procalcitonin in SIRS, Sepsis and Septic shock:

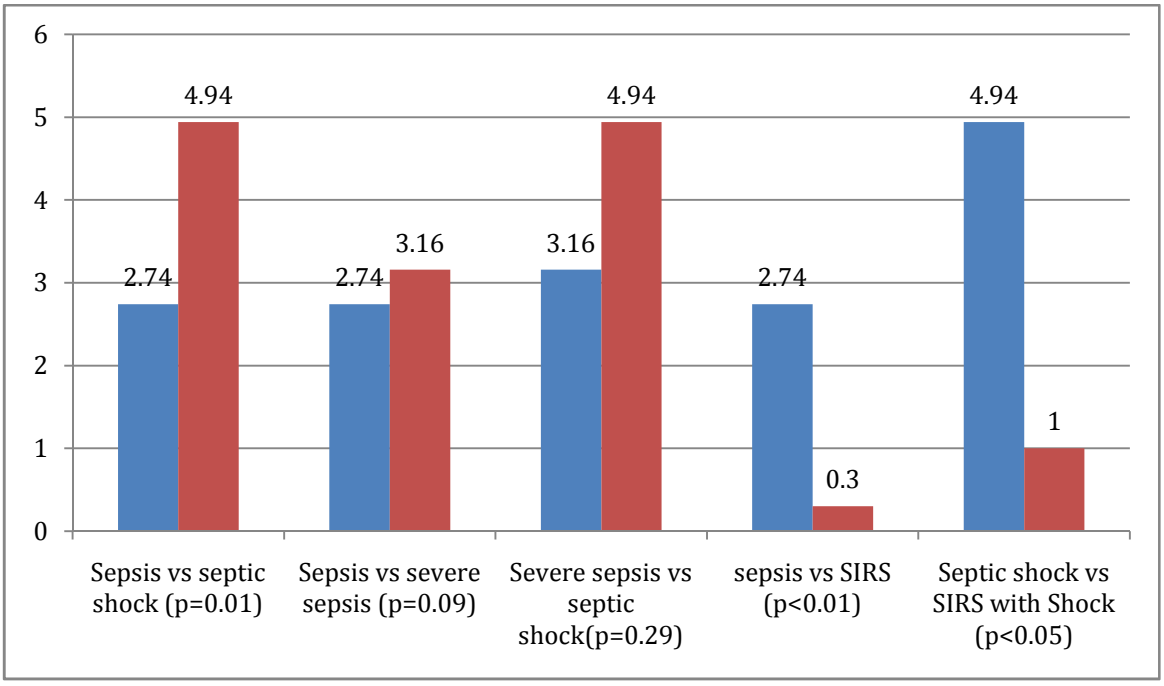
Serum Procalcitonin showed an increase in patients with sepsis (3.42ng/ml) compared to those with SIRS (0.48ng/ml, $p<0.01$). Also, the elevation of PCT in patients with Septic shock (4.94ng/ml) was significantly more than in patients with Sepsis (2.74ng/ml, $p=0.01$)



Co-relation of Procalcitonin with sespsis and SIRS:

Our study shows that, there is a significant elevation of serum PCT in patients with Septic shock compared to sepsis (4.94 v/s 2.74ng/ml, p=0.01). Also, there is more increase in serum PCT values in patients with septic shock compared to severe sepsis, in those with Severe sepsis compared to Sepsis, and in patients with Sepsis compared to SIRS, although these were statistically not significant. There is also a significant rise of PCT in patients with Septic shock compared to patients with SIRS and shock.

Figure 17: Co-relation of PCT levels with Sepsis severity



DISCUSSION

We analyzed the plasma concentrations of various markers with respect to their potential use in differentiating between patients suffering from SIRS and those suffering from sepsis. This assessment is of potential interest because systemic inflammation is a common problem in the ICU, which often leads to shock and death. The diagnostic repertoire for identifying SIRS is poor. Verification of infection site, and even the presence of infection, remains problematic in sepsis. In 20–30% of patients, the infection site is never identified. Neither imaging studies nor blood culture analysis can rule out the presence of infection.[1]

Moreover, there are classes of patients with unconfirmed infection, or for whom cultures are negative yet who develop similar symptoms, rates of organ failure and survival outcomes as do those patients in whom infection is confirmed. The availability of laboratory tests for accurate and rapid identification of septic patients by isolation of micro-organisms from body fluid specimens would be of considerable value. Thus, there is a clear need for a reliable diagnostic procedure that allows early discrimination between patients suffering from SIRS and those with sepsis.

