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Role of procalcitonin in predicting etiology in bacteremic patients: Report from a large single-center experience

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ABSTRACT

Background: Procalcitonin (PCT) is routinely used for an early recognition of severe infections and for promoting appropriate use of antibiotics. However, limited data correlating values of PCT with etiology of infection has been reported.
Methods: During 2016, all positive blood cultures (BC) were retrospectively extracted in a 1100-beds Italian tertiary-care hospital. PCT and C-reactive protein (CRP) values were recorded within 24 h from BC collection. Primary endpoint of the study was to investigate the correlation between PCT and CRP values and the occurrence of bloodstream infections (BSI) caused by bacteria or fungi.
Results: During the study period, 1296 positive BC were included: 712 (54.9%) due to Gram-positive (GP), 525 (40.5%) due to Gram-negative (GN) strains, and 59 (4.6%) caused by fungi. Among GN isolates, enterobacteriaceae were reported in 453 (86.3%) cases. PCT values were higher in patients with GN etiology (26.1 ± 14.2 ng/mL) compared to GP (6.9 ± 4.5) and fungi (3.3 ± 2.4). Mean values for CRP in GN, GP, and fungi were not different. Receiver Operating Characteristic (ROC) curves showed an area under curve (AUC) of 0.71 for PCT and 0.51 for CRP among GN isolates; an AUC of 0.7 for PCT and 0.52 for CRP among enterobacteriaceae. Lower AUC for PCT were reported for GP and fungi.
Conclusions: PCT showed moderate performance in early detection (within 24 h) of Gram-negative infections, especially those caused by enterobacteriaceae. Further prospective studies are mandatory to confirm these observations.

Introduction

Rapid identification of bacterial infections and early initiation of antibiotic regimens are recognized as independent factors associated with favorable outcome [1–3]; therefore, immediate recognition of sepsis may be essential to start an appropriate antibiotic regimen [4,5]. However, in clinical practice a rapid identification of pathogens is often delayed due to available standard microbiological tests. The early identification of etiologies is crucial to overcome treatment delays and inappropriate therapies [6].

Procalcitonin (PCT) is a biomarker with a potential role in diagnosis and prognosis of bacterial infections, since its values appeared strictly correlated with the development of severe bacterial infections [7–9]. Systematic use of PCT has been proposed as part of the initial diagnostic pathway and for monitoring antibiotic treatment response and duration, especially in critically ill patients [10,11].

Recent studies showed the potential role of PCT for discriminating between severe infections caused by Gram-negative (GN) and Gram-positive (GP) bacteria and fungi [12,13].

Aim of this study was evaluation of PCT levels in predicting occurrence of BSI due to GN, especially enterobacteriaceae, GP, and fungi in a large population of patients with positive blood cultures (BC).

Materials and methods

Design of the study

All positive BC were retrospectively extracted, from January 1st to December 31st 2016, at a 1100-beds teaching hospital in Udine, Italy. Microorganisms detected in BC were considered as

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clinically relevant pathogens in following conditions: (1) isolation of a pathogen in ≥2 BC, considered as etiology of infection; (2) detection of pathogen in one set of BC, but consistent with cultures from other suspected foci of infection at the same time of BC collection; and (3) detection in one set of BC, reported by clinician as cause of infection based on clinical, radiological, and laboratory data. Coagulase-negative staphylococci (CoNS) and other skin commensals were not considered as etiology of infection when isolated from one BC set alone, and in absence of clinical data supporting a pathogenic role. For every positive BC sample included in the study were extracted PCT and C-reactive protein (CRP) values recorded ±24 h from BC collection.

All methods were carried out in accordance with local and international guidelines and regulations. The study was approved by local ethical committee (Department of Medicine, University of Udine, Piazzale Santa Maria della Misericordia 15, 33100, Udine, Italy). At time of BC acquisition, an informed consent was obtained from all subjects; if subjects were under 18 years from a parent and/or legal guardian.

