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Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial

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Abstract

Introduction

Sepsis, a leading cause of death in critically ill patients, is the result of complex interactions between the infecting microorganisms and the host responses that influence clinical outcomes. We evaluated the prognostic value of presepsin (sCD14-ST), a novel biomarker of bacterial infection, and compared it with procalcitonin.

Methods

This is a retrospective, case–control study of a multicenter, randomized clinical trial enrolling patients with severe sepsis or septic shock in ICUs in Italy. We selected 50 survivors and 50 non-survivors at ICU discharge, matched for age, sex, and time from sepsis diagnosis to enrolment. Plasma samples were collected 1, 2 and 7 days after enrolment to assay presepsin and procalcitonin (PCT). Outcome was assessed 28 and 90 days after enrollment.

Results

Early presepsin (day 1) was higher in decedents (2269 (1171–4300) pg/mL, median (Q1-Q3)) than in survivors (1184 (875–2113) pg/mL, $P = 0.002$) while PCT was not different (18.5 (3.4-45.2) and 10.8 (2.7-41.9) μg/L, $P = 0.31$). The evolution of presepsin levels over time

was significantly different in survivors compared to decedents (*P* for time-survival interaction = 0.03) while PCT decreased similarly in the two groups (*P* = 0.13). Presepsin was the only variable independently associated with ICU and 28-day mortality in Cox models adjusted for clinical characteristics. It showed prognostic accuracy in the range of the sequential organ failure assessment (SOFA) score (area under the curve (AUC) from 0.64 to 0.75) but better than PCT (AUC 0.53 to 0.65).

Conclusions

This is the first evidence in a multicenter clinical trial that presepsin measurements may provide useful prognostic information in patients with severe sepsis or septic shock. These preliminary findings suggest that presepsin may be of clinical importance for early risk stratification.

Introduction

Sepsis is the leading cause of death in critically ill patients and requires early goal-directed management to reduce its high burden of mortality and morbidity [1]. During sepsis, the combination of severe infection and the subsequent non-localized inflammatory and immune-mediated systemic responses may result in a clinical condition with lethality as high as 40% [2]. Despite efforts to improve early recognition and clinical treatment, sepsis often evolves to septic shock (reduced tissue perfusion despite fluid therapy and vasoactive drugs) and multiorgan failure, which are the most frequent causes of death in the septic patient. The host's innate and adaptive immune responses are fundamental in defense against the infecting microorganism(s), but also contribute to the amplification of pro-inflammatory mechanisms, coagulation imbalance and endothelial dysfunction, that participate in organ injury [3].

Since optimal management requires early goal-oriented therapies, in principle it could benefit from individualized circulating biomarkers for early risk stratification. Circulating biomarkers may help in the diagnosis and guidance for antimicrobial therapy of sepsis [4,5], but few have proved to be useful for individual prognostic stratification. Presepsin (sCD14-ST) is a soluble N-terminal fragment of the cluster-of-differentiation (CD) marker protein CD14 that is released into the circulation during monocyte activation on the recognition of lipopolysaccharide (LPS) from infectious agents [6]; it shows promise for diagnostic purposes [7] and powerful prognostic information in septic patients already at admission [8]. To date, no multicenter study has ever evaluated the prognostic value of presepsin during severe sepsis. We therefore set out to examine the relations between early plasma presepsin concentrations and mortality in patients with severe sepsis and septic shock, comparing its prognostic performance with that of procalcitonin.

Material and methods

Study design

This is a retrospective case–control study for the multicenter, randomized Albumin Italian Outcome Sepsis (ALBIOS) trial that enrolled patients with severe sepsis or septic shock from 100 intensive care units (ICU) in Italy (Clinicaltrials.gov #NCT00707122). The primary aim was to verify whether volume replacement with albumin and the maintenance of serum

albumin levels within the physiologic range during the first 28 days (or until ICU discharge, whichever came first) improved 28-day and 90-day survival, compared to crystalloids; both arms of the study were treated according to the early-goal directed therapy and the surviving sepsis campaign guidelines for the treatment of severe sepsis [1,9].

We selected 50 survivors and 50 non-survivors at ICU discharge (21 ± 18 days) matched for age, sex, source center and time of enrolment after confirmation of the inclusion criteria (within 6 h, between 6 and 24 h) which were at least one focus of infection (known or suspected), two or more signs of systemic inflammatory reaction syndrome (core temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or arterial partial pressure of carbon dioxide <32 mmHg or requirement for mechanical ventilation for an acute pathological process, white blood cell count >12,000/μL or <4,000/μL or more than 10% immature neutrophils), and at least one severe, acute sepsis-related organ dysfunction, assessed using the Sequential Organ Failure Assessment (SOFA) score [10]. Exclusion criteria were age lower than 18 years, terminal state, a known adverse reaction to albumin, a proved or suspected and clinically active brain injury, congestive heart failure (NYHA class III or IV), a pathological condition in which albumin could be clinically indicated (such as cirrhosis with ascites, intestinal malabsorption syndrome, nephrosic syndrome, burns), more than 24 hours elapsed since the presence of inclusion criteria, religious objection to the administration of human blood products, and inclusion in other experimental studies. Assignment to the randomization arm was not known when patients were selected and the study was performed.