A relatively new marker that has been associated with inflammation and sepsis is PCT, a 116-amino-acid protein that is the precursor to calcitonin. The PCT plasma level in healthy individuals is low, usually below 0.1 ng/ml.[2] That PCT concentration is significantly elevated in patients with organ dysfunction is undoubted. However, the difference in PCT between patients with SIRS and those with sepsis may be small.

Not surprisingly, the diagnostic sensitivity and specificity of PCT has been compared with other acute phase reactants in their ability to diagnose sepsis.[3,4]

The present study was undertaken to estimate the levels of serum Procalcitonin in patients with SIRS and Sepsis and to estimate PCT levels with different degrees of severity of Sepsis.

The present one year hospital based cross sectional study was done on a total of 50 patients with SIRS or Sepsis, based on American College of Chest Physicians/Society of Critical Care Medicine Consensus criteria, from January 2012 to December 2012 in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

In the present study 62% of patients were males and 38% were females. The male to female ratio was 1.63:1. In the present study of the 27 patients with sepsis, 18 (66.67%) were males and 9 (33.33%) were females. Among 23 patients with SIRS, 13 (56.52%) were males and 10 (43.48%) were females. No statistically significant difference was observed between sex and PCT levels.

In this study 18 to 30 years was the commonest age group, which comprised of 36% patients, followed by 51 to 60 years with 24% of patients. The mean age among males was 41.70 ± 14.73 years while in females it was 42.73 ± 20.45 years. The incidence of Sepsis was less in people aged ≤ 50 years compared to those >50 years of age, while that of SIRS was more in the younger age group, ≤ 50 years. 16 out of 18 people (88.89%) aged >50 years had sepsis, while 11 out of 32 people (34.38%) ≤ 50 years of age had sepsis.

In the present study serum PCT levels were significantly higher in patients with Sepsis compared to patients with SIRS. The mean PCT levels were 2.07 ± 2.12

ng/ml. The mean Serum PCT values in patients with SIRS and Sepsis were 0.48 ± 0.57 ng/ml and 3.42 ± 2.07 ng/ml respectively ($p<0.01$).

Summing up, the Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of PCT (≥2ng/ml) were 85.2%, 95.8%, 95.6% and 88% respectively. A review to explore the association between PCT and Sepsis in humans found that, patients with sepsis have, on average, higher serum levels of PCT than matched patients with SIRS.

High serum PCT concentrations were first described by Assicot and coworkers[5] in children with severe bacterial infections, and were suggested to be a specific marker for bacterial infection. Al-Nawas and coworkers[6] reported higher PCT levels in patients with clinically documented infection than in those fulfilling the criteria for SIRS.

Two studies compared PCT and CRP in ICU patients and found that PCT had poorer sensitivity, specificity and AUC than did CRP as a marker of sepsis.[7,8] In order to assess the diagnostic utility of PCT and CRP in a medical ICU, prospective measurements were conducted in 101 consecutive patients with acute SIRS or sepsis. PCT did not clearly discriminate SIRS from sepsis.[7] Another group from Germany reported average PCT concentrations of 0.4 ± 3.0 ng/ml for SIRS, 0.5 ± 2.9 ng/ml for sepsis and 6.9 ± 3.9 ng/ml for severe sepsis. On the basis of their findings, the investigators concluded that PCT, CRP, white blood cell count, and body temperature does not discriminate SIRS from sepsis, and PCT was the only parameter to discriminate between sepsis and severe sepsis.[9]

Selberg and coworkers[10] studied discrimination of sepsis and SIRS by determination of circulating plasma concentrations of PCT, IL-6 and C3a in a medical ICU. Their data indicated that of PCT, IL-6 and C3a concentrations are more reliable parameter for differentiating between septic and SIRS patients than are CRP and elastase.

Muller *et al*,[3] enrolled 101 consecutive adult patients admitted to a medical intensive care unit with a predicted length of stay greater than 24 hr and divided them according to diagnoses: no SIRS and no infection, SIRS and no infection, sepsis, severe sepsis and septic shock. At a cut-off of 1.0 ng/mL, PCT levels were significantly elevated in patients with sepsis, severe sepsis and septic shock compared with those without SIRS or infection. PCT was the most accurate laboratory test variable for the diagnosis of infection with a sensitivity of 89%, specificity 94%, negative predictive value 90% and positive predictive value 94%, and was superior to CRP, IL-6 and serum lactate levels. PCT levels were also significantly higher in non-survivors.

