Accuracy of Biomarkers for the Diagnosis of Adult Community-acquired Pneumonia: A Meta-analysis

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ABSTRACT

Background: Biomarkers such as C-reactive protein (CRP) and procalcitonin may help distinguish community-acquired pneumonia (CAP) from other causes of lower respiratory tract infection.

Methods: We performed a systematic review of the literature to identify prospective studies evaluating the accuracy of a biomarker in patients with acute cough or suspected CAP. We performed parallel abstraction of data regarding study inclusion, characteristics, quality, and test accuracy. Study quality was evaluated using QUADAS-2. Bivariate meta-analysis was performed using the mada package in R, and summary receiver operating characteristic (ROC) curves were created.

Results: Fourteen studies met our inclusion and exclusion criteria; three were at low risk of bias and four at moderate risk of bias, largely due to failure to prespecify diagnostic thresholds. Considering all studies regardless of the cutoff used, CRP was most accurate (area under the ROC curve = 0.802), followed by leukocytosis (0.777) and procalcitonin (0.771). Lipopolysaccharide-binding protein and fibrinogen are promising, but were only studied in a single report. For CRP and procalcitonin, the positive and negative likelihood ratios (LR+ and LR–, respectively) varied inversely based on the cutoff. For CRP, LR+ and LR– were 2.08 and 0.32 for a cutoff of 20 mg/L, 3.64 and 0.36 for a cutoff of 50 mg/L, and 5.89 and 0.47 for a cutoff of 100 mg/L. For procalcitonin, LR+ and LR– were 2.50 and 0.39 for a cutoff of 0.10 μg/L, 5.43 and 0.62 for a cutoff of 0.25 μg/L, and 8.25 and 0.76 for a cutoff of 0.50 μg/L. The combination of CRP >49.5 mg/L and procalcitonin >0.1 μg/L had LR+ of 2.24 and LR– of 0.44.

Conclusions: The best evidence supports CRP as the preferred biomarker for diagnosis of outpatient CAP given its accuracy, low cost, and point-of-care availability.

Community-acquired pneumonia (CAP) is a significant source of morbidity and mortality in adults, with an annual incidence of nine to 30 per 1,000 persons per year[1] and leading to nearly 50,000 deaths in the United States alone in 2017.[2] Accurate diagnosis can potentially lead to earlier initiation of treatment for patients with CAP, while avoiding unnecessary antibiotics for patients with a nonpneumonia lower respiratory tract infection (LRTI). Individual signs and symptoms have limited accuracy in the diagnosis of

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CAP.[3] However, a recent meta-analysis of nine studies (six in the ED, three in primary care) found good accuracy of the overall clinical impression of physicians in patients with acute lower respiratory symptoms or suspected CAP found a positive likelihood ratio (LR+) of 7.7 and a negative likelihood ratio (LR–) of 0.54.[4]

The diagnosis is usually based on an abnormal chest radiograph (or increasingly lung ultrasound) in a patient with signs and symptoms of LRTI such as cough, fever, chest pain, sputum production, chills, sweats, and abnormal lung sounds.[5] There are limited data regarding the accuracy of chest radiograph compared to a reference standard of chest computed tomography (CT), one study found sensitivity of 83% in a group of 280 patients with CAP confirmed by chest CT[6] and another found a sensitivity of 90% in a group of 718 patients receiving both chest CT and chest X-ray (CXR).[7] These studies were not able to calculate specificity.

Biomarkers potentially associated with an increased likelihood of CAP include the white blood cell count, C-reactive protein (CRP), and procalcitonin. Two previous studies have included the inflammatory biomarker CRP in clinical prediction rules (CPRs) for the diagnosis of CAP.[8,9] Procalcitonin is another inflammatory biomarker and is associated with an increased likelihood of bacterial pneumonia.[10] Recently, the National Institute for Health and Care Excellence (NICE) endorsed the use of CRP at the point of care to diagnose CAP and reduce inappropriate antibiotic use.[11] These biomarkers are readily available in the emergency department (ED) setting in the United States, as well as in the primary care setting in other countries in Europe. Their cost is only $5.75 for CRP and $29.77 for procalcitonin based on the Center for Medicare and Medicaid Services Clinical Laboratory Fee Schedule (https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Clinical-Laboratory-Fee-Schedule-Files-Items/19CLABQ1.html). Previous systematic reviews have been limited by year of publication,[12,13] using qualitative rather than quantitative synthesis,[14] and including only a single biomarker.[12] In this study, we perform an updated systematic review and meta-analysis of the accuracy of biomarkers for the diagnosis of CAP.

METHODS

Our meta-analysis adhered to the PRISMA guidance for reporting of a meta-analysis; the checklist is provided in Data Supplement S1, Appendix S1 (available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13889/full). The PROPERO systematic review registration number is CRD42018108036.