Clinical data on hemodynamic parameters, vasoactive drug administration, blood gas analysis, ventilatory status, fluid balance, antibiotic therapy and standard laboratory exams were obtained daily, from study enrolment to day 28 (or ICU discharge, whichever came first). The Simplified Acute Physiology Score (SAPS II) was recorded within the first 24 hours after enrollment, and the SOFA score was calculated daily. For consistency between the indications provided by the current guidelines for the management of severe sepsis and septic shock [1] and the calculation of the SOFA score [10], cardiovascular SOFA sub-score was modified lowering to 65 mmHg the mean arterial pressure limit for point 1. Moreover, the aggregate SOFA score did not include neurological function, as cerebral failure was not assessed during the study [11-13]. Data on the initial site of infection and on infecting microorganisms (site and blood culture) were collected periodically. Septic shock at the time of randomization was defined as a cardiovascular component of the SOFA score of 1, 3 or 4 [11].

A complete list of centers and investigators participating to the ALBIOS substudy on biomarkers is presented in Additional file 1. The study was compliant with the 1975 Declaration of Helsinki as revised in 2008, and approved first by the Institutional Review Board of the Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy (coordinating center), and subsequently by the appropriate Institutional Review Boards of all the other participating centers [see Additional file 2]. Written informed consent was obtained for all participants.

Sample collection and circulating biomarkers measurement

EDTA-plasma samples were serially collected 1, 2 and 7 days after enrolment (or at ICU discharge, whichever came first), shipped on dry ice to a central repository and stored at −70°C until assayed. A central laboratory, blind to patients' characteristics, measured

presepsin (chemiluminescent enzyme immunoassay, PATHFAST Presepsin, Mitsubishi Chemical) [14], and procalcitonin (Elecsys BRAHMS Cobas® PCT, Roche Diagnostics). For imprecision determination, 4 plasma samples were assayed in duplicate at 20 non-consecutive days. The PATHFAST presepsin assay revealed an intra-assay and inter-assay coefficient of variation (CV) of 4.4% at 445 pg/mL. At 4901 pg/mL intra- and inter-assay CVs of 3.2% and 3.9% were obtained, respectively. The limit of detection was 20 pg/mL. The Elecsys BRAHMS Cobas® PCT assay yielded a limit of detection of 0.02 μg/L. The intra-assay and inter-assay CVs were 9.9% and 16.3% at a procalcitonin concentration of 0.06 μg/L and 2.1% and 4.2% at 41.2 μg/L, respectively. Reference values (95th percentile) measured in a control group of 110 healthy volunteers, were 320 pg/mL for presepsin (upper limit of normality, ULN) and 0.046 μg/L for procalcitonin.

Outcome and statistical analysis

The primary outcome of the ALBIOS trial was death, as assessed 28 and 90 days after enrolment; we also evaluated the association between circulating biomarkers and survival at ICU discharge. Categorical variables are presented as proportions and continuous variables as mean (standard deviation) or median (Q1-Q3). Differences in clinical characteristics according to survival status were analyzed with the Chi-square test or Fishers' exact test for categorical variables; continuous variables were compared by two-sample *t*-test or by the non-parametric Mann–Whitney *U* test for non-normally distributed data. Changes over time of biomarker concentrations in survivors and decedents were compared with two-way analysis of variance for repeated measurements on log-transformed data, when appropriate.

The comparison of presepsin and procalcitonin concentration at 1, 2, and 7 days between decedents and survivors at ICU discharge was performed by the Mann–Whitney *U* test in both the overall study population and in the subgroup of patients with septic shock.

The relation between circulating biomarker concentrations, entered as log-transformed continuous variables, and mortality was first assessed with univariate Cox proportional hazards models and data are presented as hazard ratio and 95% confidence interval for a one-unit increase on a log scale. Cumulative sums of martingale-based residuals plot and testing was used to evaluate whether an independent continuous covariate could be entered directly into the model or if a transformation was necessary as well as the absence of the time dependence of the ability to predict outcomes was confirmed by the numerical method proposed by Lin and colleagues [15] derived from the same analysis of cumulative sums of martingale residuals.

Cox multivariable models were used to establish the independent prognostic value of circulating biomarkers, after adjustment for a set of clinically relevant variables set *a priori*: SAPS II; SOFA score and serum lactate concentration, both measured on day 1; mean arterial pressure and central venous oxygen saturation, both measured at 6 hours after enrolment and randomized treatment (Albumin *vs.* Crystalloids). All these covariates have been directly included into the model. The prognostic discrimination of each biomarker and of two clinical risk scores (SOFA score and SAPS II) was established from the area under the receiver operating characteristic (ROC) curve (AUC) which is equivalent to the c-index. The optimal cut-off was chosen as the highest product of sensitivity and specificity. Statistical analysis was done using SAS software, version 9.2 (SAS Institute). A two-sided p value of <0.05 was deemed to be statistically significant.

