REVIEW ARTICLE

Serum Procalcitonin and C-Reactive Protein Levels as Markers of Bacterial Infection: A Systematic Review and Meta-analysis

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A meta-analysis was performed to evaluate the accuracy of determination of procalcitonin (PCT) and C-reactive protein (CRP) levels for the diagnosis of bacterial infection. The analysis included published studies that evaluated these markers for the diagnosis of bacterial infections in hospitalized patients. PCT level was more sensitive (88% [95% confidence interval {CI}, 80%–93%] vs. 75% [95% CI, 62%–84%]) and more specific (81% [95% CI, 67%–90%] vs. 67% [95% CI, 56%–77%]) than CRP level for differentiating bacterial from noninfective causes of inflammation. The Q value for PCT markers was higher (0.82 vs. 0.73). The sensitivity for differentiating bacterial from viral infections was also higher for PCT markers (92% [95% CI, 86%–95%] vs. 86% [95% CI, 65%–95%]); the specificities were comparable (73% [95% CI, 42%–91%] vs. 70% [95% CI, 19%–96%]). The Q value was higher for PCT markers (0.89 vs. 0.83). PCT markers also had a higher positive likelihood ratio and lower negative likelihood ratio than did CRP markers in both groups. On the basis of this analysis, the diagnostic accuracy of PCT markers was higher than that of CRP markers among patients hospitalized for suspected bacterial infections.

Bacterial infections are a major cause of morbidity and mortality [1–3]. Diagnosis of bacterial infections is sometimes challenging, because clinical presentation of infections from different causative agents can be similar; for example, it may be difficult to differentiate viral from bacterial infections in certain instances [1, 3]. Inflammatory states, such as trauma, pancreatitis, transplant rejection, and vasculitis, might also have a clinical presentation similar to that for an infection. Although untreated bacterial infections may cause serious complications, treating viral illnesses or noninfective causes of inflammation with antibiotics is not only ineffective, but also contributes to the development of resistance [4], increases costs, and adds the risks of toxicity and allergic reactions. Studies undertaken by the World Health Organization indicate that, for every 100 respiratory infections, only 20 require antibiotic treatment [4]. It is estimated that physicians in Canada and the United States overprescribe antibiotics by 50% [4]. The most precise way to diagnose bacterial infections is by culture; tests to confirm viral infections include determination of acute- and convalescent-phase antibody titers and tests for viral antigens. However, there is often a delay until results are known, and rapid immunological or genomic tests require prior knowledge of the infectious agent. The identification of markers for the early recognition of bacterial infections could guide treatments, reduce misuse of antibiotics, and possibly improve long-term outcomes [5].

Among several markers of inflammation and sepsis, procalcitonin (PCT) and C-reactive protein (CRP) markers are being studied to investigate their accuracy for the diagnosis of bacterial infections. PCT is the prehormone of calcitonin, which is normally secreted by the C cells of the thyroid in response to hyper-

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Table 1. Summarized quality assessment of the 12 included studies.

Criterion[a]	Maximum score for each category	Study: Aouifi et al. [117]	Enguix et al. [118]	Hatherill et al. [119]	Lorrot et al. [120]	Muller et al. [121]	Penel et al. [122]	Rothenburger et al. [123]	Schwarz et al. [124]	Selberg et al. [125]	Suprin et al. [126]	Ugarte et al. [127]	Viallon et al. [128]
Study protocol	45	32.3	27.3	34.5	36	34	37.3	25	33.5	28.8	33.5	35.2	38.5
Statistical analysis	48	21.3	25.3	31	24.4	20	15.7	19	17.6	26	20.3	27	28.5
Presentation of results	8	7.3	4	1	6	7	6.7	5.7	7.3	5.3	7.3	6.7	8
Total	101	60.9	56.6	66.5	66.4	61	59.7	49.7	58.4	60.1	61.1	68.9	75

NOTE. Studies were assessed using the criteria of Chalmers et al. [12].

[a] For each category, results are expressed as the average of scores from 3 reviewers.

calcemia; under these normal conditions, negligible serum PCT concentrations are detected [6]. The mechanism proposed for PCT production after inflammation and its role are still not completely known. It is believed that PCT is produced by the liver [7] and peripheral blood mononuclear cells [8], modulated by lipopolysaccharides and sepsis-related cytokines. CRP is an acute-phase reactant, and CRP level measurements are frequently used to aid in the diagnosis of bacterial infections. CRP is synthesized by the liver, mainly in response to IL-6, which is produced not only during infection but also in many types of inflammation [9]. It binds to polysaccharides in pathogens, activating the classical complement pathway. The reported diagnostic accuracy of PCT and CRP for the diagnosis of bacterial infections has varied across studies. To adequately evaluate their accuracy, we systematically reviewed and performed a meta-analysis of studies that simultaneously investigated PCT and CRP levels as markers for bacterial infection.

METHODS

A protocol was written before this study was undertaken, as recommended by the Quality of Reporting of Meta-analyses (QUORUM) statement [10].

