ORIGINAL RESEARCH

Levels of Procalcitonin in the Patients of Sepsis- Pilot Study

[1]Dr. Vinita Singh, [2]Dr. Sneha Wadalkar

[1]Associate Professor, Department of Biochemistry, Terna Medical College, Nerul, Navi Mumbai, India
[2]Assistant Professor, Department of Biochemistry, MGM Medcial College, Vashi, Navi Mumbai, India

Corresponding Author
Dr. Sneha Wadalkar
Assistant Professor, Department of Biochemistry, MGM Medical College &Hospital, Vashi, Navi Mumbai, India
Email: sneha.wadalkar@gmail.com

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ABSTRACT

Background-Sepsis, a life-threatening complication of an infection, resulting from release of cytokines in the bloodstream to fight an infection, ultimately triggering inflammation throughout the body. This can cause a cascade of changes that damage multiple organ systems, leading them to fail, sometimes even resulting in death.Crucial steps for a successful treatment and positive outcomes, are an early diagnosis and differentiation from non-infectious causes. PCT is biomarker that has diagnostic, therapeutic and prognostic significance. The study was undertaken to identify whether serum pro-calcitonin can act as a superior marker in septicaemia. **Material Method-**This is prospective case control Pilot study.Total 60 subjects were included, Case group comprised of 30 IPD patients of sepsis, whereas 30 heathy individuals were included in control group. Levels of PCT, CRP levels and neutrophil count were analysed in both the groups.PCT levels were analysed by electrochemiluminescence method using commercially available kit & CRP levels by Nephelometry method respectively. Neutrophil counts were done on Sysmex five-part cell counter. **Result-** The levels of Neutrophils (%), PCT (ng/ml) and CRP (mg/L) were significantly high is study group with mean of 79.94 ± 16.9, 7.27±18.6 and 64.2±49.9 respectively in study group with p value <0.001.CRP and PCT are similarly significant markers with co-relation coefficient of 0.518. **Conclusion-** Procalcitonin can be used as an inflammatory marker for sepsis with added significance of diagnostic as well as a prognostic marker.

Keywords- Sepsis, Procalcitonin, C-reactive Protein, Inflammatory marker

Abbreviations- PCT (Procalcitonin), CRP (C-reactive protein), ICU (Intensive care unit),HIC (high-income countries), CAP (community-acquired pneumonia), TNF (Tumour necrosis factor)

INTRODUCTION

Sepsis is the most common cause of admission to an ICU and is associated with significant morbidity and mortality, particularly in elderly, immunocompromised and critically ill patients.[1] Itis reported to be the most common cause of death in non-coronary Intensive Care Unit (ICU). The Global Burden of Disease Study indirectly estimated sepsis cases in India to number 11 million, with close to 3 million deaths.[2]Approximately, 25–35% of patients with severe sepsis and 40–55% of patients with septic shock die within 30 days.[1]

Sepsis is a serious condition that happens when the body's immune system has an extreme response to an infection.[3]Patientswith systemic infection and organ dysfunction or shock are often difficult to distinguish from patients with similar clinical signs and lab finding, but without infection. The established biological markers of inflammation (leukocytes, C-reactive protein) are often used to assess the progression of infection. These may oftenget influenced by parameters other than infection and only be slowly released during progression of an infection. There is no specific maker which shows one to one co-relation between patients' clinical condition and infectious etiology. Since these common clinical and lab measurements lack sensitivity and specificity, other tests are needed to give an early marker of the infectious cause for a generalized inflammatory response to allow early diagnosis and also for the use of specific treatment.[4]

One such parameter is Procalcitonin (PCT), which has recently become of interest as a possible marker of the systemic inflammatory response to infection.[1] Procalcitonin [PCT] belongs to the calcitonin superfamily of peptides consisting of 116 amino acids and 14.5 KD molecular weight. It is the precursor of calcitonin and synthesized by thyroid C cells. In

normal physiological conditions,serum level of PCT is low (0.1 ng/ml).[4]Its expression occurs in a tissue specific manner. In absence of infection, transcription of CALC-1 gene for PCT in the non-neuroendocrine tissue is suppressed. In presence of microbial infection, non-neuroendocrinal tissue express the CALC-1 gene to produce PCT.[9]

PCT is stable marker whose concentration is not affected by neutropenia, immunodeficiency condition & use of NSAIDS which is not the case with CRP. [6]PCT is produced in tissues like lungs, liver, kidney, adipose tissue etc. particularly in bacterial infections, under the influence of inflammatory cytokines and bacterial endotoxin. It is released in circulation, which can even increase up to 1000 times. The first measurable values can be found even 2-4 hours after stimulation and peak up within 6-24 hours. In comparison, the levels of CRP (C-reactive protein) start to rise 12-24 hours after stimulation, reaching a maximum value after 48 hours.[7] Crucial steps for a successful treatment and positive outcomes, are an early diagnosis and differentiation from non-infectious causes. [11]PCT is biomarker that has diagnostic, therapeutic and prognostic significance. The study was undertaken to identify whether serum pro-calcitonin can act as a superior marker in septicaemia.

