Dynamic Changes in Heparin-binding Protein as a Prognostic Biomarker in Patients with Sepsis

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Research

Abstract

BACKGROUND

We aimed to investigate the prognostic value of dynamic changes in heparin-binding protein (HBP) within the first 48 hours of hospital admission in sepsis patients.

Methods

We conducted a prospective observational study in the emergency intensive care unit of a tertiary care center. Patients who met SEPSIS-3 criteria were prospectively enrolled from August 2019 to January 2020. Serum levels of HBP were measured at admission, 24 hours, and 48 hours. Dynamic change in HBP was calculated as a percentage change between admission and 24 hours, and between admission and 48 hours. Accuracies of absolute level of HBP, dynamic change of HBP, and other biomarkers were compared with ROC analysis.

Results

A total of 245 patients were enrolled. After excluding patients not fulfilling the eligibility criteria and those died before 48 hours of admission, 185 patients were included for final analysis, of which 117 had sepsis, 68(36.76%) had septic shock, and 48(30%) died in the hospital. Day 1-HBP was correlated with procalcitonin (r2=0.21, p=0.004). Of all predictors of 30-day mortality, HBP clearance within 48 hours had the highest predictive accuracy (AUC: 0.82), followed by Day 1-HBP (AUC: 0.79), PCT (AUC: 0.75) and HBPc-24(AUC: 0.6). HBPc-48 > -17.14% had an independent impact on 30-day survival after adjusting for age, gender, shock status, and requirement of mechanical ventilation support.

Conclusions

HBPc-48 can predict survival in critically ill patients with sepsis and can assist clinicians with risk stratification of these patients. Future multicenter studies are necessary to assess the generalizability of these findings.

Introduction

Sepsis is a major public health concern, as it is one of the most expensive conditions to treat and is a leading cause of death.[1,2] The incidence of sepsis has steadily increased in the past decade, from 143,000 admissions in 2000 to 343,000 in 2007(3). The new SEPSIS-3 consensus defines sepsis as a "life-threatening organ dysfunction caused by a dysregulated host response to infection". In clinical research, organ dysfunction can be defined as a change in SOFA score by more than 2 points for ICU patients. A recent prospective observational cohort study of 130 patients, however, has shown that the change in SOFA score at 48 hours is only 61.3% sensitive in predicting the 30-day mortality.

Heparin-binding protein (HBP), also called azurocidin or cationic antimicrobial protein, is a 37 kDa multifunctional protein contained within the secretory and azurophilic granules of polymorphonuclear leukocytes. HBP acts as an amplifier of inflammatory responses and induces capillary leakage, both of which are highly dysregulated in severe sepsis. A rapid increase of HBP can be explained by its location within the secretory granule, which is the first to be mobilized upon neutrophil activation. After release, HBP contributes to the neutrophil-mediated permeability changes of the endothelium, leading to vascular leakage. Recently, HBP has been shown to be a robust predictor of the progression to organ dysfunction due to infection. HBP also rises earlier than other inflammatory markers and increased plasma HBP was observed in over 90% of the patients who developed severe sepsis.

Dynamic changes in HBP may reflect both the severity of the disease at presentation and the response to the initial treatment. HBP clearance measures the relative changes in HBP compared to the baseline HBP and is postulated to be a better predictor of outcomes. In this study, we aimed to prospectively evaluate the predictive value of day 1 (baseline), 24-hour, and 48-hour HBP clearance for sepsis mortality. Additionally, we aimed to assess whether or not 48-hour HBP clearance, in addition to clinical variables or severity scores, had independent prognostic value in this cohort.

Methods

Patient Population and Design

This was a prospective observational study conducted in the Emergency Department Intensive Care Unit (EICU) of People's Hospital of Baoan District of ShenZhen. Patients admitted to the EICU between August 2019 and January 2020 who fulfilled the SEPSIS-3 criteria were enrolled.[6] Exclusion criteria included pregnancy, do-not-resuscitate orders, and age under 20 years. The study was approved by the local ethics committee, and written informed consents were obtained from patients or patient representatives. All septic patients were treated based on guidelines from the current Surviving Sepsis Campaign with modifications as deemed appropriate by the treating physicians. The duration of antimicrobial therapy was guided by culture data, site of infection, and the treating physician. Patient data collected included: age, gender, vital signs, comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, site(s) of infection, laboratory tests findings (basic biochemistry, complete blood count, coagulation, and arterial blood gases), microbiological culture results, duration of hospitalization (length of stay in ICU and in total), and clinical outcomes. Infection was diagnosed by clinical, laboratory, and microbiological parameters. APACHE II scores and SOFA scores were assessed on the first day of admission (day 1). Serum concentrations of procalcitonin (PCT) were measured on the first day of EICU admission. HBP was measured at admission (baseline HBP) and was repeated at 24 and 48 hours. The patients were followed for 28 days, until death, discharge, or end of follow-up, whichever came first. The primary endpoint was all-cause mortality at 28 days.

