Role of Serial change in Serum Procalcitonin Levels as a Marker to Predict 28th Day Mortality in Patients with Sepsis and Septic Shock

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Abstract

Objectives

Worldwide, the estimated incidence of sepsis is >30 million cases every year with approximately 6 million deaths annually. Studies have shown that procalcitonin can be a reliable marker for diagnosis and predicting mortality in sepsis patients. In this study, we have tried to determine the role of serial changes in procalcitonin levels in predicting 28th day mortality in patients with sepsis and septic shock.

Methods

A prospective observational study was conducted at ABVIMS and Dr RML Hospital from 1st November 2017 to 31st March 2019. Adults who were diagnosed with sepsis or septic shock and admitted to ICU, emergency or ward of the hospital were included. Sample for procalcitonin was taken at admission (day-1), and on day-5. Patients were followed telephonically to record final outcome at 28 days.

Results

Fifty-seven patients were enrolled in the study. 35 (61.4%) patients had sepsis and 22 (38.6%) were in septic shock. 10 (17.54%) patients died over a period of 28 days follow up. The level of serum procalcitonin on day-1 was significantly higher in non survivors as compared to survivors (7.66±2.07 vs. 5.78±2.48, p-value -0.029). Percentage change in procalcitonin (ΔPCT) from day 1 to day 5 was significantly low among non survivors as compared to survivors (29.94 ± 38.29 vs 70.33±34.56, p- value-0.006). Of 10 patient who died, 8 (32%) had ≤80% decrease in (ΔPCT) and only 2 (6.25%) had >80%decrease in (ΔPCT) (p= 0.016). SOFA, q-SOFA and serum lactate were significantly higher among non survivors and were also significant in predicting mortality on univariate analysis. But multivariate analysis showed that only (ΔPCT) had significant correlation with mortality (OR: 0.972, p=0.022) and hence can hence can be used as an independent marker of mortality in sepsis patient.

Conclusion

This study determined that more than baseline values of procalcitonin, the change in serial procalcitonin (ΔPCT) was significant in predicting mortality in patients with

sepsis and septic shock.

KEY WORDS: Procalcitonin, sepsis, serial change, mortality

Introduction

Sepsis and septic shock are common indications for the admission in the Intensive Care Unit and it carries high morbidity and mortality. Worldwide, the estimated incidence of sepsis is more than 30 million cases every year, leading to approximately 6 million deaths annually. [1] Early diagnosis of sepsis and septic shock is essential for treatment and to reduce mortality. There is an ongoing effort to improve the ability to predict mortality in sepsis and septic shock. Different biomarkers have been studied like CRP, IL-6, IL-2, lipo-polysaccharides binding protein (LBP), pentraxin-3, TNF-α, co-peptin, soluble urokinase plasminogen activator, soluble CD14 (presepsin) and TREM-1 etc. There are multiple studies on sepsis-related biomarkers and it has been seen that procalcitonin can be used as a reliable marker for predicting mortality in sepsis. Procalcitonin is a 116 amino acid prohormone of calcitonin found in the blood. [2,3] Its synthesis is stimulated by various inflammatory cytokines released during sepsis, like tumor necrotic factor-alpha and IL-6.[4] Procalcitonin is a host response marker because it is increased by microbial toxins and various pro-inflammatory mediators like, tumour necrosis factor-α, IL-6,IL-1b and decreased after recovery.[5] Expression of procalcitonin is reduced by some cytokines like interferon -γ which is released due to viral infection, thus elevated serum procalcitonin is indicative of bacterial aetiology.[6] Apart from diagnosis, serum Procalcitonin kinetics are also be used for prediction of mortality and treatment failure. Bacterial infection increases the expression of procalcitonin by producing CALC-1 gene in extra-thyroidal tissues all over the body.[7] Besides bacterial infection procalcitonin increases in various other conditions like multiple trauma, cardiogenic shock, drug sensitivity reaction, major surgery, thyroid malignancy etc.[8,9,10,11] Patient without any infection or inflammation usually have a low level of serum procalcitonin concentration (< 0.05 ng/mL). In patient with severe sepsis and septic shock, procalcitonin concentration can be so high as up to 1000 ng/mL. [3] The cutoff value of procalcitonin for sepsis has been set at 0.44 to 1.0 ng/mL in multiple studies. [12,13] It has also been evaluated to shorten the course of antibiotic therapy in septic patients. [14] In our study, we have tried to find the role of serum procalcitonin levels as a marker to predict 28th day mortality in patients with sepsis and septic shock and to find the association between the decrease in serum procalcitonin levels by more than 80% between day 1 and day 5 with increased 28th day mortality in patients diagnosed with sepsis and septic shock. The objectives of the present study are:

