MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2023; 29: e938538
DOI: 10.12659/MSM.938538

Received: 2022.10.01
Accepted: 2022.12.12
Available online: 2022.12.29
Published: 2023.01.25

Changes in Heparin-Binding Protein, Procalcitonin, and C-Reactive Protein Within the First 72 Hours Predict 28-Day Mortality in Patients Admitted to the Intensive Care Unit with Septic Shock

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG Hui Xue
AFG Feng Yu

Department of Emergency Medicine, Intensive Care Unit, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, PR China

Corresponding Author: Feng Yu, e-mail: fengyu653410@163.com
Financial support: None declared
Conflict of interest: None declared

Background: This study aimed to evaluate the possible associations of heparin-binding protein (HBP), procalcitonin (PCT), and C-reactive protein (CRP) levels with 28-day mortality in septic shock patients admitted to Intensive Care Units (ICUs).

Material/Methods: Blood samples were taken at ICU admission and measured again 72 h later to calculate changes in HBP (ΔHBP), changes in PCT (ΔPCT), changes in CRP (ΔCRP), and changes in Sequential Organ Failure Assessment (ΔSOFA) relative to baseline.

Results: Variables included in the univariable logistic regression model for survival were age, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, decreasing ΔSOFA, decreasing ΔHBP, decreasing ΔPCT, and decreasing ΔCRP. Survival was directly related to decreasing ΔHBP with odds ratio (OR)=9.95 (95% confidence interval [CI] 4.63 to 21.35; *P*<0.001), decreasing ΔPCT with OR=7.85 (3.74 to 16.49; *P*<0.001), decreasing ΔCRP with OR=5.83 (2.84 to 11.97; *P*<0.001), decreasing ΔSOFA with OR=1.93 (1.00 to 3.75; *P*=0.051) and APACHE II score with OR=1.93 (1.14 to 1.68; *P*=0.001). In a multivariable logistic regression model for survival, only decreasing ΔHBP with OR=7.18 (2.91 to 17.69; *P*<0.001), decreasing ΔPCT with OR=5.17 (2.12 to 12.56; *P*<0.001), and decreasing ΔCRP with OR=4.33 (1.77 to 10.61; *P*=0.001) remained significant.

Conclusions: Measuring changes in HBP, PCT, and CRP within 72 h of admission may aid in predicting 28-day mortality for patients with septic shock in ICUs.

Keywords: Antimicrobial Cationic Peptides • Biomarkers • Procalcitonin • Sepsis • Shock, Septic

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/938538

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Septicemia is defined as an aberrant immune reaction to an infection that results in life-threatening organ dysfunction, based on SEPSIS-3 consensus criteria [1]. Septic shock refers to cases of sepsis characterized by abnormalities in the circulatory, molecular, and metabolic systems. Approximately 5.3 million people have sepsis each year, making it a severe public health problem [2]. Guidelines for evidence-based management have emphasized serum biological markers as indicators of the context of sepsis, as well as scoring systems based on risk factors associated with patient mortality [3,4]. Among patients with sepsis, reliable predictive biomarkers and scoring systems can aid clinicians in making rapid yet appropriate treatment decisions. Indeed, several studies have emphasized the value of conventional biological markers for detecting sepsis and its outcomes, like procalcitonin (PCT) or C-reactive protein (CRP) [5-7]. Although elevated serum PCT levels are associated with bacterial infection and sepsis, a meta-analysis of 18 studies found that PCT did not distinguish between sepsis and non-septic systemic inflammation [8,9]. CRP, an acute-phase reactive protein, is the most commonly used clinical biomarker, and its level in the plasma of healthy individuals is less than 1 mg/L [10]. Not only do bacterial infections and sepsis lead to increased levels of CRP, but so does injury [11]. Several studies have shown that changes in biochemical markers, and not only absolute values, can predict therapeutic response and survival following the diagnosis of sepsis [12,13].

CAP37, also known as heparin-binding protein (HBP), is produced within the vesicles and azurophil granules in human polymorphonuclear leukocytes, and neutrophils rapidly secrete it under bacterial stimulation [14]. The release of HBP causes vessel leakage or swelling, which is commonly dysregulated in cases of septic shock due to its potent chemoattractant capacity for the monocytes and macrophages [15,16]. As a result of its versatility, HBP may be able to serve as an inducible biological marker in the case of septic shock [17,18]. Although effective control of sepsis may lead to rapid decreases in HBP levels, whether kinetics in HBP can provide greater insight into treatment responses and outcomes remains unclear.

