Lack of admission biomarkers' clinical utility in outcomes prediction in patients suspected with infection in the emergency department

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ABSTRACT

Introduction

Initial procalcitonin (PCT) levels may fail in mortality and septic shock prediction and raise cost-effectiveness issues. Since measurement of lactate, C-reactive protein (CRP), white blood cells and neutrophils is common in the emergency department (ED), we compared prediction abilities of these biomarkers to PCT.

Methods

From January 1st to December 31st, 2018, an observational, single center, retrospective study was conducted in the adult ED of the XXX University Hospital (XXX). Endpoints were bacteremia, septic shock, and in-hospital mortality, related to the same ED visit.

Results

Over one year, 459 patients suspected with infection were included, of mean age 60.4 years (SD: 22.0), with 50.8% male, and 364 (79.3%) were hospitalized following ED visit. Overall, 45 (9.8%) patients had a bacteremia, 39 (8.5%) a septic shock and 54 (11.8%) died during their hospitalization.

PCT and CRP showed the best discrimination for bacteremia, with an area under curve (AUC) of 0.68 for PCT and 0.65 for CRP. PCT and lactate showed similar good discriminative power for septic shock, with an AUC of 0.78 for both, and poor discrimination for in-hospital mortality, with an AUC of 0.62 for PCT and 0.69 for lactate.

Systolic blood pressure and pulse oximetry showed similar discrimination for septic shock as PCT or lactate, while they showed higher discrimination for in-hospital mortality than PCT.

Conclusion

Usual admission biomarkers lack clinical utility in predicting septic shock or in-hospital mortality. CRP and PCT are poorly efficient in predicting bacteremia.

CLINICIANS' CAPSULE

What is known about the topic ?

- PCT has shown some interest in clinical outcome prediction and early risk stratification.

What did this study ask ?

- Is there a difference in clinical outcome prediction ability between PCT, lactate, CRP, leukocytes and neutrophils ?

What did this study find ?

- Similar discriminative value between PCT and CRP for bacteremia, and between PCT and lactate for septic shock and in-hospital mortality.
- Similar discriminative value between systolic blood pressure + pulse oximetry and PCT or lactate for septic shock, and higher discriminative value of systolic blood pressure + pulse oximetry, than PCT for in-hospital mortality.

Why does this study matter to clinicians ?

- The lack of admission biomarkers' clinical utility, especially in predicting septic shock or in-hospital mortality, may make emergency physicians reconsider their initial prescriptions for patients suspected with infection in the emergency department.

KEY WORDS

Procalcitonin; Infection; Lactate; Outcome prediction; Emergency Department.

INTRODUCTION

The biomarker procalcitonin (PCT) has shown some interest in clinical outcome prediction [1,2]of sepsis and bacteremia in infected patients [3-5]. Used in association with other biomarkers, PCT

improves early risk stratification and bacteremia prediction [5-7], helping emergency physicians (EPs) to make quick decisions in an increasingly crowded emergency department (ED).

Yet, initial low PCT levels are not uncommon among patients diagnosed with septic shock [8], and initial PCT levels may fail in mortality, sepsis and septic shock prediction [9-11]. Consequently, since suspected infections are a frequent reason for ED visits, PCT prescriptions for clinical outcome prediction may raise cost-effectiveness issues, encouraging EPs to reasonably adapt their prescriptions to each patient clinical presentation.

On the other hand, measurement of lactate, C-reactive protein (CRP), white blood cells (WBC) and neutrophils, is common in infected patients during ED visits, with inferior laboratory dosing costs compared to PCT. Lactate seems as efficient as PCT in bacteremia prediction [5], CRP has shown diagnostic accuracy equal to PCT in sepsis [12], WBC count has similar sepsis and in-hospital mortality prediction abilities as PCT [3], and neutrophils seem to predict septic shock and mortality [11].

In the context of ED visits for patients suspected with infection, no study compared the clinical outcome prediction ability of initial PCT levels to initial lactate, CRP, WBC and neutrophils levels, separately and all together, in terms of bacteremia, septic shock and in-hospital mortality. The purpose of this study, conducted in the ED of a University Hospital, was to compare these prediction abilities.

METHODS

Aim and outcomes

The first aim of this study was to investigate the association of initial PCT, lactate, CRP, WBC and neutrophils levels, and major clinical outcomes, in ED patients suspected with infection. The second aim was to compare the discriminative ability of each admission biomarker, alone or in combination, regarding the clinical outcomes, and to determine their sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), considering specific cut-offs.

Endpoints were bacteremia, septic shock, and in-hospital mortality, related to the same ED visit. Blood cultures performed in the ED or in the first days after admission in hospitalization wards were used. Only bacteremia associated with the infection site related to the ED visit were considered. The 2016 Surviving Sepsis Campaign criteria were used to diagnose septic shocks [13]. In-hospital

mortality corresponded to patients not surviving at hospital discharge ; analysis was confined to hospitalized patients (we did not consider patients discharged from the ED directly to home).