Retrieving the literature. All studies published in the MEDLINE database from 1 January 1970 through 30 May 2002 that evaluated serum PCT and/or CRP markers for the diagnosis of bacterial infections were identified. With use of a Boolean strategy, cross-searching of the following 5 categories was done: (1) type of study ("descriptive study" OR "diagnosis" OR "epidemiological study" OR "meta-analysis" OR "multicenter study" OR "prospective" OR "review-literature" OR "reproducibility" OR "test" OR "validation"); (2) site ("critical care" OR "hospital" OR "intensive care"); (3) subjects ("human"); (4) test ("C-reactive protein" OR "interferon" OR "interleukin" OR "procalcitonin" OR "white blood cell count" OR "sedimentation") and (5) disease ("infection" OR "cross infection" OR "hospital acquired infection" OR "meningitis" OR "multiple organ dysfunction syndrome" OR "MODS" OR "pneumonia" OR "sepsis" OR "septicemia" OR "septic shock" OR "systemic inflammatory response syndrome" OR "SIRS"). The bibliographies of relevant articles were further cross-checked to search for articles not referenced in the MEDLINE database.

Selection of studies and data extraction. Studies of patients from all age groups that prospectively and simultaneously evaluated PCT and CRP levels as diagnostic markers for bacterial infection in hospitalized patients were evaluated. Retrospective studies, reviews, animal studies, and studies for which complete data was unavailable were excluded. No limitation was placed on the language of the article. The selection and data extraction was performed by 3 independent reviewers (L.S., F.G., and J.L.), and disagreements, if any, were resolved by consensus. Raw data from the articles were used to construct

Table 2. Summarized quality assessment using the Standards for Reporting of Diagnostic Accuracy checklist of the 12 included studies.

Section[a]	Maximum score for each category	Study: Aouifi et al. [117]	Enguix et al. [118]	Hatherill et al. [119]	Lorrot et al. [120]	Muller et al. [121]	Penel et al. [122]	Rothenburger et al. [123]	Schwarz et al. [124]	Selberg et al. [125]	Suprin et al. [126]	Ugarte et al. [127]	Viallon et al. [128]
Title and introduction	2	2	2	2	2	2	2	2	2	2	2	2	2
Methods	11	9	5	7	7	7	7	6	8	7	7	8	8
Results	11	5	4	5	5	7	6	6	7	6	5	7	5
Discussion	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	25	17	12	15	15	17	16	15	18	16	15	18	16

NOTE. The Standards for Reporting of Diagnostic Accuracy criteria are from [13, 14].

[a] For each section, results are derived from consensus between 3 reviewers as the number of items from the checklist present in the original article.

Table 3. Description of individual studies included in the meta-analysis.

Study	Year	Population/study setting	Control group (no. of control patients vs. no. of patients with bacterial infection)	Type of bacterial infection	Means of diagnosis of infection	Timing of inclusion/ tests	PCT level, ng/mL		CRP level, mg/L	
							Median (range)	Best cutoff value	Median (range)[a]	Best cutoff value
Aouifi et al. [117]	2000	Adults who underwent cardiac surgery/ICU	Patients with SIRS (43 vs. 54)	Pneumonia, bacteremia, mediastinitis, septic shock	Clinical examination; CXR; WBC, blood, ETT, and/or intra-operative mediastinal culture	<48 h after operation or when there is suspicion of infection	No infection, 0.41 (0.08–1.67); all infections, 24.3 (0.25–356)	1	No infection, 111 ± 83;[b] infection, 180	15
Enguix et al. [118][c]	2001	Neonates/NICU	Patients with SIRS (46 vs. 20)	Sepsis	For SIRS and evidence bacterial infection: blood culture, characteristic meningococcal rash, and/or clinical recovery with antibiotic therapy	ICU admission or when infection was suspected	No infection, 0.81 (0.2–5.3); sepsis, 50.3 (5–834)	6.1	No infection, 5.0 (5.0–42.1); sepsis, 77 (32.4–144)	23.1
Hatherill et al. [119][c]	1999	Children/PICU	2 groups: noninfected patients (43) and patients with viral infection (14 vs. 112)	Septic shock, pneumonia, tracheitis, UTI, bacterial meningitis/ encephalitis	For documented infection: bacterial isolation; characteristic meningococcal or staphylococcal rash; CSF, bronchoalveolar, or peritoneal fluid profile consistent with bacterial infection	Admission to the PICU	No infection, 0 (0–4.9); viral infection, 0.8 (0–4.4); localized infection, 2.9 (0–24.3); septic shock, 94.6 (3.3–759.8)	5	No infection, 8 (2–47); viral infection, 12 (7–76); localized infection, 20 (7–213); septic shock, 101 (3–335)	20
Lorrot et al. [120]	2000	Children/hospitalized from ER	Patients with viral infection (274 vs. 162)	Sepsis, meningitis, pneumonia, UTI, otitis, diarrhea	Blood culture, CXR, bacterial culture of sputum, serological test revealing mycoplasma, viral immunofluorescence or culture, PCR for enterovirus, serum antibody titers	Hospitalization for suspected bacterial or viral infection as cause for fever	Viral infection, 0.4 (0–5.2); localized infection, 3.9 (0.1–44); sepsis, 41.3 (0.15–432.6)	1	Viral infection, 18 (4–220); localized infection, 94 (0–400); sepsis, 139 (9–400)	40
Muller et al. [121][c]	2000	Adults/ICU	Patients with SIRS (46 vs. 55)	Pneumonia, UTI, gastrointestinal infection	Clinical examination, CXR; ETT, bronchoalveolar, blood, CSF, stool, and/or urine culture, serum antibody titers	ICU admission with an , anticipated stay of >24 h	No infection, 6.6; bacterial infection, 36.9	1	No infection, 140; bacterial infection, 252	100
Penel et al. [122][c]	2001	Adults with cervicofacial cancer/ oncology service	Patients with paraneoplasic fever (19 vs. 43)	Pneumonia, sepsis, abscess, peritonitis, catheter-related infection	Clinical examination; CXR; blood, catheter, and/or urine culture	Hospital admission	No infection, 0.26 (0.05–1.17); bacterial infection, 0.44 (0.09–57.4)	1	No infection, 154 (26–267); bacterial infection, 131 (20–596)	6

