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Biomarkers in Sepsis: A study of Procalcitonin as a diagnostic and prognostication tool in Sepsis in a tertiary care hospital

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Abstract

Background: *The incidence and mortality from sepsis has been on a rising trend worldwide. Early diagnosis and intervention are key to reducing morbidity and mortality from sepsis. Biomarkers are gaining prominence in this regard. Of these, procalcitonin (PCT) which is elaborated by the tissues in response to the inflammatory response of sepsis, has high sensitivity and specificity to diagnose sepsis.*

Aims and Objectives: *The study was done with the aim to assess the prevalence of elevated serum procalcitonin levels in patients with sepsis, and to evaluate for correlation of procalcitonin levels with severity of sepsis, clinical course, prognosis (assessed by prognostication scores like qSOFA, SOFA, APACHE II scores) and treatment outcome of sepsis.*

Methods: *40 patients admitted with sepsis in the medical ICU of Rajah Muthiah Medical College Hospital during the period from September 2018 to August 2020 were studied. Demographic characteristics, history and physical examination details of the patients were entered in a case proforma. qSOFA score was calculated from GCS, respiratory rate and systolic BP. Shock index was calculated from heart rate and systolic BP. A venous sample for procalcitonin estimation was obtained in first 12 hours. Investigations from workup of the patient and clinical status were used to calculate SOFA and APACHE II score. The clinical course and treatment of the patients were followed up. Statistical analysis of the above data was performed.*

Results: *Among the 40 sepsis patients studied, 20% had sepsis (n=8), 40% each severe sepsis and septic shock (n=16 in each category). The overall mortality was 25% (n=10), with highest mortality in patients with septic shock. The mean PCT of study subjects was 5.64 ± 15.05 ng/ml. PCT may be used to predict mortality as survivors had mean PCT of 2.75 ± 4.10 ng/ml compared to 14.29 ± 28.57 ng/ml in non-survivors ($p < 0.05$). Greater PCT values were associated with need for ventilatory support (mean 8.86 ± 21.78 ng/ml, $p <0.05$). PCT levels were greater with greater severity of sepsis: the mean PCT was 1.77 ± 2.66 ng/ml in sepsis, compared to 3.05 ± 4.29 ng/ml in severe sepsis, and 10.16 ± 22.90 ng/ml in septic shock. qSOFA score and CRP were good independent predictors of mortality ($p < 0.05$ and $p < 0.0001$ respectively) and showed positive correlation with PCT.*

Conclusion: *Serum PCT may be used to diagnose sepsis at an early stage. In addition, it is useful to categorize severity of sepsis, predict mortality and need for ventilatory support in patients with sepsis.*

Keywords: *Sepsis, procalcitonin, biomarkers, septic shock, CRP, SOFA, APACHE II score, shock index, prognostic indicator.*

Introduction

Sepsis is a dysregulated immune response to infection resulting in organ dysfunction.13 million cases of sepsis occur each year globally, with 4 million people dying of it. The mortality rate is as high as 29% in Asian countries[1].

The risk factors for sepsis include age over 65 years, lower socioeconomic status, male gender, African or Afro-American race, immunosuppressed states like AIDS, malignancy, conditions like diabetes, renal failure and genetic defects in immune functions.

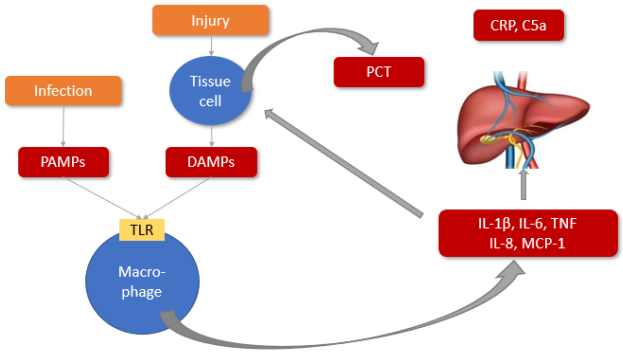
Sepsis develops with the initiation of a proinflammatory cascade in the body following an infection. This results in a systemic inflammatory response syndrome (SIRS). In recent years, a compensatory anti-inflammatory response syndrome (CARS)[2] has been described, which is associated with decompensation in the immunosuppressed, culminating in severe sepsis and death.

