Diagnostic and prognostic performances of serum procalcitonin in patients with bloodstream infections: A parallel, case-control study comprising adults and elderly

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Summary

Objective: To examine the diagnostic and prognostic performances of serum procalcitonin (PCT) in adult and elderly patients with bloodstream infections (BSIs).
Method: A total of 176 patients with culture-proven BSIs and 200 healthy counterparts were studied prospectively. Participants were studied in two adult (age≤65 years, n=92) and elderly (age>65 years, n=84) groups. Admission serum PCT level was measured using a standard enzyme-linked immunosorbent assay (ELISA) technique.
Results: The mean serum PCT level (in ng/mL) was significantly higher in cases than in controls (0.18 vs. 0.07, p=0.01 in adults; 0.20 vs. 0.07, p=0.002 in elderly). At cut-off values of 0.09 ng/mL in adults and 0.08 ng/mL in the elderly, the corresponding sensitivity and specificity were 82.6 and 82.0% in adults, and 69.1 and 70.0% in elderly, respectively. At a cut-off value of 0.2 ng/mL, the sensitivity and specificity of serum PCT in predicting 28-day mortality were 81 and 81.7% in adults, and 75 and 80.4% in elderly, respectively.
Conclusion: Although admission serum PCT is a sensitive and specific biomarker for the diagnosis of BSIs in patients younger than 65 years old, its short-term prognostic value is comparable between adults and the elderly.

Keywords: procalcitonin, bloodstream infections, age.

Introduction

Bloodstream infections (BSIs) are very common and potentially lethal, particularly in the elderly and among immunocompromised patients.[1] Early diagnosis and implementation of an appropriately therapy, however, could reduce the morbidity and mortality associated with BSIs.[2]

Blood culture is generally considered the method of choice for the diagnosis of sepsis, but it is time-consuming, i.e., results are typically available only after 12-48 hours. In addition, skin contamination may mislead physicians in some cases.[3,4] As a result, since uncertain exclusion of sepsis from a differential diagnosis list in acute stages is risky, the administration of empiric antibiotics is usually inevitable and has untoward consequences.[5]

To preclude this shortcoming, researchers have tried to find an accurate test for the diagnosis of BSI at early stages. In 1993, Assicot et al.[6] found that serum procalcitonin (PCT) levels rise when sepsis or other significant bacterial infections occur. Soon later, several studies suggested that serum PCT could be used as a sensitive biomarker to detect or rule out BSIs in patients with suspected bacterial infections and systemic inflammatory response syndrome (SIRS).[7,8] Despite many studies and even some meta-analyses, the topic is still a matter of heated debate due to inconsistent findings.[9-14] Such heterogeneity might arise from using different subgroups of patients,[9] inconsistency in defining bacteremia and septicemia[10-12] and severe methodological flaws (such as using a small sample size and problematic grouping).[13]

A factor that has been neglected in previous studies is the patients' age.[12] This may also affect the prognostic value of PCT in patients with BSIs.[15] As to address this limitation, we have performed this study to examine diagnostic and prognostic values of serum PCT in the management of adult and elderly patients with BSIs, separately.

METHOD

From April 2013 through June 2016, a total of 206 adult hospitalized patients with culture-proven BSIs and 200 healthy random volunteers from patients' families were prospectively enrolled into this case-control study. Patients with renal disease/malignancy (n=14), immune problems (n=6), recent trauma/surgery (n=6) and a history of recent antibiotic therapy for more than 48 hours (n=4) were excluded, yielding 176 patients in the case group for final analysis (Figure 1). The ethics committee of our university approved our study and informed written consents were obtained from all of the participants.

Participants were divided into groups based on age, namely adults (up to 65 years) and elderly (65 plus years), with both case and control sets as follows: 92 cases vs. 100 controls and 84 cases vs. 100 controls, respectively.

