

# Should serial monitoring of procalcitonin be done routinely in critically ill patients of ICU: A systematic review and meta-analysis

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## Abstract

Sepsis is a life-threatening condition with dysregulated host response to infection. It is a major determinant of mortality in the intensive care unit (ICU). Procalcitonin (PCT) is widely investigated for prognosis in patients with sepsis. Most of the studies have cited that elevated PCT concentrations and PCT non-clearance are associated with poor outcomes in patients with sepsis and some studies have cited as having no additional benefit. Most of the studies have evaluated single PCT measurement and correlated with prognosis and outcome in septic patients. Limited literature is there about serial PCT levels and its impact on the outcome of patients with sepsis. We searched literature through PubMed, Embase, Web of Knowledge, and the Cochrane Library from 2007 to 2017 and present a systematic review and meta-analysis of studies evaluating the utility of serial measurement of PCT for prognosis in critically ill patients. Articles that assessed PCT non-clearance as a marker of mortality data were included. The primary objective of this meta-analysis was to pool the results of all the available studies on serial PCT non-clearance as a mortality predictor and formulate overall area under receiver operating curve (AUROC). To find out the overall proportion of mortality in PCT non-clearance was our secondary objective. To detect the mortality using PCT non-clearance, ROC curve analysis was done. Area under curve (AUC) of the studies was varying between 0.52 and 0.86. Overall AUC was observed 0.711 (95% confidence interval (CI): 0.662–0.760) under fixed effect model and 0.708 (95% CI: 0.648–0.769) under random effect model. There was moderate variation among the studies, i.e.,  $I^2$  50.80% (95% CI: 0.00–80.42%). The overall proportion of mortality was 37.54% with much heterogeneity ( $I^2$  88.24%) among the studies. PCT non-clearance is a fair predictor of mortality. Further studies are needed to define optimal cut off point for PCT non-clearance in ICU patients with sepsis.

**Keywords:** Procalcitonin, sepsis, septic shock

## Introduction

Sepsis is a life-threatening condition that arises when a host responds to an infection and damages its organs.<sup>[1]</sup> It is a major determinant of mortality in an intensive care unit (ICU). Early identification of septic patients with poor clinical outcome is a constant clinical challenge for intensivists. Severity scores like Acute Physiology and Chronic Health Evaluation (APACHE

II) and Sequential Organ Failure Assessment (SOFA) score have been validated for risk stratification.<sup>[2,3]</sup> Studies have identified that blood biomarkers may provide additional information for disease progression in sepsis.<sup>[4-8]</sup> No single biomarker in sepsis has been proven as a gold standard.

Procalcitonin (PCT) has been widely investigated in infectious diseases. PCT is a 116 amino acid prohormone of calcium

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metabolism regulator calcitonin. This precursor of calcitonin is produced by the C-cells of thyroid under the control of calcitonin gene-related peptide 1 (CALC-1) gene. Normally, the expression of this gene is found in neuroendocrine cells of the thyroid.<sup>[9]</sup> During microbial infection, there is overexpression of the CALC-1 gene in various extrathyroidal cells and tissues including kidney, liver, pancreas, leukocytes, and adipose tissue.<sup>[10]</sup> Therefore, unlike calcitonin, this prohormone is synthesized in numerous extrathyroidal tissues in response to bacterial lipopolysaccharide, endotoxins, and cytokines induced by a bacterial infection like IL-1 and TNF- $\alpha$ .<sup>[11,12]</sup> Plasma PCT levels rise within 3 hours, peak between 6 and 24 hours of sepsis onset, and decrease with the control of infection. Multiple studies have evaluated the diagnostic role of PCT in sepsis. Limited studies are there about the prognostic role of PCT in patients with sepsis. Regarding the prognostic value of PCT in sepsis, most of the studies have evaluated the effect of single PCT concentration on mortality in septic patients.<sup>[13-27]</sup> Limited number of studies have evaluated serial PCT levels and the effect of its kinetics on prognosis and outcome in ICU patients with sepsis.<sup>[28-37]</sup> In this systematic review and meta-analysis, we pooled results of all the available studies where serial monitoring of PCT was done and PCT non-clearance was used for mortality prediction in ICU patients with sepsis and septic shock. The primary objective of this meta-analysis was to pool the results of all the available studies on serial PCT non-clearance as a mortality predictor and formulate overall area under receiver operating curve (AUROC). To find out the overall proportion of mortality in PCT non-clearance was our secondary objective.

