Diagnostic accuracies of procalcitonin and C-reactive protein for bacterial infection in patients with systemic rheumatic diseases: a meta-analysis

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Abstract

Objective

The purpose of this study was to compare the diagnostic performance of procalcitonin and C-reactive protein (CRP) for bacterial infection in patients with systemic rheumatic diseases.

Methods

We searched Medline, Embase, and the Cochran library, and performed two meta-analyses on the diagnostic accuracy of procalcitonin and CRP for bacterial infection in systemic rheumatic disease patients.

Results

A total of eight studies including 668 patients in whom the patients with bacterial infection were 208 were available for the meta-analysis. The pooled sensitivity and specificity of procalcitonin were 66.8% (95% confidence interval [CI] 60.0–73.2) and 89.8% (86.6–92.4), respectively, and those of CRP were 81.3% (75.3–86.3) and 63.0% (58.5–67.5). Procalcitonin PLR, NLR, and DOR were 5.930 (3.593–9.786), 0.352 (0.229–0.539), and 19.33 (10.25–36.45), respectively, and those for CRP were 2.228 (1.376–3.608), 0.367 (0.252–0.534), and 7.066 (3.559–14.03), respectively. The AUC of procalcitonin was 0.884 and the Q^* index was 0.814, while the AUC of CRP was 0.789 and the Q^* index was 0.726, which indicated that the diagnostic accuracy of procalcitonin in patients with systemic rheumatic diseases is higher than that of CRP (difference of AUC 0.095, 95% CI 0.004–0.185, p=0.039). When the data were limited to SLE, the specificity of procalcitonin was also significantly higher than that of CRP (difference 0.219, 95% CI 0.127–0.310, p<0.0001).

Conclusion

Our meta-analysis of published studies demonstrates that procalcitonin is more specific and has better diagnostic accuracy than CRP for bacterial infection in systemic rheumatic diseases.

Key words

rheumatic diseases, bacterial infection, procalcitonin, CRP, diagnostic accuracy, meta-analysis

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Introduction

Bacterial infection is a common cause of morbidity and mortality in systemic rheumatic diseases. The patients with systemic rheumatic diseases have a higher risk for bacterial infection, because they were immunosuppressed due to the diseases itself and its treatments (1). It is sometimes challenging to differentiate bacterial infection from disease flare in patients with systemic rheumatic diseases, because clinical presentations of bacterial infection and disease flare can be similar and both conditions show elevation of acute phase reactants. Increasing or additional dosages of immunosuppressive agents decrease disease flare, but aggravate infection. Thus it is very important to distinguish bacterial infection from disease flare in febrile patients with systemic rheumatic diseases.

C-reactive protein (CRP) is a well-known marker for infection and inflammation. CRP is synthesised in the liver, mainly in response to IL-6, which is produced in both bacterial infection and inflammation (2). CRP is not specific and has low diagnostic accuracy for bacterial infection, because CRP is elevated in systemic diseases due to inflammation, even lack of bacterial infection (3). Procalcitonin is a precursor peptide of calcitonin that is normally secreted by the calcitonin cells of the thyroid gland, and procalcitonin is not detectable in normal individuals (<0.05 ng/ml) (4). However, bacterial infection increases production of procalcitonin in the liver and peripheral blood mononuclear cells (5). Procalcitonin is produced in response to endotoxin or IL-1β induced by bacterial infections (5). Thus, procalcitonin may be useful in distinguishing bacterial infection from other non-infectious diseases.

Procalcitoin has been studied in the context of systemic rheumatic diseases in comparison with CRP with respect to diagnostic accuracy for bacterial infection. However, published studies on the diagnostic accuracies of procalcitonin and CRP showed controversial results (6-13). This may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. In order to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false positives or false negatives (14-17), we performed this diagnostic meta-analysis on the sensitivities and specificities of procalcitonin and CRP for the diagnosis of bacterial infection in patients with systemic rheumatic diseases in order to assess the diagnostic accuracies of procalcitonin and CRP to differentiate infection from disease flare using published data.