Design

We conducted an observational, single center, retrospective study, in the adult ED of the XXX University hospital (XXX) from January 1st to December 31st, 2018. All PCT assays were considered, except in the following situations: duplicates, patients under 18 years old or with active malignancy or final non-infectious diagnosis, and patient files with relevant missing data. In a second time, patients who did not have all the above-mentioned biomarkers obtained were excluded. All considered biomarkers were issued from the first set of blood testing.

Biological data were collected using Haemonetics software. PCT, lactate and CRP concentrations were performed with a Cobas 8000 biochemistry analyzer (Roche diagnostic). The serum concentrations of PCT were measured by Elecsys BRAHMA PCT electrochemiluminescence immunoassay, the serum concentrations of lactate were determined using lactate oxidase specific enzyme, and the serum concentrations of CRP were determined by latex-enhanced turbidimetric immunoassay according to the manufacturer's instructions. WBC count and neutrophils levels were measured with ADVIA analyzer (Siemens-healthineers). Blood cultures were carried out using BACTALERT analyzer (Biomérieux), maintained on average five days in the incubator (maximum ten days if an endocarditis was suspected) and considered sterile beyond these deadlines. Blood culture vials with color change (due to pH variation promoted by bacteria), were analyzed by a bacteriologist to determine the bacterial type and the antibiogram. Clinical data were collected using Easily software. They included demographic data, ED nurse triage level using the FRench Emergency Nurses Classification in Hospital scale (FRENCH) [14], initial vital signs, patient comorbidities, infection site, and occurrence of the outcomes.

Before or during the study, emergency physicians and nurses were given no specific recommendations and followed no prescription algorithm regarding ED patient management.. Biomarkers were prescribed at physician's discretion.

The study was authorized by the French national commission for data privacy (Commission Nationale Informatique et Libertés, CNIL), and performed in accordance with the Helsinki Declaration.

Statistical analysis

Frequencies for qualitative data and mean with standard deviation (SD) or median with interquartile range (IQR) for quantitative data, were used as appropriate to describe the population. Associations between bacteremia, septic shock, in-hospital mortality and socio-demographic, clinical and biological data were investigated using the Chi square or Fisher's exact test, Student's t-test or Mann Whitney, as appropriate.

The discriminative ability of admission biomarkers was assessed for each outcome, using the area under the receiver operating characteristics curve (AUC) and 95% confidence interval. The discriminative ability of vital signs significantly associated with outcomes was further assessed. Forest plots were used to present the data.

Se, Sp, PPV and NPV of PCT, lactate, CRP, WBC count and neutrophils, were calculated using the following cut-offs, according to usual biochemistry laboratory cut-offs and previous studies [1,15]:

- PCT ($ng.mL^{-1}$): 0.25 or 0.5
- Lactates ($mmol.L^{-1}$): 2
- CRP ($mg.L^{-1}$): 20 or 100
- WBC count ($.10^9$ $cells.L^{-1}$): 4 and 12
- Neutrophils ($.10^9$ $cells.L^{-1}$): 9 or 75% of the WBC count

Analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Population

In 2018, 1711 PCT assays were performed at the request of the ED. Four hundred and fifty-nine patients benefited from simultaneous assays of PCT, lactate, CRP, WBC count and neutrophils. Flow chart is detailed in Figure 1.

Patient characteristics and clinical outcomes

The mean age of patients was 60.4 years (SD: 22.0) and 50.8% were male. Main acute infection sites leading to ED visits were bronchopulmonary in 31.4%, urogenital in 19.0%, intra-abdominal in 16.1%, skin and soft tissue in 10.0%, and undetermined in 13.5%. Other specified infection sites included ear, nose, throat, eye, tooth, cardiovascular, bone and neurological infection sites. Diabetes and obesity concerned 25.7% and 14.2% of patients, respectively. Among the 459 patients, 361 (78.6%) were hospitalized following ED visit. Patient characteristics stratified by outcome are shown in Table 1.

Overall, 45 (9.8%) patients had a bacteremia, 39 (8.5%) a septic shock and 54 (11.8%) died during their hospitalization. Bacteremia was associated with higher temperature (p = 0.0260), obesity (p = 0.0113), higher PCT (p < 0.0001), CRP (p = 0.0014) and neutrophils (p = 0.0492) levels. Septic shock and in-hospital mortality were associated with older patients (p = 0.0060 and p = 0.0012, respectively), higher FRENCH level, lower systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, pulse oximetry, and Glasgow coma scale (GCS), higher PCT (p < 0.0001 for bacteremia and septic shock, p = 0040 for in-hospital mortality) and higher lactate (p < 0.0001 for septic shock and in-hospital mortality) levels. In addition, septic shock was associated with diabetes (p = 0.0221) and higher CRP levels (p = 0.0006).

Characteristics of the 393 patients excluded due to lack of simultaneous essays of admission biomarkers, are presented in the Appendix.

Admission biomarkers discriminative ability for clinical outcomes

PCT and CRP showed equal poor discrimination for bacteremia, with an area under curve (AUC) of 0.68 (0.59-0.77) for PCT and 0.65 (0.56-0.73) for CRP (Figure 2). No other biomarker (lactate, WBC count, neutrophils) alone or in association, showed significantly better discrimination for bacteremia (Table 2). The added value of vital signs for bacteremia discrimination was not studied as it did not show any significant difference between groups (bacteremia *versus* no bacteremia).

