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Diagnostic and predictive values of procalcitonin in bloodstream infections for nosocomial pneumonia

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ABSTRACT

Purpose: We evaluated the diagnostic accuracy of PCT to distinguish between gram-negative (GN) and gram-positive (GP) bloodstream infections nosocomial pneumonia (NP) patients and compared PCT levels with the pneumonia severity index (PSI) for predicting mortality.
Methods: Data were collected retrospectively for blood culture-positive NP patients between January 2014 and August 2016. PCT levels were compared between patients with GN versus GP infections. Outcome variables included 28- and 60-day mortality.
Results: PCT level was higher in GN infections than in GP infections. PCT could differentiate between GN and GP infections with an AUC value of 0.706. At a PCT cutoff of 5.4 ng/mL, the specificity for GN infections were 80.3%. The AUCs for 28- and 60-day mortality were 0.758 and 0.759 for PSI, and 0.620 and 0.634 for PCT. Serum PCT level was less predictive of mortality in GN NP patients compared with that for GP NP patients. There was a significantly positive correlation between PCT and PSI, and the correlation in GP NP patients was better than that in GN NP patients.
Conclusions: PCT could differentiate between GN and GP bloodstream infections in patients with NP. However, PCT levels were less predictive of mortality compared with the PSI.

1. Introduction

Pneumonia is a serious illness and common cause of death. Community-acquired pneumonia (CAP) is associated with a mortality rate of ~20% for patients admitted to hospital in the United Kingdom [1]. Nosocomial pneumonia (NP) (including hospital-acquired and ventilator-associated pneumonia) has a point prevalence of ~1% in hospital inpatients and is associated with a higher mortality rate compared with CAP [2,3]. Rapid recognition of severe bacterial infections and prompt initiation of therapeutic regimens might decrease patient mortality. Current pneumonia and sepsis management guidelines emphasize early initiation of fluid resuscitation and appropriate antimicrobial therapy to improve patient outcomes [4,5]. Immediate pathogen recognition would be ideal to facilitate appropriate antibiotic selection. However, in real-life clinical practice pathogen identification is often delayed due to current microbial diagnostic techniques. Identifying infection biomarkers with high sensitivity and specificity would be useful to overcome treatment delays.

Procalcitonin (PCT) is a blood biomarker that might have potential as a diagnostic and prognostic indicator of bacterial infection. Recent studies [6,7] have demonstrated the utility of the PCT level for discriminating between gram-negative (GN) and gram-positive (GP) bacteria. This issue could be of particular relevance in bloodstream infections, in which PCT could assist clinicians in setting the most appropriate early therapeutic approach that is essential for NP patients outcome. Assessment of disease severity is an important early step in the management of patients. As recommended by the American Thoracic Society and the Infectious Disease Society of America [8], the Pneumonia Severity Index (PSI) was introduced to evaluate the severity and prognosis of CAP. However, there are limited data on usefulness of PSI in patients with NP. Therefore, we also evaluated the prognostic value of PSI for predicting mortality and compared the accuracy of PSI with PCT for the prediction of 28- and 60-day mortality in inpatients with NP.

The present study investigated whether PCT levels over the clinical course of NP with bacterial blood infection could serve as an early diagnostic biomarker for NP. We evaluated whether PCT levels could distinguish between GN and GP bacterial bloodstream infections in patients with NP. We also assessed the potential of PCT for identifying NP patients at risk of short- and long-term mortality.

Abbreviations: AUC, area under the curve; BC, blood culture; CAP, community-acquired pneumonia; CI, confidence interval; GN, gram-negative; GP, gram-positive; IQR, interquartile range; NP, nosocomial pneumonia; PCT, procalcitonin; PSI, Pneumonia Severity Index; ROC, receiver operating characteristic.

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Table 1
Demographic and clinical characteristics of patients.