Materials and methods

Identification of eligible studies and data extraction

We utilised Medline, Embase, and the Cochrane library to identify articles published through July 2014 in which diagnostic accuracies of procalcitoin and CRP were performed in patients with systemic rheumatic diseases. In addition, all references mentioned in the identified articles were reviewed to identify studies not indexed by electronic databases. The following keywords and subject terms were used in the search: "procalcitonin", "CRP", "sensitivity", "specificity", "lupus", "rheumatoid arthritis", "adult-onset Still's disease", "vasculitis", and "rheumatic diseases" (Search strategy S1). Studies were included in the analysis if: 1. they examined diagnostic accuracies of both procalcitonin and CRP, 2. included sufficient data to calculate sensitivity and specificity, and 3. the study included patients diagnosed with systemic rheumatic diseases as based on each classification or diagnostic criteria. No language restriction was applied. We excluded the following: 1. studies including overlapping data and 2. studies in which there was no data for CRP. Data regarding the methods and results were extracted from the original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus or a third reviewer. We conducted a meta-analysis in accordance with the guidelines provided by PRISMA statement (18). We extracted information on author, publication year, and demographic characteristics of participants, cut-off values of procalcitonin and CRP from each study. Procalcitoin and CRP raw data were ex-

tracted from all primary studies to fill the four cell values of a diagnostic 2 x 2 table (true positives, false positives, true negatives, and false negatives). We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) to assess the quality of each study (19).

Evaluation of statistical associations

We used two meta-analysis methods to assess the overall diagnostic ability of procalcitonin and CRP. Within- and between-study variations and heterogeneities were assessed using Cochran's Q-statistic. Cochran's Q-statistic test assesses the null hypothesis that all studies evaluated the same effect. The effect of heterogeneity was quantified using I^2 with a range between 0 and 100%, representing the proportion of between-study variability attributable to heterogeneity rather than to chance (20). I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. The fixed effects model assumes that a genetic factor has a similar effect on disease susceptibility across all studies investigated and that observed variations among studies are caused by chance alone (21). The random effects model assumes that different studies show substantial diversity and assesses both within-study sampling error and between-study variance (22). When study groups are homogeneous, the two models are similar. If the study groups lack homogeneity, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is most appropriate in the presence of significant between-study heterogeneity (22). We used a random effects model to combine sensitivity, specificity, positive and negative likelihood ratios (PLR, NLR), and diagnostic odds ratio (DOR) estimates, and summary receiver-operating characteristic curves (SROC) were analysed. DOR is a unitary measure of diagnostic performance that encompasses both sensitivity and specificity or both PLR and NLR, and DOR is regarded as a suitable global measure of accuracy for comparing the overall diagnostic accuracies of different tests (23). Because sensitivity and specificity are inter-dependent variables, independent calculations may sometimes underestimate both. SROC curve analysis is more appropriate because it accounts for this mutual dependence. Area under the curve (AUC) (in this case, area under the SROC curve) presents an overall summary of test performance and displays the trade-off between sensitivity and specificity, and an AUC of 1.0 (100%) indicates perfect discriminatory ability for a diagnostic test (13). In addition, the Q^* index is another useful global estimate of test accuracy for comparing SROC curves. The Q^* index is defined at the point where sensitivity equals specificity on an SROC curve, and is the point on a SROC curve intersected by the anti-diagonal. A Q^* value of 1.0 indicates 100% accuracy (*i.e.* sensitivity and specificity of 100%) (13). Statistical manipulations for this meta-analysis were performed using MetaDiSc, version 1.4 (Hospital Universitario Ramon y Cajal, Madrid) (16).