Variables analyzed

Patient data were collected from medical charts and from hospital computerized databases or clinical charts according to a pre-established questionnaire. The following information were reviewed: demographics; clinical and laboratory findings; comorbid conditions; microbiological data; source of infection; PCT and CRP values (±24 h from BC collection); duration of intensive care unit (ICU) and hospital stay; the simplified acute physiology score (SAPS II); development of septic shock; 30-day mortality.

CRP, PCT and BC analysis

PCT concentration was measured by using ADVIA Centaur® BRAHMS Procalcitonin assay on Advia Centaur XP instrument (Siemens Healthineers), with functional sensitivity of 0.02 ng/mL; CRP concentration by using C-Reactive Protein gen.3 (CRPL3) assay on Cobas c 702® instrument (Roche), with functional sensitivity of 1 mg/L. BC were processed using the automated BD BACTECTM FX system (Becton-Dickinson Microbiology Systems).

Primary endpoint and statistical analysis

Primary endpoint of the study was to investigate the correlation between PCT and CRP values (±24 h from BC collection) with pathogens causing BSI.

Continuous variables are presented as mean ± SD, and differences were evaluated by t-test. Categorical variables were expressed as count and percentages and compared by chi-square test or Fisher's exact test, as appropriate. We evaluated discrimination using receiver operating characteristic curves (ROC). We compared ROC curves for CRP and PCT values. The calibration of the model was evaluated by the goodness-of-fit Hosmer-Lemeshow χ^2 statistic. The suggested cut-off values were determined by the Youden index; then, we calculated sensitivity, specificity, negative (NPV) and positive predictive values (PPV) for the cut-off point of PCT and CRP in predicting etiology of infection. To calculate these values were randomly extracted patients, hospitalized in the same wards during the study period, with negative BC in which were reported CRP and PCT values ±24 h from BC collection. Finally, we performed logistic regression analysis on CRP and PCT cut-off values predicting etiology of infection. All tests were two-tailed, and a P value < 0.05 was considered significant. All computations were carried out with SPSS 20.0 for Windows (SPSS Inc., Chicago, IL).

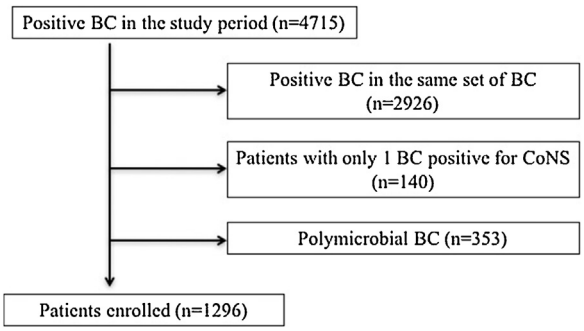

Fig. 1. Study flow diagram.
BC: blood cultures; CoNS: coagulase-negative stafilococci.

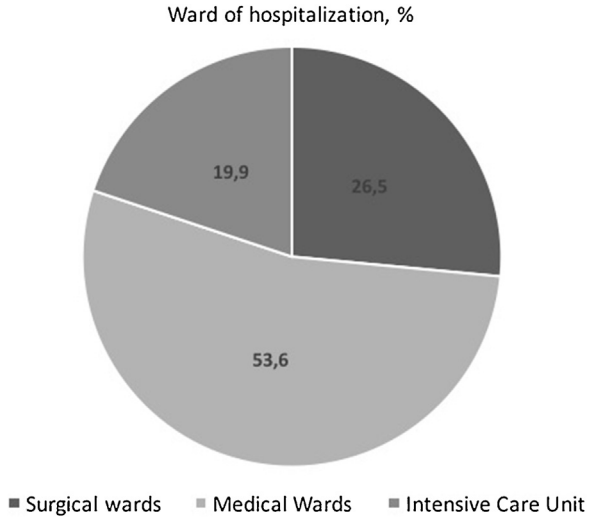

Fig. 2. Wards of hospitalization at time of BC positivity. BC: blood cultures.