Characteristics	Values
Age (years)	73.5 (62–82)
Males (%)	171 (59.79)
Females (%)	115 (40.21)
Ward of hospitalization	
ICU (%)	236 (68.41)
EICU (%)	109 (31.59)
BCs	
Monomicrobial (%)	325 (94.20)
GN (%)	163 (50.15)
GP (%)	139 (42.77)
Fungi (%)	23 (7.08)
Polymicrobial (%)	20 (5.80)
PSI	
≤ 50	5 (1.45)
51–70	13 (3.77)
71–90	25 (7.25)
91–130	115 (33.33)
> 130	187 (54.20)
Death within 28 d	101 (29.28)
Death within 60 d	124 (35.94)
Leukocyte count, 10^9cells/L	10.26 (6.96–14.40)
Platelet count ($\times 10^9$/L)	169 (107–247)
Hematocrit, %	29.1 (24.91–34.0)
BUN (mg/dL)	9.73 (6.13–16.54)
Creatinine, mg/dL	84.7 (55.85–139.05)
Total bilirubin (μmol/l)	11.8 (77.51–19.64)
Sodium, mEq/L	138 (134.3–143.0)
Potassium, mg/dL	4.1 (3.7–4.6)
Glucose, mg/dL	7.73 (5.91–9.85)

Data are expressed as *n* (%) or median (25th to 75th range).
BC, blood culture; ICU, intensive care unit; EICU, emergency intensive care unit; GN, Gram-negative; GP, Gram-positive; BUN, blood urine nitrogen; PSI, Pneumonia Severity Index.

2. Materials and methods

2.1. Study population

Patients with pneumonia who were hospitalized in the China-Japan Friendship Hospital (a 1600-bed teaching hospital; Beijing, China) from January 2014 through August 2016 were enrolled. Inclusion criteria were as follows: [1] fulfillment of diagnostic criteria for NP as proposed by American Thoracic Society/Infectious Diseases Society of American [9]; [2] at least one positive blood culture (BC) during the NP episode; [3] consecutive blood samples for BC and PCT collected simultaneously; [4] age ≥ 18 years; and [5] a single bloodstream infection episode alone (the first sample of the episode was considered). An episode was defined as the period associated with one or more positive BCs for the same organism(s) [10, 11]. PCT levels can be affected by some non-infectious diseases, such as autoimmune diseases [12-16] and malignant tumors [17-19]. Therefore, the exclusion criteria were: [1] a medical history of immune system disease (adult-onset Still's disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, or multiple sclerosis) [12-16]; and [2] a history of malignant tumor (thyroid carcinoma or lung cancer) [17-19].

2.2. PCT levels and blood cultures

Serum PCT levels were measured using an automatic analyzer (Vidas B.R.A.H.M.S.; bioMérieux, Marcy l'Etoile, France), according to the manufacturer's instructions. The lower detection limit of the assay was 0.05 ng/mL, and the assay sensitivity was 0.09 ng/mL.

For each sample, an aliquot of 5–10 mL whole blood was inoculated into Bactec aerobic and anaerobic bottles (Becton Dickinson, Sparks, MD, USA) that were then incubated in a Bactec FX automated blood culture system (Becton Dickinson). Aliquots were removed from positive cultures for Gram staining and were streaked on solid medium for subsequent analysis. Microorganisms were identified by conventional methods and matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

2.3. Pathogen identification

Microorganisms detected in BCs were considered as clinically relevant pathogens rather than contaminants if they met the following conditions: [1] detection in ≥2 BCs and reported by the clinician as the cause of the NP episode; [2] detection in one set of BCs but consistent with the results of cultured samples from suspected infectious foci collected from the same patient during the same infectious episode; [3] detection in one set of BCs of a species included among the etiopathogenic agents of the patient's infectious disease; and [4] detection in one set of BCs reported by the clinician as the cause of the NP episode in the final diagnosis based on clinical, instrumental, and laboratory data. Coagulase-negative staphylococci, *Corynebacterium* spp., and other skin commensals were considered as contaminants when isolated from one set of BCs alone [20] and in the absence of clinical and/or laboratory data suggesting a pathogenic role.

2.4. Statistical analyses

Values are expressed as counts and percentages or medians and inter-quartile ranges (IQR). The Kruskal-Wallis test was used for multigroup comparisons. Receiver operating characteristic (ROC) curve analysis and calculation of the area under the curve (AUC) were performed to determine the diagnostic utility of various PCT cut-offs and to assess the ability for predicting mortality. Youden's indices (sensitivity + specificity − 1) were calculated to determine the ideal discriminatory cut-off values. Correlations between PCT and PSI were examined using the Spearman test. All tests were two tailed, and a p-value of <.05 was

Table 2
Median PCT levels corresponding to pathogens isolated from ≥2 BCs with monomicrobial infection.