A case with BSI (bacteremia or sepsis) was reported when any pathogenic bacterial species excluding coagulase-negative staphylococci, aerobic and anaerobic diphtheroids, *Micrococcus* species, and *Bacillus* species[16] was recovered in 1 or 2 sets of aerobic and anaerobic blood cultures.

Bacteremia was defined as the presence of viable bacteria in the blood; and sepsis was defined when the bacteremia was accompanied by the systemic inflammatory response syndrome (SIRS) as recognized by the presence of at least two of the following: (i) body temperature > 38°C or < 36°C, (ii) heart rate > 90 beats/min, (iii) respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mmHg, and (iv) white blood cell count > 12,000 cells/mm³, < 4,000 cells/mm³, or > 10% band.[17] Most probable sources of BSIs and the types of isolated microorganisms were also reported.

The admission serum PCT level was measured in ng/mL with enzyme-linked immunosorbent assay (ELISA) using a standard autoanalyzer (Elecsys 2010, Roche, Switzerland) according to the manufacturer's guideline.

All patients were followed up for 28 days and the prognostic ability of PCT for predicting 28-day mortality was also examined.

Statistical analysis

The statistical analyses were performed using the SPSS software version 22.0 (IBM Inc., USA). A normal distribution of quantitative data was assured using the Kol-
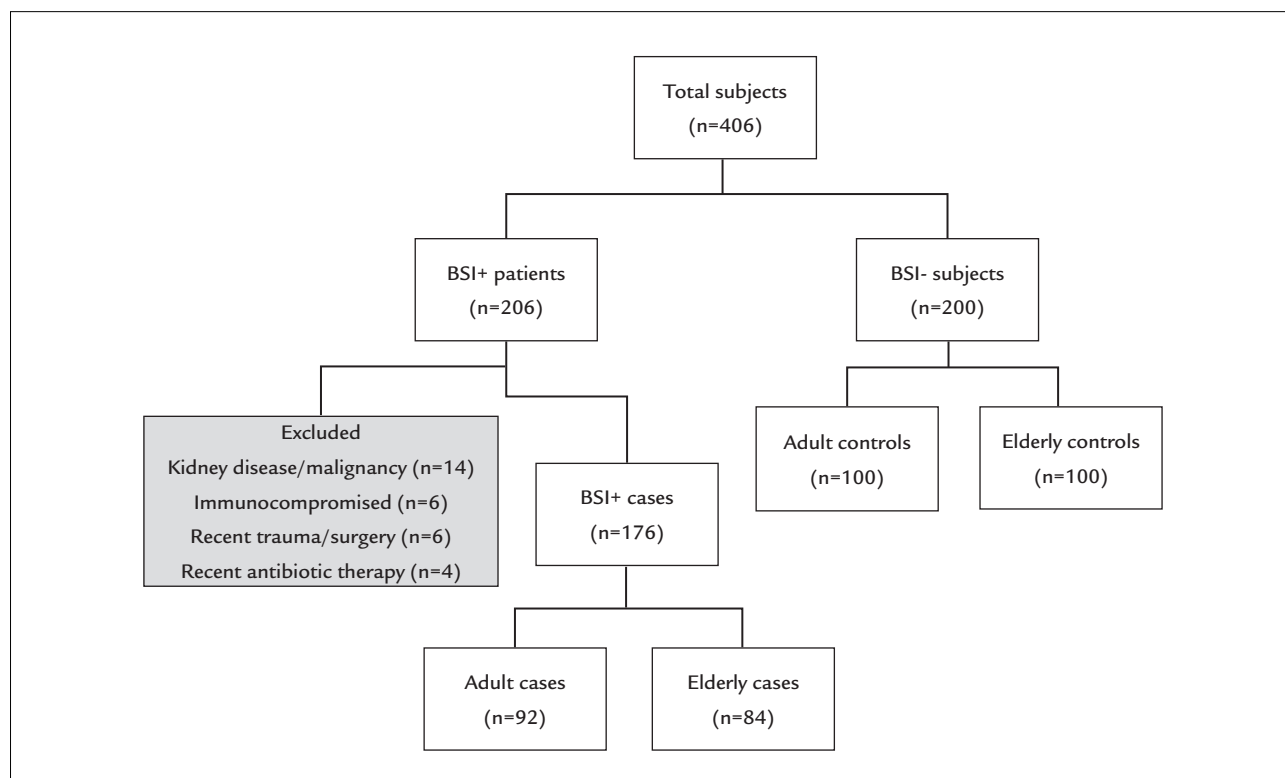