1. To study the role of serum procalcitonin levels as a marker to predict 28th day mortality in patients with sepsis and septic shock
2. To find the association between decrease in serum procalcitonin levels by more than 80% between day 1 and day 5 and 28th day mortality in patients diagnosed with sepsis and septic shock.

Methods

This was a prospective observational study conducted in the department of medicine, ABVIMS and Dr RML Hospital, New Delhi from 1st November 2017 to 31st March 2019. Diagnosis of sepsis was based on standard clinical, laboratory and microbiological parameters and organ dysfunction was based on the definitions proposed by the Society of critical care medicine (SCCM), third international consensus definition for sepsis and septic shock (sepsis-3), 2016.[15]

Patients more than 18-year of age, who were diagnosed with sepsis or septic shock and admitted to ICU, ward or emergency of the hospital were included, after taking an informed consent. Those patients who underwent surgery, had trauma or malignancy and were less than 18 years of age were excluded. Patients without initial blood draw i.e., blood sampling done after 12 hours of diagnosis of sepsis or septic shock and those who died or were discharged from the hospital prior to the day 5 of blood sampling were also excluded. Detailed clinical history, examination and investigations were performed as per the case record performa. All patients were followed up telephonically for 28 days to record the final outcome.

Sample collection and Procalcitonin Measurement

After taking written informed consent from patient or surrogate, approximately 3-5ml of blood was collected from patient within 12 hours of diagnosis of sepsis and

septic shock, using aseptic technique. Sample taken at the time of admission or within 12 hours of diagnosis of sepsis and septic shock was considered as day-1 sample (DAY-1) and repeat sample was taken on day-5 (DAY-5). So, a total of two samples were taken, and sent to microbiology department of Dr RML Hospital where it was measured quantitatively by ELISA kit manufactured by BIO-VENDOR RESEARCH AND DIAGNOSTIC PRODUCTS. The serial change in procalcitonin i.e., PCT was calculated as change in absolute values, and subtraction of PCT (day1-day5) and percentage values were calculated as (day 5/day 1×100).All patients were followed up for 28 days to record the outcome. Ethical approval was taken from hospital's ethical review board.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Quantitative variables were compared using Mann-Whitney Test between the two groups. Demographic data was analyzed between groups with student t-test and non parametric data with Mann Whitney U-test. Association of decreased serum procalcitonin levels by more than 80% between day 1 and day 5 with 28^{th} day mortality was done by using the Chi square test/Fisher exact test. Receiver operating characteristic curve was used to find out the area under curve of procalcitonin for predicting mortality. To find out different predictors of mortality in sepsis and septic shock univariate analysis was applied and factors with p value < 0.05 in univariate analysis were subjected to multivariate regression analysis to determine the independent role of different predictors of mortality in sepsis and septic shock. A p value of <0.05 was considered statistically significant. The sensitivity, specificity, positive predictive and negative predictive values were compared by their 95% confidence intervals. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 86 patients were screened in the study, 29 patients were excluded because of negative consent, missing initial blood sampling on day-1 of admission and death/LAMA (left against medical advice) before day 5. The main intention to diagnose analysis consisted of 57 patients. Among 57 patients, 35 (61.4%) patients were diagnosed with sepsis and 22 (38.6%) were in septic shock, out of these 10 (17.54%) patients died over a period of 28 days follow up. Patients enrolled in the study had a mean age of 57.14±15.77 years and 57.89% were male. Table 1, shows the baseline characteristics in overall intention to diagnose population stratified by 28 day survival status. The baseline severity of illness score i.e., SOFA score and qSOFA scores were significantly higher among the non survivors as compared to survivors. The lactate level were also higher (3.23±0.67 mmol/L) in non survivors as compared to survivors (2.82±0.67 mmol/L). Among the biomarkers, the level of serum procalcitonin on day 1 was significantly higher in non survivors as compared to survivors (7.66±2.07 vs 5.78±2.48, p=0.029). Percentage change in procalcitonin from day 1 to day 5 was significantly low in non survivors as compared to survivors (29.94±38.29 vs 70.33±34.56, p=0.006). (Table 1)