PCT and lactate showed similar good discriminative power for septic shock, with an AUC of 0.78 (0.70-0.85) for PCT and 0.78 (0.70-0.86) for lactate. CRP discriminative ability for septic shock, was lower than PCT and lactate ones. WBC count and neutrophils showed no discrimination for septic shock.

PCT and lactate showed poor discrimination for in-hospital mortality, with and AUC of 0.62 (0.55-0.70) for PCT and 0.69 (0.61-0.77) for lactate (non-significant difference between PCT and lactate, p = 0.0711). CRP, WBC count and neutrophils showed no discrimination for in-hospital mortality.

Sensitivity, specificity, positive predictive value and negative predictive value of admission biomarkers

PCT cut-off of 0.5 $ng.mL^{-1}$ and CRP cut-off of 100 $mg.L^{-1}$ predicted bacteremia with similar Se (55.6% both) and Sp (66.4% and 64.0%, respectively), closed to lactate cut-off of 2 $mmol.L^{-1}$ (Se: 51.1%, Sp: 67.4%). CRP cut-off of 20 $mg.L^{-1}$ and neutrophils cut-off of 75% WBC, showed the highest Se in bacteremia prediction (86.7% and 82.2%, respectively), but very low Sp (26.6% and 27.3%, respectively) (Table 3). Leukopenia accounted for 12 (2.6%) patients in the overall population, and 1 (2.4%) patient in the immunosuppressed population.

PCT cut-off of 0.5 ng.mL^{-1} showed better Se in septic shock prediction than lactate cut-off of 2 mmol.L^{-1} (76.5% and 66.7%, respectively), but similar Sp (68.1% and 68.6%, respectively). PCT cut-off of 0.25 ng.mL^{-1}, CRP cut-off of 20 mg.mL^{-1} and neutrophils cut-off of 75% WBC, showed the highest Se in septic shock prediction (84.6%, 87.2% and 84.6%, respectively), with higher Sp for PCT (56.0%, 26.4% and 27.4%, respectively).

PCT cut-off of 0.5 ng.mL^{-1} and lactate cut-off of 2 mmol.L^{-1} predicted in-hospital mortality with similar Se (57.4% both) and Sp (62.3% and 64.8%, respectively).

PCT, lactate and vital signs discrimination in septic shock and in-hospital mortality

Considering table 1 with significant differences in patients' vital signs in the groups septic shock and in-hospital mortality, further investigations were carried out about the discriminative ability of vital signs for the two outcomes (Table 2 and Figure 3). SBP showed good discrimination for septic shock, with AUC of 0.76, very close to PCT and lactate. SBP, pulse oximetry and temperature, with AUC of 0.70, 0.70 and 0.69, respectively, showed higher discrimination for in-hospital mortality than PCT (p = NS). In addition, combined SBP and pulse oximetry showed significant higher discrimination for in-hospital mortality than PCT (p = 0.0021) (Table 2 and Figure 2).

DISCUSSION

This first study investigating the prognostic value of both PCT, lactate, CRP, WBC count and neutrophils, alone and combined, in terms of bacteremia, septic shock and in-hospital mortality, in ED patients suspected with infection, has 3 key findings. First, considering the cut-off of 0.5 ng.mL^{-1} for PCT, 100 mg.L^{-1} for CRP, and 2 mmol.L^{-1} for lactate, PCT and CRP showed similar poor discriminative value for bacteremia, and PCT and lactate showed similar good discriminative value for septic shock and poor discriminative value for in-hospital mortality, with no significant added value of admission biomarker combinations, thus differentiating their usefulness in the context of clinical outcome prediction. Second, Se and Sp of PCT, CRP and lactate were relatively low, while they showed their highest discriminative value for the three outcomes, differentiating again the usefulness of these biomarkers. Third, several vital signs were as efficient as (and sometimes even better than) PCT and lactate in septic shock and in-hospital mortality predictions, emphasizing the interest of clinical examination over biomarkers measurements.

PCT has been extensively studied as a predictive biomarker, with contrasting findings. For Sager et al., PCT was a strong and independent outcome predictor for 30-day mortality across different medical diagnosis in unselected medical ED patients [1]. For Magrini et al. PCT was strongly useful as

sepsis biomarker in patients suspected with infection [3]. But on the other hand, Chloe et al. found initial low PCT levels to be common among patients diagnosed with severe sepsis or septic shock in the ED [8], and Karon et al. showed poor diagnostic utility of PCT for septic shock prediction [11]. For Ljungström et al., the neutrophil-lymphocyte count ratio had equivalent performance to PCT for bacterial sepsis diagnosis [15], and for Shim et al., PCT was equivalent to lactate in predicting bacteremia and 28-day mortality [16].

Heterogenicity in the studied populations, in objectives to achieve, and sometimes disconnections from the ground truth, had made it difficult for emergency physicians to bring out a clear idea of what PCT could add in risk stratification in patients suspected with infection. It appeared that an observational study such as this one, reflecting aspects of routine care, could help emergency physicians with their medical reasoning. Moreover, as CRP is a historic biomarker of inflammation, as WBC are part of the systemic inflammatory response syndrome, as lactate is overproduced in sepsis, and as bacteremia, septic shock and in-hospital mortality are three major outcomes in infected patients, a simultaneous evaluation of these biomarkers, with admission biomarkers prescribed on purpose by emergency physicians, was necessary.