FIGURE 1 Flowchart of case and control study groups.

mogorov-Smirnov test. The quantitative data were presented as mean±standard deviation or mean (standard error of the mean). Independent samples t-test and the Chi-square test were used for comparisons. The Pearson coefficient (r) was employed to assess correlations. Receiver operator characteristic (ROC) curves were plotted to detect area under the curve (AUC) and optimal cut-off levels. A p-value of less than 0.05 (two-tailed) was considered statistically significant.

RESULTS

Demographics of the study population in two adult and elderly groups are summarized and compared between cases and controls in Table 1. Accordingly, the groups were comparable in terms of sex and age of participants.

Sepsis was diagnosed in 42 patients (45.7%) in the adult group and in 44 patients (52.4%) in the elderly group. Within a 28-day follow-up time, 21 patients (22.8%) died in the adult group and 28 patients (33.3%) died in the elderly group.

Most probable sources and microbial etiologies of BSI in the case groups are shown in Table 2. Accordingly, both in the adult and elderly groups, urinary tract and respiratory infections were the most frequent possible sources of BSIs and *Staphylococcus aureus* and *E. coli* were the most commonly isolated bacteria, respectively.

There was no significant difference between males and females for the mean serum PCT level (0.13 [0.02] ng/mL vs. 0.18 [0.03] ng/mL, respectively; p=0.18). Patients' age and serum PCT level did not correlate significantly in the case groups (r=0.5, p=0.60). No significant correlation was found between serum procalcitonin level and age in adult (r=0.2, p=0.19) or elderly (r=0.02, p=0.91) groups.

In both the adult and elderly groups, mean serum PCT levels were significantly higher in cases than in controls (p=0.01 and 0.002, respectively). Between patients in adult and elderly groups, however, no significant difference was found for the mean serum procalcitonin level (p=0.54).

The AUC of serum PCT level for predicting BSI was 0.81 (95% confidence interval [95CI] 0.71-0.91; p<0.001) in the adult group and 0.73 (95CI 0.63-0.84; p<0.001) in the elderly group. Accordingly, the optimal cut-off level of serum PCT was 0.09 ng/mL (sensitivity, 82.6%; specificity, 82.0%) in the adult group and 0.08 ng/mL (sensitivity, 69.1%; specificity, 70.0%) in the elderly group.

In both the adult and elderly groups, mean serum PCT levels were significantly higher in dead versus surviving patients after 28 days (p<0.001 for both).

TABLE 1 Demographic data of the study population.

Variable		Adults		p-value	Elderly		p-value
		Cases (n=92)	Controls (n=100)		Cases (n=84)	Controls (n=100)	
Sex	Male	54 (58.7)	56 (56)	0.79	50 (59.5)	56 (56)	0.73
	Female	38 (41.3)	44 (44)		34 (40.5)	44 (44)	
Age (y)		42.96±11.16 (19-63)	44.74±12.63 (23-65)	0.47	74.14±7.11 (66-90)	72.18±5.86 (66-91)	0.15

Data are presented as frequency (%) or mean±standard deviation (minimum-maximum).

TABLE 2 Probable sources and etiologies of bloodstream infection in adult and elderly patients.