In another well-conducted prospective blinded trial by Harbarth *et al*,[11] the investigators measured PCT, IL- 6, IL-8 and CRP levels in 78 consecutive patients admitted to a joint medical and surgical intensive care unit with SIRS. Sixty patients (77%) had clinically suspected infection of which 44 had microbial infection and 23 had bacteraemia. Median PCT concentrations were 0.6 (range 0 - 5.3) ng/mL in SIRS, 3.5 (range 0.4 - 6.7) ng/mL in sepsis, 6.2 (range 2.2 - 85) ng/mL in severe sepsis and 21.3 (range 1.2 - 654) ng/mL in septic shock. At a cut-off value of 1.1 ng/mL, PCT was shown to yield a sensitivity of 97%, specificity of 78% and area under the reciever operating curve 0.92 (CI 0.85 - 1.0) to differentiate patients with SIRS from

those with sepsis, severe sepsis and septic shock. The serum level of PCT was a stronger predictive marker than IL-6 and IL-8. The authors also noted that a slow decrease or no decrease in PCT levels 48 hr after admission was correlated with a poor outcome. In those who died, the serum PCT level never fell below 1.1 ng/mL except for one time point in one patient. Four patients had a recurrent sepsis, which were associated with further spikes in PCT levels.

There is no agreement, however, regarding the benefit of PCT compared with C-reactive protein for investigation of SIRS. In a study of 101 patients, Suprin *et al*,[12] concluded that although C-reactive protein and PCT levels were both significantly elevated in patients with sepsis, C-reactive protein, at a cut-off of 100 mg/L had a greater sensitivity and specificity than PCT (cut- off 2 ng/mL) for discriminating between sepsis and non- septic SIRS: 70% vs 65% and 74% vs 70%. A prospective observational study by Ugarte *et al*,[13] showed that as a marker of infection and compared with C-reactive protein, PCT had a lower sensitivity (67.6% vs 71.8%) and specificity (61.3% vs 66.6%). In contrast to C-reactive protein, however, PCT was significantly elevated in bacteraemic patients and in non-survivors leading the authors to conclude that although PCT was inferior as a marker for infection, it was a useful prognostic indicator. The authors also suggested that combining PCT and C-reactive protein measurements might improve the diagnostic specificity of PCT.

One category of patients in whom infection is notoriously difficult to diagnose is the post chemotherapy neutropenic group. Giamarellos- Bourboulis *et al*,[14] examined the sensitivity of PCT as a marker of infection in 115 post-chemotherapy neutropaenic patients presenting with fever. The value of PCT as a marker of infection was strongest on the first day of febrile neutropaenia. Median values for

bacteraemic patients and those with localised bacterial infections were 8.23 ng/mL and 0.86 ng/mL respectively (p = 0.017). At a cut-off of 2 ng/mL, PCT had a sensitivity of 91%, specificity of 87% and a negative predictive value of 77% for the diagnosis of severe sepsis. In addition, 60% of patients with a pyrexia of unknown origin who responded clinically to empirical antibiotic therapy had PCT levels > 0.5 ng/mL, compared with 6.7% of those with a pyrexia of unknown origin who did not respond to antibiotics. In all cases, clinical resolution of infection was accompanied by a rapid fall in PCT levels to values similar to control values by the second day of treatment. Conversely, persistence of infection was associated with a higher PCT level.

PCT levels are also modestly elevated in a variety of non- infectious conditions including burns (especially electrical and inhalation burns),[15] cardiopulmonary bypass,[16,17] heat stroke[18] and in cardiogenic shock.[19]

Wanner *et al*,[20] studied 405 patients to ascertain the usefulness of PCT in the posttraumatic period to diagnose sepsis and the multiple organ dysfunction syndrome. They confirmed that PCT correlated with injury severity according to the ISS but determined that in low-ISS (> 25) and high-ISS (< 25) groups, PCT values at days 1 and 3 were significantly elevated in those who developed sepsis compared with those who did not. They concluded that at a cut-off of 1.5 ng/mL (peak values day 1 or day 3), PCT could be used to discriminate sepsis from non-infectious SIRS with 3 or 4 criteria with a sensitivity of 76% and a specificity of 77%.

