American Journal of Emergency Medicine 35 (2017) 579–583

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria

Sheng Tao Yan [a], Li Chao Sun [b], Hong Bing Jia [c], Wen Gao [d], Jian Ping Yang [e], Guo Qiang Zhang [f,*]

[a] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[b] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[c] Clinical Microbiology Unit, China-Japan Friendship Hospital, Beijing, China
[d] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[e] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China
[f] Department of Emergency Medicine, China-Japan Friendship Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 4 September 2016
Received in revised form 20 November 2016
Accepted 9 December 2016

Keywords:
Sepsis
Procalcitonin
Positive blood culture
Gram-positive bacteria
Gram-negative bacteria
Bacterial species
Infection sites

ABSTRACT

Objective: The aim of this study was to evaluate procalcitonin (PCT) diagnostic accuracy in discriminating gram-negative (GN) from gram-positive (GP) bloodstream infections and determining the relationship between PCT levels, infection sites, and pathogen types.

Methods: Clinical and laboratory data were collected from patients with blood culture (BC)-positive sepsis between January 2014 and December 2015. PCT levels at different infection sites were compared, as was the presence of GN and GP bloodstream infection. A receiver operating characteristic (ROC) curve was generated to assess diagnostic accuracy.

Results: Of the 486 monomicrobial BCs, 254 (52.26%) were positive for GN bacteria (GNB), and 202 (42.18%) for GP bacteria (GPB). Median PCT levels were higher in BCs positive for GN (2.42 ng/ml, IQR: 0.38–15.52) than in those positive for GPB (0.49 ng/ml, IQR: 0.13–5.89) ($P < 0.001$). In the ROC analysis to differentiate between GNB and GPB, the area under the curve was 0.628 (95% CI: 0.576–0.679). When the cutoffs for PCT were 10.335 and 15.000 ng/ml, the specificity of GNB infection was 80.2% and 84.2%, respectively. PCT levels caused by GNB differed between *Escherichia coli* and *Acinetobacter baumanni*/*Burkholderia cepacia*, *Klebsiella pneumonia* and *Acinetobacter baumanni*. PCT levels caused by GPB differed between *Staphylococcus epidermidis*/*Staphylococcus aureus* and *Staphylococcus hominis*/*Staphylococcus haemolyticus*, *Enterococcus faecium* and *Enterococcus faecalis*/*S.hominis*/*S. haemolyticus*. Among patients with known infection sites, there were statistical differences in PCT levels between abdominal infection and pneumonia/infective endocarditis, urinary tract infection and pneumonia/catheter-related infection/infective endocarditis.

Conclusion: PCT can distinguish between GNB and GPB infection, as well as between different bacterial species and infection sites.

1. Introduction

Sepsis is a life-threatening condition that can result from infections. The global incidences between 1995 and 2015 were 437 and 237 per 100,000 persons per year for sepsis and severe sepsis, respectively [1], and sepsis contributed to one in every two to three deaths in two complementary hospital cohorts [2]. Early diagnosis and rapid bacterial identification are essential for timely and appropriate clinical management [3-5]. Blood cultures (BCs) are considered the gold standard for detecting pathogens in patients with sepsis; however, given the time required, it cannot be applied to make early therapeutic decisions [6]. Identifying biomarkers with high sensitivity and specificity would be useful for overcoming this problem.

Procalcitonin (PCT) is a 116-amino acid protein with a molecular mass of 13 kDa that is produced by thyroid C cells and converted to calcitonin before being released into the bloodstream. Circulating levels of PCT—which are produced by liver monocytes, macrophages, and lung and intestinal lymphocytes—are generally very low in healthy individuals, but can increase by 100 to 1000 fold in response to systemic bacterial infections [7].

