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The role of serum procalcitonin in the differential diagnosis of pneumonia from pulmonary edema among the patients with pulmonary infiltrates on chest radiography

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Abstract

The aim of this study is to evaluate the usefulness of serum procalcitonin (PCT) as a diagnostic biomarker for distinguishing pneumonia from pulmonary edema in patients presenting with pulmonary infiltrates on chest radiography.

A comparative study was performed retrospectively in a university-affiliated hospital, from May, 2013 to April, 2015. Adult patients (≥18 years) who showed pulmonary infiltrates on chest radiography and had blood tests with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), PCT, and N-terminal pro-b-type natriuretic peptide (NT-proBNP) on admission were included in the study. Clinical parameters collected on admission were compared between the case group (n = 143) with pneumonia and the control group (n = 88) with pulmonary edema alone.

During the study period, a total of 1217 patients were identified. Of them, a total of 231 patients were included in analyses based on exclusion criteria. In the multivariate logistic regression analysis, PCT ≥0.25 ng/mL, ESR ≥35 mm/h, CRP ≥18 mg/L, NT-proBNP ≤200 pg/mL, underlying neurologic diseases, fever, sputum, absence of cardiomegaly, and a low Charlson comorbidity index were independently associated with pneumonia. For this model, the sensitivity, specificity, positive predictive value, and negative predictive value in distinguishing between the 2 groups were 90.2%, 79.6%, 87.8%, and 83.3%, respectively, with an area under the curve of 0.93.

This study suggests that the practical use of PCT in conjunction with clinical data can be valuable in the differential diagnosis of pulmonary infiltrates and guidance for clinicians to prevent antibiotic misuse.

Abbreviations: AP = anterior-posterior, AUC = area under the curve, BACH = Biomarkers in Acute Heart Failure, BT = body temperature, CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IQR = interquartile range, LOOCV = leave-one-out cross-validation, NPV = negative predictive value, NT-proBNP = N-terminal pro-b-type natriuretic peptide, OR = odds ratio, PA = posterior-anterior, PCT = procalcitonin, PACS = picture archiving and communication system, PPV= positive predictive value, ROC = receiver-operating characteristic, WBC, white blood cell.

Keywords: pneumonia, procalcitonin, pulmonary edema

1. Introduction

Although antibiotic therapy can lead to dramatic reduction in mortality and morbidity rates in the case of bacterial infection, the overuse of antibiotics contributes greatly to the development and spread of multidrug-resistant microorganisms. Selective antibiotic pressure and insufficient measures for infection control and prevention are 2 key factors associated with the development of multidrug-resistant pathogens.[1] Previous studies have suggested that tailoring antibiotics based on the evidence of clinical symptoms and signs augmented by biomarker grounds of infection may be helpful for curtailing antibiotic consumption.[2–4]

Establishing a true "gold standard" for the diagnosis of pneumonia is often troublesome.[5] The practical use of sputum and blood cultures has a significant limitation due to the delay in reporting of culture results and issues with colonization and contamination, and also the inability to grow atypical pathogens in standard cultures. In current practice, the rate of microbiological diagnosis of pneumonia is at most 40%.[6,7] Meanwhile, finding new infiltrates on chest x-ray is regarded as the diagnostic cornerstone for the diagnosis of pneumonia. However, the interpretation of chest radiography has wide variations even among radiologists.[8] Therefore, for the differential diagnosis of pulmonary infiltrates on chest radiography, clinicians should try to integrate clinical, laboratory, and radiological data.

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The symptoms, signs, and radiographic findings of congestive heart failure overlap substantially with those of pneumonia.[9] An erroneous diagnosis of pneumonia can cause a delay in the precise diagnosis and appropriate treatment, and also unnecessary antibiotic use, and it may worsen the clinical outcomes. In a population-based study that included 48,000 patients, lower respiratory infection had a 15.3% prevalence in patients with congestive heart failure.[10] A reliable and rapid tool to subsidize the differential diagnosis of the findings of new infiltrates on chest x-rays is definitely needed.