If PCT did not fail in predicting the above-mentioned outcomes, it failed in significantly outperforming CRP in bacteremia prediction and lactate in septic shock and in-hospital mortality prediction. In the context of a generalized ED overuse, it raises the cost-effectiveness issue of PCT prescriptions, while usual “low-cost” admission biomarkers can reach the same goal. To go further, we wonder about the real interest of these biomarkers in septic shock and in-hospital mortality predictions, while a simple clinical examination may be as efficient or even better.

This study has some limitations. First, the bacterial or viral etiology of each infection was not investigated due to lack in gold standard criteria. Second, the cause of in-hospital mortality was not assessed, and death may have not been directly related to the infection. Third, blood cultures were not performed in all patients, and antibiotics may have been administered before blood cultures. Therefore, the statistical link between bacteremia and the biomarkers may have been misestimated. Fourth, only ED patients suspected with infection whose PCT was prescribed were included. Even if we designed the study on purpose, we set aside other infected patients, limiting these results from being applied to all infected patients. Fifth, as we considered only patients with simultaneous measurements of PCT, lactate, WBC and neutrophils, we selected patients with a more severe clinical presentation, since lactate is more often measured in such clinical conditions.

CONCLUSIONS

In patients suspected with infection in the ED, usual admission biomarkers, alone or in combination, lack any clinical utility in predicting septic shock or in-hospital mortality, while CRP and PCT are poorly efficient in predicting bacteremia.

FUNDING

None

CONFLICT OF INTEREST

None

ACKNOWLEGEMENTS

We thank Miss Jenny Pirot who provided help in editing the manuscript.