MATERIAL AND METHODS

This is prospective, case-control, Pilotstudy conducted in Department of Biochemistry, MGM Medical College, Navi Mumbai.Thirty indoor patients of MGM Hospital diagnosed with sepsis admitted in ICU, within age group of 30-60 years were included in Study group.30 healthy individuals acted as control group.Purpose of the study was explained and informed written consent was taken from patients before inclusion in study.Ethical committee clearance was obtained from Institutional Ethical Committee.

All sampleswere collected as per routine sample collection protocol under aseptic conditions.Sample for neutrophil estimation was collected in EDTA tube and in gel separating tube for estimation of Pro-calcitonin and CRP.Gel tubes were centrifuged at 2800 RPM for 12 minutes.PCT levels were measured by electrochemiluminescence method using commercially available kit & CRP levels by Nephelometry method. Neutrophil counts were done on Sysmexfive-part cell counter.

STATISTICAL ANALYSIS

These biochemical parameters were compared and co-related statistically using SPSS 13.0 version. Results are expressed in Mean±SD and parameters are co-related by using Pearson co-relation coefficient.

RESULT

In our study Total 60 participants were included. Out of that,Case group comprised of 30 IPD patients of sepsis, whereas 30 heathy individuals were included in control group.Levels of PCT, CRP levels and neutrophil count were analysed in both the groups.

Table no. 1. Mean and SD of parameters in Control andStudygroup

Parameters	Control Group (n=30)	Case Group (n=30)	P value
Neutrophil count (%)	51.84 ± 7.72	79.94 ± 16.9	< 0.001
PCT (ng/ml)	0.03 ± 0.01	7.27 ± 18.6	< 0.05
CRP (mg/L)	3 ± 1.30	64.2 ±49.9	< 0.001

Figure 1- Mean of Neutrophil count in study and control group

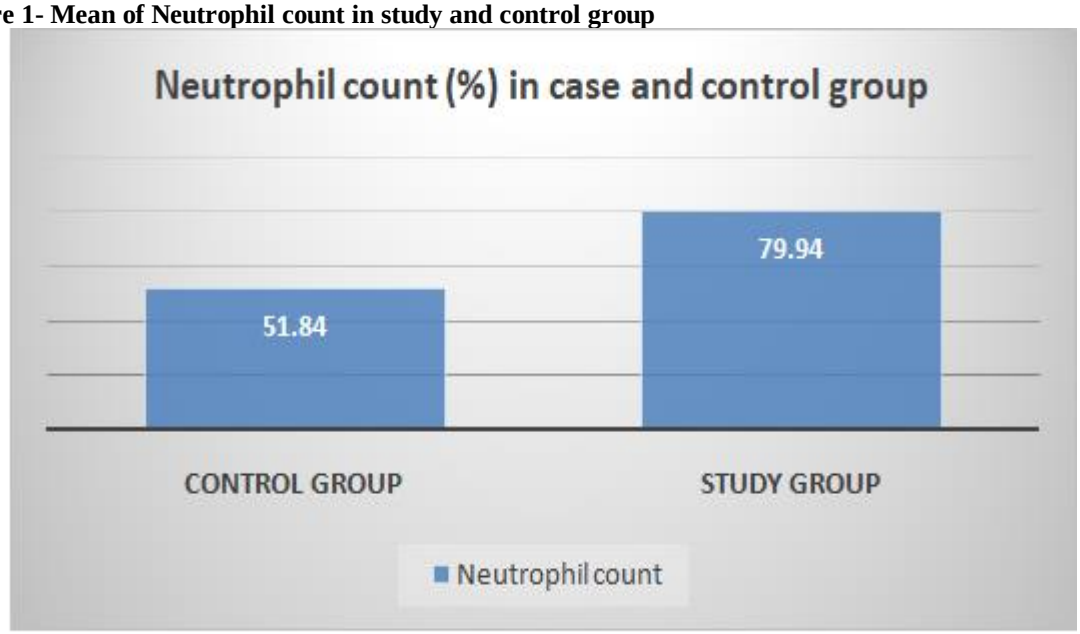


Figure 2- Mean of Procalcitonin (ng/ml) levels in study and control group.