Scores such as SOFA and APACHE II are commonly used in ICUs to assess patient disease severity and predict outcomes [19]. The APACHE II score is calculated based on the worst values within the first 24 h of ICU admission [20]. According to some studies, organ failure is associated with a high mortality rate, and dynamic assessment of organ dysfunction in critically ill patients after ICU admission can be used to predict the outcome [21]. Therefore, this prospective, single-center study of 146 patients admitted to the intensive care unit with septic shock conducted between July 2020 and June 2022, aimed to evaluate the prognostic value of kinetics of heparin-binding protein, procalcitonin, C-reactive protein levels, SOFA scores, and APACHE II scores as factors associated with in-hospital mortality.

Material and Methods

Ethics Statement

Anhui Medical University First Affiliated Hospital's Emergency Intensive Care Unit (EICU) was the site of this prospective study, which took place between July 2020 and June 2022. Anhui Medical University's First Affiliated Hospital's ethics review committee approved this study (No. PJ2022-12-13), and all authorized delegates of the included patients signed consent forms.

Participants

We included patients who met the third version of the diagnostic criteria for septic shock as defined by the International Guidelines [1]. We excluded patients with these criteria: (1) age <18 years, (2) incomplete clinical records, and (3) ICU stay <72 h. We excluded some patients with malignancies as well as hematological diseases, autoimmune diseases, immune deficiency diseases, and patients who received a transplant. Our institution's standard management protocol is derived from the Surviving Sepsis Campaign (SSC) guidelines, and this was followed for all enrolled patients [22].

Data Collection

As part of our ICU admission process, patients received a preliminary evaluation that included the gathering of data on age, sex, underlying disease, type of infection, and comorbidities. APACHE II scores were calculated within the first 24 h of ICU admission, and SOFA scores were calculated after admission and again at 72 h. Blood samples were taken after admission to the ICU and measured again 72 h later. Blood samples was used to measure levels of serum HBP, serum PCT, serum CRP, white blood cells (WBC), platelets, and biochemistry, and for arterial blood gas analysis. Before antibiotic use, blood cultures and drug sensitivity tests (bilateral and double sets) were done. The primary endpoint was 28 days of ICU admission. Non-survivors were identified as those who died before 28 days, while survivors were identified as those who had been discharged from the ICU before 28 days. ICU stays were measured as the time spent in the ICU prior to transfer or death.

Biomarker Assays

The lower reference limit for serum HBP concentration was 5.9 ng/ml, as measured via an immunofluorescence assay (Joinstar Biomedical Technology Co., LTD, Hangzhou, China). PCT levels were detected using a semi-quantitative solid-phase