Results

Presepsin concentration and baseline clinical characteristics

Selected clinical characteristics of patients at the time of study enrollment according to median levels of presepsin as assessed on day 1 (1494 pg/mL) are shown in Additional file 3. Higher levels of presepsin were significantly associated with worse SOFA score and reduced diuresis.

Time-course of presepsin levels during study period

Baseline clinical characteristics and circulating biomarker concentrations as measured at day 1 in survivors and non-survivors at ICU discharge are presented in Table 1. The only significant difference between the two groups was a higher concentration of presepsin in decedents (p = 0.0015). The main clinical characteristics, risk scores (SOFA at enrollment and SAPS II) as well as procalcitonin levels were not statistically different.

Table 1 Baseline clinical characteristics and biomarkers in survivors and in decedents at ICU discharge

Characteristics	**Survivors** (n = 50)	**Decedents** (n = 50)	**P**
Age (years)	71.6 ± 10.8	71.3 ± 13.6	0.63
Females (no. (%))	23 (46)	23 (46)	1.00
BMI (kg/m^2)	25.5 ± 4.9	28.4 ± 7.6	0.09
Randomized allocation to albumin (no. (%))	27 (54)	27 (54)	1.00
Source of severe sepsis *(no. (%))*			
Lungs	19 (38)	19 (38)	1.00
Abdomen	26 (52)	20 (40)	0.23
Urinary tract	8 (16)	10 (20)	0.60
Other	7 (14)	10 (20)	0.42
SAPS II	50 ±14	51 ±12	0.75
SOFA score	8 [6-10]	9 [7-11]	0.10
Reason for ICU admission *(no. (%))*			
Medical	25 (50)	28 (56)	0.55
Emergency surgery	23 (46)	17 (34)	0.22
Elective surgery	2 (4)	5 (10)	0.44
Shock (no. (%))	40 (80)	34 (68)	0.17
Mechanical ventilation (no. (%))	44 (88)	45 (90)	0.75
Vasoactive drugs (no. (%))	37 (74)	36 (72)	0.82
Heart rate (beats/min)	102 ±27	103 ±21	0.91
Mean arterial pressure (mmHg)	73 ±16	73 ±14	0.78
Central venous pressure (mmHg)	8.0 [6.0-13.7]	9.9 [7.3-12.5]	0.54
Central venous oxygen saturation (%)	75 [66–81]	73 [66–80]	0.53
Urine output (mL/hr)	40 [16–100]	50 [20–90]	0.94
Serum lactate (mmol/L)	2.6 [1.6-4.2]	2.5 [1.8-4.2]	0.67
Plasma presepsin on day 1 (pg/mL)	1184 [875–2113]	2269 [1171–4300]	0.0015
Plasma procalcitonin on day 1 (μg/L)	10.8 [2.7-41.9]	18.5 [3.4-45.2]	0.31

Continuous variables are presented as mean ± SD or median and interquartile range when not normally distributed; categorical variables as number (%). Abbreviations: *ICU*, intensive care unit, *SAPS* II, simplified acute physiology score II; *SOFA*, sequential organ failure assessment score.

The evolution of presepsin levels over time was significantly different in survivors compared to decedents (Figure 1; p for time-survival interaction = 0.03). At all the three 3 time-points, presepsin levels were significantly higher in the decedents than survivors ($p < 0.005$). There was no statistical difference in presepsin concentrations measured on days 2 or 7 compared to that of the first day, both in decedent and survivors. Conversely, PCT levels fell rapidly and similarly in survivors and non-survivors (Figure 1), and concentrations were significantly different between the two groups only on day 7 ($p = 0.01$). PCT levels measured on days 2 or 7 were significantly lower than that of the first day ($p < 0.0001$ for survivors, $p < 0.001$ for decedents). The interaction between seven-day time course and survival was significant for the SOFA score ($p = 0.008$), but not for serum lactate concentration ($p = 0.08$) or mixed venous oxygen saturation (SvO_2, $p = 0.49$).

Figure 1 Time course of plasma concentrations of presepsin and procalcitonin during ICU stay by survival status. Plasma concentrations of presepsin and procalcitonin 1, 2 or 7 days after enrollment in decedents (n = 50, black) and survivors (n = 50, grey) at ICU discharge. Data are shown as median and interquartile range. Two-way ANOVA for repeated measurements on log-transformed biomarker concentrations. ** $p < 0.005$, *$p = 0.01$ for Mann–Whitney *U* test.

Plasma concentrations of presepsin were similar between patients with severe sepsis and those with septic shock at the time of study enrollment, both on day 1 (1571 [793–2440], n = 26, *vs.*1485 [960–3501] pg/mL, n = 74, p = 0.51, respectively) and at subsequent times (data not shown). The same was true for SOFA score and procalcitonin (data not shown).

In the 74 patients with septic shock, presepsin was significantly higher in decedents than survivors, both at baseline (2590 [1631–4310] *vs.* 1170 [890–1799] pg/mL, p = 0.0007, Figure 2) and the next days ($p < 0.001$). In contrast, early procalcitonin levels (days 1 and 2) were not different between the two groups with septic shock.