In recent years, procalcitonin (PCT) has emerged as a promising biomarker for the diagnosis of bacterial infections because higher levels are revealed in severe bacterial infections than in viral infections and nonspecific inflammatory diseases.[11] PCT has been extensively evaluated in clinical research studies targeted at subjects with pneumonia,[5,12–14]. In addition to bacterial infectious diseases, multiple studies have investigated the possible usefulness of PCT in patients with cardiovascular diseases.[15,16] A large study that included 4698 patients with congestive heart failure demonstrated the PCT level to be 4-fold higher in patients when pneumonia was present.[17] A recent pooled analysis showed its ability to facilitate the diagnosis and exclusion of pneumonia in patients in the Emergency Department presenting with dyspnea.[18] Interestingly, the multinational Biomarkers in Acute Heart Failure (BACH) trial that included 1641 patients presenting with dyspnea demonstrated that patients with a diagnosis of acute heart failure and PCT level >0.21 ng/mL had a worse outcome if not treated with antibiotics, whereas patients with low PCT level <0.05 ng/mL had a better outcome if they did not receive potentially unnecessary antibiotic therapy.[19,20]

However, PCT has not been studied for its ability to discriminate pneumonia in patients presenting with pulmonary infiltrates on chest radiography in a clinical setting. The purpose of this study was to evaluate the clinical performance of PCT as a marker of pneumonia in patients with pulmonary infiltrates on chest x-ray, with particular focus on the differential diagnosis of pneumonia from pulmonary edema.

2. Materials and methods

2.1. Study design and patients

A retrospective comparative study was conducted in a university-affiliated hospital in the Republic of Korea, from May, 2013 to April, 2015. Adult patients (≥18 years) who had developed new pulmonary infiltrates and underwent blood tests for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), PCT, and N-terminal pro-b-type natriuretic peptide (NT-proBNP) on admission were eligible for this study. Patients with any of the following comorbid conditions that alter CRP level were excluded: trauma, burn, myocardial infarction or unstable angina within 2 weeks, autoimmune disease, malignancy disease, chronic inflammatory disease, active pulmonary tuberculosis, foci of infection other than pneumonia, and systemic steroid therapy. Only the first episodes were included in the analysis.

The study protocol was approved before study initiation by the institutional review board of the Korea University Anam Hospital (No. AN15096–001).

2.2. Definitions

Presence of a new radiologic infiltrate was determined based on the consensus of 2 investigators: an expert radiologist and an infectious diseases specialist. Pneumonia was diagnosed based on the detection of a new, persistent pulmonary infiltrate compatible with pneumonia and at least 2 of the following clinical criteria: fever or hypothermia (body temperature >38°C or <35.5°C); leukopenia or leukocytosis (white blood cell [WBC] count <4000/μL or >12,000/μL); acute respiratory symptoms; or microbiological confirmation with an isolated microorganism known to be a possible pulmonary pathogen.[16] Pulmonary edema was defined as lung edema with a usual radiologic appearance or with an unusual radiologic appearance, but with clinical findings that are usually associated with a well-known cause of pulmonary edema.[21,22]

2.3. Variables

Data collected for this analysis included demographic characteristics, comorbidities, Charlson comorbidity index,[23] clinical manifestations, microbiological data, laboratory and radiologic data at onset, clinical severity, antimicrobial therapy, hospital stay, and in-hospital mortality. CRP level was determined using a high-sensitivity assay (Beckman Coulter CRP Latex, Beckman Coulter, Brea, CA). Serum PCT level was measured by an ultrasensitive immunofluorescence assay (Elecsys BRAHMS PCT, Roche Diagnostics, Mannheim, Germany). Serum NT-proBNP level was determined by an electrochemiluminescence assay (Elecsys proBNP II STAT, Roche Diagnostics, Mannheim, Germany).

2.4. Radiologic evaluation

Chest radiographs were obtained as posterior-anterior (PA) or anterior-posterior (AP) projection, depending on the status of the patient. The exposure parameters were 120 kVp, 4 mAs (PA projection), and 75 kVp, 5 mAs (AP projection). The mobile unit was from Hitachi, Japan, and the standing unit was from Shimadzu, Japan. Images were obtained and recorded in a picture archiving and communication system (PACS). The evaluation points of chest radiographs were as follows: measurement of cardiothoracic ratio for assessment of cardiomegaly; presence of pulmonary infiltrations in the lung fields for radiologic diagnosis of pneumonia; pleural effusion based on blunting of the costophrenic angle or asymmetric diffuse hazy opacities in the AP projection; and the presence of pulmonary congestion, determined by visualization of septal lines, dominantly shown in the basal lung fields or hilar and vascular engorgements.

