

REVIEW

Prognostic value of procalcitonin in pneumonia: A systematic review and meta-analysis

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ABSTRACT

This meta-analysis was performed to determine the accuracy of procalcitonin (PCT) in predicting mortality in pneumonia patients with different pathogenic features and disease severities. A systematic search of English-language articles was performed using PubMed, Embase, Web of Knowledge and the Cochrane Library to identify studies. The diagnostic value of PCT in predicting prognosis was determined using a bivariate meta-analysis model. The Q-test and I^2 index were used to test heterogeneity. A total of 21 studies comprising 6007 patients were included. An elevated PCT level was a risk factor for death from community-acquired pneumonia (CAP) (risk ratio (RR) 4.38, 95% confidence interval (CI) 2.98–6.43), particularly in patients with a low CURB-65 score. The commonly used cut-off, 0.5 ng/mL, had low sensitivity (SEN) and was not able to identify patients at high risk of dying. Furthermore, the PCT assay with functional SEN <0.1 ng/mL was necessary to predict mortality in CAP in the clinic. For critically ill patients, an elevated PCT level was associated with an increased risk of mortality (RR 4.18, 95% CI: 3.19–5.48). The prognostic performance was nearly equal between patients with ventilator-associated pneumonia (VAP) and patients with CAP.

Key words: meta-analysis, mortality, pneumonia, procalcitonin, prognosis.

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; CR, consecutive recruitment; DOR, diagnostic odds ratio; ED, emergency department; FN, false negative; FP, false positive; HW, hospital ward; ICU, intensive care unit; LR, likelihood ratio; NLR, negative likelihood ratio; PCT,

procalcitonin; PLR, positive likelihood ratio; PR, prospective recruitment; RR, relative risk; SEN, sensitivity; SPE, specificity; SROC, summary receiver operator characteristic; TN, true negative; TP, true positive; VAP, ventilator-associated pneumonia.

INTRODUCTION

The lung is the most frequent site of infection in people worldwide. Pneumonia may manifest as a wide range of possible outcomes because of different disease severities and pathogenic features. For critically ill patients, community-acquired pneumonia (CAP) and ventilator-associated pneumonia (VAP) are associated with high mortality.¹ The unpredictable disease course and uncertain outcomes are challenges for clinicians, hindering the early identification of patients at risk of dying. However, for CAP, a considerable proportion of patients in the emergency department (ED) can be treated as outpatients. Therefore, risk stratification is a key issue for the management of this population, allowing the selection of the most appropriate care setting, whether outpatient treatment, admission to a hospital ward (HW) or the intensive care unit (ICU). Several risk scores, such as the pneumonia severity index (PSI) and CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥ 65 years), can be used to assess the severity of pneumonia and predict mortality.^{2–6} However, they tend to be used more for research than clinical decision making and have several limitations.

A growing number of clinical research studies have identified blood biomarkers that may reveal additional information about the prognosis of patients with pneumonia.^{7–10} Procalcitonin (PCT), the prohormone of calcitonin, mirrors the severity of infection and has emerged as the most studied and promising blood biomarker for the risk stratification of patients. However, whether the PCT level is an ideal index to predict the prognosis of pneumonia remains debatable, particularly in patients with different types and severities of pneumonia.^{11,12} For this reason, a meta-analysis was performed to systematically and quantitatively evaluate the prognostic accuracy of the PCT level in different types and severities of pneumonia.

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METHODS

Search strategy and study selection

Two investigators (L.D. and G.W.) independently performed the search strategy and assessed the studies. Any disagreement was resolved by a third opinion (S.L.X.). A systematic search of English-language articles was performed using Medline (via PubMed), Embase (via OvidSP), Web of Knowledge and the Cochrane Library (see Supplementary Appendix 1 for an example of the search strategy). No publication date restrictions were applied to the search.

Studies were included if they assessed the accuracy of PCT levels associated with mortality in adult (>18 years old) patients with pneumonia. To be eligible, they had to have a well-defined diagnostic reference standard for pneumonia. Furthermore, the studies had to provide sufficient information to construct a 2×2 contingency table. For CAP, low risk was defined as PSI score classes I to III and CURB-65 score class 1. High risk was defined by PSI score classes IV-V and CURB-65 score classes 2–5 according to previous criteria.^{13,14} For studies providing multiple PCT cut-off points for prognostic accuracy, the data giving the maximum overall accuracy were selected. And if multiple studies reused the same sample of patients, the most recent or most informative article was included.

