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ORIGINAL ARTICLE

Pancreatic stone protein and soluble CD25 for infection and sepsis in an emergency department

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ABSTRACT

Background Infection is a common problem in emergency departments (EDs) and is associated with high mortality, morbidity and costs. Identifying infection in ED patients can be challenging. Biomarkers can facilitate its diagnosis, enabling an early management and improving outcomes. In the critical care setting, two emerging biomarkers, pancreatic stone protein (PSP) and soluble CD25 (sCD25), have demonstrated to be useful for diagnosis of sepsis. We aimed to assess the diagnostic value of these biomarkers, in comparison with procalcitonin (PCT), for infection and sepsis in an ED population with suspected infection.

Materials and methods Through a prospective, observational study, we investigated the utility of serum PCT, PSP and sCD25 levels, measured on admission, for diagnosis of infection and sepsis, defined according to the recently updated for sepsis (Sepsis-3), in patients presenting to the ED for suspected infection. Diagnostic accuracy was evaluated by using receiver operating characteristic curves (ROC) analysis.

Results Of the 152 patients enrolled in this study, 129 had a final diagnosis of infection, including 82 with noncomplicated infection and 47 with sepsis. Median PCT, PSP and sCD25 levels were significantly higher in patients with infection and sepsis. The ROC curve analysis revealed a similar diagnostic accuracy for infection (ROC area under the curve (AUC) PCT: 0·904; sCD25: 0·869 and PSP: 0·839) and for sepsis (ROC AUC: PCT: 0·820; sCD25: 0·835 and PSP: 0·872).

Conclusions Pancreatic stone protein and sCD25 perform well as infection and sepsis biomarkers, with a similar performance than PCT, in ED patients with suspected infection. Further larger studies investigating use of PSP and sCD25 are needed.

Keywords Emergency department, infection, pancreatic stone protein, procalcitonin, sepsis, soluble CD25.

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Introduction

Infectious diseases are a major health problem and are associated with high mortality and morbidity in all areas of health care, including emergency department (ED) [1]. Besides, infection has a great impact on the need for microbiological tests and antibiotic treatments, involving increased human and economic cost. Although in most individuals the host response is adequate to deal with the potential threat, in some cases, infection gives rise to an inappropriate host response, and when this results in the development of organ dysfunction, the term 'sepsis' is used according to the updated definition for sepsis (Sepsis-3) [2]. Despite advances in antibiotic therapy and cardiovascular and respiratory support, sepsis represents a major cause of morbidity and mortality [3]. Guidelines by the Surviving Sepsis Campaign (SCC) emphasize the importance of an early diagnosis and appropriate therapy in the initial hours because both have a significant impact on outcomes [4]. Delays in the beginning of the antimicrobial treatment are associated with worse prognosis [5,6]. Therefore, clinicians are faced with two primary challenges: first, identifying infection and targeting patients who should be given antibiotic therapy and second, assessing the severity of disease.

In the clinical practice, diagnosis of infection is based on the onset of characteristic clinical signs and symptoms of a host response, an increase in inflammatory and/or infection biomarkers levels and the results of cultures and other microbiological tests [7]. However, different aetiologies often exhibit overlap in the clinical presentation, and classic signs and symptoms of infection are not always present, especially in

patients with multiple comorbidities, such as elderly population [8] or immunocompromised patients [9]. Moreover, culture-dependent diagnosis of infection is slow. Therefore, biomarkers may provide a more rapid means to rule-in or rule-out infection and to make a decision about the need for antibiotics and to assess the need for admission to ward or intensive care unit (ICU) [7].

In 2010, Pierrakos and Vincent [10] identified 178 sepsis biomarkers evaluated in 3370 studies; however, only two of them have been widely used in clinical practice: C-reactive protein (CRP) and procalcitonin (PCT). CRP has been in use for over 20 years. Despite its sensitivity for infection, it is not very specific, unless high cut-off levels are used which in turn reduces sensitivity. PCT has been identified as having the highest performance among biomarkers for the diagnosis and prognosis of sepsis [11], although the evidence presented by Tang *et al.* [12] does not support its widespread use for sepsis diagnosis. PCT has some limitations because its elevations are not as specific for infection as was once believed [13]. This biomarker may be elevated in a number of disorders in the absence of infection, especially following surgery and trauma [14]. Moreover, false-negative results can be observed in the early course of infection [15]. Wacker *et al.* [16] concluded that PCT cannot be recommended as the single definitive test for sepsis diagnosis. There remains a need for better infection biomarkers.