## Methodology

We systematically searched studies using PubMed, Embase, Web of Knowledge, and the Cochrane Library. The search terms were: (procalcitonin or PCT or "PCT clearance" or "PCT-c" or "PCT decrease" or "PCT kinetics") and (sepsis or septicemia or septic shock) and (mortality or prognosis). We searched articles over 10 years, i.e, from 2007 to 2017. We included articles written in English only. We further reviewed the reference list of the selected articles to obtain potentially relevant articles. For the study, articles in which PCT non-clearance was used as a prognostic marker were taken into account. Only original articles were included. PCT non-clearance was noted in percentage. Articles that assessed PCT non-clearance as a marker of mortality data were included. The primary objective of this meta-analysis was to pool the results of all the available studies on serial PCT non-clearance as a mortality predictor and formulate overall AUROC. To find out the overall

proportion of mortality in PCT non-clearance was our secondary objective. PCT non-clearance and its effect on mortality or non-survival were assessed with sensitivity and specificity. Reviews, letters, commentaries, correspondences, case reports, conference abstracts, expert opinions, editorials, and animal experiments were excluded. Articles involving pediatric patients ( $\leq 18$  years) were also excluded.

The summary of the above studies is being presented in Table 1.

## Statistical analysis

Mortality of the PCT non-clearance patients and AUROC of the PCT non-clearance was assessed for the individual study as well as a pooled measure was estimated according to fixed-effects model or random-effects model as appropriate. Q-test and  $I^2$  indexes were calculated to assess inter-study heterogeneity. Values of 25%, 50%, and 75% for the  $I^2$  test considered as low, medium, and high heterogeneity, respectively.  $I^2$  values of less than 50% were considered as acceptable between-study heterogeneity, and the fixed-effects model was selected. Otherwise, the random-effects model was selected. AUC of the individual study, as well as pooled AUC, was obtained and represented using Forest plot. Similarly, Funnel plot was used to present the publication bias in terms of standard error with corresponding measures. The same exercise was done and the forest plot as well as funnel plot was presented for the proportion of the mortality of the non-clearance patients. Statistical analyses were performed using the software MedCalc Version 17.2. A  $P$  value of less than 0.05 was considered statistically significant.

## Results

After inclusion of all relevant articles, 10 studies with a total sample size of 1974 patients were included in this systematic review.<sup>[28-37]</sup> Cut off for PCT non-clearance was different in all studies. Overall mortality, sensitivity, and specificity of PCT non-clearance as a predictor of mortality in individual studies are represented in Table 1.

Five studies had done a ROC curve of the ability of PCT non-clearance to predict mortality.<sup>[28,31,33,34,36]</sup> To detect the mortality using PCT non-clearance, ROC curve analysis was done. Forest plot analysis was used to evaluate AUC of the studies where PCT non-clearance was used as a mortality predictor [Figure 1]. AUCs of the studies were varying between 0.52 and 0.86. Overall AUC observed was 0.711 (95% CI = 0.662–0.760) under fixed effect model and 0.708 (95% CI = 0.648–0.769) under random effect model. Moderate heterogeneity was observed among the studies [ $Q = 10.17$ , d.f = 5,  $P = 0.071$ ,  $I^2$  (inconsistency) =

**Table 1: Characteristic of studies showing sensitivity and specificity of PCT non-clearance as a mortality predictor in ICU patients with sepsis and its severity**