Figure 2 Time course of plasma concentrations of presepsin and procalcitonin in patients with septic shock during ICU stay by survival status. Plasma concentrations of presepsin and procalcitonin 1, 2 or 7 days after enrollment in decedents (n = 34, black) and survivors (n = 40, grey) with septic shock at ICU discharge. Data are shown as median and interquartile range. Two-way ANOVA for repeated measurements on log-transformed biomarker concentrations. ** $p < 0.001$, *$p = 0.007$ for Mann–Whitney *U* test.

Presepsin levels did not significantly differ in relation to the type of infection, determined by either site or blood cultures (bacterial, fungal, mixed or undetermined), or the type of bacterial infection (purely gram negative, purely gram positive, mixed or undetermined – data not shown).

By study protocol, patients were stratified according to the time from fulfillment of inclusion criteria and study enrolment (within 6, or between 6 and 24 hours). In patients with early enrolment (within 6 hours), plasma concentrations of presepsin on day 1 were not significantly different in decedents (2138 [1062–3101] pg/mL, n = 24) and survivors at ICU discharge (1335 [879–2856] pg/mL, n = 25, p = 0.17). The same was true for procalcitonin (23.2 [3.3-64.1] *vs.* 10.9 [2.8-30.8] µg/L, p = 0.20). However, the plasma concentration of presepsin on day 1 was significantly higher in decedents randomized between 6 and 24 hours after the onset of inclusion criteria (2621 [1223–4959] pg/mL, n = 26) than in the survivors at

ICU discharge (1044 [875–1331] pg/mL, n = 25, p = 0.003), while procalcitonin did not differ (16.2 [3.4-40.6] *vs.* 7.1 [2.7-41.8] µg/L, p = 0.88).

Plasma presepsin concentration in relation to mortality

The prognostic value of presepsin was evaluated at ICU discharge and during follow-up period on days 28 and 90 after study enrollment, according to pre-specified study endpoints. In univariate Cox proportional hazard models (Table 2), presepsin on day 1 was associated with mortality at ICU discharge ([HR [95%CI] = 1.65 [1.22-2.24] for one unit increase of log-transformed concentration, p = 0.0012), at 28 days (1.73 [1.32-2.27], p < 0.001) and at 90 days (1.50 [1.18-1.91], p = 0.001). The corresponding HR for procalcitonin were 1.01 [0.87-1.18] (p = 0.88), 1.07 [0.92-1.25] (p = 0.40), and 1.03 [0.91-1.18] (p = 0.63). After adjustment for clinically relevant variables including SAPS II, SvO_2 and mean arterial pressure 6 hours after study enrollment, and SOFA score and serum lactate on day 1, presepsin on day 1 remained independently related to outcome at ICU discharge, and after 28 days (1.48 [1.04-2.11] (p = 0.03), and 1.54 [1.12-2.12] (p = 0.01), Table 2), but not after 90 days (1.29 [0.96-1.72], p = 0.09).

Table 2 Univariate and multivariable Cox models for mortality

Time	Biomarker	ICU mortality				28-day mortality				90-day mortality			
		Univariate		*Multivariable*		*Univariate*		*Multivariable*		*Univariate*		*Multivariable*	
Day 1	Presepsin	1.65 [1.22-2.24]	0.001	1.51 [1.05-2.17]	0.03	1.73 [1.32-2.27]	<0.0001	1.55 [1.12-2.13]	0.008	1.50 [1.18-1.92]	0.001	1.28 [0.96-1.71]	0.09
	Procalcitonin	1.01 [0.87-1.18]	0.88	0.89 [0.75-1.05]	0.15	1.07 [0.92-1.25]	0.40	0.97 [0.84-1.12]	0.68	1.03 [0.91-1.18]	0.63	0.94 [0.83-1.06]	0.32
Day 2	Presepsin	1.84 [1.33-2.54]	0.0002	1.83 [1.19-2.81]	0.006	2.02 [1.49-2.75]	<0.0001	1.93 [1.27-2.92]	0.002	1.73 [1.31-2.28]	0.0001	1.47 [1.02-2.12]	0.04
	Procalcitonin	1.00 [0.86-1.16]	0.97	0.82 [0.68-0.98]	0.03	1.05 [0.90-1.23]	0.54	0.85 [0.70-1.02]	0.08	1.06 [0.92-1.21]	0.43	0.86 [0.73-1.02]	0.08
Day 7	Presepsin	1.77 [1.30-2.41]	0.0003	1.83 [1.22-2.74]	0.004	2.11 [1.55-2.89]	<0.0001	2.13 [1.41-3.21]	0.0003	1.84 [1.41-2.41]	<0.0001	1.75 [1.23-2.48]	0.002
	Procalcitonin	1.12 [0.93-1.33]	0.23	0.97 [0.78-1.21]	0.78	1.29 [1.06-1.57]	0.01	1.11 [0.87-1.42]	0.39	1.25 [1.05-1.47]	0.01	1.08 [0.88-1.33]	0.46

Risk presented as hazard ratio and 95% CI with an increment of 1 unit after logarithmic transformation of the biomarker concentration. The following covariates, deemed as important clinical variables, were considered in the multivariable models: SAPS II score, SOFA score, serum lactate concentration, mean arterial pressure, central venous oxygen saturation and randomized treatment (albumin *vs.* crystalloids).