Procalcitonin Kinetics and 28-Day Mortality

We measured and analysed the change in S-Procalcitonin concentration (ΔPCT) on day 1 and day 5 in all patients. The mean ΔPCT in survivor and non-survivor was 70.33% and 29.94% respectively (Figure 1). We divided the patients into two groups, first who had ≥80% decrease in S-procalcitonin on day 5 as compared to day 1 and the second who had < 80% decrease of S-procalcitonin on day 5 compared to day 1. ΔPCT of ≤ 80% was seen in 43.86% and > 80% in 56.14% (Figure 1).

Out of 10 patient who died due to sepsis and septic shock at 28 day follow up, 8 (32%) had ≤ 80% decrease and 2 (6.25%) had > 80% decrease in serum procalcitonin levels (p= 0.016**)** (Table 2).

Comparison in AUROC curve of various parameter

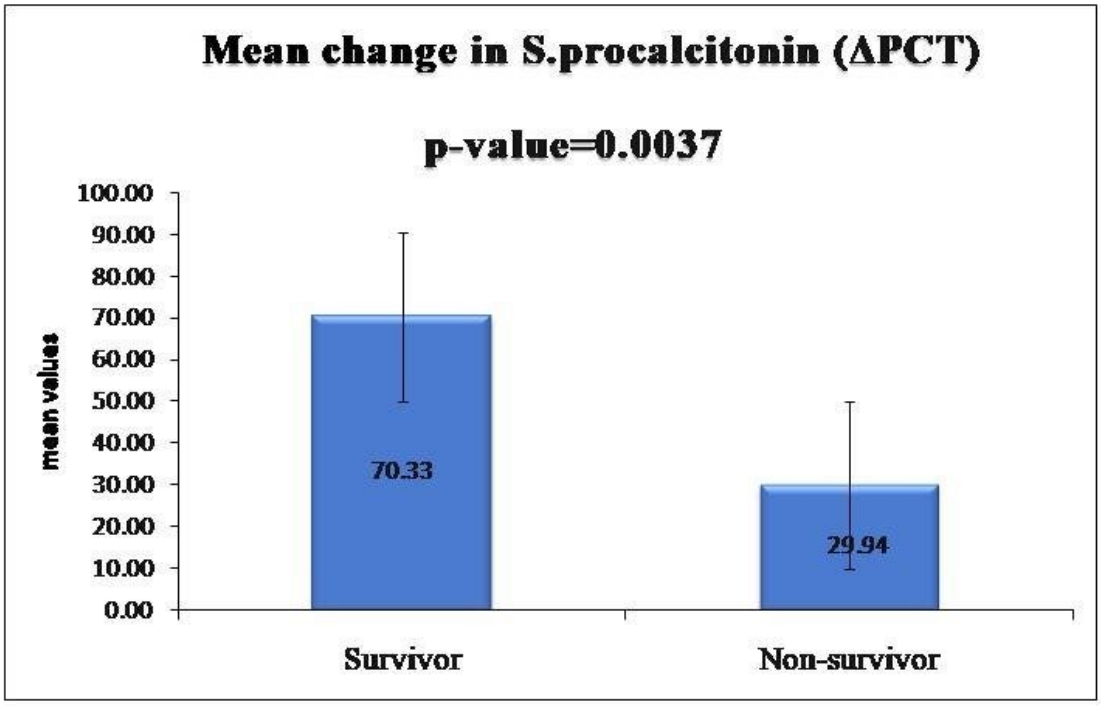
AUROC of various predictors of prognosis in relation to mortality in sepsis, showed percentage change in S-procalcitonin (ΔPCT) having AUROC, sensitivity and specificity 0.719, 80 and 63.8 respectively (p=0.037), having a positive predictive value of 32% and a negative predictive value of 93.8%. For serum PCT on day-1 AUROC, sensitivity and specificity was 0.736, 60.0 and 85.11 respectively (p=0.0096). For qSOFA score AUROC,