PCT is used as a biomarker for initiating or terminating antibiotic therapy in various clinical settings, including the emergency department, intensive care unit (ICU), and primary care [8-10]. The present study investigated whether PCT levels in the clinical course of bacterial blood infection can serve as an early diagnostic marker for sepsis. We examined whether the levels differed according to bacterial species

* Corresponding author at: Department of Emergency Medicine, China-Japan Friendship Hospital, No 2 east Yinghua street, Chaoyang district, Beijing 100029, China.
E-mail address: zhangchong2003@vip.sina.com (G.Q. Zhang).

http://dx.doi.org/10.1016/j.ajem.2016.12.017

and site of infection, and evaluated the utility of PCT levels for distinguishing between gram-negative and -positive bacteria (GNB and GPB, respectively) in patients with bloodstream infection.

2. Materials and methods

2.1. Patients and samples

This retrospective study was carried out using clinical and routine laboratory data collected at the Clinical Microbiology Unit of China-Japan Friendship Hospital, China, between January 2014 and December 2015. Inclusion criteria were as follows: (1) fulfillment of diagnostic criteria for sepsis in 2012 [11]; (2) at least one positive blood culture; (3) consecutive blood samples for BC and PCT collected simultaneously; (4) age ≥ 18 years; and (5) only a single bloodstream infection episode (only the first sample of the episode was considered). An episode was defined as the time period associated with one or more positive BCs for the same organism(s) [12,13]. PCT levels may be altered in some non-infectious diseases, such as autoimmune disease [14-18] and malignant tumors [19-21]. Therefore, our 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) [14-18]; and (2) history of malignant tumor (thyroid carcinoma or lung cancer) [19-21].

2.2. Measurement of PCT level

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 assay sensitivity was 0.09 ng/ml.

2.3. BCs

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 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).

2.4. Pathogen identification

Microorganisms detected in BCs were considered as clinically relevant pathogens rather than contaminants if they met the following conditions: (i) detection in two or more BCs and reported by the clinician as the cause of the sepsis episode; (ii) detection in only 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; (iii) detection in only one set of BCs and belonging to a species included among etiopathogenic agents of the patient's infectious disease; and (iv) detection in only one set of BCs reported by the clinician as the cause of the sepsis episode in the final diagnosis based on clinical, instrumental, and laboratory data. Coagulase-negative staphylococci, *Corynebacterium* spp., and other skin commensals were considered as

Table 1
Demographic and clinical characteristics of patients.

Variable	Value
Age (years)	70 (IQR: 59–80)[a]
Males (%)	253 (61.11)
Females (%)	161 (38.89)
Ward of hospitalization	
ICU (%)	309 (74.64)
EM (%)	105 (25.36)
BCs	
Monomicrobial (%)	486 (92.75)
GNB (%)	254 (52.26)
GPB (%)	202 (42.18)
Fungi (%)	30 (6.17)
Polymicrobial (%)	38 (7.25)
SOFA	4 (IQR: 1–7)[a]
Platelet count ($\times 10^9$/l)	154 (IQR: 75–228)[a]
Creatininemia (mg/dl)	73.70 (IQR: 50.90–137.05)[a]
Total bilirubin (μmol/l)	11.90 (IQR: 7.51–20.84)[a]

BC, blood culture; EM, emergency department; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; ICU, intensive care unit; IQR, interquartile range; PCT, procalcitonin; SOFA, sequential organ failure assessment.
[a] Median value and IQR.

Table 2
Median PCT levels corresponding to pathogens isolated from two or more BCs with monomicrobial infection.