Previous studies compared CRP, and many other biomarkers with PCT separately for differentiating SIRS from sepsis. In the present study, many of the routinely available biochemical markers were measured at the same. PCT (>0.5ng/ml)

had the highest sensitivity for differentiating SIRS from sepsis, followed by PCT (≥2ng/ml), A:G ratio, CRP, and WBC count, 96.3%, 85.2%, 85.2%, 81.5%, and 74.1% respectively. PCT (≥2ng/ml) had the highest specificity (95.8%) for differentiating SIRS from sepsis, followed by PCT (>0.5ng/ml), Lactate and WBC count, 73.9%, 47.8%, 43.5%. CRP had a poor specificity of 34.8%. In our study, average PCT concentrations were 0.48 ± 0.57 ng/ml for SIRS, 2.74 ± 0.71 ng/ml for sepsis, 3.16 ± 1.74 ng/ml for severe sepsis, and 4.94 ± 3.15 ng/ml for septic shock. Thus, in agreement with previous studies,[21,10] PCT was a more reliable marker in the diagnosis of sepsis than other measures.

Overall, increase in serum Procalcitonin was found to be more in patients with sepsis and was found to be better predictor for differentiating SIRS from Sepsis, compared to CRP, WBC count and other routine markers. There is also a relationship between increasing values of PCT and increasing severity of sepsis, with Septic shock patients having much higher increase in PCT values compared to those with Sepsis and SIRS.

Limitations:

The present study included consecutive unselected patients who were representative of an ICU population, with baseline characteristics similar to those reported in the literature, and strict objective criteria for the diagnosis of infection were employed.

However, several criticisms of the study should be addressed. First, PCT was not monitored every day, and a shorter monitoring interval may improve its performance as an aid for diagnosis and follow up of sepsis. Second, with the use of

clinical criteria and microbiological evidence, it might have been difficult to ascertain the exact etiology of SIRS in all patients. This may have introduced some misclassification bias. Third, antimicrobial therapy may have an impact on PCT values. Our study design did not allow us to explain the exact relationship between antimicrobial therapy and PCT values. The temporal relationship between PCT and antibiotic treatment should be assessed in further studies.

CONCLUSION

The advent of serum PCT as a marker of infection represents a new strategy in the diagnosis of sepsis. The usefulness of serum PCT measurements as a marker may be summarised as,

- To distinguish between infectious and non infectious causes of SIRS,
- To differentiate between bacterial and viral sepsis, and
- To assess the severity of infection and judge the response to therapy.

However, there are caveats. Firstly, a number of non-infectious conditions can give rise to elevations in PCT levels and should not necessarily be used as an indication to commence antimicrobial therapy. Secondly, the cut off value of PCT giving the optimum sensitivity and specificity for the diagnosis of infection varies with different conditions. Thirdly, localised infections may cause no increase in PCT levels. Finally, a falling PCT level in response to antibiotic therapy does not necessarily imply eradication of infection, but merely that the systemic response is under control.

In the present study, PCT appeared to be a more accurate diagnostic parameter for differentiating between patients suffering from SIRS and those with sepsis. Routine determination of PCT may improve management of patients, for example by preventing the use of unnecessary antibiotics that are known to select resistance strains. Further studies of the early phases of sepsis are necessary to define the role of PCT in possible therapeutic strategies, such as antimicrobial and immunological therapies, and cost implications.

Concerning the function of PCT, a number of unanswered questions remain. For example, what is the biological role of PCT? What are its target receptors? Does it have any protective value? Answers to these questions might enhance the value of assaying this peptide.

SUMMARY

This is a prospective study conducted over a period of one year from January 2012 to December 2012.

50 consecutive patients admitted with Sepsis or SIRS admitted in MICU were included in the study. Males were 31 (62%) and females were 19 (38%). Among the 50 patients, most number of patients were seen in age group of 18-30 years (36%), followed by those between 51-60 years (24%)

Out of 50 patients, SIRS was seen in 23 (46%) of cases, sepsis was observed in 13 (26%) of cases, Severe Sepsis in 7 (14%) cases and septic shock was observed in 7 (14%).