Rothenburger et al. [123][c]	1999	Patients who had undergone cardiac surgery with CPB/ICU	Patients without sings of infection (15 vs. 43)	Systemic infection, wound infection	Clinical examination, CXR, ETT, bronchoalveolar, blood, and/or urine culture	Suspected onset of infection	No infection, 0.46 (0.26–0.77); localized infection, 0.58 (0.24–2.07); systemic infection, 10.86 (3.28–15.13)	4	No infection, 97.5 (74.5–120); localized infection, 165.9 (96.6–181.6); systemic infection, 164.5 (137–223)	18
Schwarz et al. [124][c]	2000	Adults with meningitis/neurology service	Patients with viral meningitis (14 vs. 16)	Meningitis	Clinical examination, CSF or blood culture, identification of bacteria with Gram staining, antigen test, CSF pleocytosis	Hospital admission	Viral meningitis, 0.24 (0.12–0.29); bacterial meningitis, 1.75 (0.16–59.92)	0.5	Viral meningitis, 7 (2–65); bacerial meningitis, 174 (7–400)	8
Selberg et al. [125]	2000	Adults/ICU	Patients with SIRS (11 vs. 22)	Sepsis	Clinical examination; CXR; ETT, catheter, blood, and/or peritoneum fluid culture	<8 h after clinical onset of SIRS or sepsis	No infection, 3.0 (0.7–29.5); severe sepsis, 19.1 (2.8–351.2); spetic shock: 16.8 (0.9–351.2)	3.3	No significant difference (data not shown)	60
Suprin et al. [126][c]	2000	Adults/ICU	Patients with SIRS (24 vs. 77)	Sepsis, pneumonia, catheter-related infection, pyelonephritis, cellulitis	Clinical examination; CXR; ETT, bronchoalveolar, blood, catheter, CSF, stool, and/or urine culture	Within 48 h of hospital admission	No infection, 4.8; infection, 25.2	2	No infection, 71; infection, 159	100
Ugarte et al. [127][c]	1999	Adults/ICU	Patients with SIRS (79 vs. 111)	Sepsis	Clinical examination; CXR; ETT, bronchoalveolar, blood, catheter, CSF, stool, skin, and/or urine culture	At hospital admission and on day infection was suspected	No infection, 0.5 (0.8–8.1); bacterial infection, 2.5 (0.8–32)	0.6	No infection, 56 (24–210); bacterial infection, 12.1 (2.7–26.4)	79
Viallon et al. [128][c]	2000	Adults with cirrhosis/admitted to ER	Patients with non inflammatory sterile ascitic fluid (40 vs. 21)	Spontaneous bacterial peritonitis	Infection of the ascitic fluid in the absence of any intra-abdominal source of infection, with an ascitic fluid neutrophil count of >250 cells/mm^3, and/or positive culture result	At baseline, before initiation of antibiotic therapy	No infection, 0.09 (0.0–0.23); infection, 10.10 (2.6–24)	0.75	No infection, 26 (11.5–57); infection, 92 (43–171)	80

NOTE. CPB, cardiopulmonary bypass; CXR, chest radiograph; ER, emergency department; ETT, endotracheal tube; ICU, intensive care unit; NICU, newborn intensive care unit; PICU, pediatric intensive care unit; SIRS, systemic inflammatory response syndrome; UTI, urinary tract infection.

[a] Unless otherwise indicated.

[b] Mean ± SD.

[c] Data confirmed by original author.

Table 4. Results derived from the 2 × 2 tables of individual studies involving procalcitonin and C-reactive protein levels as markers for bacterial infections versus noninfective causes of inflammation.

	Procalcitonin markers				C-reactive protein markers			
	No. of results		Sensitivity,	Specificity,	No. of results		Sensitivity,	Specificity,
Study	TP/FN	FP/TN	% (95% CI)	% (95% CI)	TP/ FN	FP/TN	% (95% CI)	% (95% CI)
Aouifi et al. [117]	46/2	8/41	96 (85–99)	84 (70–92)	50/33	4/10	60 (49–71)	71 (42–90)
Enguix et al. [118][a]	19/3	1/23	86 (64–96)	96 (77–100)	19/4	1/22	83 (61–94)	96 (76–100)
Hatherill et al. [119][a]	103/3	9/40	97 (91–99)	82 (68–91)	73/0	37/43	100 (95–100)	54 (42–65)
Muller [121][a]	52/3	6/40	95 (84–99)	87 (73–95)	41/9	17/34	82 (68–91)	67 (52–79)
Penel et al. [122][a]	43/14	0/5	75 (62–85)	100 (48–100)	43/24	0/1	64 (52–75)	100 (3–100)
Rothenburger et al. [123][a]	12/2	3/42	86 (56–97)	93 (81–98)	14/30	1/14	32 (19–48)	93 (66–100)
Selberg et al. [125]	19/5	3/6	79 (57–92)	67 (31–91)	19/9	3/2	68 (48–83)	40 (7–83)
Suprin et al. [126][a]	49/6	26/14	89 (77–95)	35 (21–52)	55/5	19/14	92 (81–97)	42 (26–61)
Ugarte et al. [127][a]	75/31	36/48	71 (61–79)	57 (46–68)	80/26	3/53	75 (66–83)	63 (52–73)
Viallon et al. [128][a]	19/2	2/38	90 (68–98)	95 (82–99)	13/3	8/37	81 (54–95)	82 (67–91)
Total[b]	…	…	88 (80–93)	81 (67–90)	…	…	75 (62–84)	67 (56–77)

NOTE. FN, false negative; FP, false positive; TN, true negative, TP, true positive.