Pathogen	Number of BCs	Median PCT level (IQR) (ng/ml)
GNB		
Escherichia coli [1-5]	97	4.48 (0.86–23.32)
Acinetobacter baumannii [1,6-9]	39	0.94 (0.17–8.44)
Klebsiella pneumoniae [2,6,10-12]	36	3.42 (0.61–21.96)
Pseudomonas aeruginosa [3,7,10,13,14]	17	1.48 (0.42–10.69)
Burkholderia cepacia [4,8,11,13,15]	18	0.44 (0.24–4.57)
Enterobacter cloacae [5,9,12,14,15]	13	1.50 (0.46–19.10)
Serratiamarcescens	6	1.06 (0.08–2.34)
Klebsiellaoxytoca	2	8.32 (1.57–15.06)
Acinetobacterlwoffii	2	0.45 (0.29–0.61)
Proteus mirabilis	4	0.44 (0.24–9.68)
Salmonella spp.	2	1.90 (0.05–3.74)
Stenotrophomonasmaltophilia	4	9.54 (4.31–16.95)
Aeromonashydrophila	2	2.54 (0.61–4.47)
GPB		
Staphylococcus epidermidis 16,17,18,19,20,39	39	0.31 (0.08–5.32)
Staphylococcus aureus [16,21,22,23,24]	35	1.18 (0.3–11.97)
Staphylococcus hominis [17,21,25,26,27]	35	0.21 (0.08–1.17)
Enterococcus faecium [18,22,25,28,29]	25	3.36 (0.48–23.07)
Enterococcus faecalis [19,23,26,28,30]	18	1.24 (0.24–2.28)
Staphylococcus haemolyticus [20,24,27,29,30]	11	0.41 (0.1–0.82)
Staphylococcus capitis	9	0.44 (0.25–3.54)
Streptococcus mutans	2	0.12 (0.10–0.14)
Paratyphoid C coli	2	0.20 (0.16–0.24)
Streptococcus viridans	2	4.19 (1.42–6.96)
Streptococcus pneumoniae	3	7.39 (5.90–19.58)
Streptococcus mitis	2	0.17 (0.05–0.29)
Streptococcus oralis	3	0.05 (0.05–0.16)
Streptococcus salivarius	2	31.97 (29.32–34.62)
Streptococcus agalactiae	2	9.36 (0.28–18.43)
Fungi		
Candida albicans	19	1.11 (0.41–2.24)
Candida parapsilosis	5	0.79 (0.40–1.70)
Candida tropicalis	2	5.37 (0.29–10.45)

1, $Z = -2.909$, $P = 0.004$; 2, $Z = -0.468$, $P = 0.639$; 3, $Z = -1.042$, $P = 0.297$; 4, $Z = -2.152$, $P = 0.031$; 5, $Z = -0.935$, $P = 0.350$; 6, $Z = -2.321$, $P = 0.020$; 7, $Z = -0.849$, $P = 0.396$; 8, $Z = -0.115$, $P = 0.908$; 9, $Z = -0.726$, $P = 0.468$; 10, $Z = -0.696$, $P = 0.487$; 11, $Z = -1.798$, $P = 0.072$; 12, $Z = -0.589$, $P = 0.556$; 13, $Z = -0.306$, $P = 0.318$; 14, $Z = -0.126$, $P = 0.902$; 15, $Z = -0.601$; $P = 0.567$; 16, $Z = -0.028$, $P = 0.978$; 17, $Z = -3.055$, $P = 0.002$; 18, $Z = -0.998$, $P = 0.318$; 19, $Z = -1.246$, $P = 0.213$; 20, $Z = -2.014$, $P = 0.044$; 21, $Z = -2.933$, $P = 0.003$; 22, $Z = -0.967$, $P = 0.333$; 23, $Z = -1.259$, $P = 0.208$; 24, $Z = -2.03$, $P = 0.043$; 25, $Z = -3.190$, $P = 0.001$; 26, $Z = -1.665$, $P = 0.096$; 27, $Z = -0.490$, $P = 0.629$; 28, $Z = -2.143$, $P = 0.032$; 29, $Z = -2.456$, $P = 0.013$; 30, $Z = -1.237$, $P = 0.220$.
BC, blood culture; GNB, Gram-negative bacteria; GPB, Gram-positive bacteria; IQR, interquartile range; PCT, procalcitonin.

contaminants when isolated from only one set of BCs [22] and in the absence of clinical and/or laboratory data suggesting a pathogenic role.

2.5. Statistical analysis

Values are expressed as counts and percentages or median and inter-quartile range (IQR). Statistical significance was assumed if the null hypothesis could be rejected at $P < 0.05$. The χ [2] test was performed to analyze associations between categorical variables. Multiple comparisons of continuous variables were carried out with Kruskal–Wallis one-way analysis of variance. Receiver operating characteristic (ROC) curve analysis was performed to determine the diagnostic utility of various PCT cut-offs, and Youden's indices were calculated to determine the ideal discriminatory cut-off value (i.e., Youden's index = sensitivity + specificity − 1). Data were analyzed using SPSS v.13.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Patients' demographic characteristics and BC results are shown in Table 1. A total of 524 positive BCs were obtained from 414 patients; 309 were from the ICU and 105 were from the emergency department. Among 486 monomicrobial BCs, 254 (52.26%) were positive for GNB, 202 (42.18%) for GPB, and 30 (6.17%) for fungal pathogens.

