Research Article

Procalcitonin kinetics as a prognostic marker in severe sepsis/septic shock

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Abstract

Background and Aims: To evaluate the prognostic value of change (fall) in serum procalcitonin level (PCT) in critically ill adults with severe sepsis/septic shock. **Methods:** This was a prospective observational study in a general purpose Intensive Care Unit of a teaching Institute. PCT was measured at admission (D0) and after 72–96 h (D4) by electrochemi-luminescence immunoassay (BRAHMS PCT kit) in adults (>18 years) admitted with severe sepsis or septic shock. Change in procalcitonin values from D0 to D4 was correlated with the primary outcome, that is, 28 days mortality. All results are reported as median (interquartile range). **Results:** A total of 171 (100 males) of 181 patients were included. The median age was 46 years (range 19–79). 137 patients were in septic shock and 34 in severe sepsis. The sequential organ failure assessment (SOFA) score in all patients was 11 (9–14). 91 (53.2%) patients survived at 28 days (survivors). The baseline procalcitonin was similar in two groups (3.48 [1.04–15.85] vs. 5.27 [1.81–23.57] ng/ml in survivors and nonsurvivors [NS] respectively). The procalcitonin change was 1.58 (0.20–8.52) in survivors and 0.28 (–1.38–6.17) in NS (P = 0.01). The C-statistic of percentage change in procalcitonin from D0 to D4 to predict survival was 0.73 (95% confidence interval [CI]: 0.65–0.82) when compared to 0.78 (95% CI: 0.71–0.86) for change of SOFA score. For an absolute fall in procalcitonin of >1 ng/ml, a 70% fall predicted survival with 75% sensitivity and 64% specificity. **Conclusions:** In critically ill-patients with severe sepsis/septic shock, change (fall) in procalcitonin is associated with good outcome.

Keywords: Biomarker, critical illness, organ dysfunction score, prognosis, septic, shock

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Introduction

Sepsis is one of the important reasons for Intensive Care Unit (ICU) admission and carries a high morbidity and mortality. To be able to quickly identify the prognosis of sepsis is of vital importance to allocate appropriate resources.[1] Several biomarkers have been studied in this regard; of them, procalcitonin seems promising. Procalcitonin, a precursor of the thyroid hormone calcitonin, remains very low in physiological conditions (level <0.1 ng/ml). Following systemic bacterial infections, the level rises rapidly and peaks by 6–12 h after the onset of infection; and falls with a control in the infection.

Procalcitonin in sepsis has been studied in various different roles. It was considered a novel biomarker that could differentiate between infectious and noninfectious causes (sepsis vs. systemic inflammatory response syndrome [SIRS]) in critically ill patients; however, this is not supported by the current literature.[2,3] Nevertheless, it continues to find utility in guiding the duration of antibiotics;[1,4,5] procalcitonin guidance significantly reduced antibiotic duration without increasing infection relapse or mortality.[6] Procalcitonin levels have been found to be higher in patients with more serious illnesses; hence it was believed that this can be used to assess the prognosis.[7,8] When this was attempted in critically ill patients, however, no correlation was found.[1] Rather, it

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was found that a change in procalcitonin level correlates better with prognosis.

Available literature on change in procalcitonin level as a prognostic marker in critically ill patients is on small groups of patients with specific illnesses (ventilator-associated pneumonia [VAP], postoperative sepsis, etc.). In these studies, the number of patients with severe sepsis or septic shock is even smaller. Hence, we planned to evaluate the prognostic value of change (or fall) in procalcitonin level in a group of critically ill patients with severe sepsis/septic shock.

Methods

Consecutive adults (age >18 years) with severe sepsis/septic shock on admission to the general ICU of a tertiary care teaching hospital were prospectively included. Severe sepsis was defined as the presence of sepsis (2 or more SIRS criteria associated with suspected or proven infection) along with organ dysfunction, hypoperfusion or hypotension.[9] Septic shock was defined as sepsis-induced hypotension despite fluid resuscitation along with evidence of hypoperfusion. Patients on immunosuppressive therapy and those in the terminal stage of any chronic disease (e.g., cirrhosis Child C) were excluded.

After obtaining written informed consent from the close relatives, two ml of blood was collected from the patient soon after admission (D0); and a repeat sample was obtained after 72–96 h (D4). Serum was separated and stored at −80°C for further analysis. The study was approved by the Institutional Ethics committee.