[a] Data confirmed by original author.

[b] Pooled data from a random effects model.

2 × 2 tables; when unavailable, the tables were constructed using given measures of sensitivity and specificity. Some studies reported the sensitivity and specificity at many cutoff points; we then chose the cutoff point with the best efficiency value [11], which was estimated by dividing the sum of true-positive and true-negative cases by the total number of cases. Authors of individual articles were contacted to verify data extracted from the original article and to provide supplementary information pertaining to the criteria used for diagnosing infection. They were also asked to review the list of references collected from the MEDLINE database and the manual search and to report known studies that were not on the list.

Quality assessment. We evaluated the methodological quality of the included studies by applying the criteria for assessing design-related bias in randomized clinical trials described by Chalmers et al. [12] (table 1). Four aspects of each study were evaluated: (1) the basic descriptive material, (2) the study protocol, (3) the statistical analysis, and (4) the presentation of results. The latter 3 aspects were graded for 27 items in total, with a score awarded to each item under each aspect. Subsequently, an overall quality index for each study was obtained by adding the item scores and normalizing by the total possible score. The 25-item criteria developed by the Standards for Reporting of Diagnostic Accuracy (STARD) committee [13, 14] was also applied. A consensus was obtained among the reviewers for both criteria (tables 1 and 2), and the rate of agreement was calculated.

Meta-analysis. The meta-analysis approach of Moses and Shapiro [15], using linear regression to combine data from independent studies evaluating similar test/criteria, was used. To create the summary receiver operating characteristic (SROC) curve, we first calculated the true-positive rate (TPR) and false-positive rate (FPR) from each individual study from the reconstructed 2 × 2 tables. These rates were then converted to their logarithmic transform: log [TPR/1 − TPR] and log [FPR/1 − FPR].

The sum and the difference of these logarithmic transforms were calculated for each study, as well as a regression line fitted to these points, with difference as the dependent variable and sum as the independent variable (difference = a + b.sum). The values of sensitivity and specificity required to construct the SROC curve were calculated as sensitivity = $1/[(1 + 1/e^{a/(1-b)})(1 - \text{specificity}/\text{specificity})^{(1+b)/(1-b)}]$.

The resulting values were plotted in the SROC space to obtain the SROC curve. The difference in sample size among the studies was taken into account by weighing each observation by the reciprocal of the variance of difference and performing weighted regression. To further compare the accuracy between PCT and CRP markers, the Q values from the SROC curves were calculated; this value represents the intersection point of the SROC curve with a diagonal line of the ROC space at which sensitivity equals specificity. A higher Q value indicates higher accuracy. All analyses were performed using Stata software, version 7 (StataCorp) [16], and the Meta-test programs [17].

Positive and negative likelihood ratios (LRs) were calculated for both tests in each group: PositiveLR = sensitivity/(1 − specificity) and NegativeLR = (1-sensitivity)/specificity. The LRs are a semiquantitative measure of the performance of diagnostic tests, expressing the magnitude by which the probability of a diagnosis in a given patient is modified by the result of a test [18]. A test with a higher positive LR and lower negative LR is considered a better test.

Table 5. Results derived from the 2 × 2 tables of individual studies involving procalcitonin and C-reactive protein levels as markers for bacterial infections versus viral infections.

Study	Procalcitonin markers				C-reactive protein markers			
	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)
	TP/FN	FP/TN			TP/FN	FP/TN		
Hatherill et al. [119][a]	103/6	9/8	94 (88–98)	47 (24–71)	73/2	36/12	97 (90–100)	25 (14–40)
Lorrot et al. [120]	126/16	36/258	89 (82–93)	88 (83–91)	122/30	40/244	80 (73–86)	86 (81–90)
Schwarz et al. [124][a]	11/0	5/14	100 (72–100)	74 (49–90)	14/6	1/8	70 (46–87)	89 (51–99)
Total[b]	…	…	92 (86–95)	73 (42–91)	…	…	86 (65–95)	70 (19–96)

NOTE. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a] Data confirmed by original author.

[b] Pooled data from a random effects model.

RESULTS

From the search of the MEDLINE database, 351 publications were retrieved. Of these, 110 studies that suggested that PCT and/or CRP levels were determined in hospitalized patients with bacterial infection were retained [19–128]. Twenty-one articles [108–128] that prospectively and simultaneously evaluated PCT and CRP values were identified. Another article [129] was found while searching the bibliographies. Detailed review of these 22 articles indicated that 12 were deemed appropriate for the meta-analysis [117–128]. Four [111, 113–115] of the 22 studies were excluded because study design was not geared towards the evaluation of PCT and CRP levels as markers of infection; other outcomes (prognosis, mortality, or kinetics) were evaluated. Six studies were excluded because data extraction was unclear [116, 129], the study population was an extension of another published study [108, 109, 112], or no control group was evaluated [110].

