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RESEARCH ARTICLE

Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection

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Abstract

Objective: To study the contribution of lactate and procalcitonin (PCT) serum measurements for the diagnosis and the risk-stratification of patients with suspected infection presenting to the ED.

Methods: Single-center one year observational study on 462 consecutive patients. Multivariate analysis to assess variables associated with sepsis, severe sepsis, septic shock and severe outcome.

Results: Multivariate analysis (Odds ratio [95% CI]), showed that PCT was the best independent variable to identify sepsis (3.98 [2.60–6.10]), while lactate was the best to diagnose severe sepsis (10.88 [6.51–18.19]). Patients with both lactate above 2 mmol·L^{-1} and PCT above 0.8 ng·mL^{-1} had an enhanced risk of severe outcome.

Conclusions: the dosages of lactate and PCT are complementary for the diagnosis and risk-stratification of patients evaluated in the ED for suspected infection.

Keywords: Lactate, procalcitonin, sepsis, septic shock, diagnosis, prognosis, ED

Introduction

The accurate evaluation of patients with suspected infection is a major concern for emergency physicians, since early specific therapeutic management correlates with better outcome (Rivers et al. 2001). However, signs of organ dysfunction or cryptic shock may not be obvious for the physician at the time of patient's presentation. Moreover, the wide clinical polymorphism and the earlier presentation of septic patients at the emergency department (ED) (in comparison to intensive care units, ICU) and the organizational features and constraints (as overcrowding) may contribute to misdiagnosis. Therefore, sepsis biomarkers may be useful in addition to clinical evaluation to improve both the diagnosis and severity assessment of septic patients. High serum lactate level reflects critical tissue hypoperfusion and is associated with increased morbidity and mortality in critically ill patients and particularly in patients with severe sepsis or septic shock (Bakker et al. 1996, Vincent et al. 1983, Nguyen et al. 2004, Jansen et al. 2009). The usefulness of serum lactate measurement, as a severity biomarker, has been well established in intensive care units (ICU) but has only recently been confirmed in the ED (Shapiro et al. 2005, Howell et al. 2007, Mikkelsen et al. 2009). Procalcitonin (PCT) is a sepsis biomarker that exhibits enhanced specificity for the bacterial origin of infection (Assicot et al. 1993, Hausfater et al. 2002, Christ-Crain et al. 2004, Hausfater et al. 2007). Morevorer, PCT levels

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Abbreviations

AUCROC, area under the ROC;
CRP, C reactive protein;
ED, emergency department;
HIV, human immunodeficiency virus;
ICU, intensive care unit;
PCT, procalcitonin;
ROC, receiver operating curve;
SBP, systolic blood pressure;
SD, standard deviation;
SIRS, systemic inflammatory response syndrome;

have been reported to be associated with the severity of infection either in ED or in ICU settings (Ugarte et al. 1999, Hausfater et al. 2002, Hausfater et al. 2007). However, the respective performance of lactate and PCT measurement, as well as the added-value of their concomitant dosages for the evaluation of patients suspected to have sepsis, has not been extensively studied in ED.

The aim of the present study was to determine the respective contribution of lactate and PCT measurement for the diagnosis and the prognosis of patients with suspected infection presenting to the ED. We made the hypothesis that these two biomarkers may provide complementary information that could be useful in a multiple biomarkers approach.

