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Letter to the Editor

Early serum procalcitonin, but not C reactive protein, might improve the prediction of sepsis in multiple trauma patients. A prospective observational study

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To the Editor:

Prediction of clinical outcome in critically ill patients is assessed by the use of composite scores that comprise physiological variables and laboratory measurements, together with the degree of impairment.

Leukocyte count is the only laboratory inflammatory biomarker included in these scores to highlight the severity of inflammation. However, in the past two decades, other biomarkers of inflammation have been studied and validated to enter the clinical practice. C reactive protein (CRP) and procalcitonin (PCT) have been investigated and used by clinicians to appreciate the extent of the pro- and anti-inflammatory processes, which are not uncommon in multiple trauma patients. As the severity of the initial physiological variables and laboratory measurements alterations are linked to the outcome, we hypothesized that PCT and CRP concentrations might predict the occurrence of sepsis, the main cause of late mortality in polytrauma patients.

After approval of the Ethics Committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca (Approval 549/2012), a total number of 65 multiple trauma patients admitted to the Intensive Care Unit (ICU) were prospectively included in this observational study between November 2012 and November 2013. Inclusion criteria were age above 18 years and Injury Severity Score (ISS) higher than 16. Only patients who survived over 12 hours after the traumatic injury were included in the statistical analysis. All patients or the next of kin gave written informed consent. Exclusion criteria were: chronic renal disease, thyroid or liver dysfunction, autoimmune diseases, treatment with glucocorticoids or other immunosuppressive drugs and burned patients.

Baseline collected data were: age, sex, preexisting chronic disease, ISS, Revised Trauma Score (RTS), Acute Physiology and Chronic Health Evaluation II score (APACHE II), SOFA score (Sequential Organ Failure Assessment), Glasgow Coma Scale (GCS), mean blood pressure, amount of blood products administered in the first 24 hours, serum lactate, blood pH, and core temperature. The complications investigated during follow-up were the occurrence of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis or septic shock [1]. PCT and CRP dosing was performed upon admission, and subsequently in days 1,2,3,4,5,7,10 and 14 after the traumatic injury.

Serum PCT concentration was determined using Enzyme-Lynked Flurorescent Assay, on VIDAS BRAHMS apparatus (BioMerieux, Marcy l'Etoile, France, 2010). Serum CRP concentration was determined using the immunoturbidimetric technique on Konlab 30.I apparatus (Thermo ElectronCo., Vantaa, Finland, 2001).

The patients were divided into two groups of interest: group T (patients with multiple trauma who did not develop sepsis) and group T&S (patients with multiple trauma who developed sepsis) in order to compare the inflammatory biomarkers' kinetics and their discriminative value.

All clinical and laboratory results were recorded in a File MakerPro 5 database and the analysis was performed using MedCalc (MedCalc Software, Ostend, Belgium). We used the U Mann Whitney test and the Fisher exact tests

for comparisons, with p-values <0.05 considered statistically significant.

We investigated the time to infections from admission rates using Kaplan Meier plots [2]. The cutoffs were determined by correlating the dichotomized biomarker (either PCT or CRP) with the binary outcome variable (infection-free= patients in the T group and patients who developed sepsis= T&S group) using Cox proportional hazard models. The optimal cutoffs were defined as the points with the most significant split (log-rank test). The infection-free rates for multiple trauma patients were considered as end-points and were calculated for PCT and CRP levels lower and higher than the optimal identified cutoff values.

A total number of 65 multiple trauma patients (48 male and 17 female patients, mean age 47 years) were prospectively included in the study, with the majority suffering blunt trauma (48 patients, 73.8%). Mean severity scores were: ISS 28 (16-75), RTS 6,271 (1,314-7,841), SOFA 3 (0-15), while the mean APACHE II score was 12 (1-42) upon admission. The mean ICU admission period was 10 days (range: 1-44 days).

Patients in the T&S group presented significantly higher baseline severity scores compared to the T group, as well as more severe lactic acidosis, a more severe altered neurological status and higher blood glucose levels on admission (U Mann-Whitney test, p<0.05). In the same time, patients from the T&S group suffered more often from previous chronic diseases, presented more often hypotension in the prehospital setting, and required more often mechanical ventilation or massive transfusion during their ICU stay (Fisher exact test, p<0.05).

We found no significant differences in mean PCT concentrations between T and T&S patients' groups upon admission and in days 1,2,3 and 5, but later on, in days 7 and 10 the mean PCT levels were significantly higher in the T&S group (Day 7: PCT 0.5 ng/dL for the T group versus 19.8 ng/dL for the T&S group, p=0.04; Day 10: PCT 0.19 ng/dL for the T group versus 10.93 ng/dL for the T&S group, p= 0.04).

With regard to CRP, we found no significant differences between the T and T&S groups upon admission or in days 1, 2 and 3. In days 5 and 7 serum CRP concentrations were significantly different between the two groups, with the T&S group having higher levels (Day 5: CRP 7.43 mg/dL for the T group versus 14.01 mg/dL for the T&S group, p=0.04; Day 7: CRP 6.82 mg/dL for the T group versus 12.95 mg/dL for the T&S group, p=0.002).

For PCT, by using the Kaplan Meier plot analysis, we identified an optimal cutoff concentration of 1.5ng/dL to be discriminative. From the patients with serum PCT <1.5ng/dL, 81% were infection free at 14 days, while from the patients with PCT >1.5 ng/dL, 56% did not present infections at 14 days (p=0.02) (Figure).