On contact with the infecting organism, the cells of the innate immunity,*via* their Pattern Recognition Receptors (PRRs) (like Toll-like receptors) recognize and bind Pathogen-Associated Molecular Patterns (PAMPs) on the surface of the organism. This binding stimulates signalling through cytosolic nuclear factor – kappa B (NF-κB), promoting transcription and synthesis of proinflammatory cytokines, including TNFα and IL-1.

The proinflammatory cytokines mediate vasodilatation, activate phagocytes and recruit the coagulation and complement system. The high-mobility group protein HMGB1, produced by monocytes and macrophages, has been recognized as a late-acting cytokine[3], which further aggravates the inflammatory process resulting in severe sepsis.

These cytokines trigger production of C-reactive protein (CRP) by the liver[4], procalcitonin (PCT) by parenchymal tissues[5], and themselves may be considered biomarkers of sepsis (e.g., IL-6, IL-8, MCP-1). Bacterial infection[6] triggers production of PCT via TNFα[7], IL-1β and IL-6*(Figure 1)*.Other biomarkers in sepsis include acute phase reactants like pentraxin 3, complements like C3b, C5a, neutrophil markers like CD64, CD11b, sTREM1 (soluble form of triggering receptor expressed on myeloid cells-1), Heparin binding protein (HBP) and lipopolysaccharide-binding protein (LBP).

Figure 1: Stimulation of PCT production



Studies have shown that PCT levels rise early, at the onset of sepsis, in comparison to CRP which has conventionally been in use as a biomarker[8,9]. Our study was conducted to assess elevated PCT levels in sepsis and its correlation with prognosis. PCT levels in healthy individuals, localized infection, sepsis and severe sepsis are shown in *Figure 2*[10].

Figure 2: Interpretation of PCT levels

PCT <0.05 µg/L	
Healthy individuals	Determination of normal values with a high sensitive assay revealed normal values to be below 0.05 µg/L.
PCT <0.5 µg/L	
Systemic infection (sepsis) is not likely. Local bacterial infection is possible.	Low risk for progression to severe systemic infection (severe sepsis). **Caution:** PCT levels below 0.5 µg/L do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. Also if the PCT measurement is done very early after a following bacterial challenge (usually < 6 hours), these values may still be low. In this case, PCT should be re-assessed 6-24 hours later.
PCT ≥0.5 – <2 µg/L	
Systemic infection (sepsis) is possible, but various conditions are known to induce PCT as well.[1]	Moderate risk for progression to severe systemic infection (severe sepsis). The patient should be closely monitored both clinically and by re-assessing PCT within 6-24 hours.
PCT ≥2 – <10 µg/L	
Systemic infection (sepsis) is likely, unless other causes are known.[1]	High risk for progression to severe systemic infection (severe sepsis).
PCT ≥10 µg/L	
Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.	High likelihood of severe sepsis or septic shock.

Objectives

1. To assess the prevalence of elevated serum procalcitonin in patients with sepsis
2. Correlation of elevation in serum procalcitonin with patient characteristics, clinical course, severity, prognosis (assessed using qSOFA and SOFA score) and treatment outcome of sepsis.

Inclusion Criteria

Patients -

- More than 18 years of age,
- for whom consent is obtained from patient or attendant,
- Meeting the ACCP/SCCM/ESICM International Consensus Definitions criteria for diagnosis of sepsis, and, with blood samples drawn within 12 hours of presentation with/ diagnosis of sepsis.

Exclusion Criteria

Patients with –

- major burns
- severe trauma
- acute inhalational injury
- major abdominal or cardiothoracic surgery
- acute multiorgan failure
- medullary thyroid carcinoma
- pancreatitis
- untreated end-stage renal failure.

Materials and Methods

A prospective, observational study was conducted among 40 patients admitted with a diagnosis of sepsisin the medical ICU of Rajah Muthiah Medical College Hospital during the study period from September 2018 to August 2020.

A detailed patient history along with examination findings were entered in the case proforma. qSOFA score was calculated from GCS, respiratory rate and systolic blood pressure. Shock index was calculated using heart rate and systolic blood pressure.

Laboratory Method: A venous sample of 2.5ml blood drawn within 12 hours of admission or diagnosis of sepsis was sent for estimating serum procalcitonin levels. These samples were processed by an automatic blood analyser which employed chemiluminescenceas method of analysis.

Routine investigations done as part of the workup of patient were considered. Using clinical data and investigations, SOFA score and APACHE II score were calculated.

The course of each patient during their ICU stay, the need for ventilatory support, inotropes and higher antibiotics, and treatment outcomes were followed up. Radiology and culture/sensitivity reports pertaining to the localization and causative organism of sepsis were recorded.