Regards to source of sepsis, 11 (22%) had respiratory system involvement, 9 (18%) had Genitourinary involvement, 9 (18%) had gastrointestinal tract related problems, 7 (14%) had CNS related problems, 4 (8%) had skin and soft-tissue infections, while 14 (28%) had other focus of sepsis or SIRS.

Procalcitonin (cut-off ≥2ng/ml) was positive in 25 (50%). CRP was positive in 37 (74%) and negative in 13 (26%).

7 (14%) of cases had blood culture positive and Escherichia coli was the commonest organism isolated (6%)

Total count was <4000 in 6 (12%) patients and, >11,000 was noted in 27(54%) of patients and in the remaining 17 (34%) WBC count was normal.

Procalcitonin (≥2ng/ml) in comparison with CRP, had a sensitivity of 85.2%, specificity was 95.8%, PPV was 95.6%, and NPV was 88%.

CRP in comparison with Procalcitonin, sensitivity was 81.5%, specificity was 34.8%, PPV was 59.5%, and NPV was 61.5%.

Serum Procalcitonin showed an increase in patients with sepsis (3.42ng/ml) compared to those with SIRS (0.48ng/ml, $p<0.01$). Also, the elevation of PCT in patients with Septic shock (4.94ng/ml) was significantly more than in patients with Sepsis (2.74ng/ml)

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ANNEXURE I – CONSENT FORM

"ESTIMATION OF SERUM PROCALCITONIN LEVELS IN PATIENTS WITH SYSTEMIC INFLAMMATORY RESPONSE SYNDROME AND SEPSIS – A ONE YEAR CROSS-SECTIONAL STUDY."

Objective and purpose of the study:

This research is intended to estimate the Serum Procalcitonin levels in patients with Systemic Inflammatory Response Syndrome and Sepsis.

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample and get a chest x ray done for the same study.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn. You may also face some radiation hazards while getting an x ray done.

Alternatives

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

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

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

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

Financial incentives for participation

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

Authorization to publish the results

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

If you have any questions about my rights as a participant you may call:

CONSENT FORM

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

ANNEXURE II – PROFORMA

Patient Name: I.P number:

Age: Sex:

Address: Occupation:

Date of admission: Date of discharge:

SYMPTOMS:

Fever	Yes/No
Cough with expectoration	Yes/No
Breathlessness	Yes/No
Burning micturition	Yes/No
Headcahe	Yes/No
Vomiting	Yes/No
Altered consciousness	Yes/No
Abdominal Pain	Yes/No
Decreased urine output	Yes/No
Bleeding Diathesis	Yes/No

PAST HISTORY:

Blood transfusion	Yes/No
Trauma, Burns, Surgery	Yes/No
History of HIV infection	Yes/No

TREATMENT HISTORY:

Immunosuppressant therapy Yes/No

Chronic Antibiotic use Yes/No

PERSONAL HISTORY:

Habits: h/o smoking Yes/No

H/o Alcohol consumption Yes/No

PHYSICAL EXAMINATION:

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

SYSTEMIC EXAMINATION:

R. S.:

C.V.S.:

P.A.:

C.N. S:

DIAGNOSIS:

ANNEXURE III – KEY TO MASTER CHART

- A:G r: Albumin:Globulin ratio
- AFLP: Acute Fatty Liver of Pregnancy
- Alb: Serum Albumin
- Bili: Total Bilirubin
- Creat: Serum Creatinine
- CRP: C-reactive Protein
- DHF: Dengue Hemorrhagic Fever
- E.coli: Escherichia coli
- Eo: Absolute Eosinophil count
- ESR: Erythrocyte Sedimentation Rate
- Hb: Hemoglobin
- HIV: Human Immunodeficiency Virus
- Kleib: Kleibsella
- Lepto: Leptospirosis
- Lt.: Left
- OPP: Organophosphorous poisoning
- Panc.: Acute Pancreatitis
- PCT: Procalcitonin
- Pl.El: Pleural effusion
- Plt: Platelets
- PMN: Neutrophils
- Pn: Pneumonia
- Pseudo: Pseudomonas

- PTB: Pulmonary Tuberculosis
- RBS: Random Blood Sugar
- Rt.: Right
- SLE: Systemic Lupus Erythematosus
- SN: Serial number
- Staph h: Staphylococcus hemolyticus
- TBA: Peritoneal (Abdominal) Tuberculosis
- TBM: Tubercular Meningtis
- TC: Total WBC count
- UTI: Urinary Tract Infection