Results

During the study period 4715 BC resulted positive. Positive BC in same BC set (n = 2926), patients with only 1 BC positive for CoNS (n = 140), and polymicrobial BC (n = 353) were excluded (see Fig. 1). A total of 1296 positive BC were retrieved: of these, 695 (53.6%) episodes were recorded in medical wards, 343 (26.5%) in surgical wards, and 258 (19.9%) in ICU, as reported in Fig. 2. Finally, BC were positive in 712 (54.9%) cases for GP strains, in 525 (40.5%) for GN strains, and in 59 (4.6%) for fungi.

In Table 1 are reported pathogens isolated from BC during the study period: the most frequent isolate was *Escherichia coli* (19.9%), followed by *Staphylococcus aureus* (19.2%), and CoNS (16.9%); *Candida albicans* was isolated in 40 (3.2%) samples. Among GN isolates, enterobacteriaceae were reported in 453 (86.3%) cases.

According with etiology of infection in Table 2 are reported age, sex, comorbidities, source of infection, length of hospital and ICU stay, severity of clinical condition, incidence of septic shock, and 30-day mortality in the three study groups. Differences were observed about PCT concentrations, that were higher in patients with GN etiology (26.1 ± 14.2 ng/mL), if compared to GP (6.9 ± 4.5 ng/mL) and to fungal (3.3 ± 2.4 ng/mL) isolates. Conversely, similar mean values were reported for CRP in GN, GP, and fungal etiology.

As reported in Fig. 3, ROC curves showed an area under curve (AUC) of 0.71 (CI 95% 0.65–0.75, p < 0.001) for PCT and 0.51 (CI 95% 0.45–0.56, p = 0.71) for CRP among GN isolates (Fig. 3-A); an AUC of 0.7 (CI 95% 0.64–0.75, p < 0.001) for PCT and 0.52 (CI 95% 0.46–0.58, p = 0.4) for CRP among enterobacteriaceae (Fig. 3-B); an AUC of 0.31 (CI 95% 0.26–0.36, p < 0.001) for PCT and 0.48 (CI 95% 0.42–0.53,

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Table 1
Pathogens isolated from BC during study period.

Etiologies	N = 1296 (%)
Escherichia coli	258 (19.9)
Staphylococci	
- CoNS	218 (16.9)
- *Staphylococcus aureus*	247 (19.2)
Klebsiella spp.	86 (6.7)
Enterococci	
- *E. faecalis*	58 (4.5)
- *E. faecium*	28 (2.1)
Candida spp.	
- *albicans*	40 (3.2)
- non-albicans	16 (1.2)
Pseudomonas aeruginosa	42 (3.2)
Enterobacter spp.	42 (3.2)
Streptococcus pneumoniae	18 (1.3)
Streptococcus gallolyticus (bovis)	14 (1.1)
Proteus spp.	12 (0.9)
Corynebacterium spp.	12 (0.9)
Serratia marcescens	9 (0.7)
Streptococcus pyogenes	7 (0.5)
Stenotrophomonas maltophilia	4 (0.3)
Acinetobacter baumannii	2 (0.1)
Other etiologies	183 (14.1)

BC: blood cultures; MDR: multidrug-resistant; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

p = 0.53) for CRP among GP isolates (Fig. 3-C); an AUC of 0.44 (CI 95% 0.33–0.55, p = 0.39) for PCT and 0.53 (CI 95% 0.42–0.65, p = 0.54) for CRP among fungi (Fig. 3-D).