Micro-organism	Values	PCT ≥ 0.5 ng/mL	PCT value*
GN	163	109	1.65 (0.30–10.16)[a,b]
Escherichia coli	41	32	3.41 (0.53–15.72)
Klebsiella pneumonia	27	20	2.07 (0.49–16.09)
Acinetobacter baumanni	33	21	0.74 (0.17–4.24)
Burkholderia cepacia	21	10	0.49 (0.25–5.60)
Pseudomonas aeruginosa	12	8	1.18 (0.16–26.98)
Enterobacter cloacae	9	6	1.06 (0.09–65.69)
Corus acinetobacter	2	1	0.45 (0.29–0.61)
Proteus mirabilis	2	1	9.48 (0.22–18.73)
Stenotrophomonas maltophilia	4	4	9.54 (4.31–16.95)
Serratia marcescens	3	2	1.92 (1.08–2.13)
GP	139	73	0.82 (0.16–4.10)[a,c]
Staphylococcus epidermidis	27	13	0.43 (0.11–2.36)
Staphylococcus hominis	30	12	0.25 (0.11–2.21)
Staphylococcus aureus	19	13	2.51 (0.30–9.59)
Staphylococcus haemolyticus	9	3	0.41 (0.09–1.09)
Staphylococcus capitis	9	4	0.27 (0.11–4.02)
Enterococcus faecium	14	9	2.40 (0.88–15.07)
Enterococcus faecalis	8	4	1.35 (0.10–4.78)
Streptococcus viridans	2	2	4.19 (1.42–6.96)
Streptococcus pneumoniae	3	3	7.39 (5.90–19.58)
Parahaemolyticus streptococcus	2	2	38.01 (3.49–72.53)
Streptococcus gordonii	2	1	2.96 (0.25–5.66)
Streptococcus agalactiae	2	1	9.36 (0.28–18.43)
Streptococcus constella	2	2	29.49 (2.96–56.02)
Fungi	23	7	0.42 (0.22–1.61)[b,c]
Candida albicans	18	5	0.97 (0.19–1.78)

Kruskal-Wallis test was used for comparison of PCT levels between gram-positive (GP) bacteria, gram-negative (GN) bacteria and Fungi groups.
[a] $Z = 2.510$, $p = .036$.
[b] $Z = -1.883$, $p = .179$.
[c] $Z = -0.738$, $p = 1.000$.
* Data are expressed as median (25th to 75th range).

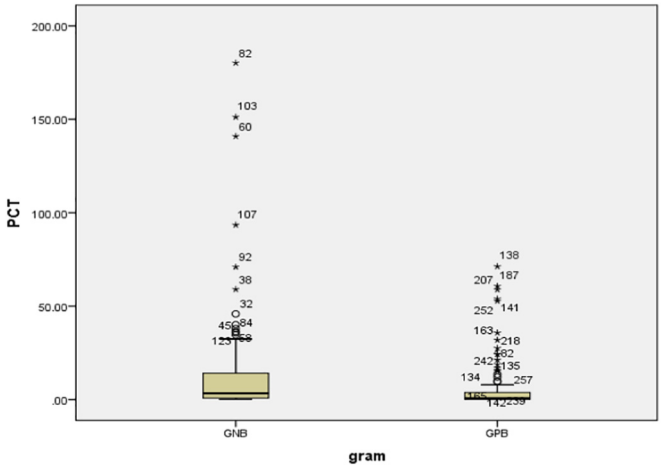


Fig. 1. PCT level differences between GN and GP infections. GN, Gram-negative; GP, Gram-positive.

considered significant. Data were analyzed using SPSS v.23.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Clinical characteristics

During the entire study period, a total of 3302 BCs were collected, and only 502 (15.2%) BCs were positive. Among which 157 (31.3%) BCs were excluded because of PCT was not drawn concomitantly. A total of 345 positive BCs were enrolled in the study. Patients' demographic and clinical characteristics are shown in Table 1.

