Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

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See Comment page 382

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Summary

Background Procalcitonin is a promising marker for identification of bacterial infections. We assessed the accuracy and clinical value of procalcitonin for diagnosis of sepsis in critically ill patients.

Methods We searched Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct, from inception to Feb 21, 2012, and reference lists of identified primary studies. We included articles written in English, German, or French that investigated procalcitonin for differentiation of septic patients—those with sepsis, severe sepsis, or septic shock—from those with a systemic inflammatory response syndrome of non-infectious origin. Studies of healthy people, patients without probable infection, and children younger than 28 days were excluded. Two independent investigators extracted patient and study characteristics; discrepancies were resolved by consensus. We calculated individual and pooled sensitivities and specificities. We used I^2 to test heterogeneity and investigated the source of heterogeneity by metaregression.

Findings Our search returned 3487 reports, of which 30 fulfilled the inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0·77 (95% CI 0·72–0·81) and specificity of 0·79 (95% CI 0·74–0·84). The area under the receiver operating characteristic curve was 0·85 (95% CI 0·81–0·88). The studies had substantial heterogeneity (I^2=96%, 95% CI 94–99). None of the subgroups investigated—population, admission category, assay used, severity of disease, and description and masking of the reference standard—could account for the heterogeneity.

Interpretation Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.

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Introduction

Worldwide, sepsis and its sequelae are still a common cause of acute illness and death in patients with community-acquired and nosocomial infections.[1,2] The American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference (Northbrook, IL, USA; August, 1991) defined sepsis as systemic inflammatory response caused by infection.[3] However, no gold standard exists for proof of infection. Bacteraemia is identified in only about 30% of patients with sepsis, depending on previous antibiotic treatment.[4,5] Furthermore, early clinical signs of sepsis, such as fever, tachycardia, and leucocytosis, are non-specific and overlap with signs of systemic inflammatory response syndromes of non-infectious origin, especially in patients who have undergone surgery. Other signs, such as arterial hypotension, thrombocytopenia, or increased lactate concentrations suggest, too late for life-saving treatment, progression to organ dysfunction. Thus, delay in diagnosis and treatment of sepsis increases mortality, prolongs length of hospital stay, and increases costs,[6,7] highlighting the need for early and reliable diagnostic biomarkers for sepsis.

Several humoral and cellular systems are activated during sepsis, with a subsequent release of various molecules that mediate the host response to infection. Several potential bloodstream biomarkers have been investigated for their ability to diagnose sepsis, estimate its severity, and provide a prognosis. The 116-aminoacid polypeptide procalcitonin had been termed the "the champion so far" for identification of bacterial infections[8] because it has several advantages over other potential biomarkers—ie, wide biological range, short time of induction after bacterial stimulus, and long half-life.[9]

However, only two meta-analyses have investigated the accuracy of procalcitonin for the diagnosis of sepsis, with conflicting results.[10,11] Both were limited by selected populations, did not include a heterogeneous patient population, and, most importantly, were biased by the choice of a gold standard for the definition of sepsis. Additionally, new studies of procalcitonin have been done since the publication of the meta-analyses and our understanding of procalcitonin is still developing.

We did a meta-analysis to investigate the ability of procalcitonin to differentiate between sepsis and systemic inflammatory response syndromes of

non-infectious origin in critically ill patients and address the heterogeneity of patients and the affect of individual covariates.

Methods

Search strategy and selection criteria

We systematically searched Medline (via PubMed), Embase (via OvidSP), ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct for studies that assessed the accuracy of procalcitonin for the diagnosis of sepsis.

Our medical subject heading terms (for Medline), EMTREE terms (for Embase), and text (for others) were "(procalcitonin OR PCT) AND (sepsis OR "bacterial infection" OR "systemic inflammatory response syndrome" OR SIRS)". To reduce the number of results, for searches in Science Direct, Embase, and Scopus, we also used the search terms "NOT (review OR letter OR editorial OR "animal experiment" OR "meeting abstract" OR "proceeding paper" OR "poster presentation" OR "meta-analysis" OR "case report")". We searched the databases between inception and Feb 21, 2012. We also searched the reference list of each primary study identified and of previous systematic reviews.

Studies were included if they assessed the accuracy of procalcitonin for differentiation between critically ill patients with sepsis from those who have a systemic inflammatory response syndrome without infection.

To be eligible, studies had to have a well defined reference standard for sepsis, which included the use of definitions established by the American College of Chest Physicians and Society of Critical Care Medicine Consensus Conference[3] or the German Sepsis Society.[12] In accordance with these definitions, the presence of infection had to be microbiologically confirmed or at least clinically suspected because of one or more characteristics: white blood cells in a normally sterile body fluid, perforated viscus, radiographic evidence of pneumonia in association with production of purulent sputum, and syndrome associated with a high risk of infection (eg, ascending cholangitis).

Furthermore, the studies had to provide sufficient information to construct the 2×2 contingency table—ie, false and true positives and negatives were provided.

We only included publications written in English, German, or French. Animal experiments, reviews, correspondences, case reports, expert opinions, and editorials were excluded. We also excluded all studies that involved healthy people, patients without probable infection, and children younger than 28 days.

Procedures

Two investigators (CW, AP) independently extracted data, including the quality assessment from the retrieved studies. Discrepancies were resolved in a consensus meeting or, if agreement could not be reached, they were resolved by referral to a third investigator (FMB).

The extracted data were general and detailed methodology characteristics, characteristics of the study population (adults or children), setting (emergency department, general ward, or intensive care unit), admission category (surgical or medical), severity of illness (sepsis, severe sepsis, or septic shock), and details of the procalcitonin assays and cutoffs used.

Each investigator also recorded the number of true and false positives and negatives. We contacted the corresponding authors if further information was needed. If no response was received after sending a reminder, the study was excluded.

We assessed the methodological quality of the studies with the Quality Assessment of Diagnostic Accuracy Studies checklist.[13] We tailored the guidelines for scoring each item of the checklist to our review.[14] Because overall quality scoring is difficult and should not be included in meta-analyses,[15] we included only item 9 (description of the reference standard) and item 11 (diagnostic review bias) of the 14 individual quality-related items as covariates in a bivariate random-effects model to test them as possible sources of variation and bias.

Statistical analysis

We tabulated true positives, false negatives, false positives, and true negatives in patients with sepsis and systemic inflammatory response syndrome, stratified by study. We used the numbers to calculate sensitivity and specificity and a corresponding CI.

To synthesise data, we used an exact binomial rendition[16] of the bivariate mixed-effects regression

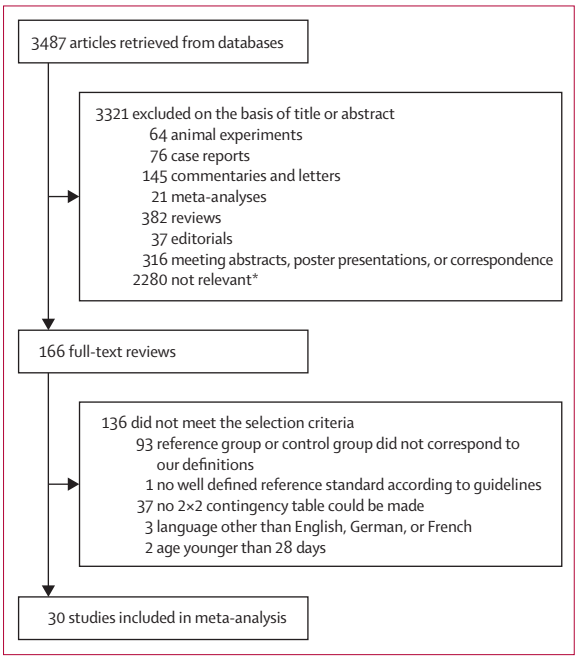

Figure 1: **Study selection**
Some studies were excluded for more than one reason. *Did not investigate the diagnostic accuracy of procalcitonin as a marker for sepsis.

model developed by van Houwelingen[17,18] for meta-analysis of treatment trials, modified for synthesis of diagnostic test data.[19,20] This model does not transform pairs of sensitivity and specificity of individual studies into a single indicator of diagnostic accuracy, but preserves the two-dimensional nature of the data taking into account any correlation between the two.