Informed written consent was obtained from the patients or attendants before including them in the study. Approval from the Institutional Human Ethics Committee was obtained prior to the study. The data obtained was entered into a Microsoft Excel worksheet and statistical analyses were performed using a statistical software package (Statistical Package for Social Sciences, SPSS). Comparisons of continuous data and categorical data between two groups were performed by t- test and Chi-square test respectively. Comparisons of continuous data among more than two groups were performed by ANOVA test. Pearson's correlation was used for correlation analysis. P value less than 0.05 were considered as statistically significant.

Results

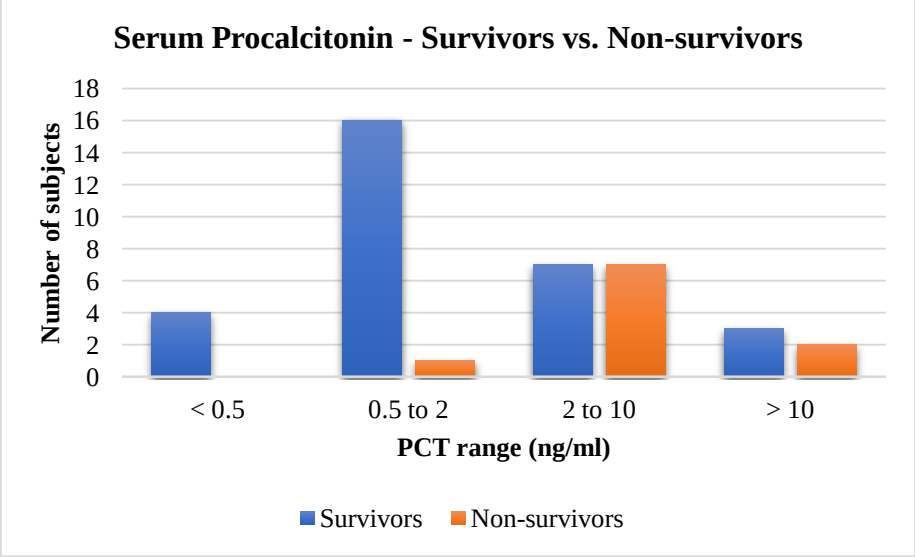
Table 1: Patient Characteristics

Variables		Study subjects (n=40)	Survivors (n=30)	Non-survivors (n=10)	p-value
Age (mean)		62.1 (±14.25)	66.07 (± 11.89)	50.2 (± 14.64)	< 0.05
Sex	**Male**	19 (48%)	16 (53%)	3 (30%)	> 0.05
	Female	21 (52%)	14 (47%)	7 (70%)	> 0.05
Source of infection					> 0.05
○ Respiratory tract		18 (45%)	13 (43.3%)	5 (50%)	
○ Soft tissue		9 (22.5%)	8 (26.7%)	1 (10%)	
○ GIT		5 (12.5%)	2 (6.7%)	3 (30%)	
○ Urinary tract		5 (12.5%)	5 (16.7%)	0 (0%)	
○ Others		3 (7.5%)	2 (6.6%)	1 (10%)	
Causative organism					> 0.05
○ Gram positive		6 (15%)	5 (16.7%)	1 (10%)	
○ Gram negative		17 (42.5%)	13 (43.3%)	4 (40%)	
○ Anaerobic		1 (2.5%)	1 (3.3%)	0 (0%)	
○ Mixed		6 (15%)	4 (13.4%)	2 (20%)	
○ Others		2 (5%)	1 (3.3%)	1 (10%)	
○ Not isolated		8 (20%)	6 (20%)	2 (20%)	
Comorbid illnesses					> 0.05
○ Diabetes		7 (17.5%)	4 (13.4%)	3 (30%)	
○ Hypertension		2 (5%)	1 (3.3%)	1 (10%)	
○ CKD		1 (2.5%)	1 (3.3%)	0 (0%)	
○ COPD/ Asthma		2 (5%)	2 (6.7%)	0 (0%)	
○ Multiple		21 (52.5%)	18 (60%)	3 (30%)	
○ None		5 (12.5%)	3 (10%)	2 (20%)	
○ Other		2 (5%)	1 (3.3%)	1 (10%)	
Severity of sepsis					<0.001
○ Sepsis		8 (20%)	8 (26.7%)	0 (0%)	
○ Severe sepsis		16 (40%)	16 (53.3%)	0 (0%)	
○ Septic shock		16 (40%)	6 (20%)	10 (100%)	
Serum PCT (ng/ml)					< 0.05
○ < 0.5		4 (10%)	4 (13.3%)	0 (0%)	
○ ≥ 0.5 to < 2		17 (42.5%)	16 (53.4%)	1 (10%)	
○ ≥ 2 to < 10		14 (35%)	7 (23.3%)	7 (70%)	
○ ≥ 10		5 (12.5%)	3 (10%)	2 (20%)	
SOFA score					< 0.05
○ 0 to 3		8 (20%)	8 (26.7%)	0 (0%)	
○ 4 to 5		5 (12.5%)	5 (16.7%)	0 (0%)	
○ 6 to 7		6 (15%)	5 (16.7%)	1 (10%)	
○ 8 to 9		11 (27.5%)	7 (23.3%)	4(40%)	
○ 10 to 11		5 (12.5%)	3 (10%)	2 (20%)	
○ > 11		5 (12.5%)	2 (6.6%)	3 (30%)	
CRP (mg/dl)					< 0.05
○ 1 to 10		20 (50%)	18 (60%)	2 (20%)	
○ 11 to 20		12 (30%)	8 (26.7%)	4 (40%)	
○ 21 to 30		7 (17.5%)	4 (13.3%)	3 (30%)	
○ > 30		1 (2.5%)	0 (0%)	1 (10%)	
qSOFA score					> 0.05
○ 0		4 (10%)	4 (13.3%)	0 (0%)	
○ 1		19 (47.5%)	14 (46.7%)	5 (50%)	
○ 2		13 (32.5%)	11 (36.7%)	2 (20%)	
○ 3		4 (10%)	1 (3.3%)	3 (30%)	
APACHE II score					>0.05
○ 0 to 9		4 (10%)	3(10%)	1 (10%)	
○ 10 to 19		16(40%)	11 (36.7%)	5 (50%)	
○ 20 to 29		14 (35%)	11 (36.7%)	3 (30%)	
○ ≥ 30		6 (15%)	5 (16.6%)	1 (10%)	