MASETR CHART

SN	IP No.	Sex	Age	Diagnosis	Hb	TC	PMN	Eo	Plt	RBS	Creat	Bili	Alb	CRP	ESR	Lactate	A:G r	Hiv	culture	PCT
1	528948	F	45	UTI	12	16400	82	492	343000	1260	5.6	0.8	1.8	+	27	1.1	0.4	-	E.coli	3.4
2	529380	F	48	UTI	10.8	11700	94	20	123000	218	2.85	0.34	1.3	+	36	6.4	0.61	-	-	1.9
3	529148	F	21	DIC	11.5	10700	68	32	75000	140	4.02	0.35	1.8	+	28	4.5	0.55	-	Staph. he	0.9
4	530535	M	64	Rt.Pn.	12.3	18800	85	36	489000	258	1.43	1.16	2.7	+	27	3.3	0.55	-	Kleib	2.8
5	530169	F	46	B/L Pn.	10.3	34900	92	30	302000	79	0.61	0.23	1.8	+	49	1.6	0.5	-	E.coli	4.2
6	532002	M	44	Hepatitis	13.4	15,200	67	24	88000	86	9.03	27.82	1.9	+	42	1	0.7	-	-	2.8
7	530851	M	52	cellulitis	13.4	22700	98	28	23000	112	0.89	2.86	2.6	-	26	3.9	1.1	-	-	3.4
8	531701	M	44	UTI	17	24000	91	34	230000	121	9.46	0.76	4.3	-	10	1.5	0.9	-	E.coli	2.4
9	533057	M	20	Dengue	16.5	4000	60	32	9000	109	0.73	0.68	3.5	+	1	2.4	1.29	-	-	0.3
10	533097	M	27	Dengue	12.8	6700	53	20	67000	92	0.75	1.07	2.9	+	58	1.4	0.88	-	-	0.3
11	533268	M	35	DHF	17.2	5800	60	26	10000	128	0.86	0.62	3.3	-	5	1.8	0.83	-	-	0.3
12	533057	M	55	UTI	12.5	6400	61	28	235000	132	1.94	0.69	2.5	+	8	1.3	0.78	-	-	0.5
13	533117	F	20	DHF	12.8	3200	56	32	14000	106	0.38	0.35	3.2	-	4	1.4	1.14	-	-	0.4
14	533469	M	18	DHF	12.8	7700	63	36	71000	119	1.3	0.67	3.5	+	28	2	1.06	-	-	0.1
15	533404	M	27	DHF	14.1	3500	42	245	9000	122	0.82	0.41	3.4	+	7	2.4	1.18	-	-	0.2

SN	IP No.	Sex	Age	Diagnosis	Hb	TC	PMN	Eo	Plt	RBS	Creat	Bili	Alb	CRP	ESR	Lactate	A:G r	Hiv	culture	PCT
16	530729	M	53	UTI	15.1	20700	71	412	233000	306	1.94	0.77	2.8	+	60	3	0.9	-	-	3.4
17	532688	F	56	snake bite	6.5	22400	89	28	20000	161	6.12	16.74	2.4	+	112	3.2	0.82	-	-	5.4
18	532161	M	64	cellulitis	6.9	13700	85	137	31000	78	2.86	19.66	1.6	+	24	3.3	0.5	-	-	6.1
19	532843	F	54	DHF	14.1	25700	95	36	260000	397	0.81	0.95	3.3	+	11	2.1	0.94	-	-	0.9
20	533465	M	62	UTI	13.2	20600	82	38	392000	140	1.22	0.92	2.9	+	62	1.6	0.67	-	Kleib.	3
21	500926	M	55	Pl.Ef.	10.4	10000	80	100	403000	100	0.61	0.28	2.1	-	8	1.8	0.5	-	-	2.4
22	493940	M	57	Rt.Pn.	16.3	11800	82	132	218000	145	1.09	0.87	3.7	+	22	1.6	0.9	-	-	2.1
23	496769	M	35	UTI	14.9	14800	78	92	430000	56	0.9	1.16	4.1	+	18	2.4	1.1	-	-	2.8
24	548851	F	19	Enteric	10	2600	15	75	40000	92	0.53	0.43	3.1	+	10	2.4	0.5	-	-	1.8
25	509028	M	38	Lt pn.	8.3	13700	93	126	205000	96	0.59	1.72	1.9	+	22	2.4	0.5	-	-	2.4
26	497925	M	48	meninigtis	14.5	10600	80	110	183000	105	1.12	0.67	3	-	18	2.2	0.7	-	-	3.2
27	494458	M	54	Rt pn.	12.4	11500	85	118	23000	248	2.15	0.69	1.4	+	32	3.8	0.4	-	Pseudo	4.1
28	550495	F	97	UTI	11.4	9100	85	30	204000	135	0.73	0.18	1.9	+	18	2.2	0.5	-	E.Coli	6.1
29	495475	F	65	Rt.Pn.	9.6	33800	94	26	325000	493	1.41	0.72	3.2	+	26	4.6	0.5	-	-	11.2
30	494906	F	54	UTI	9.8	8200	75	12	40000	192	3.76	1.68	2.3	+	32	2.1	0.7	-	-	2.4
31	496770	F	64	Cellulitis	10.6	20900	78	208	444000	78	1.14	0.34	2.4	+	68	3	0.6	-	-	3.6