Based on this model, we estimated mean logit sensitivity and specificity with their standard error and 95% CIs, the between-study variability in logit sensitivity and specificity, and the covariance between them. We back-transformed these quantities to the original receiver operating curve scale to obtain summary sensitivity, specificity, and diagnostic odds ratios. We then used the derived logit estimates of sensitivity, specificity, and respective variances to construct a hierarchical summary receiver operating curve for procalcitonin with summary operating points for sensitivity and specificity on the curves and a 95% confidence contour ellipsoid (two-dimensional CI).

We calculated I^2 to assess heterogeneity. If heterogeneity among studies was recorded, the potential source of heterogeneity was investigated by metaregression. Study-level covariates can be used in metaregression to combine results from multiple studies with attention to between-study variation. We used study-specific covariates such as population or admission category. To investigate publication bias, we constructed effective sample size funnel plots versus the log diagnostic odds ratio and did a regression test of asymmetry.[21]

We calculated κ statistics to assess the agreement between the two investigators for assessment of methodological quality.

	Year	Population	Admission category	Setting	Procalcitonin assay	Cutoff (ng/mL)	n	Prevalence (%)	Severity	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
Ahmadinejad[24]	2009	Adult	Medical and surgical	ED	PCT-Q	0·5	120	59%	No information	63	11	38	8	0·89 (0·79–0·95)	0·78 (0·63–0·88)
Al-Nawas[25]	1996	Adult	Medical	..	PCT-LIA	0·5	337	36%	Sepsis, severe sepsis, and septic shock	73	45	170	49	0·60 (0·51–0·69)	0·79 (0·73–0·84)
Arkader[26]	2006	Paediatric	Medical and surgical	PICU	PCT-LIA	2	28	50%	No information	12	0	14	2	0·86 (0·57–0·98)	1·00 (0·77–1·00)
Bell[27]	2003	Adult	Medical and surgical	ICU	PCT-LIA	15·75	83	75%	No information	47	2	19	15	0·76 (0·63–0·86)	0·90 (0·70–0·99)
Castelli[28]	2004	Adult	Medical and surgical	ICU	PCT-LIA	1·2	49	69%	Sepsis, severe sepsis, and septic shock	21	2	13	13	0·62 (0·44–0·78)	0·87 (0·60–0·98)
Clec'h[29]	2006	Adult	Medical	ICU	PCT-Kryptor	1	76	47%	Septic shock	29	2	38	7	0·81 (0·64–0·92)	0·95 (0·83–0·99)
Clec'h[29]	2006	Adult	Surgical	ICU	PCT-Kryptor	9·7	67	46%	Septic shock	28	9	27	3	0·90 (0·74–0·98)	0·75 (0·58–0·88)
Dorizzi[30]	2006	Adult	Medical and surgical	ICU	PCT-LIA	1	83	61%	Sepsis, severe sepsis, and septic shock	42	6	26	9	0·82 (0·69–0·92)	0·81 (0·64–0·93)
Du[31]	2003	Adult	Medical and surgical	ICU	PCT-LIA	1·6	51	39%	Sepsis, severe sepsis, and septic shock	16	8	23	4	0·80 (0·56–0·94)	0·74 (0·55–0·88)
Gaini[32]	2006	Adult	Medical	HW	PCT-Kryptor	1	93	80%	Sepsis, severe sepsis, and septic shock	56	9	10	18	0·76 (0·64–0·85)	0·53 (0·29–0·76)
Gibot[33]	2004	Adult	Medical	ICU	PCT-LIA	0·6	76	62%	Sepsis, severe sepsis, and septic shock	39	9	20	8	0·83 (0·69–0·92)	0·69 (0·49–0·85)
Groselj-Grenc[34]	2009	Paediatric	Medical and surgical	PICU	PCT-LIA	0·28	36	67%	Sepsis, severe sepsis, and septic shock	20	3	9	4	0·83 (0·63–0·95)	0·75 (0·43–0·95)
Harbarth[35]	2001	Adult	Medical and surgical	ICU	PCT-LIA	1·1	78	77%	Sepsis, severe sepsis, and septic shock	58	4	14	2	0·97 (0·88–1·00)	0·78 (0·52–0·94)
Hsu[36]	2011	Adult	Medical	ICU	PCT-Kryptor	2·2	66	83%	Severe sepsis and septic shock	31	0	11	24	0·56 (0·42–0·70)	1·00 (0·72–1·00)
Ivancevic[37]	2008	Adult	Surgical	..	PCT-LIA	1·1	63	65%	No information	34	5	17	7	0·83 (0·68–0·93)	0·77 (0·55–0·92)
Jimeno[38]	2004	Adult	Medical	..	PCT-LIA	0·5	104	39%	No information	17	5	58	24	0·41 (0·26–0·58)	0·92 (0·82–0·97)
Kofoed[39]	2007	Adult	Medical	HW and ED	PCT-Kryptor	0·25	151	64%	No information	77	23	32	19	0·80 (0·71–0·88)	0·58 (0·44–0·71)
Latour-Perez[40]	2010	Adult	Medical and surgical	ICU	PCT-Q	0·5	114	63%	Sepsis, severe sepsis, and septic shock	53	5	37	19	0·74 (0·62–0·83)	0·88 (0·74–0·96)
Meynaar[41]	2011	Adult	Medical and surgical	ICU	PCT-Kryptor	2	76	42%	Sepsis, severe sepsis, and septic shock	31	9	35	1	0·97 (0·84–1·00)	0·80 (0·65–0·90)

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	Year	Population	Admission category	Setting	Procalcitonin assay	Cutoff (ng/mL)	n	Prevalence (%)	Severity	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)
(Continued from previous page)															
Naeini[42]	2006	Adult	Medical and surgical	..	PCT-Q	0·5	50	50%	Sepsis, severe sepsis, and septic shock	22	1	24	3	0·88 (0·69–0·97)	0·96 (0·80–1·00)
Oshita[43]	2010	Adult	..	..	PCT-Q	0·5	168	67%	No information	76	11	45	36	0·68 (0·58–0·76)	0·80 (0·68–0·90)
Pavcnik-Arnol[44]	2007	Paediatric	Medical and surgical	PICU	PCT-Kryptor	5·79	49	61%	Sepsis, severe sepsis, and septic shock	17	2	17	13	0·57 (0·37–0·75)	0·89 (0·67–0·99)
Ruiz-Alvarez[45]	2009	Adult	Medical and surgical	ICU	PCT-Kryptor	0·32	103	76%	Sepsis, severe sepsis, and septic shock	65	9	16	13	0·83 (0·73–0·91)	0·64 (0·43–0·82)
Sakr[46]	2008	Adult	Surgical	ICU	PCT-LIA	2	327	36%	Sepsis, severe sepsis, and septic shock	82	92	116	37	0·69 (0·60–0·77)	0·56 (0·49–0·63)
Selberg[47]	2000	Adult	Medical	ICU	PCT-LIA	3·3	33	67%	Sepsis and severe sepsis	19	5	6	3	0·86 (0·65–0·97)	0·55 (0·23–0·83)
Simon[48]	2008	Paediatric	Medical and surgical	PICU	PCT-LIA	2·5	64	39%	No information	17	10	29	8	0·68 (0·46–0·85)	0·74 (0·58–0·87)
Suprin[49]	2000	Adult	Medical	ICU	PCT-LIA	2	95	79%	Sepsis, severe sepsis, and septic shock	49	6	14	26	0·65 (0·53–0·76)	0·70 (0·46–0·88)
Tsalik[50]	2011	Adult	..	ED	PCT-Kryptor	0·1	336	74%	Sepsis, severe sepsis, and septic shock	168	33	56	79	0·68 (0·62–0·74)	0·63 (0·52–0·73)
Tsangaris[51]	2009	Adult	Medical and surgical	ICU	PCT-Kryptor	1	50	54%	Sepsis, severe sepsis, and septic shock	19	2	21	8	0·70 (0·50–0·86)	0·91 (0·72–0·99)
Tugrul[52]	2002	Adult	Medical and surgical	ICU	PCT-LIA	1·31	85	88%	Sepsis, severe sepsis, and septic shock	55	2	8	20	0·73 (0·62–0·83)	0·80 (0·44–0·97)
Wanner[53]	2000	Adult	Surgical	ED and ICU	PCT-LIA	1·5	133	34%	No information	34	20	68	11	0·76 (0·60–0·87)	0·77 (0·67–0·86)

All assays made by BRAHMSGmbH (Hennigsdorf, Germany). TP=true positive. FP=false positive. TN=true negative. FN=false negative. ED=emergency department. ICU=intensive care unit. PICU=paediatric intensive care unit. HW=hospital ward.