Inclusion Criteria

The following inclusion criteria were used: original data collection in patients presenting with symptoms of acute respiratory infection as well as patients with clinically suspected pneumonia based on physician order of a CXR and reporting sufficient information to calculate sensitivity and specificity for the diagnosis of CAP for at least one biomarker. Data collection could be prospective or retrospective, but studies had to obtain the biomarker and reference standard on all patients. Studies were limited to adults identified in the inpatient or outpatient setting, with no limit by country, year, or language. The reference standard had to be imaging (radiography or CT) performed in all participants.

Studies were excluded if they enrolled patients because they had dyspnea or sepsis rather than suspected CAP. They were also excluded if patients were in a specialized population such as only patients with chronic lung disease, patients in skilled nursing facilities, or patients who were immunosuppressed or had HIV disease. We did include studies limited to older adults. Studies of ventilator-associated or hospital-acquired pneumonia, studies of the diagnosis of a specific pathogen (i.e., mycoplasma or legionella), and studies that did not use a cohort design (i.e., recruited patients with known CAP and healthy controls) were also excluded.

Search Strategy

This report is the first of three planned systematic reviews (biomarkers to diagnose CAP, biomarkers for prognosis in CAP, and signs and symptoms to diagnose CAP) that used a single search strategy. The search of PubMed was built around the concepts of "signs, symptoms, and biomarkers"; "community-acquired pneumonia"; and "accuracy or prognosis" linked by Boolean AND joins and is shown in Data Supplement S1, Appendix S2. The limits "has abstract," "human," and adult age ranges were applied to the search. In addition, the reference lists of included studies were reviewed for additional articles, as were several older systematic reviews identified by

our search.[3,12–15] Only published, peer-reviewed studies were included.

Data Abstraction

All abstracts were reviewed for inclusion in parallel, with the lead author comprising one reviewer and the four other authors acting as the second reviewer. Any abstract potentially of interest was reviewed in full by two reviewers. Studies meeting inclusion criteria that were included in systematic review were again reviewed in parallel as described above to abstract study characteristics, study quality, and accuracy data. Discrepancies were resolved through consensus discussion.

Quality Assessment

The QUADAS-2 tool was adapted for our study and definitions for low, unclear, and high risk of bias prespecified for each domain.[16] The full tool is shown in Data Supplement S1, Appendix S3.

Analytic Strategy

Similar cutoffs were combined where clinically reasonable, i.e., white blood cell count cutoffs of >9.5, 10, and 10.5 were combined into a single cutoff of ">9.5-10.5." Data were imported into R (version 3.5.2) using the R Studio framework (version 1.1.463). We performed bivariate meta-analysis where there were two or more studies of a test using the same or similar cutoff to define a positive test, using the mada package (version 0.5.8) to calculate receiver operating characteristic (ROC) curves and measures of accuracy with 95% confidence intervals (CIs).[17] Where only a single study described the accuracy of a test and cutoff, we used the diagti procedure[18] in Stata version 15.1 (StatCorp) to calculate measures of accuracy with 95% CIs. For ROC curves, the 95% CI was calculated using the midas procedure in Stata.

A threshold effect occurs when sensitivity decreases and specificity increases as the diagnostic threshold or cutoff increases.[19] When a threshold effect occurs, it is generally inappropriate to calculate or report a single summary estimate of sensitivity, specificity, or LRs. Therefore, when we observed a threshold effect based on inspection of the summary ROC curve, we instead presented the ROC curve and calculated separate summary estimates of diagnostic accuracy parameters for each cutoff. Where appropriate, the area under the ROC curve is reported, and summary estimates of diagnostic accuracy are accompanied by 95% CIs, which were used to assess heterogeneity. In addition, visual inspection of summary ROC curves was used to determine the presence of threshold effects and heterogeneity.

RESULTS

The results of our search are summarized in the PRISMA diagram in Figure 1.[20] Our initial combined search for the three planned meta-analyses was performed in August 2018 and identified 792 abstracts. This review identified a total of 139 studies to be reviewed in full, of which 10 met our inclusion criteria.[9,15,21–28] We identified eight additional potentially relevant studies from the reference lists of included studies and previous meta-analyses, of which four met our inclusion criteria.[29–32] A bridge search performed in July 2019 identified 29 articles, of which one was reviewed in full and did not meet inclusion criteria. The total number of included studies is therefore 14, with a total of 6,599 patients.

The characteristics of included studies are summarized in Table 1. One study was set in the United States, one in Chile, and the remainder in Europe. The oldest study was published in 1986, and the most recent in 2016. Half of the studies identified patients in the ED, and the other half patients in a primary care setting. CRP was studied in 13 studies, leukocytosis in seven studies, and procalcitonin in five studies. The accuracy of the combination of CRP and procalcitonin was evaluated in a single study.[25] Nine studies recruited a broad range of patients with lower respiratory symptoms, while five only included patients if the clinician suspected CAP and ordered a CXR.