Variable		Groups	
		Adults (n=92)	Elderly (n=84)
Source of infection	Urinary tract	38 (41.3)	32 (38.1)
	Respiratory system	22 (23.9)	24 (28.6)
	Abdomen	14 (15.2)	11 (13.1)
	Neuromeningeal	3 (3.3)	4 (4.8)
	Multiple	15 (16.3)	13 (15.5)
Bacteria	*Staphylococcus aureus*	44 (47.8)	41 (48.8)
	E. coli	40 (43.5)	37 (44)
	Klebsiella	3 (3.3)	0 (0)
	Enterobacter	2 (2.2)	2 (2.4)
	Pseudomonas	1 (1.1)	0 (0)
	Miscellaneous	2 (1.1)	4 (4.8)

Data are presented as frequency (%).

The AUC of serum PCT level for predicting 28-day mortality was 0.82 (95% confidence interval [95CI] 0.70-0.94; p<0.001) in adults and 0.83 (95CI 0.73-0.92; p<0.001) in the elderly. Accordingly, the optimal cut-off level of serum PCT was 0.2 ng/mL in both the adult and elderly groups, with a sensitivity of 81 and 75% and specificity of 81.7 and 80.4%, respectively.

DISCUSSION

Conventional strategies such as using clinical symptoms and biological markers of inflammation, e.g. leukocytes and C-reactive protein, have had poor diagnostic value to detect or rule out bacteremia and sepsis in previous reports, with an estimated false-negative rate of 15-50%.[1,18]

In normal conditions, serum PCT is produced by the C-cells in the thyroid gland and all is cleaved to calcitonin, catacalcin and an N-terminal residue. During clinically significant infections such as bacteremia and sepsis, however, the serum level of PCT rises dramatically. Although the exact source of this acute-phase reactant protein is not known, it is thought to be related to extra-thyroid tissues, because patients with previous total thyroidectomy still exhibit high levels of procalcitonin in their serum during infection.[19]

Some investigators have suggested serum PCT as an appropriate tool to differentiate bacterial infections from SIRS caused by viruses or noninfectious conditions such as trauma, burns and organ malfunction.[20] Even though, for the purpose of BSI management, PCT has been found superior to conventional diagnostic methods in terms of test speed and accuracy in several studies, there is still no general consensus in this regard or in suggesting a widely accepted cut-off value despite the availability of several case-control studies and large meta-analyses.[9-14] For example, in a study by Liaudat et al.[21] that included 50 hospitalized bacteremic patients and 150 controls, at cut-off values of 0.5 and 0.2 ng/mL the sensitivity and specificity of PCT to detect BSIs were 56-92% and 83-43%, respectively. Sudhir et al.[1] included 100 patients with sepsis in their study and reported a high sensitivity value (94%) for serum PCT to detect BSIs. In a recent study, Wang et al.[22] used serum PCT for the diagnosis of BSIs in a retrospective design. The best cut-off value was reported at 0.80 ng/mL, with a sensitivity and specificity of 83 and 65%, respectively. They suggested serum PCT as a reliable marker to exclude bacteremia in patients with suspected BSIs. In another series by Riedel et al.[23] comprising 295 patients with symptoms suggestive of systemic infection and 16 patients with definite diagnosis of BSIs, the sensitivity and specificity of PCT assay with a calcu-

lated threshold of 0.1475 ng/mL to detect BSIs were 75 and 79%, respectively. Accordingly, they suggested PCT as a useful marker to rule out sepsis and systemic inflammation in emergency departments. In other studies,[24,25] the suggested optimal cut-off points for serum PCT varied between 0.1 to 2.0 ng/mL, with sensitivity and specificity values ranging from 35 to 97% and 78 to 99%, respectively. In a recent meta-analysis by Hoeboer et al.,[14] the diagnostic accuracy of serum procalcitonin for bacteremia was examined. In all, 58 studies including 3,420 patients with bacteremia were reviewed. At a cut-off value of 0.5 ng/mL, the overall sensitivity and specificity of this biomarker were 76 and 69%, respectively. The authors, however, concluded that due to the heterogeneity of available studies, further research is needed in this regard.