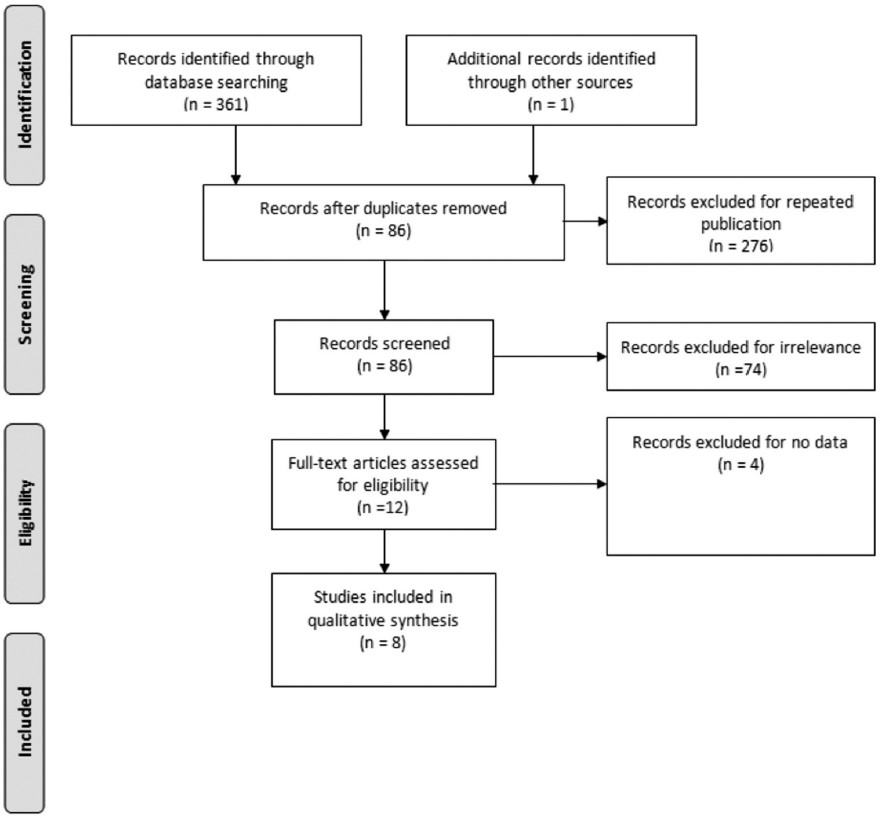

Fig. 1. Flow diagram of study selection.

Results

Studies included in the meta-analysis

We identified 362 studies by electronic and manual searching, and 12 were selected for full-text review based on title and abstract (6-13, 24-27). Four of these were excluded because they had no data on CRP (24-27) (Fig. 1). Thus, eight studies that reported on the diagnostic accuracies of procalcitonin and CRP met our study inclusion criteria (6-13), and these studies included in total 668 patients in whom the patients with bacterial infection were 208. These studies consisted of three SLE, three systemic autoimmune diseases, one adult-onset Still's disease (AOSD), and one acute arthritis. The characteristic features of the participants in the studies included in the meta-analysis are given in Table I, and the quality assessments of the diagnostic accuracy of the studies are shown in Figure 2.

Diagnostic accuracy of procalcitoin and CRP in systemic rheumatic diseases

When all eight studies were considered together, the sensitivity estimates of procalcitoin ranged from 38.2% to 100%, and the specificity estimates ranged from 75.0% to 100% (Fig. 3).

Table I. Characteristics of individual studies included in meta-analysis.

Authors	Country	Disease	Numbers		Outcomes	Cut-off value		PCT		CRP	
			Bacterial infection	Non-infection		PCT (ng/ml)	CRP (mg/dl)	Sensitivity	Specificity	Sensitivity	Specificity
Yu, 2013 (6)	China	SLE	47	67	MDI, CDI	0.38	0.71	74.5	95.5	70.2	62.7
Bador, 2012 (7)	Malaysia	SLE	10	58	MDI	0.12	0.48	80	78	80	55
Kim, 2012 (8)	Korea	SLE	34	39	MDI, CDI	0.025	1.35	38.2	93.3	100	90
Joo, 2011 (9)	Korea	Autoimmune diseases[a]	32	47	CDI	0.09	7.18	81.3	78.7	71.9	68.1
Sleglova, 2010 (13)	Czech	Autoimmune diseases[b]	42	170	MDI, CDI	0.5	2.0	52.4	94	76.2	67.9
Chen, 2009 (11)	Taiwan	AOSD	12	24	MDI	1.4	10.1	100	100	73.1	83.3
Scire, 2006 (10)	Italy	Autoimmune diseases[c]	20	24	MDI	0.5	6.0	75	75	95	8.3
Martinot, 2005 (12)	France	Acute arthritis	11	31	MDI	0.3	5.0	72.7	93.5	100	40

PCT: procalcitoin; CRP: C-reactive protein; SLE: systemic lupus erythematosus; AOSD, adult onset Still's disease; MDI: microbiologically documented infection; CDI: clinically documented infection; [a]: AOSD, n=3; ankylosing spondylitis (AS), (n=9); Behçet's disease (BD), (n=8); microscopic polyangitis (MPA), (n=1); polyarteritis nodosa (PAN), (n=1); rheumatoid arthritis (RA), (n=33); Sjögren's disease (SD), (n=2); SLE, (n=16); systemic sclerosis (SSc), (n=5); Wegener's granulomatosis (WG), (n=1); [b]: Data on each autoimmune disease (not available); [c]: ANCA-associated vasculitis (AAV) (n=3); AOSD (n=1); cryoglobulinaemic vasculitis (CV) (n=1); polymyositis (PM) (n=2) PMR: polymyalgia rheumatic (PR) (n=1); RA: (n=4); SLE (n=7); SSc: (n=1).