Median PCT levels corresponding to microbial species isolated from ≥2 NP patients with monomicrobial bacteremia are shown in Table 2. Elevation of serum PCT (≥0.5 ng/mL) was more frequently observed in subjects whose causative pathogen was GN (66.87%) compared to those with GP (52.52%) or fungal infections (30.43%) ($p = .011$ and .001, respectively). *Escherichia coli* (41 isolates, 25.15%) and *Staphylococcus hominis* (30 isolates, 21.58%) were the most frequently isolated GN and GP bacteria, respectively. The median PCT level was higher in

Table 3
Diagnostic ability of PCT at various cutoff values for differentiating between NP caused by GN and GP bacteria.

PCT cutoff value (ng/mL)	0.465	0.570	1.05	5.400	10.160	15.90
Sensitivity	0.854	0.800	0.700	0.408	0.331	0.238
Specificity	0.492	0.508	0.568	0.803	0.871	0.902
LR+	1.681	1.633	1.620	2.071	2.566	2.429
LR−	0.297	0.394	0.528	0.737	0.768	0.845
PPV	0.624	0.615	0.615	0.671	0.717	0.705
NPV	0.774	0.720	0.702	0.579	0.569	0.546

PCT, procalcitonin; NP, nosocomial pneumonia; GN, gram-negative; GP, gram-positive; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value;

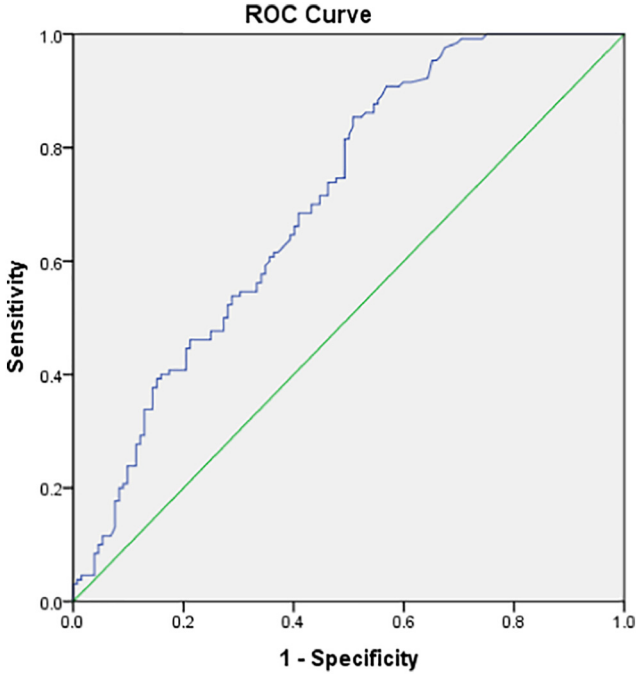


Fig. 2. ROC curve of PCT level to differentiate between GN and GP infections in patients with NP. Area under the curve, 0.706; 95% confidence interval, 0.643–0.768.

