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RESEARCH ARTICLE

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Heparin binding protein as a reliable prognostic biomarker for severity of sepsis in the intensive care unit

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ABSTRACT

Background: It is still challenging to identify people who are at risk for developing sepsis quickly and early. Heparin-binding protein (HBP) has been demonstrated a promising data that can be used as predictive qualities in identifying organ failure.

Methods: This prospective observational investigation of 55 adult patients who have been proven to have sepsis, and were hospitalized into the intensive care unit. By carrying out HBP, procalcitonin (PROCAL), C-reactive protein (CRP), serum lactate, SOFA score on admission and after 72 hours and detecting 28-day mortality.

Results: Despite PROCAL and HBP were higher in survival than non-survival patients at day 0 (1010.32 ± 341.72 vs 770.21 ± 327.97, $p = 0.0112$) (16.73 ± 7.19 vs 13.19 ± 7.26, $p = 0.077$) respectively, It was significantly lower in survival than non-survival at day 3 (542.09 ± 191.98 vs 995.00 ± 333.74, $p = <0.0001$) (9.03 ± 2.92 vs 16.67 ± 7.55, $p = <0.0001$) respectively. Our main marker HBP decreased significantly from day 0 to day 3 for survival patients with paired difference -7.69 ± 6.78 with p value < 0.0001, while it is increased with non-significant value for non-survival patients with paired difference 3.48 ± 9.45 with p value 0.084. ROC analysis for mortality showed for HBP that AUC at day 0 was 0.323 (p=0.025). At cut-off value of>15.5ng/ml, sensitivity was 29.2%, specificity was 64.5%, while at day 3 was 0.831 (p=0.000). At cut-off value of>9.5ng/ml, sensitivity was 83.33%, specificity was 77.42%.

Conclusion: HPB showed a strong prognostic marker of mortality in ICU septic patients at day 3 more than day 0 with important value and trend.

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KEYWORDS
Heparin-binding protein; prognostic; biomarker; sepsis; ICU; mortality

1. Introduction

More than 30 million people around the world get sepsis every year, and it is one of the main reasons why critical patients die around the world. Sepsis can happen to anyone who has an infection, and it affects as many as 1–2% of all hospitalized patients. Sepsis is described as "a life-threatening organ failure caused by an infected host's bad response to the infection." The new factors for diagnosing sepsis are different for patients in the ICU and those who are not in the ICU [1].

It is still difficult to determine whether individuals have a greater mortality risk and might benefit from closer observation or more intensive therapy. Given the complexity of sepsis and the challenges in its clinical evaluation, the introduction of new biomarkers to identify such individuals seems appealing. However, single biomarkers generally give incorrect information due to the variety and complicated pathophysiology of sepsis, and biomarkers which consistently qualify as predictors of prognosis in sepsis patients remain limited [2].

Current diagnostic indicators for detection of sepsis and septic shock include bacterial culture, levels of procalcitonin (PROCAL), CBC, and CRP are inadequate due to time delays, low sensitivity, and lack of specificity. When bacteria are present, the secretory and azurophilic granule of neutrophils produce heparin binding protein (HBP) [3].

Monocytes and macrophages, both kinds of immune cells, are drawn to and activated by HBP, which works as both a chemoattractant and an activator. Studies conducted in clinical settings have shown that a wide range of bacteria, which are responsible for a wide range of infectious diseases, release HBP [4].

2. Patients and methods

In compliance with protocols established by the Institutional Review Board (IRB) of the Faculty of Medicine Ain Shams University hospitals in Cairo, Egypt, under code number FMASU M D 159/2021, and registered at clinicaltrails.gov (ID: NCT05610020). Under the direction of the anesthesia and critical care

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department, a prospective observational study was carried out in the emergency, medical, and surgical intensive care units at Ain Shams University Hospital. Using the third worldwide consensus criteria for sepsis and septic shock, 55 adults have been shown to have confirmed sepsis. Who required intensive care unit admission were sought out for participation. Elsayed et al., [5] reported Pearson correlation coefficient between HBP and SOFA score in sepsis case at different points of time after admission. Adopting their results a sample size of 46 achieves at least 80% power to detect a different of −0.40. Between the null hypothesis correlation of 0.05 The sample size should be increased by 20% to be 55 cases. Exclusion criteria: Aged less than 18 and more than 70 years old, pregnancy, neutropenic from malignancy, on immunosuppressive therapy and confirmed hematological malignancy.

- Our primary object is to evaluate the level of HBP in relation to 28 days mortality among septic patients.

- secondly, is to compare HBP level to other sepsis bio markers (PCT,WBCs, lactate, and CRP) and Make a correlation variant between bio markers, organ dysfunction (measured by SOFA score), and mortality.

All participants included in the study were subjected to the following: Full medical history, Clinical examination, Data were collected from the studied septic patients included the following: complete blood count (CBC), coagulation profile, arterial blood gases (ABGs), electrolytes, serum creatinine and urea, liver and kidney functions.