On the other hand, the sensitivity estimates of CRP ranged from 70.2% to 100%, and the specificity estimates ranged from 40.0% to 90.0% (Fig. 4). The pooled sensitivity and specificity of procalcitonin were 66.8% (95% confidence interval [CI] 60.0–73.2) and 89.8% (86.6–92.4), respectively, and those of CRP were 81.3% (75.3-86.3) and 63.0% (58.5–67.5) (Table II, Fig. 3-4). In summary, procalcitonin PLR, NLR, and DOR were 5.930 (3.593–9.786), 0.352 (0.229–0.539), and 19.33 (10.25–36.45), respectively, and those for CRP were 2.228 (1.376–3.608), 0.367 (0.252–0.534), and 7.066 (3.559–14.03), respectively (Table II). Figure 4 shows the performance of procalcitoin and CRP testings in the form of SROC curves. The AUC of procalcitonin was 0.884 and the Q^* index was 0.814, indicating modest accuracy, while the AUC of CRP was 0.789 and the Q^* index was 0.726, which indicated that the diagnostic accuracy of procalcitonin in patients with systemic rheumatic diseases is higher than that of CRP (Table III, IV). The cut-off values of PCT and CRP were quite different among the reports, especially in the report of Chen *et al*. (11) including patients with AOSD. Thus, we performed a Spearman rank correlation test for threshold effect and a subgroup analysis of homogenous disease such as SLE. Spearman rank correlation test showed no presence of threshold effects in the PCT and CRP meta-analyses (PCT: Spearman correlation coefficient=0.024; p=0.966; CRP: Spearman correlation coefficient=0.143; p=0.736).

Diagnostic accuracy of procalcitonin and CRP in SLE

Data that were limited to studies of SLE were similar to those from all 8 studies. When all three SLE studies were considered together, the pooled sensitivity and specificity of procalcitonin were 61.3% (95% CI 50.8–71.6) and 88.4% (82.5–92.9), respectively, and those for CRP were 82.4 (73.0–89.6) and 66.5 (58.7–73.6) (Table II). In summary, procalcitonin PLR, NLR, and DOR were 6.332

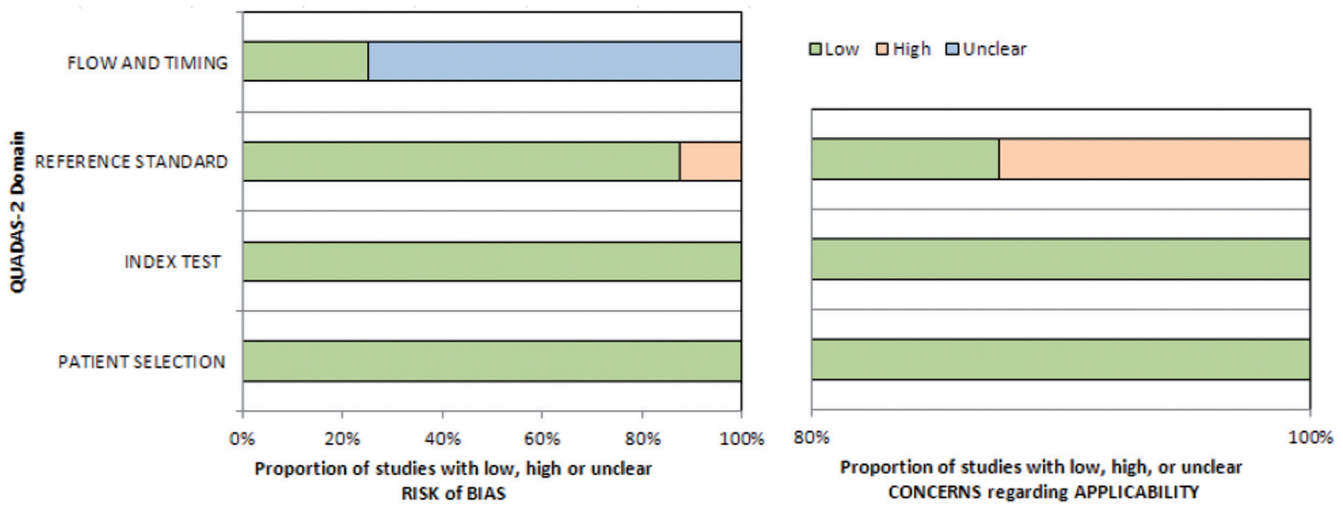

Fig. 2. Quality assessment of diagnostic accuracy studies.