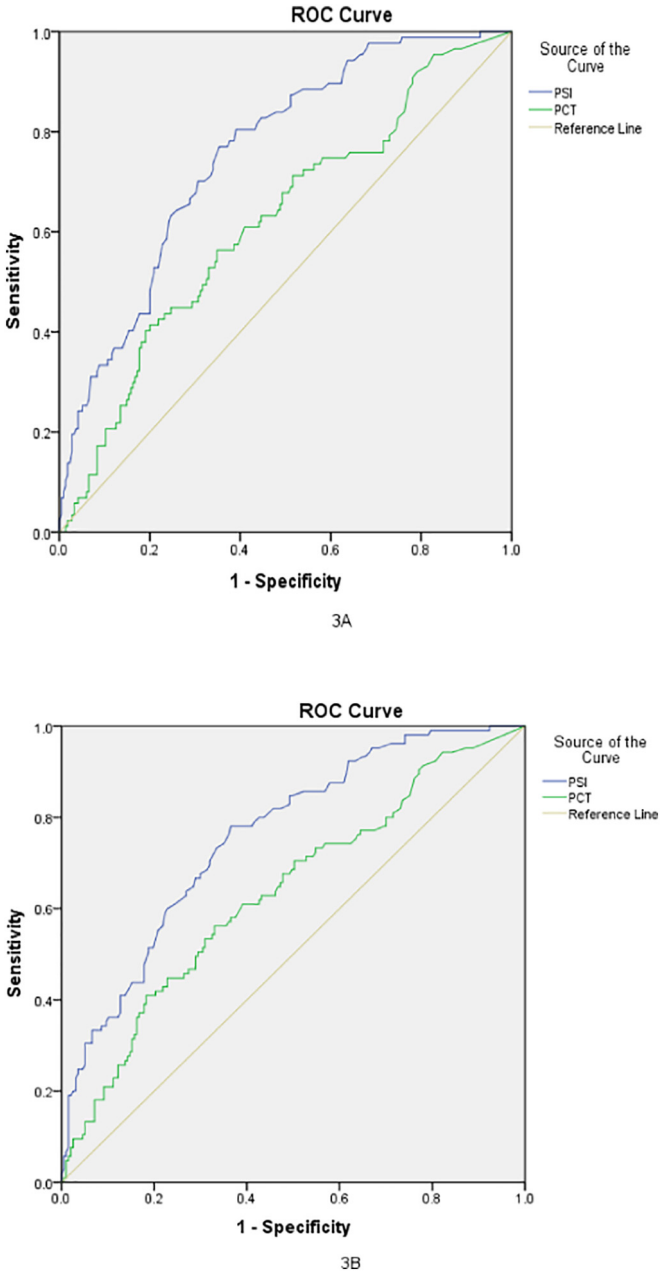
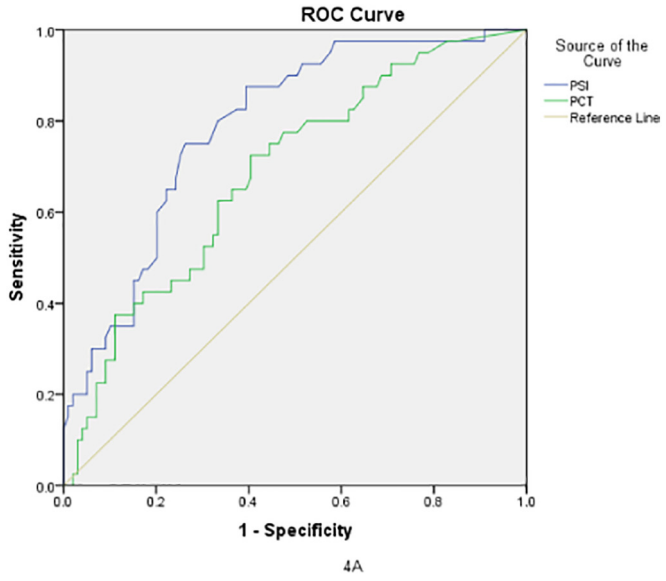
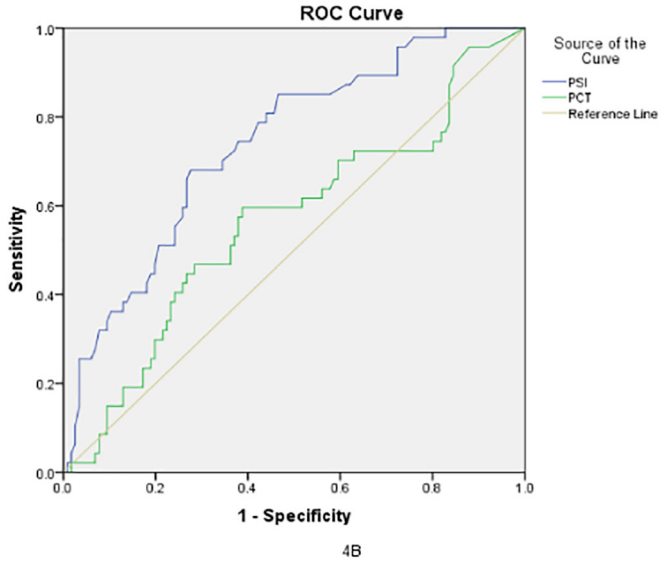


Fig. 3. Inpatient mortality prediction ROC curves of the PCT level and PSI. (A) 28-day mortality. (B) 60-day mortality.



