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Utility of Procalcitonin as a Diagnostic Tool for Sepsis in Intensive Care Units

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ABSTRACT

Introduction/Objective: Sepsis is one of the leading causes of mortality in the intensive care unit (ICU). Its diagnosis is often complex and represents a real clinical challenge. The objective of this study was to evaluate the usefulness of procalcitonin (PCT) as a diagnostic marker of sepsis.

Methods: This prospective cohort study included 65 patients hospitalized in the ICU. Demographic and clinical data were collected according to a specific information sheet. All patients underwent an inflammatory assessment including PCT, hypersensitive C - reactive protein (hsCRP), and complete blood count. The Sequential Organ Failure Assessment (SOFA) score was calculated. Patients were classified into septic (SOFA ≥ 2 points) and non-septic (SOFA < 2 points). The Receiver Operating Characteristic (ROC) curve was used to evaluate the diagnostic performance of inflammatory parameters.

Results: Of 65 included patients, 46 had developed sepsis. Among the investigated inflammatory markers, PCT has the best discriminative capacity; its area under the curve (AUC), of 0.78, was the highest, followed by the neutrophils to lymphocytes ratio (NLR) and hsCRP with a lower but statically significant AUC. The optimal PCT threshold for sepsis diagnosis was 4.5ng/ml with a specificity of 83% and a sensitivity of 60%. A positive correlation between the PCT levels and the SOFA score was also found (p=0.002).

Conclusion: This study provides additional evidence of the performance of PCT in the diagnosis of septic states in patients admitted to ICU. The newly established cut-off value provides the best balance between specificity and sensitivity. Its superiority over conventional inflammatory markers has been demonstrated.

Keywords: Procalcitonin, Sepsis, C-reactive Protein, NLR, SOFA Score, Intensive Care.

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INTRODUCTION

Sepsis is a life-threatening multi-organ dysfunction caused by a maladaptive response to infection. According to recent reports, the incidence of sepsis is estimated to be around 50 million cases worldwide annually [1]. Sepsis is one of the most frequent causes of hospitalization, particularly in intensive care units (ICU). It is also one of the main causes of mortality in these wards, with rates ranging from 25% to 70% in severe forms of septic shock [2-4].

Accurate and early diagnosis with appropriate antimicrobial therapy is crucial to ensure a better prognosis of septic patients [4-6]. However, due to its pathophysiological mechanism, its diagnosis is often complex and represents a challenge for the clinician [7]. Traditionally, blood culture is regarded as the "gold standard" [2]. It provides a reliable diagnosis of systemic bacterial infection and an effective selection of the appropriate antibiotic therapy. However, the delay required to establish such identification does not favor its implementation in emergencies. Thus, several inflammatory biomarkers have been proposed as diagnostic alternatives, such as hypersensitive C - reactive protein (hsCRP), pro-calcitonin (PCT), and some interleukins (IL1 and IL6). However, their diagnostic value and cost-performance ratio remain to be evaluated [2, 4, 6].

PCT is the immediate precursor of calcitonin, the main hypo-calcemic hormone. It is a polypeptide composed of 116 amino acids, mainly synthesized by the C-cells of the thyroid gland, but also, to a lesser extent, by the neuroendocrine tissue of other organs such as the lungs and the guts [6, 8].

Over the last decades, PCT has attracted growing interest. It has been particularly proposed as an early, sensitive, specific, and reliable marker of bacterial infections. Its quantification can also be used to differentiate a local infection from a systemic one. Moreover, it could have a substantial prognostic value; its level positively correlates with the infection's severity [6, 9]. However, there is still no consensus, and the recent sepsis definition does not involve any reference biomarker. The diagnostic performance and the cut-off value of PCT to define the likely septic states vary widely from one study to another. Hence, the main objective of the present study was to evaluate PCT as a diagnostic marker of sepsis in intensive care units and to define the threshold value above which this diagnosis is most likely.

METHODS

Patients and study design

This is a single-center prospective cohort study performed at the Frantz Fanon Hospital, University Hospital Center of Blida, Algeria. All patients admitted to the ICU from January to June 2019 who had inflammatory markers testing were included in this study.

The exclusion criteria were: age <18 years, cardiovascular diseases, pregnancy, dialysis during hospitalization, current tumor process, and death within 48 hours of admission. These exclusion conditions were applied since they may be associated with a non-specific elevation of PCT without septic states.

This study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee.

