

ORIGINAL RESEARCH

50 SHADES OF GREY: DOES SERUM PROCALCITONIN PREDICT ALL CAUSE MORTALITY IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK?

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ABSTRACT:

Background: The concept, definition and understanding of sepsis may have undergone several changes in the past years, but its omniscient nature in modern day critical care medicine has made accurate diagnosis, early initiation of therapy and relatively accurate prognostication, imperative. In recent times, procalcitonin has been used to initiate, de-escalate and guide antibiotic therapy. However, the data on its ability to predict all cause mortality in patients with sepsis remains nebulous. There is adequate evidence to merit considering both sides of the story.

Methods: We studied 99 consecutive patients meeting the diagnostic criteria for sepsis according to Sepsis 3 consensus criteria. Serum procalcitonin levels were compared head to head with 30-day all-cause mortality. Chi square paired and unpaired T and Pearson's coefficient were used to analyze the data.

Results: Our study showed that patients with a higher baseline value of serum procalcitonin had higher rate of in-hospital mortality (SD – 1.8 vs SD - 0.68, 2-tailed P<0.001). However, no statistically significant association was noted between baseline PCT and duration of ICU stay.

Conclusions: The predictive value of serum PCT, for mortality has been a matter of debate and controversy with compelling evidence to both sides of the story available in

contemporary literature. Our study re-enforces the dictum of early diagnosis and treatment of sepsis in conjunction with the judicious use of serum procalcitonin. On the horizon, the authors see a plethora of newer biomarkers (SUPAR and sTREM-1) which may be used standalone or in combination to improve outcomes.

Keywords: Sepsis, septic shock, Procalcitonin

INTRODUCTION:

Sepsis is defined as a life threatening, dysregulated immune response to infection that results in organ dysfunction(1-3). Clinical features include signs of infection, altered mentation, hypotension and hepatic, renal or hematologic dysfunction. According to the Sepsis 3 criteria, this condition has been described as an acute increase in > 2 sepsis organ failure assessment points. Septic shock was defined as the need for vasopressors to maintain a mean arterial pressure to >65 mmHg, with a serum lactate concentration >2 mmol/L despite adequate fluid resuscitation(2).

Sepsis can be both community and hospital acquired(4-6). Pneumonia is the most common source(6), with abdominal or genitourinary sources being the second and third most common. About one third patients would have a positive blood culture, thereby contributing to the enigma in diagnosis.

Patients with sepsis can have cardiorespiratory complications, neurologic and hematological sequelae, acute kidney injury and additional manifestations like adrenal crisis, sick euthyroid illness, dysfunction of hypothalamic-pituitary axis and DIC.

Procalcitonin is a serum biomarker that rises in bacterial infection and may therefore be of utility in prediction and prognostication in such infections(7). In healthy individuals, its synthesis is limited to thyroid neuroendocrine cells and therefore not detectable in normal individuals. In patients with infection, synthesis of procalcitonin is upregulated in nearly all tissues. Triggers for procalcitonin synthesis in infected individuals include TNF alpha, endotoxins, IL-1 and IL-6. Specific etiological agents associated with procalcitonin rise include Streptococcus pneumoniae, Hemophilus influenzae, Pneumocystis jirovecii, Candida and Malaria are all known to cause significant elevations in procalcitonin.

Serum procalcitonin rises within 4 hours of an inflammatory stimulus and peaks at 24 to 48 hours(8). Peak levels correlate with severity of infection and levels of procalcitonin decline by 50% every day after resolution of infection. The rate of fall is less predictable in patients with renal dysfunction.