Serum lactate, total leucocyte count (as a part of CBC), CRP to be compared with procalcitonin and our marker (HPB) on admission (day 0) and after 72 hours (day 3) cultures withdraw on clinical suspicion that were obtained to identify source of sepsis. Assay of serum Human Azurocidin (HBP) levels by quantitative enzyme linked immunosorbent assay (ELISA) technique on admission and after 72 hours. Assay of serum Human Procalcitonin levels (PROCAL) by quantitative enzyme linked immunosorbent assay (ELISA) technique on admission and after 72 hours.

All the laboratory assays were conducted at the Clinical Pathology Department of Ain Shams University Hospitals.

Then, the patients were divided to non-survival and survival to compare the results data between them.

2.1. Statistical methods

Data were analyzed using Statistical package for Social Science (SPSS) version 27.0., data were expressed as meant standard deviation (SD), Median (IQR) and frequency and percentage when indicated. The following tests were used: Independent-samples t-test, paired samples *t*- test, Chi-square (X2) test, Mann–Whitney U test, ROC analysis Pearson's correlation coefficient the confidence interval was set to 95%, P-value <0.05 was considered significant.

3. Results

-Demographic and laboratory parameters of the non-survival patients (24 patients) and survival patients (31 patients). It showed that age, gender, diabetes, Ischemic Heart Disease, Chronic Kidney Disease, Chronic Liver Disease, Sequential organ failure assessment (SOFA) at day 0, CRP at day 0, lactate at day 0, WBCs at day 0 were comparable in both groups. However, non-survival patients had statistically significant lower proportion of hypertension [Percentage = 33.3% versus (vs.) 61.3%, p-value (p) = 0.04].Compared with survival patients and statistically significant higher values of SOFA at day 3 [Median/interquartile range (IQR) = 10.0 (8.0–14.0) vs. 2.0 (1.0–4.75), p =<0.0001], CRP at day 3 [Mean± SD = 217.88 ± 101.78 vs. 100.74 ± 67.22, p =<0.0001], lactate at day 3 [Mean± SD = 4.92 ± 3.69 vs. 1.84 ± 0.89, p =<0.0001], WBCs at day 3 [Mean± SD = 22.58 ± 7.55 vs. 12.73 ± 5.68, p =<0.0001], HPB at day 3 [Mean± SD = 16.67 ± 7.55 vs. 9.03 ± 2.92, p =<0.0001] and PROCAL at day 3 [Mean± SD = 995.00 ± 333.74 vs. 542.09 ± 191.98, p =<0.0001] compared with survival patients and also showed that PROCAL at day 0 was significant higher in survival than non-survival (1010.32 ± 341.72 vs 770.21 ± 327.97, p = 0.0112) (as shown in Table 1).

- Paired data are done for both groups (Survival Patients and Non-survival Patients) between D0 and D3 showed; increased SOFA Score for non-survival patients with paired difference 3.500 with p-value = 0.005 while decreased SOFA Score for survival patients with paired difference-4.0000 with p-value = 0.0001.Also showed increased CRP for non-survival patients with paired difference 21.04 ± 122.11 with p-value = 0.41, while decreased for survival patients with paired difference-110.90 ± 99.10 with p-value= <0.0001. Additionally, the following parameters were detected; increased Lactate level for non-survival patients with paired difference 1.81 ± 3.15 mmol/L with p-value = 0.009, while decreased for survival patients with paired difference −2.58 ± 2.62 mmol/L with p-value= <0.0001. Increased WBCs counts ($X10^3$) for non-survival patients with paired difference 1.33 ± 10.89 cells/mm^3 with p-value = 0.55, while decreased for survival patients with paired difference −8.98 ± 6.39 cells/mm^3 with p-value= <0.0001, PROCAL Increased for non-survival patients with paired difference 224.79 ± 406.01 pg/ml with p-value = 0.012, while decreased for survival patients with paired difference −468.23 ± 364.19 pg/ml with p-value= <0.0001. It showed that our main increased HBP for non-survival patients with paired difference 3.48 ± 9.45 ng/ml with p-value = 0.084, while decreased for survival patients with paired difference −7.69 ± 6.78 ng/ml with p-value= <0.0001 (as mentioned in Table 2, Figure 1 and 2).

Table 1. Demographic and laboratory parameters of the non-survival patients and survival patients (total 55 patients).