Table: **Study characteristics**

We used the MIDAS module[22] for STATA (version 12) for the bivariate summary receiver operating curve analysis and to calculate κ statistics. We used Proc GLIMMIX in SAS (version 9.3) to do the metaregression. Graphs were produced with the MIDAS module and the Quality Assessment of Diagnostic Accuracy Studies module for STATA.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our database search retrieved 3487 articles. After reviewing the titles and abstracts, we excluded 3321. After a full text review we excluded a further 136, leaving 30 studies for inclusion (figure 1). Because in one study investigators reported diagnostic accuracy separately for medical and surgical patients, the study was divided into two parts, thus we analysed 31 datasets. Search of the reference lists of the identified articles and previous systematic reviews[10,11,23] did not identify any more relevant articles.

The table shows the main study characteristics. 3244 critically ill patients were included in the analysis, of whom 1863 (57%) had sepsis and 1381 (43%) had systemic inflammatory response syndrome of non-infectious origin. 21 of 30 studies reported classification of severity of illness (sepsis, severe sepsis, or septic shock). Of 1173 patients, 499 (42%) had sepsis, 234 (20%) had severe sepsis, and 440 (38%) had septic shock.

The prevalence of sepsis among studies ranged between 34% and 88% (mean 60%). Only four studies were done in a paediatric setting, whereas 27 investigated adult patients (table). Sites of infection—eg, lung, abdomen, bloodstream, urinary tract—varied. The source of infection (community-acquired or nosocomial) also differed between studies.

Most studies were done in intensive care units, four of them in a paediatric intensive care unit, and most (20 of 30) were done in Europe (table). The cutoff for procalcitonin concentration differed substantially between studies (median 1·1 ng/mL, IQR 0·5–2·0).

Most studies (17 of 30) used a quantitative manual procalcitonin assay for diagnosis of sepsis (table). The appendix shows assay characteristics, the methodological quality of the included studies according to the Quality Assessment of Diagnostic Accuracy Studies

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checklist,[13] how the studies scored on each item, and how the items were assessed. We omitted item 12 of the checklist (clinical data) because the index test is fully automated and no further clinical data are needed to interpret the test results.

The inter-rater reliability for assessment of quality items was 0·59 (p<0·0001). Overall, the methodological quality was moderate. None of the studies fulfilled all of the items, but all studies fulfilled at least four items. 22 studies (73%) met at least 50% of the items.[24,26–28,30–36,39,41,43–45,47–52] Items 3 (reference standard), 5 (partial verification bias), 6 (differential verification bias), and 14 (withdrawals) were fulfilled by all studies. Reports of test review bias (item 10) and uninterpretable results (item 13) were poor (appendix). We identified publication bias by Deeks' regression test of asymmetry (t=4·12; p<0·0005; appendix).

Pooled sensitivity was 0·77 (95% CI 0·72–0·81) and pooled specificity was 0·79 (95% CI 0·74–0·84; figure 2). The area under the receiver operating characteristic curve was 0·85 (95% CI 0·81–0·88; figure 3). Substantial heterogeneity exists among the studies (overall I^2 for bivariate model 96%, 95% CI 94–99). We recorded no evidence of a threshold effect (tested with the STATA MIDAS module). The proportion of heterogeneity probably caused by different cutoffs was small (0·05). To identify the source of heterogeneity, we did metaregression analyses.

To compare medical with surgical patients we did a stratified bivariate regression analysis. We obtained data from 13 studies (nine provided data for medical patients and four provided data for surgical patients). The diagnostic accuracy in surgical patients was higher than that in medical patients as measured by the area under the summary receiver operating characteristic curve (0·83 [95% CI 0·80–0·86] *vs* 0·79 [0·75–0·83]; not tested for significance). We also compared adult with paediatric

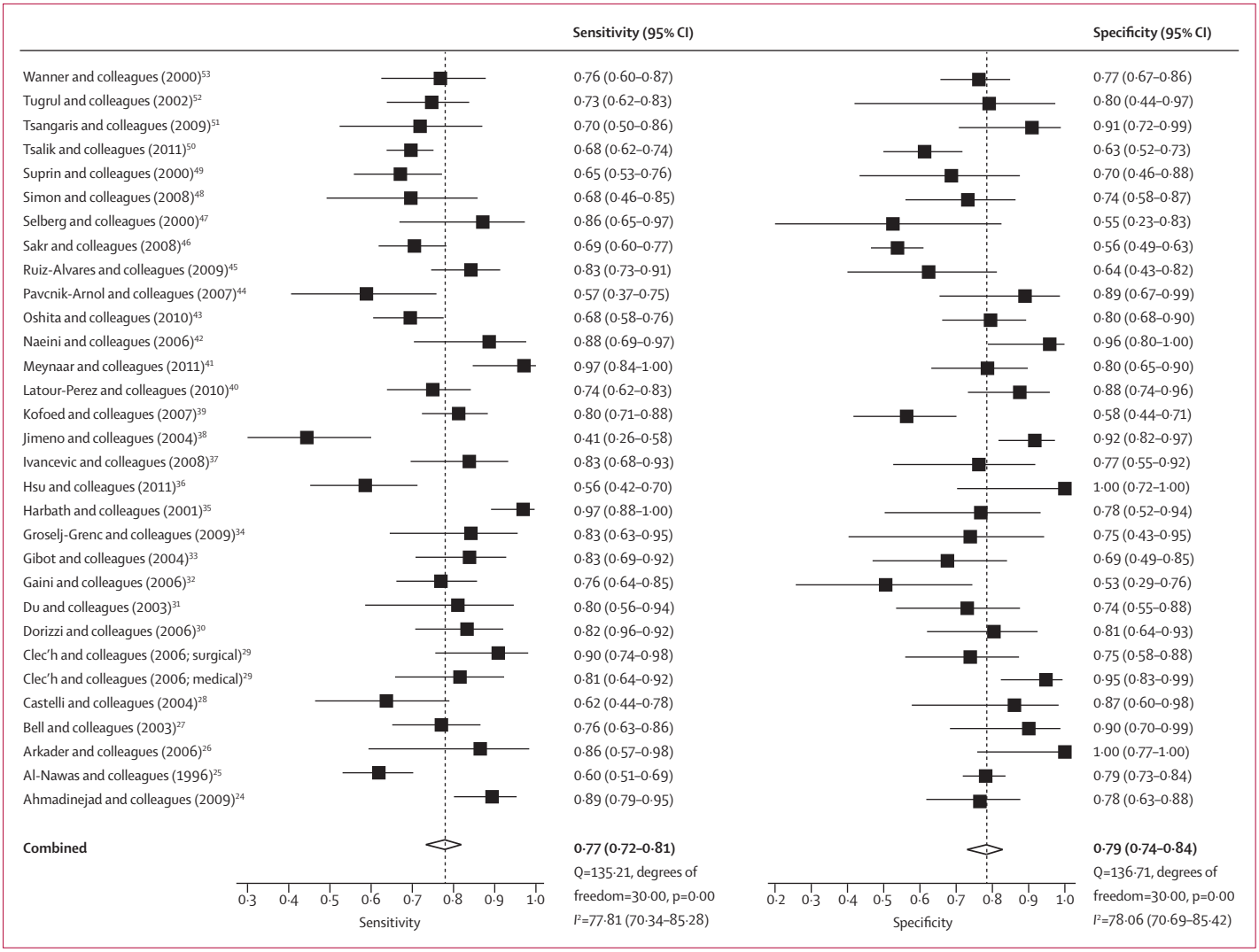

Figure 2: **Sensitivity and specificity of procalcitonin assay for diagnosis of sepsis**

patients (0·85 [0·82–0·88] *vs* 0·85 [0·81–0·88]; not tested for significance). Analysis of the other covariates yielded no significant results (data not shown). Thus, the heterogeneity could not be explained by metaregression analysis.