Methods

Patients

This was an observational cohort study of consecutive patients presenting during a 12-month period to the ED of an urban academic 1600 bed hospital with a 55,000 annual admissions to the ED. Patients 15-year-old or greater were included if they presented with a suspected diagnosis of infection to our ED during the study period and had available both lactate and PCT serum measurements blood sampled in the emergency room. PCT and lactate measurements are performed in routine practice in our ED in cases of suspected infection, and both biomarkers results are available in 1 h. All blood samples studied were drawn before any therapeutic intervention. Because of the observational design of the study, the ethical committee (CPP Ile de France Paris VI, Paris, France) authorized a waiver of informed consent. For patients with multiple measurements, only the first blood sample was taken into account. A trained research assistant reviewed each electronic ED file and recorded admission data (including first vital variables measured and routine biological data at entry and diagnosis retained in ED) and outcome (discharge, admission to a medical ward or ICU, secondary transfer into an ICU, in hospital mortality). For each patient, the presence of systemic inflammatory response syndrome (SIRS), sepsis, or severe sepsis/septic shock criteria (Levy et al. 2003) were also systematically recorded, either at ED admission or during follow-up. However, for this study we kept hyperlactatemia as a severe sepsis criterion but did not take into account PCT value for sepsis criteria. As a high lactate level is not specific of severe sepsis (Fall & Szerlip 2005), patient's electronic files were screened for associated factors that may contribute to raised serum lactate levels (cancer, alcoholic consumption, inhaled or systemic β-2 agonists, statin or antiretroviral treatment, diabetes mellitus, anemia, seizures and shock of other origin than sepsis). However, we did not exclude the patients with such associated causes of high lactate levels. We further categorized two outcome subgroups of patients defined as follows: severe outcome (any death and/or ICU admission (either primary or secondary) and/or terminal patients with therapy limitations) and secondary worsening (secondary admission in ICU and unexpected deaths, i.e. deaths that occurred in patients that were initially not considered to require ICU admission, and were not terminal patients with therapy limitations).

Biological measurements

Procalcitonin was measured by a time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor PCT; Brahms, Hennigsdorf, Germany). This assay is based on polyclonal antibody against calcitonin and a monoclonal antibody against katacalcin which bind to calcitonin and katacalcin sequence of precursor molecules. The limit of detection was 0.02 $ng.mL^{-1}$. Normal values were <0.1 $ng.mL^{-1}$ and the functional sensitivity was 0.06 $ng.mL^{-1}$.

Lactate was measured by an enzymatic method (lactate-oxidase) in whole arterial blood using a Radiometer ABL 725 blood gas analyzer (Radiometer Medical A/S, Neuilly-Plaisance, France), or in venous plasma-based assays on Roche Cobas Integra 400 plus analyzer (Roche Diagnostics, Meylan, France). The normal range was 0.5–1.8 and 0.5–2.2 $mmol.L^{-1}$ in arterial and venous blood respectively.

Statistical analysis

Data are expressed as mean ± SD or median (25–75 interquartile range) in non-normally distributed variables (Kolmogorov–Smirnov test). Comparisons between two groups were performed using the Student's *t*-test, the Mann–Whitney test, and Fisher's exact method, when appropriate. The Bonferroni correction was applied for multiple comparisons. Comparison of two medians in the same sample was performed using the Wilcoxon test.

We determined the receiver operating curve (ROC) and calculated the area under the ROC curve and its 95% confidence interval. The ROC curve was used to determine the optimal threshold for PCT and lactate to accurately identify the following criteria: sepsis, severe sepsis, septic shock and severe outcome (as defined previously). The optimal threshold was the one which maximizes the Youden index (sensitivity + [specificity – 1]) on the ROC curve (Ray et al. 2010). Comparison of areas under the

ROC curve was performed as previously described by Delong et al. (1988).

We performed a multivariate analysis to assess variables associated with sepsis, severe sepsis, septic shock and severe outcome using backward logistic regression. To avoid overfitting, we used a conservative approach and included only the significant variables in the univariate analysis (p value of entry ≤ 0.10). Interactions were not tested. The odds ratio and their 95% confidence interval of variables selected by the logistic model were calculated. The discrimination of the model was assessed using the ROC curve and the calculation of the area under the ROC curve. The percentage of patients correctly classified by the logistic model was calculated using the best threshold determined by the ROC curve. Calibration of the model was assessed using the Hosmer-Lemeshow statistics.

We also calculated the main diagnostic variables (sensitivity, specificity, negative and positive predictive values, positive and negative likelihood ratios) and their 95% confidence interval associated with a severe outcome when considering elevated PCT, elevated lactate, one of these, or both of them.

All p values were two-tailed and a p value of less than 0.05 was considered significant. Statistical analysis was performed using NCSS 6.0 software (Statistical Solutions Ltd, Cork, Ireland) and R software with specific packages (http://www.R-project.org).