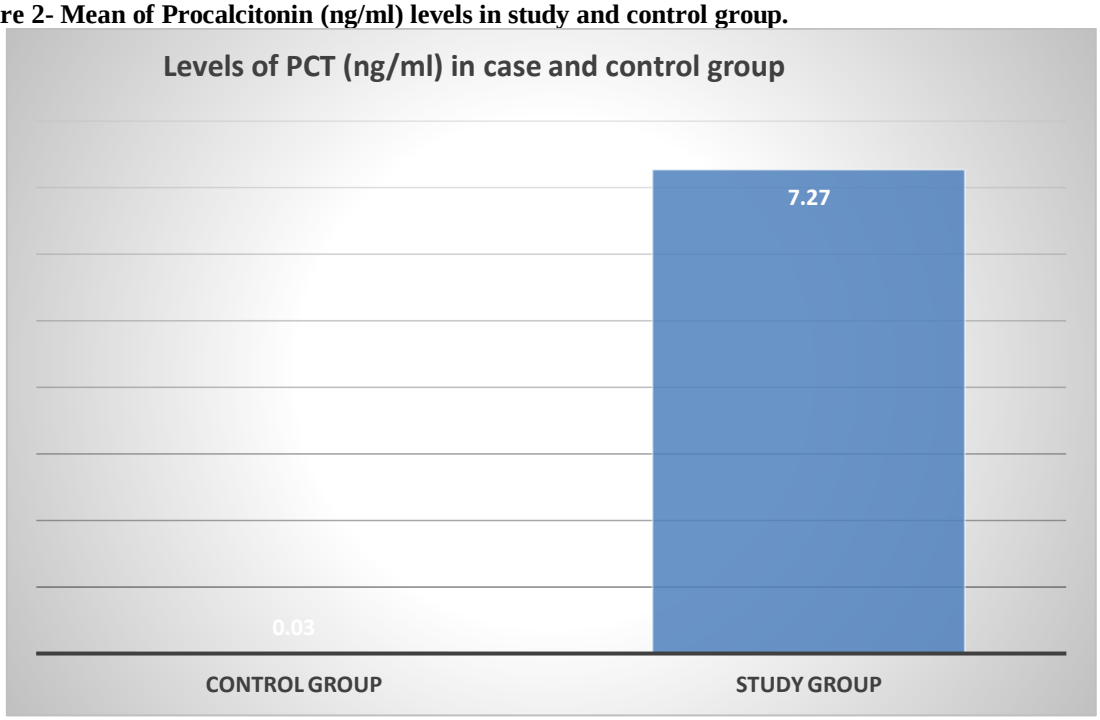


Figure 3- Mean of C-Reactive Protein(mg/L) in study and control group

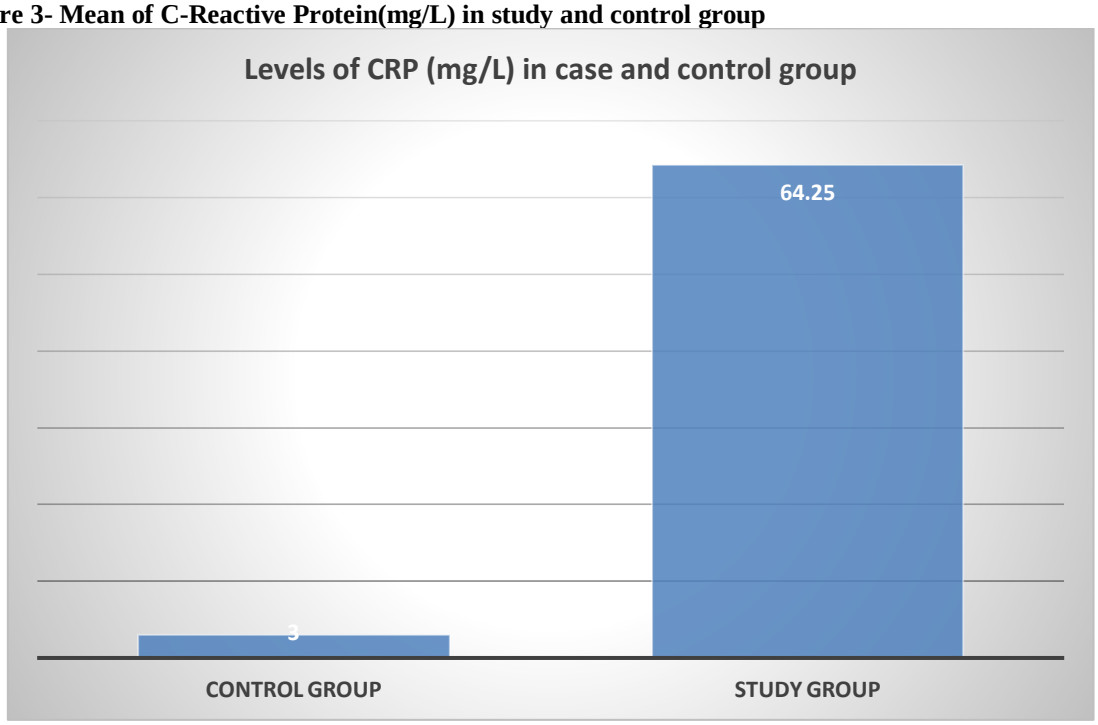


Table no. 2- Correlation coefficient of CRP and PCT with Neutrophil in study group