Discussion

Procalcitonin can differentiate effectively between sepsis and systemic inflammatory response syndrome of non-infectious origin. Previously, two meta-analyses have investigated the diagnostic accuracy of procalcitonin in critically ill patients, with conflicting results.[10,11]

In a meta-analysis from 2006, including studies published between April, 1996, and October, 2004, Uzzan and colleagues[11] reported that the summary receiver operating characteristics curve for procalcitonin was better than for C-reactive protein for identification of sepsis. However, the investigators restricted the population to surgery or trauma patients. Therefore, no conclusion can be drawn for patients other than surgical. Furthermore, the researchers did not assess the heterogeneity of patients from different settings, with different sites of infection, or other study-specific covariates.

In a meta-analysis from 2007, including 18 studies published between April, 1996, and November, 2005, Tang and colleagues[10] concluded that procalcitonin is not able to discriminate between sepsis and systemic inflammatory response syndrome. The diagnostic accuracy of procalcitonin was low; mean sensitivity and specificity were both 71% (95% 67–76) and the area under the summary receiver operator characteristic curve was 0·78 (95% CI 0·73–83). However, their findings were heavily biased because of their selection criteria. First, studies were excluded that had sites of infection typical in sepsis, such as abdominal sepsis, pancreatitis, or meningitis. Second, studies that assessed the ability of procalcitonin to diagnose septic shock were excluded. Because progression of sepsis to septic shock is associated with an increase in procalcitonin concentration,[1] exclusion of patients with septic shock could reduce the overall estimate of diagnostic accuracy. To prevent systematic bias, we included all eligible studies that investigated the diagnostic capacity of procalcitonin in the continuum from sepsis to severe sepsis and to septic shock. Third, they included studies that assessed patients who did not have systemic inflammatory response syndrome or who were not critically ill, which might cause underestimation of diagnostic accuracy.

Accordingly, 23 studies included in the previous meta-analyses[10,11] were excluded from our systematic review because 13 included healthy controls or patients who did not have systemic inflammatory response syndrome in the control group,[54–66] and seven did not provide clear definitions for the target condition or included patients who had infection without systemic inflammatory response syndrome and thus were not in accordance with our selection criteria.[54,64–69] Furthermore, four studies had insufficient information to construct the 2×2 contingency table.[70–73] One investigated the predictive value of procalcitonin for tumour necrosis factor α and interleukin 6 concentrations.[74] Another did multiple measurements in several patients[75] and one study investigated the prognostic value of procalcitonin for infection after cardiac surgery.[76]

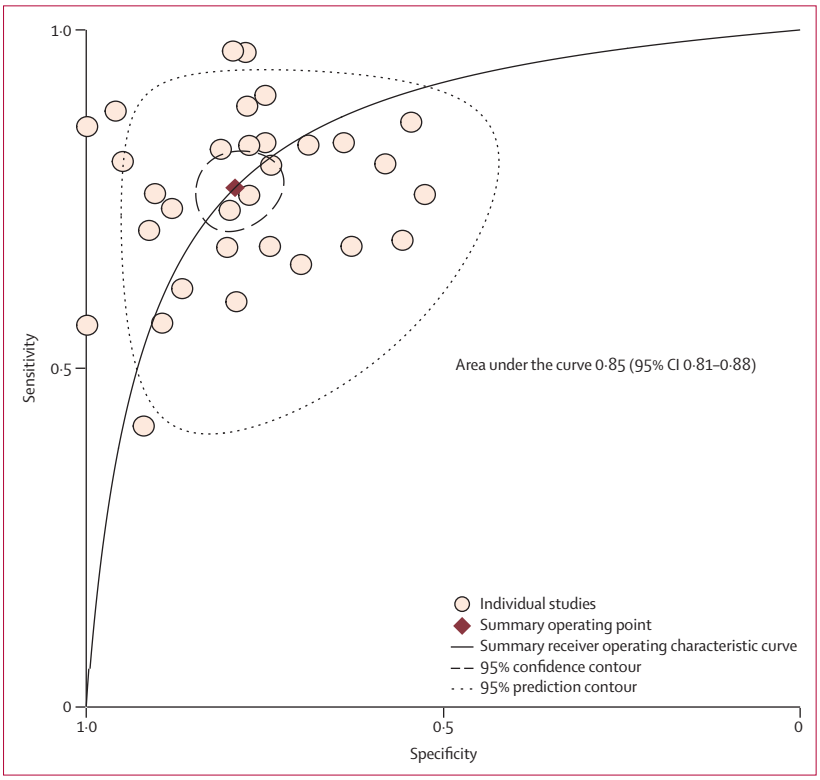

Figure 3: **Summary receiver operating characteristic curve**
Also shows 95% confidence contour and 95% prediction contour.

Furthermore, the meta-analysis of Tang and colleagues[10] has substantial shortcomings in its quantitative data analysis. It summarised pairs of sensitivity and specificity into a single measure of diagnostic accuracy. Thus, important information is missing. To retain the two-dimensional character, we used the bivariate mixed-effects regression model.

Our meta-analysis has several limitations.[77] First, we detected substantial heterogeneity between studies but none of the study characteristics were responsible for the majority of this heterogeneity. The studies differ in several ways—eg, methodological quality, patients' clinical spectrum, admission category, and procalcitonin assay used. Thus, further unrecorded differences between the studies probably contribute to the heterogeneity. Use of a more homogenous population would solve this difficulty, but would cause selection bias.

Second, a reliable test of infection is still absent, so observational studies are biased by the choice of

gold standard. According to our inclusion criteria, the presence of infection had to be microbiologically confirmed or at least clinically suspected. All included studies fulfilled this requirement (appendix), but most did not provide much detailed information about how infection was proved. Nevertheless, depending on previous antibiotic treatment, bacteraemia occurs in only about 30% of patients with sepsis.[4,5] Additionally, absence of standardisation of clinical and radiological findings could cause interobserver variability, which could lead to false-negative or false-positive judgments about the patient's medical condition. We only included studies that had a well defined reference standard for sepsis. Nevertheless, we do not know definitively whether all patients with infection were identified as such.

Third, implementation of some studies was reported poorly, especially with regard to uninterpretable results and test review bias (appendix). To minimise resultant bias and to ensure more homogeneity, investigators should use the Standards for Reporting of Diagnostic Accuracy checklist[78] and also consider using the Quality Assessment of Diagnostic Accuracy Studies checklist.[13]

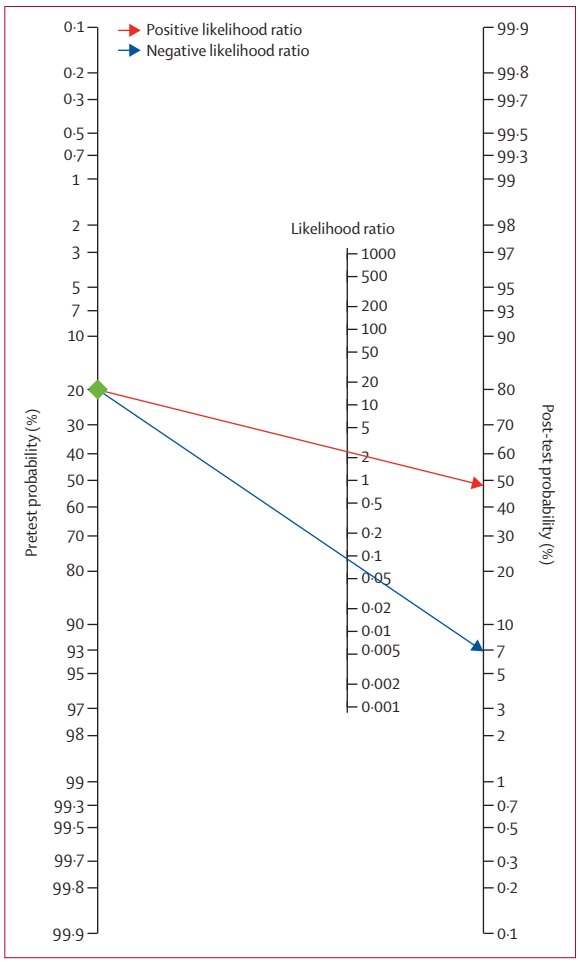

Figure 4: **Fagan nomogram of the procalcitonin test for diagnosis of sepsis**

Fourth, we detected publication bias. Studies with desirable results are more likely to be published, which can lead to an overestimation of overall diagnostic accuracy. To solve this problem, we looked again for further studies by searching the databases and reference lists of primary studies, but could not identify additional relevant articles. Finally, we only included studies written in German, English, or French, which might have affected our findings.