2.5. Statistical analysis

IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY), R 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS 9.4 (SAS Institute Inc., Cary, NC) were used for all statistical analyses. Categorical and continuous variables were indicated as count (proportion) and median (interquartile range [IQR]), respectively. Groups of categorical variables were compared using Pearson chi-square test or Fisher exact test. Groups of normally or non-normally distributed continuous variables were compared using a 2-sample Student *t* test or the Mann–Whitney *U* test, respectively. Receiver-operating characteristic (ROC) curves were constructed for each biomarker to evaluate individual predictive values, and also the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Finally, the ROC curves of CRP, ESR, PCT, and NT-proBNP were compared.

To identify predictors associated with pneumonia in patients with pulmonary infiltrates, multivariate logistic regression

Table 1

Comparison of demographic and baseline characteristics of 231 patients with pulmonary infiltration on chest x-ray.

Variables[a]	All (n = 231)	Pneumonia (n = 143, 61.9%)	Pulmonary edema (n = 88, 38.1%)	P[b]
Male sex, n (%)	132 (57.1)	80 (55.9)	52 (59.1)	.639
Age (y), median (IQR)	76 (69–82)	77 (69–83)	75 (69–82)	.424
Comorbidity, n (%)				
Cardiovascular	176 (76.2)	93 (65.0)	83 (94.3)	<.001
Cerebrovascular	64 (27.7)	51 (35.7)	13 (14.8)	.001
Diabetes mellitus	93 (40.3)	45 (31.5)	48 (54.4)	.001
Renal	48 (20.8)	17 (11.9)	31 (35.2)	<.001
Charlson comorbidity Index, median (IQR)	2 (1–4)	2 (1–3)	3 (2–6)	<.001
Symptoms, n (%)				
Fever	101 (43.7)	88 (61.5)	13 (14.8)	<.001
Cough	93 (40.3)	79 (55.2)	14 (15.9)	<.001
Sputum	98 (42.4)	83 (58.0)	15 (17.0)	<.001
Chest pain	35 (15.2)	20 (14.0)	15 (17.0)	.529
Dyspnea	160 (69.3)	93 (65.0)	67 (76.1)	.076
Clinical severity, n (%)				
Shock	51 (22.1)	35 (24.5)	16 (18.2)	.263
ICU care	75 (32.5)	48 (33.6)	27 (30.7)	.649
Mechanical ventilation	50 (21.6)	33 (23.1)	17 (19.3)	.501
Antibiotic therapy, n (%)	197 (85.3)	141 (98.6)	56 (63.6)	<.001
Outcome				
Morbidity, median (IQR)	9 (6–17)	9 (5–18)	9 (6–17)	.745
In-hospital mortality, n (%)	17 (7.4)	10 (7.0)	7 (8.0)	.800

ICU = intensive care unit, IQR = interquartile range.

[a] Values represent the number of subjects (%) or median (interquartile range).

[b] *P* values were obtained using Student *t* test, Mann–Whitney *U* test, or chi-square test as appropriate.

analysis using backward stepwise variable selection based on the Wald statistic was used. In multivariate logistic regression analysis, variables were evaluated if they had at least 10% significance as predictors of pneumonia in univariate analysis. The models were evaluated using Hosmer–Lemeshow goodness-of-fit tests. To evaluate the performance of the final logistic regression model, the predictive accuracy was calculated using leave-one-out cross-validation. The optimal cut-off values for individual biomarkers such as CRP, ESR, PCT, and NT-proBNP levels were determined at the points showing the best sensitivity and specificity. As these are not necessarily optimal in multivariate logistic regression analysis, a threshold analysis was performed in which all possible combinations of cut-off values were examined. Two-sided *P* values <.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

During the study period, in all, 1217 patients were identified initially. Of these, 231 patients were included in analyses based on exclusion criteria. Patients were diagnosed with pneumonia (n = 143) or pulmonary edema alone (n = 88).

Demographic and baseline characteristics of the 231 patients are summarized in Table 1. Of these, 132 patients (57.1%) were men. The median age was 76 years (IQR 69–82 years). Univariate analyses showed no significant age difference between the 2 groups (Table 1).