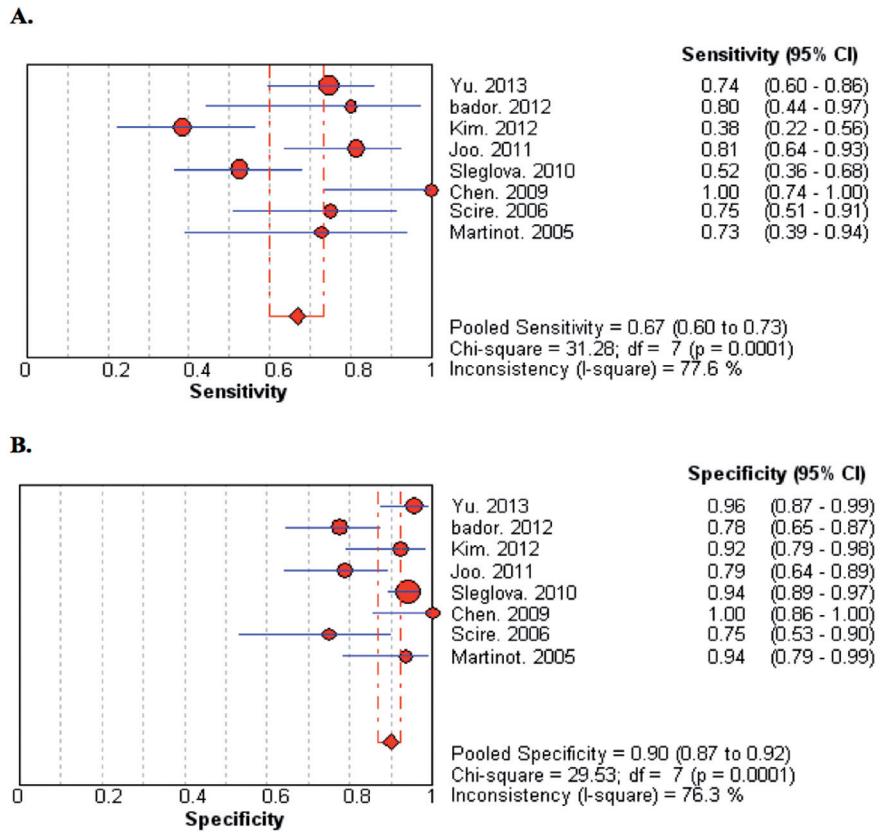

Fig. 3. Sensitivity (**A**) and specificity (**B**) estimates for PCT for the diagnosis of bacterial infection. Circles and lines represent point estimates and 95% CIs, respectively. Circle areas represent relative study sizes.

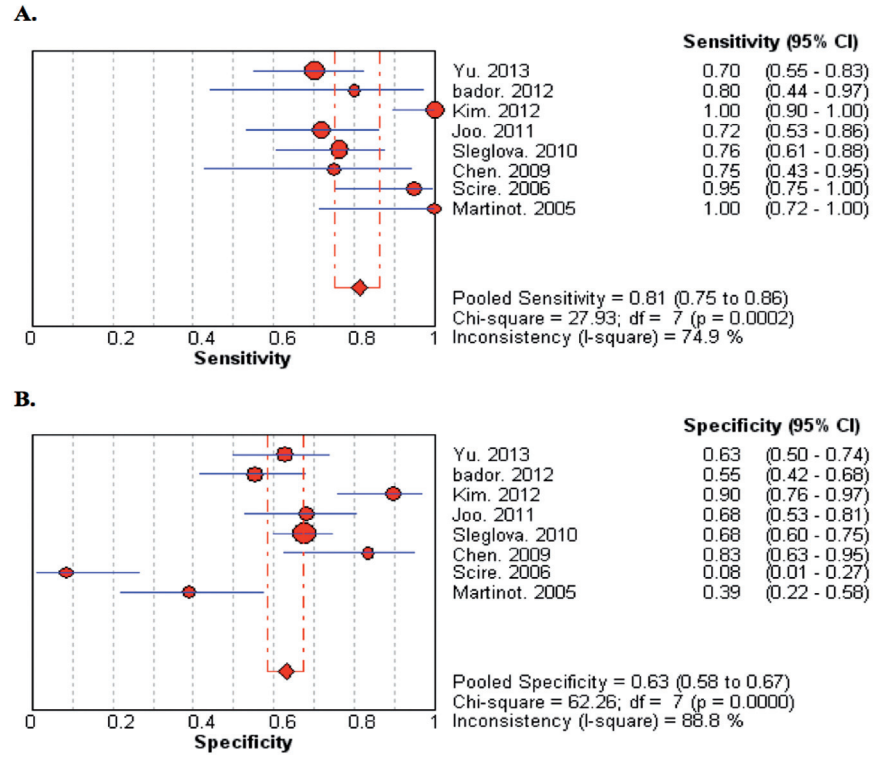

Fig. 4. Sensitivity (**A**) and specificity (**B**) estimates for CRP for the diagnosis of bacterial infection. Circles and lines represent point estimates and 95% CIs, respectively. Circle areas represent relative study sizes.