Data extraction and quality assessment

Two investigators, L.D. and G.W., independently extracted the data and assessed the quality of the included studies. Any conflict was resolved by a third opinion. The following descriptive data were extracted: name of the first author, publication year, study design, clinical setting, endpoints, assay manufacturer, sample size, prevalence of mortality, type of pneumonia, cut-off point sensitivity (SEN) and specificity (SPE). The corresponding authors were contacted if the data were not presented or needed clarification. The quality of included studies were evaluated according to the Revised Tool for Quality Assessment of Diagnostic Accuracy Studies checklist for diagnostic studies.¹⁵ Risk of bias was judged as 'low', 'high' or 'unclear'.

Statistical analysis

We chose the MIDAS module for STATA software, version 12.0 (Stata Corporation, College Station, TX) and Meta-Disc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) to perform statistical analyses. True positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) were tabulated based on the PCT levels and all-cause mortality in pneumonia. Relative risk (RR) was used to assess the predictive value of PCT and pooled using a fixed-effect or random-effect model based on DerSimonian and Laird's method.¹⁶ The Q-test was performed and the I^2 index was calculated to assess inter-study heterogeneity.^{17,18} Values of 25%, 50% and 75% for the I^2 test represented low, medium and high heterogeneity, respectively.¹⁹ An I^2 value less than 50% was consid-

ered to be acceptable heterogeneity between studies, in which case the fixed-effect model was selected. Otherwise, the random-effect model was chosen. A P value less than 0.05 was considered statistically significant.

The presence of a threshold effect on the prognostic accuracy of PCT in pneumonia was evaluated using the Spearman correlation coefficient between the logits of SEN and SPE. If no threshold effect existed, a bivariate random-effect regression model^{20,21} was used to calculate the pooled SEN, SPE, diagnostic odds ratio (DOR), positive likelihood ratio (PLR) and negative likelihood ratio (NLR). If a threshold effect did exist, the summary receiver operating characteristic (SROC) curve was constructed by plotting the individual and summary points of SEN and SPE to assess the overall diagnostic accuracy.²²

A subgroup analysis restricted to both CAP and critically ill pneumonia patients was performed to explore the prognostic accuracy of PCT. A univariate meta-regression analysis was performed to explore the sources of potential heterogeneity between studies. The covariates included the year of publication, sample size, prevalence of mortality, endpoints, high-quality methodology (if the data were collected consecutively), different cut-off points and the proportion of high-risk patients identified based on the PSI (classes IV-V) and CURB-65 scores (classes 2–5). Publication bias was tested using Deeks' funnel plot.

RESULTS

Six-hundred and thirty-seven articles were retrieved from databases, of which 21 studies with a total of 6007 patients were eventually included (Fig. 1). No additional relevant articles were identified in the bibliographies of the original articles. The characteristics of the included studies are listed in Table 1.

Characteristics of included studies

The included studies were published from 2002 to 2014. Eleven were conducted in Europe,^{23,25,28–33,36,37,42} seven in Asia;^{24,26,35,38–40,43} two in North America,^{34,41} and one in South America.²⁷ The mean age of the patients varied between 53 and 82 years, and the proportion of men ranged from 18–98%. Thirteen studies included patients with CAP^{23,24,32–42} 11 with VAP;^{25–31} and one with nursing home-acquired pneumonia.⁴³ Nine studies, which included critically ill patients, were performed in ICU;^{23–31} six in ED;^{34,37–39,41,42} and six in HW.^{32,33,35,36,40,43} Nineteen studies collected blood samples within 24 h after patients were diagnosed with pneumonia.^{24–30,32–43} One study collected blood samples within 48 h because of limited laboratory availability.²³ One study measured the PCT level on day 3.³¹ The endpoints differed across studies, including 14-day mortality,²⁴ 28-day mortality,^{25–27,30,33,36–40} 30-day mortality,^{32,34,35,41} ICU mortality,²³ hospital stay⁴³ and adverse outcomes.^{29,42} Three studies used the VIDAS method,^{32,37,38} four the Kryptor PCT assay^{34,36,41,42} and one the PCT-LIA assay;³⁹ these assays had functional SEN less than 0.1 ng/mL. One study