Blood sample collection and analysis

The blood samples were collected in 5 ml sodium citrate anticoagulation tubes (BD vacutainer) and centrifuged at 3,000 rpm for 10 min and biochemistry markers were analyzed immediately. The HBP level was determined by a commercial enzyme-linked immunosorbent assay kit (Joinstar Biomedical Technology Co., LTD, Hangzhou, China). The HBP detection range was 5.9–300 ng/mL. The intra-assay coefficient of variation was 11% at 21 ng/mL and 7% at 81 ng/mL. In addition, we investigated the prognostic ability of baseline PCT levels for mortality prediction. PCT level was measured via an automatic analyzer, the VIDAS® B.R.A.H.M.S PCT assay (bioMérieux, Marcy L'Etoile, France). The lower limit of detection of the assay was 0.01 ng/mL.

Serum dynamic change of HBP

Changes in serum HBP (ΔHBP) was defined as the difference between a given timepoint and baseline (Day 1). In particular, we measured the 24 hour change (ΔHBP 24) and the 48 hour change (ΔHBP 48), both relative to the baseline (Day 1) measurement. The relative change of HBP was calculated by dividing the ΔHBP24 and ΔHBP48 by the baseline HBP, respectively, and was presented as a percentage. Baseline APACHE II score, Sequential Organ Failure Assessment (SOFA) score, primary source of infection, culture results, ICU, and hospital mortalities were recorded. Clinical parameters such as body temperature, heart rate, white cell count (WCC), and clinical signs of infection were recorded on admission and repeated daily.

Statistical Analysis

We compared the characteristics between survivors and nonsurvivors among patients with sepsis or septic shock. Categorical variables were expressed as a number and proportion and compared with Chi-square tests. Continuous variables were presented with mean ± standard deviation for data with a normal distribution and compared using Student t-tests. Data with non-normal distributions was presented with a median with interquartile range and compared with an independent sample using Mann-Whitney U test. Spearman's rank correlation coefficient was used to examine the relationship between the serum concentration of HBP and PCT. The prognostic accuracy of different biomarkers, clinical score, or HBP clearance at 24 or 48 hour was assessed by area under the receiver operating characteristic (ROC) curves. The best cutoff in terms of sensitivity and specificity was identified by the Youden's Index. The Youden index is the maximum vertical distance or difference between the ROC curve and the diagonal or chance line; it occurs at the cut point that optimizes the test's differentiating ability when equal weight is given to sensitivity and specificity. To assess whether the 48 hour HBP clearance has independent prognostic meaning in addition to age, gender, requirement of mechanical ventilation, and shock status, we performed a multivariate Cox-proportional hazard model analysis. We also plotted Kaplan-Meier survival curves at the optimal cutoff for three markers. For all statistical analyses, P < 0.05 was considered statistically significant. Data analysis and graphing were conducted with R statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics and clinical presentations

During the study period, a total of 245 patients were admitted for sepsis or septic shock. In the first stage, 6 patients were excluded from the study due to age < 20 years, 4 excluded due to pregnancy, 9 due to leukopenia or hyperleukocytosis, 6 due to hemolysis, and 10 had received albumin or heparin treatment before HBP measurement. A total of 206 patients were initially included, but 21 patients died within 48 hours of admission. Thus, the remaining 185 patients were included for analysis Fig. 1).

We compared the demographic, comorbidity, laboratory results, site of infection, clinical severity, and various outcome variables between survivors and nonsurvivors. Compared to survivors, non-survivors were older, had higher serum levels of procalcitonin and lactate, and had more bloodstream but more pulmonary infection. Nonsurvivors had higher APACHE II or SOFA scores and required mechanical ventilation support more frequently. The comparison of patient characteristics across the two groups is summarized in Table 1.