Author	Year	Place	Study design	Clinical setting	Follow up	PCT assay	PCT non-clearance	Sample size	Overall mortality n (n%)	Severity of sepsis	SEN %	SPE %
Karlsson <sup>[28]</sup>	2010	Finland	Prospective	ICU	In hospital mortality	Cobas PCT	PCT ↓ <50% in 72 h	242	62 (25.6)	Severe sepsis	88.7	27.8
Guan <sup>[29]</sup>	2011	China	Prospective	ICU	28 day mortality	Lumitest PCT	PCT ↓ <25% in 5 days	37	12 (32.4)	Sepsis, sev sepsis, septic shock	100	100
Tschaikowsky <sup>[30]</sup>	2011	Germany	Prospective	SICU	28 day mortality	KRYPTOR-PCT	PCT ↓ <50% in 7 days	64	21 (32.8)	Severe sepsis, septic shock	35.3	97.1
Ruiz-Rodriguez <sup>[31]</sup>	2012	Spain	Prospective	ICU	ICU mortality	Lumitest PCT	PCT ↓ <50% in 48 h	27	18 (66.7)	Septic shock	89	72
Suberviola <sup>[32]</sup>	2012	Spain	Prospective	ICU	In hospital mortality	KRYPTOR-PCT	PCT ↓ <70% in 72 h	88	21 (23.9)	Septic shock	52.6	94.2
Schuetz (Derivation cohort) <sup>[33a]</sup>	2013	USA	Prospective	ICU	ICU mortality	VIDAS	PCT ↓ <60% in 72 h	154	45 (29.2)	Severe sepsis, septic shock	60	67
Schuetz (Validation cohort) <sup>[33b]</sup>	2013	USA	Prospective	ICU	ICU mortality	VIDAS	PCT ↓ <60% in 72 h	102	18 (17.6)	Severe sepsis, septic shock	78	61
Mat Nor <sup>[34]</sup>	2014	Malaysia	Prospective	ICU	In hospital mortality	KRYPTOR-PCT	PCT ↓ <30% in 48 h	67	27 (40.3)	Severe sepsis	74.1	55
Gracia de Guadiana-Romualdo <sup>[35]</sup>	2015	Spain	Prospective	ICU	In hospital mortality	Cobas PCT	PCT ↓ <40% in 48 h	100	28 (28)	Severe sepsis and septic shock	64.3	62.5
Poddar <sup>[36]</sup>	2015	India	Prospective	ICU	28 day mortality	Cobas PCT	PCT ↓ <50% in 4 days	171	80 (46.7)	Severe sepsis, septic shock	68	64
Schuetz (Intention to diagnose population) <sup>[37a]</sup>	2017	USA	Prospective	ICU	28 day mortality	KRYPTOR-PCT	PCT ↓ <80% in 4 days	646	107 (16.5)	Severe sepsis, septic shock	77.3	38.8
Schuetz (Subpopulation with ICU care on day 4) <sup>[37b]</sup>	2017	USA	Prospective	ICU	28 day mortality	KRYPTOR-PCT	PCT ↓ <80% in 4 days	276	73 (26.4)	Severe sepsis, septic shock	79.2	32.1

PCT: Procalcitonin, ICU: Intensive Care Unit, SICU: Surgical intensive care unit, CI: Confidence Interval, SEN: Sensitivity, SPE: Specificity

50.8%, 95% CI = 0%–80.4%]. Similarly, the Funnel plot was drawn to show the standard error of the studies corresponding to their observed AUC and is shown in Figure 2.