Results

During the 12-months study period, 462 patients suspected of being infected underwent both PCT and lactate serum measurements at admission. There were 272 (59%) men and 190 (41%) women; mean age was 64 ± 20 years (range 15–102 years). The cohort comprised 58 patients with cancer ongoing treatment, 15 HIV-infected patients, 7 patients with multiple sclerosis and 4 with systemic vasculitis ongoing corticosteroid therapy. The main ED admission characteristics of these patients are summarized in Table 1. Samples for lactate measurement were drawn mostly from arterial puncture (82%) and the remaining from peripheral venous. One hundred and forty patients (30%) had a lactate >2 mmol/L and 35 (8%) >4 mmol/L. Two hundred and fifty-six patients (55%) had, at admission 2 or more SIRS criteria, 283 (61%) had sepsis, 117 (25%) severe sepsis and 10 (2%) septic shock.

Overall, there were 86 patients who were initially considered to be critically ill (at least one vital failure) including 12 terminal patients with therapy limitations, 15 patients who secondarily became so (2 unexpected deaths and 13 secondary ICU admissions) and 361 patients who remained definitely noncritically ill. Finally, 87 (19%) patients were admitted to the ICU (74 directly from the ED and 13 in the following days after initial admission on a medical bed) (Figure 1). Overall, 20 patients (4%) died, thus generating a severe outcome subgroup size of 101 (22%) patients (Figure 1). The secondary worsening subgroup comprised 15 patients with

Table 1. Main baseline characteristics of patients at ED admission (n = 462).

Variables	N	n (%) mean ± SD median (25–75 IQR)
Age	462	64 ± 20
Age > 75 years	462	173 (37%)
Sex male		272 (59%)
Baseline characteristics		
Temperature (°C)	462	37.3 ± 1.1
Heart rate (beats per minute bpm)	462	98 ± 23
Systolic blood pressure (mmHg)	459	127 ± 25
Pulse oximetry	457	95 (92–98)
Temperature > 38°C or < 36°C		130 (28%)
Heart rate > 90 bpm		283 (61%)
Systolic blood pressure < 90 mmHg		25 (5%)
Pulse oximetry < 90%		76 (17%)
Biology		
White blood cell count (per mm^3)	458	11 313 ± 7162
Creatinine (μmol.L^{-1})	459	111 ± 113
Lactate (mmol.L^{-1})	462	2.02 ± 1.71
Lactate > 2		140 (30%)
Lactate > 4		35 (8%)
Procalcitonin (PCT) (ng.mL^{-1})	462	0.25 (0.11–1.14)
PCT > 0.25		236 (51%)
PCT > 2		88 (19%)
nSIRS Criteria	462	
0		73 (16%)
1		133 (29%)
2		153 (33%)
3		81 (17%)
4		22 (5%)

Data are expressed as mean ± SD, median [25–75% Interquartile, IQR], or number (percentage).

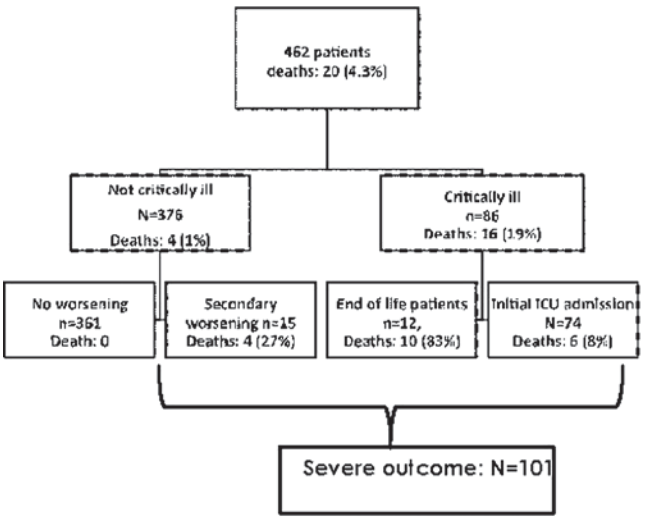

Figure 1. Study flow chart (n = 462).

Table 2. Area under ROC curves (AUC_{ROC}) of lactate, PCT and number of SIRS criteria (nSIRS) for severe outcome, sepsis, severe sepsis and septic shock.