	Neutrophil	PCT
PCT	0.237	1.000
CRP	0.399*	0.518**

***: Significant at 5% level, **: Significant at 1% level**

Figure 4- correlation between Neutrophil and PCT

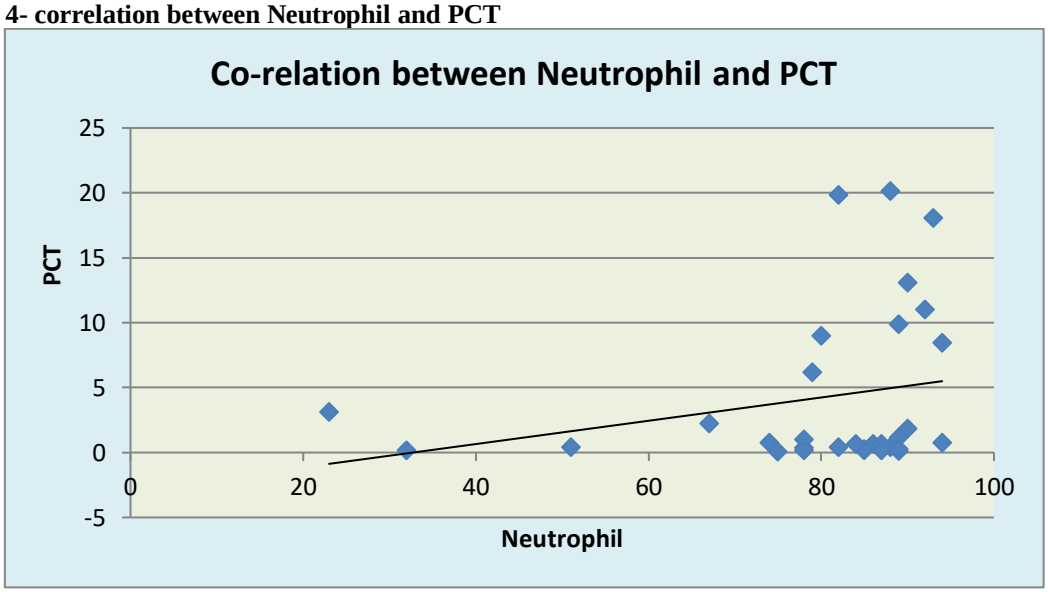


Figure 5- correlation between Neutrophil and CRP

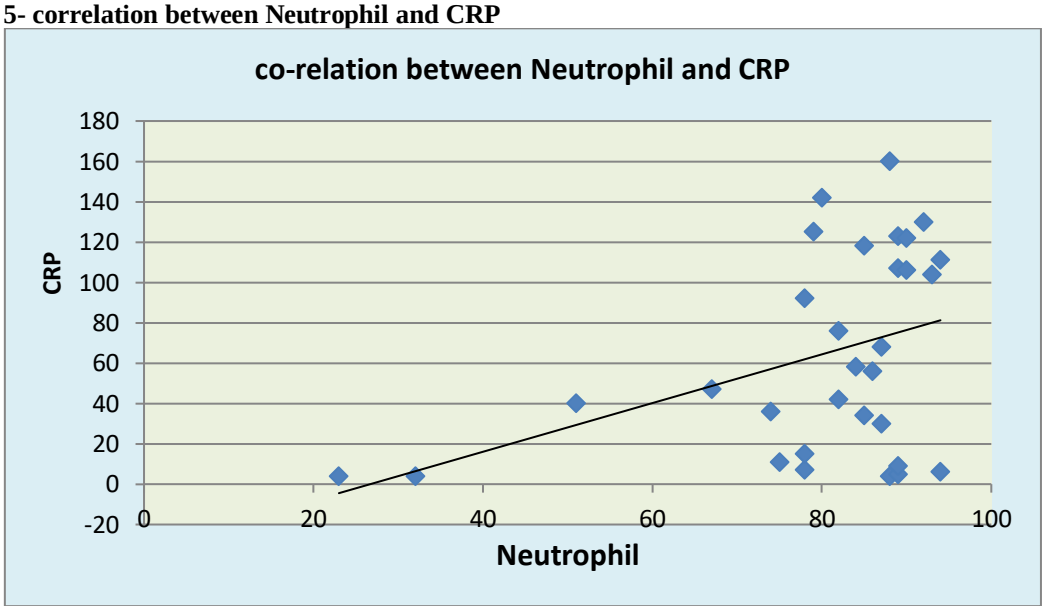
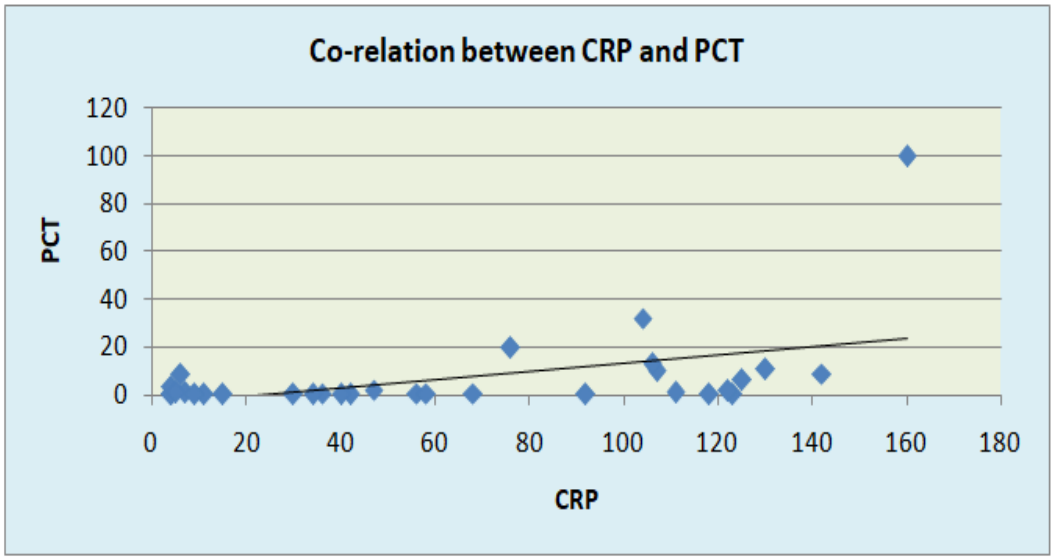


Figure 6- correlation between CRP and PCT



DISCUSSION

[8] Estimates of the global burden of sepsis and resulting mortality (based on a global population of 7.2 billion people) all comes from high-income countries (HIC) whereas data from Low- and Middle-Income Countries (LMIC) is scarce or non-existent. This is problematic as approximately 87% of the world's population resides in LMIC. In developing countries such as India, with a population of 1.34 billion people, the epidemiology of sepsis is poorly understood despite high mortality and morbidity rate.[8]

Sepsis refers to the systemic response to infection by microbial agents, such as bacteria, fungi, and yeast, where the patient typically develops fever, tachycardia, tachypnoea, and leucocytosis. Microbiologic cultures from the blood or the infection site are frequently, although not invariably, positive. Severe sepsis is associated with the hypoperfusion or dysfunction of at least oneorgan. [9]Important aspects of sepsis management are early diagnosis as well as timely and specific treatment (e.g. antibiotics) in the first few hours of triage. However, the correct diagnosis and differentiation form non-infectious causes is challenging. The positive microbiological results can be due to contamination or a negative result does not always rule out infection.Moreover, the correct use of antibiotics, still represents a major issue for treating physicians. [10]

No gold standard exists for the detection of sepsis caused by bloodstream infections. The use of conventional diagnostic approaches such as blood cultures and inflammatory blood markers [i.e., C-reactive protein (CRP), white blood count (WBC)] in patients with a clinical suspected infection or sepsis is restricted by some limitations, such as microbiological cultures require longer duration. One of the most investigated host-directed markers is PCT.[11]It is a peptide precursor of calcitonin, synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis.