(2.000–20.04), 0.383 (0.157–0.935), and 19.01 (5.072–71.31), respectively, and those for CRP were 2.798 (1.265–6.189), 0.217 (0.041–1.146), and 14.36 (1.501–137.40), respectively (Table II). The AUC of procalcitonin was 0.883 and the Q^* index was 0.813, indicating modest accuracy. The AUC of CRP was 0.860 and the Q^* index 0.791 (Table III).

Comparison of diagnostic accuracy of procalcitonin versus CRP

The sensitivity of procalcitonin was lower than that of CRP in systemic rheumatic diseases (difference -0.145, 95% CI -0.231 – -0.058, p=0.001), but the specificity of procalcitonin was significantly higher than that of CRP (difference 0.268, 95% CI 0.214–0.351, p<0.0001) (Table IV). In overall, the AUC of procalcitonin was significantly higher than that of CRP (difference 0.095, 95% CI 0.004–0.185, p=0.039) (Table IV). When data that were limited to studies of SLE, the specificity of procalcitonin was significantly higher than that of CRP in SLE (difference 0.219, 95% CI 0.127–0.310, p<0.0001) (Table IV). However, the difference of the AUC in procalcitonin *versus* CRP was not significant in SLE (difference 0.023, 95% CI 0.193 – 0.239, p=0.834) (Table IV).

Discussion

Distinguishing bacterial infection from disease flare-up is important in clinical practice. However, the early detection and differentiation of bacterial infection in febrile patients with systemic diseases are challenging. Studies of the diagnostic accuracies of procalcitonin and CRP for the diagnosis of bacterial infection in systemic rheumatic diseases have reported inconsistent findings (6-12). These inconsistent findings may be due to false positives, false negatives, or low statistical power due to small sample size. Meta-analysis integrates previous research, and increases statistical power and resolution by pooling the results of independent analyses (28), and thus provides a powerful means of overcoming the small sample size problem and inadequate statistical power.

In this meta-analysis, we combined evidence of the diagnostic accuracies

Table II. Summary results of meta-analysis.

Biomarkers	Population	Study no.	Numbers		Sensitivity	Specificity	PLR	NLR	DOR
			Bacterial infection	Non-infection					
PCT	Overall	8	208	460	0.668 (0.600-0.732)	0.898 (0.866-0.924)	5.930 (3.593-9.786)	0.352 (0.229-0.539)	19.33 (10.25-36.45)
PCT	SLE	3	91	164	0.613 (0508-0.716)	0.884 (0.825-0.929)	6.332 (2.000-20.04)	0.383 (0.157-0.935)	19.01 (5.072-71.31)
CRP	Overall	8	208	460	0.813 (0.753-0.863)	0.630 (0.585-0.675)	2.228 (1.376-3.608)	0.367 (0.252-0.534)	7.066 (3.559-14.03)
CRP	SLE	3	91	164	0.824 (0.730-0.896)	0.665 (0.587-0.736)	2.798 (1.265-6.189)	0.217 (0.041-1.146)	14.36 (1.501-137.40)

PCT: procalcitoin; CRP: C-reactive protein; SLE: systemic lupus erythematosus; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; DOR: Diagnostic OR. 1 means 100% in sensitivity and specificity.

Table III. Estimates of summary receiver operating characteristic curve parameters.

Antibody	Population	Study no.	Numbers		AUC	SE(AUC)	Q*	SE(Q*)
			Bacterial infection	Non-infection				
PCT	Overall	8	208	460	0.884	0.023	0.814	0.024
PCT	SLE	3	91	164	0.883	0.050	0.813	0.051
CRP	Overall	8	208	460	0.789	0.040	0.726	0.034
CRP	SLE	3	91	164	0.860	0.098	0.791	0.095

PCT: procalcitoin; CRP: C-reactive protein; SLE: systemic lupus erythematosus; AUC: Area under the curve; SE : Standard error, 1 means 100% in sensitivity and specificity.

Table IV. Paired comparison of diagnostic accuracy for bacterial infection in systemic rheumatic diseases.