We identified a cutoff value of 4.25 mg/dL for CRP concentration, but there was no significant difference between the infection free rates in patients with CRP <4.25 mg/dL relative to those with CRP > 4.25 mg/dL (74% versus 67%, p=0.67) (Figure).

Severe traumatic lesions are triggers for the early activation of systemic inflammation, aimed to maintain homeostasis, but which may lead to development of the possibly lethal multiple organ dysfunction syndrome [3,4]. The initial pro-inflammatory syndrome is soon followed by an anti-inflammatory response that may lead to immune suppression and carries a high risk for the development of severe infections and sepsis, the main cause of late mortality in trauma [5].

In our study, baseline severity scores were significantly higher in patients who later on developed sepsis, confirming the prediction function for the use of these scores in ICU patients. In the same time, this group of patients presented more often previous chronic diseases, prehospital haemodynamic instability and lactic acidosis,

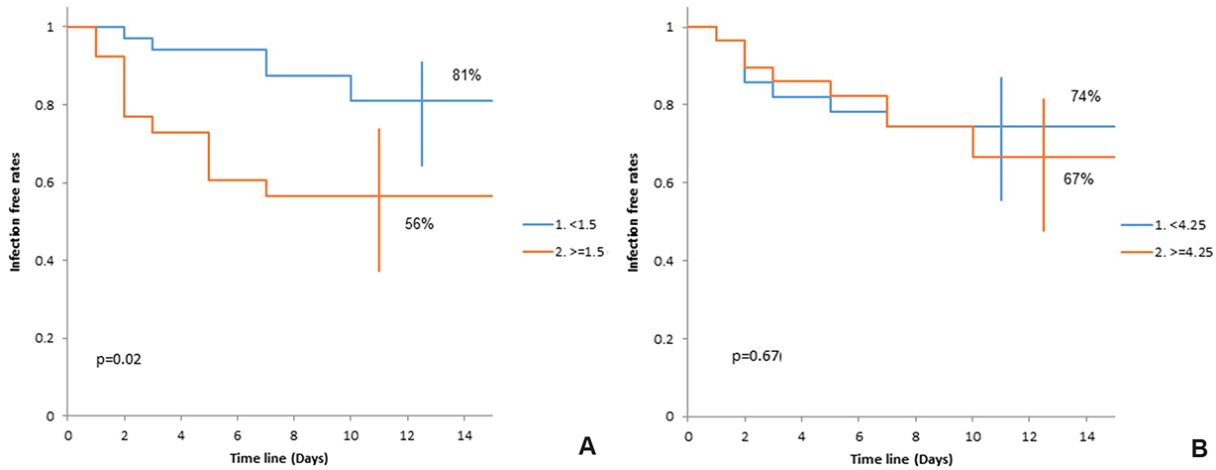

Figure. Kaplan-Meier survival curve for serum procalcitonin (PCT) in patients with PCT<1.5 ng/dL and PCT>1.5 ng/dL (A) and for serum C reactive protein (CRP) in patients with CRP<4.25 mg/dL and CRP>4.25 mg/dL (B).

a severely altered neurological status as assessed by the GCS, and they required more often mechanical ventilation and massive transfusion, a well-known trigger for immune suppression during the ICU stay, suggesting that these might be independent risk factors for the occurrence of sepsis after suffering severe traumatic injuries.

In our patients, CRP discriminated earlier the patients who developed sepsis from those without septic complications (U Mann Whitney test, p=0.04 on Day 5), compared to PCT (U Mann Whitney test, p=0.04 on Day 7). Thus, CRP might be more valuable in the early diagnosis of sepsis.

The prognostic relevance of PCT and CRP is still controversial [6]. There have been efforts to measure plasma biomarkers concentrations in order to predict the clinical outcome and the response to therapy. PCT and CRP are non-specific biomarkers that respond to both inflammation and infection [7].

As both PCT and CRP are severity markers for the initial inflammatory syndrome induced by severe injuries and for the presence of sepsis, we hypothesized that early serum concentrations are linked to the clinical outcome, which is strongly related to the occurrence of sepsis, infectious complications being the main determinant of late mortality in trauma.

We found a PCT serum concentration of 1.5 ng/dL to discriminate between two categories of patients. Those with higher levels than this optimal threshold have significantly lower infection free rates compared to those with levels <1.5ng/dL (p=0.02). For CRP, we could not identify such an optimal threshold. The use of PCT serum concentration in the first 24 hours after the traumatic event might improve the prognostic information that currently available scores offer to the intensive care unit physician, as it reflects the severity of the initial inflammatory response. The study of altered neuroendocrine responses and autonomic nervous system imbalance, both linked to immune suppression in response to trauma and sepsis, might reveal other valuable biomarkers to estimate the severity of the disease and the risk of death [8,9].

In conclusion, early serum PCT, but not CRP, discriminates between patients with different rates of sepsis occurrence when an optimal

discriminative cutoff point of 1.5ng/dL is used. Further studies, including larger cohorts of patients, are requested to evaluate whether the inclusion of PCT dichotomized by the cutoff concentration of 1.5ng/dL aids in the prediction of sepsis development and sepsis-related late mortality in the polytrauma population.

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Abbreviations

CRP= C-reactive protein
PCT= Procalcitonin
ICU= Intensive Care Unit
ISS= Injury Severity Score
RTS= Revised Trauma Score
APACHE II= Acute Physiology, Age and Chronic Health Evaluation II score
SOFA= Sequential Organ Failure Assessment score
GCS= Glasgow Coma Scale
SIRS= Systemic Inflammatory Response Syndrome
T= Patients with multiple trauma who did not develop sepsis
T&S= Patients with multiple trauma who developed sepsis

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