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

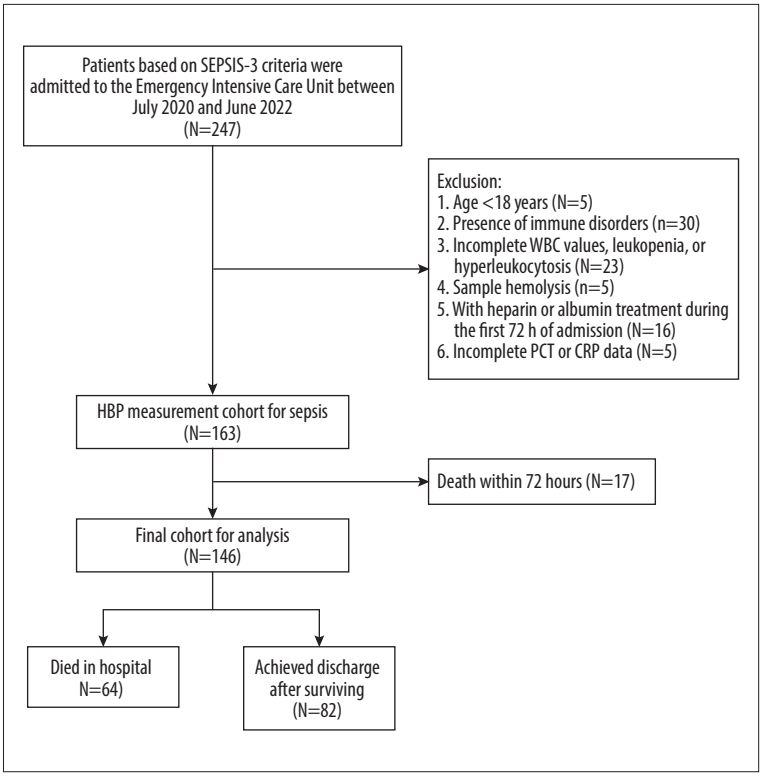

Figure 1. Flow chart of inclusion and exclusion process. PCT – procalcitonin; CRP – C-reactive protein; HBP – heparin-binding protein; WBC – white blood cell counts; (GraphPad Software, San Diego, CA, USA).

immunoassay (Brahms Diagnostica GmbH, Berlin, Germany) (limit of detection, 0.5 ng/ml). CRP concentration was measured using latex immunoturbidimetry (Lifotronic Technology Co., LTD, Shenzhen, China), and the normal reference range was 0-10 mg/L. Kinetics in HBP, PCT, and CRP (ΔHBP, ΔPCT, and ΔCRP, respectively) were calculated by subtracting baseline levels from 72-h levels [16]. Therefore, ΔHBP=HBP72H–HBP0H, ΔPCT=PCT72H–PCT0H, ΔCRP=CRP72H–CRP0H, and ΔSOFA=SOFA72H–SOFA0H. Δ >0 indicates an increasing trend, while Δ ≤0 indicates a decreasing trend or no change [23].

Statistical Analysis

All experimental data were analyzed using SPSS 26.0 v. (IBM, Armonk, N.Y., USA). For normally distributed continuous variables, including SOFA scores and APACHE II scores, the results are presented as mean±standard deviation (mean±S.D). We used *t* tests to compare the 2 groups. Non-normally distributed variables, including age, ICU stay, WBC, serum HBP, serum PCT, serum CRP, and changes in each marker, are expressed using medians and interquartile ranges (IQRs). The Mann-Whitney U test, was used for comparisons between the 2 groups. Percentages are reported for qualitative variables such as sex, comorbidities, and type of infection. These data were compared between groups using chi-square testing. Statistical significance was defined as a *P* value <0.05 (95% confidence interval [CI]). The effect of clinical characteristics and important variables on prognosis was assessed using logistic regression. For the univariable model, we included biologically significant variables. For the multivariable model, variables with $P<0.10$ in univariable logistic regression were entered. Multivariable models were considered significant if they had $P<0.05$ [23].

Results

Baseline Characteristics

We prospectively screened 247 patients with septic shock admitted to our ICU between July 2020 and June 2022. After eligibility evaluation, 146 patients finally participated in the study, of whom 82 (56%) and 64 (44%) were survivors and non-survivors, respectively. The reasons for the exclusion are shown in **Figure 1**. Thirty patients presented with immunodeficiency. Twenty-three patients with missing WBC values, leukopenia (WBC $<3\times10^9$/L), or hyperleukocytosis (WBC $>50\times10^9$/L) were excluded from the study. Other exclusions included 5 patients whose samples hemolyzed, 16 patients who had received heparin or albumin treatment before HBP measurements, 5 patients with incomplete PCT or CRP data, 5 patients aged <18 years, and 17 who died less than 72 h after enrollment. Therefore, 146 patients participated in the final study.

Table 1 summarizes the main baseline characteristics of the patients included in the study. A comparison was made between those who survived and those who did not survive regarding

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. Baseline characteristics of survivors and non-survivors following septic shock.

