Prognostic Value of Variations in Serum Biomarkers and Prognostic Scores Values between Admission and Second day in Intensive Care Unit Septic patients

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Abstract

Background: To determinate the prognostic value of procalcitonin (PCT) and C-reactive protein (CRP) changes during the first two days of admission to the ICU with sepsis and/or septic shock, and to compare it with changes in Acute Physiology And Chronic Health Evaluation II (APACHE-II) and Sepsis-related Organ Failure Assessment (SOFA) prognostic scores.

Methods: Prospective cohort observational study. 50 consecutive patients admitted to a single-center ICU.

Results: Aged 67(52-75) years with APACHE-II 19(14-25) and SOFA scores 7(5-11) points on admission, and a recorded 28-day mortality of 42%. There were no significant differences observed between APACHE II, SOFA, PCR nor PCT in the survival versus the non-survival group on the day of admission. APACHE II (p=0,001) and SOFA (p=0,002) between admission and second day raised significantly in no survivors, with no significant changes in CRP and PCT. Mortality was significantly associated with a raise in APACHE-II and SOFA scores between admission and second day (OR:2.13,1.18-3.86) but not with PCT nor CRP changes.

Conclusions: Changes in SOFA and APACHE II scores between admission and second day in ICU septic patients are more sensitive mortality predictors than the observed changes in CRP and PCT values.

Background

Mortality related to sepsis and septic shock continues to be high in the medical literature despite advances in early diagnosis and appropriate treatment. Advanced life support and resuscitation together with prompt antibiotic treatment constitutes the fundamental aspect of sepsis management (1).

Sepsis biomarkers are molecules that support the diagnosis of a septic condition, being used as prognostic and follow-up indicators as well (2). They have been also used as guide for detection of complications in surgical and trauma patients (3). Among these biomarkers, procalcitonin (PCT) and C-reactive protein (CRP) are the most commonly used ones. PCT has shown a significant prognostic value even since admission, as lower serum levels have been associated with a higher probability of survival in patients with sepsis (4). On admission, PCT levels are strongly related to the severity of the inflammatory reaction. PCT *per se* impairs the endothelial barrier function, causing capillary leak and refractory hypotension with subsequent multiple organ failure during sepsis (5).

Randomized studies support the use of decision-making algorithms based on PCT blood levels when guiding antibiotic therapy. A favourable response in PCT levels could shorten the length of antibiotic treatment in critically-ill septic patients, but this statement is only supported by a moderate level of evidence with controversy over it. Neither can it be considered a pattern in current clinical management (6). De-escalation of antibiotic treatment in septic patients according to PCT changes seems a safe and useful practice, although it still has not been associated with an improvement in mortality figures (7,8).

Recently, we published a paper about predictive usefulness of several biochemical parameters in patients with severe sepsis and septic shock admitted to the Intensive Care Unit (ICU). We found that a decrease of more than 50% in PCT serum levels from days 0 to 5 of admission was an independent factor associated with mortality. However, changes in levels from days 0 to 2 did not show a prognostic value (9). Also, Schuetz et al. found an increased mortality in septic patients who did not show a significant decrease in PCT values on the fifth day of admission (2). We believe that five days is a too long period to be used as a predicting time in sepsis, mostly when diagnostic and therapeutic tools must be reinforced earlier to improve a patient´s evolution towards a satisfactory trend.

On the other hand, validated clinical prognostic scores (PS) have proved to be reliable enough when establishing prognosis in critically ill patients since their admission to ICU. Sepsis-related Organ Failure Assesment (SOFA) is a PS used in mortality prognosis for patients admitted to medical and surgical ICUs (10–12). The APACHE-II (Acute Physiology And Chronic Health Evaluation II) system (13) is validated to establish prognosis on admission of critical patients.

The objective of our study is to assess the prognostic value of routine used severity scores (SOFA and APACHE-II) and biochemical markers (CRP and PCT) between admission and the second day of admission in ICU patients with sepsis and septic shock.