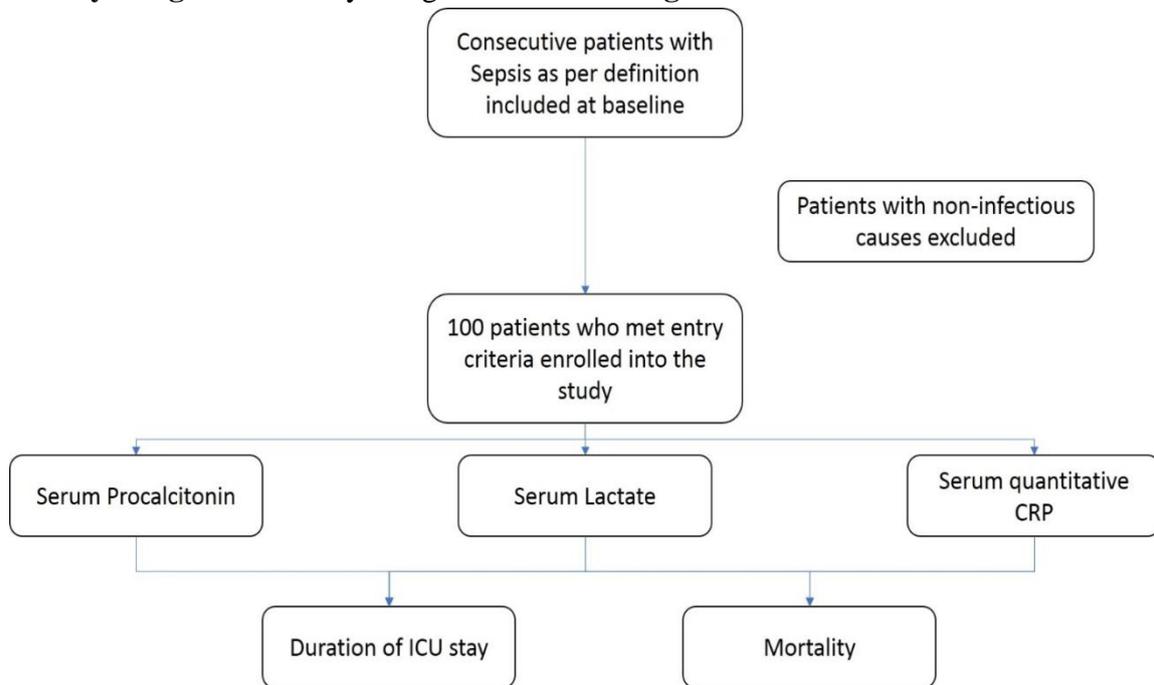
As on date, serum procalcitonin may be used for antibiotic initiation, discontinuation and prognostication in patients with sepsis. In this study we aim to correlate the levels of serum procalcitonin with duration of ICU stay and mortality.

METHODS:

1. **Study design and setting** - This study was a single center prospective cross-sectional study carried out over a period of 18 months at a resource limited service hospital.
2. **Study participants and inclusion criteria** - 100 consecutive patients who were admitted to the hospital with signs of sepsis, defined by the Sepsis 3 consensus, as a qSOFA of 2 or more on admission. The patients were monitored for signs of progressive organ

dysfunction and were managed according to existing standard of care. Each of these patients were subjected to investigations as detailed in Table 1.

3. **Exclusion criteria** – Patients with a known prior non-infectious cause, which could independently contribute to mortality were excluded. These include, but were not limited to autoimmune conditions (SLE, Sjogren's, Dermatomyositis), advanced cardiovascular disease (DCM with EF<20%), neutropenic patients and transplant patients.
4. **Study design** – The study design is detailed in **Figure 1**.



Additionally, other baseline and relevant investigations were carried out on all patients. As the patients were all managed according to existing standard of care, consent was waived. The data was analyzed and P value of < 0.05 was considered. Correlation co-efficient, Unpaired T test and Chi square test was used to analyze the data.

RESULTS:

The mean age of patients was 56.48 ± 13.85 , with 31% females and the rest were males(**Figure 1**).The mean TLC was 18644 ± 3030.3 . Other parameters are discussed in **Table 2**.

Age (years)	56.48 ± 13.85
Gender (Male/Female)	69 % Male
TLC	$18,644 \pm 3030.92$
CRP	83.649 ± 51.3
Procalcitonin	1.29 ± 0.35
Organ failure estimates	1.08 ± 1.11
Outcome	

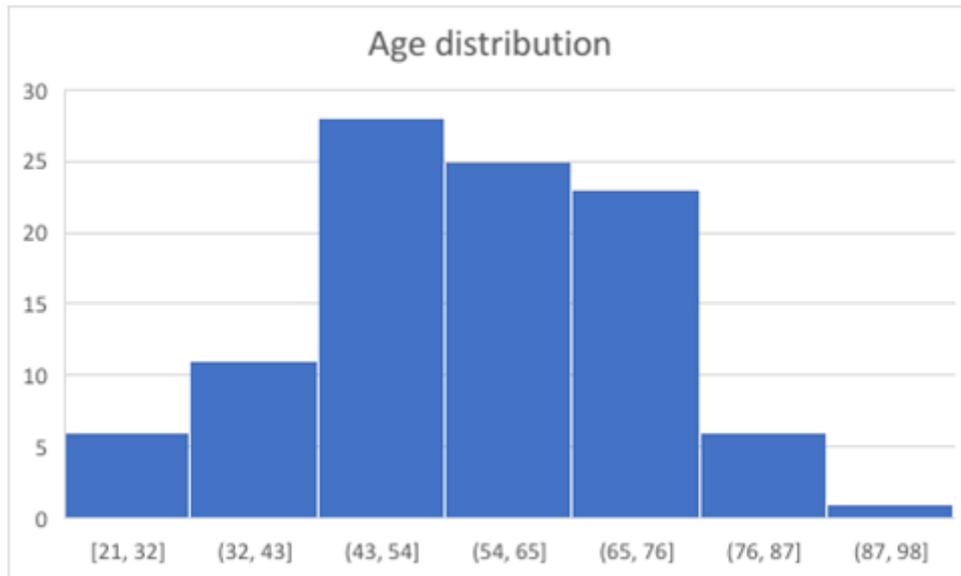


Figure 1 - Age distribution in patients with Sepsis / septic shock

RESEARCH QUESTION 1 - IS THERE A DIRECT CORRELATION BETWEEN PROCALCITONIN AND OUTCOME?