Sensitivity, specificity, NPV and PPV of CRP and PCT in predicting BC positive for GN strains and enterobacteriaceae are summarized in Table 3. Among Gram-negative isolates, a CRP value >5 mg/L showed a sensitivity of 96.2%, a specificity of 6.2%, a NPV of 7.6%, and a PPV of 95.3%; a PCT value >0.5 ng/mL showed a sensitivity of 93.3%, a specificity of 29.8%, a NPV of 79.5%, and a PPV of 60.2%. Among enterobacteriaceae, a CRP value >5 mg/L showed a sensitivity of 95.4%, a specificity of 5.6%, a NPV of 5.5%, and a PPV of 95.4%; a PCT value >0.5 ng/mL showed a sensitivity of 97.9%, a specificity of 29.2%, a NPV of 92.2%, and a PPV of 61.9%; a PCT concentration >10 ng/mL showed a sensitivity of 64.6%, a specificity of 71.9%, a NPV of 73.4%, and a PPV of 63%.

Table 3
Sensitivity, specificity, NPV and PPV of CRP and PCT in BC positive for Gram-negative strains and enterobacteriaceae.

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Gram-negative (n = 525)				
CRP > 5 mg/L	96.2	6.2	7.6	95.3
PCT > 0.5 ng/mL	93.3	29.8	79.5	60.2
PCT > 2 ng/mL	76.7	50	73.4	54.5
PCT > 10 ng/mL	55	70.2	80.1	41.6
Enterobacteriaceae (n = 453)				
CRP > 5 mg/L	95.4	5.6	5.5	95.4
PCT > 0.5 ng/mL	97.9	29.2	92.2	61.9
PCT > 2 ng/mL	81.2	49	76.2	56.4
PCT > 10 ng/mL	64.6	71.9	73.4	63

CRP: C-reactive protein; PCT: procalcitonin; NPV: negative predictive value; PPV: positive predictive value; BC: blood cultures.

Finally, logistic regression analysis performed on CRP and PCT values predicting positivity of BC showed that a PCT value >10 ng/mL (OR 3.84, CI 95% 2.18–6.75, p < 0.001) was independently associated with GN isolation, while a PCT value >0.5 ng/mL (OR 6.01, CI 95% 1.16–31.72, p = 0.03), a PCT value >2 ng/mL (OR 2.52, CI 95% 1.28–3.96, p = 0.03), and a PCT value >10 ng/mL (OR 3.88, CI 95% 2.15–7.03, p < 0.001) were independently associated with BC positive for enterobacteriaceae (see Table 4).

Discussion

The main findings of this analysis confirm recent data on bacteremic patients with proven GN bacteremia, where higher PCT concentrations have a significant role to predict GN etiology, if compared with patients with GP bacteremia or fungal infection.

The association of GN bacteremia with high PCT concentrations, reported in our analysis, is in line with other studies performed among different patient populations [12,14–23]. As previously

Table 2
Clinical characteristics and outcome of patients according with etiology of infection.

Variables	Gram-positive bacterial etiology n = 712 (%)	Gram-negative bacterial etiology n = 525 (%)	Fungal etiology n = 59 (%)
Age, mean ± SD	58.1 ± 22.8	58.9 ± 24.2	61.1 ± 27.1
Male sex	350 (49.1)	259 (49.3)	28 (47.4)
Comorbidities			
Chronic liver disease	20 (2.8)	16 (3)	6 (10.1)
Neoplasm	71 (9.9)	68 (12.9)	9 (15.2)
Diabetes	163 (22.8)	142 (27.1)	22 (37.2)
Heart failure	247 (34.7)	212 (40.4)	15 (25.4)
Coronary artery disease	101 (14.2)	56 (10.6)	6 (10.1)
Chronic renal disease	86 (12.1)	62 (11.8)	8 (13.5)
COPD	187 (26.2)	141 (26.8)	17 (28.8)
Source of infection			
Primary bacteremia	268 (37.6)	207 (39.4)	22 (37.2)
CVC-related bacteremia	110 (15.4)	82 (15.6)	10 (16.9)
Pneumonia	302 (42.4)	218 (41.5)	0
Catheter-related urinary tract	103 (14.4)	144 (27.4)	16 (27.1)
SSTI	101 (14.2)	55 (10.4)	0
Intra-abdominal	68 (9.5)	66 (12.5)	12 (20.3)
Length of hospital stay	31.2 ± 27.1	33.6 ± 24.2	29.3 ± 26.5
Length of ICU stay, mean ± SD	27.7 ± 22.8	30.2 ± 20.2	18.9 ± 16.5
PCT concentration (ng/mL), mean ± SD	6.9 ± 4.5	26.1 ± 14.2	3.3 ± 2.4
CRP concentration (mg/L), mean ± SD	127.1 ± 113.1	126.9 ± 99.4	122 ± 98.9
SAPS II at time of infection onset, mean ± SD	25.1 ± 22.1	24.6 ± 21.4	24.3 ± 22.1
Sepsis or septic shock	121 (16.9)	92 (17.5)	11 (18.6)
30-day mortality	101 (14.2)	102 (19.4)	11 (18.6)