Pancreatic stone protein (PSP) and soluble CD25 (sCD25) have recently emerged as promising sepsis biomarkers. PSP, also known as lithostathine and regenerating protein (PSP/reg), is a lectin-binding protein [17]. It is constitutively secreted by pancreatic acinar cells into pancreatic juice along with zymogens, and it is also secreted by subsets of intestinal and gastric cells [18]. Its physiological role is not clear. PSP levels increase in acute and chronic pancreatitis, chronic renal failure and gastrointestinal malignancy [19,20]. Studies focusing on infection and inflammation postulated that PSP would be a pro-inflammatory mediator that binds and activates neutrophils, thereby acting as an acute-phase protein that responds to injury during the early phase of infection [21]. Soluble CD25 (sCD25) is the soluble form of CD25 which is shed into the blood. $CD4^{+}CD25^{+}Foxp^{3+}$ regulatory T cells (Treg cells) play an important role in the immune response, exerting a pronounced anti-inflammatory effect through contact-mediated direct inhibition of other immune cells and produce high levels of sCD25, interleukin-4 and IL-10 [22]. Sepsis is associated with the increased percentages of Treg cells and elevated plasma levels of sCD25 [23].

Recent studies have demonstrated that PSP and sCD25 performed well to identify sepsis [24] and to predict the mortality in ICU septic patients [25,26]. However, the performance of infection biomarkers may vary between different clinical settings, such as the ED, ICU and ward [15]. Therefore, in this study, we aimed to evaluate the diagnostic utility of two emergent biomarkers, PSP and sCD25, in comparison with a traditional biomarker, PCT, for diagnosis of infection and sepsis, defined according to recently published Sepsis-3 definition [2], in an unselected cohort of patients admitted to ED for suspected infection.

Materials and methods

Study design and population

This observational prospective single-centre study was conducted at the ED of Hospital General Universitario Santa Lucía of Cartagena, Spain, from October to November 2013. It was approved by the local ethics committee. Informed consent was obtained from all participating patients or from their close relatives.

All consecutive adult (≥ 14 years) patients fulfilling all the following inclusion criteria: (i) suspicion of infection, as judged by the ED physician on admission, and (ii) clinical request of body fluid cultures (blood culture and others, according to suspected source of infection) drawn at the time of admission, were included in the study. Exclusion criteria were the following: (i) age less than 14 years old, (ii) evidence of an immunocompromised stage (e.g. malignancy), terminal stage of disease, and (iii) pregnancy.

Classification of patients

Infection was defined by using both clinical and laboratory patients' data recorded in ED and hospital documentation. All final patient classifications were determined by using a majority rule among two physicians, all blinded to biomarker results. Patients designated as 'infected' included all patients with clinically relevant positive bacterial microbiological cultures collected within 48 h of enrolment. Of note, those patients with strong evidence for infection in the absence of positive cultures were also included in the 'infected' designation. These cases included such findings as radiographic evidence (computed tomography scan, chest X-ray, etc.) or physical examination findings strongly suggesting bacterial infection in the absence of positive cultures. All other subjects were classified as 'noninfected'.

For further classification of infected patients, Sepsis-3 definitions were used [2]. Organ dysfunction was identified as an acute change in sequential [sepsis-related] organ failure assessment (SOFA) score of ≥ 2 points or more resulting from infection. Septic shock was defined as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mm Hg and having a serum lactate level > 2 mM

despite adequate volume resuscitation [2]. According to these criteria, infected patients were classified into 'sepsis' and 'noncomplicated infection' subgroups.

Sampling and laboratory analysis

Venous blood samples were collected on admission to ED for white blood count, neutrophil count, blood chemistry and coagulation tests, as required, and analysed in a central laboratory within 2 h. Leftover serum was immediately frozen and stored at −80 °C until the end of study when all samples were analysed for PSP and sCD25.