The cutoffs that separated patients who had sepsis from those who did not varied greatly between studies. Some had a cutoff that led to the most favourable results for diagnostic accuracy. Others gave sensitivity and specificity at different thresholds. The difficulty is that the cutoffs were not subsequently validated. The values of diagnostic accuracy are correlated negatively with each other. To change the cutoff means changing sensitivity at the cost of specificity or vice versa. False-negative results leading to denial of treatment could be fatal in sepsis.[6] However, to prevent the development of antibiotic resistance, and increased side-effects and costs, critically ill patients without bacterial infection should be identified correctly. Thus, a rational threshold is needed. We recommend different phases in testing diagnostic accuracy. First, investigators should examine the validity of procalcitonin in a selected group of patients to find a rational cutoff. Second, to ascertain diagnostic value in everyday clinical practice, the established cutoff has to be validated in a diagnostic controlled trial.

The most important feature of a biomarker is its potential to change clinical decision making. In recent years, cutoffs between 0·1 and 0·5 ng/mL have been calculated in patients with lower respiratory tract infections.[79] Our meta-analysis provides important information for critically ill patients, for whom diagnostic decision making is of upmost importance. The median cutoff of the studies included was 1·1 ng/mL (IQR 0·5–2·0). The absence of a clinical threshold effect suggests that a cutoff of between 1·0 and 2·0 ng/mL is helpful for discrimination of patients with sepsis from other inflammatory conditions, in accordance with recommendations.[80]

Likelihood ratios and post-test probabilities are also relevant for clinicians. They provide information about the likelihood that a patient with a positive or negative test actually has sepsis or not. In our study, both likelihood ratio and post-test probability were moderate (figure 4). A positive likelihood ratio of 4 implies that a person with disease is four-times more likely to have a positive test result than is a healthy person. Given a pretest probability of 20%, the post-test probability for a positive test result is 48% (figure 4). Likewise a negative likelihood ratio of 0·29 reduces the post-test probability to 7% for a negative test result. However, these likelihood ratios are calculated from dichotomised data. The result of the procalcitonin test is either positive or negative. The disadvantage of making data dichotomous is that

useful information is lost.[81] Because procalcitonin concentrations rise as disease severity advances,[56] patients with a high procalcitonin concentration are more likely to have sepsis than are patients with a low procalcitonin concentration. To provide more precise information about the reliability of the test, we suggest calculating likelihood ratios based on multiple cutoffs.

As our results show, procalcitonin is not a perfect marker for diagnosis of sepsis, but an ideal marker does not exist. Sepsis is a pathophysiological process rather than a specific syndrome and is too complex to be described by a single measure. Nevertheless, procalcitonin is one of the most promising parameters. Several other mediators and molecules of the host response to infection—C-reactive protein, soluble TREM1, interleukin 6, interleukin 8, and soluble PLAUR—have been investigated, but with no outstanding result.[23,35,40,82]

In conclusion, procalcitonin is a helpful marker for diagnosis of sepsis in critically ill patients. However, it cannot be recommended as the single definitive test for sepsis diagnosis, but rather it must be interpreted in context with information from careful medical history, physical examination, and when feasible, microbiological assessment. Moreover, continuing re-evaluation during the course of disease is advisable.

Contributors

CW had the idea for and designed the study, searched the scientific literature, collected, analysed, and interpreted data, and wrote and critically revised the report. AP searched the scientific literature, collected data, and drafted and critically revised the report. FMB had the idea for and designed the study, interpreted data, drafted and critically revised the report, supervised the study, and gave administrative, technical, and material support. PS had the idea for and designed the study, statistically analysed and interpreted the data, drafted and critically revised the report, supervised the study, and gave administrative, technical, and material support.

Conflicts of interest

We declare that we have no conflicts of interest.

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Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

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Procalcitonin is widely reported as a useful biochemical marker to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome. In this systematic review, we estimated the diagnostic accuracy of procalcitonin in sepsis diagnosis in critically ill patients. 18 studies were included in the review. Overall, the diagnostic performance of procalcitonin was low, with mean values of both sensitivity and specificity being 71% (95% CI 67–76) and an area under the summary receiver operator characteristic curve of 0·78 (95% CI 0·73–0·83). Studies were grouped into phase 2 studies (n=14) and phase 3 studies (n=4) by use of Sackett and Haynes' classification. Phase 2 studies had a low pooled diagnostic odds ratio of 7·79 (95% CI 5·86–10·35). Phase 3 studies showed significant heterogeneity because of variability in sample size (meta-regression coefficient –0·592, p=0·017), with diagnostic performance upwardly biased in smaller studies, but moving towards a null effect in larger studies. Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients. The findings from this study do not lend support to the widespread use of the procalcitonin test in critical care settings.

Introduction

Sepsis is the leading cause of mortality in critically ill patients.[1] Delay in diagnosis and treatment often results in rapid progression to circulatory collapse, multiple organ failure, and eventually death.[2,3] Therefore, accurate and timely diagnosis will limit morbidity, reduce costs, and improve patients' outcome.[4–6]

The diagnosis of sepsis is difficult, because clinical signs of sepsis often overlap with other non-infectious causes of systemic inflammation.[7,8] These signs include tachycardia, leucocytosis, tachypnoea, and pyrexia, which are collectively termed a systemic inflammatory response syndrome (SIRS). SIRS is very common in critically ill patients, being found in various conditions including trauma, surgery, and hypoxic injuries.[8–11] Microbiological culture can be used to distinguish sepsis from non-infectious conditions. However, this method lacks sensitivity and specificity, and there is often a substantial time delay.[12]

Procalcitonin, a 116-aminoacid peptide involved as a precursor in calcium homeostasis, has been studied as a marker to differentiate sepsis from other non-infectious causes of SIRS. Early studies were encouraging,[13–16] and procalcitonin has been proposed as a diagnostic marker to be included in the international definition of sepsis.[17] However, more recent studies have produced conflicting results.[18–24] Furthermore, many studies included patients who did not have SIRS or who were not critically ill. This has added further uncertainty in assessing the diagnostic accuracy of procalcitonin in the critical care setting. The aim of this review was therefore to systematically and quantitatively evaluate all the published studies that assessed the diagnostic use of procalcitonin in critical care settings.

Methods

Data source

We searched Medline, Embase, and Current Contents from January, 1966, to November, 2005, for all studies of diagnostic accuracy of procalcitonin for sepsis. The search strategy used medical subject heading terms and text words, including the following: "procalcitonin"; "sepsis", "sepsis syndrome", "septicemia", "infection", "systemic inflammatory response syndrome", and "SIRS"; and "sensitivity", "specificity", "predictive value", "likelihood ratio", "review", "meta-analysis", "false positive", and "false negative".

The reference lists of each primary study were searched for additional publications. Further searches were done by manually reviewing abstract booklets, conference proceedings, and review articles. Investigators were contacted for further study details if needed. No language restriction was used and all foreign language publications were translated.

Study eligibility

We included all studies that met the following criteria: assessed the diagnostic accuracy of procalcitonin for sepsis; provided sufficient information to construct the 2×2 contingency table; and had a well-defined reference standard for the target condition (sepsis), which included use of accepted definitions by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference,[8] and confirmed the presence of infection by microbiological culture.

Studies were excluded if they included patients who did not have SIRS or were not critically ill; included too narrow spectrum of patients, such as abdominal sepsis or septic shock; were duplicated studies; were paediatric studies; were limited to very restrictive subgroups, such as cardiac surgery, pancreatitis, meningitis, or burns; or were risk stratification or prognosis studies.

Data extraction

Two reviewers (BMPT, GDE) independently abstracted data in each study to obtain information on year of publication, country of origin, clinical setting, patients'

Methodological variable	Information required in each study	Studies that met criteria (n)
Did investigators use additional information (other than consensus definition of sepsis and microbiological culture) to confirm diagnosis, thus minimising misclassification bias?	Using all available information to diagnose sepsis/SIRS, including images studies, response to antibiotics, necropsy reports, and surgical findings	14
Was there a time delay between the index test and reference test (disease progression bias)?	Both procalcitonin and reference test to be done at the same time	18
Did the result of index test influence whether patients receive reference test (work-up bias)?	All patients should receive reference test regardless of procalcitonin test results	18
Were different reference tests used in patients (differential verification bias)?	Consistent use of international consensus criteria to diagnose sepsis in all patients	18
Was the interpretation of the reference test made without the knowledge of the index test (blinding)?	Diagnosis of sepsis/SIRS was made independent of the result of procalcitonin test	8
Description of reference test	Sufficient details provided in how the diagnosis was made	18
Description of index test	Sufficient details provided in how the procalcitonin was measured	18
Description of study population	Sufficient details provided for the case mix and demographic information of the patients enrolled	18
Method of recruitment	Patients were prospectively or consecutively recruited	18

SIRS=systemic inflammatory response syndrome.