Variables	Non-survival patients ($n = 24$)	Survival patients ($n = 31$)	p-value
Age [1]	56.13 ± 8.95	56.23 ± 8.53	0.966
Sex [3]			0.732
Male	16 (66.7%)	22 (71%)	
Female	8 (33.3%)	9 (29%)	
Diabetes [3]	16 (66.7%)	26 (83.9%)	0.136
Hypertension [3]	8 (33.3%)	19 (61.3%)	**0.04**
Ischemic Heart Disease [3]	12 (50%)	11 (35.5%)	0.279
Chronic Kidney Disease [3]	3 (12.5%)	5 (16.1%)	0.705
Chronic Liver Disease [3]	1 (4.2%)	0 (0%)	0.251
SOFA (Day 0) [2]	7.5 (5.0–9.0)	6.0 (5.0–8.75)	0.402
SOFA (Day 3) [2]	10.0 (8.0–14.0)	2.0 (1.0–4.75)	**<0.0001**
CRP (Day 0) (mg/L) [1]	196.83 ± 145.88	211.65 ± 104.98	0.663
CRP (Day 3) (mg/L) [1]	217.88 ± 101.78	100.74 ± 67.22	**<0.0001**
Lactate (Day 0) (mmol/L) [1]	3.11 ± 1.66	4.42 ± 3.00	0.059
Lactate (Day 3) (mmol/L) [1]	4.92 ± 3.69	1.84 ± 0.89	**<0.0001**
WBCs (Day 0) ($X10^3$) ($cells/mm^3$) [1]	21.25 ± 9.39	21.71 ± 8.08	0.846
WBCs (Day 3) ($X10^3$) ($cells/mm^3$) [1]	22.58 ± 7.55	12.73 ± 5.68	**<0.0001**
HBP (Day 0) (ng/ml) [1]	13.19 ± 7.26	16.73 ± 7.19	0.077
HBP (Day 3) (ng/ml) [1]	16.67 ± 7.55	9.03 ± 2.92	**<0.0001**
PROCAL (Day 0) (pg/ml) [1]	770.21 ± 327.97	1010.32 ± 341.72	**0.0112**
PROCAL (Day 3) (pg/ml) [1]	995.00 ± 333.74	542.09 ± 191.98	**<0.0001**

CRP: C-reactive protein; HBP: heparin binding protein; SOFA: sequential organ failure assessment; WBCs: white blood cells.

1= Data was expressed as mean ± standard deviation (SD), *p* value done by student t-test; 2= Data was expressed as median/interquartile range (IQR), *p* value done by Mann–Whitney test; 3= Data was expressed as number (percentage) *p* value done by Chi-square (X2) test.

Bold values indicate statistically significant results.

Table 2. Descriptive statistics and comparison for different studied variables in the studied non-survival patients and patients with survival patients.

Variables	(Day 0)	(Day 3)		Paired differences	p- value
SOFA [2]	7.5 (5.0–9.0)	10.0 (8.0–14.0)	**Non-survival patients**	3.5000	**0.005**
	6.0 (5.0–8.75)	2.0 (1.0–4.75)	**Survival patients**	−4.0000	**<0.0001**
CRP (mg/L) [1]	196.83 ± 145.88	217.88 ± 101.78	**Non-survival patients**	21.04 ± 122.11	0.41
	211.65 ± 104.98	100.74 ± 67.22	**Survival patients**	−110.90 ± 99.10	**<0.0001**
Lactate (mmol/L) [1]	3.11 ± 1.66	4.92 ± 3.69	**Non-survival patients**	1.81 ± 3.15	**0.009**
	4.42 ± 3.00	1.84 ± 0.89	**Survival patients**	−2.58 ± 2.62	**<0.0001**
WBCs ($X10^3$) ($cells/mm^3$) [1]	21.25 ± 9.39	22.58 ± 7.55	**Non-survival patients**	1.33 ± 10.89	0.55
	21.71 ± 8.08	12.73 ± 5.68	**Survival patients**	−8.98 ± 6.39	**<0.0001**
HBP (ng/ml) [1]	13.19 ± 7.26	16.67 ± 7.55	**Non-survival patients**	3.48 ± 9.45	0.084
	16.73 ± 7.19	9.03 ± 2.92	**Survival patients**	−7.69 ± 6.78	**<0.0001**
PROCAL (pg/ml)[1]	770.21 ± 327.97	995.00 ± 333.74	**Non-survival patients**	224.79 ± 406.01`	**0.012**
	1010.32 ± 341.72	542.09 ± 191.98	**Survival patients**	−468.23 ± 364.19	**<0.0001**

CRP: C-reactive protein; HBP: heparin binding protein; SOFA: *sequential organ failure assessment; WBCs: white blood cells*.

1= Data was expressed as mean ± standard deviation (SD) *p* value done by paired t-test; 2= Data was expressed as median/interquartile range (IQR), *p* value done by Wilcoxon test.

Bold values indicate statistically significant results.

-Correlations of the different variables at day 0 in the studied patients. It showed that SOFA at day 0 had statistically significant positive correlation with lactate at day 0 [Pearson's correlation coefficient (r) = 0.486, p = 0.0002] and WBCs at day 0 [r = 0.426, p = 0.0012]. Also, it showed that lactate at day 0 had statistically significant positive correlation with WBCs at day 0 [r = 0.399, p = 0.003]. Furthermore, it showed that WBCs at day 0 had statistically significant positive correlation with PROCAL at day 0 [r = 0.295, p = 0.029]. Moreover, it showed that PROCAL at day 0 had statistically significant positive correlation with HBP at day 0 [r = 0.588, *p*= <0.0001] (as shown in Table 3).