End point and variables	Threshold	AUC_{ROC} [95% CI]	*p* value
Severe outcome			
Lactate ($mmol.L^{-1}$)	2.0	0.679 [0.604–0.731]	<0.001
PCT ($ng.mL^{-1}$)	0.80	0.664 [0.594–0.724]	<0.001
nSIRS (*n*)	2	0.605 [0.545–0.659]	<0.001
Sepsis			
Lactate ($mmol.L^{-1}$)	1.4	0.565 [0.508–0.616][a,b]	0.02
PCT ($ng.mL^{-1}$)	0.25	0.748 [0.701–0.788][a]	<0.001
nSIRS (*n*)	2	0.678 [0.625–0.722][b]	<0.001
Severe sepsis			
Lactate ($mmol.L^{-1}$)	2.0	0.792 [0.736–0.838][a]	<0.001
PCT ($ng.mL^{-1}$)	0.5	0.722 [0.659–0.775][a]	<0.001
nSIRS (*n*)	2	0.638 [0.582–0.688][b]	<0.001
Septic shock			
Lactate ($mmol.L^{-1}$)	2.60	0.840 [0.719–0.912][a]	<0.001
PCT ($ng.mL^{-1}$)	0.60	0.865 [0.737–0.933][a]	<0.001
nSIRS (*n*)	2	0.675 [0.573–0.757][b]	<0.001

p value refers to the comparison vs 0.50 (i.e. no discrimination).
[a]$p < 0.05$ vs nSIRS.
[b]$p < 0.05$ vs PCT.

2 unexpected deaths and 13 secondary admissions to ICU (including 4 septic shocks).

On the 462 patients included, 90 (19%) had co-morbidities and/or treatments that could contribute to raised lactate levels, comprising 43 patients with cancer, 10 with alcoholic intoxication, 12 on β-2 agonist treatment, 7 with HIV infection, 6 with diabetes mellitus, 4 with anemia, 4 cases of shock of other origin than sepsis, and 5 patients with seizures.

Prediction of sepsis, severe sepsis, septic shock and severe outcome

The performances of PCT, lactate and number of SIRS criteria were evaluated according to the area under ROC curve (Table 2 and Figure 2). Although PCT appeared more effective in predicting sepsis (threshold: 0.25 ng/mL), lactate was superior in identifying severe sepsis or severe outcome (threshold: 2.0 mmol/l) and was equivalent to PCT in predicting septic shock. For each clinical group studied, the number of SIRS criteria performed less well than PCT and lactate.

Multivariate analysis showed that PCT was the best independent variable to identify sepsis while lactate was the best for the diagnosis of severe sepsis (Table 3). PCT and lactate performed similarly to identify septic shock but less well than systolic blood pressure (SBP) <90 mmHg (Table 3). Finally, severe outcome was more appropriately identified by clinical variables (SBP < 90