Characteristics	Non-survivors (n=64)	Survivors (n=82)	P value
Age (years)*	66.50 (53.00, 72.00)	64.5 (53.00, 72.00)	0.698
Male (n, %)	34 (53.1%)	45 (54.9%)	0.833
Length of ICU stay (days)*	12.50 (9.00, 15.00)	11.50 (8.00, 15.00)	0.214
Comorbidities (n, %)			
Hypertension	29 (45.3%)	34 (41.5%)	0.641
Diabetes	12 (18.7%)	16 (19.5%)	0.908
Coronary heart disease	23 (35.9%)	29 (35.4%)	0.943
Cerebrovascular disease	10 (15.6%)	16 (19.5%)	0.542
COPD	9 (14.1%)	10 (12.2%)	0.739
Cirrhosis	4 (6.2%)	6 (7.3%)	0.800
Chronic kidney disease	12 (18.7%)	11 (13.4%)	0.380
Trauma	6 (9.4%)	9 (11.0%)	0.752
Infection subclass (n, %)			
Pulmonary infection	41 (64.1%)	55 (67.1%)	0.704
Intra-abdominal infection	18 (28.1%)	21 (25.6%)	0.723
Urinary tract infection	13 (20.3%)	16 (19.5%)	0.904
Skin/soft tissue	3 (4.7%)	5 (6.1%)	0.710
Bloodstream	34 (53.1%)	30 (36.6%)	0.046
Other	5 (7.8%)	9 (11.0%)	0.520
WBC (10^9/L)*	12.15 (7.67, 19.45)	10.50 (7.30, 15.53)	0.311
SOFA (mean±SD)	10.70±2.96	10.05±0.90	0.060
APACHE II (mean±SD)	21.06±2.97	19.77±0.92	0.000

* Median (interquartile range); EICU – Emergency Intensive Care Unit; COPD – Chronic Obstructive Pulmonary Disease; WBC – white blood cell counts; SOFA – Sequential Organ Failure Assessment; APACHE II – Acute Physiology and Chronic Health Evaluation.

demographics, comorbidities, type of infection, blood tests, clinical scores, and ICU stay. Of the patients who were in septic shock, 43.8% died, and 65.7% of infections originated in the lungs. Bloodstream infection was diagnosed in approximately half of the included patients with septic shock (43.8%), and the rate of bloodstream infection was significantly higher in non-survivors than in survivors (53.1% vs 36.6%; *P*=0.046). APACHE II scores were markedly higher for non-survivors than for survivors (*P*<0.001), with other indicators not showing statistically significant differences.

The Evolution of HBP Levels, PCT, and CRP Levels Among Survivors and Non-Survivors Following Septic Shock

The kinetic data of HBP, PCT, and CRP between admission and the first 72 h of admission are shown in **Figure 2**. Non-survivors showed an increasing trend in HBP levels, which were significantly higher than the survivor group at 72 h of admission (**Table 2**, *P*<0.001). PCT levels increased in non-survivors but not in survivors. PCT levels can discriminate survivors from non-survivors on admission (**Table 2**, *P*<0.001) or at the first 72 h of admission (**Table 2**, *P*<0.001). CRP levels showed no difference between survivors and non-survivors on admission (**Table 2**, *P*=0.557) and at 72 h (**Table 2**, *P*=0.245).

Comparison Accuracy of Biomarkers and Clinical Score

In the univariable logistic regression model for survival, age, APACHE II score, decreasing ΔSOFA, decreasing ΔHBP, decreasing ΔPCT, and decreasing ΔCRP were the main variables. The results are shown in **Table 3**. Survival was directly related to decreasing ΔHBP, with an odds ratio (OR)=9.95 (95% confidence