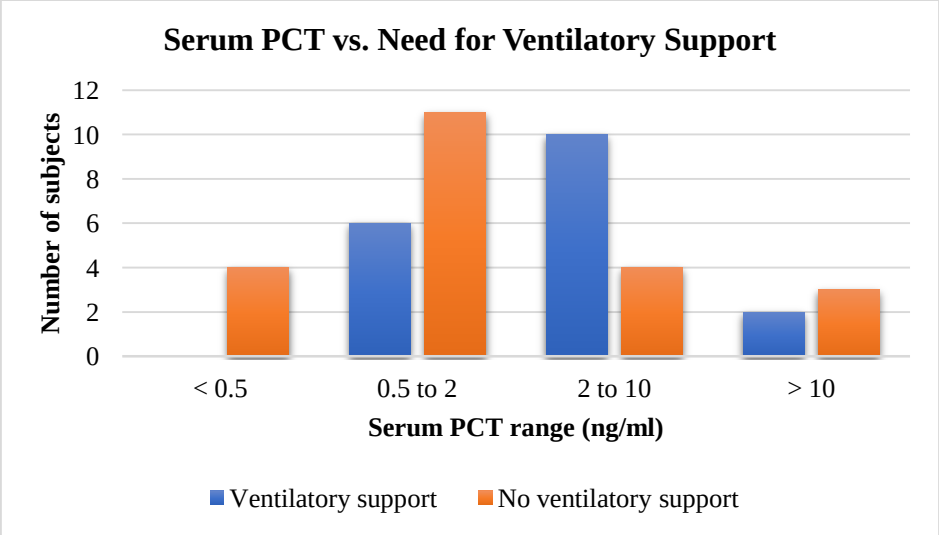
ICU stay (days) ○ 1 to 5 ○ 6 to 10 ○ 11 to 15 ○ > 15	 20 (50%) 17 (42.5%) 1 (2.5%) 2 (5%)	 13 (43.3%) 16 (53.4%) 1 (3.3%) 0 (0%)	 7 (70%) 1 (10%) 0 (0%) 2 (20%)	 > 0.05
Shock index ○ < 0.8 ○ ≥ 0.8	 11 (27.5%) 29 (72.5%)	 9 (30%) 21 (70%)	 2 (20%) 8 (100%)	 > 0.05
MAP ○ <65 ○ ≥ 65	 9 (22.5%) 31 (77.5%)	 5 (16.7%) 25 (83.3%)	 4 (40%) 6 (60%)	 > 0.05