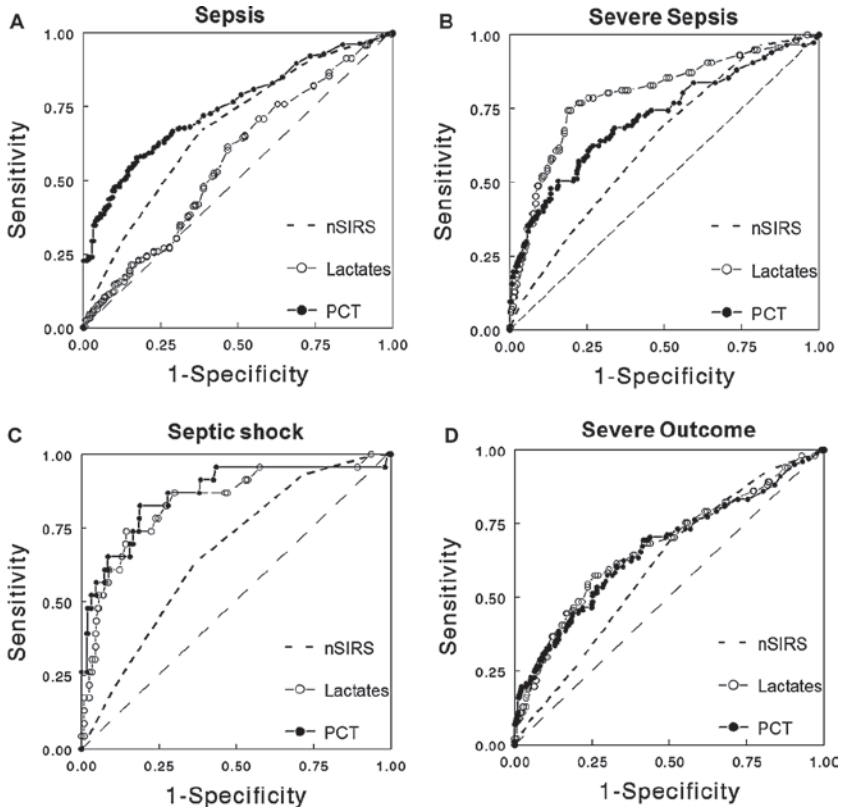

Figure 2. Receiver operating characteristic (ROC) curves of procalcitonin (PCT), lactate and the number of SIRS criteria (nSIRS) for the diagnosis of sepsis (A), severe sepsis (B), septic shock (C) and severe outcome (death or ICU admission during hospital course) (D). The dotted line is the identity line (no discrimination).

Table 3. Variables independently associated with severe outcome (death or ICU admission during hospital course), sepsis, severe sepsis and septic shock.

Clinical group and variables	OR [95% CI]	*p* value
Severe outcome		
SAP < 90 mm Hg	7.13 [2.58–19.69]	<0.001
SpO2 < 90%	3.32 [1.84–5.99]	<0.001
Lactate > 2 mmol.L^{-1}	2.95 [1.76–4.94]	<0.001
Creatinine > 120 µmol.L^{-1}	2.95 [1.70–5.15]	<0.001
PCT > 0.80 ng.mL^{-1}	1.73 [1.02–2.94]	0.04
Sepsis		
PCT ≥ 0.25 ng.mL^{-1}	3.98 [2.60–6.10]	<0.001
Temperature > 38 or < 36°C	2.42 [1.47–3.98]	<0.001
WBC count > 12,000 mm^{-3}	1.83 [1.17–2.86]	0.008
Severe sepsis		
Lactate > 2 mmol.L^{-1}	10.88 [6.51–18.19]	<0.001
PCT ≥ 0.25 ng.mL^{-1}	4.42 [2.59–7.54]	<0.001
Septic shock		
SAP < 90 mm Hg	14.44 [4.34–48.05]	<0.001
Lactate > 2 mmol.L^{-1}	6.36 [1.87–21.62]	0.003
SpO2 < 90%	4.99 [1.62–15.35]	0.005
PCT > 0.80 ng.mL^{-1}	6.71 [1.99–22.69]	0.002

Multivariate analysis. Data are expressed as odds ratios (OR) and their 95% confidence interval [95% CI].

nSIRS, number of SIRS criteria; SAP, systolic arterial pressure; SpO2, peripheral pulse oximetry; WBC, white blood cell.

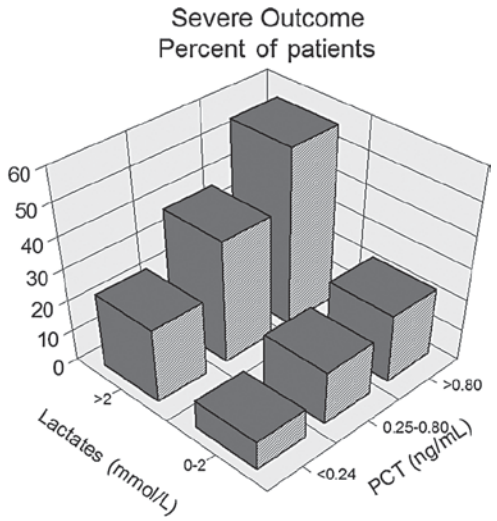

Figure 3. Percentage of patients with a severe outcome (death or ICU admission during hospital course) according to the presence of elevated lactate and/or procalcitonin ($n = 462$, $\chi^2 = 59.1$, $p < 0.001$).

mmHg and pulse oximetry <90%) although PCT, lactate and high creatinine levels remained independent predictive variables, PCT exhibiting the lowest odd ratio (Table 3). The respective contribution of PCT and lactate (according to their serum level) for the prediction of severe outcome is shown in Figure 3. Lastly, we calculated main diagnostic variables associated with an elevated PCT (>0.8 mg/L), an elevated blood lactate (>2 mM/L), one of these two variables, and both of them in predicting severe outcome (Table 4).