Table 1: **Quality assessment of the 18 studies included, by methodological variable**

demographics, sample size, diagnostic cut-off points, and disease prevalence. Each reviewer extracted the data to construct a 2×2 table. Any disagreements were resolved by consensus.

Quality assessment

The methodological quality of each study was assessed by a checklist, by use of adapted criteria from the Cochrane Collaboration guidelines,[25] a study by Lijmer and colleagues,[26] and the QUADAS tool.[27,28] Details of the methodological assessment are shown in table 1.

Statistical analysis

Studies were grouped according to Sackett and Haynes' classification of diagnostic studies.[29] In this classification, phase 1 studies are those that compare the difference in test results between patients with the target disorder and healthy individuals. Phase 2 studies are those that examine how the index test discriminates between patients with and without the target disorder. Phase 3 studies are those that assess the test's real-life performance in patients suspected to have the disorder.

For each study, positive and negative likelihood ratios and a diagnostic odds ratio (OR) were calculated. The likelihood ratio expresses the magnitude by which the probability of sepsis in a given patient is modified by the results of the procalcitonin test. It incorporates both sensitivity and specificity and has the advantage of being less affected by prevalence. The diagnostic OR is the ratio of the odds of a positive result in a patient with sepsis compared with a patient without sepsis: [sensitivity/(1–sensitivity)]/[(1–specificity)/specificity]. The diagnostic OR is a measure of overall accuracy and has the advantage of allowing the inclusion of covariates to examine heterogeneity in a regression model.[30] Pooling of the summary indices was done using DerSimonian and Laird's random-effects model.[31] Each study was weighted by use of an inverse variance method.

To detect heterogeneity, the likelihood ratios and diagnostic ORs were graphically displayed using forest plots and analysed using Cochran's Q test. A p value of less than 0·05 by Cochran's Q test indicated significant heterogeneity. To quantify the extent of heterogeneity, the I^2 statistic was used to measure the percentage of variability among summary indices that were caused by heterogeneity rather than chance. A study with an I^2 greater than 50% indicated substantial heterogeneity.

We constructed summary receiver operator characteristic (SROC) curves to summarise the study results, by use of a regression model described by Littenberg and Moses.[32] In this method, the true-positive and false-positive rates of each study were logarithmically transformed and calculated in a regression model. The data were then back-transformed into the SROC space. A smoothed curve was then fitted across studies to represent the relation between sensitivity and the proportion of false positives (1–specificity).

To ensure that variation in the diagnostic threshold did not affect the shape of the SROC curve, the threshold effect was tested using the regression equation $D=a+bS$, where D is the log of the diagnostic OR and S is a measure of the diagnostic threshold. Estimation of the variables a and b was then done using a least-squares method, weighted by inverse variance. The absence of a threshold effect was indicated by $b=0$.

A Q^* point on the SROC curve was used to obtain the maximum joint sensitivity and specificity. The Q^* point is the intersection between a symmetrical SROC curve and the antidiagonal line, at which sensitivity equals specificity. This point represents a single-number summary of the

test performance and has the advantage of being less affected than other parameters by heterogeneity.[32,33]

To explore sources of heterogeneity among studies, the Littenberg-Moses method[32] was extended by adding covariates to the model. The covariates included spectrum characteristics (eg, study setting, prevalence), clinical and demographic variables (eg, disease severity, age), and methodological features (eg, sample size).

Publication bias was examined visually by inspecting funnel plots and statistically by using Egger's regression model.[34] If publication bias was present, the effect of such bias on the final summary estimate was assessed by using the trim and fill method.[35] This method imputes the missing studies and re-calculates a new summary estimate. The difference between the calculated and observed value was then used to determine the effect of bias on the diagnostic performance of the test.

Results

Study characteristics

We retrieved 672 abstracts, of which 39 were considered potentially suitable. After full text review, 21 studies were excluded (figure 1): one had no SIRS patients in the control group,[36] four included patients who were not critically ill,[37–40] two were case-control studies,[41,42] three used a different reference standard,[43–45] nine could not generate 2×2 tables,[14,46–53] and two had too narrow a spectrum of patients.[54,55] In total, 18 studies were included in the final analysis. Studies were grouped according to Sackett and Haynes' classification[29] for diagnostic studies: 14 phase 2 studies (group 1), four phase 3 studies (group 2). Details of all 18 studies are shown in table 2.

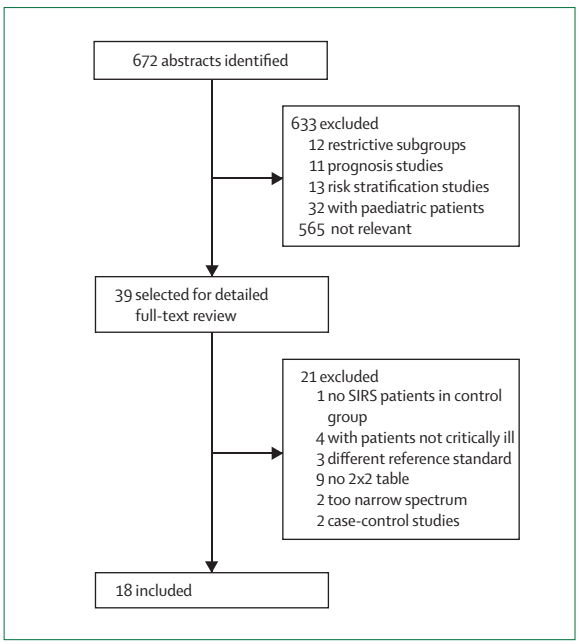

Figure 1: **Study identification, inclusion, and exclusion**
Some studies were excluded by more than one category. SIRS=systemic inflammatory response syndrome.

Study	Year	Country	Setting	Patients (n)	Mean age (years)	Cut-off point (ng/mL)	Study design	Prevalence of sepsis	Sensitivity	Specificity
Group 1 studies (1602 patients)										
Aikawa et al[56]	2005	Japan	Emergency department	176	47	0·5	PR	51%	0·64	0·86
Al-Nawas et al[16]	1996	Germany	Hospital ward/ICU	337	..	0·5	PR	36%	0·60	0·79
Baumgarten et al[57]	2002	Netherlands	ICU	35	..	3	PR	31%	0·55	0·88
Chan et al[58]	2004	Taiwan	Emergency department	69	65	0·6	PR+CR	54%	0·71	0·67
Cheval et al[59]	2000	France	ICU	60	58	20	PR+CR	53%	0·88	0·82
Du et al[60]	2003	China	ICU	51	65	1·6	PR+CR	75%	0·80	0·74
Hausfater et al[61]	2002	France	Emergency department	195	47	0·2	PR	35%	0·62	0·88
Muller et al[23]	2000	Switzerland	ICU	101	59	1·0	CR	58%	0·90	0·93
Mokart et al[62]	2005	France	ICU	50	56	1·1	PR	47%	0·81	0·74
Selberg et al[63]	2000	Germany	ICU	33	47	3·3	PR	67%	0·86	0·55
Suprin et al[64]	2000	France	ICU	95	57	2·00	PR	76%	0·65	0·70
Tugrul et al[65]	2002	Turkey	ICU	85	45	1·31	PR	88%	0·73	0·80
Ugarte et al[21]	1999	Belgium	ICU	182	63	0·6	CR	58%	0·68	0·68
Wanner et al[66]	2000	Switzerland	ICU	133	40	1·5	PR	34%	0·76	0·77
Group 2 studies (495 patients)										
Bossink et al[67]	1999	Netherlands	Hospital ward/ICU	133	60	0·5	CR	45%	0·65	0·58
Gibot et al[68]	2004	France	ICU	76	60	0·6	PR+CR	62%	0·83	0·69
Harbarth et al[22]	2001	Switzerland	ICU	78	54	1·1	CR	77%	0·97	0·78
Ruokonen et al[20]	2002	Switzerland	ICU	208	55	0·8	PR+CR	78%	0·68	0·48

ICU=intensive care unit; PR=prospective recruitment; CR=consecutive recruitment; ..=not available.