Table 2: Correlation Statistics

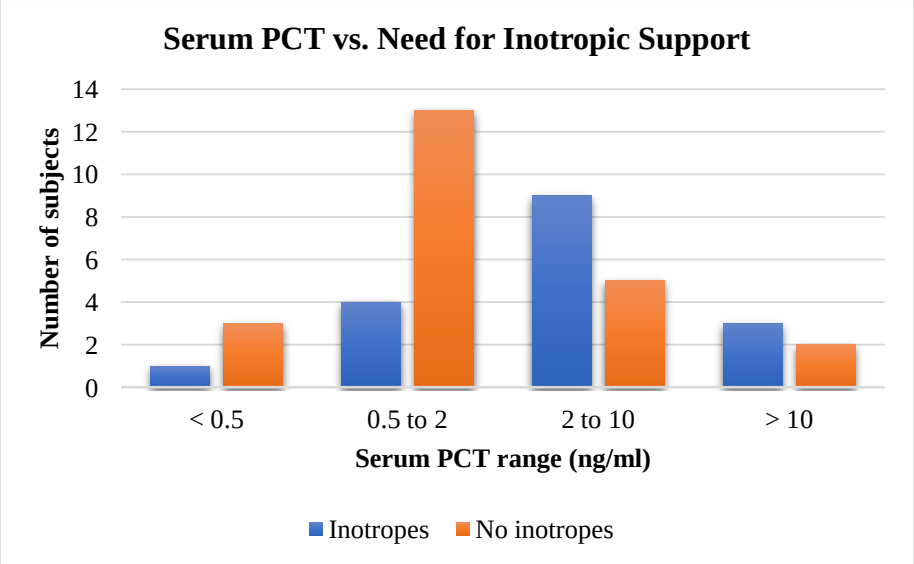
Parameters	**PCT (ng/ml)**	
	R	**P VALUE**
Severity of sepsis	1.2372 (F value)	>0.05
SOFA score	0.0679	> 0.05
CRP (mg/dl)	0.7086	< 0.001
qSOFA score	0.3467	< 0.05
APACHE II score	0.127	> 0.05
Duration of ICU stay	-0.0698	> 0.05
Shock index	0.1098	> 0.05
MAP (mmHg)	-0.1321	> 0.05



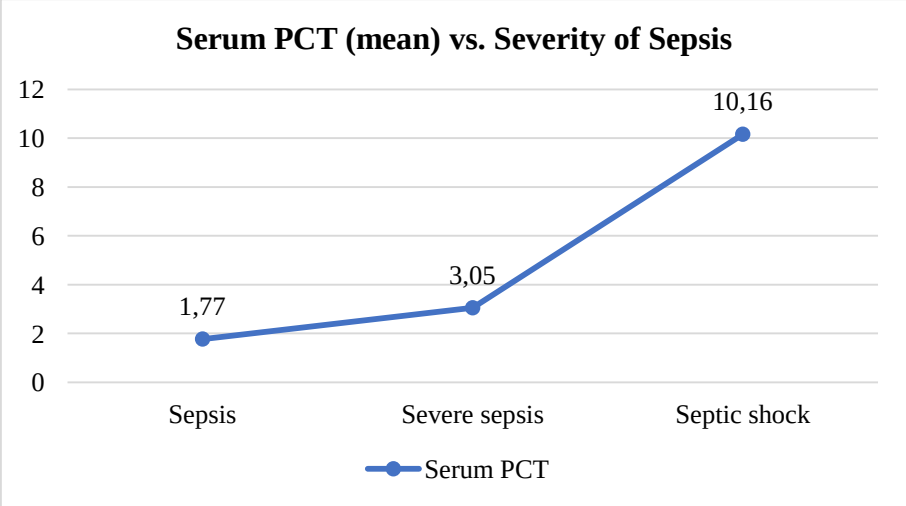
Graph 1: Serum procalcitonin levels vs. Mortality