3.2. PCT levels for infections caused by different microbial species

Median PCT levels corresponding to microbial species isolated in two or more patients with monomicrobial bacteremias are shown in Table 2. *Escherichia coli* (97 isolates, 38.19%) and *Staphylococcus epidermidis* (39 isolates, 19.31%) were the most frequently isolated GNB and GPB, respectively. To assess whether different microbial groups could be distinguished by PCT levels, median values for monomicrobial bloodstream infections caused by different species were compared (Table 2 and Fig. 1). Among GNB, PCT levels caused by *E. coli* were higher than those caused by *Acinetobacter baumanni* or *Burkholderia cepacia* infection, whereas PCT levels induced by *Klebsiella pneumonia* were higher than those caused by *A. baumanni*. Among GPB, PCT levels for *S. epidermidis*, *Staphylococcus aureus*, and *Enterococcus faecium* were higher than those associated with *Staphylococcus hominis* or *Staphylococcus haemolyticus* infection. PCT levels were higher for infections caused by *E. faecium* as compared to *Enterococcus faecalis*.

3.3. PCT levels induced by GNB vs. GPB

The median PCT level was higher for BCs positive for GNB (2.42 ng/ml, IQR: 0.38–15.52) than for those positive for GPB (0.49 ng/ml, IQR: 0.13–5.89) ($P < 0.001$). To evaluate the diagnostic accuracy of PCT level in identifying the causative organism of bloodstream infections, we carried out an ROC analysis in monomicrobial BCs (Fig 2). The best diagnostic accuracy in discriminating GNB from GPB was at a cut-off value of 0.495 ng/ml, with 72.4% sensitivity and 51.0% specificity; when the cut-off value was 25.185 ng/ml, the specificity was 90.1% (Table 3).

3.4. Comparing PCT levels for infections at different sites

Among patients with a known infection site, increases in PCT levels were correlated with the site of infection (Table 4 and Fig. 3). Patients with abdominal infection had higher PCT levels than those with pneumonia or infective endocarditis, whereas patients with urinary tract infections had levels (5.05 ng/ml; IQR: 1.14–40.60) that were higher than those with pneumonia, catheter-related infection, or infective endocarditis.

4. Discussion

The results of this study showed that in patients with sepsis, a PCT cut-off value of 10.3 ng/ml could identify infection caused by GNB, with a specificity of 80.2%. PCT levels may be correlated with infection site; the results of the multivariate regression analysis showed that after correcting for the location of primary infection, a PCT level of 10.3 was still specific for GNB infections. Increases in PCT levels differed between infections caused by GNB and GPB and according to site of