Pancreatic stone protein levels were measured on microplate assays, using a sandwich isoform-specific enzyme-linked immunoabsorbent assay (ELISA), as previously described [21]. sCD25 levels were measured on microplate assays, using also an ELISA sandwich assay, according to manufacturer's recommendations. Serum PCT levels were measured in a Cobas 411 analyser (Roche Diagnostic, Mannheim, Germany), according to the electrochemiluminescence immunoassay measurement principle, with a detection limit of 0·02 ng/mL, functional sensitivity of 0·06 ng/mL, measurement range of 0·02–100 ng/mL, intra-assay imprecision of 0·9–1·3% and total precision of 4·0–3·7%, according to manufacturer's instructions.

Statistical analyses

The normality of continuous variables was tested by Kolmogorov–Smirnov or Shapiro–Wilk tests, as appropriate. Continuous variables are presented as median (interquartile range [IQR]) for non-normally distributed data or mean (standard deviation [SD]) for normally distributed data. Comparisons of group differences for continuous variables were made by the Mann–Whitney *U*-test or the Student's *t*-test, as appropriate. Categorical variables are presented as number and percentage in each category. The significance of differences in percentages was tested by the Chi-squared test. Sensitivity, specificity and likelihood ratios of PCT, sCD25 and PSP for the diagnosis of infection and sepsis were calculated using final diagnosis categorization. A receiver operating characteristic (ROC) analysis was performed for each of the biomarkers, and their diagnostic accuracy for infection and sepsis was compared with the DeLong test. The optimal threshold value was set for each ROC curve through the Youden Index (corresponding to the maximum of the sum 'sensibility + specificity').

The statistical analyses were performed using SPSS v. 20·0 (software SPSS Inc., Chicago, IL, USA). All *P*-values < 0·05 were considered statistically significant.

Reporting of the study conforms to CONSORT-revised and the broader EQUATOR guidelines [27].

Results

Baseline characteristics of the study population

The study population consisted of a total of 152 adult patients (median age: 66 years [IQR: 33], range: 16–97 years; 88 (57·9%) male) presenting to ED and who fulfilled inclusion criteria. Thirty-six patients had received antibiotic therapy previously (23·7%). A total of 129 patients were classified as infection (84·9%). The most common sources of infection were urinary (n = 53 (41·1%) and respiratory tracts (n = 41 (31·8%). Infection was microbiologically proven in 69 patients (53·5%); in 49 patients (71%), infection was caused by gram-negative bacteria, and in 12 patients (17·4%), by gram-positive bacteria; in five patients (7·2%), gram-positive and gram-negative bacteria were isolated, and in three patients (4·2%), infection was caused by other type of microorganism. Bacteraemia was detected in 30 patients (23·3%), with *Escherichia coli* being the microorganism most frequently isolated (63·3%). Among patients with confirmed infection, the final diagnosis was noncomplicated infection and sepsis in 82 (63·6%) and 47 (36·4%), respectively. A comparison of demographic and baseline data, including the sources of infection, is summarized in Table 1.

Discrimination between noninfection and infection

There were no significant differences between the two groups regarding age, gender, antibiotic therapy prior to ED visit and infection focus. Serum levels of the different biomarkers measured in our study are shown in Fig. 1. Levels of PCT, PSP and sCD25 were significantly higher in patients with infection than in noninfected patients (Table 1).

For discrimination between infection and noninfection, ROC curve analysis revealed AUCs values of 0·904, 0·869 and 0·839 for PCT, sCD25 and PSP, respectively, without statistically significant differences between them (Table 2). ROC curves are shown in Fig. 2, and optimal thresholds and the performance of each biomarker are shown in Table 2.

Discrimination between noncomplicated infection and sepsis

When 'noncomplicated infection' and 'sepsis' groups were compared, patients with sepsis were older and the requirement for management in ICU was higher. Regarding biomarkers, serum levels of the three biomarkers were significantly higher in patients classified into sepsis group (Table 1).

For discriminating between noncomplicated infection and sepsis, ROC AUCs were 0·820, 0·872 and 0·835 for PCT, PSP and sCD25, respectively, without statistically significant differences between them (Table 3). ROC curves are shown in Fig. 2, and optimal thresholds and the performance of each biomarker are shown in Table 3.