All patients were managed as per the decision of the treating physician. Data collected included demographic and clinical characteristics of the patients, relevant laboratory results and cultures, and details of therapy. ICU prognostication scores, that is, acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were calculated in all patients and recorded. The patients were followed-up till 28 days and the outcome at 28 days was noted as the primary outcome.

Procalcitonin estimation in the serum was done using the commercially available electrochemiluminescence immunoassay (BRAHMS PCT kit) using a Cobase 411 analyzer with a sensitivity of <0.02 ng/ml and a measuring range of 0.02–100 ng/ml. Values above 100 ng/ml were not delineated further and reported as such. All such values were taken as 100 ng/ml for the purpose of calculations.

Statistical analysis

Statistical analysis was done using the statistical software SPSS 16 (IBM Corporation, USA). Those who survived till 28 days after study enrolment were considered as "survivors." Intergroup comparisons were done using nonparametric tests. Receiver operating characteristic (ROC) curves were constructed to identify the most discriminatory values of change in procalcitonin level and SOFA score. Significance level was considered at $P< 0.05$.

Results

A total of 542 patients were admitted to the ICU between March 2011 and June 2013; 181 of these with severe sepsis/septic shock fulfilled the inclusion criteria. Of these, four patients refused consent while in six patient's treatment was either withheld/withdrawn. Hence, samples of 171 patients were analyzed. Of these, a second sample could be taken on D4 in 139 patients as some patients died before the second sample could be taken while some samples clotted and some patients were missed.

The median age of the patients was 46 years (range 19–79 years, interquartile range [IQR] 30–58). The baseline characteristics of the patients are as shown in Table 1.

Among the patients included in the study, 80 died at the end of 28 days; thus 91 patients were survivors (S) and 80 nonsurvivors (NS). The severity of illness of the patients at study entry and their outcome is as shown in Table 2.

All patients required organ support in the ICU; 160 (94.1%) required mechanical ventilation, 154 (91.7%) required vasoactive drugs, 84 (49.1%) required renal replacement therapy (at least one session) and 130 (76.02%) required transfusion of any blood product. At 28 days, the median days of mechanical ventilation was 8 (IQR 4–15 days), vasoactive drug infusions were 5 (IQR 3–10 days) and antibiotics was 16 (IQR 8–24). A median of 0 renal replacement therapies was used (IQR 0–4). Regarding blood product transfusions, 113 (66.1%) patients required packed red blood cell transfusions with a median of 2 units (IQR 0–4 units); 91 (53.2) required fresh frozen plasma transfusions with a median of 2 units (IQR 0–6) and 59 (34.5%) required RDP transfusions with a median of 0 units (IQR 0–5). More NS required transfusions as compared to survivors (70/80, 87.5% vs. 60/91, 65.9% $P = 0.001$).

Among the baseline characteristics of the patients, age, gender, admission type (medical, surgical or

obstetric), primary diagnosis, patient location prior to ICU admission and presence or absence of comorbidities did not affect outcome. On the other hand, NS had more nosocomial infections as compared to community acquired infections (38/80 in NS vs. 26/91 in S; $P = 0.012$), were in septic shock more often as compared to severe sepsis (76/80 in NS vs. 61/91 in S; $P < 0.01$) and had a higher number of organ systems involved (median 4 in NS vs. 3 in S; $P < 0.01$). Gram-negative infections were predominant in both survivors and NS.

Regarding the severity of illness, APACHE II and SOFA scores were compared in the two groups. Both scores were higher in the NS [Table 2]. Parameters used to identify sepsis, that is, total leukocyte count and temperature, were similar in both groups as were the perfusion parameters, central venous oxygen saturation and base excess. The global perfusion parameter, lactate, however, was higher in NS as compared to survivors (median value 2.0 mmol/L in NS vs. 1.5 mmol/L in S, $P = 0.02$).