Discussion

The accurate identification and risk-stratification of infected patients is of major concern in emergency room, in order to implement a targeted therapy as soon as possible (Rivers et al. 2001). Apart from efforts to identify potential source of infection and recording vital parameters and clinical signs, emergency physicians may use biological tools to improve their clinical judgment. Such biological parameters may either reflect hemodynamic consequences of sepsis (such as blood lactate measurement) or the systemic host response to bacterial invasion (such as serum PCT level). In the present study, we report the respective usefulness of lactate and PCT measurements for the diagnosis and risk-stratification of patients suspected of having sepsis who present to the ED. Only 61% of patients suspected of infection had sepsis, which requires some comments. Indeed, due to the large polymorphism and sometimes cryptic presentation of infected patients at the emergency department, emergency physicians have to favor sensitivity rather than specificity. Unsurprisingly, PCT appeared to perform better for the diagnosis of sepsis while lactate was slightly more predictive of critical illness (Tables 2, 3, and 4, Figure 2). Both biological variables were predictive of severe outcome, defined as death or ICU admission during hospital course, although PCT performed less than other biological variables as creatinine (Table 3). Our data confirm that SIRS criteria are neither sensitive nor sufficiently specific (Levy et al. 2003). Rather than competing, lactate and PCT provided complementary informations on outcome. Therefore, a patient having both a lactate level above 2 mmol.L^{-1} and a PCT above 0.8 ng.mL^{-1} had an enhanced risk of severe outcome (56%) compared to patients having only one of these biomarkers raised (21.7% for PCT and 23.8% for lactate) or any (9.2%) (Figure 3, Table 4).

The prognostic value of the serum lactate level in patients admitted to the ED for a suspected infection is now well-established (Shapiro et al. 2005, Howell et al. 2007, Mikkelsen et al. 2009, Vorwerk et al. 2009) and remains of value even in patients without obvious hypoperfusion and/or organ dysfunction (Howell et al. 2007, Mikkelsen et al. 2009). The lack of early lactate clearance at 6 h seems to be more useful in predicting poor prognosis than the baseline lactate value probably because it reflects non-optimal hemodynamic resuscitation (Nguyen et al. 2004, Arnold et al. 2009, Nguyen et al. 2010). This may be particularly useful for accurately risk-stratifying septic patients who are not immediately candidates for ICU admission. Conversely, as many non-septic conditions (notably seizures) cause raised lactate levels, such results should not lead to a misdiagnosis of severe sepsis state (Fall & Szerlip 2005). Indeed, 19% of our patients had concomitant characteristics that may have contributed to high lactate levels. Therefore, beside the outcome value of lactate measurement there is a place for a sepsis diagnosis biomarker for patients suspected of infection but without obvious clinical focus. PCT has been established as a biomarker of bacterial infection (Hausfater et al. 2002,

Table 4. Diagnostic variables associated with an elevated procalcitonin (PCT > 0.8 mg/L), an elevated blood lactate (>2 mM/L), one of these two variables, and both of them in predicting severe outcome (death or ICU admission during hospital course).