Table 1 Characteristics of the study population

	Noninfection *n* = 23 (15·1%)	Infection *n* = 129 (84·9%)	*P*	Noncomplicated infection *n* = 82 (63·6%)	Sepsis* *n* = 47 (36·4%)	*P*
Age, years (Median [IQR])	66 (36)	67 (32)	0·386	64 (31)	73 (27)	0·028
Gender, male/female	12/11	76/53	0·830	49/33	20/27	0·798
Previous antibiotic therapy, *n* (%)	4 (17·4)	32 (24·8)	0·441	22 (26·8)	10 (21·3)	0·482
Infection focus, *n* (%)						
Urinary		53 (41·1)		35 (42·7)	18 (38·3)	
Respiratory		41 (31·8)		29 (35·4)	12 (25·5)	
Abdominal		19 (14·7)		9 (11)	10 (21·3)	
Skin and soft tissues		8 (6·2)		6 (7·3)	2 (4·3)	
Central nervous system		1 (0·8)		0 (0)	1 (2·1)	
Isolated bacteraemia		1 (0·8)		1 (1·2)	0 (0)	
Other/Unknown		6 (4·7)		2 (2·4)	4 (8·5)	
Biomarkers levels (Median [IQR])						
PCT (ng/mL)	0·07 (0·10)	0·54 (2·23)	< 0·001	0·33 (0·72)	3·78 (13·4)	< 0·001
PSP (ng/mL)	23 (14)	73 (173)	< 0·001	44 (62)	252 (254)	< 0·001
sCD25 (ng/mL)	3·8 (0·9)	7·5 (7·6)	< 0·001	5·8 (4·0)	12·0 (10·5)	< 0·001

IQR, Interquartile range; CRP, C-reactive protein; PCT, Procalcitonin; PSP, Pancreatic stone protein; sCD25, soluble CD25.
*Including sepsis (*n* = 37 [78·7%]) and septic shock (*n* = 10 [21·3%]).

Biomarker levels were analysed for bacteraemia. PSP, sCD25 and PCT were significantly higher in patients in which bacteraemia was detected (PSP: 133 ng/mL (219) vs. 59 ng/mL (127); $P = 0{\cdot}044$, sCD25: 12·1 ng/mL (11·1) vs. 6·9 ng/mL (5·1); $P = 0{\cdot}003$, PCT: 2·14 ng/mL (14·52) vs. 0·43 ng/mL (1·13); $P < 0{\cdot}001$). When biomarker levels were compared between patients with microbiologically proven infection and those with clinical or radiologically documented infection, no significant differences were observed.

Discussion

An accurate and timely diagnosis of infection and sepsis is critical for the optimal management of patients, and helps limiting mortality and improving patient outcomes [4]. A new definition for sepsis (Sepsis-3) has been recently published [2]. However, this definition has some limitations; among them, there was no attempt to redefine infection. Rather, it next sought to generate recommendations for clinical and other criteria, such as infection and/or inflammatory biomarkers, that could be used to identify infection and sepsis among patients with suspected infection, mainly in patients with multiple comorbidities as elderly, in which the incidence and short-time mortality of the infectious diseases have increased significantly in recent years [1] and the clinical manifestations are often nonspecific and variable [28].

Procalcitonin is widely reported as a useful biomarker to identify bacterial infection [29,30], including in elderly [31] and immunocompromised patients [32], to differentiate sepsis from other noninfectious causes of SIRS [16] and to assess the sepsis severity [33]. Its measurement is included in some guidelines and may be considered in patients with acute heart failure with suspected coexisting infection, particularly for the differential diagnosis of pneumonia [34], and for the management of adult lower respiratory tract infections [35]. Some authors have recently recommended the inclusion of PCT in guidance protocols for early stopping of antibiotics in critically ill patients [36,37]. However, although PCT is currently the biomarker most commonly used in the clinical practice, it has some limitations [15]. A previous study has reported the diagnostic value of PSP and sCD25 for sepsis in ICU setting [24], but to our knowledge, no study has evaluated the diagnostic utility of both biomarkers in ED setting.