-Correlations of the different variables at day 3 in the studied patients. It showed that SOFA at day 3 had statistically significant positive correlation with CRP at day 3 [r = 0.766, *p*= <0.0001], lactate at day 3 [r = 0.778, *p*= <0.0001], WBCs at day 3 [r = 0.751, *p*= <0.0001], HBP at day 3 [r = 0.628, *p*= <0.0001] and PROCAL at day 3 [r = 0.680, *p*= <0.0001]. Also, it showed that CRP at day 3 had statistically significant positive correlation with lactate at day 3 [r = 0.599, *p*= <0.0001], WBCs at day 3 [r = 0.712, *p*= <0.0001], HBP at day 3 [r = 0.700, *p*= <0.0001] and PROCAL at day 3 [r = 0.675, *p*= <0.0001]. Furthermore, it showed that lactate at day 3 had statistically significant positive correlation with WBCs at day 3 [r = 0.611, *p*= <0.0001], HBP at day 3 [r = 0.364, p = 0.006] and PROCAL at day 3 [r = 0.420, p = 0.001]. Moreover, it showed that WBCs at day 3 had statistically significant positive correlation

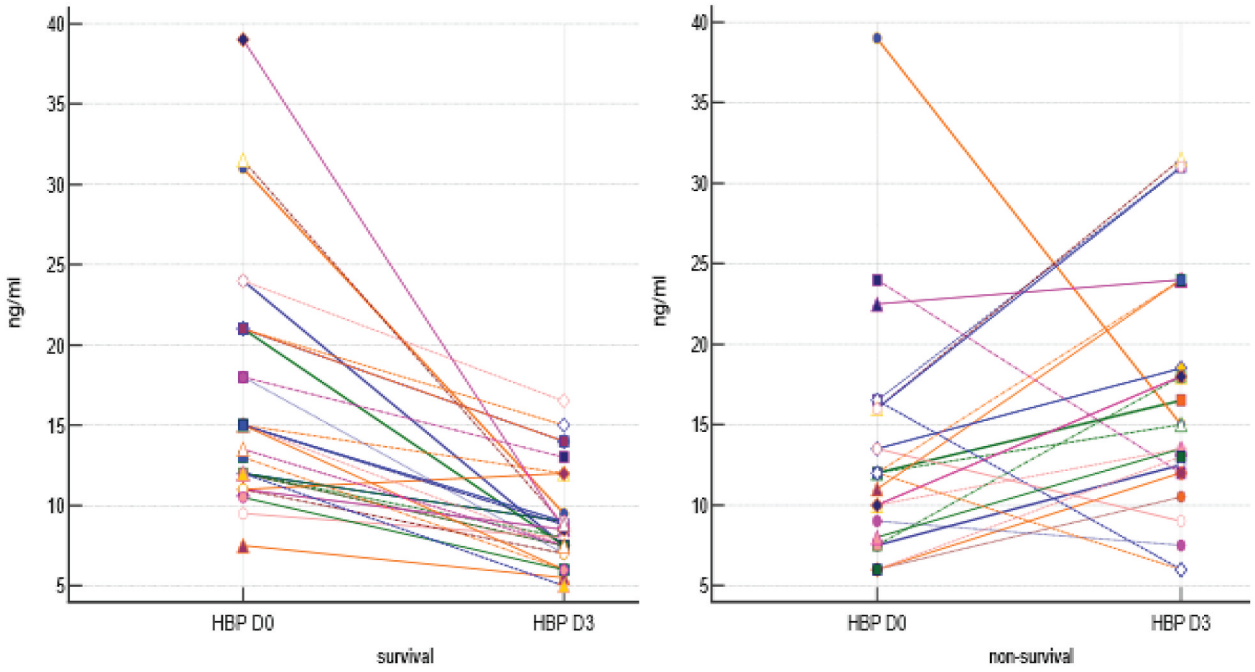

Figure 1. Serial measurement of plasma levels of HBP (ng/ml) between sepsis survival and non-survival.