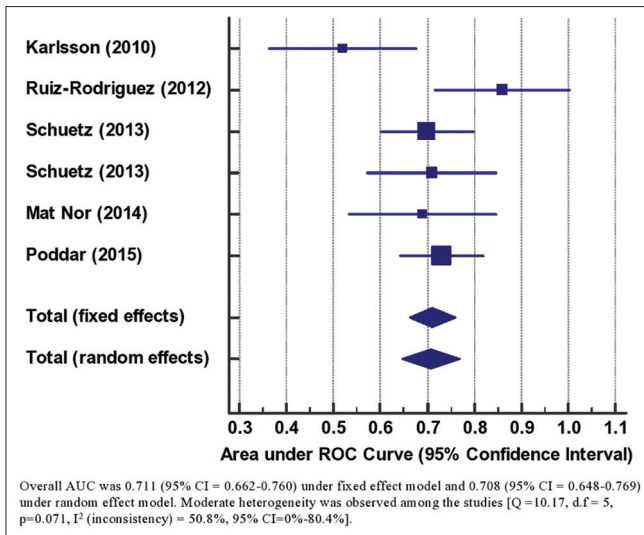
Similarly, the proportion of the mortality in the PCT non-clearance group in the studies was observed using forest plot analysis [Figure 3]. Six studies assessed the proportion of mortality in patients with PCT non-clearance.<sup>[28-30,32,33,37]</sup> The proportion of the mortality was varying among the studies between 20.09% to 100%. Overall mortality was observed as 37.54% (95% CI = 25.6–50.24) under the random effect model. Much heterogeneity was observed among the studies [Q = 59.53, d.f. = 7, P < 0.001, I<sup>2</sup> (inconsistency) = 88.24%, 95% CI = 79.12%–93.38%]. Similarly, funnel plot graph showing the standard error of the mortality of the different studies is shown in Figure 4.

## Discussion

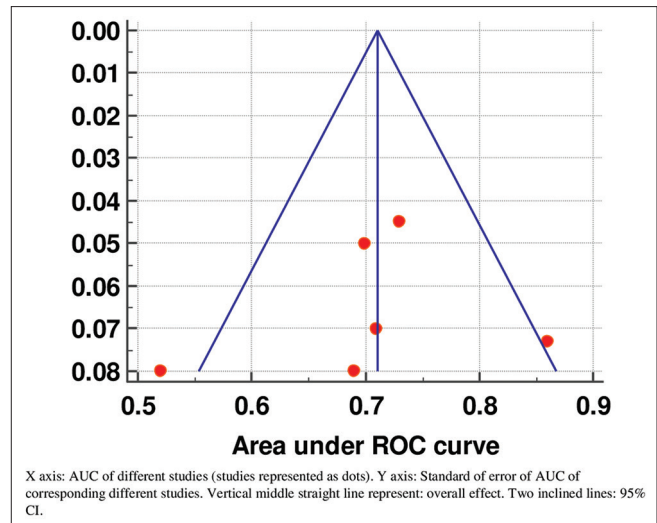
Sepsis is life-threatening organ dysfunction with the

dysregulated host response. Complex pathophysiology plays role in sepsis. Not a single biomarker can predict mortality in sepsis. PCT is a widely studied biomarker. Literature on PCT as a diagnostic marker of sepsis is well established. However, there are limited studies on PCT as a prognostic marker. Mortality is a marker of outcome in ICU. Most of the studies have evaluated single PCT as a mortality predictor in patients with sepsis.<sup>[13-27]</sup> PCT non-clearance as a predictor of mortality has also been assessed in a few studies.