Materials And Methods

A single-center prospective observational study was performed from 1st of January 2014 to 31st of January 2015, in the 16-bed mixed ICU of the “Serrania de Ronda” Hospital, Malaga (Spain), a 300-bed non-academic teaching hospital where all medical specialties except neurosurgery and cardiac surgery are available. This Hospital has an ICU-based medical emergency team. All consecutive patients admitted to the ICU, older than 18 years old, and diagnosed of severe sepsis/septic shock according to the definitions of the Surviving Sepsis Campaign 2012 (14) were included. If a patient had more than one ICU episode during the study period, only the first one was included. Diagnosis of sepsis was based on the Systemic Inflammatory Response Syndrome (SIRS) criteria in the presence of a known infection, and diagnosis of severe sepsis was based on sepsis-induced tissue hypoperfusion or organ dysfunction. In case of maintained arterial hypotension without response to volume infusion and requiring administration of vasoactive drugs, a diagnosis of septic shock was made.

Exclusion criteria were: 1) previous immunodeficiency, either of congenital origin, or caused by human immunodeficiency virus infection or hematological malignancies; 2) blood transfusion in the previous three months, as this could modify serum levels of the studied molecules; and 3) treatment with corticosteroids or immunomodulators in the previous six months.

The following variables were collected upon admission: 1) age and sex; 2) risk factors for infection (chronic obstructive pulmonary disease, diabetes mellitus, antibiotic treatment in the previous three months, central intravascular catheter, bladder catheter, active neoplasia); if the patient had no one of the considered risk factors for infection, the case was described as „absence of risk factors”; 3) previous

antibiotic therapy; 4) site of infection; and 5) severity of infection. SOFA and APACHE-II scores on admission were recorded according to available clinical and laboratory data.

Patients were treated according the guidelines of the Surviving Sepsis Campaign 2012 (14). Antibiotic therapy was considered adequate when isolated microbia were sensitive to the antibiotic used during empirical treatment. Patients were followed up until hospital discharge or death.

Blood samples were collected upon admission and sequentially after two and five days of hospitalization by venipuncture. After centrifugation, plasma was stored at -80 °C until analysis. PCT was measured by a time-resolved amplified cryptate emission assay (Kryptor PCT, Brahms Diagnostica, Berlin, Germany). CRP was measured by a inmunoturbidometry assay (CardioPhase hsCRP; Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma concentrations of sTREM-1, sCD14, sCD163 and IL-6 were also measured with specific sandwich enzyme-linked immunosorbent assays (R&D systems, Minneapolis, USA), although these data were not analyzed in this study.

STATISTICAL ANALYSIS

Quantitative variables were expressed as median and 25th–75th percentiles interval, qualitative variables as percentages and frequencies. Non-parametric tests were used to compare continuous variables, applying the Mann-Whitney U test for comparisons of two independent samples. Categorical variables were compared with the chi-square test. Multivariate analysis was performed using a multiple logistic regression model, being mortality at 28 days of hospital stay the dependent variable. The area under the ROC curve was used to analyze discrimination. PSPP (Psppire.exe 0.10.2) and 'R V.3.4.1' were used for statistical analysis. Values of $p < 0,05$ were considered statistically significant.

ETHICS

Approval for the study was granted by the Malaga Provincial Ethics Committee for Medical Research. Patients or their representatives were provided with written informed consent to participate in this study.

Results

50 patients with diagnosis of severe sepsis or septic shock were included in the study. Median (IQR) age was 67 (52–75) years, APACHE-II on ICU admission was 19 (14–25) points, and SOFA score was 7 (5–11) points (Table 1). 28-day mortality was 42%. The empiric antibiotic treatment was adequate according to culture results from samples taken on admission in 45 patients (90%), and inappropriate in 5 (10%). In the five-patients group with inappropriate antibiotic treatment, mortality during first day of admission was 60%, versus (vs.) 40% in the rest ($p = 0.390$).

Table 1
Relationship between 28-day mortality and rest of variables (age expressed in years, APACHE-II and SOFA in points)

Variables	Total (n = 50)	Survivors (n = 29)	Non-survivors (n = 21)	P values
Age	67 (52,75)	66 (48,74)	71 (63,78)	0.115
APACHE-II	19 (14,25)	18 (14,22)	19 (14,25)	0.333
SOFA	7 (5,11)	7 (5,10)	7 (4,11)	0.534
Lactate (mmol)	2.1 (1.4,3.6)	1.9 (1.4,3.4)	2.1 (1.4,3.7)	0.616
CRP (mg/l)	221 (109,280)	246 (136,285)	158 (86,240)	0.066
PCT (ng/ml)	2 (0.5,21)	8 (0.7,29)	1 (0.4,9)	0.092
Male gender *	72	75.9	66.7	0.475
Risk factors of infection *	28	41.4	9.5	0.013
Absent				
COPD	18	10.3	28.6	0.098
DM	22	20.7	23.8	0.793
Neoplasia	4	6.9	0	0.219
Bladder catheter	30	24.1	38.1	0.288
Central venous catheter	14	6.9	23.8	0.089
Number of risk factors of infection*	28	41.4	9.5	0.013
0				
> 1	42	31	57.1	0.065
Site of infection *				0.266
Respiratory	34	27.6	42.9	
Urinary	8	10.3	4.8	
Abdominal	48	55.2	38.1	

Quantitative variables are expressed as median and 25th–75th percentiles interval.