A description of studies included in the meta-analysis is shown in table 3, and results derived from their 2 × 2 tables are presented in tables 4 and 5. Sixty-seven percent of original authors responded to the request. Studies included 46 neonates, 638 children, and 702 adults in different areas of the hospital; approximately one-half of the subjects were in intensive care units.

The methodological evaluation of study quality using the criteria of Chalmers et al. [12] is presented in table 1. The average quality index for all studies was 62 of a possible score of 101. Of the 324 items rated, complete agreement between reviewers' scores was observed for 280 (86.4%) of the 324 items rated, and complete disagreement was observed for 3 (<1%). Approximately one-half of the studies included consecutive patients. Test definition, description, and value were adequately described in most of the studies. The accuracy of the tests was calculated in all studies, largely by constructing a ROC curve.

The quality evaluation using the STARD checklist is presented in table 2 as the number of items present from the checklist. A total of 300 items were tabulated (25 items for each of 12 studies); complete agreement between reviewers was observed for 189 (63%) of the 300 items. All articles were identified as studies of diagnostic accuracy, stated the research question in the introduction, and included some specification of materials and methods involved, definition and cutoffs of the index tests, and the reference standards. Most, but not all, characterized well the study population, participant recruitment, dates, and the reference standard used. No study reported the expertise of the person reading the tests, the measures of statistical uncertainty, and the estimates of test reproducibility. One study reported participants that satisfied inclusion criteria and were later excluded.

PCT levels were invariably measured using the commercially

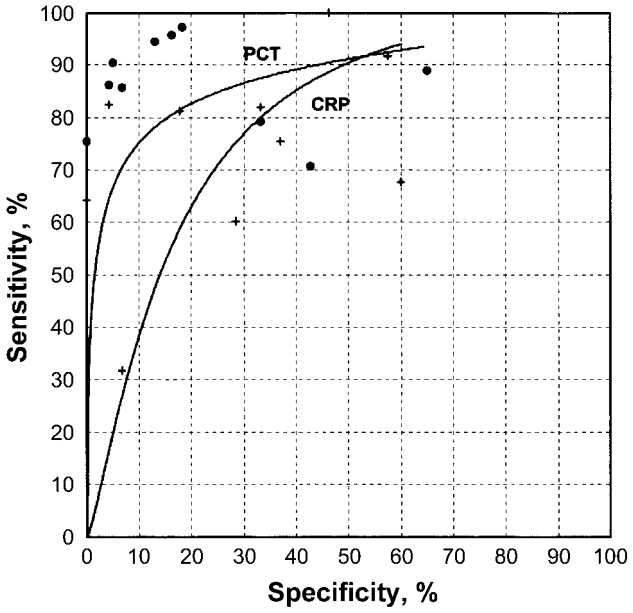

Figure 1. Summary receiver operating characteristic (SROC) curves comparing serum procalcitonin (PCT; ●) and C-reactive protein (CRP; +) markers for detection of bacterial infections versus noninfective causes of inflammation. Each point contributing to the SROC curve represents 1 study.

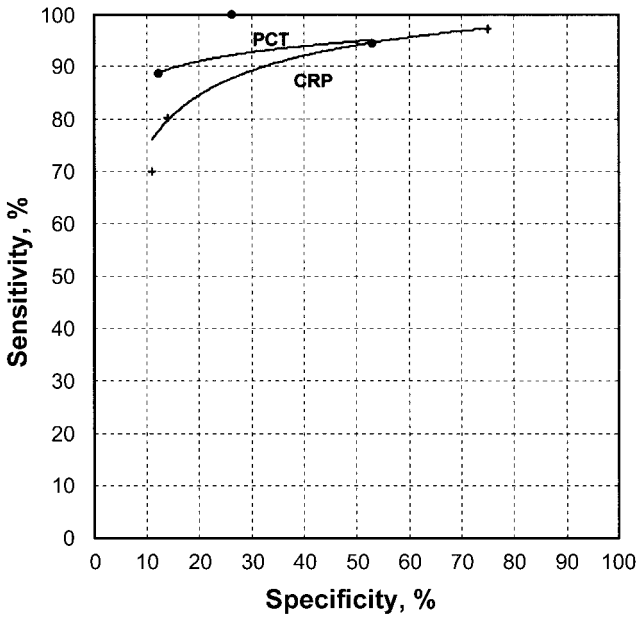

Figure 2. Summary receiver operating characteristic (SROC) curves comparing serum procalcitonin (PCT; ●) and C-reactive protein (CRP; +) markers for bacterial infections versus viral infections. Each point contributing to the SROC curve represents 1 study.

available immuno-luminometric assay (LUMItest PCT; distributed by BRAHMS Diagnostica GmbH), which has a reported detection limit of 0.08 ng/mL [130] and interassay precision of 6%–10% [117]. CRP concentrations were determined using different techniques and assays.