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Figure 1: Flow chart

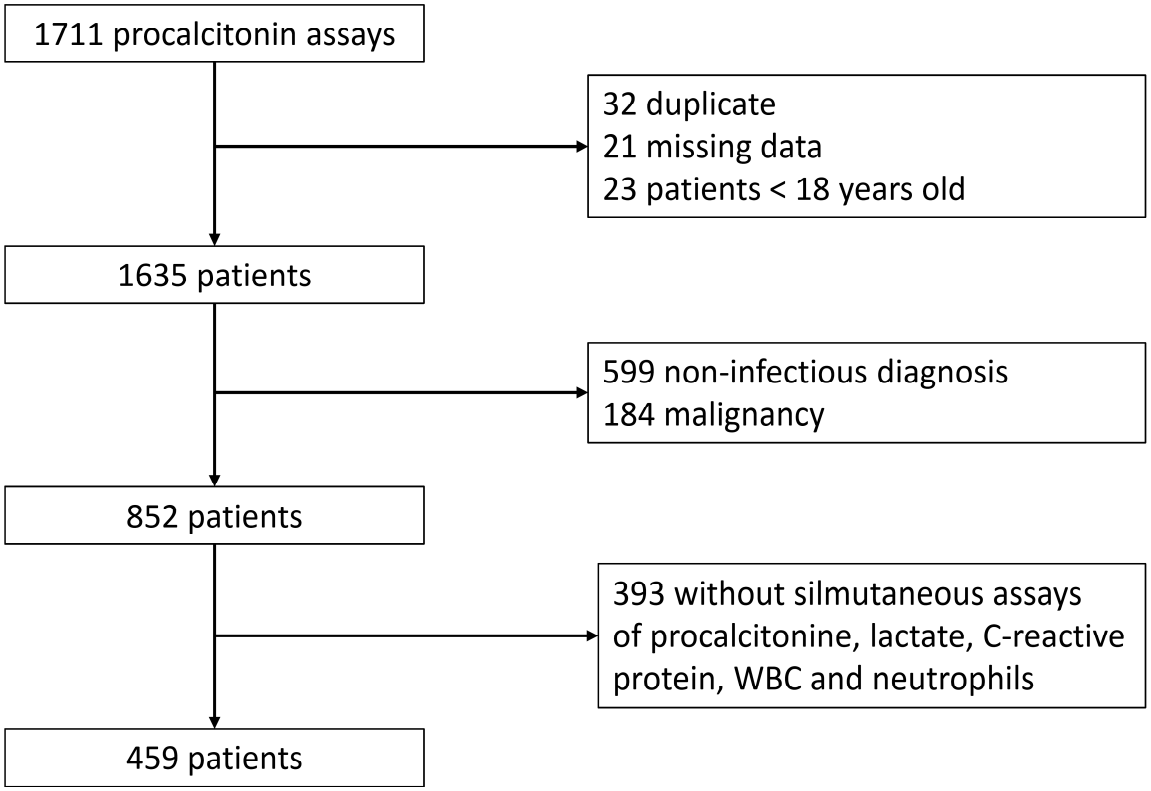
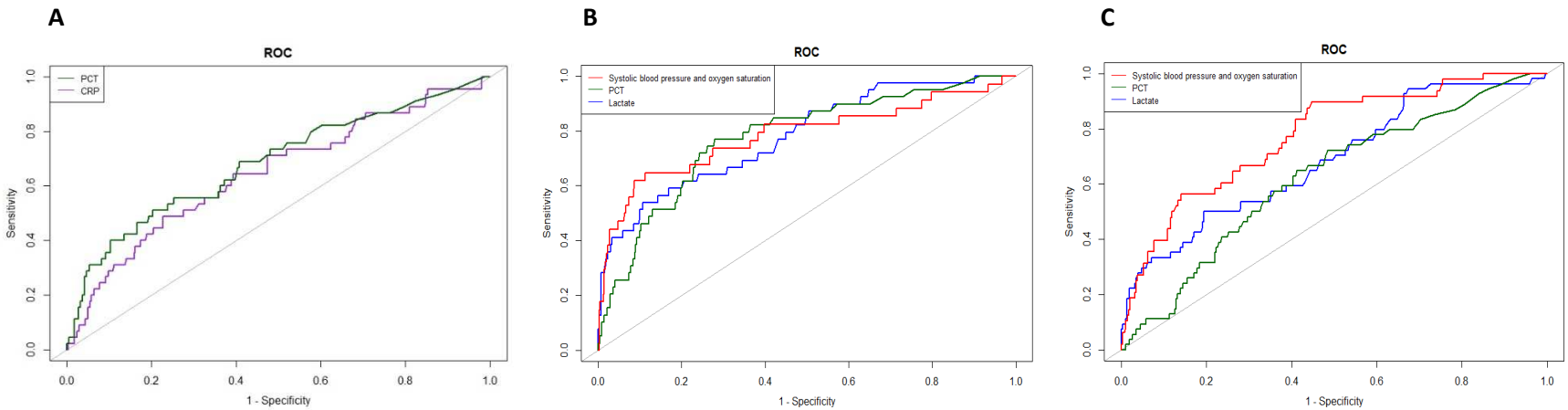
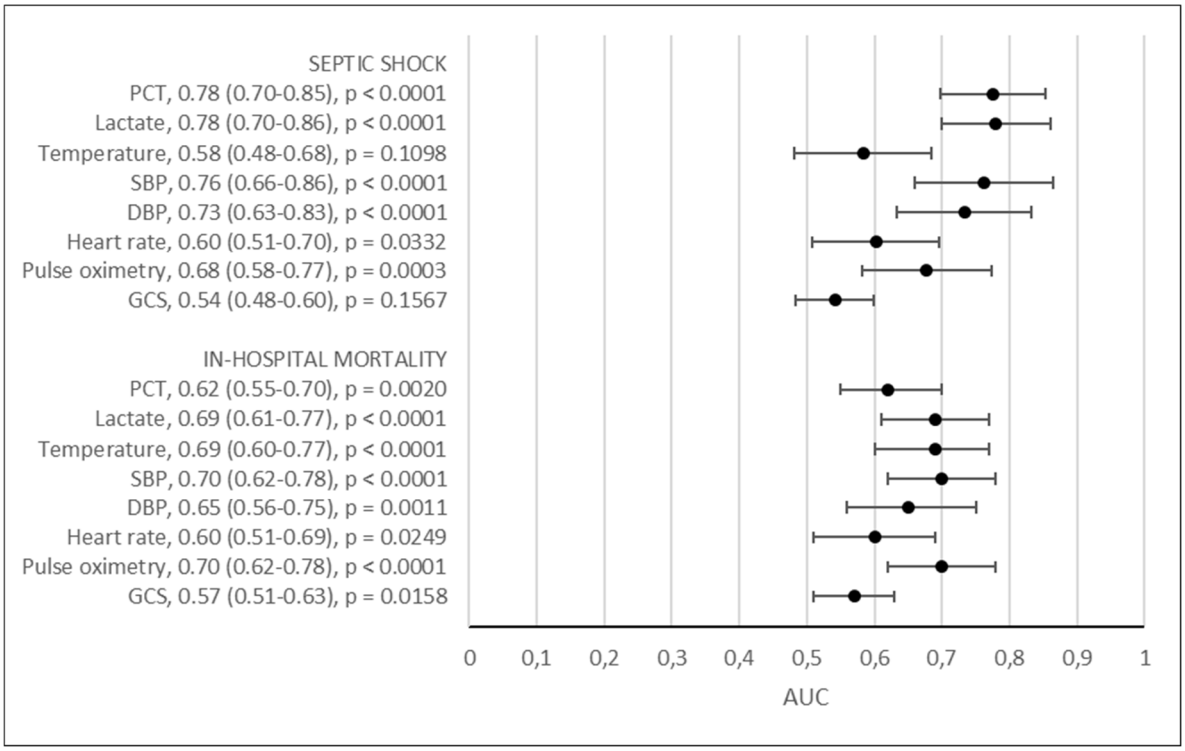


Figure 2: Area under the receiver operating characteristics curve for procalcitonin and C-reactive protein discrimination in bacteremia (A), and for procalcitonin, lactate and vital signs discrimination in septic shock (B) and in-hospital mortality (C)



Legend: CRP, C-reactive protein ; PCT, procalcitonin ; PO, pulse oximetry ; ROC, receiver operating characteristics ; SBP, systolic blood pressure.