Table 1
Comparisons of baseline characteristics between survivors and nonsurvivors in patients with severe sepsis and septic shock

	Survivors (N = 137)	non-Survivors (N = 48)	P Value
Demographic characteristics			
Age, mean ± SD, yr.	63.21 ± 19.45	63.60 ± 17.47	0.902
Female, n (%)	48 ± 35.0	17 ± 35.4	1.000
Comorbidities, n (%)			
Chronic heart failure	13 (9.5)	5 (10.4)	1.000
Diabetes mellitus	31 (22.6)	10 (20.8)	0.956
Cerebrovascular disease	27 (19.7)	8 (16.7)	0.803
Chronic kidney disease	19 (13.9)	10 (20.8)	0.362
Laboratory results, mean ± SD			
White blood cell count (109/L)	13.47 ± 14.36	12.58 ± 7.52	0.683
Neutrophil percentage (%)	83.81 ± 10.49	79.74 ± 20.30	0.078
Procalcitonin(ng/dL)	8.06 ± 18.80	22.55 ± 31.70	< 0.001
Lactate (mmol/L)	2.72 ± 2.64	5.51 ± 5.15	< 0.001
Site of sepsis, n (%)			
Bloodstream	2 (1.5)	6 (12.5)	0.005
Lung	112 (81.8)	47 (97.9)	0.011
Urinary tract	9 (6.6)	2 (4.2)	0.802
Abdomen	18 (13.1)	12 (25.0)	0.091
Soft tissue	2 (1.5)	1 (2.1)	1.000
Others	4 (2.9)	1 (2.1)	1.000
Clinical scoring, points, mean ± SD,			
APACHE II score	14.58 ± 7.36)	23.69 ± 6.43	< 0.001
SOFA score	6.47 ± 4.91)	13.42 ± 5.60	< 0.001
Number dysfunctional organs, mean ± SD	2.7 ± 1.2	4.1 ± 1.7	0.060
Organ support, n (%)			

	Survivors (N = 137)	non-Survivors (N = 48)	P Value
Mechanical ventilation	21 (15.3)	14 (29.2)	0.058
Renal replacement therapy	6 (4.4)	15 (31.2)	< 0.001
Vasopressor	36 (26.3)	32 (66.7)	< 0.001
Duration of hospitalization, mean ± SD,days			
Length of ICU stay	9.30 ± 9.53	10.79 ± 7.93	0.334
Length of hospital stay	17.37 ± 12.82	11.50 ± 8.38	0.004

Baseline and dynamic change of HBP among sepsis patients

Table 2 compares the baseline and dynamic change of HBP within 48 hours of admission between survivors and nonsurvivors. Mean serum levels of HBP were higher in nonsurvivors at admission, 24 hours and 48 hours. Survivors had significantly higher mean HBP clearance at both 24 hour and 48 hour than nonsurvivors. The time-dependent change of HBP between survivors and nonsurvivors is shown in Fig. 2. At 24 hours, both survivors and nonsurvivors showed a decreasing trend in HBP with nonsurvivors having higher admission HBP levels (Fig. 2A, 2B). At the 48 hours, the decrease was more pronounced in survivors (Fig. 2C) than nonsurvivors. Several nonsurvivors even had higher HBP levels at 48 hours compared to HBP levels at admission (Fig. 2D). The serial measurements of serum level of HBP for each patient is shown in Supplementary Fig. 1.

Table 2

Comparisons of HBP and HBPc dynamic monitoring levels between survivors and nonsurvivors in patients with sepsis or septic shock

Variables	Survivors (N = 137)	non-Survivors (N = 48)	*P* Value
HBP-initial(ng/mL) median (IQR)	117.41 (75.24-185.45)	234.95 (203.13-270.96)	< 0.001
HBP-24 h(ng/mL) median (IQR)	85.42 (51.36-119.58)	173.02 (125.77−200.70)	< 0.001
HBP-48 h(ng/mL) median (IQR)	47.72 (24.29−86.12)	196.21 (129.60-224.76)	< 0.001
HBPc-24 h(%) median (IQR)	-27.93 (-41.51,-17.25)	-21.87 (-35.86,-14.16)	0.142
HBPc-48 h(%) median (IQR)	-53.88 (-71.83,-35.65)	-15.24 (-38.65,-3.13)	< 0.001

Comparative accuracy of biomarkers and clinical score

We compared the predictive accuracies of absolute levels and relative changes of various biomarkers. HBPc-48 h had the highest predictive accuracy with an AUC of 0.82, followed by admission HBP (0.79), admission PCT (0.75), admission CRP (0.68) and HBPc-24 h (0.60). Supplementary Fig. 2 shows the ROC curves of each predictive marker. The AUC with 95% confidence intervals, optimal cutoff points, and corresponding sensitivity and specificity are shown in Table 3. At the optimal cutoff of -17.14%, HBPc-48 h can predict 30-day mortality with a sensitivity of 0.58 and a specificity of 0.91. HBP is weakly correlated with PCT concentrations (Spearman correlation 0.21, P = 0.004, Supplemental Fig. 3).