4A



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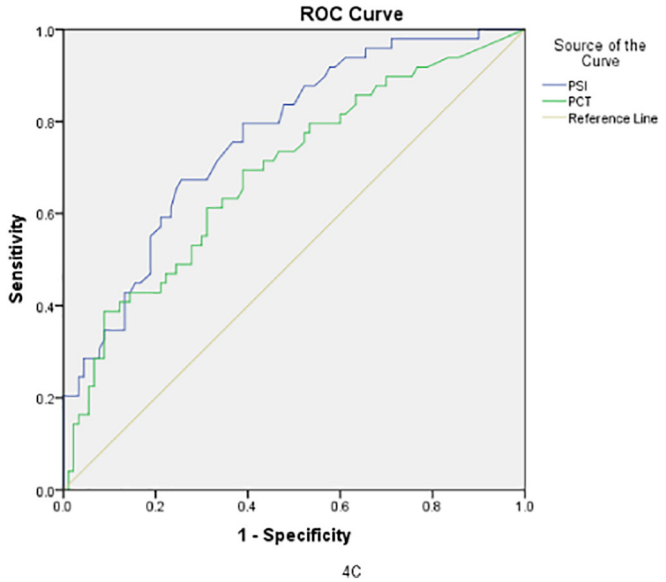

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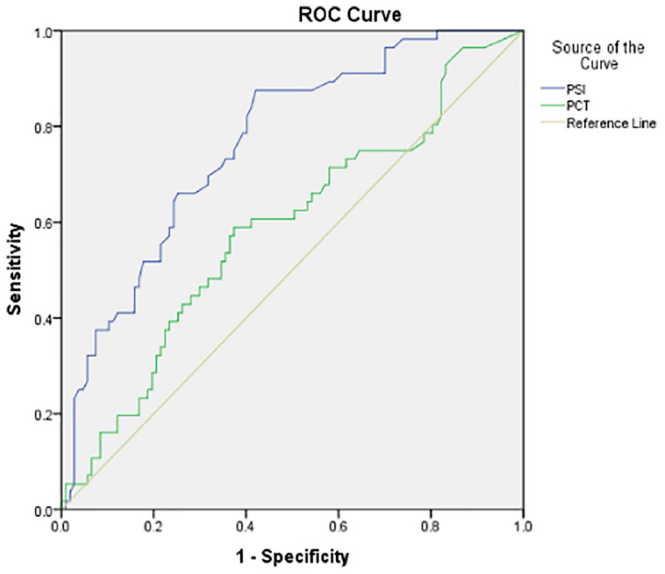

4D

Fig. 4. Inpatient mortality prediction ROC curves according to infection type.ROC curves of the PCT level and PSI score system to predict inpatient mortality. (A) 28-day mortality for GP NP. (B) 28-day mortality for GN NP. (C) 60-day mortality for GP NP. (D) 60-day mortality for GN NP.

those with GN infections (1.65 ng/mL; IQR, 0.30–10.16) compared to those with GP infections (0.82 ng/mL; IQR, 0.16–4.10; $p < .05$; Fig. 1) when there was no statistical difference with PSI score between GN infections (134.46 ± 35.87, 95%CI 128.67–140.25) and GP infections (126.75 ± 45.92, 95%CI 119.05–134.45, $t = -1.583$, $p = .115$). ROC analysis was conducted for monomicrobial BCs to evaluate the diagnostic accuracy of PCT levels in identifying the causative organism of NP (Fig. 2). The diagnostic accuracies of different PCT cutoff values for discriminating between GN and GP infections are shown in Table 3.

3.2. PCT Predictive value for mortality

The ROC curves for predicting mortality within 28 days of the onset of NP are shown in Fig. 3A. The AUC values were 0.758 (95% CI, 0.701–0.815) for the PSI class and 0.620 (95% CI, 0.550–0.690) for serum PCT. Fig. 3B shows the ROC curves for predicting mortality within 60 days of the onset of NP. The AUC values were 0.759 (95% CI, 0.704–0.814) for the PSI class and 0.634 (95% CI, 0.568–0.700) for serum PCT.

3.3. Mortality associated with infection type

The ROC curves for predicting mortality within 28 days of the onset of GP NP are shown in Fig. 4A. The AUC values were 0.788 (95% CI, 0.709–0.867) for the PSI class and 0.685 (95% CI, 0.590–0.781) for serum PCT. Fig. 4B shows the ROC curves for predicting mortality within 28 days of the onset of GN NP. The AUC values were 0.739 (95% CI, 0.657–0.820) for the PSI class and 0.563 (95% CI, 0.464–0.663) for serum PCT.