Table 1: Admission characteristics of the patients

Characteristic	Number (%)
Male:female	100:71
Admission type	
Medical	149 (87.1)
Surgical	12 (7.2)
Obstetric	10 (5.8)
Patient location prior to ICU admission	
Emergency	47 (27.5)
Any ward	32 (18.7)
Another ICU	92 (53.8)
Type of sepsis	
Community acquired	107 (62.6)
Nosocomial	64 (37.4)
Diagnostic category	
Pneumonia	47 (27.5)
Pancreatitis	27 (15.8)
Tropical infections	26 (15.2)
Other GI conditions	21 (12.3)
Urinary tract infections	13 (7.6)
Miscellaneous	37 (21.6)
Organ systems involved	
Respiratory	155 (90.6)
Cardiovascular	131 (76.6)
Renal	110 (64.3)
Hematological	58 (33.9)
Neurological	37 (21.6)
GI including hepatic	36 (21.1)
Endocrine/metabolic	10 (5.8)
Comorbidities	
Diabetes	36 (21.1)
Hypertension	40 (23.4)
Hypothyroidism	15 (8.8)
Cardiac conditions	16 (9.4)
Respiratory conditions	19 (11.1)
Hepatobiliary diseases	9 (5.3)
Obesity	06 (3.5)
Others	10 (5.8)
None	80 (46.8)
Microbiologic data	
Gram-negative	65 (38)
Gram-positive	6 (3.5)
Mixed bacterial	10 (5.8)
Fungal	10 (5.8)
Vector borne	9 (5.3)
Possible colonizations	14 (8.2)
All tests negative	57 (33.3)

ICU: Intensive Care Unit; GI: Gastrointestinal

Median procalcitonin level in the entire group of patients at study entry was 3.83 ng/ml (IQR 1.24–29.17); it was 3.48 ng/ml (IQR 1.04–15.85) in survivors as against 5.27 (IQR 1.81–23.57) in NS ($P = 0.14$). Procalcitonin level decreased to a median of 1.48 ng/ml (IQR 0.66–11.08) on D4 with values of 0.98 ng/ml and 6.09 ng/ml in survivors and NS respectively ($P < 0.01$). The procalcitonin level in the patients with different diagnostic categories was similar (data not shown).

Comparison of the change in procalcitonin levels in survivors and NS is shown in Table 3 along with the change in values of SOFA score, lactate levels, central venous oxygen saturation, pH and base excess over the same period (i.e, 72–96 h). Change in procalcitonin level and SOFA score are significant while the rest are not significant. Change in procalcitonin level in survivors from D0 to D4 (3.48 ng/ml to 0.98 ng/ml) is significant while there is no change in NS (5.27 ng/ml to 6.09 ng/ml).

To better quantify the fall in procalcitonin levels, we looked at the percentage change in the procalcitonin value from the baseline value as a prognostic marker. Overall, the procalcitonin value decreased by a median of 59.7% in the entire group (IQR 2.9–79.0%). The median value in survivors and NS was 73.5% (IQR 35–85) and 24.4% (IQR −40.3–63.9); this difference was statistically significant ($P < 0.01$). This is depicted graphically in the box plot at Figure 1.