Figure 3: Forest plot of area under the receiver operating characteristics curve for PCT, lactate and vital signs discrimination in septic shock and in-hospital mortality



Legend: AUC, area under the receiver operating characteristics curve ; DBP, diastolic blood pressure ; GCS, Glasgow coma scale ; PCT, procalcitonin ; SBP, systolic blood pressure.
Data are expressed with 95% confidence interval.

Table 1: Patient characteristics stratified by outcome

	Overall	Bacteremia			Septic shock			In-hospital mortality ‡		
		Yes	No	*p* value	Yes	No	*p* value	Yes	No	*p* value
	N = 459	N = 45	N = 414		N = 39	N = 420		N = 54	N = 310	
Demographic										
Male gender, n (%)	233 (50.8)	22 (48.9)	211 (51.0)	0.7912	24 (61.5)	209 (49.8)	0.1594	26 (48.2)	156 (50.3)	0.7681
Age, mean (SD)	60.4 (22.0)	64.2 (20.6)	60.0 (22.1)	0.2781	70.2 (15.2)	59.5 (22.3)	0.0060	72.0 (18.8)	62.0 (20.9)	0.0012
Nurse triage level and vital signs										
FRENCH 1 or 2, n (%)	64 (13.9)	6 (13.3)	58 (14.0)	0.9010	16 (41.0)	48 (11.4)	< 0.0001	21 (38.9)	40 (12.9)	< 0.0001
Temperature, °C, mean (SD)	37.5 (1.2)	37.9 (1.2)	37.5 (1.2)	0.0260	37.2 (1.2)	37.6 (1.2)	0.1079	36.8 (1.2)	37.6 (1.2)	< 0.0001
SBP, mmHg, mean (SD)	126.4 (25.2)	124.8 (26.0)	126.6 (25.2)	0.6501	101.5 (31.6)	128.7 (23.3)	< 0.0001	108.0 (27.9)	128.3 (24.6)	< 0.0001
SBP ≤ 100 mmHg, n (%)	68 (14.8)	9 (20.0)	59 (14.4)	0.3164	23 (60.5)	45 (10.8)	< 0.0001	22 (41.5)	38 (12.3)	< 0.0001
DPB, mmHg, mean (SD)	72.0 (16.7)	69.8 (16.4)	72.3 (16.7)	0.3527	59.4 (21.3)	73.2 (15.7)	0.0004	63.5 (23.1)	71.9 (15.3)	0.0134
Heart rate, bpm, mean (SD)	97.8 (24.6)	96.7 (21.1)	97.9 (24.9)	0.7620	89.3 (22.8)	98.6 (24.6)	0.0260	88.7 (28.9)	98.7 (24.6)	0.0095
Pulse oximetry, %, mean (SD)	94.0 (7.1)	94.6 (5.2)	93.9 (7.3)	0.8191	90.9 (7.2)	94.3 (7.0)	0.0006	89.1 (9.2)	93.9 (7.1)	< 0.0001
Pulse oximetry < 95%, n (%)	161 (35.1)	22 (51.2)	139 (36.3)	0.0565	21 (61.8)	140 (35.7)	0.0027	33 (68.8)	111 (38.8)	0.0001
GCS, mean (SD)	14.7 (1.3)	14.7 (1.4)	14.7 (1.3)	0.8204	14.6 (1.3)	14.8 (1.3)	0.0454	14.2 (2.1)	14.8 (1.3)	0.0006
GCS < 15, n (%)	27 (5.9)	3 (6.8)	24 (6.0)	0.8293	5 (13.9)	22 (5.4)	0.0571	10 (19.6)	17 (5.7)	0.0021
Comorbidities										
Diabetes, n (%)	118 (25.7)	17 (37.8)	101 (24.4)	0.0511	16 (41.0)	102 (24.3)	0.0221	13 (24.1)	91 (29.4)	0.4279
Immunosuppression, n (%)	41 (8.9)	4 (8.9)	37 (8.9)	0.9914	5 (12.8)	36 (8.6)	0.3757	6 (11.1)	30 (9.7)	0.7447
Obesity, n (%)	65 (14.2)	12 (26.7)	53 (12.8)	0.0113	6 (15.4)	59 (14.1)	0.8188	10 (18.5)	49 (15.8)	0.6177
Infection site				0.0554			0.5740			0.3784
Bronchopulmonary, n (%)	144 (31.4)	10 (22.2)	134 (32.4)		16 (41.0)	128 (30.5)		25 (46.3)	103 (33.2)	
Urogenital, n (%)	87 (19.0)	14 (31.1)	73 (17.6)		5 (12.8)	82 (19.5)		9 (16.7)	63 (20.3)	
Intra-abdominal, n (%)	74 (16.1)	9 (20.0)	65 (15.7)		7 (18.0)	67 (16.0)		6 (11.1)	62 (20.0)	
Skin and Soft Tissue, n (%)	46 (10.0)	3 (6.7)	43 (10.4)		5 (12.8)	41 (9.8)		5 (9.3)	27 (8.7)	
Other (specified), n (%)	46 (10.0)	7 (15.6)	39 (9.4)		3 (7.7)	43 (10.2)		6 (11.1)	27 (8.7)	
Undetermined, n (%)	62 (13.5)	2 (4.4)	60 (14.5)		3 (7.7)	59 (14.1)		3 (5.6)	28 (9.0)	
Biology										
PCT, $ng.mL^{-1}$, median (IQR)	0.22 (1.06)	1.26 (20.72)	0.19 (0.83)	< 0.0001	2.27 (24.34)	0.19 (0.73)	< 0.0001	0.84 (2.78)	0.25 (1.15)	0.0040
Lactate, $mmol.L^{-1}$, median (IQR)	1.6 (1.2)	2.0 (1.6)	1.6 (1.2)	0.0500	3.1 (7.3)	1.6 (1.1)	< 0.0001	2.4 (3.7)	1.6 (1.2)	< 0.0001
CRP, $mg.L^{-1}$, median (IQR)	64.6 (133.1)	128.0 (245.0)	58.6 (122.1)	0.0014	138.0 (287.1)	58.6 (122.9)	0.0006	73.7 (159.8)	76.6 (156.7)	0.7038
WBC count, $.10^9$ $cells.L^{-1}$, median (IQR)	12.7 (7.9)	13.7 (7.5)	12.3 (8.0)	0.1339	14.7 (11.1)	12.7 (7.9)	0.4848	13.1 (8.2)	13.0 (7.6)	0.5664
Neutrophils, $.10^9$ $cells.L^{-1}$, median (IQR)	10.1 (7.6)	11.8 (7.5)	9.9 (7.6)	0.0492	12.3 (8.6)	10.1 (7.5)	0.2133	11.1 (6.1)	10.5 (7.3)	0.4213