*Qualitative variables are expressed as percentages (%)

APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assesment; CRP, C-Reactive Protein; PCT, Procalcitonine; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

Variables	Total (n = 50)	Survivors (n = 29)	Non-survivors (n = 21)	P values
Central nervous system	2	3.4	0	
Cardiovascular	2	0	4.8	
Soft tissues and bone	2	3.4	0	
Unknown	4	0	9.5	
Nosocomial origin*	30	20.7	42.9	0.123
Previous antibiotic therapy *	34	34.5	33.3	1
Septic shock *	66	65.5	66.7	1
Urgent surgery	30	34.5	23.8	0.537
Mechanical ventilation *	52	48.3	57.1	0.578
Cathecolamine therapy *	72	65.5	81.1	0.341
Quantitative variables are expressed as median and 25th–75th percentiles interval.				
*Qualitative variables are expressed as percentages (%)				
APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assesment; CRP, C-Reactive Protein; PCT, Procalcitonine; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus				

Patients in the non-survival group scored higher on admission in APACHE-II: 19 (14–25) vs. 18 (14–22) points, and in SOFA: 7 (4–11) vs. 7 (5–10) points, with no significant statistical difference (n.s.) observed for both scores. Values of analyzed inflammatory biomarkers were lower in the non-survival group, being CRP 158 (86–240) vs. 246 (136–285), p = 0.066 (n.s.); and PCT 1 (0.4-9) vs. 8 (0.7–29), p = 0.092 (n.s.). Changes between recorded values on admission and the day after, and their relationship with mortality were analyzed. Patients in the survival group showed a more noticeable decrease in CRP : -3 (-48,18) vs. -9 (-53,36) and PCT: 0 (-1,1) vs. 0 (-6, 2), with no significant statistical difference (n.s.) observed for both decreases.

Variations in PSs between first and second day of admission (Value day of admission – Value second day) showed a significant statistical difference for both scores, with a variation in APACHE-II of 2 (-2, 4) points in the non-survivors group, and an observed decline in the survivals of -3 (-6,0) points, (p = 0.001), with similar observed findings in SOFA, increasing this in the non-survivals 1 (-1,3) points, and − 1(-2,0) points in the survival group, (p = 0.002) (Table 2).

Table 2
Relationship between 28-day mortality and changes in main studied variables from admission to day after (Parameter Value of admission day – Parameter Value of second day). APACHE-II and SOFA are expressed in points.

Variables	Total (n = 48)	Survivors (n = 29)	Non-survivors (n = 19)	P values
APACHE-II	-1 (-5,2)	-3 (-6,0)	2 (-2,4)	0.001
SOFA	0 (-1,1)	-1 (-2,0)	1 (-1,3)	0.002
Lactate (mmol)	0 (-0.7,0.5)	0 (-0.6,-0.3)	0.1 (-0.6,1.3)	0.499
CRP (mg/l)	-5 (-50,20)	-9 (-53,36)	-3 (-48,18)	0.974
PCT (ng/ml)	0 (-1,1)	0 (-6,2)	0 (-1,1)	0.57
Quantitative variables are expressed as median and 25th–75th percentiles interval.				
APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assesment; CRP, C-Reactive Protein; PCT, Procalcitonine.				

The area under the ROC curve was used to analyse discrimination of changes in values of parameters and scores between first and second day of admission in relation to mortality, being 0.77 (0.62–0.93) for APACHE-II changes, 0.68 (0.5–0.85) for SOFA score changes, and just 0.52 for CRP and 0.51 for PCT changes respectively.

We categorized APACHE II and SOFA scores variations between first and second day of admission and we analyzed its relationship with mortality. Patients were classified according to scores variations > 0 (deterioration) or ≤ 0 (improvement). 28-day mortality of 28 patients with APACHE II score variation ≤ 0 was 21.4% vs. 65% of 20 patients with score variation > 0 (p = 0.002). 28-day mortality of 35 patients with SOFA score variation ≤ 0 was 25.7% vs 76.9% of 13 patients with score variation > 0 (p = 0.001).