Presepsin concentrations on days 2 and 7, but not procalcitonin, were independently related to mortality in ICU, and on days 28 and 90 (Table 2). The SOFA score was the only clinical variables independently associated with mortality in the multivariable models including procalcitonin; when presepsin was included in place of procalcitonin in these models, the SOFA score was no longer significantly associated with mortality (data not shown).

Prognostic accuracy of presepsin

Finally, the prognostic accuracy of presepsin was evaluated with ROC curves, yielding area-under the curves for ICU survival of 0.69, 0.70 and 0.74 on days 1, 2 and 7 (Table 3). The SOFA score had similar accuracy. Corresponding values for procalcitonin were 0.56, 0.55 and 0.64.

Table 3 Prognostic accuracy of presepsin, procalcitonin and clinical risk scores

	ICU survival								*28-day survival*								*90-day survival*						
	AUC [95%CI]	**Optimal cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+**	**LR-**	**AUC [95%CI]**	**Optimal cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+**	**LR-**	**AUC [95%CI]**	**Optimal cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**LR+**	**LR-**
Presepsin																								
Day 1	0.69 [0.58-0.79]	1631	66.7	74.0	71	70	2.56	0.45	0.72 [0.61-0.82]	1631	67.4	70.9	64	74	2.32	0.46	0.66 [0.55-0.77]	1631	62.5	71.4	76	58	2.19	0.53
Day 2	0.70 [0.59-0.87]	1718	69.4	73.5	72	71	2.62	0.42	0.74 [0.64-0.85]	1718	74.4	72.7	68	78	2.73	0.35	0.68 [0.57-0.79]	1407	77.2	61.0	73	66	1.98	0.37
Day 7	0.74 [0.64-0.84]	1606	72.0	70.0	71	71	2.40	0.40	0.74 [0.64-0.84]	2028	63.6	76.8	68	73	2.74	0.47	0.70 [0.60-0.81]	1453	70.7	64.3	73	61	1.98	0.46
Procalcitonin																								
Day 1	0.56 [0.44-0.68]	14.27	60.4	58.0	58	60	1.44	0.68	0.55 [0.44-0.67]	14.27	60.5	56.4	52	65	1.39	0.70	0.53 [0.41-0.65]	14.27	57.1	57.1	64	50	1.33	0.75
Day 2	0.55 [0.44-0.67]	8.88	60.4	55.1	57	59	1.35	0.72	0.53 [0.41-0.65]	8.88	59.5	52.7	49	63	1.26	0.77	0.55 [0.43-0.67]	8.88	60.7	58.5	67	52	1.46	0.67
Day 7	0.64 [0.54-0.75]	1.51	56.0	74.0	68	63	2.15	0.59	0.65 [0.54-0.76]	1.47	61.4	73.2	64	71	2.29	0.53	0.63 [0.52-0.74]	1.47	55.2	76.2	76	55	2.32	0.59
SOFA score																								
Day 1	0.69 [0.59-0.80]	9	65.3	68.8	68	66	2.09	0.50	0.68 [0.58-0.79]	9	67.4	66.7	62	72	2.02	0.49	0.68 [0.57-0.79]	9	61.4	70.0	74	57	2.05	0.55
Day 2	0.67 [0.56-0.78]	8	73.9	54.2	61	68	1.61	0.48	0.72 [0.61-0.82]	9	70.0	64.8	60	74	1.99	0.46	0.64 [0.53-0.76]	8	70.4	55.0	68	58	1.56	0.54
Day 7	0.75 [0.65-0.85]	7	59.6	83.0	78	67	3.50	0.49	0.75 [0.65-0.85]	7	61.0	79.2	69	72	2.94	0.49	0.71 [0.60-0.81]	6	66.7	65.0	72	59	**1.91**	0.51
SAPS II																								
Day 1	0.51 [0.39-0.62]	49	56.0	48.0	52	52	1.08	0.92	0.63 [0.52-0.74]	51	61.4	60.7	55	67	1.56	0.64	0.58 [0.47-0.70]	49	60.3	54.8	65	50	1.33	0.72

The areas under the receiver-operating characteristics curves (AUC) are shown as mean [95% confidence interval]. NPV, negative predictive value; PPV, positive predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Discussion

Severe sepsis is still a major challenge for critical care medicine. Over the past ten years, many efforts have improved several aspects of its treatment and prognosis, such as earlier identification of the potential infection, early etiologic therapy, and early implementation of adequate supportive therapy, avoiding potential harmful effects [1,16]. Nonetheless, the early stratification of its severity and prognosis, and accurate monitoring of the effects of clinical treatment, is still an unsolved issue. Several clinical scores have been introduced in clinical practice to partially satisfy this task, the SOFA score [10] or the APACHE score [17], but the state of the art in diagnosing and monitoring severe sepsis with circulating biomarkers relies on procalcitonin at the onset and in the course of the disease [18]. However, despite all the data available and the widespread clinical implementation, procalcitonin has shown limited value for risk stratification and prognostication.