	Population	Study no.	Numbers		PCT	CRP	Difference (PCT *vs*. CRP)	*p*-value
			Bacterial infection	Non-infection				
Sensitivity	Overall	8	208	460	0.668 (0.600-0.732)	0.813 (0.753-0.863)	-0.145 (-0.231 - -0.058)	0.001
	SLE	3	91	164	0.613 (0.508-0.716)	0.824 (0.730-0.896)	-0.211 (-0.344 - -0.077)	0.002
Specificity	Overall	8	208	460	0.898 (0.866-0.924)	0.630 (0.585-0.675)	0.268 (0.214-0.351)	< 0.0001
	SLE	3	91	164	0.884 (0.825-0.929)	0.665 (0.587-0.736)	0.219 (0.127-0.310)	< 0.0001
AUC	Overall	8	208	460	0.884	0.789	0.095 (0.004-0.185)	0.039
	SLE	3	91	164	0.883	0.860	0.023 (0.193-0.239)	0.834

PCT: procalcitoin; CRP: C-reactive protein; SLE: systemic lupus erythematosus; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; AUC : Area under the curve; SE : Standard error, 1 means 100% in sensitivity and specificity.

of procalcitonin and CRP for bacterial infection in systemic rheumatic diseases. This meta-analysis of eight studies including 668 patients shows that the sensitivity of procalcitonin is lower than that of CRP, but that the specificity of procalcitonin is higher than that of CRP, and that the overall diagnostic accuracy of procalcitonin is better than that of CRP for diagnosing bacterial infection in systemic rheumatic diseases. When sensitivity and specificity were considered independently, the sensitivity of procalcitonin was 66.8% and its specificity was 89.8%, whereas respective values for CRP were 81.3% and 63.0%. AUC provides an index of the overall discriminative ability of a test. When sensitivity and specificity were considered simultaneously, the AUC for procalcitonin was 0.884, whereas that for CRP was 0.789. When the data were limited to SLE, the specificity of procalcitonin was also significantly higher than that of CRP in SLE. These results are consistent with that of previous relevant meta-analyses showing a higher diagnostic accuracy of procacitonin compared with CRP for bacterial infection (29).

Our data confirmed that procalcitonin is a useful biomarker for discrimination between bacterial infection and noninfectious condition in febrile patients with systemic rheumatic diseases. Procalcitoin has a useful positive LR (5.930, 95% CI 3.593–9.786), in contrast to CRP (2.228, 95% CI 1.376–3.608). However, procalcitonin