Table 3 shows variations of SOFA, APACHE-II, CRP, PCT and lactate between admission days 1st and 5th (Value day of admission – Value 5th day) and we analysed its relationship with mortality. Variations of the prognostic scores for clinical severity (APACHE-II and SOFA) between 1st and 5th day showed a significant statistical differences between survival and non-survival groups, with decreasing figures in the survival group, and mildly increasing in non-survivals. Variations of the laboratory parameters (CRP, PCT, lactate) showed a significant statistical differences between survival and non-survival groups for PCT and without statistical differences between survival and non-survival groups for CRP and lactate.

Table 3
Relationship between 28-day mortality and changes in main studied variables from admission to 5th day (Parameter Value admission day – Parameter Value day 5). APACHE-II and SOFA are expressed in points.

Variables	Total (n = 42)	Survivors (n = 28)	Non-survivors (n = 14)	P values
APACHE II	-5 (-10,0)	-7 (-10,-3)	2 (-5,6)	0.002
SOFA	-1 (-5,1)	-4 (-6,-1)	1 (-1,3)	< 0.001
Lactate (mmol)	-0.3 (-1.3,0.2)	-0.7 (-1.3,-0.19)	0 (-0.58,0.33)	0.325
CRP (mg/l)	-117 (-186,-2)	-140 (-205,-20)	-32 (-145,26)	0.065
PCT (ng/ml)	-2 (-18,0)	-4.5 (-21,-0.4)	-0.3 (-2.4,0.4)	0.012
Quantitative variables are expressed as median and 25th–75th percentiles interval.				
APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sepsis-related Organ Failure Assesment; CRP, C-Reactive Protein; PCT, Procalcitonine				

Multivariate analysis was performed using a multiple logistic regression model, showing that mortality was significantly related to changes in recorded APACHE-II scores between date of admission and second day, odds ratio (OR): 1.33 (1.1–1.63). In this model we did not include analyzed variables that showed high statistical significance in univariate analysis, as changes in SOFA scores between date of admission and first day after it, or presence of one or more risk factors, or changes in PCT and CRP.

According to the strong observed relationship between mortality and changes in SOFA scores between date of admission and second day, with similar discriminative values observed in comparison to APACHE-II score changes, a second multivariate analysis was performed, excluding this time APACHE-II score changes, trying to create an easier model to be used in the clinical practice, as SOFA score is easier to estimate than APACHE-II score. This second model showed that mortality was related to changes in SOFA score, OR: 2.13 (1.18–3.86), and to the presence of one or more risk factors, OR: 6.01 (1.01–35.78). The discrimination of this model, evaluated with the area under the ROC curve was 0.84 (0.72–0.95).

Simplifying and making even more intuitive the statistical model, a third multivariate analysis was performed classifying SOFA score evolution between admission and second day in worsening of the SOFA score, and improving or maintenance of its initial value, showing an OR: 12.26 (2.18–68.82), according to the presence of risk factors the OR was 8.19 (1.17–57.31). The area under the ROC curve for this model was 0.78 (0.65–0.91).

Discussion

We found in this study that changes in APACHE-II and SOFA prognostic scores during first two days of admission are more sensitive for prognosis of septic patients admitted to ICU than the evolution of biochemichal inflammatory markers (PCT and CRP), with statistically significant differences observed

between the survival and the non-survival group for these PSs changes between first and second days, and between first and fifth days of admission. Multivariate analysis showed that only changes in SOFA and APACHE-II scores were the variables significantly associated to mortality when the study was restricted just to the first two days of admission.

In septic patients admitted to ICU is essential an early assesment of response to treatment. A potential parameter that matches short-term evolution with mortality could guide us to search other sources of sepsis or broaden treatment when the evolution is unsatisfactory.

A recent paper from our research group (9) have addressed the topic of prognostic reliability concerning different studied biochemical markers in septic patients, as the soluble triggering receptor expresed on myeloid cell 1 (sTREM 1), soluble cluster of differentiation 14 (sCD14), soluble cluster of differentiation 163 (sCD163), Interleukin 6 (IL 6), PCT and CRP. In this paper we correlated basal value of STREM 1, SCD 163, IL6, and PCT with SOFA score on admission, basal values of SCD14, decrease in PCT and IL 6 figures from admission to 5th day of ICU stay with mortality, and serum levels of sTREM-1 with severity of sepsis. Multivariate analysis showed in this paper that a 50% of decrease in PCT value from 1st to 5th day of admission was significantly associated to mortality. We did not find a prognostic significance in changes of studied biochemical markers between first and second day of admission. Although severity PSs as SOFA or APACHE II were evaluated, we did not compare its prognostic reliabilty with that coming from biochemical markers levels in this previous paper.