In this study, performed in patients at the time of admission to ED, we have investigated the diagnostic accuracy of PSP and sCD25 for infection and sepsis, as compared with PCT, and the main finding is that PSP and sCD25 perform at least

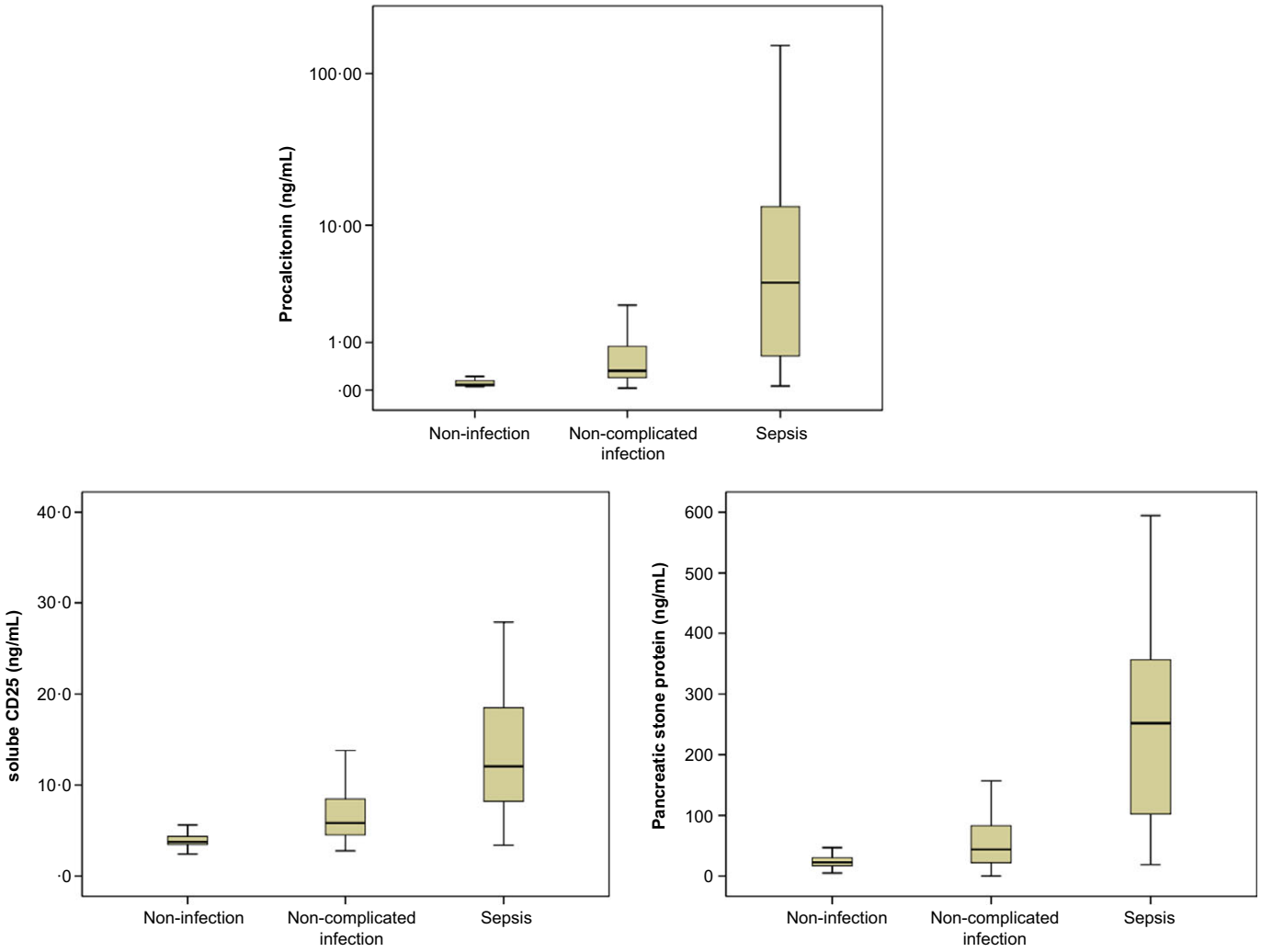

Figure 1 Median (boxplots) values of procalcitonin, pancreatic stone protein and soluble CD25 in different conditions.