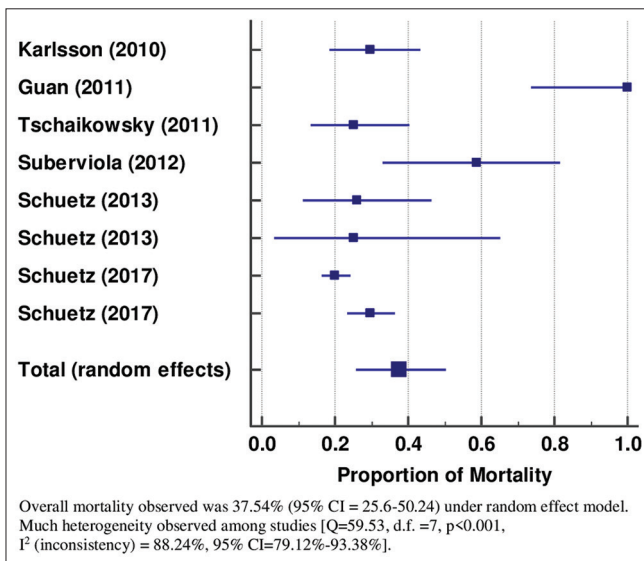
In a prospective study by Karlson *et al.*,<sup>[28]</sup> in 2010, the predictive value of PCT for survival in 242 adult patients with severe sepsis and septic shock was investigated. Patients with septic shock had higher PCT concentrations (P = 0.02). Though PCT concentrations did not differ between hospital survivors and non survivors, mortality was lower in patients whose PCT concentration decreased by >50% by 72 hours compared to those with less than 50% decrease (12.2% vs. 29.8%, P = 0.007) in 72 hours. It was concluded that PCT



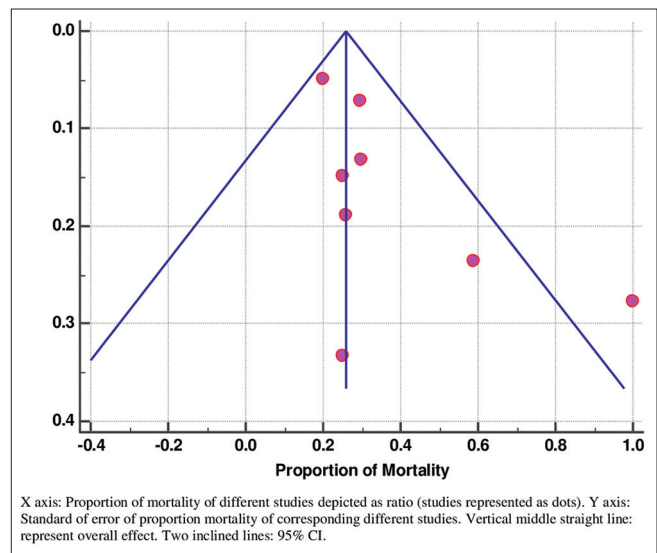
**Figure 1:** Forest plot showing the area under curve (95% CI) of the studies to detect procalcitonin non-clearance as a predictor of mortality



**Figure 2:** Funnel plot showing the area under curve of the different studies with their corresponding standard error



**Figure 3:** Forest plot showing proportion of mortality in patients with procalcitonin non-clearance



**Figure 4:** Funnel plot showing proportion of mortality in PCT non-clearance patients of different studies with their corresponding standard error

concentrations were higher in more severe forms of sepsis, but a substantial concentration decrease was more important for survival than the absolute values.

In a prospective cohort study in 2011, Guan *et al.*<sup>[29]</sup> enrolled 37 septic shock patients of ICU with PCT > 10 ng/ml. PCT was measured at enrollment and 5 days thereafter. All survivors had a decrease in PCT concentration (median decrease of 9.73 ng/ml) and an increase was seen in non-survivors (median increase of 5.95 ng/ml). A significant decrease in PCT concentration (>25%) was observed in 25 survivors but none in 12 non-survivors. Kinetics of PCT and SOFA correlated with each other. The authors concluded that a significant decrease in PCT

concentration rather than PCT concentration itself is a useful indicator of survival in septic shock patients when PCT concentration is greater than 10 ng/ml.

In a prospective study, Tschakowsky *et al.*<sup>[30]</sup> evaluated the performance of PCT, as a percentage of baseline (POB) in predicting hospital survival in 64 postoperative patients with severe sepsis. Plasma PCT was serially measured from day 1 to day 14 in parallel with clinical data until day 28. In survivors, PCT significantly decreased from days 1 to 14. The authors suggested that a decrease in PCT-POB on day 7 in combination with C-Reactive Protein (CRP-POB) may serve to monitor efficacy and guide duration of therapy in critically ill patients.