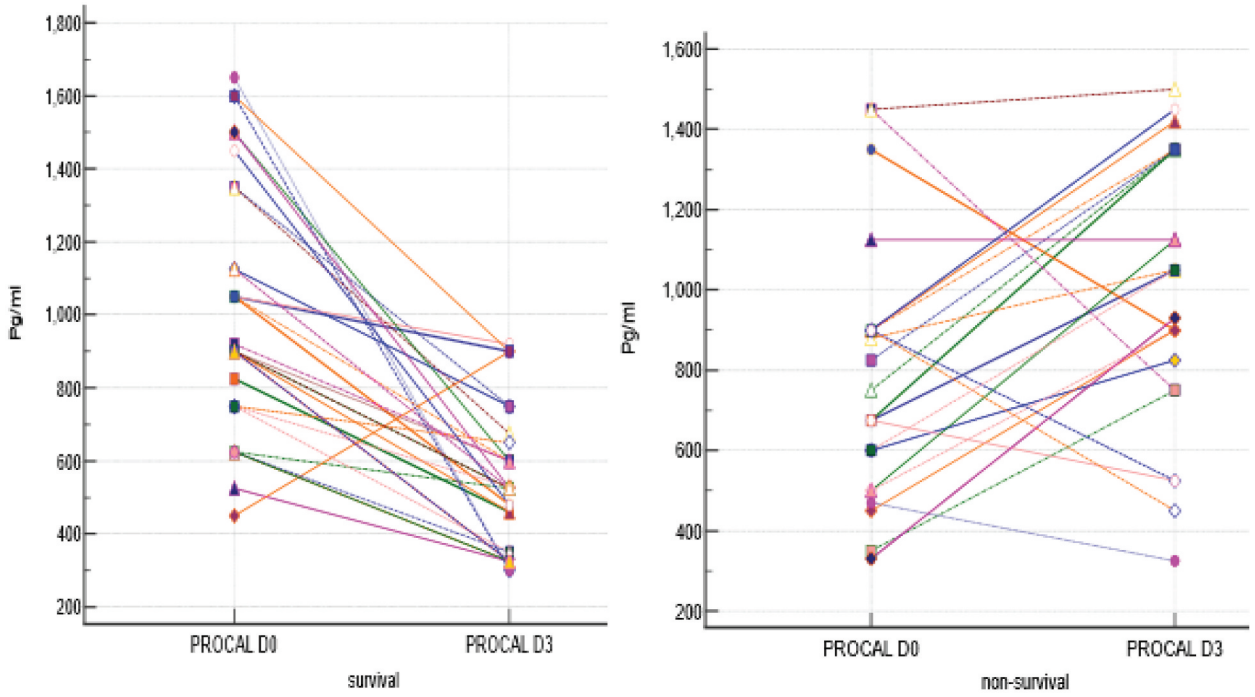

Figure 2. Serial measurement of plasma levels of PCT (pg/ml) between sepsis survival and non-survival.
Abbreviations: procal: procalcitonin

with HBP at day 3 [r = 0.641, *p*= <0.0001] and PROCAL at day 3 [r = 0.714, *p*= <0.0001]. Finally, it showed that HBP at day 3 had statistically significant positive correlation with PROCAL at day 3 [r = 0.792, *p*= <0.0001] (as shown in Table 4).

-The current study detected that The AU-ROC curve analysis for HBP at day 0 was 0.323 (*p* = 0.025). At cut-off value of > 15.5, sensitivity was 29.2%, specificity was 64.5%, while the AU-ROC curve analysis for HBP at day 3 was 0.831 (*p* = 0.000). At cut-off value of > 9.5, sensitivity was 83.33%, specificity was 77.42% (as shown in Table 5 and Figure 3).

4. Discussion

Using the Third International Consensus Conference's criteria of septic shock and sepsis, 55 adult patients hospitalized to the intensive care unit at Ain Shams

Table 3. Correlations of the different variables at day 0 in the studied patients (total 55 patients).

Variables		SOFA (Day 0)	CRP (Day 0)	LACTATE (Day 0)	WBCs (Day 0)	HBP (Day 0)
CRP (mg/L)	**r**	0.126				
(Day 0)	**p**	0.360				
LACTATE (mmol/L)	**r**	**0.486**	0.024			
(Day 0)	**p**	**0.0002**	0.865			
WBCs ($X10^3$) (cells/mm^3)	**r**	**0.426**	0.138	**0.399**		
(Day 0)	**p**	**0.0012**	0.316	**0.003**		
HBP (ng/ml)	**r**	0.053	0.149	0.100	0.060	
(Day 0)	**p**	0.702	0.277	0.468	0.666	
PROCAL (pg/ml)	**r**	0.116	0.125	0.163	**0.295**	**0.588**
(Day 0)	**p**	0.399	0.362	0.235	**0.029**	**<0.0001**

r: Pearson's correlation coefficient p: p-value
CRP: C-reactive protein; HBP: heparin binding protein; SOFA: sequential organ failure assessment; WBCs: white blood cells.
Bold values indicate statistically significant results.

Table 4. Correlations of the different variables at day 3 in the studied patients (total 55 patients).