Flow Diagram

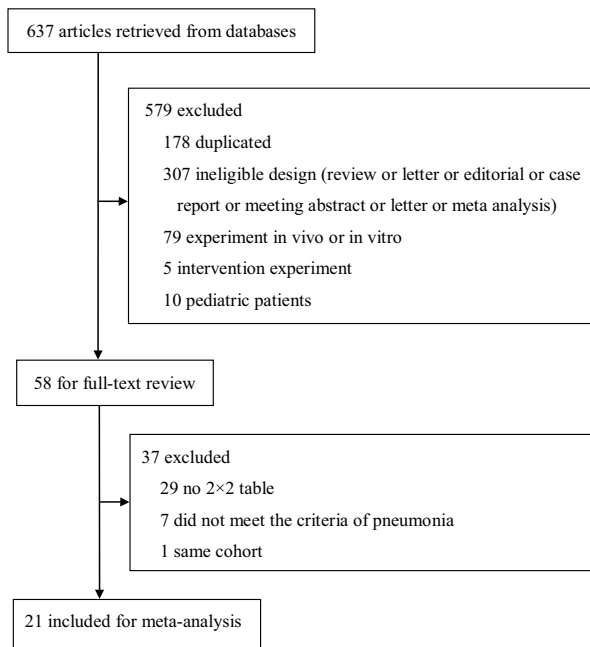


Figure 1 Flowchart of study selection.

used the LUMItest PCT assay,³³ and two the PCT-Q;^{35,40} these assays had functional SEN greater than 0.1 ng/mL.

Study quality and publication bias

The quality of each included study is shown in Supplementary Table S1. The overall Deeks' funnel plot of the included studies is shown in Table 2.

Data analysis for patients with CAP

Prognostic performance of PCT in patients with CAP

There were 14 studies with 5532 patients in the CAP group.^{23,24,32–42} Two included patients diagnosed with severe pneumonia.^{23,24} The random-effect model was used to pool the RR ($I^2 = 62.7\%$). An elevated PCT level was associated with an increased risk of mortality in CAP (risk ratio (RR) 4.38, 95% CI: 2.98–6.43) (Fig. 2a).

No statistically significant difference was observed for the threshold effect (Spearman correlation coefficient = 0.545; $P = 0.054$). The pooled SEN and SPE were 0.69 (95% CI: 0.57–0.79) and 0.74 (95% CI:

Table 1 Characteristics of the included studies

Author	Year	Study design	Clinical setting	Endpoint	Assay	Sample size (n)	Prevalence (%)	Type of pneumonia	Cut-off (ng/mL)	SEN (95% CI)	SPE (95% CI)
Boussekey ²³	2005	PR + CR	ICU	ICU mortality	LUMItest PCT	110	27.3	CAP	2	76.7	60
Tseng ²⁴	2008	PR	ICU	14-day mortality	Kryptor PCT	22	22.8	CAP	21.91	80	88.2
Hillas ²⁵	2010	PR + CR	ICU	28-day mortality	PCT-LIA	45	35.6	VAP	0.42	87.5	65.5
Su ²⁶	2012	PR	ICU	28-day mortality	VIDAS	26	53	VAP	9.47	66.7	90.9
Seligman ²⁷	2011	PR + CR	ICU	28-day mortality	LUMItest PCT	71	36.6	VAP	0.74	84.6	57.8
Duflo ²⁸	2002	PR + CR	ICU	Mortality	LUMItest PCT	44	64	VAP	2.6	74	75
Luyt ²⁹	2005	PR + CR	ICU	Adverse outcomes	Kryptor PCT	76	61.8	VAP	1	83	64
Savva ³⁰	2011	MPR + CR	ICU	28-day mortality	Kryptor PCT	180	38.5	VAP	0.92	80	88.5
Zielinska ³¹	2012	PR	ICU	Mortality	LUMItest PCT	34	21	VAP	0.62	100	66.3
Andrijevic ³²	2014	PR	HW	30-day mortality	VIDAS	101	24.8	CAP	2.56	76	61.8
Masia ³³	2005	PR	HW	28-day mortality	LUMItest PCT	185	4.87	CAP	0.5	55.6	90.9
Huang ³⁴	2008	MPR	ED	30-day mortality	Kryptor PCT	1651	6.4	CAP	0.1	92.5	34.6
									0.25	64.2	55.7
									0.5	49.1	65.6
Kasamatsu ³⁵	2012	PR	HW	30-day mortality	PCT-Q	170	11.8	CAP	0.5	25.8	96.3
Krueger ³⁶	2008	PR	HW	28-day mortality	Kryptor PCT	1508	4.5	CAP	0.228	84.3	66.6
Lacoma ³⁷	2012	PR	ED	Mortality	VIDAS	75	8	CAP	0.115	50	83.3
Liu ³⁸	2014	PR + CR	ED	28-day mortality	VIDAS	359	22	CAP	0.955	58.7	71.1
Park ³⁹	2012	PR	ED	28-day mortality	PCT-LIA	126	12.7	CAP	0.35	68.75	92.73
Ugajin ⁴⁰	2014	PR + CR	HW	28-day mortality	PCT-Q	213	9.4	CAP	0.5	60	49.2
Schuetz ⁴¹	2011	PR + CR	ED	30-day mortality	Kryptor PCT	924	5.4	CAP	0.1	94	12.7
									0.25	78	37.76
									0.5	58	51.95
									1	48	61.1
									5	26	83.75
Haeuptle ⁴²	2009	RR	ED	Adverse outcomes	Kryptor PCT	29	17.2	CAP	1.5	82	75
Porfyridis ⁴³	2014	PR	HW	Hospital mortality	Kryptor PCT	58	17.2	NHAP	1.1	80	82