The SROC curves for PCT and CRP values are plotted over the domain of TPR and FPR in figure 1 for the 10 studies (905 patients) that evaluated these tests markers for bacterial infections, compared with noninfective causes of inflammation, providing evidence of the individual contribution of each study to the regression analysis. PCT markers have significantly higher accuracy than do CRP markers for discriminating bacterial infections from noninfective causes of inflammation. Pooled sensitivity for PCT markers was 88% (95% CI, 80%–93%), compared with 75% (95% CI, 62%–84%) for CRP markers. There was a statistically significant difference between the sensitivities (13%; 95% CI, 8%–17%; $P < .05$). Pooled specificity for PCT markers was also higher than for CRP markers (81% [95% CI, 67%–90%] vs. 67% [95% CI, 56%–77%]), and this difference was statistically significant (14%; 95%, CI 8%–20%; $P < .05$). This was confirmed by calculation of the Q value, which was higher for PCT markers (Q = 0.82; 95% CI, 64%–99%) than that for CRP markers (Q = 0.73; 95% CI, 64%–82%). The likelihood ratios were better for PCT markers (positive LR, 3.58; [95% CI, 2.99–4.28]; negative LR, 0.18 [95% CI, 0.15–0.23]) than for CRP markers (positive LR, 2.43 [95% CI, 2.03–2.92]; negative LR, 0.42 [95% CI, 0.36–0.49]).

In figure 2, the SROC curves for PCT and CRP markers are plotted over the domain of TPR and FPR for the 3 studies (592 patients) that evaluated these diagnostic markers for bacterial infections versus viral infections. PCT markers were also significantly better than CRP markers at differentiating bacterial infections from viral infections. Pooled sensitivity for PCT markers was 92% (95% CI, 86%–95%), compared with 86% (95% CI, 65%–95%) for CRP markers, and the difference was statistically significant (6%; 95% CI, 5%–11%; $P < .05$). However, pooled specificities were comparable (73% [95% CI, 42%–91%] vs. 70% [95% CI, 19%–96%] for PCT vs. CRP markers, respectively; difference, 3% [95% CI, −4% to 10%]; $P > .05$). The Q value calculated was higher for PCT markers (Q = 0.89; 95% CI, 0.82–0.96) than for CRP markers (Q = 0.83; 95% CI, 0.81–0.85), suggesting that, in terms of overall accuracy, PCT markers are better than CRP markers for differentiating between bacterial and viral infections. The LRs were better for PCT markers (positive LR, 6.05 [95% CI, 4.67–7.82]; negative LR, 0.10 [95% CI, 0.06–0.15]) than for CRP markers (positive LR, 3.75 [95% CI, 3.06–4.59]; negative LR, 0.20 [95% CI, 0.15–0.27]).

DISCUSSION

Early identification of infections is still a challenge for clinicians. The general consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a marker specific for bacterial infection will be most helpful. Based on this meta-analysis, we observed that PCT levels were more accurate markers for bacterial infection than were CRP levels, both when differentiating bacterial infections from noninfective causes of inflammation and when differentiating bacterial infections from viral infections.

The kinetics of a prospective marker should be considered along with its sensitivity and specificity. PCT secretion begins within 4 h after stimulation and peaks at 8 h [7, 131, 132], clearing when the insult is under control [133]. PCT is stable in samples, the assay is relatively easy to perform, with a moderate cost (~$10), and the result is available within 2 h [118]. CRP secretion starts within 4–6 h after stimulation, peaking only after 36 h. The assay for determing CRP levels is easy to perform, often automated, and has a low cost (~$5) [118].

As would be expected, none of the studies included in this review were completely free from all potential biases and limitations. Study population and patient selection were not fully reported; however, there was minimal withdrawal from the studies, minimizing selection bias. Few studies reported information on blinding and test reproducibility, which could potentially have altered the trustworthiness of the data. Results are susceptible to spectrum bias, because diagnostic tests may have different accuracies in distinctive phases of the disease [134, 135]. Classification bias in the original studies was pos-

sible, because even in the face of positive culture results, there is not always enough evidence to discriminate between infection and colonization.

PCT measurements were performed using the same commercially available specific antibody system. However, means of measuring CRP levels largely varied, with 8 different methods used among the 12 included studies. The implications of multiple assay methods are unknown in the final result of this meta-analysis. However, each study was included using its own best cutoff value, and the linear regression methods used in the analysis accounted for possible threshold differences between studies.

When performing a literature review, one must always consider some degree of publication bias; studies have a higher likelihood of being published when they show encouraging results [136]. Such a selective publication policy could lead to an inflation of the associations that were found; there is no method to control for this bias. The limited number of studies precluded the statistical control for differences in study populations, designs, etc., in the analysis.

After candidly mentioning possible limitations, we must underline the strengths of this study. Giving more credibility to the results is the fact that all decisions and data collections involved the consensus of 3 independent reviewers, among whom there was a high agreement rate; authors of individual papers were contacted to confirm or correct the information from the original articles, with notably high response rates.

There was no verification bias in the studies included in this meta-analysis, because PCT level determinations, CRP level determinations, and tests to diagnose infection were performed simultaneously, and patients were allocated to the infected or noninfected group without prior knowledge of PCT and CRP data.

In the meta-analysis technique, pooling of results across studies or averaging sensitivity and specificity causes underestimation of test performance, because the relationship between sensitivity and specificity is not linear. However, the underestimation is no more than 2% for each parameter [137]. The ROC curve method used in this meta-analysis, rather than a single point, is the best summary of the results when diagnostic threshold varies among the studies [138]. We selected a random effects model that assumes that the included studies belong to a random sample of a universe of studies. A large spectrum of the population was covered in the meta-analysis, allowing generalization of the results. All age groups were included in this study, because kinetics of PCT follow similar pattern in children and adults, with some evidence that PCT levels vary in a similar way during the first 48 h of life [118, 139, 140].