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

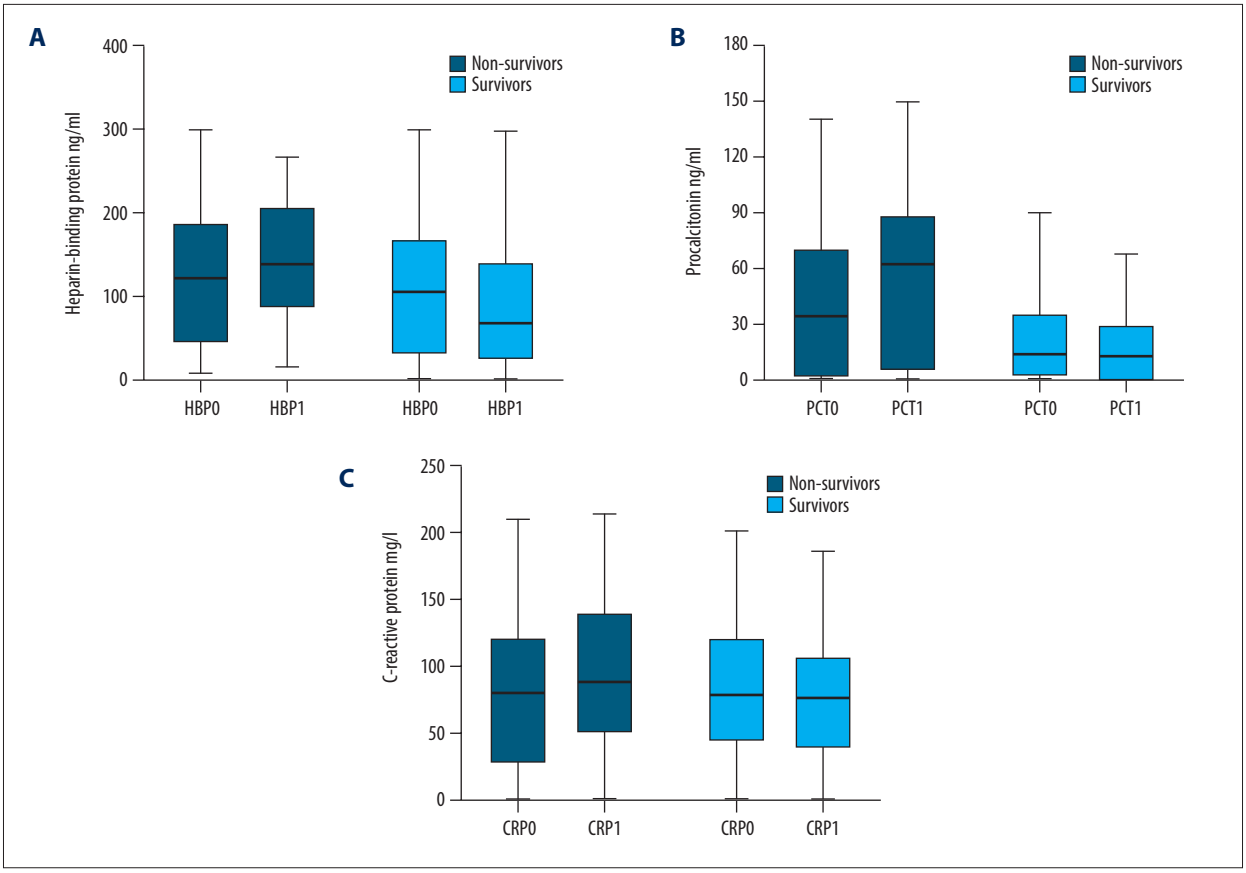

Figure 2. Kinetics of serum HBP, PCT, and CRP in survivors and non-survivors. The upper and lower edges of the box plot represent the 25th and 75th percentiles, respectively. The inner horizontal line represents the median and the whiskers represent the 10th and 90th percentiles. (**A**) Box plot represents kinetics of serum HBP (HBP0: HBP measurement at the time of admission; HBP1: HBP measurement at the first 72 h of admission). Comparing between groups, *P*=0.301 at the time of admission and *P*<0.001 at the first 72 h of admission for heparin-binding protein (HBP). (**B**) Box plot represents kinetics of serum PCT (PCT0: PCT measurement at the time of admission; PCT1: PCT measurement at the first 72 h of admission). *P*<0.001 at the time of admission and *P*<0.001 at the first 72 h of admission for procalcitonin (PCT). (**C**) Box plot represents kinetics of serum CRP (CRP0: CRP measurement at the time of admission; CRP1: CRP measurement at the first 72 h of admission). *P*=0.557 at the time of admission and *P*=0.245 in the first 72 h of admission for CRP. HBP – heparin-binding protein; PCT – procalcitonin; CRP – C-reactive protein. (GraphPad Software, San Diego, CA, USA).

Table 2. Evolution in biomarkers in patients with septic shock.

Variables	Non-survivors (n=64)	Survivors (n=82)	P value
HBP0	122.25 (43.68, 189.62)	105.55 (30.93, 168.87)	0.301
HBP1	139.15 (85.00, 208.27)	67.85 (23.90, 141.85)	0.000
PCT0	34.00 (1.38, 70.25)	13.35 (1.92, 35.84)	0.000
PCT1	62.15 (4.91, 88.30)	12.51 (0.86, 29.22)	0.000
CRP0	80.05 (27.08, 120.07)	78.83 (44.42, 121.07)	0.557
CRP1	88.66 (50.59, 138.97)	76.35 (39.25, 106.63)	0.245

All results are expressed in the median (interquartile range); HBP – heparin-binding protein; PCT – procalcitonin; CRP – C-reactive protein; HBP0 – HBP measurement at the time of admission; HBP1 – HBP measurement at the first 72 h of admission; PCT0 – PCT measurement at the time of admission; PCT1 – PCT measurement at the first 72 h of admission; CRP0 – CRP measurement at the time of admission; CRP1 – CRP measurement at the first 72 h of admission.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. logistic regression model for survival in patients with septic shock.