The median Charlson comorbidity index was 2 (IQR 1–4), and univariate analyses revealed that patients with pulmonary edema alone had significantly higher indices than those with pneumonia. Underlying cardiovascular or renal diseases and diabetes mellitus were significantly more common in patients with pulmonary edema, while neurologic diseases were significantly less common in the same patients (Table 1).

3.2. Clinical characteristics

A fever exceeding 38.0°C, cough, and purulent sputum were more common in patients with pneumonia compared with those with pulmonary edema (Table 1). Between the 2 groups, there were no statistically significant differences in clinical severity based on frequency of shock, application of mechanical ventilation, or intensive care unit care stay. Seventeen patients (17.0%) showed mortality, without a significant difference in frequency between the 2 groups (Table 1).

Of the 88 patients with pulmonary edema alone, 56 (63.6%) received antibiotic therapy on admission.

3.3. Radiologic findings and laboratory data

On radiologic finding, cardiomegaly and pleural effusion were more common in patients with pulmonary edema alone compared with those with pneumonia. Table 2 demonstrates

Table 2

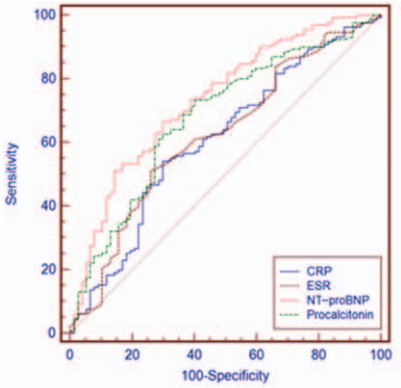
Comparison of radiologic and laboratory characteristics of 231 patients with pulmonary infiltration on chest x-ray.

Variables[a]	All (n = 231)	Pneumonia (n = 143, 61.9%)	Pulmonary edema (n = 88, 38.1%)	P[b]
Pathogens isolated from sputum, n (%)	92 (39.8)	71 (49.7)	21 (23.9)	<.001
Laboratory results, median (IQR)				
WBC ($\times 10^3/\mu L$)	7.8 (6.0–10.3)	7.6 (5.9–10.6)	8.2 (6.1–10.3)	.501
CRP (mg/dL)	15.0 (6.5–38.8)	18.8 (7.6–40.6)	11.8 (4.9–36.3)	.018
CRP ≥18.0 mg/dL, n (%)	105 (45.5)	75 (52.4)	30 (34.1)	.007
ESR (mm/h)	31 (20–46)	35 (23–50.5)	29 (13–39)	.003
ESR ≥35.0 mm/h, n (%)	94 (40.7)	72 (50.3)	22 (25.0)	<.001
PCT (ng/mL)	0.27 (0.09–1.03)	0.40 (0.14–1.91)	0.15 (0.07–0.49)	<.001
PCT ≥0.25 ng/mL, n (%)	118 (51.1)	89 (62.2)	29 (33.0)	<.001
PCT ≥0.50 ng/mL, n (%)	81 (35.1)	60 (42.0)	21 (23.9)	<.001
Platelets ($\times 10^3/\mu L$)	194 (154–270)	198 (160–270)	186 (148–261)	.158
Albumin (mg/dL)	3.3 (2.9–3.7)	3.2 (2.8–3.5)	3.5 (3.1–3.8)	.001
Albumin ≤3.0 mg/dL, n (%)	172 (74.5)	100 (69.9)	72 (81.8)	.044
NT-proBNP (pg/mL)	1930 (458–5574)	861 (280–3326)	4549 (1603–11901)	<.001
NT-proBNP ≥200 pg/mL	201 (87.0)	117 (81.8)	84 (95.5)	.003
Creatinine (mg/dL)	0.95 (0.72–1.43)	0.81 (0.67–1.11)	1.27 (0.92–2.23)	<.001
Chest x-ray, n (%)				
Cardiomegaly	159 (68.8)	79 (55.2)	80 (90.9)	<.001
Pleural effusion	103 (44.6)	51 (35.7)	52 (59.1)	.001

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IQR = interquartile range, NT-proBNP = N-terminal pro-b-type natriuretic peptide, PCT = procalcitonin, WBC = white blood cell.

[a] Values represent the number of subjects (%) or median (interquartile range).

[b] *P* values were obtained using Student *t* test, Mann–Whitney *U* test, or chi-square test as appropriate.