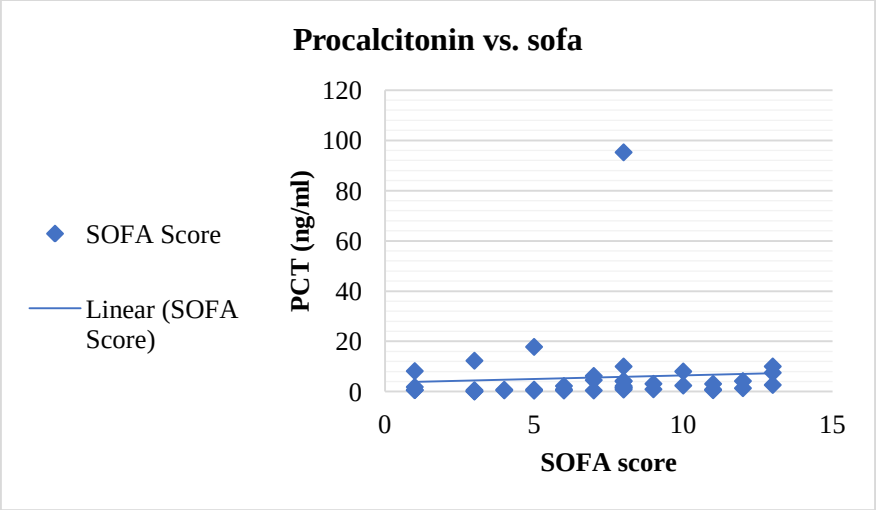
Graph 2: Serum procalcitonin levels and ventilatory support



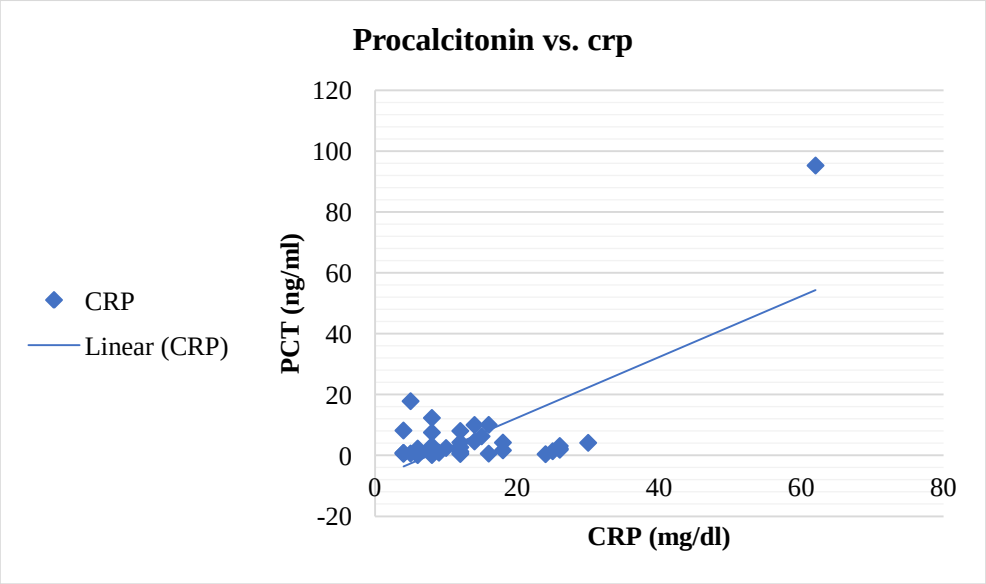
Graph 3: Serum procalcitonin levels and inotropic support



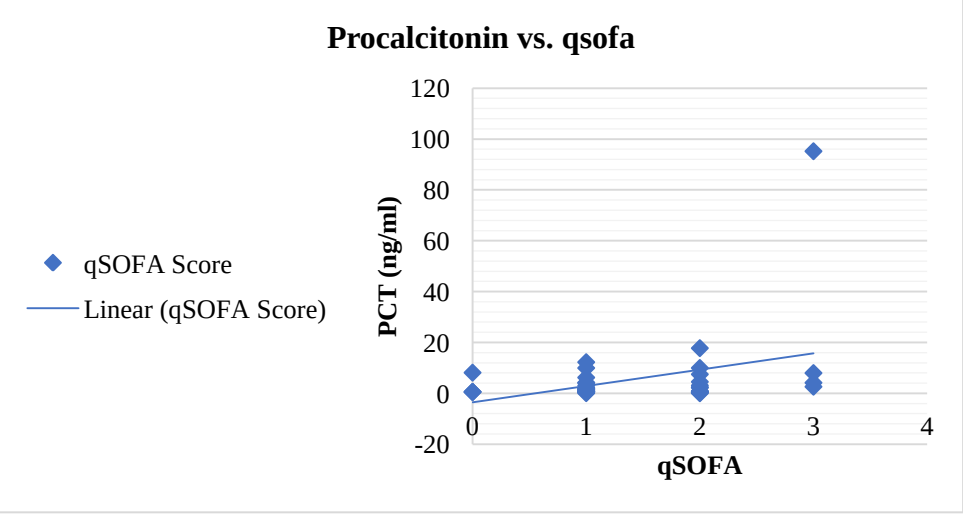
Graph 4: Serum procalcitonin levels (mean) vs. severity of sepsis