In our study, we have evaluated the combined role of serum PCT and other clinical indicators of inflammation as predictors of sepsis in which we explored the diagnostic accuracy of these different parameters from a clinical perspective.Total 60 participants of age group between 35 to 60 years of age were enrolled. Out of 60 participants, 30 were patients of Sepsis admitted in ICU of MGM Hospital and 30 healthy individuals included in control group. As confirmatory in sepsis, neutrophil count is high with mean of 79.94 ± 16.9 % compared to control group (51.84 ± 7.72 %) (Table 1 and Fig 1). It has shown statistical significance with p value <0.000 in both the groups.Positive correlation wasobtained betweenPCT levels, neutrophil count and CRP with co-relation coefficient 0.237and 0.399 respectively (Table 2 and Figs 4 &5). Co-relation coefficient of 0.237 between PCT and Neutrophilsuggest that PCT is better marker for clinical co-relation in study group.

The levels of PCT and CRP are quite high in cases of sepsis with mean of 7.27 ±18.6 ng/ml and 64.2 ± 49.9 mg/L respectively (Table 1, Fig 2 &3). CRP values are statistically more significant (<0.001) compared to value of PCT (<0.05) in both the groups.PCT and CRP has shown a positive co-relation with co-relation coefficient of 0.518. (Table 2, Fig 6)

In healthy individuals, serum PCT is not detectable, since the protein is not released into the blood in absence of systemic inflammation.[10] In case of a sepsis caused by bacterial infections and inflammatory states, PCT synthesis is induced in alltissues, local procalcitonin production rises, and because the tissues cannot further process PCT to calcitonin, serum levels increase.[5] Also, it's synthesis is triggered by bacterial toxins, such as endotoxin and cytokines [e.g., interleukin (IL)-1beta, interleukin-6 and tumour necrosis factor (TNF)-alpha].PCT has a wide biological range, a short time to induction after bacterial stimulation and a long half-life. [10]

Procalcitonin is a prognostic biomarker for the risk assessment in patients with severe infection and sepsis.[10] Decreasing PCT values correlate with good outcomes and increasing values are associated with adverse outcomes which also include mortality.A PCT decrease >80% within 72 hours after initial assessment had a negative predictive value of around 90% for the exclusion of ICU mortality, which probably can help to identify patients with a reduced riskor for whom a therapy de-escalation and an early ICU discharge could be considered. In contrast, no decrease or an increase of PCT in the same timeframe had a positive predictive value of around 50%, indicating patients at high risk who probably require treatment escalation. [11] These results were also confirmed by the MOSES-Study, a prospective multicentre FDA study, conducted in different U.S based hospitals.[12]

Thestudy of de Jager and colleaguesobserved high PCT levels in the blood of patients infected with community-acquired pneumonia (CAP) caused by Legionella pneumophila in comparison to other conventional parameters such as CRP and WBC counts.[9]Jacquot and colleagues demonstrated that rapid measurement of PCT could help to rule out nosocomial infection in newborns.[13]Brunkhorst et al. reported from their study that serum PCT levels increase with the increasing severity of the inflammatory response to infection.[14]Initial high levels of PCT were indicative of more severe diseases in comparison to other conventional parameters such as CRP and WBC count. [9]

Along with some positive responses, some studies reported low levels of PCT as well. According to study conducted by Gendrel and Bohuon, they demonstrated that PCT levels are minimal in viral infections.[15]Due to cytokines released during viral infections that inhibit the production of TNF-alpha, PCT synthesis is not induced in the most viral infections.The precise role which PCT plays as part of

the immune response remains unclear. [10]Thus, PCT has good discriminatory properties for the differentiation between bacterial and viral inflammations with rapidly available results. [10]
Our Study concluded that CRP and PCT are similarly significant markers with co-relation coefficient of 0.518.

CONCLUSION

It is concluded from the observation of significant high levels PCT in study group, that Procalcitonincan be used as an inflammatory marker for sepsiswith added significance of diagnostic as well as a prognostic marker.

Conflict of Interest- None

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