Table 3
Evaluation of the prognosis of severe sepsis and septic shock patients

Variables	Cut-off level	Sensitivity (%)	Specificity (%)	AUC	95%CI
PCT (ng/dL)	1.79	0.82	0.65	0.75	0.68, 0.83
HBP (mg/dL)	201.69	0.79	0.80	0.79	0.72, 0.86
CRP	91.77	0.66	0.70	0.68	0.58, 0.78
HBPc-24 h (%)	-23.26	0.63	0.60	0.60	0.51, 0.70
HBPc-48 h (%)	-17.14	0.58	0.91	0.82	0.75, 0.89

Thereafter, we plotted Kaplan-Meier survival curve at optimal cutoff for baseline HBP (Cutoff: 201.69 ng/mL), HBPc-24 h (Cutoff: -23.26%), and HBPc-48 h (Cutoff: -17.14%) in Fig. 3. In three markers, HBPc-48 h showed the best performance to differentiate survivor and non-survivor groups in 30-day cumulative probability of death (p < 0.0001). For clinical use, we select two cutoff points that can inform clinical decision. Patients who had a HBPc-48 h greater than 50% had a 91.5% survival rate, while patients who had a HBPc-48 h less than 4% had a 86.7% mortality rate.

Lastly, we explored whether or not HBPc-48 h has independent predictive value in addition to common demographic and clinical predictiors. The Cox model showed that HBPc-48 h was independently associated with increased risk of mortality after adjusting for age, gender, shock status, and requirements of mechanical ventilation support. (Table 4)

Table 4
Multivariate binary Cox regression analysis of prognosis in patients with severe sepsis or septic shock

Variables	HR	95%CI	P value
Age > 70	1.20	0.63,2.29	0.575
Sex (F V.S. M)	1.33	0.70,2.50	0.382
Shock	2.37	1.29,4.33	0.005
Mechanical ventilation	1.38	0.18,10.68	0.760
HBPc-48 h > -17.4%	6.34	3.46,11.63	<0.0001

Discussion

Sepsis remains a leading cause of morbidity and mortality in the ICU with variable in-hospital mortality rates (18%-50%).[14-15] In the present study, mortality due to severe sepsis or septic shock was 25.94%, which is consistent with prior studies. Clinically, once the diagnosis of sepsis is made, predicting survival

among sepsis patients is important to properly risk stratify patients and guide treatment decisions. Our pilot study reveals HBPc-48 h may have the best discriminative capability among several widely used biomarkers such as CRP or PCT. We also found patients with a HBPc-48 h greater than 50% had a greater than 90% chance of survival, while patients with a HBPc-48 h less than 4% had a nearly 90% mortality rate. These findings support the routine measurement of serum HBP at ICU admission and 48 hours later.

HBP has been shown to be a valuable prognostic marker for patients with sepsis[16-17]. Linder et al.[18] reported that plasma HBP levels of ≥ 15 ng/mL served as a better indicator of severe sepsis (with or without septic shock) than various other laboratory parameters investigated, including PCT, IL-6, CRP, WBC and lactate (sensitivity, 87.1%; specificity, 95.1%). Subsequently, a number of studies verified that plasma HBP levels were significantly elevated in sepsis associated with circulatory failure[19-20]. Another international multicenter study demonstrated that HBP was the best predictor of progression to organ dysfunction (AUC-ROC = 0.80)[21].

To our knowledge, this is the first study that dynamically analyzed HBP concentrations and established that HBP-c can be a useful biomarker for prompt prognostication of patients with sepsis. In this prospective observational study, we found that serum levels of HBP dramatically decreased at 48 hours after ICU admission in survivors, but decreased at a slower rate or even remained elevated in nonsurvivors. In contrast, the initial serum concentration of HBP and HBPc-24 h poorly correlated with prognosis. The 48-hour HBP-c of survivors was − 53.88% (IQR, -71.83 to -35.65), which was substantially higher than that of nonsurvivors (-15.24%; IQR, -38.65 to -3.13, P<0.001). Several prognostic indices are used in ICUs. The two most widely used were the APACHE II score and SOFA score; however, the utility was limited to the first 24 hours of treatment in other studies[22]. In our study, we showed HBPc-48 h has an independent prognostic value compared to common predictors such as shock status, age, or gender. Therefore, the use of clinical scores alone may not replace serial measurement of HBP in risk stratification. The HBP clearance has the additional benefit of providing information about initial treatment success. Our data shows that for those patients with inadequate clearance of HBP at 48 hours, the clinicians may adjust their initial treatment. Further clinical trials are needed to help determine the best strategy that how HBP clearance information can guide clinical treatment.