This meta-analysis provides a thorough comparison between PCT and CRP markers; we can conclude that the overall accuracy of PCT markers is higher than that of CRP markers both to differentiate bacterial infections from viral infections and to differentiate bacterial infections from other noninfective causes of systemic inflammation. In trying to apply these findings to the clinical practice, we calculated LRs. PCT markers were particularly good for differentiating bacterial infections from viral infections, which is probably the most frequent dilemma encountered in clinical practice. Although the cost of performing an assay for determination of PCT levels is double that for determination of CRP levels, the differences in accuracies and LRs seem to be sufficiently great for PCT markers to be considered for widespread use in clinical practice. The application of assays for PCT could guide treatment and reduce unnecessary antibiotic use. The next step is to evaluate the true impact of use of PCT markers on outcomes with prospective studies.

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ERRATUM

In an article in the 15 July 2004 issue of the journal (Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 2004; 39:206–17), several errors were made in the data presented, requiring corrections to the text, the abstract, tables 4 and 5, and figures 1 and 2.

The data in the sixth and seventh paragraphs of the Results section require a number of corrections and adjustments. In the sixth paragraph, the estimations of sensitivity and specificity for bacterial infections compared with noninfective causes of inflammation require the following corrections. Pooled sensitivity for procalcitonin (PCT) was 85% (95% CI, 0.76–0.91), compared with 78% (95% CI, 0.70–0.85) for C-reactive protein (CRP); there was a statistically significant difference between the sensitivities: 7% (95% CI, 0.23–0.11; $P < .05$). Pooled specificity for PCT was also higher than for CRP: 83% (95% CI, 0.68–0.92) versus 60% (95% CI, 0.38–0.79), respectively, and this difference was statistically significant: 23% (95% CI, 0.18–0.28; $P < .05$). This was confirmed on calculation of the Q value, which was higher for PCT (Q = 0.82; 95% CI, 0.64–0.95) than that for CRP (Q = 0.75; 95% CI, 0.68–0.82).

In the seventh paragraph of Results, the data for evaluation of these markers for bacterial infections versus viral infections requires the following corrections. Pooled sensitivity for PCT was 82% (95% CI, 0.65–0.92), compared with 73% (95% CI, 0.62–0.82) for CRP, and the difference is statistically significant: 9% (95% CI, 0.02–0.16; $P < .05$). Pooled specificities were also higher for PCT than for CRP: 88% (95% CI, 0.50–0.98) versus 81% (95% CI, 0.55–0.93), respectively, with a difference of 7% (95% CI, −0.01 to 0.13; $P > .05$). The Q value calculated from the curves was slightly higher for PCT (Q = 0.85; 95% CI, 0.83–0.87) than for CRP (Q = 0.82; 95% CI, 0.74–0.90), suggesting that, in terms of overall accuracy, PCT is somewhat better than CRP in differentiating between bacterial and viral infections.

In addition, corrections similar to those made in the text are required in the abstract. The corrected abstract should read as follows:

> A meta-analysis was performed to evaluate the accuracy of determination of procalcitonin (PCT) and C-reactive protein (CRP) levels for the diagnosis of bacterial infection. The analysis included published studies that evaluated these markers for the diagnosis of bacterial infections in hospitalized patients. PCT level was more sensitive (85% [95% confidence interval {CI}, 0.76–0.91] vs. 78% [95% CI, 0.70–0.85]) and more specific than CRP level (83% [95% CI, 0.68–0.92] vs. 60% [95% CI, 0.38–0.79]) for differentiating bacterial from noninfective causes of inflammation. The Q value for PCT markers was higher (0.82 vs 0.75). The sensitivity for differentiating bacterial from viral infections was also higher for PCT markers (82% [95% CI, 0.65–0.92] vs. 73% [95% CI, 0.62–0.82]), as was the specificity (88% [95% CI, 0.50–0.98] vs. 81% [95% CI, 0.55–0.93]). The Q value was higher for PCT markers (0.85 vs. 0.82). PCT markers also had a higher positive likelihood ratio and lower negative likelihood ratio than did CRP markers in both groups. On the basis of this analysis, the diagnostic accuracy of PCT markers was higher than that of CRP markers among patients hospitalized for suspected bacterial infections.

In tables 4 and 5, the false positive (FP) and the false negative (FN) values were inadvertently interchanged. The resultant changes in the estimation of the sensitivities and specificities (along with their 95% CIs) are presented here in corrected tables (tables 4 and 5, below, on page 1387).

As a result of these changes, figures 1 and 2 need to be slightly modified, as well. The corrected figures are presented here (figures 1 and 2, below, on page 1388).

These corrections do not alter the interpretation or the conclusions of the meta-analysis. The authors sincerely apologize for these errors.

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Table 4. Results derived from the 2 × 2 tables of individual studies involving procalcitonin and C-reactive protein levels as markers for bacterial infections versus noninfective causes of inflammation.