SD: standard deviation; ns: not significant; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CVC: central venous catheter; SSTI: skin and soft-tissue infection; PCT: procalcitonin; CRP: c-reactive protein; SAPS: simplified acute physiology score.

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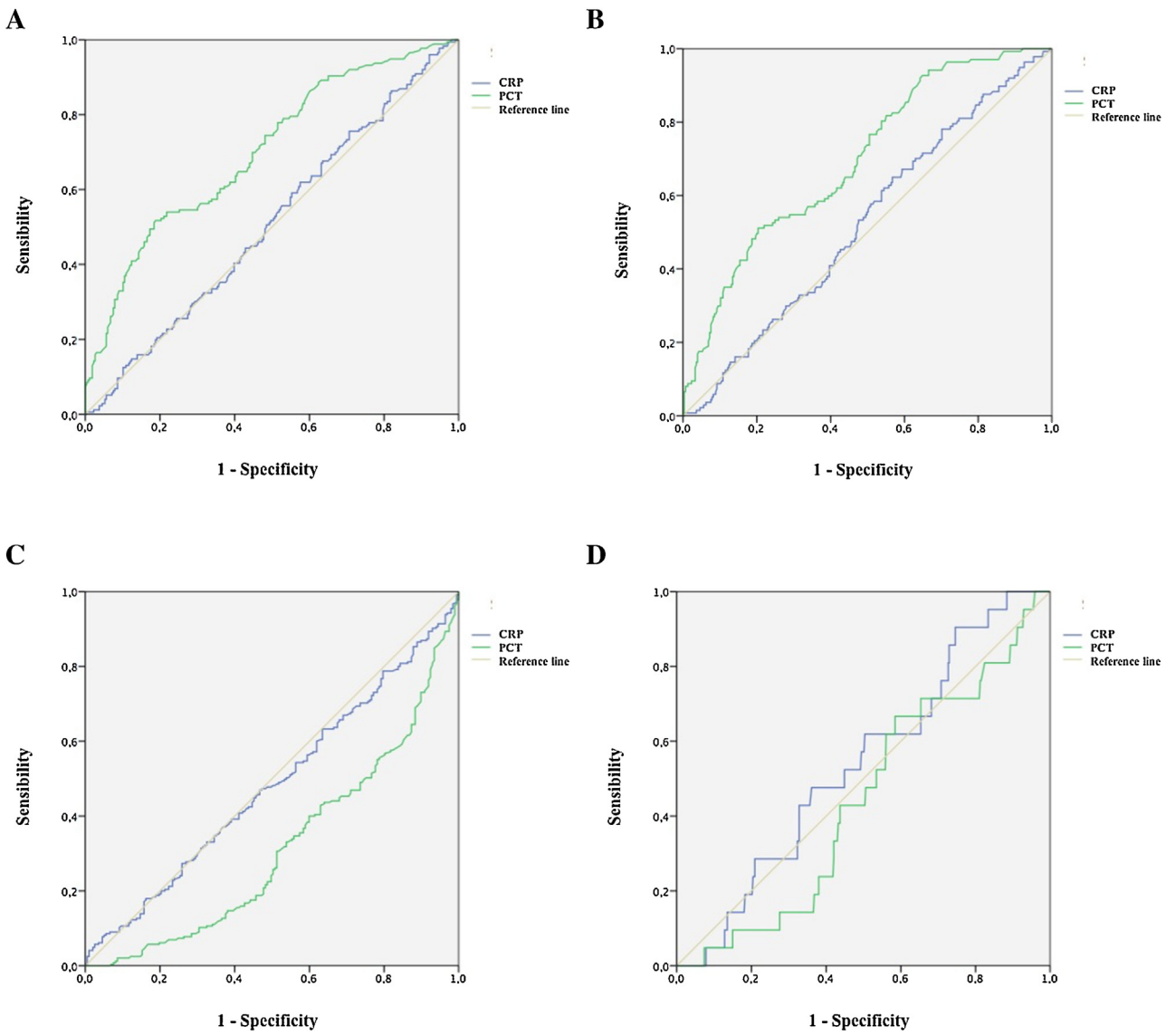