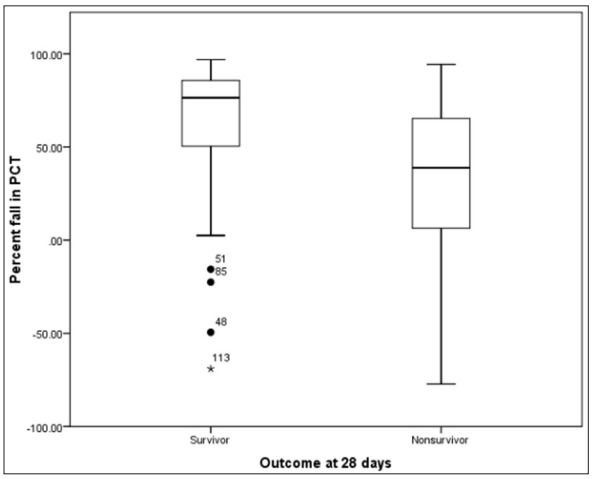

Figure 1: Percentage fall in procalcitonin levels in survivors and nonsurvivors

Table 2: Severity of illness at study entry and 28-day outcome

Characteristic	All patients (*n*=171)	Survivors (*n*=91)	Nonsurvivors (*n*=80)
Severity of sepsis*			
Severe sepsis	34	30	4
Septic shock	137	61	76
Length of ICU stay* (days)	12 (8-23)	19 (10-33)	9 (4-14)
Length of hospital stay* (days)	16 (9-28.5)	23.5 (13-44.5)	11 (5-17)
APACHE II score*	18 (15-21)	16 (12-21)	19 (17-22.3)
SOFA score*	11 (9-14)	10 (8-13)	13 (11-15)
Total leucocyte count (×1000/cmm)	16.6 (11.7-23.5)	15.8 (11.7-23.4)	16.7 (11-24.0)
Lactate (mmol/L)*	1.8 (1.2-2.6)	1.5 (1.1-2.2)	2.0 (1.4-3.1)
$ScvO_2$ (%)	72 (67-79)	73 (68-80)	72 (65-78)
Base excess	−5.7 (−8.4-−1.5)	−5.5 (−8.2-−0.5)	−6.0 (−9.2-−2.2)
pH	7.31 (7.25-7.37)	7.33 (7.27-7.38)	7.30 (7.22-−7.36)
Procalcitonin D0 (ng/ml)	3.83 (1.24-21.17)	3.48 (1.04-15.85)	5.27 (1.81-23.57)
Procalcitonin D4* (ng/ml)	1.48 (0.66-11.08)	0.98 (0.44-4.64)	6.09 (1.03-18.75)

Comparison between survivors and nonsurvivors *P<0.05. Values expressed are median values and IQR, except severity of sepsis where patient numbers are given. APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential organ failure assessment; $ScvO_2$: Central venous oxygen saturation; IQR: Interquartile range; ICU: Intensive Care Unit

Table 3: Median (IQR) change (day 0 minus day 4) in different parameters

Parameter	All patients (*n*=171)	Survivors (*n*=91)	Nonsurvivors (*n*=80)
Procalcitonin*	1.18 (0.02–7.86)	1.58 (0.20–8.52)	0.28 (−1.38–6.17)
SOFA score*	2 (0–4)	3 (1–5)	0 (−1–2)
Lactate (mmol/L)	0.2 (−0.4–0.8)	0.2 (−0.4–0.8)	0.2 (−0.3–0.9)
$ScvO_2$ as %	0 (−7–6)	1 (−5.1–6.6)	−2.0 (−9–5.3)
Base excess	−1.6 (−7.8–0.2)	−1.9 (−8.2–−0.1)	−1.2 (−6.8–0.9)
pH	−0.03 (−0.11–0.01)	−0.03 (−0.12–0.0)	−0.03 (−0.08–0.02)

Comparison between survivors and nonsurvivors *P<0.05. SOFA: Sequential organ failure assessment; IQR: Interquartile range; $ScvO_2$: Central venous oxygen saturation

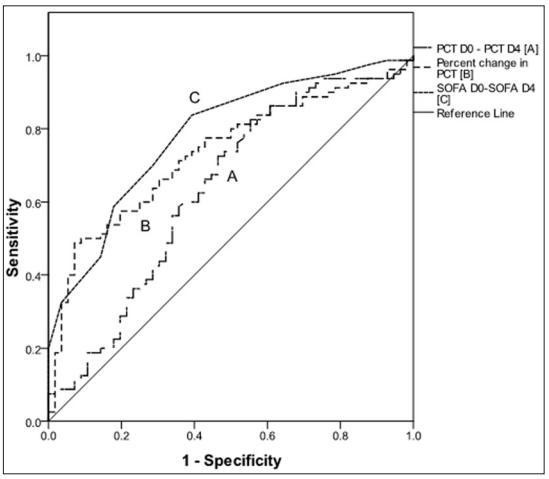

Figure 2: Receiver operating characteristic curves of change in procalcitonin level (PCT D0-PCT D4), sequential organ failure assessment score (SOFA D0–SOFA D4) and percentage change in procalcitonin level (percent change in PCT)

Receiver operating characteristic curves were constructed to identify the most discriminatory values of change in procalcitonin and change in SOFA score [Figure 2]. The area under the curve (AUC) for change in PCT to predict survival was 0.64 (95% confidence interval [CI]: 0.54–0.73; P = 0.007) as compared to 0.78 (95% CI: 0.71–0.86; P < 0.01) for change in SOFA score. Percentage change in PCT gives a C-statistic of 0.73 (95% CI: 0.65–0.82; P < 0.01). 50% and 75% fall in PCT value yielded 68% and 47% sensitivity and 64% and 93% specificity respectively to predict survival at 28 days. Among those patients in whom the absolute fall in procalcitonin was >1 ng/ml, a 70% fall in procalcitonin predicted survival with 75% sensitivity and 64% specificity.