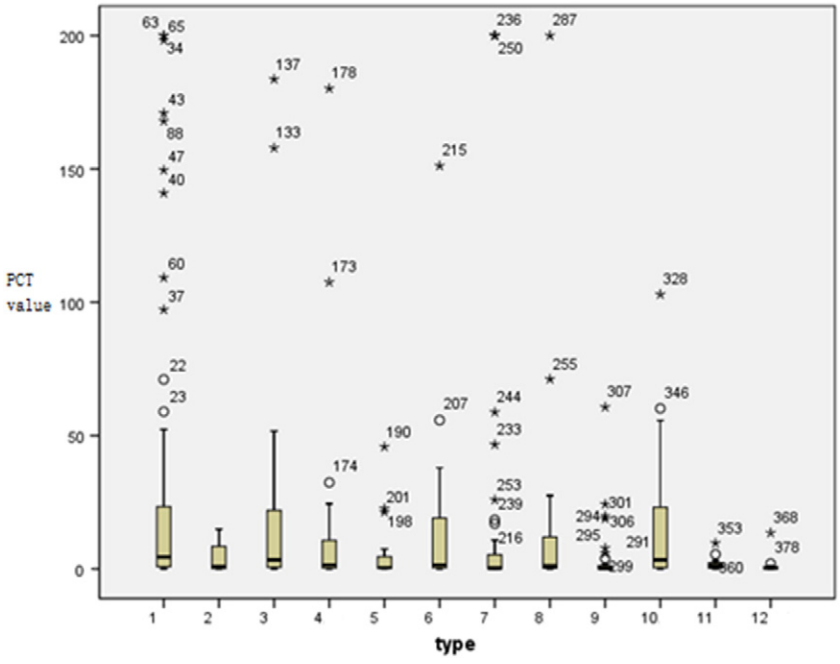

Fig. 1. PCT levels corresponding to GNB and GPB ($n = 6$ each) isolated from two or more BCs with monomicrobial bloodstream infection. 1, *E. coli*; 2, *A. baumanni*; 3, *K. pneumonia*; 4,*Pseudomonas aeruginosa*; 5, *B. cepacia*; 6, *Enterobacter cloacae*; 7, *S. epidermidis*; 8, *S. aureus*; 9, *S. hominis*; 10, *E. faecium*; 11, *E. faecalis*; 12, *S. haemolyticus*.

infection. Thus, PCT levels can provide useful information for selecting the most appropriate antimicrobial therapy when BC results are not available or the infection site is unclear.

PCT is a relatively specific biomarker for severe bacterial infection and sepsis. It is produced in response to bacterial endotoxins and inflammatory cytokines [23]. GNB and GPB activate different Toll-like receptor signaling pathways, resulting in the production of distinct proinflammatory cytokines that stimulate PCT release [24]. Thus, infection by different pathogens can induce different levels of PCT production. GNB can produce endotoxins that can also be released upon cell death, resulting in persistently high levels of PCT [25,26]. A few recent studies have demonstrated the utility of PCT level for discriminating between GNB and GPB infections; one prospective study found that a PCT cut-off value of 10.8 ng/ml can discriminate between sepsis caused by GNB and GPB, with a sensitivity of 0.60 and specificity of 0.82 [27]. Similarly, a retrospective study found that a PCT cut-off of 15 ng/ml could discriminate between the two types of infection, with a specificity of 87.8% [28]. Our cut-off values differed from those reported in these previous studies, which could be attributed to differences in the proportions of bacterial species and infection sites.

This is the first study demonstrating significant differences in PCT levels between bloodstream infections caused by *E. coli* and *A. baumanni*/*B. cepacia*, *K. pneumonia* and *A. baumanni*, *S. epidermidis*/*S. aureus* and *S. hominis*/*S. haemolyticus*, *E. faecium*, and *E. faecalis*/*S. hominis*/*S. haemolyticus*. Our findings are consistent with those of previous studies showing that a greater increase in PCT levels is induced by Enterobacteriaceae as compared to that by non-fermentative GNB [27]. Enterobacteriaceae such as *E. coli* and *K. pneumoniae* at concentrations of 10^4 cells/ml induced greater interleukin-6 production by human umbilical vein endothelial cells than *P. aeruginosa* (10^6 cells/ml), which produced low levels of this cytokine [29] that is known to induce PCT [30].

We also found that PCT levels are correlated with infection site; that is, there was a significant difference between abdominal infection and pneumonia/infective endocarditis, and between urinary tract infection and pneumonia/infective endocarditis/catheter-related infection. This can be explained by the fact that the site of colonization differs among