Table 1: Baseline characteristics of patients

Characteristics	All Patients (n=57)	Survivors (n= 47)	Non survivors (n=10)	p- value
Age	57.14±15.77	55.3±15.65	65.8±13.99	0.055*
Male sex	33(57.89%)	26(78.79%)	7(21.21%)	
Female sex	24(42.11%)	21(87.5%)	3(12.50%)	
Sepsis	35(61.4%)	30(85.71%)	5(14.29%)	0.415
Septic shock	22(38.60%)	17(77.27%)	5(22.73%)	0.415
Lactate level (mmol/l)	2.98±0.67	2.82±0.67	3.23±0.67	0.19
Sofa score	4.95±2.17	4.55±1.93	6.8±2.35	0.006*
qSOFA	2.02±0.72	1.92±0.72	2.5±0.53	0.02*
Procalcitonin (Day-1)	6.11±2.5	5.78±2.48	7.66±2.07	0.029*
Procalcitonin (Day-5)	2.41±2.93	1.76±2.43	5.45±3.28	0.003*
Percentage change in Procalcitonin	63.25±38.17	70.33±34.56	29.94±38.29	0.006*

Values as mean ± SD, n(number), % (percentage), SOFA (Sequential organ functional assessment), qSOFA (quick sepsis related organ failure assessment).

Figure 1: The Mean change in S.PCT (Δ PCT) between Day –1 and Day –5 in survivor and non-survivor



sensitivity and specificity was 0.718, 100.0 and 29.8 respectively, (p=0.002). For SOFA score AUROC, sensitivity and specificity was 0.776, 70.0 and 85.11 respectively, (p=0.0035). For lactate AUROC, sensitivity and specificity was 0.626,70 and 57.45 respectively, (p=0.2061) (Figure 2, Table 3).

To assess whether the procalcitonin decrease provides prognostic information beyond that of other clinical outcome predictors, we calculated univariate (Table 4) and multivariate cox regression analysis (Table 5) among all predictors. SOFA score, q-SOFA levels were found to be significantly associated with mortality on univariate analysis but not on multivariate analysis**.** Final model derived by multivariate logistic regression suggested a significant and independent correlation of percentage change in S-Procalcitonin (ΔPCT) and mortality (OR: 0.972, p=0.022)**.** (Table 5).

Discussion

In present era of antibiotic resistance, sepsis is one of the major causes of mortality and morbidity in ICUs. Prompt diagnosis of sepsis is required to start antibiotics early so that we can manage the patient at the initial stages and prevent further complications. There are various markers for predicting outcomes of sepsis. In present study, we have tried to find the prognostic value of serum procalcitonin level and its serial change as a marker to predict 28th day mortality in patients with sepsis and septic shock. Other parameters studied were age, gender, SOFA score, q-SOFA and serum lactate levels. In our study the mean age of survivors was 55.3 years and non survivors were 65.8 years. Similarly in the studies conducted by Ros – Torro JJ et al and Huang MY et al it was 68 yrs and 70 years respectively. [16,17] These findings were similar to other studies. [18,19] However, age was not found to be the significant predictor of mortality. No significant association was found between gender and mortality in sepsis patients as seen in previous studies also. [10,20] Majority of patients who had high SOFA score had high mortality which was found statistically significant by chi square test (p=0.013) and univariate logistic regression analysis (p= 0.007; OR 1.735). However, SOFA score was not found to be an independent predictor of mortality on multivariate logistic regression analysis. The findings corroborated with the studies done earlier by Saransh Jain and Sanjeev Sinha in MICU of AIIMS which stated that procalcitonin levels of less than 7 ng/mL showed higher cumulative survival as compared to those with higher level (69.1% vs. 39.5%, p = 0.02). The baseline mean SOFA scores were 8.3 in the study patients and were significantly higher among those who did not survive. [20]

A study conducted by Karlsson S et al also showed that patients with SOFA score of 4 and above had higher level of serum procalcitonin measured on day one [6.5 ng/mL (1.6-29.0)] and three [2.3 ng/ml (0.7-7.4)] respectively, as compared to those without sepsis. [21]

Similar to our study, q SOFA score did not have independent role in prediction of mortality as found in study done by Jiang et al. [22]

The mean serum lactate level was higher in non survivor group as compared to the survivor group but this was statistically not significant (p= 0.20). This was similar to one previous study done by Saransh Jain et al which also predicted that lactate levels were higher in those who died due to sepsis than those who survived, 2.4 mmol/L