Of the 14 included studies, eight were judged to be at low risk of bias and six at moderate risk of bias (at least one of four QUADAS-2 domains at high risk of bias). Overall study quality is summarized in Table 2, with detailed results in Data Supplement S1, Appendix S2. The most common limitation was a failure to clearly prespecify diagnostic cutoffs for an abnormal test and instead specify them post hoc or not describe when cutoffs were set. Blinding of the person performing the index test to the reference standard and vice versa were often unclear, but are unlikely to affect accuracy given the nature of the index tests as objective biomarkers. The person interpreting the reference standard test was clearly described as masked to the index test result in eight studies, uncertain masking in five studies, and not masked in one study. Spectrum bias was unlikely as we excluded

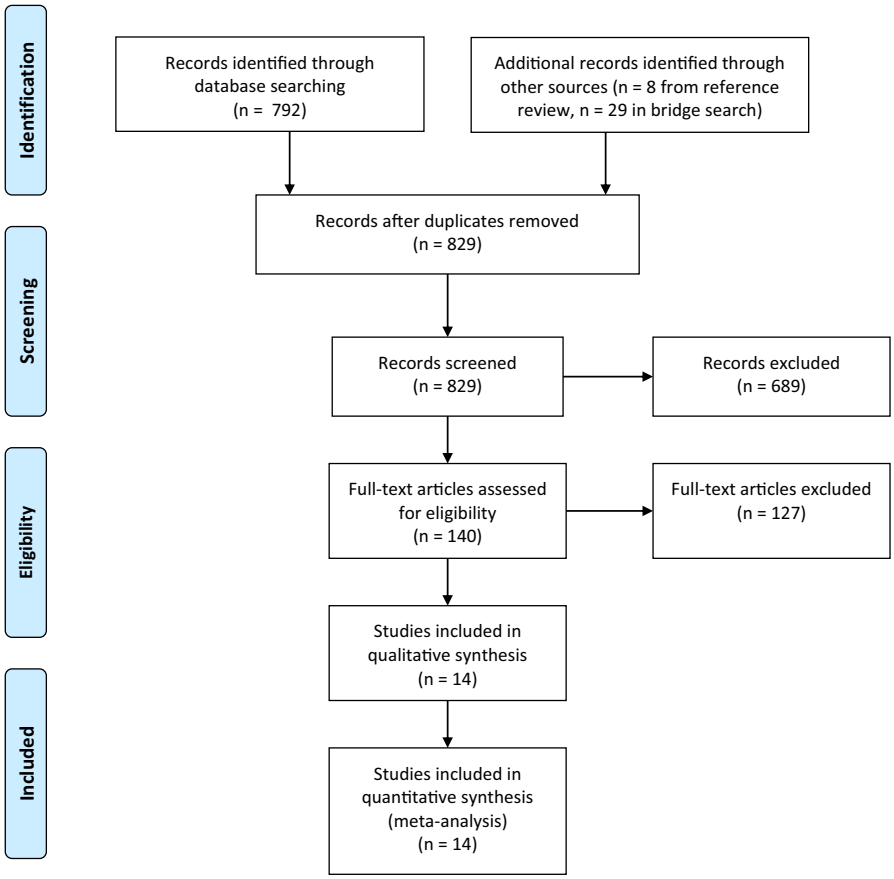

Figure 1 Diagram showing identification of studies for the systematic review. From Moher et al.[20]

diagnostic case–control studies, and in 13 of 14 studies all patients received the same reference standard test. Most studies were funded by a university, institution, or foundation ($n = 6$) or the federal government ($n = 5$) or were unfunded ($n = 1$). Two studies did not report a funding source but did not appear to have been industry funded. Thus, we feel that bias due to industry support is unlikely.

Summary ROC curves for CRP, procalcitonin, and leukocytosis are shown in Figures 2A–2C. In each case a threshold effect is present, with sensitivity increasing as specificity decreases. Therefore, summary estimates of accuracy are not shown in the plot. The area under the ROC curve is 0.80 for CRP (95% CI = 0.78 to 0.85), 0.78 (95% CI = 0.74 to 0.81) for leukocytosis, and 0.77 (95% CI = 0.74 to 0.81) for procalcitonin.

Summary estimates of sensitivity, specificity, and LRs are shown for different cutoffs for each test in Table 3. Among tests and cutoffs reported by two or more studies, CRP >10 mg/L had the highest sensitivity and lowest LR–. CRP >20 mg/L, CRP >50 mg/L and CRP >100 mg/L had LR+ of 2.08, 3.68, and 5.79, respectively, and LR– of 0.32, 0.36, and 0.48 (see Figures 3A–3C). While procalcitonin >0.25 μg/L and procalcitonin >0.50 μg/L had good LR+ (5.43 and 8.25, respectively), LR– were higher (worse) than for CRP (0.62 and 0.76, respectively). Leukocytosis defined as a white blood cell count $>9.5 \times 10^9$ to 10.5×10^9 cells/L had modest accuracy (LR+ 3.15, LR– 0.54) with good homogeneity around this estimate (see Figure 3D).