Variables		SOFA (Day 3)	CRP (Day 3)	LACTATE (Day 3)	WBCs (Day 3)	HBP (Day 3)
CRP (mg/L)	**r**	**0.766**				
(Day 3)	**p**	**<0.0001**				
LACTATE (mmol/L)	**r**	**0.778**	**0.599**			
(Day 3)	**p**	**<0.0001**	**<0.0001**			
WBCs ($X10^3$) (cells/mm^3)	**r**	**0.751**	**0.712**	**0.611**		
(Day 3)	**p**	**<0.0001**	**<0.0001**	**<0.0001**		
HBP (ng/ml)	**r**	**0.628**	**0.700**	**0.364**	**0.641**	
(Day 3)	**p**	**<0.0001**	**<0.0001**	**0.006**	**<0.0001**	
PROCAL (pg/ml)	**r**	**0.680**	**0.675**	**0.420**	**0.714**	**0.792**
(Day 3)	**p**	**<0.0001**	**<0.0001**	**0.001**	**<0.0001**	**<0.0001**

r: Pearson's correlation coefficient p: p-value
CRP: C-reactive protein; HBP: heparin binding protein; SOFA: sequential organ failure assessment; WBCs: white blood cells.
Bold values indicate statistically significant results.

Table 5. Receiver operating characteristics (ROC) curve analysis of the studied markers for mortality prediction in the studied patients (total 55 patients).

Variables	Optimal cut off	AUC	p-value	Sensitivity	Specificity
SOFA (Day 0)	>7	0.566	0.406	50%	67.74%
SOFA (Day 3)	>7	0.940	**<0.0001**	83.33%	96.77%
CRP (Day 0) (mg/L)	>171.5	0.406	0.235	58.3%	54.2%
CRP (Day 3) (mg/L)	>119	0.836	**<0.0001**	83.33%	80.65%
LACTATE (Day 0) (mmol/L)	>4.1	0.347	0.054	29.2%	77.4%
LACTATE (Day 3) (mmol/L)	>2.6	0.858	**<0.0001**	70.83%	87.1%
WBCs (Day 0) ($X10^3$) **(cells/mm^3)**	>18.5	0.464	0.647	54.2%	48.4%
WBCs (Day 3) ($X10^3$) (cells/mm^3)	>17	0.860	**<0.0001**	75%	77.42%
HBP (Day 0) (ng/ml)	>15.5	0.323	**0.025**	29.2%	64.5%
HBP (Day 3) (ng/ml)	>9.5	0.831	**<0.0001**	83.33%	77.42%
PROCAL (Day 0) (pg/ml)	>650	0.288	**0.008**	62.5%	19.4%
PROCAL (Day 3) (pg/ml)	>675	0.864	**<0.0001**	83.33%	80.65%

AUC: Area under curve; CI: Confidence interval; CRP: C-reactive protein; HBP: heparin binding protein; NPV: negative predictive value; PPV: positive predictive value; SOFA: sequential organ failure assessment; WBCs: white blood cells.
Bold values indicate statistically significant results.

University Hospitals in Cairo, Egypt, participated in this prospective observational research.

As regard demographic, patients with nonsurvivor had statistically significant lower proportion of hypertension [Percentage = 33.3% versus (vs.) 61.3%, p-value (p) = 0.04].

Concerning clinical and laboratory parameters, SOFA, CRP, lactate, WBCs at day 0 were comparable in both groups (survivor and non- survival patients). Despite PROCAL and HBP were higher in survival than non-survival patients at day 0 (1010.32 ± 341.72 vs 770.21 ± 327.97, p = 0.0112) (16.73 ± 7.19 vs 13.19 ± 7.26, p = 0.077) respectively, It was significantly lower in survival than non-survival at day 3 (542.09 ± 191.98 vs 995.00 ± 333.74, p =<0.0001) (9.03 ± 2.92 vs 16.67 ± 7.55, p =<0.0001) respectively. Additionally, non-survivor has significant higher values in day 3 for SOFA, CRP, WBCs, lactate, with p =<0.0001.

In the same line to our results, a prospective observational study done by ***Dou et al.*** [6]. Patients exhibiting septic shock or sepsis accounted for 245 admissions. Non-survivors had greater median plasma HBP levels than survivors in this research. Upon admission, (235 vs 117 (ng/mL), $p < 0.001$), while for a period