Parameter	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age	1.00 (0.98-1.03)	0.82		
APACHE II score	1.39 (1.14-1.68)	0.001	1.10 (0.88-1.37)	0.410
ΔSOFA decreasing values	1.93 (1.00-3.75)	0.051	1.93 (0.79-4.69)	0.146
ΔHBP decreasing levels	9.95 (4.63-21.35)	0.000	7.18 (2.91-17.69)	0.000
ΔPCT decreasing levels	7.85 (3.74-16.49)	0.000	5.17 (2.12-12.56)	0.000
ΔCRP decreasing levels	5.83 (2.84-11.97)	0.000	4.33 (1.77-10.61)	0.001

The results show univariate and multivariate logistic regression analyses of the kinetics of biomarkers and clinical scores. APACHE II – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment; HBP – heparin-binding protein; PCT – procalcitonin; CRP – C-reactive protein; OR – odds ratio; CI – confidence interval. ΔSOFA=SOFA72H–SOFA0H; ΔHBP=HBP72H–HBP0H; ΔPCT=PCT72H–PCT0H; ΔCRP=CRP72H–CRP0H.

interval 4.63 to 21.35), *P*<0.001; decreasing ΔPCT with OR=7.85 (3.74 to 16.49), *P*<0.001; decreasing ΔCRP with OR=5.83 (2.84 to 11.97), P<0.001; decreasing ΔSOFA with OR=1.93 (1.00 to 3.75), *P*=0.051; APACHE II score with OR=1.39 (1.14 to 1.68), *P*=0.001. Age was not significant and was excluded from the multivariate analysis because *P*=0.1 was an inclusion condition.

A multivariable logistic regression model for survival was developed by screening the variables from the univariate analysis. Only decreasing ΔHBP with OR=7.18 (2.91 to 17.69), *P*<0.001, decreasing ΔPCT with OR=5.17 (2.12 to 12.56) *P*<0.001, and decreasing ΔCRP with OR=4.33 (1.77 to 10.61) *P*=0.001 remained significant (**Table 3**).

Discussion

Our study demonstrated that patient prognosis, including treatment response and survival, were not always related to HBP, PCT, or CRP absolute values, but were closely linked to their kinetics. PCT levels clearly differentiated between survivors and non-survivors on admission to the ICU and the first 72 h after admission, while HBP just showed this difference in the first 72 h after admission. Decreasing values of HBP, decreasing values of PCT, and decreasing values of CRP were able to predict, respectively, a 7-fold, 5-fold, and 4-fold greater chance for patients with septic shock to survive.

CRP is often used clinically as a marker to support the diagnosis of sepsis [10]. In our results, absolute CRP levels could not differentiate survivors from non-survivors on admission and the first 72 h of admission (**Table 2**, *P*=0.557 and 0.245, respectively). Previous studies have demonstrated that changes in CRP levels, but not absolute levels, can forecast death rates in patients with sepsis [13]. CRP levels in ventilator-associated pneumonia patients varied significantly between day 1 and day 4. According to Seligman et al [23], these decreases in CRP levels were also associated with higher survival rates. A decrease in CRP by 25% or more from the previous day was shown by Yentis et al to be a good indicator of regression of sepsis, with a sensitivity of 97% and specificity of 88% [24]. A decline in CRP prior to the clinical resolution of sepsis and was related to the severity of the disease. Hoeboer et al reported that rapid decreases in CRP were most predictive of the antibiotic response in seriously ill patients with fever [13]. Our results agree with the results of Yentis et al in patients with sepsis; in our septic shock patients, the decrease of CRP levels was significantly predictive of survival, with OR=5.83 (**Table 3**, *P*<0.001) in the univariable, with OR=4.33 (**Table 3**, *P*<0.001) in the multivariable logistic regression.