	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Elevated lactate	0.54 [0.45–0.64]	0.76 [0.72–0.81]	0.39 [0.32–0.47]	0.86 [0.81–0.89]	2.31 [1.78–2.98]	0.59 [0.47–0.53]
Elevated PCT	0.51 [0.41–0.60]	0.75 [0.70–0.79]	0.35 [0.28–0.44]	0.84 [0.80–0.88]	2.00 [1.53–2.59]	0.66 [0.53–0.80]
Elevated lactate and/or PCT	0.72 [0.63–0.80]	0.58 [0.53–0.63]	0.33 [0.27–0.39]	0.88 [0.84–0.92]	1.74 [1.45–2.06]	0.47 [0.33–0.54]
Elevated lactate and PCT	0.33 [0.24–0.42]	0.93 [0.90–0.95]	0.56 [0.42–0.69]	0.83 [0.79–0.87]	4.54 [2.86–7.27]	0.73 [0.62–0.82]

Data are expressed as values and their 95% confidence interval [95% CI].
NLR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; PLR, positive likelihood ratio.

Hausfater et al. 2007) and there is growing evidence for its usefulness as an indicator for starting or stopping antibiotics, notably in lower respiratory tract infections (Christ-Crain et al. 2004, Arnold et al. 2009, Bouadma et al. 2010). The outcome predictor value of PCT in sepsis, although remaining controversial, has been reported in the ICU and ED settings (Hausfater et al. 2002, Clec'h et al. 2004, Hausfater et al. 2007, Phua et al. 2008, Viallon et al. 2008). In 72 patients with septic shock, Phua, Koay and Lee studied the prognostic value of lactate, PCT and several cytokine levels (from day 1 to day 3 following ICU admission) and reported that elevated baseline lactate levels exhibited superior prognostic accuracy than baseline PCT levels, although both remained inferior to baseline cytokine levels and APACHE II and SOFA scores (Phua et al. 2008). This is in accordance with our results as PCT and lactate levels were independent variables associated with severe outcome but performed less well than systolic blood pressure and pulse oximetry (Table 3). However, the clinical context is quite different between patients already admitted to the ICU with the highest level of care (Phua et al. 2008) and patients in the ED being evaluated and risk-stratified for suspected infection. In other words, without questioning the fundamental role of clinical variables in evaluating septic patients, having the use of biological data with added-value for prognosis may be of particular value for the physician to warn or highlight the potential severity of the infection. To date, lactate and PCT measurement appeared to be the best candidates as cytokine levels are not routinely performed and still controversial (Lvovschi et al. 2011). Recently, Green et al. studied the contribution of C-reactive Protein (CRP) stratification to lactate levels for the prognosis of patients admitted through the ED for suspected infection, and found that patients with both a lactate level greater than or equal to 4.0 mmol.L^{-1} and a CRP greater than 10.0 mg.dL^{-1} had an increased risk of short-term mortality (Green et al. 2011). Although we did not study CRP in the current study, due to the enhanced specificity of PCT for bacterial infection and its close relation to severity, we think that PCT may be more suitable than CRP when measured together with lactate for risk-stratification of septic patients (Hausfater et al. 2002, 2007, Claeys et al. 2002, Simon et al. 2004, Claessens et al. 2010a, 2010b).

Several limitations of our study should be noted. First, since the criteria of inclusion specified the availability of both PCT and lactate measurements, we cannot confirm that all patients with sepsis were indeed taken into account. However, since lactate and PCT levels are part of normal practice in our ED when caring for patients suspected of being infected (Hausfater et al. 2002, Hausfater et al. 2007), we think that most of our septic patients over a period of one year have been included. Secondly, as we took into account hyperlactatemia as an already relevant criteria for severe sepsis definition (Levy et al. 2003), this should have overestimated the diagnostic properties of lactate. Thirdly, this was a single-center study, the results may not be applicable to other EDs. Fourthly, it cannot be excluded that the knowledge of baseline lactate and PCT results by emergency physician affected some diagnostic decisions, which was unavoidable in this observational study. Finally, the subgroup with secondary worsening was not large enough (15 patients) to allow statistical analysis of the predictive variables, although this was potentially the most clinically-relevant group of interest. Additional large scale studies are needed to explore this particular subgroup of patients.

Conclusions

For patients evaluated in the ED for suspected infection, the combination of lactate and PCT measurements together with clinical data and vital variables provide complementary informations for diagnosis and risk-stratification. Patients with lactate above 2 mmol.L^{-1} and a PCT above 0.8 ng.mL^{-1} may be at highest risk for severe outcome.

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Declaration of interest

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