Table 2 Diagnostic accuracy of pancreatic stone protein (PSP), soluble CD25 (sCD25) and procalcitonin (PCT) for infection

Biomarker	PSP (ng/mL)	sCD25 (ng/mL)	PCT (ng/mL)
AUC (95% CI)	0·839 (0·773–0·904) $P < 0·001$	0·869 (0·796–0·942) $P < 0·001$	0·904 (0·852–0·955) $P < 0·001$
Optimal cut-off*	41·5	4·4	0·2
Sensitivity (%) (CI 95%)	67·4 (58·6–75·4)	85·3 (78·0–90·9)	79·8 (71·9–86·4)
Specificity (%) (CI 95%)	95·7 (78·1–99·9)	78·3 (56·3–92·5)	91·3 (72·0–98·9)
LR + (95% CI)	15·5 (2·3–105·9)	3·9 (1·8–8·5)	9·2 (2·4–34·6)
LR − (95% CI)	0·34 (0·3–0·4)	0·19 (0·1–0·3)	0·22 (0·2–0·3)

AUC, area under the curve; CI, confidence interval; LR (+), likelihood ratio positive; LR (−), likelihood ratio negative.
Comparisons between biomarkers: PSP vs. sCD25 $P = 0·456$; PSP vs. PCT $P = 0·094$; sCD25 vs. PCT $P = 0·465$.
*According Youden index.

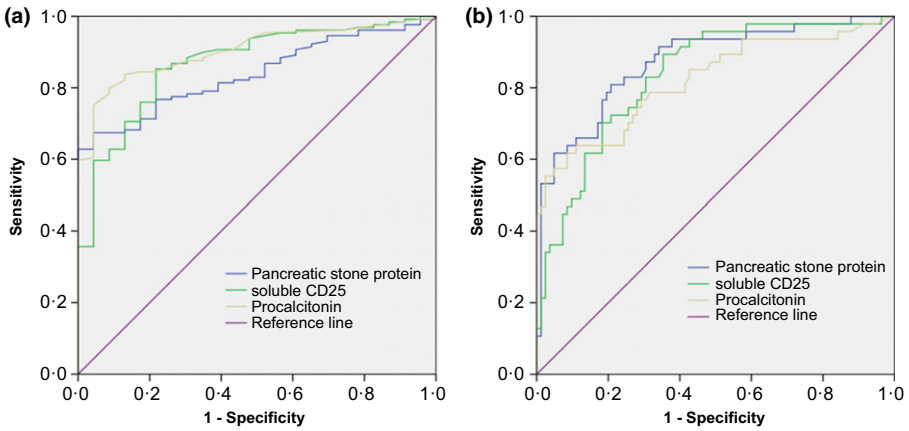

Figure 2 Receiver operating characteristic for procalcitonin, pancreatic stone protein and soluble CD25 for diagnosis of infection (a) and for diagnosis of sepsis (b).

Table 3 Diagnostic accuracy of pancreatic stone protein (PSP), soluble CD25 (sCD25) and procalcitonin (PCT) for sepsis

Biomarker	PSP (ng/mL)	sCD25 (ng/mL)	PCT (ng/mL)
AUC (95% CI)	0·872 (0·807–0·937) $P < 0·001$	0·835 (0·764–0·906) $P < 0·001$	0·820 (0·739–0·901) $P < 0·001$
Optimal cut-off*	96·6	6·87	2·02
Sensitivity (%) (CI 95%)	80·9 (66·7–90·9)	89·4 (76·9–96·5)	61·7 (46·4–75·5)
Specificity (%) (CI 95%)	79·3 (68·9–87·4)	64·6 (53·3–74·9)	91·5 (83·2–96·5)
LR + (95% CI)	3·90 (2·5–6·1)	2·53 (1·9–3·4)	7·23 (3·4–15·2)
LR − (95% CI)	0·24 (0·1–0·4)	0·16 (0·07–0·4)	0·42 (0·3–0·6)

AUC, area under the curve; CI, confidence interval; LR (+), likelihood ratio positive; LR (−), likelihood ratio negative.
Comparisons between biomarkers: PSP vs. sCD25 $P = 0·297$; PSP vs. PCT $P = 0·218$; sCD25 vs. PCT $P = 0·749$.
*According Youden index.

comparably with PCT to detect infection and to identify sepsis among infected patients.