The 55 kDa glycoprotein CD14 is expressed on the membrane of monocytes/macrophages and facilitates the toll-like receptor (TLR) 4-specific inflammatory reaction, whereby soluble CD14 (sCD14) is released into the circulation and serves as a mediator of the response to lipopolysaccharide (LPS) from infectious agents. Simultaneously, a 13 kDa fragment of sCD14 is formed, named sCD14-ST or presepsin [19]. Although its biological function remains unclear, it appears to be released in the plasma as a consequence of cellular phagocytosis after bacterial infection, and is therefore an indirect marker of sepsis [20]. It has been identified less than a decade ago in patients with sepsis, appearing superior to other biomarkers (IL-6 and procalcitonin), as well as to site and blood culture for the diagnosis of severe sepsis of bacterial origin [7,20].

In this case-controlled study, we investigated in a multicenter setting the potential prognostic power of presepsin during ICU stay in patients with severe sepsis. A recent study carried out in106 patients presenting at the ED of two hospital centers with suspected sepsis or septic shock showed that presepsin measured at first medical evaluation (but not successively) was associated with 60-day mortality at univariate analysis [21]. In our study, presepsin levels on day 1 remained independently associated with mortality at early stages (at ICU discharge and after 28 days) even after correction for the individual clinical variables considered the most important parameters of the resuscitation phase (mean arterial pressure, serum lactate levels, central venous oxygen saturation) [1,11]. The models were also adjusted for widely used clinical scores of overall severity (such as the SAPS II) [22], or multi-organ failure (such as the SOFA score) [10]. No independent association was observed between any of these variables and mortality when presepsin was included in the models. Taken together, these findings suggest that presepsin is a robust circulating biomarker for early stratification of the severity of sepsis, as well as for prognosis. Though there are contrasting evidences on the independent prognostic value of procalcitonin in septic patients [23,24], there is a consensus that its main clinical use is for helping in the monitoring of antibiotic therapy. Sepsis is a complex syndrome, with an initial phase (usually the first 48 hours), in which appropriate etiological therapy and adequate supportive treatment must be established, followed by a second phase when multiple organ failures may occur. Presepsin, being superior as an early prognostic factor to clinical parameters in both phases, may have unique characteristics encompassing the complexity of the whole syndrome.

When looking at the time-course of presepsin, we observed a significant difference between survivors and decedents. In contrast, procalcitonin decreased in both groups, as already observed by others [25]. This suggests that presepsin may be also used for monitoring the

efficacy of the therapy adopted, either etiologic, supportive or both, as previously suggested [6,20]. Although the study design meant we could not demonstrate any direct association between the treatment applied and late levels of presepsin, one may speculate that the drop in presepsin levels in patients who survived indicates a beneficial effect of the treatment, reducing the "activity" of the bacterial infection, or controlling its systemic reactivity. Since presepsin has previously been identified as a promising biomarker for the diagnosis of sepsis, even superior to conventional markers and blood culture [6,7], it is conceivable that early assessment of circulating presepsin will help in early, correct diagnosis, as well as in monitoring the appropriateness of the therapy implemented.

When we compared presepsin levels to clinical scores, its prognostic accuracy appeared to be similar to that of the SOFA score, both for early (ICU discharge and after 28 days) and late outcomes (90-day mortality). This seems reasonable since the SOFA score, the most commonly used clinical score to assess the development of organ failures, relies on the concept that the higher the severity and the number of organ failures during the course of sepsis, the greater is the likelihood of death [10]. It is tempting to speculate too, that the greater the host's biological response to the microorganism (either due to its virulence or to the immune reaction), and therefore, indirectly, the higher the levels of plasma presepsin, the greater the severity of sepsis, the risk of multiple organ dysfunction, and ultimately the risk of death.

Some limitations of the present study deserve consideration. First, the relatively small sample size did not allow in-depth analysis of the relations between presepsin levels and disease characteristics (infecting organism, source of sepsis) or severity (physiological score, multi-organ failure), as well as the therapy applied. Second, this was a retrospective, case–control study with inherent selection bias, and possibly overlooked some confounding factors. Although we cannot exclude that selecting the study population according to early ICU survival might have partially affected our findings, the evaluation of outcome even after 28 and 90 days likely have further supported the plausibility of our observations, which await for further validation. Third, although extensive daily monitoring of circulating biomarkers is important during the early management of sepsis [26], only 3 measurements (on days 1, 2 and 7) were available.

Conclusion

In conclusion, we show here for the first time that presepsin is an early marker of mortality, with better prognostic performance than procalcitonin, and may be proposed as a aid in risk stratification strategies in the septic patient. These preliminary findings provide solid bases for future, more extensive evaluation of presepsin as a biomarker for severe sepsis. We need to gain more insights on the pathophysiological conditions associated with presepsin release, both in experimental models of sepsis and in well-characterized patients. We should also delineate the added value of this biomarker for clinical decision making, in terms of diagnosis, risk stratification, or therapy monitoring. Finally, the clinical indications of presepsin should be confirmed and validated in large-scale, independent cohorts of unselected patients with severe sepsis or septic shock.