Fig. 3. ROC curves about PCT and CRP to predict BC positive for Gram-negative (A), enterobacteriaceae (B), Gram-positive (C), and fungi (D).
ROC: Receiver Operating Characteristic; CRP: C-reactive protein; PCT: procalcitonin; BC: blood cultures.

Table 4
Logistic regression analysis about CRP and PCT values in predicting positivity of BC for Gram-negative strains and enterobacteriaceae.

Gram-negative	OR	CI 95%	*p*
CRP > 5 mg/L	1.89	0.53–6.73	0.32
PCT > 0.5 ng/mL	3.12	0.62–15.71	0.16
PCT > 2 ng/mL	0.73	0.41–1.29	0.28
PCT > 10 ng/mL	3.84	2.18–6.75	**<0.001**
Enterobacteriaceae			
CRP > 5 mg/L	1.65	0.41–6.69	0.48
PCT > 0.5 ng/mL	6.01	1.16–31.72	**0.03**
PCT > 2 ng/mL	2.52	1.28–3.96	**0.03**
PCT > 10 ng/mL	3.88	2.15–7.03	**<0.001**

CRP: C-reactive protein; PCT: procalcitonin; BC: blood cultures.
In bold are reported p-value statistically significant.

reported, PCT production can be directly induced by inflammatory cytokines [24] and lipopolysaccharide, that is one of the most important cell wall component of GN bacteria, is precociously recognized by innate immune system via toll-like receptor 4 (TLR4), while lipoteichoic acid (LTA), a cell wall component of GP bacteria, is recognized by toll-like receptor 2 (TLR2) [25,26]. These differences in activation of TLR4, for GN bacteria, and TLR2, for GP bacteria, result in different production of inflammatory cytokines, with a different gene expression also in leukocytes [27]. Moreover, higher levels of IL-6 and IL-8 have been reported in patients with GN bacteremia probably contributing to these observed differences in PCT response during GN or GP bacteremia [28]. These mechanisms are directly related to PCT values reported in positive BC for enterobacteriaceae have been explored only in few studies [13]. Previous studies reported observations that enterobacteriaceae, such as *E. coli* and *K. pneumoniae*, at high concentrations (10^4 cells/mL) induce a greater IL-6 production compared to *P. aeruginosa* (10^6 cells/mL), in which production of IL-6 is lower [29]. Moreover, data reported in literature show as PCT values in GP are similar to those observed in fungal infection in almost all studies analyzing the role of PCT to predict BC results in bacteremic patients.

As matter of fact, collection of BC samples is universally reported as gold standard for etiological diagnosis of BSI, considering the high sensitivity and specificity to identify etiology of infection and then to test antimicrobial sensitivity; for these reasons, the delayed acquisition of BC can stop process for an early diagnosis of sepsis

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[30]. PCT can be a useful biomarker to detect bacterial etiology at initial stages of infection, but a major limitation is represented by the lack of identification of causative bacteria. A study conducted in acutely febrile patients reveals that PCT levels could be helpful also in differentiating bacterial from non-bacterial infections [24], and other studies have reported association between higher PCT levels and GN bacteremia, if compared to GP bacteremia [31–33]. Of interest, Thomas-Rüddel et al. recently assessed the correlation between PCT concentrations, in ICU patients, with different foci of infection during sepsis: in multivariate analysis focus of infection and etiology were independently associated with PCT concentration; therefore, variations in host response during bacteremia could depend from site of infection, giving another possible explanation for differences in PCT concentrations during different types of infection [19].