In a prospective, observational study by Ruiz-Rodriguez *et al.*,<sup>[31]</sup> in ICU patients with septic shock and multiorgan dysfunction, serum concentrations of PCT were determined within 12 h of onset of septic shock and serial levels were measured after 24, 48, and 72 h. PCT clearance (PCT-c) was calculated as initial PCT minus PCT at subsequent hours and then multiplied by 100. It was found that PCT clearance was higher in survivors than that in non-survivors, with significant differences at 24 and 48 hr. ( $p < 0.05$ ). The AUROC was 0.74 for PCT clearance at 24 h, and 0.86 at 48 h.

In 88 patients with septic shock admitted to an ICU of a tertiary care teaching hospital in Spain, Suberviola *et al.*<sup>[32]</sup> found that PCT level at admission was comparable between survivors and nonsurvivor ( $P = 0.6$ ). The PCT level was recorded on admission to ICU and again after 72 hours. Those patients with increasing PCT levels showed higher hospital mortality than those with decreasing levels (58.8% vs 15.4%,  $p < 0.01$ ). The best AUC for prognosis (0.79) was found for PCT clearance [(initial PCT- final PCT) ÷ (initial PCT)] × 100. A PCT clearance of 70% or higher offered a sensitivity and specificity of 94.7% and 53%, respectively for survival. Serial PCT measurements were more predictive of the prognosis of septic shock patients than single measurements.

In a retrospective analysis by Schuetz *et al.*,<sup>[33]</sup> in 2013 in adult patients with sepsis from critical care units in two independent institutions in the USA, cohorts were used for derivation or validation to study the association between PCT change over the first 72 critical care hours and mortality. The authors found that PCT change was strongly associated with ICU and in-hospital mortality independent of clinical risk scores. When PCT decreased by at least 80%, the negative predictive value for ICU/in-hospital mortality was 90%/90% in the derivation cohort and 91%/79% in the validation cohort. It was concluded that PCT kinetics over the first 72 hours of critical care provides prognostic information about ICU and in-hospital mortality in patients with confirmed or likely sepsis independent of clinical severity scores.

Mat Nor *et al.*<sup>[34]</sup> in 2014 evaluated the prognostic value of dynamic changes of PCT in sepsis patients by conducting a prospective observational study in adult ICU. Daily PCT was measured for 3 days. A 48-h PCT clearance (PCTc-48) was defined as POB PCT minus 48 h PCT over baseline PCT. Day 1-PCT was associated with the diagnosis of sepsis but was not predictive of mortality. In sepsis patients, PCTc-48 was associated with the prediction of survival (AUC 0.69 (95% CI: 0.53 to 0.84)). Patients with PCTc-48 >30% were independently associated with survival (Hazard Ratio (HR) 2.90 (95% CI: 1.22–6.90)).

In a single-center prospective observational study in 2015 by Gracia de Gadiana-Romualdo *et al.*,<sup>[35]</sup> in ICU of a university hospital, 100 severe sepsis and septic shock patients were included to assess the prognostic value of serial measurements of PCT in relation to hospital mortality and to determine whether their addition to severity scores (APACHE II and SOFA) was able to improve prognostic accuracy. Measurements were done on admission and after 48 hours. The best AUC for predicting in-hospital mortality corresponded to APACHE II on admission and SOFA after 48 hours (AUC ROC: 0.75 for both). PCT clearance was higher among survivors. (AUC ROC: 0.66). A combination of severity scores and PCT clearance did not result in superior AUCs. They concluded that PCT levels on admission showed no prognostic value but PCT clearance was predictive of in-hospital mortality.