According to a report, age and past medical history are two important parameters that might contribute to such heterogeneity.[26] For instance, it has been shown that false-positive results of PCT testing are frequent among patients with renal problems.[23]

To exclude these potential confounding factors, we only included patients with intact renal function and normal immune system. In addition, the diagnostic performance of serum PCT was examined separately in adults (18-65 years) and the elderly (over 65 years) in our study. Based on our findings, at optimal cut-off values of 0.09 ng/mL for adults and 0.08 ng/mL for the elderly, serum PCT was accompanied with a better diagnostic performance in the former (sensitivity and specificity of 82.6 and 82% in adults versus 69.1 and 70% in the elderly, respectively).

The usefulness of serum PCT to manage patients with suspected BSIs has rarely been examined in the elderly.[27] It is still not clear how the age of patients may affect serum levels of PCT during BSIs. In a recent study by Stucker et al.,[28] and, in accordance with our findings, the authors concluded that serum PCT should not be considered a reliable indicator of BSIs among the elderly.

Whenever sepsis occurs, the innate immune response is activated by releasing various cytokines such as interleukins 1, 6 and 8, tumor necrosis factor-α, and interferon-γ from the endothelial and epithelial cells and macrophages.[29] When this reaction is extensive and diffused, endothelial cell damage may ensue, which in turn may cause hemodynamic changes and organ failure.[27] Among the elderly and immunocompromised patients, however, the classic signs of sepsis may be missing because of decreased inflammatory responses in such patients.[30] In addition, it has been shown that serum PCT levels correlate positively with the severity of inflammatory responses to infections.[31] This can explain why serum procalcitonin is a more reli-

able indicator of BSIs under 65 years of age. To the best of the authors' knowledge, ours is the first study in the literature that assesses the diagnostic performance of serum PCT among adults and the elderly in parallel.

It should be kept in mind that BSIs are more common among the elderly. Besides a high prevalence, comorbid chronic diseases that usually develop with advanced age, a compromised immune system, inability to communicate adequately with the physician, and nonspecific signs and symptoms of infection further deteriorate the prognosis of BSIs in the elderly.[8] So, as a second goal, we examined the prognostic utility of serum PCT in predicting 28-day mortality among adult and elderly patients. In conformity with some recent studies,[15,32-34] we showed that, at a cut-off value of 0.2 ng/mL in both groups, this biomarker is a good indicator of short-term mortality (sensitivity and specificity of around 80%). Again, our study is the first in the medical literature to report an almost equal performance of serum PCT to predict mortality in both adult and the elderly patients with BSIs.

In addition to its high accuracy to detect BSIs, serum PCT has been suggested as an inexpensive biomarker that is not affected by viral infections or inflammatory reactions of non-infectious origin. It is capable to detect bacteremia rapidly (< 1 hour) and has an established prognostic significance as well as longer half-life in the systemic circulation (25-30 h) compared to other conventionally used cytokines. In addition, analyzing the serum level of this biomarker requires only a small amount of blood sample.[23,35,36]

Despite significant advantages of our study, such as using matching groups of patients and controls as to age, past medical history and ethnicity,[1] a state-of-the-art, up-to-date technology to determine serum PCT levels, culture-proven final diagnosis in all participants, and the study on a rather large number of patients, it may be found limited in terms of not incorporating the severity of BSIs in the final conclusion.

Finally, since in the elderly the studied variable is prognostic rather than diagnostic, it is likely that the rise of procalcitonin is time-dependent in this age group. So, further longitudinal studies should be considered in the future.

Conclusion

We showed that serum PCT can be used more reliably in adults than in the elderly with suspected BSIs. The short-term prognostic value of this biomarker, however, does not differ considerably between old and younger patients.

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