CAP, community-acquired pneumonia; CR, consecutive recruitment; ED, emergency department; FN, false negative; FP, false positive; HW, hospital ward; ICU, intensive care unit; MPR, multi-centre prospective recruitment; MRCT, multi-centre randomized controlled trial; NHAP, nursing home-acquired pneumonia; PR, prospective recruitment; RR, retrospective recruitment; SEN, sensitivity; SPE, specificity; TN, true negative; TP, true positive; VAP, ventilator-associated pneumonia.

Table 2 Subgroup analysis

Variable	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic odds ratio (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	AUC (95% CI)	Test for heterogeneity (<i>I</i> ²)	Deeks' funnel test (<i>P</i> value)
CAP patients	14	5532	0.69 (0.57–0.79)	0.74 (0.60–0.84)	6 (4–10)	2.6 (1.8–3.8)	0.42 (0.32–0.55)	0.77 (0.73–0.80)	62.7	0.46
Overall										
Cut-off = 0.5 ng/mL	5	3143	0.46 (0.33–0.59)	0.77 (0.52–0.91)	3 (1–6)	2.0 (1–3.9)	0.70 (0.60–0.83)	0.56 (0.52–0.61)	70.9	0.2
FAS > 0.1 ng/mL	3	568	0.44 (0.20–0.68)	0.86 (0.70–1.00)	4 (1–20)	3.37 (1–12.4)	0.75 (0.60–0.94)	0.64 (0.60–0.66)	76.3	0.6
FAS < 0.1 ng/mL	8	4773	0.75 (0.63–0.84)	0.68 (0.52–0.81)	6 (4–11)	2.3 (1.6–3.4)	0.36 (0.26–0.51)	0.78 (0.75–0.82)	70	0.63
HW patients	6	2235	0.65 (0.46–0.80)	0.79 (0.60–0.90)	7 (3–14)	3.1 (1.8–5.4)	0.45 (0.30–0.67)	0.77 (0.74–0.81)	66	0.74
ED patients	6	3165	0.73 (0.56–0.85)	0.69 (0.47–0.85)	6 (3–12)	2.4 (1.4–4.0)	0.39 (0.26–0.60)	0.77 (0.73–0.81)	66.6	0.56
Overall	9	608	0.80 (0.75–0.85)	0.74 (0.63–0.82)	12 (7–20)	3.1 (2.2–4.3)	0.27 (0.20–0.35)	0.83 (0.79–0.86)	49.2	0.98
ICU patients	7	476	0.81 (0.75–0.87)	0.74 (0.63–0.83)	13 (7–23)	3.2 (2.1–4.7)	0.25 (0.18–0.34)	0.85 (0.81–0.87)	59.2	0.49

AUC, area under the curve; CAP, community-acquired pneumonia; CI, confidence interval; ED, emergency department; FAS, functional assay sensitivity; HW, hospital ward; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

0.60–0.84), respectively (Fig. 3a). The PLR and NLR were 2.6 (95% CI: 1.8–3.8) and 0.42 (95% CI: 0.32–0.55), respectively. The DOR was 6 (95% CI: 4–10). The overall area under the SROC curve (AUC) was 0.77 (95% CI: 0.73–0.80) (Fig. 4a).