In our study, PCT, PSP and sCD25 performed well as markers for infection and for sepsis, with ROC AUCs above 0·8. Llewelyn *et al.* [24] reported higher serum PSP, PCT and sCD25 levels in patients with sepsis, defined as SIRS in presence of infection (Sepsis-2 definition), than in patients with noninfective SIRS, with ROC AUCs in distinguishing both conditions of 0·93, 0·84 and 0·90, respectively, slightly higher than ROC AUCs found in our study in differentiating infected from noninfected patients; this difference could be due to the different criteria used to classify the patients and a generally higher severity of disease expected in a ICU setting.

In the ED setting, several recent studies using the previous sepsis definition support the use of PCT for diagnosis of sepsis. Indeed, for Hur *et al.* [38] PCT-based sepsis diagnosis was more reliable and discriminating than clinical sepsis diagnosis. Magrini *et al.* [39] reported a ROC AUC value of 0·79 for sepsis in patients with symptoms of infection, improving this diagnostic accuracy when PCT was combined with other biomarkers such as CRP and WBC. However, comparison of our results with those obtained in these studies is not possible due to differences in the criteria for classification of patients. Also in ED patients, Liu *et al.* [40] reported a ROC AUC value for PCT of 0·741 (95% CI: 0·703–0·779) for severe sepsis, term similar to sepsis in the new Sepsis-3 definition, which is lower than in our study (ROC AUC: 0·820). Recently, PCT was reported as an accurate diagnostic marker, with a ROC AUC value of 0·84, for pneumonia in patients presenting to ED with dyspnoea [41]. In other setting, Klouche *et al.* [42] have reported a ROC AUC value of 0·80 for PCT to differentiate infected from noninfected patients in ICU patients, which is also lower than in our study (ROC AUC: 0·904). A similar performance (ROC AUC: 0·780) has been reported by Koch *et al.* [43] to discriminate between sepsis and nonsepsis in critically ill patients. This performance was lower in Godnic *et al.* [44] study, in which PCT showed a ROC AUC value of 0·630 to detect bacterial infection between ICU patients with SIRS.

Our study has several important strengths. First, the updated definition for sepsis has been used to classify the patients. Second, we have evaluated the biomarkers in unselected patients who were considered by their ED physicians to have

an infection. Patients with inflammatory response but without suspected infection were not included in the study, thereby allowing a challenging, real-life assessment of biomarkers, because our study population closely resembles the one ED physicians face in their daily practice.

Our study has also some limitations. First, it was a single-centre study, so the results may not be applicable to other settings, and with a small sample size. Second, we have assessed the diagnostic accuracy for infection and sepsis at the time of sampling and we cannot draw conclusions about the value of biomarkers as predictors for later development of sepsis or the impact of serial measurements. Further investigation is necessary to determine whether these biomarkers could predict the development of sepsis or the progression of severity. Third, we did not exclude from the analysis patients with chronic renal failure or gastrointestinal diseases, conditions in which increases in PSP have been reported [19,20]. Fourth, the small number of patients classified as septic shock (n = 10) does not allow us to evaluate reliably the utility of biomarkers to reflect the severity of sepsis. Finally, in our study, to classify the patients, mandatory organ dysfunction was the definition used for sepsis; this makes difficult the comparison with previous studies using the former definition of sepsis.

In conclusion, our results suggest that two novel biomarkers, PSP and sCD25, performed well to detect infection and to identify patients with sepsis in the ED setting when applying the recently revised sepsis definitions [2]. Our findings support the assessment of both biomarkers by further larger studies to aid in the clinical decision process in ED patients with suspected infection.

Conflict of interest

Abbott Diagnostics supported the study providing PSP and sCD25 reagents. MB (now at Philips Handheld Diagnostics, Eindhoven, The Netherlands) was employee of Abbott GmbH & Co. KG. Wiesbaden, Germany, when study was performed. All other authors declare that there is no conflict of interest. Abbott GmbH and Co. KG did not participate in the protocol development or interpretation of the results.

Authors' contributions

LGG and MDA designed the study. EJS, AHH and PET recruited the subjects for the study. SRA, RJS and AOF compiled the clinical data and categorized the subjects. EJS was responsible for measuring PSP and sCD25. LGG and MB analysed the data and wrote the manuscript.

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