Data collection

A specially designed data sheet was used to collect clinical records related to the infection risk and severity. This sheet included: first: demographic characteristics. Second: Dates of admission, discharge, and death. Third: Hospitalization pattern: medical or surgical. Fourth: infection risk factors: intubation, ventilation, central catheterization, and other devices. Fifth: Personal medical history: hypertension and diabetes. Sixth: Clinical records during hospitalization: body temperature, hemodynamic status (systolic, diastolic and mean arterial pressure (SBP, DBP, MAP)), heart rate (HR), respiratory status (respiratory rate, partial oxygen pressure (PaO2), inspired oxygen fraction (FiO2) and use of artificial ventilation), and neurological status (Glasgow score).

Sepsis definition and endpoint

Sepsis was diagnosed according to the new Task Force group definition by an acute change in the total Sequential Organ Failure Assessment (SOFA) score (≥2 points) [10, 11].

Biomarkers, assay methods and clinical definitions

PCT was assessed by a quantitative enzymatic immunoassay method (VIDAS® PCT). According to the reference values provided by the assay kits of this technique, levels between 0.05ng/ml and 2ng/ml indicate a very probable bacterial infection. However, levels above 2ng/ml are highly suggestive of severe sepsis. They need to be interpreted according to the clinical context.

In addition to PCT, all included patients were also tested for the following inflammatory markers: hsCRP measured by an immuno-turbidimetric method on Selectra Pro M®, a total blood count on Sysmex® Hematology Analyzer, with a focus on total white blood cells (WBC), neutrophils (Neut), lymphocytes (Lym), as well as calculation of the Neut to Lym ratio (NLR).

A biological evaluation was performed using routine assay methods on Selectra Pro M®, including 1) blood glucose and renal functions markers: urea, serum creatinine, and electrolytes (sodium and potassium). 2) Nutritional status markers: albumin and total protein. 3) Liver enzymes and markers: total bilirubin (BT), lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), γ-glutamyl transferase (GGT), and alkaline phosphatases (ALP). All biological markers were assessed at admission and evaluated at an interval of 48 hours. All the laboratory testing was performed at the same center.

The regularly recorded clinical parameters include the determination of PaO2, FiO2, and measurement of systolic and diastolic blood pressure (SBP and DBP), mean arterial pressure (MAP), and Glasgow score.

The SOFA score was calculated by assessing, according to the recommendations, the number and severity of organ dysfunctions in six systems: respiratory, coagulant, hepatic,

cardiovascular, renal, and neurological [12]. The diagnosis of sepsis was made by a SOFA score >2 points.

The prognosis was stratified within 24 hours of admission using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. This score has 15 components to which a scoring system ranging from 1 to 4 is assigned according to its deviation from the normal value [4, 9].

Statistical analysis

Statistical analyses were performed using SPSS® software, version 23. Quantitative variables were expressed as means ± standard deviation and compared by Student's t-test. In univariate analysis, the qualitative variables are expressed as frequencies and compared by the Chi2 test. The non-parametric Spearman's Rho test was used to test the correlation between inflammatory markers and stratification indices.

To evaluate the performance of inflammatory biomarkers in the diagnosis of sepsis, Receiver Operating Characteristic (ROC) curves were constructed; the areas under the curves (AUC) were compared with that of the SOFA score. The cut-off of each parameter was selected according to the best balance between sensitivity and specificity, as expressed by the Youden index (IY).

RESULTS

Sepsis incidence rate

During the study duration, 73 patients were enrolled, of whom eight were excluded. Sixty-five patients were included in this analysis. Among them, 46 developed a sepsis event, representing an incidence rate of 70.7% (Figure 1).

The overall 30-day mortality rate was 58.4%, with a significantly higher incidence in patients who had developed sepsis (34 patients Vs. 04 patients, p= 0.001) (Figure 1).