Meta-regression analysis

A meta-regression analysis was performed to identify the sources of heterogeneity between studies. The results indicated that only consecutive collection and the CURB-65 score (classes 2–5) were statistically significant for heterogeneity (*P* = 0.001 and *P* = 0.024, respectively).

Subgroup analysis

When analyzing the different mortalities of CAP patients in the ICU and other clinical settings, we excluded two studies which were restricted to critically ill patients with severe CAP.^{23,24} In the analysed group, a significant threshold effect was observed (Spearman correlation coefficient = 0.620; *P* = 0.032). Therefore, we calculated the overall AUC to be 0.76 (95% CI: 0.73–0.80).

A subgroup analysis restricted to different cut-offs, different clinical settings and PCT assays with different SEN values was performed (Table 2). It was found that studies which chose the commonly used cut-off of 0.5 ng/mL had a low SEN for PCT predicting mortality in CAP and were unable to identify patients at high risk of dying.^{33–35,40,41} Two studies provided prognostic accuracy using a cut-off in the range of 0.25–5 ng/mL.^{34,41} Both showed that the cut-off of 0.5 ng/mL was not sensitive enough to provide prognostic value to clinicians and had lower overall prognostic performance compared with a cut-off of <0.5 ng/mL. It was also found that studies with functional assay SEN (FAS) less than 0.1 ng/mL had superior prognostic performance.

Data analysis for ICU patients with pneumonia

There were nine studies including 608 patients in this group.^{23,31} They were conducted in the ICU and focused on critically ill patients. Two studies included patients with CAP^{23,24} and seven with VAP.^{25–31} The mean prevalence of mortality was 40.1% (interquartile range 21–64). The heterogeneity between studies was acceptable (*I*² = 49.2%), and a fixed-effect model was used to pool the RR. An elevated PCT level was associated with an increased risk of mortality in critically ill patients with pneumonia (RR 4.18, 95% CI: 3.19–5.48) (Fig. 2b).

The pooled SEN and SPE were 0.80 (95% CI: 0.75–0.85) and 0.74 (95% CI: 0.63–0.82), respectively (Fig. 3b). The PLR and NLR were 3.1 (95% CI: 2.2–4.3) and 0.27 (95% CI: 0.20–0.35), respectively. The DOR was 12 (95% CI: 7–20). The overall AUC was 0.83 (95% CI: 0.79–0.86) (Fig. 4b), indicating moderate diagnostic accuracy. Meta-regression analysis indicated that only the sample sizes were statistically significant for heterogeneity (*P* = 0.034). The subgroup analysis is shown in Table 2. The performance in VAP patients was nearly equal to the overall performance in ICU patients.