Table 2: **Characteristics of the studies included (2097 patients)**

2097 patients were included in the analysis, with 1452 from intensive care units, 440 from emergency departments, and 205 from hospital wards. Studies included a wide case mix, including cardiac, pulmonary, neurological, gastrointestinal, renal, trauma, and surgical illnesses. SIRS criteria were fulfilled in 2092 patients. The mean age of patients in the studies was 54 years (range of study means 40–65 years). The prevalence of sepsis across studies ranged from 31% to 88%. All studies used LumiTest PCT, a commercially available immunolumino-metric assay (Brahms Diagnostica, Berlin, Germany). Test threshold ranged from 0·2 ng/mL to 20 ng/mL.

Quantitative data synthesis

14 studies were included in group 1 (1602 patients). The pooled summary indices showed that the diagnostic performance of procalcitonin was low, with positive likelihood ratio 3·03 (95% CI 2·51–3·65), negative likelihood ratio 0·43 (95% CI 0·37–0·48), and diagnostic OR 7·79 (95% CI 5·86–10·35; figure 2). There was no evidence of a threshold effect (b=0·451, p=0·66). The SROC curve yielded a maximum joint sensitivity and specificity of 73% (95% CI 69–77), an area under the curve of 0·79, and Q* point of 0·73, consistent with low diagnostic accuracy of procalcitonin.

One study had an unusually high summary estimate and accounted for most of the heterogeneity (52·6%).[23] Heterogeneity diminished significantly after this study was excluded (14·7%), thus allowing statistical pooling of the summary estimates. This study was therefore treated as an outlier and the results were reported with the exclusion of this study. However, subsequent sensitivity analysis showed that the pooled summary estimates did not differ significantly with inclusion of the outlier.

Four studies were included in group 2 (495 patients). These studies were highly heterogeneous (Cochran's Q=21·57, p<0·001), with an I^2 value of 86·1%. Statistical pooling was therefore not done for this group.

Finally, all 18 studies were pooled. There was no evidence of a threshold effect (b=–0·21, p=0·40). The SROC curve (figure 3) yielded a maximum joint sensitivity and specificity of 71% (95% CI 67–76), an area under the curve of 0·78, and Q* point of 0·72, indicating that the performance of procalcitonin was low even when all studies were combined.

As expected, when pooling all studies, significant heterogeneity was introduced by the group 2 studies (Cochran's Q=60·21, p<0·001). The source of heterogeneity was explored by univariate meta-regression analysis. Sample size was significant in group 2 as a source of heterogeneity (p=0·017), but only weakly suggestive in group 1 (p=0·09; table 3). None of the variables, such as clinical settings, disease severity, patient demographics, or prevalence, were statistically significant as a source of variability in either group 1 or 2. Within group 2, smaller studies showed a higher diagnostic performance of procalcitonin (eg, a decrease of 40 patients overestimated the relative diagnostic OR by a factor of 1·82). By contrast, the largest study (208 patients) had a diagnostic OR of 1·94 and a 95% CI that included the null effect of 1·0 (figure 4).

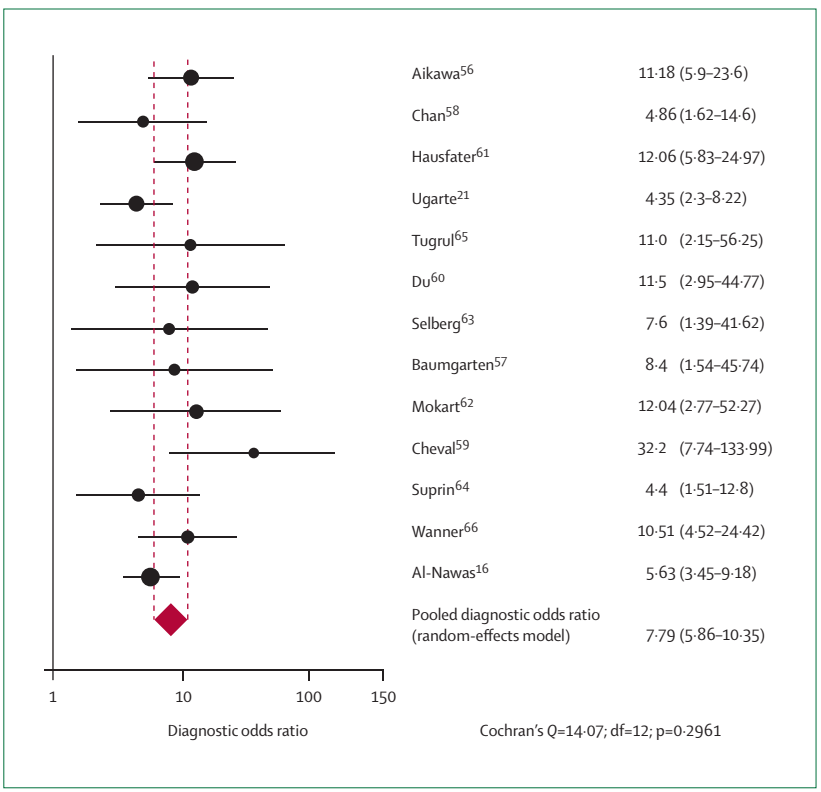

***Figure 2*: Diagnostic odds ratios of group 1 studies**
Circles represent individual studies. Error bars represent 95% CIs. Diamond represents pooled diagnostic odds ratio, with dashed lines representing its 95% CI. Size of circles is proportional to weighting by inverse variance. SE=standard error.

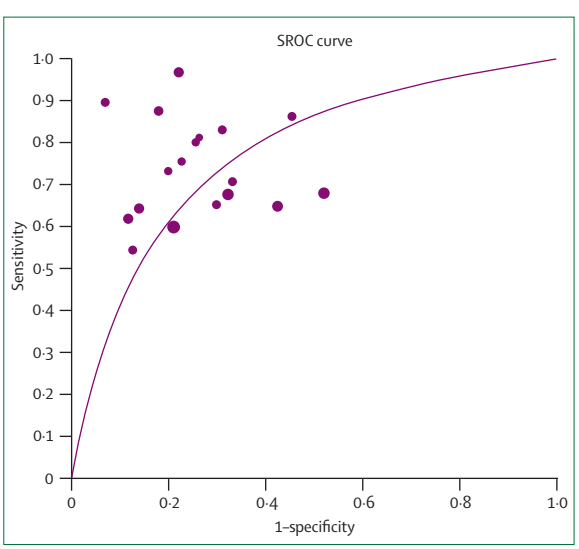

***Figure 3*: Summary receiver operator characteristic (SROC) curve of all studies**
Circles indicate individual study estimates of sensitivity and 1–specificity. Size of circles is proportional to inverse variance of each study.

	Group 1		Group 2	
	Relative DOR (95% CI)	p	Relative DOR (95% CI)	p
Sample size*	1·00 (0·72–1·03)	0·092	0·55 (0·45–0·67)	0·017
Disease severity	..	..	0·93 (0·37–2·37)	0·480
Age	0·97 (0·91–1·03)	0·333	1·49 (0·73–3·08)	0·089
Study setting	1·04 (0·98–1·10)	0·217	0·90 (0·09–9·30)	0·660
Prevalence	1·00 (0·96–1·04)	0·926	0·94 (0·62–1·44)	0·321

..=not available. *The change in relative diagnostic odds ratio (DOR) is for an increase of 40 patients.

***Table 3*: Source of heterogeneity in univariate meta-regression analysis**

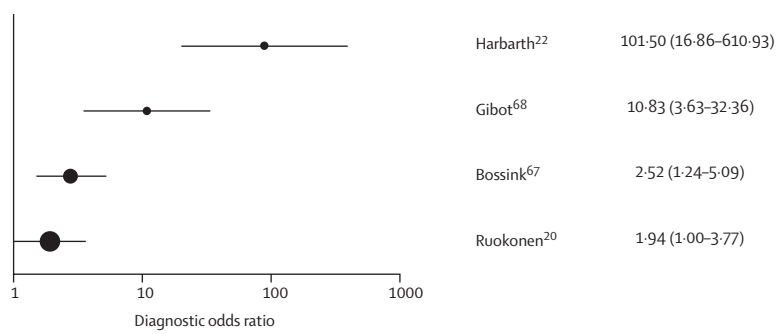

***Figure 4*: Diagnostic odds ratios of group 2 studies**
Circles represent individual studies. Error bars represent 95% CIs. Size of circles is proportional to sample size.