To test whether there was significant difference in Procalcitonin with respect to final outcome; t test for two independent samples is used.

Group Statistics					
	Final Outcome	N	Mean	Std. Deviation	Std. Error Mean
Procalcitonin	Death	25	2.7116	1.82667	.36533
	Discharged	75	.7996	.68459	.07905

Independent Samples Test						
		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	P value (2-tailed)
Procalcitonin	Equal variances assumed	24.391	.000	7.651	98	.000
	Equal variances not assumed			5.115	26.281	.000

Summary: Since p value < 0.05, the level of significance; Procalcitonin differs significantly with respect to outcome. The mean values suggest that Procalcitonin is higher for the patients who died than that for patients who were discharged.

RESEARCH QUESTION 2 - IS THERE A DIRECT CORRELATION BETWEEN PROCALCITONIN AND DURATION OF ICU STAY?

The Pearson's correlation coefficient between Procalcitonin & Duration of ICU stay is as given below & its significance is tested by t test.

PROCALCITONIN		
Length Of ICU Stay	Pearson Correlation	.163
	p value (2-tailed)	.106
	N	100
*. Correlation is significant at the 0.05 level (2-tailed).		
**. Correlation is significant at the 0.01 level (2-tailed).		

Summary: Since $p \text{ value} > 0.05$, the level of significance; the correlation between Procalcitonin & Duration of ICU stay is not significant.

Summary of results –

Our study showed that patients with a higher baseline value of serum procalcitonin had higher rate of in-hospital mortality (SD – 1.8 vs SD - 0.68, 2-tailed $P < 0.001$). However, no statistically significant association was noted between baseline PCT and duration of ICU stay.

DISCUSSION:

The ability of serum procalcitonin at being able to predict mortality is a matter of controversy in modern critical care medicine. In the past decade there have been several studies on the subject, with no clear consensus reached. We explore both sides of the story in the following paragraphs. The authors realize that these studies may not be comparable head to head, however, serve to reflect the conceptually dubious nature of the findings on the subject.

In 2019 *Akagi et al*(9) suggested that procalcitonin was not independent predictor of 30-day mortality, although they did find a correlation between procalcitonin levels and severity of pneumonia. *Andriolo et al* (10) were similarly unable to correlate PCT levels with overall mortality. *Khanna et al* attempted to summarize various organ failure scores and PCT levels to predict mortality in patients with acute pancreatitis(11).

The evidence to the contrary is equally overwhelming. *Chiwakata et al* demonstrated a statistically significant relationship between PCT and mortality in patients with Plasmodium falciparum malaria (12). *Cotoi et al* demonstrated a relationship between PCT levels and all cause mortality in patients with a previously diagnosed condition (13). *Gul et al* demonstrated an association, but not a direct correlation between procalcitonin levels and mortality in Crimean Congo Hemorrhagic fever(14). This study was unique in being to associate a viral infection with serum procalcitonin levels. *Kenzaka et al* demonstrated a significant correlation between PCT levels and mortality (15). Their study was also able to comment on the predictive ability of PCT.

Hanah Kim et al opined that a multi-marker approach to predict mortality in sepsis which included PCT, presepsin, and galectin 3 may be used to predict mortality in sepsis (16). *Matsumura et al* definitively stated that mortality in patients with higher PCT levels and that it was able to predict post ICU discharge mortality as well (17). *John Victor Peter et al* were able to correlate the levels of increased mortality in patients with scrub typhus infection and

in those who would need ICU admission(18).*Pierrali et al* were able to demonstrate the rise of PCT in the first 72 hours and all cause mortality in patients with sepsis (8).

CONCLUSION:

The predictive value of serum PCT, for mortality has been a matter of debate and controversy with compelling evidence to both sides of the story available in contemporary literature. Our study re-enforces the dictum of early diagnosis and treatment of sepsis in conjunction with the judicious use of serum procalcitonin. On the horizon, the authors see a plethora of newer biomarkers (SUPAR and sTREM-1) which may be used standalone or in combination to improve outcomes.

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