Finally, the combination of two biomarkers was studied in a single study.[25] It used a cutoff of >49.5 mg/L for CRP and a range of cutoffs for procalcitonin from 0.1 to 0.5 μg/L. For all four combinations, accuracy was poor with a range of LR+ from 1.62 to 2.24 and a range of LR– from 0.44 to 0.80.

The diagnostic odds ratio (LR+/LR–) is a measure of overall diagnostic accuracy and discrimination. In general, higher cutoffs for each test were associated with higher diagnostic odds ratios (Table 3).

Finally, potential sources of heterogeneity were explored by comparing the accuracy of studies in a broad population of patients presenting with acute respiratory tract infection versus patients specifically referred for chest radiography due to clinical suspicion of CAP (Data Supplement S1, Figure S1) and primary

Table 1
Characteristics of Included Studies

First Author, Year	Design	Number of Patients Included	Female (%)	Inclusion Criteria	Setting	Mean or Median Age	Reference Standard for Pneumonia Diagnosis	Country	Year(s) Patients Recruited
Heckerling, 1986[29]	Retrospective chart review	464	NR	Patients age 18 years or older who had a CXR for fever or respiratory symptoms; excluded if heart failure.*	ED	Mean 50 years	CXR with pulmonary infiltrate suggestive of pneumonia	United States	1983 to 1984
Melbye, 1988[27]	Prospective cohort	71	48%	Patients age 15 years or older with LRTI suspected to be CAP.*	Primary care	Mean 48 years	CXR with new infiltrate that resolved at 4 weeks	Norway	1986
Melbye, 1992[30]	Prospective cohort	402	NR	Patients age 18 years or older presenting with symptoms of respiratory or throat infection; excluded if severe dyspnea or pregnant.	ED	NR	CXR suggestive of pneumonia†	Norway	1988 to 1989
Gonzalez Ortiz, 1995[31]	Prospective cohort	141	NR	Patients age older than 14 years presenting with fever (>38°C) and respiratory symptoms; excluded if focal signs suggesting other infection such as meningitis.	ED	NR	CXR with findings suggestive of pneumonia	Spain	NR
Stolz, 2006[32]	Prospective cohort	243	48%	Adult patients with suspected LRTI.	ED	Mean 64 years	CXR showing new infiltrate in a patient with respiratory symptoms	Switzerland	2003
Lagerström, 2006[24]	Prospective cohort	177	NR	Adult patients with respiratory symptoms and clinically suspected pneumonia; excluded if severe illness.*	Primary care	Mean 51 years	CXR with infiltrate showing acute pneumonia	Sweden	1995 to 1998
Müller, 2007[15]	Prospective cohort	545	37%	Consecutive adults 18 years or older with suspected LRTI; excluded if cystic fibrosis, active pulmonary TB, HAP, or severely immunocompromised.	ED	Mean 67 years	CXR with new infiltrate	Switzerland	2002 to 2005
Holm, 2007[21]	Prospective cohort	364	51%	Consecutive adults 18 years or older with GP diagnosed LRTI; excluded if recent hospitalization, severe illness requiring immediate hospitalization, pregnancy, or already in study.	Primary care	Median 50 years	CXR with new infiltrate	Denmark	2002 to 2003

(Continued)

Table 1. (continued)

First Author, Year	Design	Number of Patients Included	Female (%)	Inclusion Criteria	Setting	Mean or Median Age	Reference Standard for Pneumonia Diagnosis	Country	Year(s) Patients Recruited
Holm, 2007[22]	Prospective cohort	364	51%	Consecutive adults 18 years or older with GP diagnosed LRTI; excluded if recent hospitalization, severe illness requiring immediate hospitalization, pregnancy, or already in study.	Primary care	Median 50 years	CXR with new infiltrate	Denmark	2002 to 2003
Hopstaken, 2009[23]	Prospective cohort	95	55%	Consecutive adults 18 years or older with signs and symptoms of LRTI; excluded if pregnant, severe illness, or recent antibiotics.	Primary care	Mean 52 years	CXR with new infiltrate	Netherlands	1998 to 1999
Steurer, 2011[28]	Prospective cohort	613	50%	Patients 18 years and older with new or worsened cough and subjective or measured fever.	Primary care	Mean 47 years	CXR with infiltrate	Switzerland	2006 to 2009
van Vugt, 2013[9]	Prospective cohort	2,820	60%	Patients 18 years and older with acute cough or clinically suspected as having LRTI.	Primary care	Mean 50 years	CXR with new infiltrate	12 European countries	2007 to 2010
Le Bel, 2015[25]	Prospective cohort	200	49%	Consecutive adults 18 years or older with clinically suspected CAP and at least one systemic symptom and at least one LRTI symptom.*	ED	Mean 64 years	CXR and thoracic CT scan; only included those with definite or excluded CAP (n = 169)	France	2011 to 2013
Moberg, 2016[26]	Prospective cohort	100	55%	Physician-suspected CAP, age 18 years or older years, and respiratory symptoms for at least 24 hours.*	Primary care	Mean 56 years	CXR with new infiltrate	Sweden	2011 to 2014

CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; LRTI = lower respiratory tract infection; NR = not reported; TB = tuberculosis.
*These studies only included patients if the clinician decided to order a CXR. The remainder included patients whether or not the clinician planned to order a chest radiograph.
†In this study, all patients where the clinician suspected pneumonia or with CRP >50 mg/L received a CXR, as well as a 25% random sample of all other patients (n = 97); none of the latter were diagnosed with pneumonia.

Table 2
Overview of Study Quality

First Author, Year	Patient Selection	Index Test	Reference Standard	Flow and Timing	Overall Risk of Bias
Holm, 2007[21]	L	L	L	L	L
Holm, 2007[22]	L	L	L	L	L
Müller, 2007[15]	L	L	L	L	L
Melbye, 1988[27]	L	L	L	L	L
Lagerström, 2006	L	L	L	L	L
Stolz, 2006[24]	L	L	L	L	L
Gonzalez Ortiz, 1995[31]	L	L	L	L	L
Steurer, 2011[28]	L	L	L	L	L
Hopstaken, 2009[23]	L	H	L	L	M
Moberg, 2016[26]	L	L	H	L	M
Le Bel, 2015[25]	L	H	L	L	M
van Vugt, 2013[9]	L	H	L	L	M
Heckerling, 1986[29]	H	L	L	L	M
Melbye, 1992[30]	L	L	L	H	M

L = low risk of bias for this domain or overall; M = moderate risk of bias; H = high risk of bias.

care versus ED settings (Data Supplement S1, Figure S2). Inspection of the summary ROC curves identifies no clear pattern of heterogeneity in diagnostic accuracy beyond that observed due to the use of different diagnostic thresholds.

DISCUSSION

We found that the biomarkers CRP, procalcitonin, and white blood cell count had fair accuracy for the diagnosis of CAP in adults. We identified a clear threshold effect for all three biomarkers, with increasing cutoffs to define an abnormal test resulting in lower sensitivity but higher specificity. Using higher cutoffs, accuracy was good for ruling in CAP (LR+ 8.8 for CRP >200 mg/L, LR+ 8.3 for procalcitonin >0.5 μg/L, and LR+ 10.5 for procalcitonin >1.0 μg/L). Thus, it may be clinically more useful to use two or more cutoffs and define low-, moderate-, and high-risk groups.

For example, CRP <20 mg/L has a LR– of 0.32 while a CRP >100 mg/L has a LR+ of 5.79. A large prospective study of patients presenting with LRTI, all of whom received a CXR, found an overall likelihood of CAP of approximately 4%.[9] Thus, using Bayes Theorem, the likelihood of CAP in patients with CRP < 20 mg/L is 1.3% and in patients with CRP >100 mg/L is 18.2%. Integration of a biomarker with signs and symptoms has the potential to further improve diagnostic accuracy, and several clinical decision rules for diagnosis or prognosis of CAP take this approach.[9,28,33] We also encourage future researchers to more completely report results by strata of biomarker value (e.g., 0 to 20, >20 to 30, >30 to 40, and >40), rather than just dichotomously, to allow a more nuanced use of these biomarkers in diagnosis and meta-analysis.

The impact of CRP and procalcitonin on antibiotic prescribing has been well studied. A Cochrane reviews concluded that CRP safely reduces antibiotic prescribing for respiratory tract infections in primary care,[34] while a second concluded that procalcitonin reduced antibiotic prescribing for respiratory infections in a range of settings (although the lead author has been asked to step down from participation in the update due to a failure to disclose conflicts of interest).[35] While a recent trial randomized physicians to being given the procalcitonin or not in patients presenting to the hospital with a LRTI found no overall difference in antibiotic-days between groups.[36] However, one would not expect a reduction in antibiotic use among those diagnosed with CAP, especially since nearly half were sick enough to be hospitalized. Importantly, in the subset with a final diagnosis of "acute bronchitis" there was a significant reduction in the procalcitonin group. Further, a recent randomized trial in 653 patients with chronic obstructive pulmonary disease found that use of CRP safely reduced antibiotic use.[37] Another validated clinical rule used CRP in conjunction with signs and symptoms and was able to identify patients with LRTI likely to have an uncomplicated course without antibiotics.[28,33]