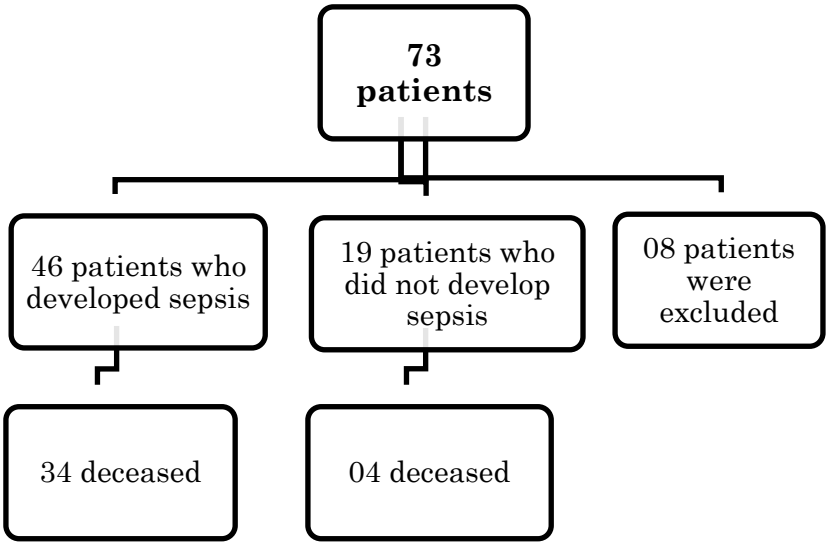

Figure1: Overall population included and incidence of sepsis and mortality.

Comparison of biological characteristics between subjects with and without sepsis

The clinic-biological characteristics of the study population are presented in Table 1. A significant difference was found between patients with and without sepsis, particularly for inflammatory markers. Indeed, subjects with sepsis had significantly higher levels of PCT, hsCRP, and NLR. These subjects also had significantly higher values of potassium, creatinine, and FiO2.

In addition, the APACHE II score, as assessed at admission, was higher in patients who developed sepsis, but this difference did not reach a significant level.

Correlation between inflammatory markers and severity scores:

The results of the correlation analysis are presented in Table 2.

PCT correlated positively and significantly with CRP, neutrophil count, NLR, and both SOFA and APACHE II scores. It also correlated significantly but inversely with lymphocyte count. However, there was no correlation between PCT and total WBC.

Performance of inflammatory markers in the diagnosis of sepsis:

The ROC curve was performed to evaluate the performance of the studied inflammatory biomarkers in the diagnosis of sepsis. The results are presented in Figure 2 and Table 3.

Table 1: Comparison of clinico-biological characteristics between patients with and without sepsis.

	Sepsis + (n=46)	Sepsis – (n=19)	P
Age (years)	44.46±25.44	36.35±24.5	0.23
PCT (ng/ml)	15.1±31.6	2.9±4.12	**0.014**
hsCRP (mg/l)	98±83.2	57.2±32.9	**0.009**
WBC (10^9/l)	13.73±7.45	12.4±4.04	0.38
Lym (%)	11.09±8.63	14.18±7.41	0.18
Neut (%)	86.91±8.63	83.82±7.41	0.18
NLR	14.5±11.6	7.7±5.8	**0.005**
Na^+ (meq/l)	142.45±8.33	140.93±9.13	0.57
K^+ (meq/l)	4.01±0.77	3.56±.067	**0.04**
BG (g/l)	1.95±1.56	1.25±0.66	0.066
Creat (mg/l)	21.21±20.42	9.11±2.78	**0.016**
T° (°c)	37.52±1.23	37.06±1.44	0.4
SBP (mmHg)	118.5±34.46	117.7±16.18	0.92
DBP (mmHg)	67.58±19.66	72.9±15.65	0.41
MAP (mmHg)	84.55±21.87	87.83±14.9	0.61
HR (bat/mn)	105.75±27.46	103.67±15.35	0.75
PaO_2 (mmHg)	104.68±21.23	105.62±18.17	0.9
FiO_2 (%)	37.21±20.71	21.00±00	**0.035**
spO_2 (%)	95.57±3.74	98.12±2.1	0.6
APACHEII (points)	15.1±8.08	12.1±8.28	0.17
APACHEII (%)	26.05±19.83	19.12±18.48	0.18
SOFA (points)	4.98±2.62	0.37±0.5	**<0.0001**

APACHE II: Acute Physiology And Chronic Health Evaluation II, Creat: Creatinine, hsCRP: hypersensitive C Reactive Protein, HR : Heart Rate, FiO2: Inspired fraction of Oxygen, WBC : White blood cells, BG: blood glucose, Lym: Lymphocytes, Neut: Neutrophiles, DBP: Diastolic Blood Pressure, MAP: Mean Arterial Pressure, PaO2: Partial Oxygen Pressure, SBP: Systolic Blood Pressure, PCT: procalcitonine, SOFA: Sequential Organ Failure Assessment, SpO2: Pulse Oxygen Saturation, T°: Body Temperature.
p : Student test. Bold p-values: statically significant p (<0.05)

Table 2: Spearman's correlation (r) between inflammatory biomarkers and severity scores.