In our results, PCT levels were significantly higher in non-survivors on admission (**Table 2**, *P*<0.001) and the first 72 h of admission (**Table 2**, *P*<0.001). PCT concentrations dramatically decreased among survivors within the first 72 h after ICU admission but only decreased very slightly or remained elevated in non-survivors. According to Guan et al [25], PCT levels above 10 ng/ml can predict survival if they decrease by more than 25% compared with the baseline value after 5 days. In a study involving 180 patients with sepsis, Charles et al determined that a more than 30% reduction in PCT from day 2 to day 3 can independently predict survival, reporting an odds ratio (OR) of 2.94 (1.22, 7.09) (*P*<0.05) [26]. According to a prospective study of 144 sepsis patients admitted to ICUs, a PCT reduction of less than 15% in the first 72 h reliably predicted death, with an OR of 3.9 (1.6, 7.09; *P*<0.001) [27]. Nevertheless, similar to the results of our analysis, the decrease in PCT levels was significantly predictive of survival, with OR=7.85 (**Table 3**, *P*<0.001) in the univariable analysis, with OR=5.17 (**Table 3**, *P*<0.001) in multivariable logistic regression analysis.

Our data suggest HBP clearance may also be a promising prognosis marker for 28-day mortality in patients with septic shock.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

HBP concentrations of 15 ng/ml were found by Linder et al to be a better indicator of a septic shock than PCT, CRP, or WBC (sensitivity 87.1%; specificity 95.1%). Additionally, 12 h prior to the onset of circulatory collapse, HBP levels were significantly higher [28]. Another international, multicenter, prospective study highlighted HBP as the best indicator to predict organ failure (AUC=0.8) [29]. HBP concentrations may have been predictive of the development of sepsis into septic shock in previous studies, but the importance of HBP clearance remains unclear. In the current study, HBP levels were significantly higher in non-survivors in the first 72 h of admission (**Table 2**, $P<0.001$). HBP concentrations dramatically decreased among survivors within the first 72 h after ICU admission but only slightly decreased or remained elevated in non-survivors. Furthermore, the decrease in HBP levels was significantly predictive of survival, with OR=9.95 (**Table 3**, $P<0.001$) in the univariable analysis, with OR=7.18 (**Table 3**, $P<0.001$) in the multivariable logistic regression analysis. Together, these results indicate that the kinetics of HBP concentrations within the first 72 h were strongly correlated with better survival following the diagnosis of sepsis. Thus, clinicians may wish to adjust the therapeutic regimen for patients exhibiting inadequate clearance of HBP.

In clinical practice, the SOFA score is a commonly used measure of multi-organ dysfunction syndrome, where high scores often indicate critical illness and poor outcomes [21]. Vincent et al demonstrated that multiple-organ dysfunction and high SOFA scores for any organ were associated with increased mortality [30]. They found that 44% of non-survivors, and only 20% of survivors ($P<0.001$), had significantly elevated SOFA scores in patients admitted to the ICU for at least 1 week. Our results with SOFA scores were similar to those of Vincent et al – decreasing SOFA scores were predictive of survival, with OR=1.93 (**Table 3**, $P=0.051$) in the univariable analysis, but not in the multivariable logistic regression analysis (**Table 3**, $P=0.146$).

This study had several limitations, including its small sample size. Thus, a prospective, multicenter, clinical study is required to confirm our findings. Moreover, data on HBP, PCT, CRP, and other parameters were collected at few time points and need to be tested and analyzed at more time points to reduce data bias. Further studies are needed to determine whether heparin or albumin treatment alters HBP measurements, as patients receiving such treatments were excluded from this study. Future studies may also need to investigate how antimicrobial therapy influences biomarker clearance and outcomes.