Variables	Cut-off values	AUC (95% CI)	% (95% CI)			
			Sensitivity	Specificity	PPV	NPV
CRP level	18.0 mg/L	0.609 (0.540-0.676)	52.4 (43.9-60.9)	65.9 (55.0-75.7)	71.4 (61.8-79.8)	46.0 (37.1-55.1)
ESR level	35.0 /mm^3	0.622 (0.553-0.688)	50.3 (41.9-58.8)	75.0 (64.6-83.6)	76.6 (66.7-84.7)	48.2 (39.6-56.9)
NT-proBNP level	200.0 mg/L	0.735 (0.669-0.793)	81.8 (74.5-87.8)	4.5 (1.3-11.2)	58.2 (51.1-65.1)	13.3 (3.8-30.7)
PCT level	0.25 ng/dL	0.680 (0.612-0.743)	62.2 (53.8-70.2)	67.0 (56.2-76.7)	75.4 (66.6-82.9)	52.2 (42.6-61.7)

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NT-proBNP, N-terminal pro b-type natriuretic peptide; PCT, procalcitonin; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio.

Figure 1. Receiver-operating characteristic curve of C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and N-terminal pro-b-type natriuretic peptide (NT-proBNP) and procalcitonin (PCT) levels to differentiate patients with pneumonia or pulmonary edema.

laboratory findings for both groups. Compared with those with pulmonary edema alone, patients with pneumonia were more frequently associated with CRP ≥18.0 mg/dL, ESR ≥35.0 mm/h, PCT ≥0.25 ng/mL, and NT-proBNP <200 pg/mL (Table 2).

Figure 1 represents the differential diagnostic accuracy of each biomarker for patients with pneumonia, estimated with the area under the curve (AUC) according to the cut-off values of the single biomarkers.

Overall, cultures from sputum yielded pathogenic bacteria in 71 patients (49.7%) with pneumonia. The most frequently isolated microorganisms were *Streptococcus pneumoniae* (n = 17), *Staphylococcus aureus* (n = 16), and *Haemophilus influenzae* (n = 11).

3.4. Factors for differential diagnosis between groups

Multiple logistic regression modeling revealed that the statistically significant factors associated with pneumonia were fever (body temperature ≥38°C, odds ratio [OR] 5.89, 95% confidence interval [CI] 2.23–15.59), purulent sputum (OR 3.80, 95% CI 1.45–9.97), underlying cerebrovascular disease (OR 4.01, 95% CI 1.44–11.16), PCT level ≥0.25 ng/mL (OR 3.96, 95% CI 1.66–9.45), CRP level ≥18.0 mg/dL (OR 2.68, 95% CI 1.07– 6.67), ESR level ≥35.0 mm/hr (OR 3.66, 95% CI 1.46–9.17), cardiomegaly on chest X-ray (OR 0.24, 95% CI 0.08–0.73), Charlson comorbidity index (per 1-point increment; OR 0.65, 95% CI 0.53–0.81), and NT-proBNP level ≥200 pg/mL (OR 0.17, 95% CI 0.04–0.73; Table 3). The *P* value for the Hosmer–Lemeshow goodness-of-fit test was 0.641, greater than the 0.05 significance threshold; therefore, there was no significant evidence for lack of fit in any of the final models.

Leave-one-out cross-validation was performed to assess the predictive accuracy of each final model. The AUCs for the clinical failure model were about 0.93 for both raw data and leave-one-out cross-validation. For this model, the sensitivity, specificity, PPV, and NPV obtained with an optimal cut-off point are described in Fig. 2.

Table 3

Multivariate logistic regression analysis for diagnosis of pneumonia among patients with pulmonary infiltration on chest x-ray.