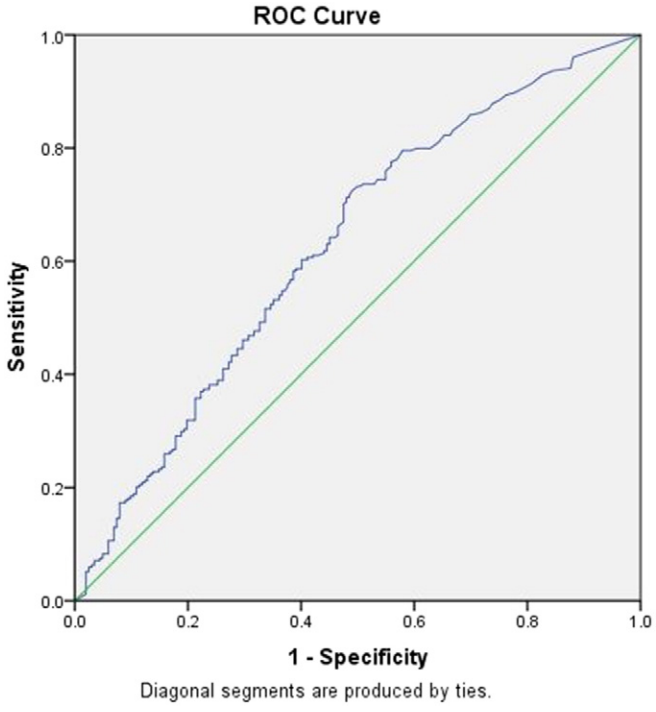

Fig. 2. ROC curve of PCT in differentiating between infections caused by GNB and GPB in patients with sepsis (area under the curve: 0.628, 95% confidence interval: 0.576–0.679).

Table 3
Sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−), positive predictive value (PPV), and negative predictive value (NPV) for various cutoff values in the ROC curve for differentiating between infections caused by GNB and GPB.

PCT cutoff value (ng/ml)	0.495	0.595	5.050	10.335	15.000	25.185
Sensitivity	0.724	0.701	0.394	0.311	0.260	0.181
Specificity	0.510	0.525	0.738	0.802	0.842	0.901
LR+	1.478	1.476	1.504	1.571	1.646	1.828
LR−	0.541	0.570	0.821	0.859	0.879	0.909
PPV	0.650	0.650	0.654	0.664	0.673	0.697
NPV	0.595	0.586	0.492	0.481	0.475	0.477

PCT, procalcitonin.

pathogens. In our study, abdominal and urinary tract infections were mainly caused by GNB (69.66% and 93.18% of cases, respectively)—including *E. coli* and *K. pneumonia*—whereas the frequencies of GNB and GPB were similar in cases of pulmonary infection (53.41% and 46.59%, respectively). About 21.21% of patients with GNB infection were infected by *E. coli* and *K. pneumonia*. Infective endocarditis and catheter-related infection were mainly caused by GPB (82.14% and 91.67% of cases, respectively). Bacteria enter the bloodstream via specific routes to reach different target sites. Urinary tract and abdominal infections are characterized by high fever and chills, which could be evidence of direct and repeated entry of pathogens into the bloodstream.

There were two clinically important findings in this study. Firstly, a PCT value >0.5 ng/ml is normally taken as the cutoff point for diagnosis of sepsis, but we found that values in 37.9% of patients with sepsis caused by bacteria were ≤0.5 ng/ml. Therefore, sepsis cannot be ruled out even when the PCT value is normal. Secondly, measuring the PCT level can raise the index of suspicion for GPB vs. GNB as the causative pathogen, which can be useful for selecting an appropriate antibiotic regimen.

This study had some limitations. Firstly, the discriminatory power determined for PCT may have been confounded by the fact that the intervals between the onset of symptoms and sampling were variable. Indeed, PCT levels can vary with infection time, especially during the first 6 h of infection [31,32]. Secondly, since the study was carried out with patients from only two departments (ICU and emergency), who experienced severe sepsis, it is unclear whether the results can be generalized to other patients. Finally, PCT levels caused by low numbers of bacteria were not compared owing to the small sample sizes.

5. Conclusion

PCT levels can be useful not only for distinguishing between GNB and GPB infections, but also between GNB or GPB bacterial species.

Table 4
PCT levels in relation to infection site.