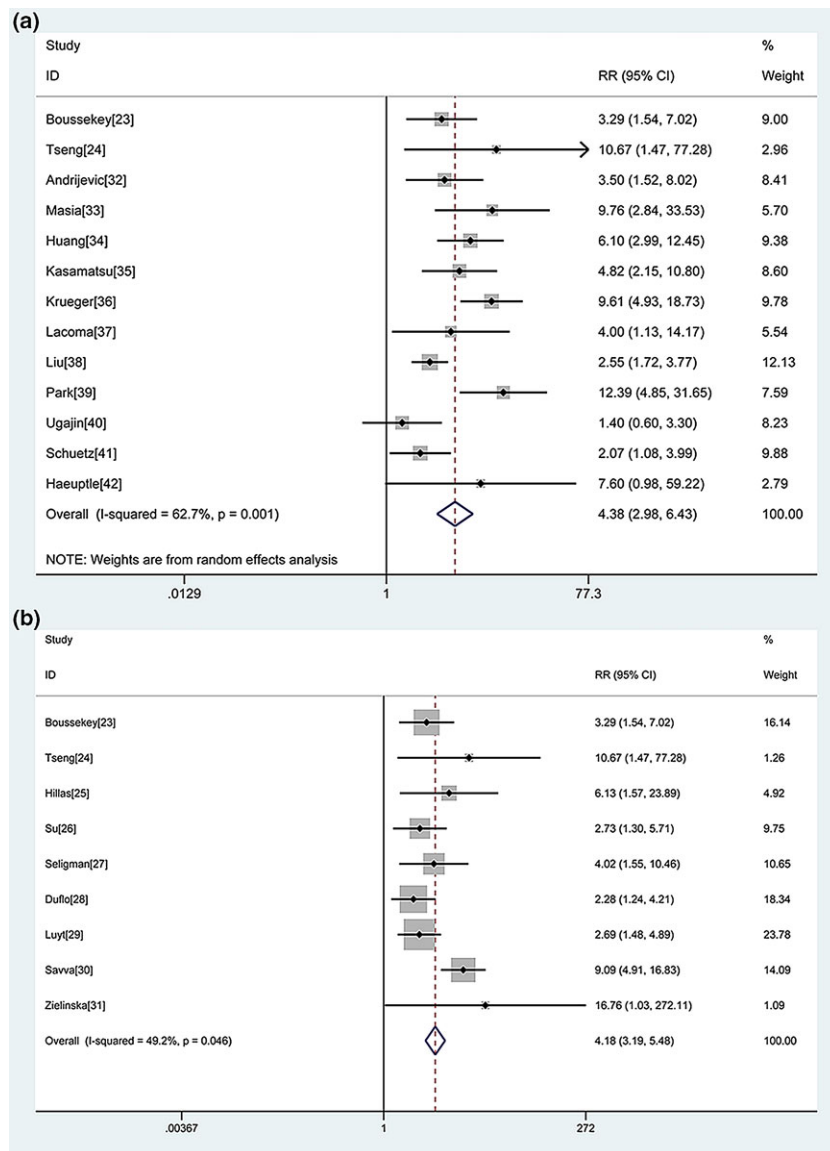


Figure 2 a. Forest plot of procalcitonin (PCT) in predicting mortality in community-acquired pneumonia (CAP). The overall pooled relative risk (RR) was 4.38 (95% CI: 2.98–6.43). b. Forest plot of PCT in predicting mortality in intensive care unit (ICU) patients with pneumonia. The overall pooled RR was 4.18 (95% CI: 3.19–5.48).

DISCUSSION

For patients with CAP, outpatient treatment significantly reduces the risk of healthcare-associated infections and frees scarce resources in many health-care settings. A vital decision for a clinician is whether to admit a patient with CAP to the ICU. Prognostic scores, such as the PSI and CURB-65, are guideline recommended to assess pneumonia severity.⁴⁴ However, some are highly complex for clinical use.¹³ In addition, many studies have shown that these clinical scores are not exempt from FP and FN results and, therefore, are not ideal. Many patients are misclassified as high-risk classes IV and V according to the PSI score.⁴⁵ A meta-analysis showed that the CURB-65 score only has a SEN of 0.62 for predicting mortality in CAP.⁴⁶

In this meta-analysis, the prognostic performance of PCT in pneumonia was first statistically calculated. It was demonstrated that an elevated PCT level is

associated with an increased risk of mortality. The CURB-65 score (classes 2–5) was statistically significant for heterogeneity, indicating that an elevated PCT level was a risk factor for death, particularly in patients with a low CURB-65 score. For this reason, PCT may provide additional information for risk scores when deciding whether to admit patients to the ICU or treat them as outpatients.

It was also confirmed that the commonly used cut-off of 0.5 ng/mL only had a SEN of 0.44 (95% CI: 0.21–0.66) and was not able to identify patients at high risk of dying. In our meta-analysis, two studies provided prognostic accuracy using a cut-off of <0.5 ng/mL as well as a cut-off of 0.5 ng/mL.^{34,41} Both studies showed that the cut-off of <0.5 ng/mL had superior prognostic performance compared with the cut-off of 0.5 ng/mL. Certain studies found lower serum PCT levels in patients with CAP and lower mortality.⁴⁷ These studies indicated that a lower cut-off point for PCT should be defined and used clinically when deciding whether to