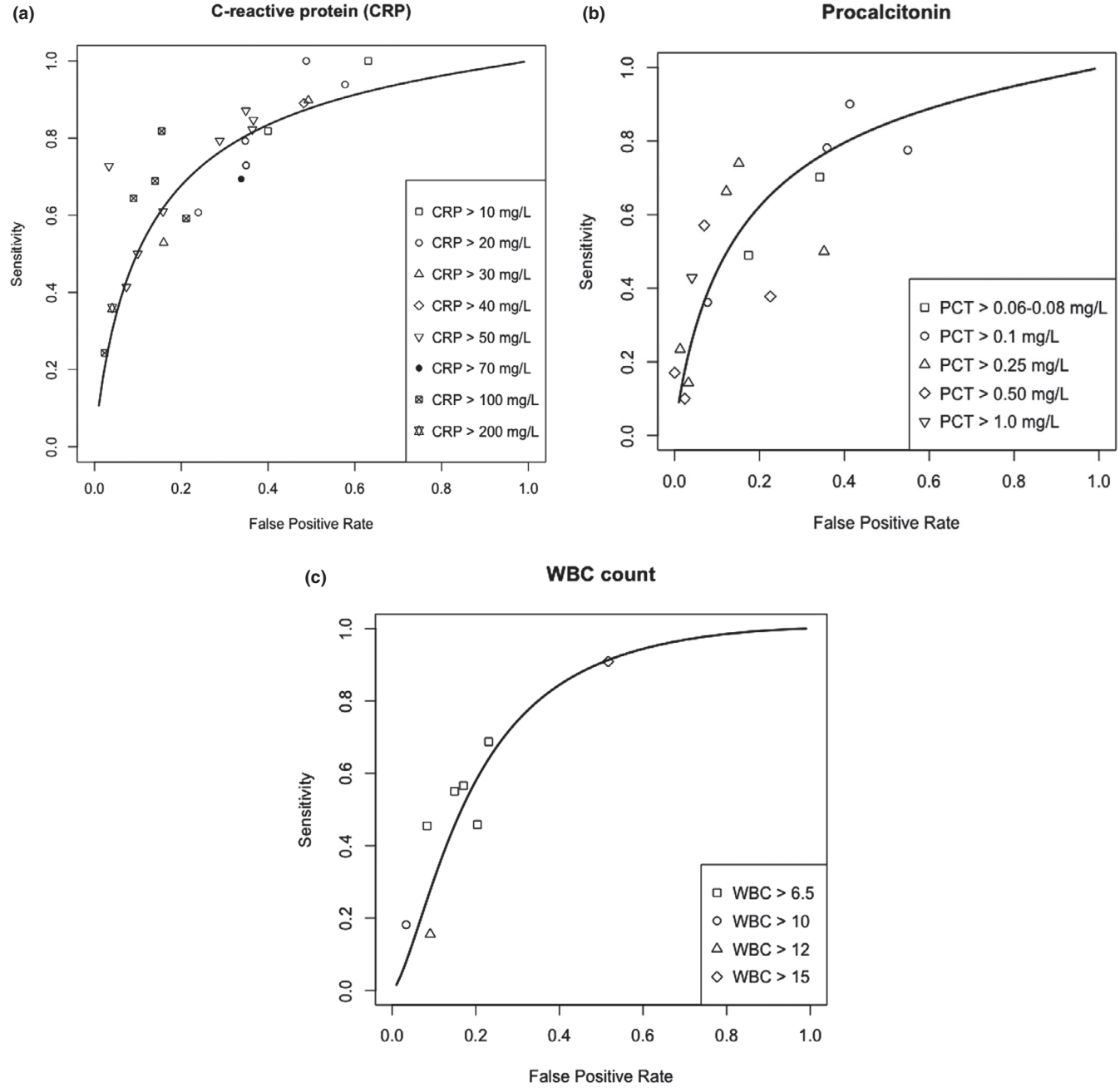

Figure 2 Summary receiver operating characteristic curves for (**A**) CRP, (**B**) PCT, and (**C**) WBC count. Due to the threshold effect, summary estimates of sensitivity and false positive rate (1 – specificity) were not calculated. CRP = C-reactive protein; PCT = procalcitonin; WBC = white blood cell.

We would argue that these biomarkers are most likely to be helpful for supporting clinical decisions about antibiotics in the outpatient setting, where chest radiography may not be readily available and where better antibiotic stewardship is needed. Unfortunately, point-of-care tests for CRP in the primary care setting, widely and successfully used in Europe,[38] have not been approved by the Food and Drug Administration in the United States as point-of-care tests. Studies in the U.S. primary care setting replicating European studies of the impact of CRP (perhaps integrated with a clinical prediction rule) on antibiotic prescribing are therefore needed. Used in conjunction with the history and physical examination, in the ED setting an abnormal CRP could identifying patients who should have a CXR, while a normal CRP could support clinical decisions not to prescribe an antibiotic. While radiographic pneumonia may be viral, it is still the standard of care in the United States to treat these patients with an antibiotic.[39]