Infection site	Number of BCs	Median PCT levels (IQR) (ng/ml)
Pneumonia [1,2,3,4,5,6]	264	0.97 (0.17–7.95)
Abdominal infection [1,7,8,9,10,11]	89	3.36 (0.46–24.22)
Urinary tract infection [2,7,12,13,14,15]	44	5.05 (1.14–40.60)
Catheter related infection [3,8,12,16,17,18]	28	0.76 (0.33–6.70)
Infective endocarditis [4,9,13,16,19,20]	12	0.21 (0.07–2.03)
Soft tissue infection [5,10,14,17,19,21]	12	0.82 (0.18–7.13)
Pelvic infection [6,11,15,18,20,21]	4	5.05 (1.02–19.48)

1, $Z = -3.241$, $P = 0.001$; 2, $Z = -3.234$, $P = 0.001$; 3, $Z = -0.030$, $P = 0.969$; 4, $Z = -1.933$, $P = 0.053$; 5, $Z = -0.290$, $P = 0.772$; 6, $Z = -1.099$, $P = 0.272$; 7, $Z = -0.861$, $P = 0.389$; 8, $Z = -1.910$, $P = 0.056$; 9, $Z = -2.950$, $P = 0.003$; 10, $Z = -1.527$, $P = 0.127$; 11, $Z = -0.218$, $P = 0.834$; 12, $Z = -2.035$, $P = 0.021$; 13, $Z = -2.867$, $P = 0.004$; 14, $Z = -1.868$, $P = 0.062$; 15, $Z = -0.336$, $P = 0.760$; 16, $Z = -1.863$, $P = 0.065$; 17, $Z = -0.236$, $P = 0.827$; 18, $Z = -1.283$, $P = 0.209$; 19, $Z = -1.160$, $P = 0.266$; 20, $Z = -1.946$, $P = 0.058$; 21, $Z = -0.971$, $P = 0.379$.
BC, blood culture; IQR, interquartile range; PCT, procalcitonin.

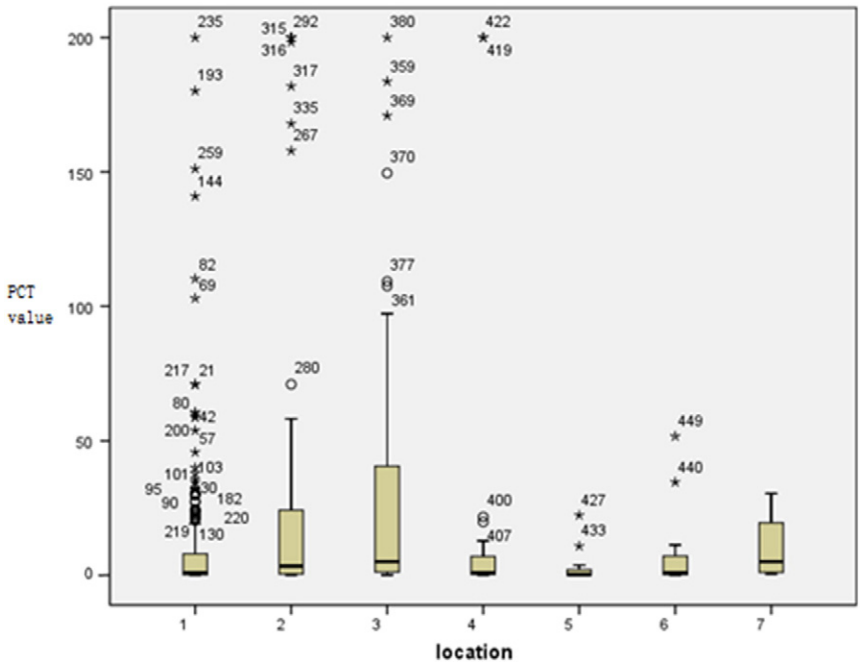

Fig. 3. PCT levels for infections at different sites. 1, Pneumonia; 2, abdominal infection; 3, urinary tract infection; 4, catheter-related infection; 5, soft tissue infection; 6, infective endocarditis; 7, pelvic infection.

Thus, PCT levels are a marker for sepsis, which can inform decisions on the ideal antimicrobial treatment for patients.