The ROC curves for predicting mortality within 60 days of the onset of GP NP are shown in Fig. 4C. The AUC values were 0.766 (95% CI, 0.686–0.846) for the PSI class and 0.689 (95% CI, 0.595–0.782) for serum PCT. Fig. 4D shows the ROC curves for predicting mortality within 60 days of the onset of GN NP. The AUC values were 0.765 (95% CI, 0.690–0.839) for the PSI class and 0.586 (95% CI, 0.493–0.679) for serum PCT.

3.4. Correlation between PCT and PSI

Correlation analysis was used to estimate the relationship between PCT and PSI score. A significantly positive correlation was observed between PCT level and PSI score ($r = 0.311$, $p = .000$, Fig. 5A). Compared with GN NP, the PCT values were moderate related with PSI scores in NP patients with GP NP ($r = 0.159$, $p = .045$; $r = 0.416$, $p = .000$; Fig. 5B and C).

4. Discussion

In patients with NP, a PCT cutoff value of 5.4 ng/mL could identify an infection caused by GN bacteria with a specificity of 80.3% and a sensitivity of 40.8%.

PCT is an established inflammatory marker indicating the presence of a bacterial infection. PCT is produced in response to the release of bacterial endotoxins and inflammatory cytokines [21]. GN and GP bacteria activate different Toll-like receptor signaling pathways resulting in the production of distinct proinflammatory cytokines that stimulate PCT release [22]. GN infections probably increase the production of TNF-alpha, IL-1,IL-6, IL-8, IL-10 and IL-18 more compared to GP microbes [23-26]. GN bacteria also produce endotoxins that are released upon cell death, resulting in persistently high PCT levels [27,28]. Therefore, infection by different types of bacteria can induce variable rates of PCT production [7, 29]. Because the infection site could influence factor for PCT levels [6], we examined levels at a single site and found that increases in PCT levels still differed significantly between GN and GP bacterial infections. To the best of our knowledge, the present study is the first to demonstrate a significant difference in PCT levels between bloodstream infections caused by GN and GP bacteria in NP patients. In the present study, the optimal PCT cut-off value was lower than that reported in previous studies [7, 29], yet resulted in the same diagnostic specificity.

Guidelines for prognosis in patients with NP patients are not well established. A severity scoring system such as the PSI, which has been widely used for patients with CAP, might be expected to be a useful tool for the prediction of NP outcome and severity. The present study found that the PSI score had fair predictive power for 28- and 60-day mortality in patients with NP (0.758 and 0.759 of the AUC, respectively), which was similar to previously reported AUCs for 30-day mortality in patients with CAP (0.79) [30]. In our trial positive correlation of serum PCT level and PSI score was found to be significant with $p < .01$. Same result was found in several trials [31-33]. Especially stronger correlation was observed between the level of PCT and PSI in GP NP than that in GN NP. That can be explained by following two reasons. Firstly, for GN infection, not only the proinflammatory cytokins, but also endotoxins released upon cell death that can stimulate PCT release [22,27,28]. Secondly, PCT values caused by different types of GNs are different. PCT value caused by Enterobacteriaceae was significantly higher than that caused by nonfermentative and obligate anaerobic bacteria [7,34].

Most previous studies have concluded that serum PCT levels might be useful for predicting the prognosis of patients with lower respiratory tract infections. Some studies reported that serum levels of PCT was an independent predictor of death in patients with NP [35-37], but also found that the predictive performance of PCT did not exceed that of well-validated clinical scoring systems, such as CURB-65 and PSI. The present study, also found that, in patients with NP, PCT had a lower predictive value for clinical outcomes compared with the PSI score system. However, owing to its complexity, PSI has limited applicability. By contrast, severing as a convenient, rapid, and cost-effective laboratory test, PCT measurements might be useful for predicting the mortality in patients diagnosed with NP.