Legend: CRP, C-Reactive Protein ; DPB, diastolic blood pressure ; ED, emergency department ; ENT, ear nose throat ; FRENCH, FRench Emergency Nurses Classification in Hospital scale ; GCS, Glasgow coma scale ; IQR, interquartile range ; SBP, systolic blood pressure ; SD, standard deviation ; WBC, white blood cells.
‡ Only hospitalized patients were considered.

Table 2: Area under the receiver operating characteristics curve for procalcitonin, lactate, C-reactive protein, white blood cells and neutrophils discrimination in bacteremia, septic shock and in-hospital mortality

	AUROC (95% CI)	***p* value**	***p* value ‡**
Bacteremia			
PCT	0.68 (0.59-0.77)	< 0.0001	
L	0.59 (0.50-0.68)	0.0471	0.0549
CRP	0.65 (0.56-0.73)	0.0016	0.3023
WBC	0.57 (0.48-0.66)	0.1308	0.0263
N	0.59 (0.50-0.68)	0.0411	0.0537
L + CRP	0.64 (0.55-0.73)	0.0017	0.2627
L + CRP + N	0.65 (0.56-0.74)	0.0015	0.3105
L + CRP + N + WBC	0.67 (0.58-0.76)	0.0001	0.7566
Septic shock			
PCT	0.78 (0.70-0.85)	< 0.0001	
L	0.78 (0.70-0.86)	< 0.0001	0.9197
CRP	0.67 (0.57-0.77)	0.0009	0.0023
WBC	0.53 (0.43-0.64)	0.5289	< 0.0001
N	0.56 (0.46-0.66)	0.2476	0.0001
L + CRP	0.77 (0.68-0.87)	< 0.0001	0.9174
L + CRP + N	0.78 (0.69-0.88)	< 0.0001	0.8686
L + CRP + N + WBC	0.81 (0.72-0.90)	< 0.0001	0.4191
SBP	0.76 (0.66-0.86)	< 0.0001	0.8344
PO	0.68 (0.58-0.77)	0.0003	0.2222
SBP + PO	0.78 (0.68-0.88)	< 0.0001	0.7566
L + SBP	0.80 (0.70-0.89)	< 0.0001	0.7106
L + PO	0.80 (0.72-0.88)	< 0.0001	0.3909
L + SBP + PO	0.81 (0.72-0.91)	< 0.0001	0.3852
In-hospital mortality			
PCT	0.62 (0.55-0.70)	0.0020	
L	0.69 (0.61-0.77)	< 0.0001	0.0711
CRP	0.52 (0.43-0.60)	0.7116	0.0047
WBC	0.52 0.44-0.61)	0.5765	0.0653
N	0.53 (0.45-0.62)	0.4229	0.0928
L + CRP	0.67 (0.58-0.75)	0.0001	0.1970
L + CRP + N	0.67 (0.58-0.75)	0.0002	0.2050
L + CRP + N + WBC	0.68 (0.59-0.76)	< 0.0001	0.1232
SBP	0.70 (0.62-0.78)	< 0.0001	0.1369
PO	0.70 (0.62-0.78)	< 0.0001	0.2001
SBP + PO	0.77 (0.70-0.84)	< 0.0001	0.0021
L + SBP	0.73 (0.66-0.81)	< 0.0001	0.0098
L + PO	0.77 (0.70-0.84)	< 0.0001	0.0015
L + SBP + PO	0.80 (0.73-0.86)	< 0.0001	< 0.0001

Legend: AUROC, area under the receiver operating characteristics ; CI, confidence intervalley ; CRP, C-Reactive Protein ; L, lactate ; N, neutrophils ; PCT, procalcitonin ; PO, pulse oximetry ; SBP, systolic blood pressure ; WBC, white blood cells.
‡ AUROC contrast Khi-2 test between PCT and the corresponding biomarker(s) and/or vital sign(s).