References

[1] Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med 2016;193:259–72.
[2] Liu V, Escobar GJ, Greene GD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014;312:90–2.
[3] Vincent JL. Clinical sepsis and septic shock—definition, diagnosis and management principles. Langenbecks Arch Surg 2008;393:817–24.
[4] Emonet S, Schrenzel J. How could rapid bacterial identification improve the management of septic patients? Expert Rev Anti Infect Ther 2011;9:707–9.
[5] Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.
[6] Peters RP, van Agtmael MA, Danner SA, et al. New developments in the diagnosis of bloodstream infections. Lancet Infect Dis 2004;4:751–60.
[7] Christ-Crain M, Muller B. Procalcitonin in bacterial infections –hype, hope, more or less? Swiss Med Wkly 2005;135:451–60.
[8] Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302:1059–66.
[9] Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
[10] Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;168:2000–7.
[11] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580–637.
[12] Pammi M, Zhong D, Johnson Y, et al. Polymicrobial bloodstream infections in the neonatal intensive care unit are associated with increased mortality: a case-control study. BMC Infect Dis 2014;14:390.
[13] Diekema DJ, Beekmann SE, Chapin KC, et al. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. J Clin Microbiol 2003;41:3655–60.
[14] Colafrancesco S, Priori R, Valesini G. Presentation and diagnosis of adult-onset Still's disease: the implications of current and emerging markers in overcoming the diagnostic challenge. Expert Rev Clin Immunol 2015;11:749–61.
[15] Liu W, Sigdel KR, Wang Y, et al. High level serum procalcitonin associated gouty arthritis susceptibility: from a southern Chinese Han population. PLoS One 2015;10:e0132855.
[16] Wallbach M, Vasko R, Hoffmann S, Niewold TB, Müller GA, Korsten P. Elevated procalcitonin levels in a severe lupus flare without infection. Lupus 2016;25:1625–6.
[17] Buhaescu I, Yoo RA, Izzedine H. Serum procalcitonin in systemic autoimmune diseases—where are we now? Semin Arthritis Rheum 2010;40:176–83.
[18] Uysal S, Meriç Yilmaz F, Boğdaycioğlu N, et al. Increased serum levels of some inflammatory markers in patients with multiple sclerosis. Minerva Med 2014;105:229–35.
[19] Bae YJ, Schaab M, Kratzsch J. Calcitonin as biomarker for the medullary thyroid carcinoma. Recent Results Cancer Res 2015;204:117–37.
[20] Trimboli P, Seregni E, Treglia G, et al. Procalcitonin for detecting medullary thyroid carcinoma: a systematic review. Endocr Relat Cancer 2015;22:R157–64.
[21] Avrillon V, Locatelli-Sanchez M, Folliet L, et al. Lung cancer may increase serum procalcitonin level. Infect Disord Drug Targets 2015;15:57–63.
[22] Weinstein MP. Blood culture contamination: persisting problems and partial progress. J Clin Microbiol 2003;41:2275–8.
[23] Simon L, Gauvin F, Amre DK, et al. 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.
[24] Kumar S, Ingle H, Prasad DVR, et al. Recognition of bacterial infection by innate immune sensors. Crit Rev Microbiol 2013;39:229–46.
[25] Castelli GP, Pognani C, Cita M, et al. Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. Crit Care Med 2009;37:1845–9.
[26] Maruna P, Frasko R, Gtirlich R. Plasma procalcitonin in patients with ileus relations to other inflammatory parameters. Physiol Res 2008;57:481–6.
[27] Leli C, Ferranti M, Moretti A, et al. Procalcitonin levels in gram-positive, gram-negative, and fungal bloodstream infections. Dis Markers 2015.
[28] Brodská H, Malíčková K, Adámková V, et al. Significantly higher procalcitonin levels could differentiate gram-negative sepsis from gram-positive and fungal sepsis. Clin Exp Med 2013;13:165–70.
[29] Elson G, Dunn-Siegrist I, Daubeuf B, et al. Contribution of toll-like receptors to the innate immune response to gram-negative and gram-positive bacteria. Blood 2007;109:1574–83.
[30] Müller B, White JC, Nylén ES, et al. Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab 2001;86:396–404.
[31] Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab 1994;79:1605–8.
[32] Limper M, de Kruif MD, Duits AJ, et al. The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. J Infect 2010;60:409–16.