SN	IP No.	Sex	Age	Diagnosis	Hb	TC	PMN	Eo	Plt	RBS	Creat	Bili	Alb	CRP	ESR	Lactate	A:G r	Hiv	culture	PCT
32	496305	M	29	Snake bite	14	10400	68	242	210000	125	0.83	0.5	3.6	+	18	1.4	1.2	-	-	1.8
33	497115	M	52	Snake bite	15.6	33300	86	306	9000	214	2.94	0.75	2.2	+	22	2.4	0.8	-	-	3.4
34	496927	M	44	Rt.Pn.	13	3200	84	26	174000	132	0.68	0.25	2.2	+	28	1.6	0.7	-	-	2.2
35	499123	M	45	Rt.Pn.	12.1	8500	78	85	78000	126	1.45	3.04	1.9	-	29	2.1	0.6	-	-	2.2
36	548870	M	58	meninigtis	16.5	17600	91	30	202000	233	1.41	1.54	3.6	+	5	2.4	1	-	-	4.1
37	498760	F	22	AFLP	9.4	42500	90	824	18000	114	0.8	3.4	2.4	-	40	2.4	1	-	-	0.5
38	508641	M	40	malaria	11	7900	82	60	79000	115	1.13	0.98	1.8	+	45	3.8	0.6	-	-	0.4
39	495529	M	18	Malaria	14.2	5800	35	172	87000	150	0.73	0.64	3.1	-	15	1.2	0.9	-	-	0.2
40	495585	F	22	Rat poison	12	19100	92	120	192000	226	0.89	0.45	2.5	-	25	4.4	0.7	-	-	0.1
41	497096	F	30	SLE	6.4	12100	75	100	127000	69	0.44	9.63	0.7	+	46	3.8	0.4	-	-	0.2
42	496805	M	17	OPP	10.6	5200	87	40	450000	162	0.82	0.89	3.7	-	10	1.6	1	-	-	0.2
43	499837	M	30	Panc.	13.1	23800	89	492	278000	119	0.72	2.21	2.3	+	32	3	0.6	-	-	0.6
44	511444	M	24	DHF	15.7	5900	49	24	11000	75	1.11	1.74	3	+	10	2.2	1	-	-	0.1
45	501555	M	55	meningitis	18.6	18000	72	36	150000	637	1.83	0.22	1.6	+	28	3.4	0.5	-	-	0.4
46	497109	F	47	meningitis	9.4	2800	70	30	171000	131	0.68	0.75	2.3	-	18	1.8	0.6	-	-	0.2
47	494019	F	49	Lepto	11.9	3500	55	50	123000	211	0.8	2.38	3.1	+	38	3	0.8	-	-	0.8

SN	IP No.	Sex	Age	Diagnosis	Hb	TC	PMN	Eo	Plt	RBS	Creat	Bili	Alb	CRP	ESR	Lactate	A:G r	Hiv	culture	PCT
48	511981	F	25	PTB	11.3	19000	92	20	398000	133	0.57	1.11	1.7	+	52	2.1	0.5	-	-	0.4
49	548862	M	29	TBM	11.1	8600	68	200	190000	97	0.48	1.21	1.9	+	32	2	0.5	-	-	0.2
50	508305	F	28	TBA	9.6	15100	70	10	267000	230	1.08	18.3	2.2	-	45	4.1	0.9	-	-	0.5