The present study also found that PCT measurements were significantly better predictors of 28- and 60-day mortality in patients with GP NP compared to patients with GN NP. By contrast, the predictive power of PSI for predicting outcome was only slightly better in patients with GP NP. The possible explanation for these differences could be

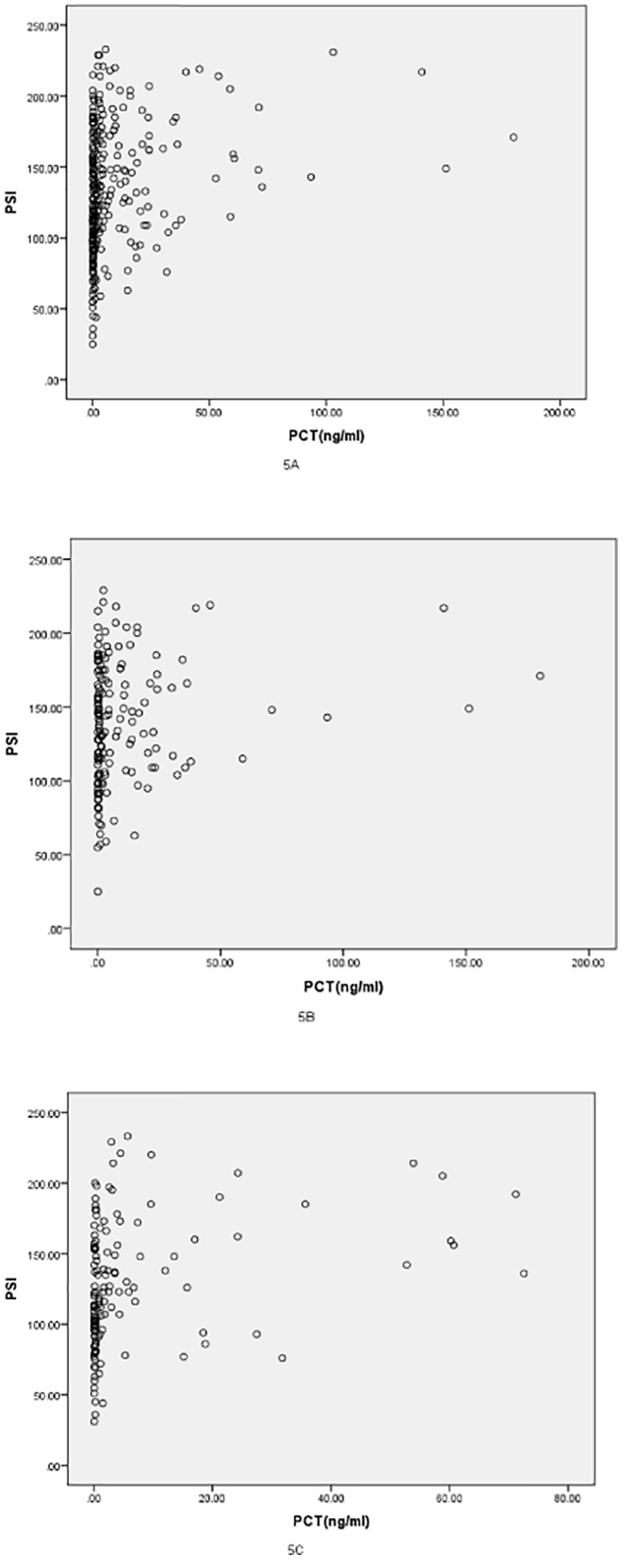

Fig. 5. Scatter diagrams of PCT and PSI in NP patients. (A) Procalcitonin (PCT - X-axis) and Pneumonia Severity Index (PSI - Y-axis) in patients with nosocomial pneumonia infected with (B) GN bacteria and (C) GP bacteria.

because of the additional release of endotoxins by GN bacteria leading to increased PCT levels [22,27,28].

The present study has limitations. First, the data were collected retrospectively from patients hospitalized in the intensive care and emergency intensive care units of a single center. Second, the discriminatory power determined for PCT might have been confounded by the fact that the intervals between the onset of symptoms and sampling were variable. Indeed, PCT levels can vary over the course of infection time, especially during the first 6 h of an infection [38, 39].Therefore, prospective, multicenter studies and samples being taken at a consistent single or multiple time point, if possible, need to conducted for patients with NP in the ICU to investigate whether real real-life measurement of PCT adds useful prognostic information and thereby improves the daily clinical management and outcomes of patients.

In conclusion, PCT can be used to differentiate between GN and GP infections in patients with NP, providing the possibility to estimate the type of microbe and consequently to consider the first-choice antibiotic treatment, but it has limited clinical usefulness when used as a prognostic marker. When used alone, PCT is not a superior predictor of mortality compared with the PSI score system.

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