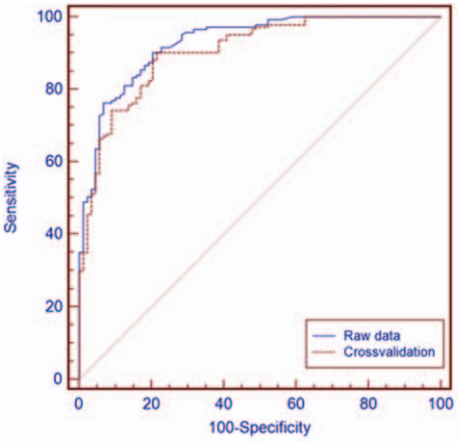
Independent variable	OR (95% CI for OR)	*P*
Fever (BT ≥38°C)	5.89 (2.23–15.59)	<.001
Purulent sputum	3.80 (1.45–9.97)	.007
Cardiomegaly on chest x-ray	0.24 (0.08–0.73)	.012
Underlying cerebrovascular diseases	4.01 (1.44–11.16)	.008
Charlson comorbidity index (per 1-point increment)	0.65 (0.53–0.81)	<.001
PCT ≥0.25 ng/mL	3.96 (1.66–9.45)	.002
CRP ≥18.0 mg/dL	2.68 (1.07–6.67)	.035
ESR ≥35.0 mm/h	3.66 (1.46–9.17)	.006
NT-proBNP ≥200 pg/mL	0.17 (0.04–0.73)	.017

BT = body temperature, CI = confidence interval, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, NT-proBNP = N-terminal pro-b-type natriuretic peptide, PCT = procalcitonin, OR = odds ratio.

4. Discussion

This study demonstrated that PCT is a useful biomarker for discriminating pneumonia from pulmonary edema alone in patients presenting with pulmonary infiltrates on chest x-ray. Our findings also suggest that it was not unusual to prescribe antibiotics for patients with pulmonary edema alone that was mistaken for pneumonia. This study indicated the necessity of antibiotic stewardship by the practical use of PCT in conjunction with clinical data to avoid misuse of antibiotic therapy.

Conventionally, chest radiography was the most common primary tool in the diagnosis and evaluation of therapeutic response according to the clinical guidelines for patients with pneumonia.[24] Although the most frequent etiology of pulmonary infiltrates is pneumonia, it also has variable causes such as alveolar edema, atelectasis, and even consolidative neoplastic lesions. Other criteria for the radiologic diagnosis of pulmonary edema include cardiomegaly, pleural effusion, and septal lines. However, despite these efforts to find differential points in the radiologic findings, the differential diagnosis of pulmonary infiltrates on initial chest radiographs can be convoluted. Sometimes, serial follow-up chest radiographs are helpful because pulmonary edema shows a quicker change of pace compared with pneumonia. Nevertheless, among the diverse causes, pneumonia can be challenging to diagnose based on clinical and radiological findings alone. Moreover, when there is concurrent acute heart failure, it is more difficult to diagnose pneumonia due to the insensitive feature of chest x-ray and



Variables	AUC (95% CI)	% (95% CI)			
		Sensitivity	Specificity	PPV	NPV
Raw data	0.929 (0.896–0.961)	90.2 (84.1–94.5)	79.6 (69.6–87.4)	87.8 (81.3–92.6)	83.3 (73.6–90.6)
LOOCV	0.904 (0.866–0.943)	90.2 (84.1–94.5)	78.4 (68.4–86.5)	87.2 (80.7–92.1)	83.1 (73.3–90.5)

AUC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; LOOCV, leave-one-out cross validation

Figure 2. Receiver-operating characteristic curve for pneumonia, obtained using the predictive probability of multivariate logistic regression model and validation results.

confusing clinical findings.[25] On the contrary, physicians have prescribed diverse broad-spectrum antibiotics for pneumonia and have had a low threshold to initiate antibiotic therapy in presumed pneumonia.[26] In our study, 56 patients (63.6%) with pulmonary edema alone received antibiotic therapy on admission. In a previous study, one-fifth of patients diagnosed with acute heart failure were treated with antibiotics, whereas only 5.1% were ultimately diagnosed with pneumonia, suggesting unnecessary antibiotic therapy.[19] Therefore, the use of biomarkers can be helpful for an antibiotic stewardship in complementing and improving clinical assessment, thereby reducing the unnecessary prescribing of antibiotics in an era of multidrug resistance.