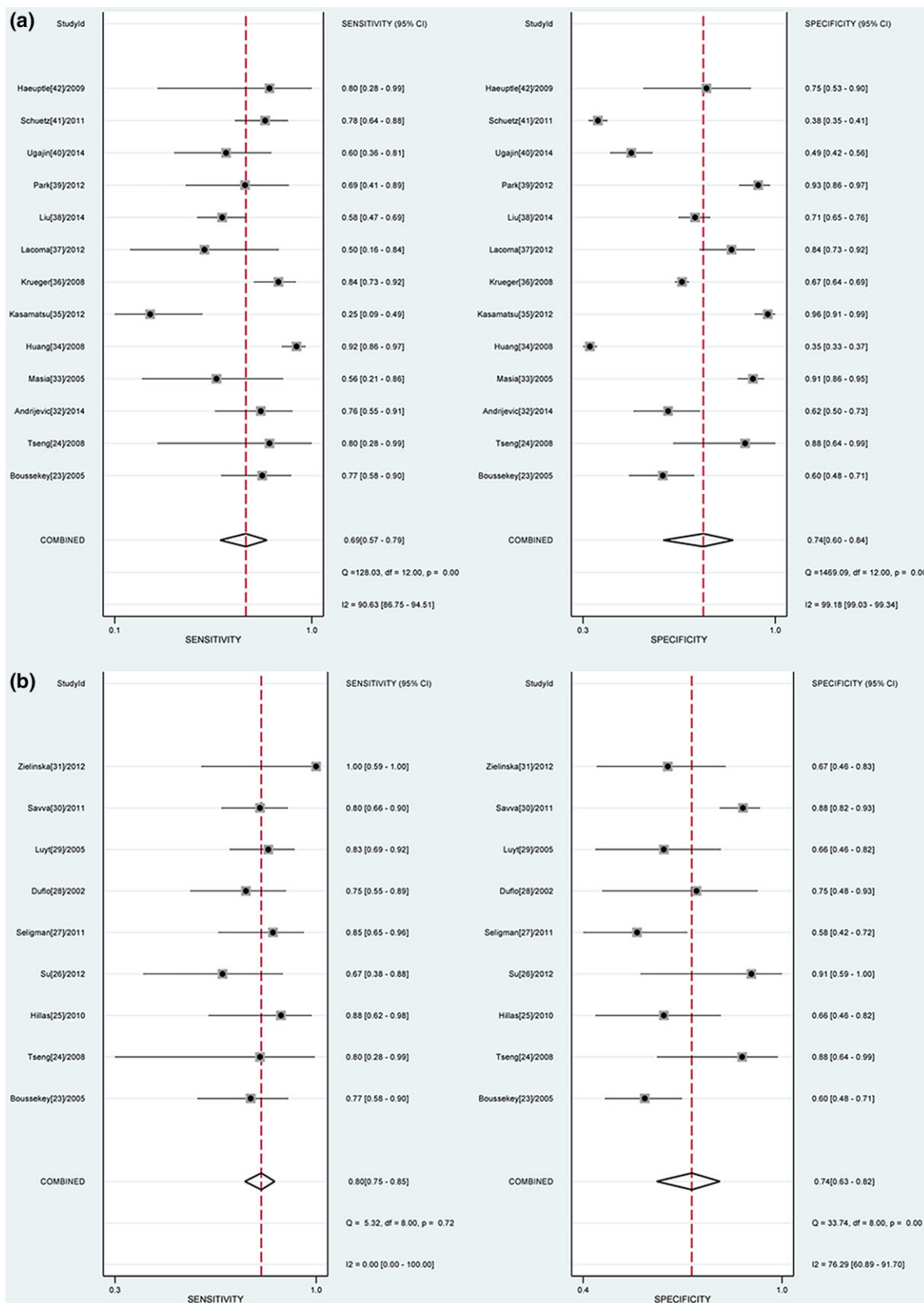


Figure 3 a. Forest plot of the sensitivity (SEN) and specificity (SPE) of procalcitonin (PCT) in predicting mortality in community-acquired pneumonia (CAP). The pooled SEN and SPE were 0.69 (95% CI: 0.57–0.79) and 0.74 (95% CI: 0.60–0.84), respectively. b. Forest plot of the SEN and SPE of PCT in predicting mortality in ICU patients with pneumonia. The pooled SEN and SPE were 0.80 (95% CI: 0.75–0.85) and 0.74 (95% CI: 0.63–0.82), respectively.