Graph 5: Correlation between SOFA score and PCT



Graph 6: Correlation between CRP and PCT



Graph 7: Correlation between qSOFA and PCT

Among the 40 sepsis patients studied, 48% were males (n=19) and 52% were females (n=21). The majority of patients belonged to the 60 to 70 years age group with a mean age of 62.1 ± 14.25 years. Diabetes was the most prevalent individual comorbidity in the study subjects (17.5%, n=7), followed by hypertension (5%, n=2). 52.5% subjects (n=21) had multiple comorbidities.

The most common source of sepsis was the respiratory tract (45%, n=18), followed by soft tissue (22.5%, n=9). Gram negative organisms were the major cause of sepsis (42.5%, n=17), followed by Gram positive organisms and mixed infections – 15%each (n=6). Anaerobic organisms caused 2.5% (n=1) of infections and 20% (n=8) were culture-negative *(Table 1)*. The above characteristics, except for age, did not have a significant association with mortality.

On grading severity of sepsis, 20% patients had sepsis (n=8), 40% each severe sepsis and septic shock (n=16 in each category). The greater the severity of sepsis, the greater was the mortality ($p < 0.001$). 100% (n=10) of non-survivors in our study succumbed to septic shock.

The overall mortality from sepsis in the study was 25% (n=10).

The mean PCT of study subjects was 5.64 ± 15.05 ng/ml. The majority of survivors (53.4%) had PCT in the range 0.5 to 2 ng/ml (n=16), in contrast to non-survivors, the majority of whom had PCT in the range 2 to 10 ng/ml (70%, n=7). The mean PCT of survivors was 2.75 ± 4.10 ng/ml compared to 14.29 ± 28.57 ng/ml in non-survivors ($p < 0.05$) *(Graph 1)*.

55.6% of the patients who needed ventilatory support had PCT between 2 to 10 ng/ml. Hence, higherserum PCT was associated with need for ventilatory support (mean 8.86 ± 21.78 ng/ml) compared to those who did not need ventilatory support (mean 2.99 ± 4.52 ng/ml, $p <0.05$) *(Graph 2)*. Similarly, the patients who needed inotropic support had higher PCT values (mean 9.61 ± 2.29 ng/ml) than those who did not (mean 2.70 ± 4.36, $p >0.05$)*(Graph 3)*. PCT levels also increased with increasing severity of sepsis: the mean PCT was 1.77 ± 2.66 ng/ml in sepsis, compared to 3.05 ± 4.29 ng/ml in severe sepsis, and 10.16 ± 22.90 ng/ml in septic shock*(Graph 4)*.

SOFA score in non-survivors was 9.80 ± 2.10, compared to 6.20 ± 3.45 in survivors ($p <0.05$). The mean CRP of survivors was 10.5 ± 6.35 mg/dl compared to 21.80 ± 16.02 mg/dl in non-survivors ($p <0.05$). SOFA score had weak positive correlation ($p >0.05$) and CRP had strong positive correlation with PCT ($p <0.05$)*(Graph 5 and 6)*.

Non-survivors had mean qSOFA of 1.80 ± 0.92 and survivors had mean qSOFA of 1.30 ± 0.75 ($p >0.05$). qSOFA score had weak positive correlation with PCT ($p <0.05$)*(Graph 7)*.Majority of survivors and non-survivors had APACHE II score in the 10 to 19 range. APACHE II score had weak positive correlation with PCT ($p >0.05$), but did not demonstrate significant association with mortality.

Median duration of ICU stay among our patients was 5.5 days. 70% (n=7) of non-survivors died within 5 days of admission in ICU, and 20% (n=2) died after more than 15 days of ICU stay. Median ICU stay in non-survivors and survivors was 2.5 days and 6.5 days respectively. In our study, duration of ICU stay had weak negative correlation with PCT ($p >0.05$).

Shock index (normal range 0.5 to 0.7, with index ≥ 0.8 indicating worse prognosis) was ≥ 0.8 in 80% (n=8) of non-survivors, compared to 70% of survivors (n=21, $p >0.05$). Shock index had weak positive correlation with PCT ($p >0.05$). 40% of non-survivors (n=4) had mean arterial pressure (MAP) < 65 mmHg (ideal target MAP for best outcome in sepsis being ≥ 65mmHg) compared to 16.7% (n=5) of survivors ($p >0.05$). MAP showed weak negative correlation with PCT ($p >0.05$) *(Graph 8)*.