Table 3
Summary Estimates of the Accuracy of Biomarkers at Different Cutoffs for the Diagnosis of Community-acquired Pneumonia

Studies (#)	Test and cutoff	Sensitivity	Specificity	LR+	LR−	DOR
3	CRP > 10 mg/L	0.90 (0.52–0.99)	0.48 (0.27–0.70)	1.71	0.27	11.40 (1.64–41.40
6	CRP > 20 mg/L	0.80 (0.68–0.89)	0.62 (0.51–0.71)	2.08 (1.77–2.40)	0.32 (0.21–0.45)	6.63 (4.52–9.34)
2	CRP > 30 mg/L	0.76 (0.29–0.96)	0.70 (0.32–0.92)	2.56 (1.38–3.91)	0.38 (0.12–0.78)	7.55 (4.22–12.50)
1	CRP > 40 mg/L	0.89 (0.85–0.92)	0.52 (0.44–0.59)	1.84 (1.59–2.17)	0.21 (0.15–0.29)	8.68 (5.59–13.48)
9	CRP > 50 mg/L	0.71 (0.56–0.82)	0.80 (0.70–0.88)	3.68 (2.70–4.92)	0.36 (0.25–0.50)	10.20 (8.16–12.70)
1	CRP > 70 mg/L	0.69 (0.59–0.78)	0.66 (0.54–0.77)	2.05 (1.44–2.92)	0.46 (0.33–0.65)	4.44 (2.32–8.50)
6	CRP > 100 mg/L	0.58 (0.39–0.74)	0.90 (0.80–0.95)	5.79 (3.49–9.07)	0.48 (0.31–0.65)	12.20 (7.98–18.00)
1	CRP > 200 mg/L	0.36 (0.31–0.41)	0.96 (0.92–0.98)	8.83 (4.22–18.47)	0.67 (0.62–0.73)	13.22 (6.13–28.46)
2	PCT > 0.06–0.08 μg/L	0.60 (0.36–0.80)	0.75 (0.55–0.88)	2.46 (1.67–3.64)	0.55 (0.35–0.75)	4.64 (2.80–7.07)
3	PCT > 0.1 μg/L	0.74 (0.48–0.90)	0.69 (0.42–0.87)	2.50 (1.50–4.31)	0.39 (0.20–0.63)	6.85 (3.58–12.00)
4	PCT > 0.25 μg/L	0.44 (0.21–0.70)	0.91 (0.76–0.97)	5.43 (2.29–10.80)	0.62 (0.38–0.83)	9.14 (3.37–19.60)
4	PCT > 0.50 μg/L	0.28 (0.11–0.53)	0.96 (0.80–0.99)	8.25 (1.85–28.20)	0.76 (0.54–0.91)	11.20 (2.32–35.50)
1	PCT > 1.0 μg/L	0.43 (0.38–0.48)	0.96 (0.92–0.98)	10.54 (5.05–21.98)	0.60 (0.54–0.65)	17.71 (8.23–38.07)
5	WBCs > 9.5×10^9–10.5×10^9 cells/L	0.55 (0.45–0.66)	0.82 (0.78–0.86)	3.15 (2.46–3.97)	0.54 (0.42–0.66)	5.92 (3.90–8.77)
1	CRP > 49.5 mg/L + PCT > 0.1 μg/L	0.69 (0.59–0.78)	0.69 (0.57–0.80)	2.24 (1.54–3.25)	0.44 (0.32–0.62)	5.05 (2.61–9.75)
1	CRP > 49.5 mg/L + PCT > 0.13 μg/L	0.63 (0.53–0.73)	0.70 (0.58–0.81)	2.14 (1.45–3.16)	0.52 (0.39–0.70)	4.10 (2.14–7.86)
1	CRP > 49.5 mg/L + PCT > 0.25 μg/L	0.48 (0.38–0.58)	0.70 (0.58–0.81)	1.62 (1.07–2.45)	0.74 (0.58–0.94)	2.19 (1.15–4.17)
1	CRP > 49.5 mg/L + PCT > 0.50 μg/L	0.37 (0.27–0.47)	0.79 (0.68–0.88)	1.74 (1.03–2.92)	0.80 (0.66–0.97)	2.17 (1.08–4.34)

CRP = C-reactive protein; DOR = diagnostic odds ratio; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; NC = not calculable; PCT = procalcitonin; WBCs = white blood cells.
*Note: where necessary, a continuity correction was used to avoid division by zero.

The threshold model of decision making identifies a test threshold below which neither testing nor treatment is indicated and treatment threshold above which treatment should generally be initiated.[40] We recently determined test and treatment thresholds of 10 and 40% to 50%, respectively, depending on whether radiography was available on site.[41] If the probability of CAP based on signs and symptoms is assessed to be no more than 25%, then a CRP < 20 mg/L (LR− 0.32) would decrease the likelihood of CAP below the test threshold. This could be clinically useful especially if radiography was not immediately available.