Table 3: Sensitivity, specificity, positive predictive value and negative predictive value of procalcitonin, lactate, C-reactive protein, white blood cells and neutrophils, for bacteremia, septic shock and in-hospital mortality

	PCT ≥ 0.25 ng.mL^{-1}	PCT ≥ 0.5 ng.mL^{-1}	Lactate ≥ 2 mmol.L^{-1}	CRP ≥ 20 mg.L^{-1}	CRP ≥ 100 mg.L^{-1}	WBC count < 4 or ≥ 12.10^{9} cells.L^{-1}	Neutrophils ≥ 9.10^{9} cells.L^{-1}	Neutrophils ≥ 75% WBC
Bacteremia								
Se, % (95% CI)	68.8 (55.4-82.4)	55.6 (41.0-70.1)	51.1 (36.5-65.7)	86.7 (76.7-96.6)	55.6 (41.0-70.1)	66.7 (52.9-80.4)	71.1 (57.9-84.4)	82.2 (71.1-93.4)
Sp, % (95% CI)	54.8 (50.0-59.6)	66.4 (61.9-71.0)	67.4 (62.9-71.9)	26.6 (22.3-30.8)	64.0 (59.4-68.6)	45.2 (40.4-50.0)	43.5 (38.7-48.3)	27.3 (23.0-31.6)
PPV, % (95% CI)	14.2 (9.6-18.9)	15.2 (9.7-20.7)	14.6 (9.1-20.1)	11.4 (8.0-14.7)	14.4 (9.2-19.6)	11.7 (7.7-15.6)	12.0 (8.1-15.9)	10.9 (7.6-14.3)
NPV, % (95% CI)	94.2 (91.2-97.1)	93.2 (90.4-96.1)	92.7 (89.8-95.6)	94.8 (90.8-98.9)	93.0 (90.0-95.9)	92.6 (89.0-96.2)	93.3 (89.7-96.8)	93.4 (89.0-97.8)
Septic shock								
Se, % (95% CI)	84.6 (73.3-95.9)	76.9 (63.7-90.1)	66.7 (51.9-81.5)	87.2 (76.7-97.7)	59.0 (43.5-74.4)	66.7 (51.9-81.5)	69.2 (54 .7-83.7)	84.6 (73.3-95.9)
Sp, % (95% CI)	56.0 (51.2-60.7)	68.1 (63.6-72.6)	68.6 (64.1-73.0)	26.4 (22.2-30.6)	64.0 (59.5-68.6)	45.0 (40.2-49.8)	43.1 (38.4-47.8)	27.4 (23.1-31.6)
PPV, % (95% CI)	15.1 (10.4-19.9)	18.3 (12.4-24.2)	16.5 (10.7-22.2)	9.9 (6.8-13.1)	13.2 (8.2-18.3)	10.1 (6.4-13.8)	10.2 (6.5-13.8)	9.8 (6.6-12.9)
NPV, % (95% CI)	97.5 (95.5-99.4)	96.9 (95.0-98.9)	95.7 (93.4-98.0)	95.7 (92.0-99.4)	94.4 (91.7-97.1)	93.6 (90.2-96.9)	93.8 (90.4-97.2)	95.0 (91.2-98.9)
In-hospital mortality								
Se, % (95% CI)	72.2 (60.3-84.2)	57.4 (44.2-70.6)	57.4 (44.2-70.6)	83.3 (73.4-93.3)	40.7 (27.6-53.8)	63.0 (50.1-75.8)	68.5 (56.1-80.9)	81.5 (71.1-91.8)
Sp, % (95% CI)	49.7 (44.1-55.2)	62.3 (56.9-67.7)	64.8 (59.5-70.2)	22.6 (17.9-27.2)	57.4 (51.9-62.9)	42.3 (36.8-47.8)	39.0 (33.6-44.5)	23.2 (18.5-27.9)
PPV, % (95% CI)	20.0 (14.4-25.6)	20.9 (14.4-27.5)	22.1 (15.3-29.0)	15.8 (11.6-20.0)	14.3 (8.8-19.8)	16.0 (11.0-20.9)	16.4 (11.5-21.2)	15.6 (11.4-19.8)
NPV, % (95% CI)	91.1 (86.8-95.4)	89.4 (85.2-93.5)	89.7 (85.8-93.7)	88.6 (81.6-95.6)	84.8 (79.9-89.6)	86.8 (81.3-92.2)	87.7 (82.2-93.2)	87.8 (80.7-94.9)

Legend: CRP, C-reactive protein ; NPV, negative predictive value ; PCT, procalcitonin ; PPV, positive predictive value ; Se, sensitivity ; Sp, specificity ; WBC, white blood cells.