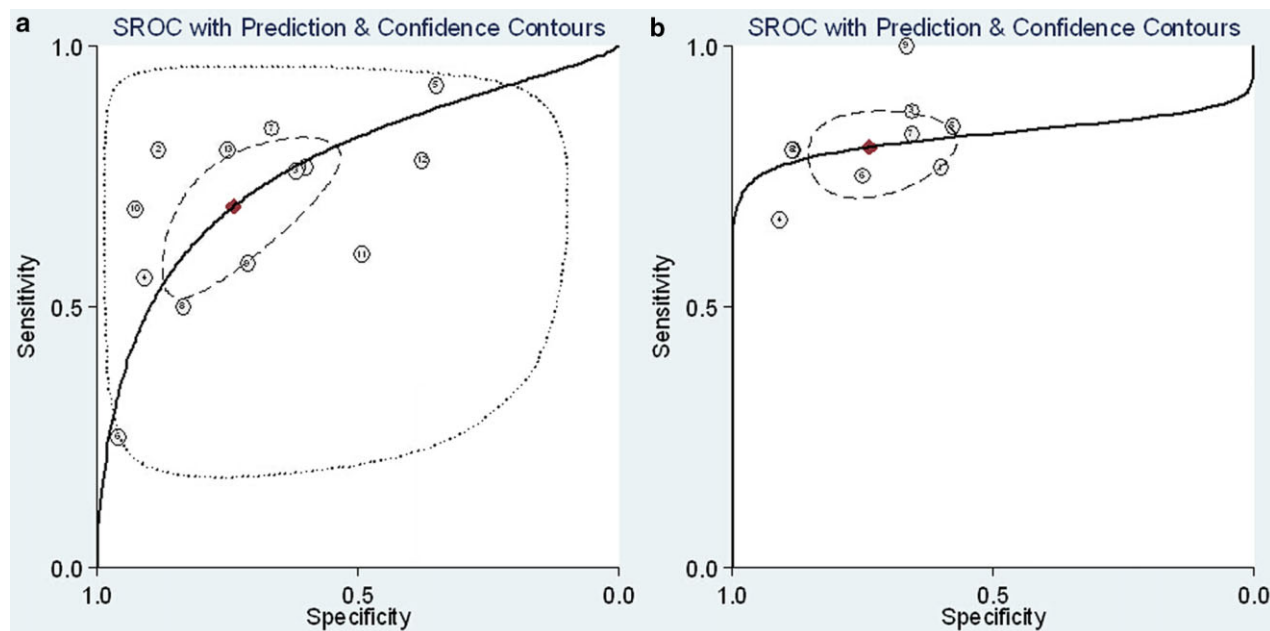


Figure 4 Summary receiver operator characteristic (SROC) graph of the included studies ((a) For CAP patients; (b) For ICU patients with pneumonia). (○) Observed Data; ◆ Summary Operating Point, SENS = 0.69 [0.57–0.79], SPEC = 0.74 [0.60–0.84]; — SROC Cune, AUC = 0.77 [0.73–0.80]; — 95% Confidence Contour; *** 95% Prediction Contour ○ Observed Data; ◆ Summary Operating Point, SENS = 0.80 [0.75–0.85], SPEC = 0.74 [0.63–0.82], — SROC Cune, AUC = 0.83 [0.79–0.88]; — 95% Confidence Contour, *** 95% Prediction Contour)

admit patients to the hospital or treat them as outpatients. Furthermore, we found that studies with FAS greater than 0.1 ng/mL have a low SEN for using PCT to predict mortality in CAP. Thus, the LUMItest assay and PCT-Q test are not sensitive enough to detect mildly elevated PCT levels, which limit their use in clinical decision making for CAP patients with low mortality. A more sensitive assay for PCT should be used clinically.

CAP and VAP may be precursors to sepsis and cause a large proportion of deaths in the ICU. For critically ill patients, the unpredictable disease course and uncertain outcomes have been a challenge for clinicians, hindering the early identification of patients at risk of dying. The identification of these patients may allow the rapid initiation of the appropriate therapeutic interventions and have a great impact on patient outcomes. In our study, it was demonstrated that an elevated PCT level was also associated with an increased risk of mortality (RR 4.18, 95% CI: 3.19–5.48) for critically ill patients. The prognostic performance in patients with CAP was nearly equal to the overall performance. However, limitations should be taken into consideration when interpreting the findings. First, the number of studies focusing on critically ill patients was small. Second, substantial heterogeneity existed in each subgroup. Thus, more studies are needed to clarify the prognostic value of PCT restricted to different pathogenic features.

CONCLUSION

For patients with mild CAP or low mortality, the commonly used cut-off of 0.5 ng/mL had low SEN and

could not be used to identify patients at high risk of dying. A more sensitive assay should be used clinically when deciding whether to admit patients to the ICU or treat them as outpatients. For critically ill patients, an elevated PCT level was also associated with an increased risk of mortality. The prognostic performance was nearly equal between patients with VAP and those with CAP. Further studies should assess whether a lower PCT threshold and more sensitive PCT assays can provide superior prognostic value for patients with pneumonia.

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Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's web-site.

Appendix S1 Example search strategy for PubMed.

Table S1 QUADAS-2 results of included studies.