Our study has to be interpreted in certain limitations. First, this is a prospective study of consecutive patients at a single center, and large prospective multicenter studies are necessary to externally validate our results. Second, we aim to use HBP to provide useful prognostic information on patients who survived the initial 48 hours, therefore patients who died within 24 hours of ICU admission were excluded from analysis. Third, we did not collect information regarding the appropriateness of antibiotic choice for the given infection. However, antibiotic selection is one of the major determinants of initial treatment success, which we believe HBP clearance indirectly measures. Adjusting this factor may underestimate the prognostic value of HBP clearance. The strength of this study was that all patients included fulfilled the SEPSIS-3 criteria. This consideration eliminates the bias that might have been caused by the inclusion of patients with heterogeneous definitions of sepsis.

Conclusions

We demonstrated that 48-hour HBP clearance is the most accurate prognostic marker compared to various markers currently used for risk stratification of sepsis patients. We demonstrated patients with a 48-hour HBP decrease greater than 50% had a greater than 90% chance of survival, while patients with a 48-hour HBP decrease less than 4% had a nearly 90% mortality rate. This dynamic information may prompt the clinician to reassess the appropriateness of treatment with the goal of improving patient outcome. Further studies are needed to validate our findings.

Abbreviations

HBP: heparin-binding protein

PCT: procalcitonin

APACHE II score: Acute Physiology and Chronic Health Evaluation Score

SOFA score: Sequential Organ Failure Assessment Score

ΔHBP: Changes in serum heparin-binding protein

ROC curves: receiver operating characteristic curves

HBPc-24h: heparin-binding protein clearance at 24 hour

HBPc-48h: heparin-binding protein clearance at 48 hour

Declarations

Ethics Approval and Consent to participate

This study was approved by the Research Committees and Institutional Review Boards for People's Hospital of Baoan District of ShenZhen, and it met the criteria for exemption from informed consent.

Consent for publication

Non-applicable

Availability of data and material

The data sets generated and/or analyzed during the current study are not publicly available due to the data confidentiality requirements of the ethics committee, but are available from the corresponding author on reasonable request and approval from the ethics committees in all institutions.

Competing interests

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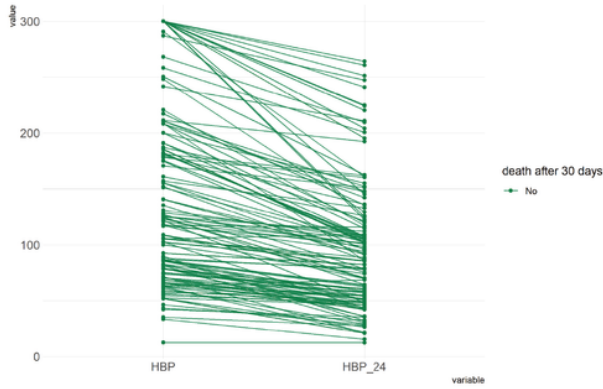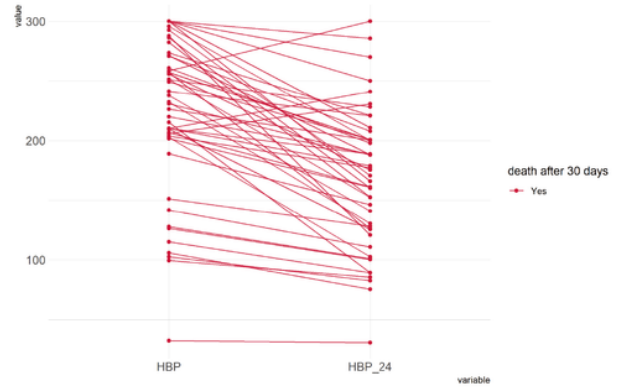
Figures

Patients admitted to ICU of Boan people's hospital fulfilling the sepsis-3 criteria
N=245