Figure 2: Showing AUROC of various parameters of prognosis

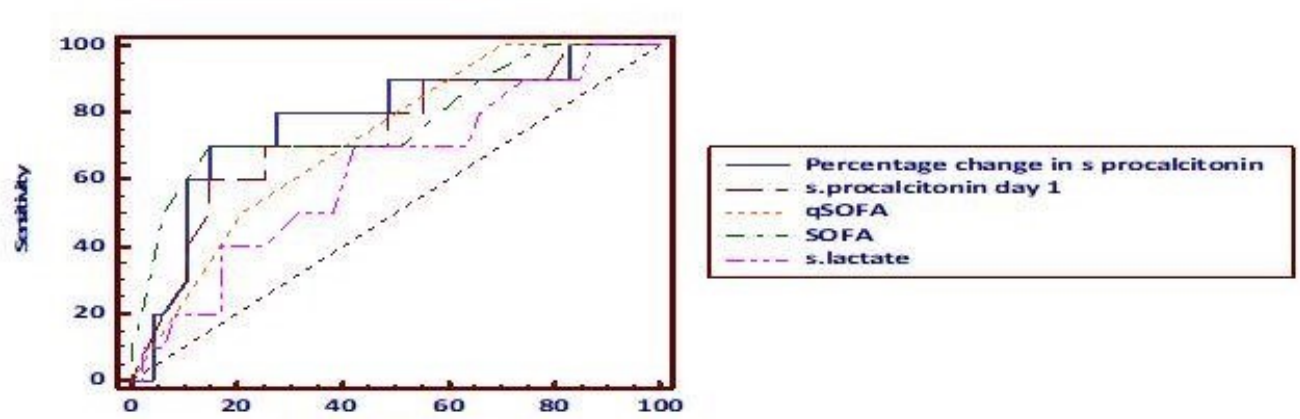


Table 2: Final outcome related to change in serum Procalcitonin (ΔPCT) levels, day-1 S. PCT compared with day-5 S. PCT levels

Percentage change in S-Procalcitonin (Δ PCT)	Final outcome		Total	p- value
	Survivor	Non-survivor		
≤ 80%	17 (68.00%)	8 (32.00%)	25 (100.00%)	0.016*
> 80%	30 (93.75%)	2 (6.25%)	32 (100.00%)	
TOTAL	47 (82.46%)	10 (17.5 4%)	57 (100.00%)	

Table 3: Area Under the Receiver Operating Characteristic curves (AUROC), sensitivity, specificity, positive and negative predictive values of various parameter of prognosis

	AUROC (95% CI)	CUT OFF	Sensitivity (95% CI)	Specificity (95% CI)	P-VALUE	Positive predictive value (95% CI)	Negative predictive value (95% CI)
S. Lactate	0.626 (0.487-0.750)	>3	70 (34.8-93.9)	57.45 (42.2-71.7)	0.2061	25.9 (11.1 - 46.3)	90 (73.5 - 97.9)
SOFA	0.776 (0.646-0.875)	>6	70 (34.8-93.3)	85.11 (71.7-93.8)	0.0035*	50 (23.0 -77.0)	93 (80.9 - 98.5)
q-SOFA	0.718 (0.583-0.829)	>1	100 (69.2-100)	29.79 (17.3 - 44.9)	0.002*	23.3 (11.8 -38.6)	100 (76.8 - 100.0)
Procalcitonin DAY -1	0.736 (0.603-0.844)	>8.3	60 (26.8-87.8)	85.11 (71.7 - 93.8)	0.0096*	46.2 (19.2-74.9)	90.9 (78.3-97.5)
Change in Procalcitonin	0.719 (0.584-0.830)	≤ 80%	80 (44.0-97.5)	63.83 (48.5-77.3)	0.0037*	32 (14.9-53.5)	93.8 (79.2-99.2)

Table 4. The various parameters associated with mortality in sepsis and septic shock determined by Univariate logistic regression