Conclusions

The present results demonstrate that changes in HBP, PCT, and CRP levels in the first 72 h after ICU admission were associated with the 28-day mortality rate of ICU patients with septic shock. In any of these marker values, a decrease is associated with survival.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10
2. Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259-72
3. Seymour CW, Kennedy JN, Wang S, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA. 2019; 321(20):2003-17
4. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):762-74
5. Clec'h C, Ferriere F, Karoubi P, et al. Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit Care Med. 2004;32(5):1166-69
6. Jensen JU, Heslet L, Jensen TH, et al. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med. 2006;34(10):2596-602
7. Garnacho-Montero J, Huici-Moreno MJ, Gutierrez-Pizarraya A, et al. Prognostic and diagnostic value of eosinopenia, C-reactive protein, procalcitonin, and circulating cell-free DNA in critically ill patients admitted with suspicion of sepsis. Crit Care. 2014;18(3):R116
8. Tang BM, Eslick GD, Craig JC, et al. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis. 2007;7(3):210-17
9. Ruiz-Alvarez MJ, García-Valdecasas S, De Pablo R, et al. Diagnostic efficacy and prognostic value of serum procalcitonin concentration in patients with suspected sepsis. J Intensive Care Med. 2009;24(1):63-71
10. Prieto MF, Kilstein J, Bagilet D, et al. C-reactive protein as a marker of mortality in Intensive Care Unit. Med Intensiva 2008;32(9):424-30
11. Gao L, Liu X, Zhang D, et al. Early diagnosis of bacterial infection in patients with septicopyemia by laboratory analysis of PCT, CRP and IL-6. Exp Ther Med. 2017;13(6):3479-83
12. Dahaba AA, Hagara B, Fall A, et al. Procalcitonin for early prediction of survival outcome in postoperative critically ill patients with severe sepsis. Br J Anaesth. 2006;97(4):503-8
13. Hoeboer SH, Groeneveld AB. Changes in circulating procalcitonin versus C-reactive protein in predicting evolution of infectious disease in febrile critically ill patients. PLoS One. 2013;8(6):e65564
14. Gautam N, Olofsson AM, Herwald H, et al. Heparin-binding protein (HBP/CAP37): A missing link in neutrophil-evoked alteration of vascular permeability. Nat Med. 2001;7(10):1123-27
15. Di Gennaro A, Kenne E, Wan M, et al. Leukotriene B4 – induced changes in vascular permeability are mediated by neutrophil release of heparin-binding protein (HBP/CAP37/azurocidin). FASEB J. 2009;23(6):1750-57
16. Chew MS, Linder A, Santen S, et al. Increased plasma levels of heparin-binding protein in patients with shock: A prospective, cohort study. Inflamm Res. 2012;61(4):375-79

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

17. Zhou Y, Liu Z, Huang J, et al. Usefulness of the heparin-binding protein level to diagnose sepsis and septic shock according to Sepsis-3 compared with procalcitonin and C reactive protein: A prospective cohort study in China. BMJ Open. 2019;9(4):e26527
18. Linder A, Akesson P, Inghammar M, et al. Elevated plasma levels of heparin-binding protein in Intensive Care Unit patients with severe sepsis and septic shock. Crit Care. 2012;16(3):R90
19. Innocenti F, Bianchi S, Guerrini E, et al. Prognostic scores for early stratification of septic patients admitted to an emergency department-high dependency unit. Eur J Emerg Med. 2014;21(4):254-59
20. Ho KM, Dobb GJ, Knuiman M, et al. A comparison of admission and worst 24-hour Acute Physiology and Chronic Health Evaluation II scores in predicting hospital mortality: A retrospective cohort study. Critical Care. 2006;10(1):R4
21. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754-58
22. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock. Crit Care Med. 2017;43(3):304-77
23. Seligman R, Meisner M, Lisboa TC, et al. Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. Critical Care. 2006;10(5):R125
24. Yentis SM, Soni N, Sheldon J. C-reactive protein as an indicator of resolution of sepsis in the Intensive Care Unit. Intensive Care Med. 1995;21(7):602-5
25. Guan J, Lin Z, Lue H. Dynamic change of procalcitonin, rather than concentration itself, is predictive of survival in septic shock patients when beyond 10 ng/mL. Shock. 2011;36(6):570-74
26. Charles PE, Tinel C, Barbar S, et al. Procalcitonin kinetics within the first days of sepsis: Relationship with the appropriateness of antibiotic therapy and the outcome. Crit Care. 2009;13(2):R38.
27. Pieralli F, Vannucchi V, Mancini A, et al. Procalcitonin kinetics in the first 72 hours predicts 30-day mortality in severely ill septic patients admitted to an Intermediate Care Unit. J Clin Med Res. 2015;7(9):706-13
28. Linder A, Christensson B, Herwald H, et al. Heparin-binding protein: An early marker of circulatory failure in sepsis. Clin Infect Dis. 2009;49(7):1044-50
29. Linder A, Arnold R, Boyd JH, et al. Heparin-binding protein measurement improves the prediction of severe infection with organ dysfunction in the Emergency Department. Crit Care Med. 2015;43(11):2378-86
30. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in Intensive Care Units: Results of a multicenter, prospective study. Crit Care Med. 1998;26(11):1793-800

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]