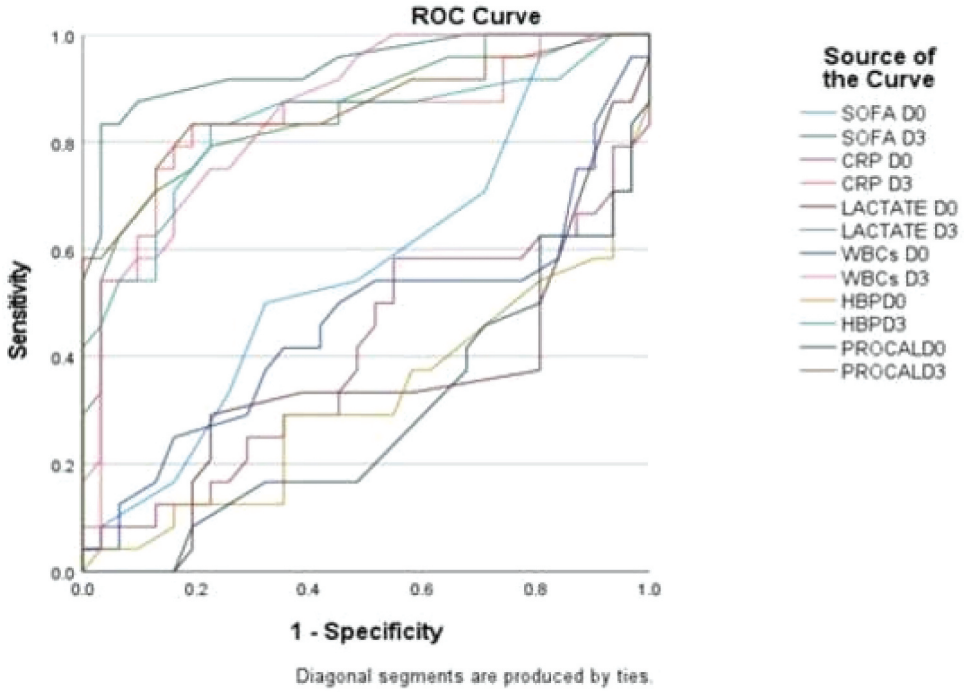

Figure 3. Receiver operating characteristics (ROC) curve analysis of the studied markers for mortality prediction in the studied patients (total 55 patients).

of 24 hours (173 vs 85 (ng/mL), $p < 0.001$) and 48 hours was (196 vs 48 (ng/mL), $p < 0.001$).

While, a single-center retrospective study included a total 349 septic patients (based on Sepsis 3.0 definition) and 250 (71.6%) of them survived more than 28 days. Comparison between survivor and non-survivor showed that the median CRP of survivor group was 61.7 (35.68–84.65) while of non-survivor was 149 (84.2–234.00) ($p < 0.001$). Also the median PROCAL of survivor group was 2.70 (0.86–6.31) and of non-survivor was 28.87 (8.37–99.40) ($p < 0.001$). While the median WBCs of survivor group was 12.82 (9.56–17.32) and of non-survivor was 14.33 (8.29–20.45) with no significant difference [7]. Additionally, a retrospective cohort study done by Zhang et al. [8] that recorded 150 patients with sepsis or septic shock and 30 patients without sepsis as control. When the median PCT and SOFA scores were compared between the non-mortality and mortality groups at the time of admission, the PCT and SOFA scores in the mortality group were considerably higher than in the surviving group. In the mortality group, the PCT level was 5.38 ng/mL, while it was 3.08 ng/mL in the group that survived ($p < 0.001$). Lastly, the mortality group's SOFA score was substantially greater than the group that survived ($p < 0.001$).

Conversely, ***Zhou et al.*** [9] based on their survival after 28 days, 93 sepsis patients (56 without shock and 37 with shock) were divided into two groups based on their survival after 28 days: the 28-d survival group ($n = 56$) and the 28-d non-survival group ($n = 37$). The plasma levels of HBP, PROCAL, and CRP did not significantly differ between the sepsis patients who survived and those who did not. However, the 28-day non-survival group's SOFA Score and lactate level were significantly higher than those of the survival group (6.0 vs. 7.0 and 1.41 mmol/L vs. 4.72 mmol/L, respectively).

In the current study, paired data are done for both groups (survival patients and non-survival patients) between D0 and D3 showed that our main HBP has significantly decreased for survival patients with paired difference -7.69 ± 6.78 with p value < 0.0001, as well as our study showed that SOFA Score, CRP value, lactate level, WBCs count, and PROCAL value were found to have decreased for survival patients with significant paired difference with p value < 0.0001.

According to *Xue and Yu* [10], HBP may also be a promising prognostic indicator for patients with septic shock who die within 28 days. At 72 hours after admission, the HBP levels of the non-survivor group were significantly higher than those of the survivor group. ***Dou et al.*** [6] showed that patients with a 48-hour HBP decrease of more than 50% had a greater than 90% chance of survival, while patients with a 48-hour HBP decrease of less than 4% had a nearly 90% mortality rate. Furthermore, ***Zhou et al.*** [9] discovered that patients who experienced septic shock and death had greater HBP levels.

As HBP increase vascular permeability, so that facilitating neutrophil extravasation and vascular leak [11]. HBP showed a sort of dynamic pattern of change in value rather than the value of the test. As HBP increase vascular permeability, so that facilitating neutrophil extravasation and vascular leak.

Correlations of the different variables at day 0 and 3 in the studied patients, it showed that at day 0, SOFA had statistically positive correlation with lactate and WBCs, additionally showed that HBP had statistically strong positive correlation with PROCAL. While at day 3.HBP showed positive correlation with Lactate, strong positive correlation SOFA, WBCs, CRP. Interestingly, HBP had a strong positive correlation with PROCAL. In line to our results, According to ***Elsayed et al.*** [5], SOFA, serum lactate, and total leucocytic count (all assessed within the first 72 hours of hospitalization) were found to be positively and statistically significantly correlated with heparin binding protein (HBP). Also, Upon admission, a correlation between the total leucocytic count and heparin binding protein was also demonstrated. [9]. **ACER et al**. [12] A prospective cross-sectional cohort research was carried out on 134 patients treated in the emergency department (ED) after being diagnosed with severe COVID-19 pneumonia. There is a moderate connection between HBP and albumin and CRP, as shown by the results of the correlation research ($r = -0.328$ and 0.278, respectively; p 0.001 for all of the correlations). Both HBP and D-dimer, as well as PROCAL and lactate, were demonstrated to have substantial connections in a study that was conducted in 2022.