Discussion

- The majority of sepsis cases were in the 50 to 70 years age group. The male-female ratio was 1.1:1.

- In concurrence with the findings of other similar studies, respiratory tract was the commonest source of infection (45% vs. 48% in the study by Harbarth *et al*[11]and 49% in the study by Suprin*et al*[12]).It was followed by soft tissue infections, gastrointestinal tract and urinary tract infections.
- Gram-negative organisms (42.5%) were the major cause of sepsis, followed by Gram-positive organisms (15%) and mixed infections (15%). Anaerobic and yeast infections constituted a minor proportion of cases. Gram negative organisms were also observed to be most commonly causative in the studies by Harbarth *et al*[11]and Suprin *et al*[12] (53% and 39% respectively). Anaerobes caused 2.5% of infections in the present study compared to 1.3% in the Suprin*et al* study[12]. The proportion of cases with mixed growth (15%) was also similar (9% in the Harbath *et al*[11] study and 8% in the Suprin *et al* study[12]). Gram positive organisms were isolated in 15% in the present study compared to 38%, 22% and 29% in the Harbath *et al* study[11], MOSES study[13] and the Suprin *et al* study[12] respectively. 20% patients were culture-negative, similar to 27% in the Harbath *et al* study[11] and 16% in the Suprin*et al* study[12]. The MOSES study[13] had greater number of culture-negative cases (67%).
- Among comorbid illnesses, diabetes (17.5%) followed by hypertension (5%) were more prevalent in our study, whereas hypertension (62%) was more common than diabetes (34%) in the MOSES study[13]. Multiple comorbid conditions existed in 53% of our study subjects. Diabetes and multiple comorbidities were each present in 30% of non-survivors in our study (p >0.05).
- The gender, source of sepsis, causative organism and comorbid illness had no statistically significant association with mortality from sepsis.
- On grading severity of sepsis, the incidence of sepsis was 20%, while incidence of severe sepsis and septic shock were 40% each.
- A significant association between mortality and severity of sepsis was observed.
- Higher PCT levels were associated with greater severity of sepsis, mortality from sepsis, increased need for ventilatory support (p <0.05) and inotropic support (p >0.05).
- SOFA score and CRP levels were found to be good independent predictors of mortality in sepsis (p <0.05), showing positive correlation with PCT values (p >0.05, p <0.001).
- Higher qSOFA score and shock index ≥ 0.8 were also seen more often in non-survivors in our study, both showing a weak positive correlation with PCT levels (p <0.05, p >0.05).
- APACHE II score was not a good predictor of mortality in our study, consistent with findings of the study by Brunkhorst *et al*[14,15].
- MAP and duration of ICU stay demonstrated negative correlation with PCT values in our study, as patients with MAP < 65mmHg andthe patients who died of sepsis in the first few days of admission had higher PCT values.

Limitations

The study did not evaluate surgical causes of sepsis as the sample was limited to patients admitted in the medical ICU. Statistical significance for some correlations could not be demonstrated due to the smaller sample size from a single centre. Serial measurements of PCT levels may be of better aid in assessing response to treatment, which could not be done due to financial constraints.

Conclusion

It may be inferred from our study findings that serum procalcitonin (PCT) is an excellent tool in early diagnosis of sepsis, where existing methods like culture, SOFA score and CRP levels fall short by a wide margin[9, 16]. A sensitivity and specificity of up to 97% and 78% respectively for PCT have been described in the literature[11].

Serum procalcitonin served as a good indicator of in-hospital mortality with > 2 ng/ml as an ideal cut-off, as 90% of patients who died of sepsis in our study had serum PCT > 2 ng/ml. Greater levels of PCT were also associated with need for ventilatory or inotropic support.

Our study also demonstrates PCT values correlate with the severity of sepsis, levels > 2 ng/ml occurring commonly in septic shock. Thus, serum PCT is also a tool to risk stratify the patient according to prognosis, so that available resources may be utilized effectively in patient care.

Levels of PCT were also found to fall with successful treatment of sepsis and improvement of the patient's condition. Hence, serial monitoring would be useful in an ICU setting[17-19].

Therefore, with the current trend of increasing morbidity and mortality from sepsis globally, a biomarker like serum procalcitonin for diagnosis and prognostication of sepsis is the need of the hour.

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