A few previous studies have provided references to assist with distinguishing pneumonia from acute decompensated heart failure. A known predictor for pneumonia is CRP level.[27–29] Prior studies have suggested diverse cut-off values of CRP level: 15 mg/L, 72.5 mg/L, and 100 mg/L.[27–29] This may be attributed to small sample sizes and different study designs, populations, and predictability. Our findings indicated a cut-off value of CRP level of 18 mg/L for ruling out a diagnosis of pneumonia. The application of the CRP test as a tool in the diagnostic work-up of patients with lung infiltrates from presumed infection is now widely used worldwide.[30] However, due to a delayed response with late peak levels and modulation from anti-inflammatory drugs, it sometimes has suboptimal practicability and diagnostic accuracy.[31]

In our study, PCT ≥0.25 ng/mL was also revealed as a valuable predictor for pneumonia in patients with pulmonary infiltrates on chest x-ray. PCT as a useful biomarker has been investigated in a number of clinical research studies and has been shown to be a more specific marker for bacterial infections compared with more traditional markers such as CRP and WBC.[4] In recent years, PCT has emerged as a promising additional diagnostic tool over CRP for the diagnosis of bacterial infections, because it shows an earlier increase upon infection, a better NPV, and a non-attenuated increase in the presence of immunosuppressive medications.[32] Several randomized controlled studies have investigated the use of PCT to assist in decisions about initiation or duration of antibiotic therapy as a clinical tool in antibiotic stewardship.[33,34] Most trials of patients with acute respiratory tract infections recommended initiation or discontinuation of antibiotic therapy based on similar PCT cut-off values around 0.25 μg/L, similar to our results.[34] In addition, in the BACH trial, PCT level was measured in 1402 patients. Of them, 12% showed a PCT >0.25 ng/mL and revealed that a cohort would potentially benefit from antibiotic therapy.[35] The BACH trial of 1641 patients presenting with dyspnea also showed that inappropriate use or withholding of antibiotics without considering the results of PCT testing may affect mortality in patients with congestive heart failure.[19,20] Therefore, PCT level may assist in diagnosing bacterial infections and improving clinical outcomes in patients with pulmonary infiltrates on chest x-ray, especially those whose diagnosis is unclear after the initial evaluation.

Our study demonstrated several predictors useful for differential diagnosis between patients with pneumonia and those with pulmonary edema alone among patients with pulmonary infiltrates on chest x-ray. In our study, apart from the known infection signs, underlying cerebrovascular diseases and a higher Charlson comorbidity index were revealed as significant predictors for pneumonia. Widely known risk factors for pneumonia include age >65 years, smoking, alcoholism, immunosuppressive conditions, and underlying diseases including chronic obstructive pulmonary diseases, cardiovascular diseases, cerebrovascular diseases, Parkinson disease, epilepsy, dysphagia, chronic liver or renal disease, diabetes mellitus, and dementia.[36] Compared with heart failure, neurologic diseases and more severe underlying diseases affecting swallowing and ambulation may be associated with a substantially increased risk of pneumonia.[37,38]

To the best of our knowledge, no study on patients with pulmonary infiltrates has ever quantitatively evaluated the usefulness of PCT in conjunction with clinical data to match the realities of a clinical setting. However, our study has certain limitations. First, this was a single-center study. The limited number of subjects who underwent laboratory tests for pulmonary infiltrates might be associated with selection bias. At the time of this study, PCT tests had been introduced into clinical practice as a nonpayment item from national health insurance claims. Therefore, some clinicians were still reluctant to prescribe it. Second, with the increase in life expectancy, the

problem of overlapping pathologies with pneumonia and pulmonary edema is common.[39] It is too difficult to differentiate patients with pneumonia alone in a clinical setting. Thus, the group of patients with pneumonia in our analysis included patients with pneumonia and pulmonary edema. Niebauer et al[40] suggested that patients with congestive heart failure showed slightly higher PCT level compared with the controls. To compensate for the confounding factors, those with cardiogenic shock or ischemic heart diseases were excluded from our analysis. Third, as this is a retrospective study, it is possible that the laboratory test results, including PCT and CRP levels, introduced a bias when distinguishing between pneumonia and pulmonary edema according to the diagnostic criteria.

5. Conclusions

In conclusion, this comparative study suggests that a combination of clinical data and laboratory findings can be useful for distinguishing patients with pneumonia among those with pulmonary infiltrates. The role of serum PCT was particularly encouraging in the differential diagnosis of pneumonia from pulmonary edema present in pulmonary infiltrations. This may help avoid the misuse of antibiotics in patients with pulmonary edema. Further prospective randomized trials with larger study populations are necessary to develop better predictive models to guide the initiation of appropriate antimicrobial therapies in patients with pulmonary infiltrates.

Author contributions

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