However, ***Zanfaly et al.*** [13] discovered a positive association between HBP and serum lactate, but they did not find a causal relationship between the two. Researchers did identify a correlation between HBP and lactate levels ($r = 0.26$, $p = 0.02$ and $r = 0.49$, P0.001) in all septic patients, but not in healthy controls. However, neither the PROCAL nor the TLC count were significantly correlated with HBP. ***Linder et al.*** [14] observed no association between HBP and either PROCAL or TLC count. In spite of positive association between HPB and lactate, this was the case. Two previous groups of researchers have drawn opposite conclusions from these findings.

Receiver operating characteristics (ROC) curve of SOFA, CRP, lactate, WBCs, PROCAL and HBP, the current study It detected that at a cut off >9.5 ng/mL, HBP at day 3 had a specificity of 77.42%, With a sensitivity of 83.33%, while at a cut off >15.5 ng/mL, HBP at day 0 had a sensitivity of 29.2% with a specificity of 64.5%.

On similar to our results, Elsayed et al. [5] stated that the optimal HBP cutoff for diagnosing septic shock at 72 hours was ≥8.852 ng/mL with area under curve 0.737 with sensitivity 87.5%, specificity 65.5%, positive predictive value (PPV) 73.7%, negative predictive value (NPV) 82.6%, accuracy 77.1% ($p < 0.05$), but on the other hand, ***Tydén et al.*** [15] discovered that the optimal HBP cutoff for diagnosing septic shock at admission was ≥15.0 ng/mL with sensitivity 87.1%, specificity 95.1%. Additionally, ***Zhou et al.*** [9] discovered that the ideal cut-off value was HBP ≥28.1 ng/mL and that the AUC of HBP was 0.893. They also reported 84.9% sensitivity, 78.3% specificity, 94.0% positive predictive value, and 78.3% negative predictive value for diagnosing septic shock.

In contrast, ***Dou et al.*** [6] found that at a cutoff of – 57.07%, the HBP change at 48 hours had a peak sensitivity of 0.92 with a specificity of 0.45, and at a cutoff of – 17.14%, the HBP change had a maximal specificity of 0.91 with a sensitivity of 0.58. HBP was also proven to be an efficient predictor of disease progression to organ dysfunction (AUC = 0.80) in a multicenter research conducted in 2015 with 759 patients [4]. Ultimately, the current investigation found that, with an AUC of 0.831 ($p = 0.000$), HBP at day 3 was a very effective marker in identifying patients who advance to septic shock with a high probability of fatality. The sensitivity was 83.33% and the specificity was 77.42% at the cut-off value of >9.5 ng/mL.

When compared to other biomarkers, ***Elsayed et al.*** [5] found that HBP was more accurate at identifying patients who developed septic shock. The best cutoff for identifying patients who progressed was ≥ 13.35, with an area under curve of 0.822, sensitivity of 90.3%, and specificity of 62.9%. This is consistent with the findings of ***Kahn et al.*** [16], who discovered that HBP had an AUC of 0.82 and a sensitivity of 64%, respectively, which was more significant than that of PROCAL, lactate, and TLC, which had AUCs of 0.76 and 36%, 0.53 and 53%, and 0.67 and 62%, respectively. ***Zhou et al.*** [9] also discovered that HBP outperformed other markers, with the PROCAL level coming in second.

In comparison to other biomarkers of sepsis (TLC, CRP, PROCAL, lactate, and IL6), ***Linder et al.*** [14] study on the prediction of HBP in septic shock found that HBP with a cutoff value of ≥ 15 had an AUC of 0.85 with a sensitivity of 87.1% and a specificity of 95.1%, which was significantly higher than other indicators.

Numerous factors have been suggested as a reason for this heterogeneity, including the different study populations (number, comorbidities, primary disease and severity), drug administration regimens to control sepsis, and methods to measure outcomes. These factors explain the contrasts and similarities between our research and the studies mentioned earlier.

At the end, we concluded from the study that HPB showed a strong prognostic marker for mortality in ICU septic patients. As HBP trend to decrease is more efficient to predict mortality than the value of the marker itself. Also, HBP has a high AUC, sensitivity, specificity to predict mortality specially in day 3.

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Ethics approval and informed consent

Approval was obtained by the Institutional Review Board with code number: FMASU MD 159/2021, Board Name: research ethical committee, Board Affiliation: faculty of medicine Ain Shams university, and registered at ClinicalTrials.gov (ID;NCT05610020).

Previous presentation in conferences

Paper has not previously presented in conference.

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