		PCT	hsCRP	WBC	Neut	Lym	NLR	SOFA	APACHE
PCT	r	-	0.31	0.12	0.32	-0.32	0.37	0.38	0.34
	p	-	**0.01**	0.4	**0.01**	**0.01**	**0.004**	**0.002**	**0.005**
SOFA	r	0.38	0.27	0.04	0.12	-0.12	0.26	-	0.35
	p	**0.002**	**0.04**	0.7	0.3	0.3	**0.048**	-	**0.005**
APACHE	r	0.34	-0.2	0.002	0.09	-0.9	0.009	0.35	-
	p	**0.005**	0.8	0.9	0.5	0.5	0.9	**0.005**	-

Among the tested inflammatory markers, PCT showed the best discriminatory capacity of sepsis, with the highest value of AUC (0.78 [0.7-0.9]). NLR, with an AUC of 0.74 [0.6-0.9], showed a comparable diagnostic capacity, followed by hsCRP with a lower but statically significant AUC (AUC = 0.69 [0.6-0.8]).

However, WBC and neutrophils had no relevance in the diagnosis of sepsis.

Table 4 shows the cut-offs values of the different inflammatory biomarkers and their corresponding diagnostic performances (sensitivities and specificities).

For PCT, an optimal cut-off of 4.5 ng/ml permitted the diagnosis of sepsis with a sensitivity of 60% and a specificity of 83% (IY=0.43). The optimal cut-offs for the remaining markers (NLR and hsCRP) were 7.49 and 94 mg/L. The sensitivity and specificity were 77%, 72% (IY=0.49) and 60%, 72% (IY=0.32) respectively.

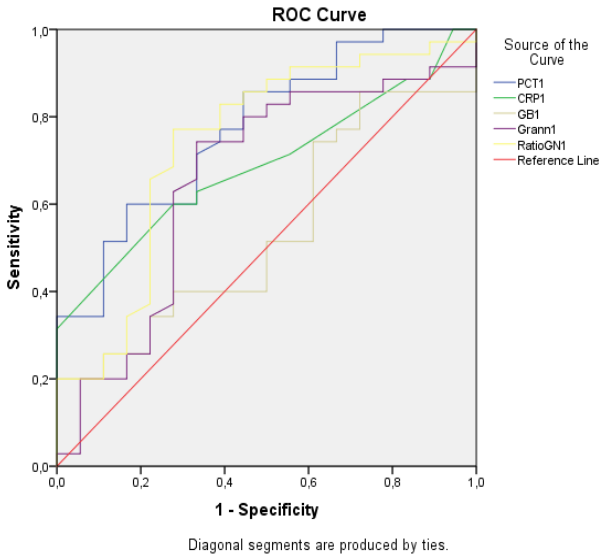

Figure 2: ROC curve of inflammatory biomarkers in the diagnosis of sepsis.

Table 3: ROC curve characteristics of inflammatory biomarkers in the diagnosis of sepsis.

	AUC	95%CI	P
PCT	0.78	[0.7-0.9]	**0.0001**
hsCRP	0.69	[0.6-0.8]	**0.025**
WBC	0.53	[0.4-0.7]	0.65
Neutrophiles	0.66	[0.5-0.8]	0.06
NLR	0.74	[0.6-0.9]	**0.005**

Table 4: Cut-offs and performance of inflammatory biomarkers in the diagnosis of sepsis.

	Cut-off	Se (%)	Sp (%)	YI
PCT	4.49	60	83	0.43
hsCRP	94	60	72	0.32
NLR	7.49	77	72	0.49

YI : Youden index, Se: sensitivity, Sp: specificity

DISCUSSION

Sepsis, a leading cause of mortality in ICU, is a serious complication that often represents a clinical challenge to screen, especially due to its etiological complexity [11]. Indeed, in most cases, sepsis is caused by bacterial infections. Still, viruses, fungi, and parasites can also be involved, thus making it difficult to establish a diagnosis of certainty in emergency settings [2].

Recently, biochemical markers, perfectly adapted to the emergency situation, have been proposed as diagnostic tools for sepsis. Among these parameters, PCT is the most promising marker, especially in the context of bacterial infections [2, 4, 5].

In our study, PCT was found to be a reliable diagnostic tool for sepsis; a cut-off value of 4.5ng/ml was defined, above which PCT had a satisfactory performance, with a sensitivity of 60% and a specificity of 83%. This exceeds the diagnostic qualities of the other studied inflammatory markers (hsCRP and NLR).