In 28 patients, the procalcitonin level remained ≤1 ng/ml on D0 and D4. When the analysis was repeated excluding these patients, the median procalcitonin level on D0 was 6.99 ng/ml (IQR 2.17–37.67) and 3.80 ng/ml (IQR 1.01–14.79) on D4. The corresponding values in survivors and NS were 7.07 ng/ml and 6.82 ng/ml on D0 (P = 0.96) and 1.67 ng/ml and 7.56 ng/ml on D4 (P = 0.001), respectively. ROC curves for PCT fall and percentage change in PCT yielded AUC of 0.66 (95% CI: 0.56–0.77) and 0.76 (95% CI: 0.67–0.85) respectively. These values, however, are not statistically different from those in the entire group.

Discussion

In this prospective study of critically ill patients with severe sepsis/septic shock, we studied the prognostic significance of the change in procalcitonin level in 72–96 h. We found that a fall in procalcitonin level predicted survival; however, a change in SOFA score did the same as well.

The most coommon primary diagnostic category was pneumonia, followed by severe acute pancreatitis and tropical illnesses (malaria, dengue, leptospirosis and others). The majority of infections were community acquired (63.2%). In 242 adults with severe sepsis/septic shock from 24 ICUs in Finland, Karlsson *et al*.[10] found higher procalcitonin levels in patients with community acquired infections as compared to those with nosocomial infections ($P = 0.001$). We did not find such an association.

A single value of procalcitonin, done at the time of admission, cannot predict the prognosis of the critically ill septic patient. This has been substantiated in several studies,[10-12] as was also found in our study. The median procalcitonin level in our patients was 3.83 ng/ml at admission; 3.48 ng/ml among the survivors and 5.27 ng/ml among the NS ($P = 0.48$). In the study by Karlsson *et al*.,[10] procalcitonin level on the day of admission did not differ among survivors and NS ($P = 0.64$). In a prospective international multicenter study by Rau *et al*. conducted in 82 surgical patients with secondary peritonitis,[11] procalcitonin level early in the course of illness predicted the presence of septic multiorgan failure and persistent sepsis, but was poorly correlated with death. Among 54 septic patients from a medical ICU in New Delhi, India, a procalcitonin level ≥ 7 ng/ml at admission predicted 28 days mortality with a hazard ratio of 2.6;[12] however, this was not significant on multivariate analysis. Similarly, in 88 patients with septic shock admitted to an ICU of a tertiary care teaching hospital in Spain[13] by Suberviola *et al*., the procalcitonin level at admission was 12.9 ng/ml and 13.5 ng/ml in survivors and NS respectively ($P = 0.6$).

The procalcitonin level is expected to fall with therapy; hence many studies looked at the value of procalcitonin at the end of 48–72 h. In the study by Karlsson *et al*.,[10] the value after 72 h did not differ among survivors and NS ($P = 0.99$). In 28 patients with severe sepsis/septic shock from Brazil, Azevedo *et al*.[14] found that the procalcitonin level after 24–48 h was significantly different among survivors and NS (median 8.2 ng/ml vs. 68.6 ng/ml at 24 h and 4.6 ng/ml and 31 ng/ml at 48 h among survivors and NS respectively). Similar findings were obtained by Suberviola *et al*.[13] with significantly different levels of procalcitonin 72 h after admission (2.2 ng/ml vs. 20 ng/ml in survivors and NS respectively; $P < 0.01$). This difference was, however, not significant on multivariate analysis. Seligman *et al*.[15] found that the procalcitonin level on D4 showed a C-statistic of 0.86 to predict mortality and was the most accurate among C-reactive protein, midregional pro-atrial natriuretic peptide and copeptin, in 71 ICU patients with VAP. The number of patients in severe sepsis/septic shock was, however, small in this study (28.4%/4.4% respectively). In a study on 340 critically ill patients with suspected sepsis, the mean PCT level after 72 h was significantly lower in survivors (0.61 ng/ml) as compared to the admission value (5.56 ng/ml; $P = 0.0012$); no such difference was seen in the NS.[16] Convincing data could not be obtained for a single value of procalcitonin on D4 to be of great prognostic significance.