Publication bias was detected using Egger's regression model (p=0·006). Visual inspection of the funnel plot suggested that missing studies were likely to fall to the left of the summary estimate. These studies were then imputed to calculate a new summary estimate (figure 5). The new diagnostic OR was 5·71 (95% CI 3·62–9·03), which was significantly lower than the observed diagnostic OR of 8·71 (95% CI 5·63–13·47). Therefore, the existing studies could have overestimated the diagnostic performance of procalcitonin.

Discussion

The results of this systematic review and meta-analysis indicate that the procalcitonin test cannot accurately distinguish sepsis from SIRS in critically ill adult patients. The study population in this review included a case mix typically seen in medical, surgical, or general intensive care units, emergency departments, and hospital wards. The findings of this review are therefore applicable to common clinical settings in which critically ill patients are managed.

The studies were grouped according to Sackett and Haynes' classification,[29] which assessed an index test on a continuum of diagnostic uncertainty. This continuum allows a stepwise, systematic progression in diagnostic evaluation from a training set (group 1), in which the index test was developed in an ideal situation, to a validation set (group 2), in which its performance was tested in a more realistic clinical context. Such classification therefore allows clinicians to make a more informed decision when assessing the generalisability of studies.[69–71]

Most patients (76%) were included in group 1 studies. The diagnostic OR and likelihood ratios were consistently low across most studies in this group. As a general rule, a diagnostic OR of greater than 100 indicates high accuracy, 25–100 indicates moderate accuracy, and less than 25 indicates an unhelpful test.[72–74] The pooled diagnostic OR of 7·79 showed that the procalcitonin test was unlikely to be helpful in assisting clinical decision making in this group of patients. With a pretest probability of 40% in adult intensive-care-unit patients, use of the procalcitonin test would only raise the post-test probability to 66%. This is insufficient to influence treatment decision (eg, to start antibiotics). Conversely, with a negative likelihood ratio of 0·43, the application of a procalcitonin test would reduce the post-test probability to only 0·23, which is not quite enough to rule out an infection.

The remaining patients (24%) were included in group 2 studies. These studies were the most informative for clinical practice, as they were designed to resemble real-life situations by restricting to patients who were most likely to be encountered by clinicians. Group 2 summary estimates showed lower accuracy and more variability. Sample size gave rise to most of the variability, with smaller studies showing higher summary estimates. Other variables, such as patient age or clinical setting, were likely to have caused variation in the diagnostic performance of procalcitonin. However, the small number of studies (n=4) means that there is a lack of power in detecting these effects. Overall, these data suggest that smaller studies tend to overestimate the effect size, a finding that has been recognised in the diagnostic study literature.[75] A well-designed prospective

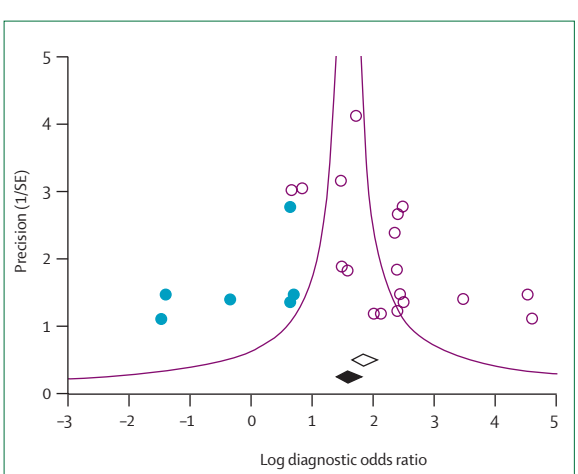

***Figure 5*: Publication bias detected by funnel plot**
Unfilled circles indicate actual studies. Filled circles indicate imputed studies. Unfilled diamond indicates observed summary estimate. Black diamond indicates new summary estimate if all imputed studies were included. SE=standard error.

study with a larger sample size will be required to address this issue.

The diagnostic accuracy of procalcitonin in some populations of patients has recently been reviewed.[76,77] Boysen and colleagues[76] assessed the diagnostic value of procalcitonin in post-operative infection. However, no conclusion could be drawn from their review because of significant heterogeneity among studies. Our analysis included one post-operative study,[62] which was left out by this review. In another review, procalcitonin concentration was found to be better than C-reactive protein in diagnosing bacterial infection.[77] However, this review included studies across a wide range of age groups, clinical settings, and disease spectrum. Additionally, nearly half of the study population (46%) included paediatric patients and many patients did not have SIRS (57%). Despite such a diverse case mix, the study did not assess heterogeneity or its effect on the pooled estimates, thus making it very difficult to interpret its findings.[77] In view of these limitations, we applied in our study more strict inclusion criteria, focusing mainly on a more homogenous population, and used a substantially larger sample size (2092 *vs* 588). We also explored systematically the issue of heterogeneity by use of meta-regression and subgroup analysis. Furthermore, sensitivity analysis confirmed that our findings were robust and consistent. These methodological strengths have therefore enhanced the validity and applicability of our findings.

Publication bias is common in diagnostic studies and is possibly more of a problem than in studies of randomised controlled trials.[78] We detected publication bias in our review. As expected, the missing studies were located to the left of the funnel plot, consistent with the general observation that studies with less optimistic estimation of diagnostic performance are less likely to get published. With imputed values, the re-calculated diagnostic OR was significantly lower than the observed value, indicating that the true diagnostic performance of procalcitonin could have been even lower. However, the statistical methods used to assess publication bias have limitations.[79,80] The above findings therefore need to be interpreted in this context.

The scope of this review means that our findings cannot be generalised to specific diseases (eg, pancreatitis, burns) or settings (eg, cardiothoracic surgical patients, neonatal/paediatric patients). Our study did not include patients who were not critically ill, or who did not fulfil the SIRS criteria. The variation in disease prevalence and severity in these patients means that the diagnostic accuracy of procalcitonin is likely to be different, depending on the chosen population or setting. Finally, we did not include studies that assessed the ability of procalcitonin to diagnose septic shock, since these conditions were usually recognised by simple clinical criteria.

The focus of this review is on the role of procalcitonin in distinguishing sepsis from SIRS in critically ill patients. However, infection can be present without any clinical manifestation of SIRS.[81] The role of procalcitonin in such a setting remains undefined, since most of the procalcitonin studies in this review used SIRS patients in the control groups. Furthermore, this review does not address the issue of prognosis. Further studies would be needed to assess the role of procalcitonin in both these settings.

Although the SIRS criteria are widely used in the literature surveyed by this review, they have been criticised for being too sensitive.[82] However, this low threshold for detection is appropriate for a test for which the consequences of overdetection are outweighed by the consequences of undetection for potentially septic patients.[83] Additionally, the SIRS criteria provide uniformity in inclusion criteria and allow valid comparison to be made across many different studies.[84] Such uniformity has ensured the validity of statistical pooling in our meta-analysis. Despite its limitations, the continuing use of the SIRS concept has recently been supported by an international sepsis definitions conference.[17] The findings of our study therefore reflect the prevalent use of the SIRS concept in sepsis research.[85,86]

Ideally, the additive value of the procalcitonin test to supplement a clinician's bedside assessment should be evaluated in any diagnostic study. Unfortunately, most of the 18 studies did not explore how procalcitonin could be used to enhance clinical assessment, which highlights a recent trend of adopting a biomarker-based approach to diagnose sepsis. In light of our findings, future research should focus on incorporating biomarkers as part of an overall assessment of critically ill patients, rather than in preference to clinical assessment.

In summary, we found that procalcitonin had a low diagnostic performance in differentiating sepsis from SIRS in critically ill adult patients. The evidence presented in this review does not lend support to the widespread use of the procalcitonin test for sepsis diagnosis in critical care settings.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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Search strategy and selection criteria

These are described in detail in the Methods section on page 210.

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