Key messages

- Circulating presepsin (sCD14-ST) levels have a significantly different trajectory over the ICU stay in decedents with severe sepsis and septic shock compared to survivors.
- Presepsin is an early marker of mortality, independent of clinical risk factors, with better prognostic performance than procalcitonin.

Abbreviations

ALBIOS, Albumin Italian Outcome Sepsis; APACHE, Acute physiology and chronic health evaluation; AUC, Area under the curve; EDTA, Ethylenediaminetetraacetic acid; ICU, Intensive care unit; LPS, Lipopolysaccharide; NYHA, New York heart association; PCT, Procalcitonin; ROC, Receiver operating characteristic; SAPS II, Simplified acute physiology score II; sCD14-ST, Soluble N-terminal fragment of cluster-of-differentiation marker protein 14; SOFA, Sequential organ failure assessment score; SvO2, Mixed venous oxygen saturation

Competing interests

SM, PC, RL and LG received a limited research support from Mitsubishi Chemical Europe GmbH, the manufacturer of the presepsin assay. RT is an employee at Mitsubishi Chemical Europe GmbH. DIAneering GmbH performed the laboratory measurements and consulted to Mitsubishi Chemical Europe GmbH.

Authors' contributions

SM and PC were involved in the acquisition of data, data processing, study design, statistical analysis, writing and manuscript drafting. ES, RT, MP, GS, RF, TM, and SI participated in the acquisition and interpretation of data and in the final revision of the manuscript. CF was involved in the data processing, performed the statistical analysis, and participated in the writing and drafting of the manuscript. RL was involved in the acquisition of data, study design and in the final revision of the manuscript. MR, GT and LG were involved in the study design and in the final revision of the manuscript. All authors read and approved the final manuscript.

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Additional files

Additional_file_1 as DOCX

Additional file 1 ALBIOS Biomarkers Substudy - Participating centers. List of participating centers.

Additional_file_2 as DOCX

Additional file 2 ALBIOS Biomarkers Substudy - Participating centers and ethical bodies. List of participating centers and their ethical bodies.

Additional_file_3 as DOCX

Additional file 3 Baseline clinical characteristics according to median presepsin concentration at study entry. Clinical characteristics at baseline are compared in patients with plasma presepsin concentration < or ≥ 1494 pg/mL.

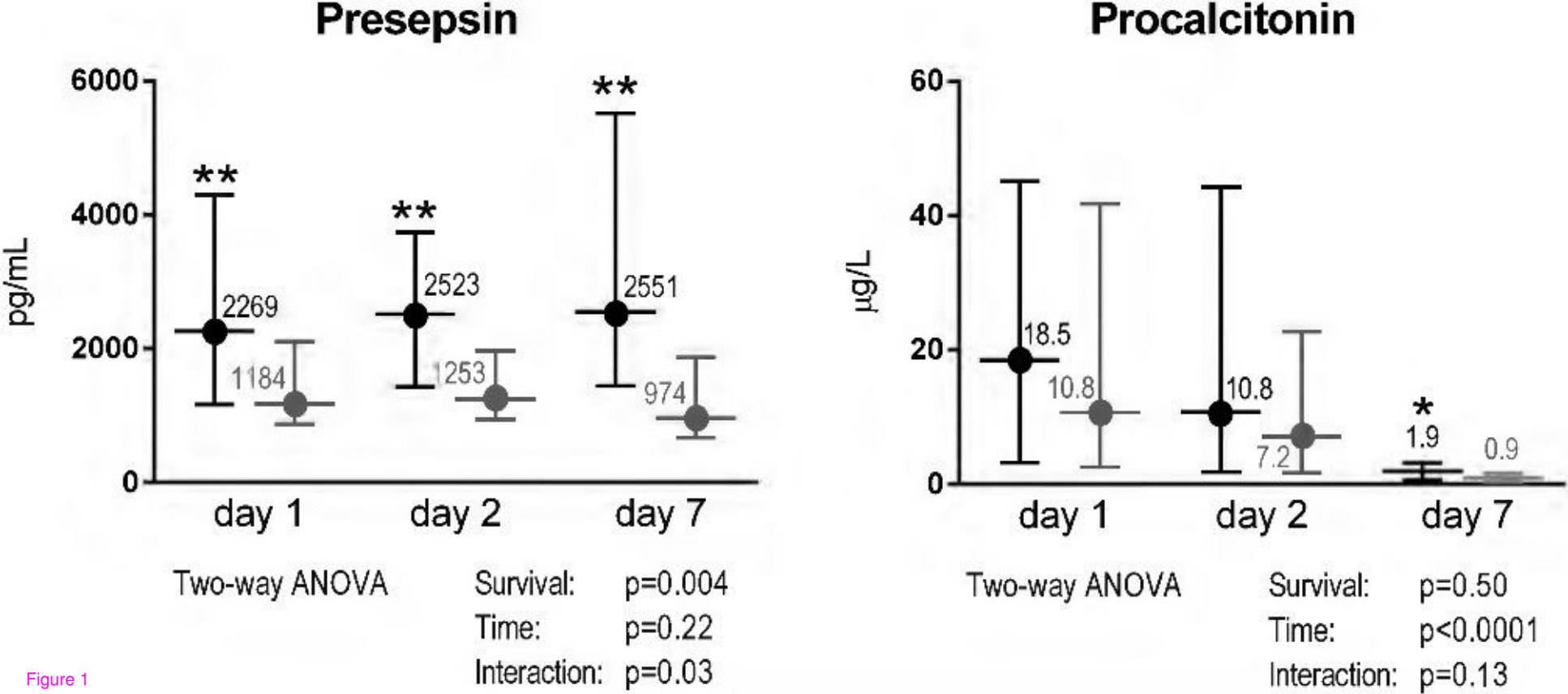
Presepsin
6000
4000
2000
0
pg/mL
**
**
**
2269
1184
2523
1253
2551
974
day 1
day 2
day 7
Two-way ANOVA
Survival: p=0.004
Time: p=0.22
Interaction: p=0.03
Procalcitonin
60
40
20
0
µg/L
18.5
10.8
10.8
7.2
*
1.9
0.9
day 1
day 2
day 7
Two-way ANOVA
Survival: p=0.50
Time: p<0.0001
Interaction: p=0.13