In a prospective observational study by Poddar *et al.*,<sup>[36]</sup> in the ICU of a tertiary care Institute in India in 2015, PCT was measured at admission (D0) and after 72–96 h (D4) in 171 adult patients admitted with severe sepsis or septic shock. Change in PCT values from D0 to D4 was correlated with the primary outcome, 28 days mortality. The C-statistic of the percentage change in PCT from D0 to D4 to predict survival was 0.73 (95% CI: 0.65–0.82) when compared to 0.78 (95% CI: 0.71–0.86) for change of SOFA score. A 75% fall in PCT value yielded 47% sensitivity and 93% specificity to predict survival at 28 days. A 50% fall predicted 28 days survival with 68% sensitivity and 64% specificity. Among patients in whom absolute fall in PCT was > 1 ng/ml, a 70% fall predicted survival with 75% sensitivity and 64% specificity. It was concluded that in critically ill patients with severe sepsis/septic, shock change (fall) in PCT was associated with good outcome and non-clearance with the worst outcome.

Schuetz *et al.*<sup>[37]</sup> in 2017 in a prospective multicenter observational clinical trial in a large sepsis patient population recruited across the United States, validated that inability to decrease PCT levels by more than 80% between baseline and day 4 was associated with increased 28-day all-cause mortality. PCT was measured daily over the first 5 days. The 28-day all-cause mortality was two-fold higher when PCT did not show a decrease of more than 80% from baseline to day 4 (20% vs 10%;  $P = 0.001$ ).

In this systematic review and meta-analysis, we highlighted those above studies.<sup>[28-37]</sup> We evaluated only the prognostic utility of serial PCT clearance. In this review, PCT non-clearance has emerged as a mortality predictor. The overall AUROC curve observed was 0.711 (95% CI = 0.662–0.760) under fixed effect model and 0.708 (95% CI = 0.648–0.769) under random effect model. There was moderate variation among the studies, i.e., 50.80% (95% CI = 0.00–80.42%), which

is acceptable. As there was moderate variation among the studies (50.80%), we focused on a random effect model and got overall AUROC curve 0.708 (95% CI = 0.648–0.769), which is acceptable. We also evaluated the proportion of mortality among different studies. Although huge variability was observed in the proportion of mortality in different studies (20.09% to 100%), it is quite expected with a different sample size of different studies. Overall mortality of almost 40% (37.54%) in the PCT non-clearance group and has its prognostic implications as highlighted above by various literature.

Our review has certain limitations. Only patients of ICU were included, thereby could not be applied to emergency department patients. Different studies that were cited had different cutoffs. Subgroup analysis was not possible due to a limited number of studies. Different confounding variables for mortality were not adjusted in this study. Optimal cutoff of PCT non-clearance could not be detected. Only articles published in English were included.

Despite being an important diagnostic marker of sepsis, PCT has its prognostic implications. It correlates with sepsis and its severity and predicts mortality in critically ill ICU patients. US Food and Drug Administration (FDA) has recently approved the use of PCT testing to guide antibiotic use in the content of acute respiratory illness and sepsis. PCT is the cornerstone of antibiotic stewardship program. In their recent consensus document, Sheutz *et al.* refined the established PCT algorithm by incorporating the severity of illness.<sup>[38]</sup> Due to the use of different cut off to discontinue antibiotic use in the emergency department, ward, and ICU patients, Sheutz *et al.* simplified the approach to discontinue antibiotic use in that document. They proposed an algorithm for PCT use in three broad categories, i.e., patient with mild illness outside ICU, patient with moderate illness outside ICU, and patient with severe illness in the ICU. Further prospective studies can be undertaken to define optimal cut off point for PCT non-clearance with respect to its various other prognostic implications. Correlation of PCT non-clearance along with clinical parameters and organ failures can guide therapeutic interventions.

## Conclusion

PCT non-clearance is a predictor of mortality in patients with sepsis. This systematic review and meta-analysis suggest that serial measurements of PCT are a valuable tool for prognosis in ICU patients. PCT non-clearance is an important predictor of mortality in critically ill ICU patients with sepsis.

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## Conflicts of interest

There are no conflicts of interest.

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