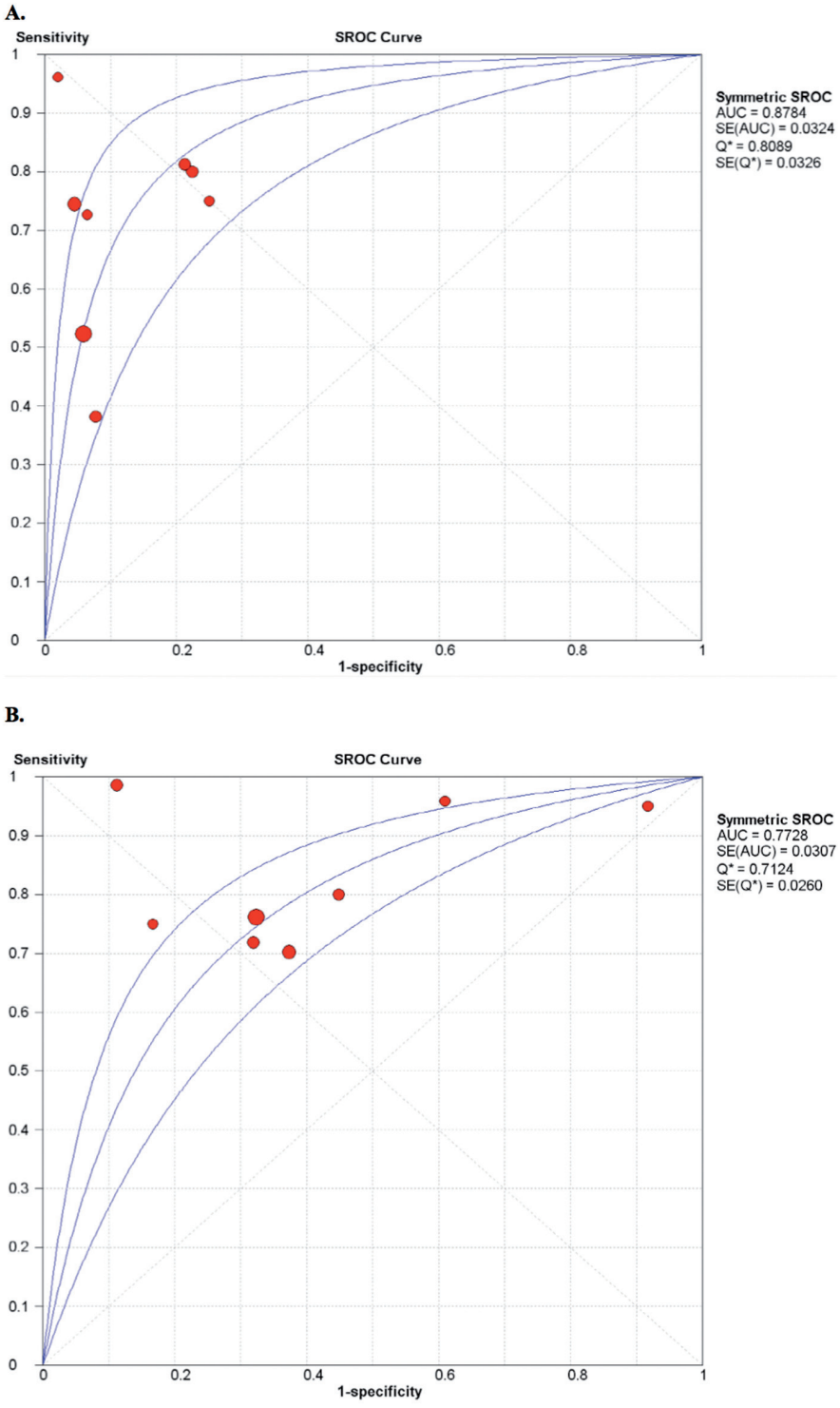

Fig. 5. SROC curves for PCT (A) and for CRP (B) for the diagnosis of bacterial infection Solid circles represent individual studies included in this meta-analysis. The curve shown is a regression line that summarises overall diagnostic accuracy. SE (AUC), standard error of AUC, Q^*, an index defined by the point on the SROC curve where the sensitivity and specificity are equal; SE(Q^*), Q^* index standard error.

is not reliable marker for the exclusion of bacterial infection, because it has a suboptimal negative LR (0.352, 95% CI 0.229–0.539) and low level of sensitivity (66.8%).

This meta-analysis differs from a previous meta-analysis on the disgnostic accuracy of procalcitoin and CRP in patients with autoimmune diseases (30), because in the present study three more studies included (6-8) and four studies were excluded because the studies examined only procalcitoin, but not CRP. Our study included studies which performed both procalcitonin and CRP tests. The result of this meta-analysis regarding higher diagnostic accuracy, AUC, specificity of procalcitonin compared with CRP is in agreement with this previous study. However, our study indicated a lower sensitivity of procalcitonin than that of CRP, while previous meta-analysis showed that sensitivity of procalcitonin is comparable with CRP. The reason of this difference is unclear, but it may be due to difference in the inclusion criteria between two meta-analyses.

The present study has limitations that should be considered. First, between-study heterogeneity was encountered in this meta-analysis. This between-study heterogeneity may have affected the results of this meta-analysis, which may be compounded by the limited information provided on clinical status and disease severity in the populations involved. We tried to overcome this limitation by using a random-effects model that incorporates uncertainties arising due to between-study variation and by doing subgroup analysis. Second, the diagnostic accuracy of procalcitonin may be different according to the cut-off levels (31). The cut-off values of PCT and CRP are quite different among the reports, especially in the report of Chen *et al*. (11) including patients with AOSD. Chen *et al*. (11) found that procalcitonin levels of 1.4 ng/ml or greater yielded the highest discriminative value for AOSD patients (11). Thus, they use 1.4 ng/ml as the cut-off value of PCP, instead of 0.5 ng/ml. However, Spearman rank correlation test showed no presence of threshold effects in the PCT and CRP meta-analyses. The cut-off levels are needed to be optimised because the best cut-off value is unclear. Further research is required to examine how the diagnostic accuracies of procalcitonin are changed due to the cut-off values. Third, given that the population is heterogeneous, the increase of other infections non-related to bacterial infection has been observed in ANCA-associated vasculitis (AAV) or AOSD. The target condition is bacterial infection, but not a whole infection.

Nevertheless, this meta-analysis also has its strengths. The number of the patients from individual studies ranged from 36 to 212. However, this pooled analysis included a total of 668 patients. In comparison with an individual study, we were able to provide more accurate data on the diagnostic tests by increasing the statistical power and resolution by pooling the results of independent analyses.

Our meta-analysis of published studies demonstrates that the sensitivity of procalcitonin is lower, but the specificity and the diagnostic accuracy of procalcitonin are higher than those of CRP for bacterial infection in systemic rheumatic diseases. We conclude that procalcitonin is more specific and has better diagnostic accuracy than CRP for differentiating bacterial infection from disease flare in patients with systemic rheumatic diseases.

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