In our present research we have gone into detail about evolution of biochemical and clinical variables during a short initial period of time (first two days), showing that clinical scores are better matched with mortality than laboratory parameters.

Prognostic validity of biochemical markers changes in this type of patients has been previously evaluated in studies as the MOSES, showing in a multicentric and prospective study in the United States, that a lack > 80% in PCT clearance from admission to 4th day of ICU stay was a factor independently associated with mortality (2). According to this finding, guided-antibiotic therapy based on PCT levels has been proposed (7), although a recent study from Cochrane Foundation did not find evidence to support this practice in the standard clinical care according to reduce mortality and days of mechanical ventilation (8). Some papers have even suggested that PCT levels could point to sepsis-source type of microorganism, being PCT significantly higher in sepsis caused by Gram-negative infections in comparison to Gram-positive or fungal infections (15, 16). Other molecules as Preserpine have proved to be more sensitive than PCT or CRP when assessing prognosis in septic patients (17).

Despites the undoubted proved prognostic value of PCT and other sepsis biochemical markers, the observed early or late decrease in PCT and CRP blood levels was not significantly related with the survival group of patients in our research. Our study includes a limited number of patients coming from a single institution, which could bias these results. Different sepsis aetiologies have been included in our study, being a potential bias influencing our results. Similar results have been reported in septic patients from our geographical setting (18). Our findings also agree with the Cochrane recommendations, as they do

not find enough evidence to support a PCT-guided policy of antibiotic treatment in septic patients (7, 8). A bigger sample of patients admitted to ICUs and coming from different centers is needed to confirm and generalize our results.

Our research was before the current agreed concept of sepsis, and our findings need to be confirmed according to the new definition. A recent study from Sterling compared two cohorts of septic patients classified according to the previous and updated sepsis-3 definition, showing that patients meeting sepsis-3 criteria scored highly in SOFA and had a higher mortality (19). This could reflect more sensitive criteria when detecting patients with sepsis, with the advantage of accordingly earlier antibiotic treatment and support measures (as energic fluid resuscitation), but it still could also exclude less severe septic patients who would have a late diagnosis and who would not benefit from antibiotic or life-support treatment, subsequently carrying a higher mortality risk (20).

We remark that the clinical scores APACHE-II and SOFA are reliable, easy and cheap to perform at patient ´s bedside. They are an early and effective prognostic tool when assessing critically-ill septic patients.

Regarding the limitations of our study, the analyzed patient sample is not very large, but sufficient to give statistically significant results in a clear way. It is also a topic of high clinical importance, given the high mortality of patients with sepsis and the high number of patients who present with sepsis. That is why we believe that it is of interest to publish our results and that they can be validated by other authors in different patients and in larger samples.

APACHE II is usually used on the first day, although it is a method used in many studies, logically some of them have used the evolution of this score score in different days (21). Our results are similar when using evolution of SOFA instead of APACHE II evolution and evolution of SOFA has been used in many studies.

Conclusions

Changes in APACHE-II and SOFA scores between the first and second day of ICU admission are a more sensitive tool than observed changes in the biochemical markers PCT and CRP when predicting mortality in septic patients. Lack of improvement in these clinical scores during the first two days of admission can be a reliable index pointing towards a non-satisfactory patient evolution that can be later confirmed and complemented by PCT changes during following days.

Declarations

Ethics approval and consent to participate:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Malaga Provincial Ethics Committee for Medical Research) and with the 1964 Helsinki declaration and its later amendments or comparable

ethical standards. Patients or their representatives were provided with written informed consent to participate in this study.

Consent for publication:

Not applicable .

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request .

Competing interests:

The authors declare that they have no competing interests .

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Authors' contributions:

JJRT, MGM and RRF: conception and design of the work

MDPG, DRR, MIRG: acquisition data

JJRT, EAA and RRF analysis and interpretation of data

JJRT, MGM, EAA ,DRR and RRF drafting

All authors read and approved the final manuscript

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