Study	Procalcitonin markers				C-reactive protein markers			
	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)
	TP/FN	FP/TN			TP/FN	FP/TN		
Aouifi [117]	46/8	2/41	85 (0.72–0.93)	95 (0.83–0.99)	50/4	33/10	93 (0.81–0.98)	23 (0.12–0.39)
Enguix [118][a]	19/1	3/23	95 (0.73–1.00)	88 (0.69–0.97)	19/1	4/22	95 (0.73–1.00)	85 (0.64–0.95)
Hatherill [119][a]	103/9	3/40	92 (0.85–0.96)	93 (0.80–0.98)	73/37	0/43	66 (0.57–0.75)	100 (0.92–1.00)
Muller [121][a]	52/6	3/40	90 (0.78–0.96)	93 (0.80–0.98)	41/17	9/34	71 (0.57–0.82)	79 (0.64–0.89)
Penel [122][a]	43/0	14/5	100 (0.92–1.00)	26 (0.10–0.51)	43/0	24/1	100 (0.92–1.00)	4 (0.00–0.22)
Rothenburger [123][a]	12/3	2/42	80 (0.52–0.95)	95 (0.83–0.99)	14/1	30/14	93 (0.66–1.00)	32 (0.19–0.48)
Selberg [125]	19/3	5/6	86 (0.64–0.96)	55 (0.25–0.82)	19/3	9/2	86 (0.64–0.96)	18 (0.03–0.52)
Suprin [126][a]	49/26	6/14	65 (0.53–0.76)	70 (0.46–0.87)	55/19	5/14	74 (0.63–0.83)	74 (0.49–0.90)
Ugarte [127][a]	75/36	31/48	68 (0.58–0.76)	61 (0.49–0.71)	80/31	26/53	72 (0.63–0.80)	67 (0.56–0.77)
Viallon [128][a]	19/2	2/38	90 (0.68–0.98)	95 (0.82–0.99)	13/8	3/37	62 (0.39–0.81)	93 (0.79–0.98)
Total	…	…	85 (0.76–0.91)	83 (0.68–0.92)	…	…	78 (0.70–0.85)	60 (0.38–0.79)

NOTE. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a] Data confirmed by original author.

[b] Pooled data from a random effects model.

Table 5. Results derived from the 2 × 2 tables of individual studies involving procalcitonin and C-reactive protein levels as markers for bacterial infections versus viral infections.

Study	Procalcitonin				C-reactive protein			
	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)	No. of results		Sensitivity, % (95% CI)	Specificity, % (95% CI)
	TP/FN	FP/TN			TP/FN	FP/TN		
Hatherill [119][a]	103/9	6/8	92 (0.85–0.96)	57 (0.30–0.81)	73/36	2/12	67 (0.57–0.75)	86 (0.56–0.97)
Lorrot [120]	126/36	16/258	78 (0.70–0.84)	94 (0.91–0.97)	122/40	30/244	75 (0.68–0.82)	89 (0.85–0.92)
Schwarz [124][a]	11/5	0/14	69 (0.42–0.88)	100 (0.77–1.00)	14/1	6/8	93 (0.66–1.00)	57 (0.30–0.81)
Total[b]	…	…	82 (0.65–0.92)	88 (0.50–0.98)	…	…	73 (0.62–0.82)	81 (0.55–0.93)

NOTE. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

[a] Data confirmed by original author.

[b] Pooled data from a random effects model.

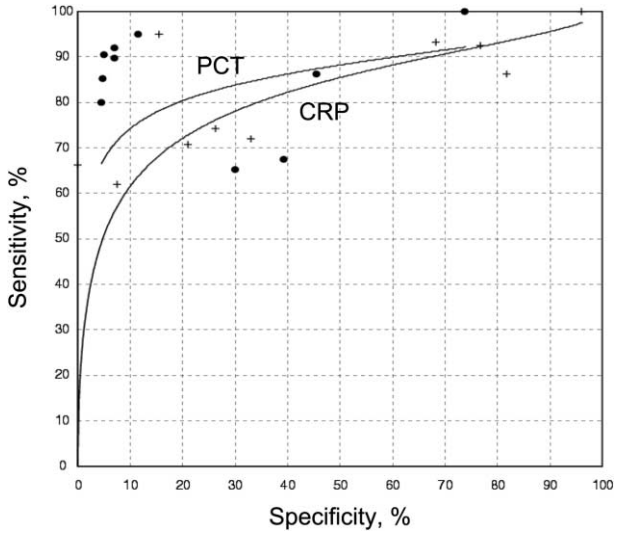

Figure 1. Summary receiver operating characteristic (SROC) curves comparing serum procalcitonin (PCT; ●) and C-reactive protein (CRP; +) markers for detection of bacterial infections versus noninfective causes of inflammation. Each point contributing to the SROC curve represents 1 study.

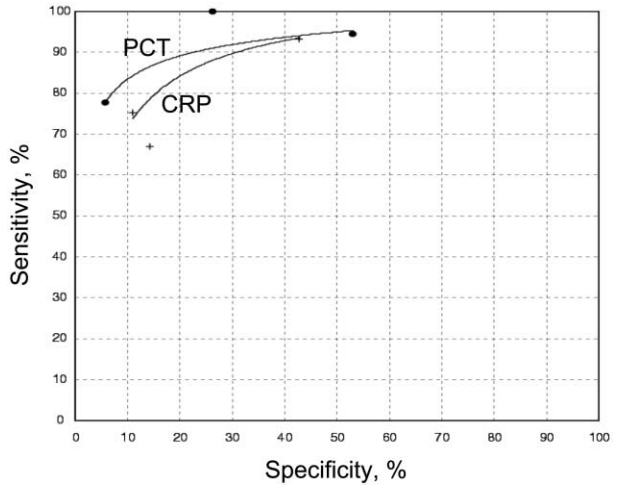

Figure 2. Summary receiver operating characteristic (SROC) curves comparing serum procalcitonin (PCT; ●) and C-reactive protein (CRP; +) markers for detection of bacterial infections versus viral infection. Each point contributing to the SROC curve represents 1 study.