Exclusion:
1. Age <20 (N=6)
2. Pregnant (N=4)
3. Leukocyte count < 10^9/L or >50 *10^9/L (N=9)
4. Hemolysis (N=6)
5. Patients having received heparin or albumin treatment (N=10)
6. Measurement outlier (N=4)

Sepsis cohort for HBP measurement
N=206

Death between 48 hours (N=21)

Final cohort for analysis
(N=185)

Died in hospital
(N=48)

Survived to discharge
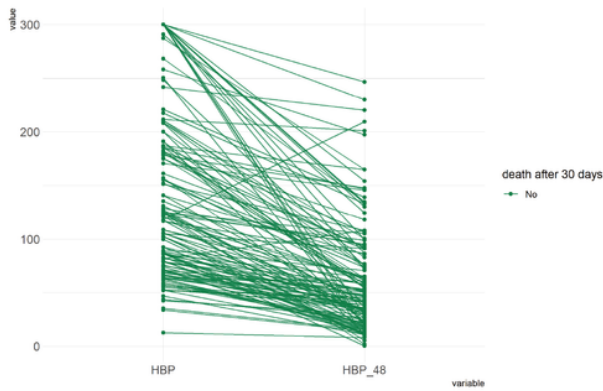(N=137)

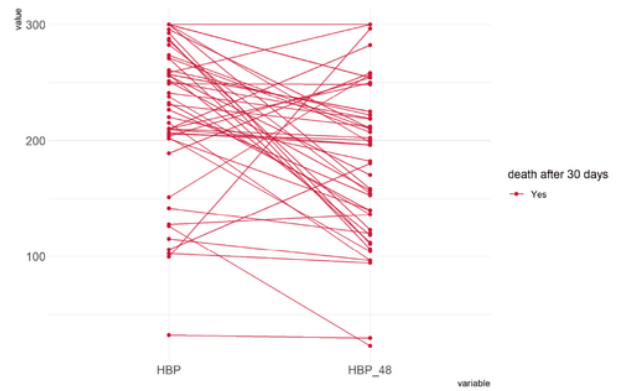**Figure 1**

Cohort inclusion and exclusion process

Figure 2

Time change plots of 24-hour serum HBP clearance between survivors (2A) and nonsurvivors (2B) and 48-hour serum HBP clearance between survivors (2C) and nonsurvivors (2D)
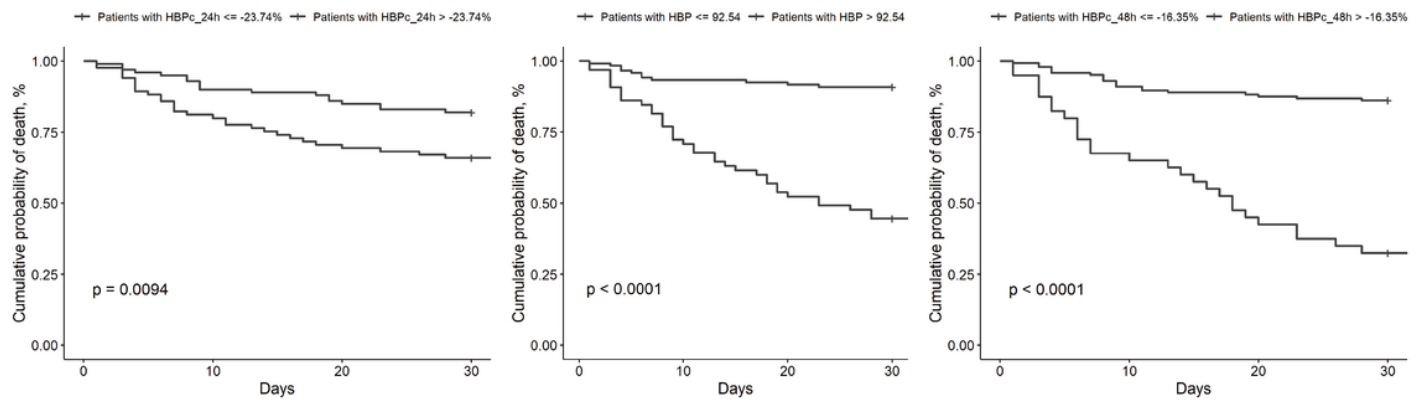

Figure 3

Kaplan-Meier survival curve for HBPc-24h (Cutoff: -23.26%), HBP (cutoff: 201.69 ng/mL), and HBPc-48h (Cutoff: -17.14%)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure1.png
- Supplementaryfigure2.png
- Supplementaryfigure3.png