LIMITATIONS

This study has several limitations. While study quality was generally good, some studies either specified cutoffs for an abnormal test post hoc or were unclear about whether it was specified post hoc. This can inflate the apparent accuracy and may not reflect performance in other populations. Masking of radiologists to the index test result was unclear in five studies and absent in one. Also, CXRs are less accurate than chest CT, and radiographic pneumonia is not the same as bacterial pneumonia, although U.S. guidelines do recommend antibiotics for patients with radiographic pneumonia.[39] In general, these potential biases are thought to inflate sensitivity and specificity. Two biomarkers were only reported in a single study, making generalizability difficult.[25]

On the other hand, our study had a number of strengths. By comprehensively reviewing all biomarkers reported in the literature for diagnosis of CAP, we enable clinicians and researchers to compare their accuracy at different cutoffs. We only included studies where all patients received the same reference standard to avoid verification bias, and we excluded diagnostic case–control studies to avoid spectrum bias. In addition, only studies performed in outpatient settings were included to assure that our findings were generalizable to the patients typically seen in primary care, urgent care, and the ED. We performed bivariate meta-analysis and complied with PRISMA recommendations for performance and reporting of our review.

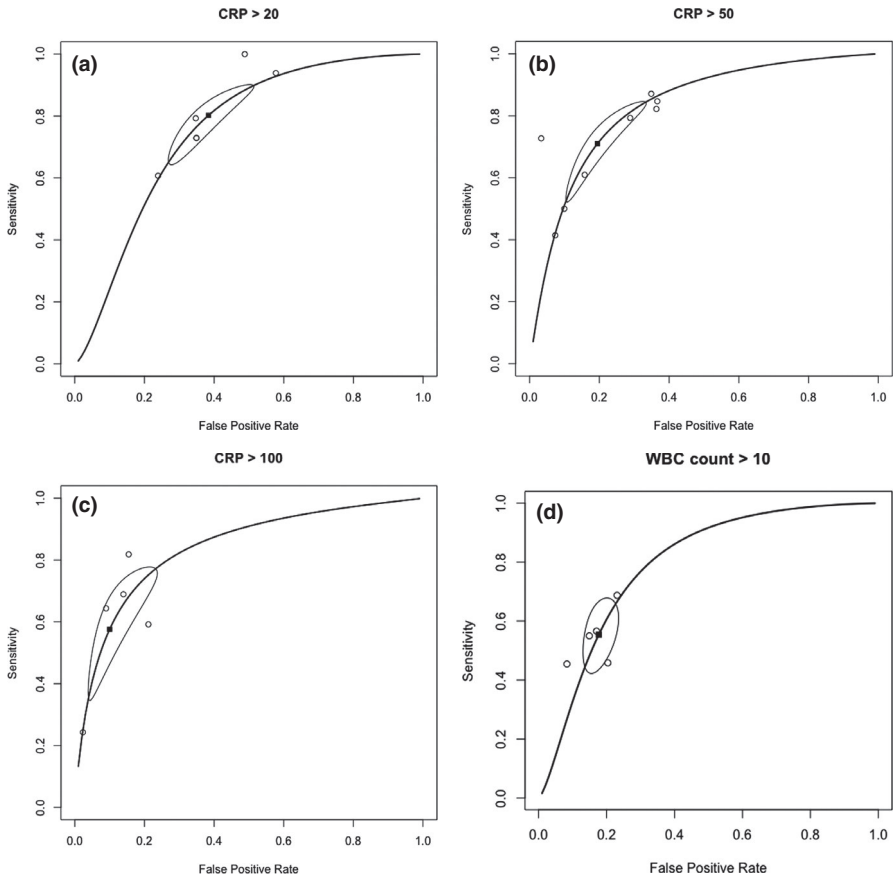

Figure 3 Summary receiver operating characteristic curves for biomarkers and cutoffs reported by at least five studies, with summary estimates for sensitivity and false-positive rate. Shown are (**A**) CRP >20 mg/L, (**B**) CRP >50 mg/L, (**C**) CRP >100 mg/L, and (**D**) WBCs >9.5 × 10^9-10.5 × 10^9 cells/L. CRP = C-reactive protein; WBCs = white blood cells.

CONCLUSIONS

In conclusion, biomarkers can be useful for the diagnosis of community-acquired pneumonia. The cutoff chosen will determine whether the test is most useful for ruling out pneumonia (e.g., C-reactive protein <10 or 20 mg/L) or for ruling in pneumonia (e.g., C-reactive protein >50 or 100 mg/L). C-reactive protein is the most accurate of the three studied biomarkers that are currently being used to assist in the diagnosis of community-acquired pneumonia. We note that C-reactive protein is inexpensive and readily available in many settings and may be easily integrated into the clinical workflow for diagnosis of community acquired pneumonia in appropriate patients.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13889/full

Data Supplement S1. Supplemental material.