For most patients with positive BC the microbiological tests and the new microbiological techniques, like MALDI-TOF, are generally available during the first 24–48 h, but data about susceptibility usually require another 1–2 days. During this time, decisions about choice of antimicrobial regimens and source control of infection are only based on clinical judgment. Considering available data, no definitive conclusions support use of PCT, compared to CRP or other markers, in management of early-stage sepsis [34,35]; moreover, the higher cost of PCT can drive physicians to use other markers like CRP, resulting in a prolonged duration of hospitalization and difficulties to decide the appropriate approach to critically-ill patients. For all these reasons the clinical use of PCT, also in predicting BC results, is limited by several factors: first of all, patients with severe infections and low PCT concentrations has a low probability of GN bacteremia, but might still have a severe GN infection without blood dissemination; then, there is a large heterogeneity in PCT levels during GN, GP bacteremia and candidemia. Although observed AUCs for GN and GP bacteremia were very different also in our analysis, it is not sufficient for a clinical application; finally, a diagnostic test guiding decisions in critical settings needs to have a better diagnostic accuracy and higher sensitivity and specificity, than values reported in literature. Further studies are mandatory to confirm these observations; however, a recent important meta-analysis showed that PCT guidance was associated with a 2–4 days reduction in antibiotic exposure (5.7 vs 8.1 days, $p < 0.0001$) and a reduction in antibiotic-related side-effects (16% vs 22%, adjusted OR 0.68, $p < 0.0001$) [36].

On this basis, the debate about the use of PCT in clinical practice is about when to use it, in which patients, and how many times. Data reported in literature support a possible use of PCT, if compared to CRP or other tests, in the diagnosis and prognosis of infection, but PCT cannot be used as a stand-alone tool. However, as part of a clinical algorithm, PCT was associated with reduction of antibiotics overuse, especially in ICU patients. In our analysis, a CRP value >5 mg/L showed a high PPV but a low NPV compared to different cut-off of PCT that were independently associated with etiology of infection. So, in our interpretation CRP value could be not associated with etiology of infection but only with the presence of an infection.

In conclusions, our data confirmed previous observations about the role of PCT in predicting BC results in a large population of bacteremic patients [37]. Of interest, CRP was not able to significantly predict BC results, while PCT values correlated with GN bacteremia and, among GN isolates, specifically identified enterobacteriaceae. High PCT values (>10 ng/mL) resulted independently associated with GN isolation; moreover, increased PCT values were not strictly related with isolation of GP strains or fungi in BC. Even with the limitation of a single centre experience and the retrospective design of the study, these results may be important to define another role of PCT, helping physicians in a rapid identification of bacteremic patients at risk of GN infection (especially enterobacteriaceae) and driving choice for a more appropriate empirical antibiotic therapy, while awaiting for definitive microbiological results [38].

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None.

Conflict of interest

In the past five years MB has participated in advisory boards and/or received speaker honoraria from Achaogen, Angelini, Astellas, AstraZeneca, Bayer, Basilea, Cidara, Gilead, Melinta, Menarini, MSD, Nabriva, Paratek, Pfizer, Roche, The Medicine Company, Shionogi, Tetraphase, VenatoRX, and Vifor. The remaining authors have no conflicts of interest.

Author contribution

MB, AR and ER wrote the main manuscript text; AR, ED and MM collected clinical data; FD performed CRP and PCT analysis; AS and FC performed BC analysis. AR performed statistical analysis. All authors reviewed the manuscript.

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