Predictors for prognosis	S.E.	P value	Odds ratio	95% C.I. for Odds ratio	
				Lower	Upper
Age	0.027	0.066	1.051	0.997	1.108
SOFA score	0.205	0.007*	1.735	1.160	2.595
q-SOFA score	0.590	0.026*	3.714	1.169	11.799
S. Lactate	0.536	0.192	2.015	0.704	5.766
S. Procalcitonin (Day-1)	0.188	0.041*	1.468	1.016	2.120
Percentage change in S- Procalcitonin (ΔPCT)	0.009	0.006*	0.975	0.957	0.993

Table 5. The factors independently associated with mortality in sepsis and septic shock determined by Multivariate logistic regression analysis

Predictors for prognosis	S.E.	p-value	Odds ratio (OR)	95% C.I. for Odds ratio	
				Lower	Upper
SOFA score	0.263	0.144	1.468	0.877	2.457
q-SOFA score	0.794	0.160	3.049	0.643	14.454
S-Procalcitonin (Day-1)	0.220	0.334	1.236	0.804	1.902
Percentage change in Procalcitonin	0.012	0.022*	0.972	0.949	0.996

(1.3-4.3) and 1.2 mmol/L (0.8-2.1) respectively (p=0.001). [20]

Several studies have investigated the prognostic role of procalcitonin in sepsis. We have tried here to find association between the percentage changes in ΔPCT from day-1 to day-5 of admission with 28-day mortality. It was seen that patients who failed to have decrease in serum procalcitonin by more than 80% on day-5 as compared to day-1 were associated with increased mortality. These results remain significant even after multivariate logistic regression analysis for other known prognostic factors. Odds ratio for ΔPCT in our study was 0.972, suggesting its neutral effect but in previous study it showed significant effect on mortality with a higher hazard ratio. A blinded, prospective multicenter observational clinical study conducted by Sheutz et al measured the prognostic performance of procalcitonin decrease from the baseline to day-4. The mortality rate was twice in those patients who did not have a fall in their Procalcitonin levels by more than 80% from baseline to da- 4 as compared to those with more than 80% decrease (p=0.001). The prognostic measures at this cutoff showed a sensitivity of 77% (95% CI) with a specificity of 39%, a negative predictive value of 90%, and a positive predictive value of 20%. It was found to be an independent predictor of mortality in Cox regression analysis (hazard ratio, 1.97 [95% CI, 1.18–3.30; p < 0.009] after adjusting for demographics. [14] These findings were also seen in various other studies. [5,17-24] In one retrospective study, procalcitonin change over 72 hours was a predictor for ICU and hospital mortality in sepsis patients, independent of ICU risk scores. [5] Another study conducted in Turkey by Cananbalci et al on thirty-three ICU patients diagnosed with SIRS, sepsis or septic shock suggested that serum PCT concentration was the most discriminatory laboratory variable and its predictive accuracy exceeded those of CRP, TNF-α, IL-2, IL-6 and IL-8 for the specific diagnosis of SIRS and sepsis. The test effectiveness was 1.84 to predict sepsis for procalcitonin with a cut off value of 2.415 ng/mL with AUC (mean ± SE) of 0.969 ± 0.016 and p value of 0.00. The sensitivity, specificity, and negative and positive predictive value being 85%, 91%, 95% and 89% respectively. [26]

Previous research data also demonstrate that procalcitonin can be used to inform antibiotic stewardship decision, mainly by reducing antibiotic initiation in low-risk patients. [25-27]

Our observation further supports serial monitoring of procalcitonin levels to predict mortality in patients with sepsis and septic shock.

Our study had certain limitations. Being a tertiary care centre the first day sample of procalcitonin was not actually reflecting the actual onset of sepsis or septic shock. Study included all patients of sepsis and septic shock irrespective of site of primary infection and organ involved thus lack specification on type of infection and organism. The procalcitonin estimation kit used in our study had upper limit of 9.6 ng/dL and hence levels could not be assessed quantitatively above this value. Our study had a small sample size of 57 cases and more studies with a larger sample size need to be done for further validation of this topic.

In conclusion, although SOFA, q-SOFA and Day-1 Serum Procalcitonin levels significantly predict mortality in patients with sepsis and septic shock, serial change in Procalcitonin (ΔPCT) levels can also be used as an independent predictor for 28-day mortality. Hence ΔPCT can guide in treatment strategy of these patients.

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Conflicts of interest: There are no conflicts of interest.

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Ethical approval: Ethical approval has been taken from hospital's ethical review board.

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