Figure 1

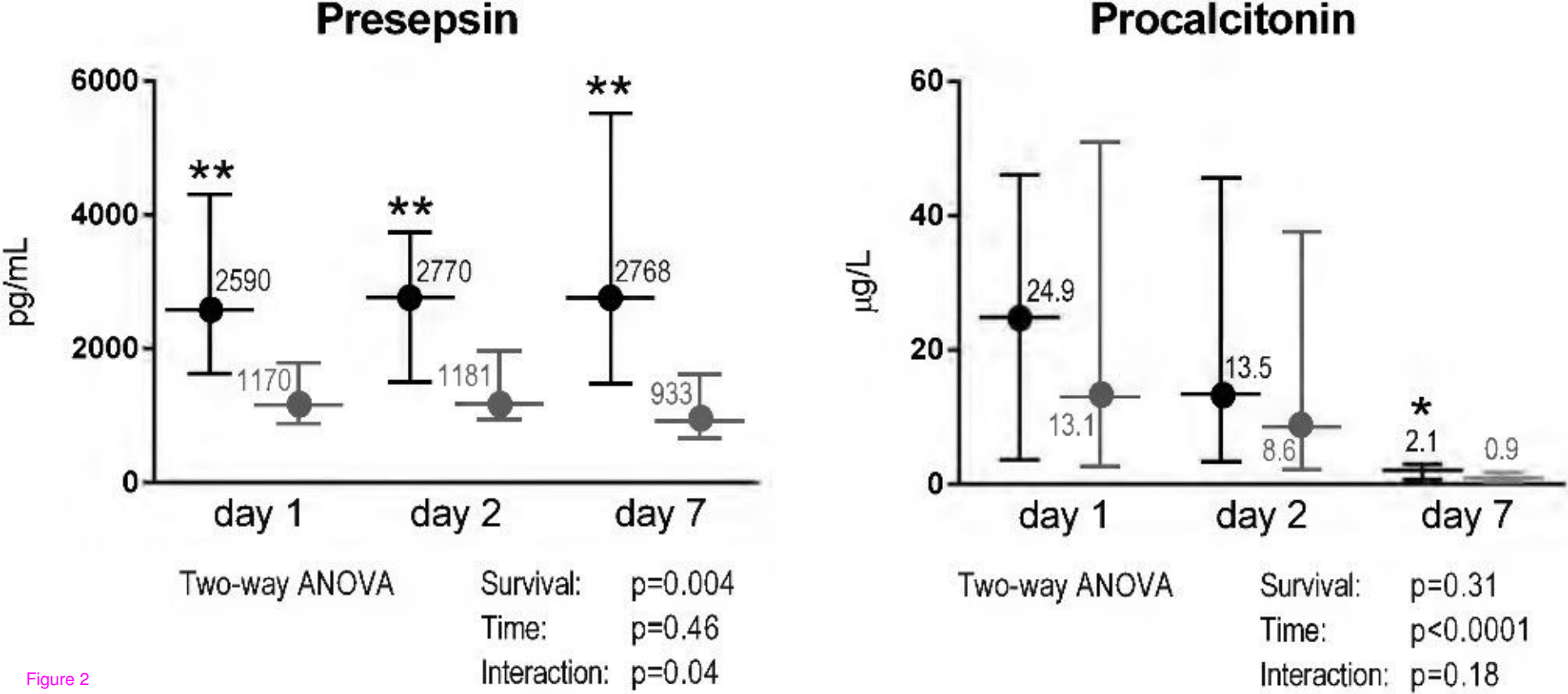
Presepsin
6000
4000
2000
0
pg/mL
**
**
**
2590
2770
2768
1170
1181
933
day 1
day 2
day 7
Two-way ANOVA
Survival: p=0.004
Time: p=0.46
Interaction: p=0.04
Procalcitonin
60
40
20
0
µg/L
24.9
13.1
13.5
8.6
*
2.1
0.9
day 1
day 2
day 7
Two-way ANOVA
Survival: p=0.31
Time: p<0.0001
Interaction: p=0.18

Figure 2

Additional files provided with this submission:

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