Most authors have attempted to correlate the change in procalcitonin level at 48–72 h after starting therapy, with outcome. In our study, the procalcitonin level decreased to 1.48 ng/ml after 72–96 h; the level fell to 0.98 ng/ml in the survivors, but remained almost same at 6.09 ng/ml in the NS. Karlsson *et al*.[10] found that a substantial decrease in the procalcitonin level at 72 h (>50% decrease) was associated with a lower hospital mortality (12.2%) as compared to those with < 50% decrease (29.8%, $P = 0.007$); however this was not an independent predictor of mortality. In a pilot study of procalcitonin clearance (decrease in value as a percentage of value at admission) among 27 critically ill ICU patients with septic shock and multiorgan dysfunction,[17] the clearance at 24 h and 48 h had AUC of 0.74 and 0.86 respectively to predict survival. Similarly, in 28 patients with severe sepsis/septic shock, Azevedo *et al*.[14] found procalcitonin clearance at 24 h was significantly higher among survivors as compared to NS ($P = 0.028$). Suberviola *et al*.[13] found that a decreasing value of procalcitonin (over 72 h) among 88 patients with septic shock was an independent predictor of survival (odds ratio 0.1); procalcitonin clearance of 70% differentiated survivors from NS with a sensitivity of 94.7% and a specificity of 53%. Seligman *et al*.,[18] in 75 ICU patients with VAP, found that a fall in procalcitonin in 4 days predicts survival with an odds ratio of 4.43 (95% CIs: 1.08–18.18; $P = 0.04$). In a study of 180 septic patients from a medical ICU in France,[19] fall in procalcitonin level between D2 and D3 after onset of sepsis was found to be an independent predictor of survival (odds ratio: 2.94; 95% CI: 1.22–7.09). Among 64 postoperative ICU patients with severe sepsis/septic shock, Tschaikowsky *et al*.[20] showed that a fall in procalcitonin level to ≤50% of the baseline was an independent predictor of survival; the sensitivity was good (97%), but the specificity was only 35%. Li *et al*., in a recent study on 102 septic patients from an ICU in China,[21] showed that the level of PCT decreased in survivors from D1 to D3 and D5 while there was no change in the level in NS ($P < 0.05$). In a small study on 37 patients with septic shock, dynamic changes in PCT and SOFA score were found to be

useful indicators of survival.[22] PCT level decreased by a median of 9.73 ng/ml in survivors but increased by 5.95 ng/ml in NS. In contrast to the studies till date, in our study, the change in procalcitonin was different in survivors and NS with fall in the median value in survivors and no change in NS. The median value of percentage fall of procalcitonin was 73.5% in survivors as against 24.4% in NS. 50% fall in procalcitonin level was 68% sensitive and 64% specific while 70% fall yielded a sensitivity of 47% with a specificity of 93%. Looking at the absolute change in procalcitonin, a fall in procalcitonin >1ng/ml identified survivors with a C-statistic of 0.78. Repeating the analysis excluding patients with a low level of procalcitonin on both days (≤1 ng/ml) increases the AUC, but this increase was not significant statistically.

Another important finding is that SOFA score fared equally well as far as prediction of prognosis is concerned. The AUC for percentage change in procalcitonin level was 0.73 while that for a change in SOFA score was 0.78. Similar findings have been found in a few other studies.[21,22]

Our study has some limitations. Firstly, many patients present late to us after being managed in other ICUs and hence the time of the first procalcitonin estimation is not necessarily the 1st day of severe sepsis or septic shock. Further, the day of illness was not noted during data collection. Secondly, many patients died before the second sample could be taken; hence our hypothesis could not be tested in all the patients. The procalcitonin estimation method used here had an upper limit of 100 ng/ml and hence, actual levels above this do not find representation. Many patients have a prolonged stay in our ICU; the final outcome may not be related to the episode of sepsis for which the patient was admitted.

Based on this study, we recommend that an estimation of procalcitonin at admission, followed by estimation within the next 72–96 h could aid the prognostic assessment of critically ill patients with severe sepsis/septic shock, along with SOFA scores calculated on the same days. A rise or no change in procalcitonin level should alert the clinician to inadequacy of therapy.

To conclude, in a group of critically ill patients with severe sepsis/septic shock, a fall in procalcitonin level is associated with a favorable prognosis. Change in SOFA score performs equally well in this group of patients in predicting prognosis.

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