Similar results have been reported in previous studies, for example, in the study conducted by Ljungstrom et al. to investigate the performance of inflammatory biomarkers, individually and in combination, in the diagnosis of bacterial sepsis, the authors found that PCT, with an AUC of 0.68, was a better predictor of sepsis, compared with CRP and NLR [9]. Comparable results were also reported in the study by Jemsa J et al., which compared the diagnostic accuracy of PCT and CRP in patients admitted to intensive care. The authors found that PCT was the best marker with an AUC of 0.92 versus 0.81 for CRP. However, the threshold of PCT was much lower than the one established by our study. Indeed, the authors had found that above the threshold of 0.42ng/ml, PCT could predict sepsis with a sensitivity of 96% and a specificity of 79% [4]. Similarly, Harbarth et al. have compared the diagnostic accuracy of PCT with that of IL-6 and IL-8 in 78 patients admitted to intensive care and have shown that above a threshold of 1.1ng/ml, PCT provided the best performance,

with a sensitivity of 97% and a specificity of 78% [13]. In another study by Müller B et al., including 101 patients admitted to the intensive care unit, the diagnostic value of PCT was compared with that of lactates, IL6, and CRP, the superiority of PCT was also demonstrated, but for a threshold value of 2ng/ml, above which the sensitivity was of 89% and the specificity of 94% [14]. In a more recent study conducted by Jekarl et al., and including 282 patients admitted to the emergency department for suspected sepsis, a lower PCT cut-off was defined at 0.18ng/ml; this threshold had a sensitivity of 84% but a lower specificity of 46% in the diagnosis of sepsis [15]. The differences in observed sensitivity can be explained by the different methodology adopted by the number of included patients but mostly by the chosen sepsis definition, which varies from one study to another. Indeed, most of the studies mentioned above [13-15] used positive microbial culture results for sepsis diagnosis. In our case, and with the lack of microbiological data, it is not excluded that some patients who were classified in the non-septic group had a bacterial infection without sepsis. This might increase the PCT levels and thus decrease its sepsis diagnostic performance.

In the last years, the sepsis definition has widely evolved; nowadays, the most common definition uses the SOFA score criteria [11]. In our study, the SOFA score was more closely correlated with PCT than with other inflammatory markers, thus supporting the relevance of PCT as a diagnostic tool for sepsis. This finding is in agreement with the results reported by Luzzani A et al. in their study, including 800 patients admitted to intensive care units. Indeed, the authors found the most significant correlation between SOFA score and PCT (r=0.73 versus r=0.41 with CRP) [16].

In addition to its use in the diagnosis of sepsis, some studies have highlighted the prognostic value of PCT in monitoring sepsis patients, particularly with regard to the decision to interrupt or extend antibiotic treatment. In this context, Kyriazopoulou et al. [17], in a recent randomized clinical trial study, found that the use of early interruption of antibiotics guided by PCT led to a reduction in 28-day mortality and early hospital discharge. The authors explained that inadequate and irrational use of antibiotics adds to the risk of acute multiple organ dysfunctions, particularly cardiovascular and renal failure [17].

Our study has some limits, especially in relation to the sample size and the lack of microbiological data from blood cultures that were not routinely performed, partly because most of the patients were already under antibiotic therapy at admission and also because these tests were not adapted to the emergencies. One other limitation is the lack of available data on some biochemical parameters that could guide the diagnosis of bacterial sepsis, such as lactate and bicarbonate levels. Therefore, further longitudinal studies are needed to clarify the relationship between inflammatory markers and both the diagnostic and prognostic aspects of sepsis in the hospital setting.

CONCLUSION

In view of the complexity of sepsis, the diversity of its etiologies, and its complications, research for efficient tools of early diagnosis is crucial to ensure adequate patient management, especially in intensive care units. Serum biomarkers offer a rapid and practical tool for diagnosis, advanced therapy prescription, and life-threatening stratification, especially in emergency departments.

This study provides additional evidence of the performance of PCT in the diagnosis of septic states in patients admitted to intensive care. A cut-off of 4.5ng/ml showed specificity 20% higher than that reported for hsCRP. The NLR has also been found to be a promising marker, its specificity was lower than that of the PCT, but in the lack of the latter, it can represent an alternative with a reasonable quality/cost ratio. Moreover, its correlation with the severity score may indicate its potential prognostic qualities.

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