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Original Research Article

Evaluation of heparin binding protein as a prognostic biomarker for diagnosis of sepsis at tertiary care hospital, North India

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ABSTRACT

Background: Sepsis is a critical condition characterized by systemic inflammation in response to infection, often leading to organ dysfunction and mortality. Heparin-binding protein (HBP) has emerged as a potential biomarker for early sepsis detection due to its rapid release and association with inflammatory processes. This study aimed to evaluate HBP as a prognostic biomarker for diagnosing sepsis, assessing its correlation with demographic characteristics, infection status, organ dysfunction, and biochemical parameters.
Methods: A prospective analytical study was conducted at G.S.V.M. Medical College, Kanpur, from December 2022 to May 2024, involving 113 patients over 18 years old suspected of sepsis. Clinical data, including demographics, infection status, organ dysfunction, and HBP levels, were collected and analyzed using statistical methods.
Results: The study cohort exhibited a mean age of 53.2±19.3 years, with balanced gender representation (49.6% male, 50.4% female) and varied infection statuses (47.8% confirmed infections, 17.7% probable, and 9.7% viral). Organ dysfunction prevalence increased from 30.1% on admission to 43.4% within 72 hours. HBP levels decreased significantly from baseline (11.28 ng/ml) to 72 hours (5.68 ng/ml), showing potential for monitoring disease progression. Significant differences in baseline HBP levels among patient groups were observed ($p \leq 0.001$).
Conclusions: The study concludes that HBP is a promising biomarker for distinguishing infection statuses, aiding in sepsis diagnosis, with significant differences observed in HBP levels across diagnostic categories, enhancing early detection and targeted treatment.

Keywords: Sepsis, HBP, Biomarker, Organ dysfunction, Infection status, Prognosis

INTRODUCTION

Sepsis is a life-threatening condition that arises when the body's response to infection causes widespread inflammation, leading to tissue damage, organ failure, and potentially death. According to the Sepsis Alliance, it is a complex syndrome resulting from an uncontrolled inflammatory response to infection, which can originate from bacteria, viruses, fungi, or parasites.[1]

In India, the prevalence of sepsis is particularly concerning due to the high burden of infectious diseases and limited healthcare resources. A study published in the Journal of Global Health in 2019 estimated that India accounts for nearly one-third of the global sepsis cases, with an incidence rate of 17.8 million cases annually.[2] Sepsis is a major contributor to mortality, with an estimated five million deaths worldwide each year.[3] It is crucial to recognize and treat sepsis early to improve outcomes.[4]

The pathophysiology of sepsis involves a complex interplay of the host immune response and the invading pathogens. Initially, the immune system detects the pathogen and activates a cascade of inflammatory responses to eliminate the infection. However, in sepsis, this response becomes dysregulated, leading to widespread inflammation, endothelial dysfunction, and increased vascular permeability.[5] This systemic inflammation results

in impaired tissue perfusion, cellular injury, and organ dysfunction. Key mediators such as cytokines, chemokines, and reactive oxygen species play crucial roles in this process, exacerbating the severity of the condition.[6]

Common symptoms of sepsis include fever or hypothermia, tachycardia (heart rate >90 beats per minute), and tachypnoea (respiratory rate >20 breaths per minute), all indicative of the body's effort to fight the infection.[5] In severe sepsis, organ dysfunction becomes more pronounced, marked by signs such as acute respiratory distress syndrome (ARDS), significant jaundice, and severe lactic acidosis. The systemic inflammation causes widespread endothelial damage and capillary leakage, leading to multiple organ failure.[7] Approximately 20-30% of severe sepsis patients do not show typical symptoms of organ dysfunction at admission but progress to severe sepsis within 24 hours.

Sepsis is diagnosed through a combination of clinical evaluation and laboratory tests. Clinicians assess signs of infection, systemic inflammation, and organ dysfunction. Common tests include blood cultures to identify the causative pathogen, complete blood count (CBC) to check white blood cell count, lactate levels to assess tissue hypoxia, and markers like C-reactive protein (CRP) and procalcitonin to detect inflammation.[8]

Identifying reliable biomarkers for sepsis has been challenging, but multiomics offers hope for a personalized approach.[9] Heparin-binding protein (HBP), also known as azurocidin or cationic antimicrobial protein of 37 KDa (CAP37), is a promising candidate. Stored in neutrophil granules, HBP is rapidly released in response to bacterial structures and inflammatory stimuli, making it one of the earliest detectable markers of infection. HBP functions as a chemoattractant, particularly for monocytes, and induces vascular leakage and edema contributing to hypotension and organ dysfunction.[10] These attributes make HBP a critical biomarker for early diagnosis, severity assessment, and prognostication in sepsis management. The present study was designed to evaluate HBP as a diagnostic parameter for the diagnosis of sepsis.

Aim and objectives

Aim of the study was to evaluate the heparin binding protein as a prognostic biomarker for diagnosis of sepsis.

Objectives of the study were to evaluate: demographic characteristics of enrolled patients, plasma levels of HBP as a prognostic biomarker for infection induced organ dysfunction, and correlation of HBP with age group and sex of patients.

METHODS

This prospective and analytical study was conducted in the Department of Medicine at G.S.V.M. Medical College, Kanpur, from December 2023 to May 2024. The study included 113 patients over 18 years old, suspected of sepsis or septic shock, presenting to the emergency department. Inclusion criteria were respiratory rate >25 breaths/min, heart rate >120 beats/min, altered mental status, systolic blood pressure <100 mm Hg, and oxygen saturation <90% without oxygen or <93% with oxygen. Exclusion criteria included patients under 18, those not consenting, prior antibiotic treatment within 24 hours before admission, neutropenia, primary coagulation abnormalities, haematological malignancy, immune-suppressive therapy, chronic infections like tuberculosis, and those on haemodialysis. Data were collected using a predetermined proforma after obtaining informed consent. Data were entered and analysed using Microsoft excel and statistical package for the social sciences (SPSS) version 20.0. Continuous variables were expressed as means and standard deviation or median and interquartile range, while categorical variables were expressed as percentages. Statistical analyses included Chi-square tests for categorical variables, one-way analysis of variance (ANOVA) for parametric continuous variables, and Pearson correlation for continuous variables, with a significance threshold of $p<0.05$.

RESULTS

The study analysed the age, sex, clinical complaints, vital signs, biochemical and haematological parameters, and HBP levels across different patient groups to determine significant associations with infection diagnosis.

The study's age distribution is as follows: 18-30 years (21.2%), 31-40 years (9.7%), 41-50 years (10.6%), 51-60 years (19.5%), 61-70 years (20.4%), and over 70 years (18.6%). The mean age is 53.2±19.3 years, with the highest representation in the 18-30 and 61-70 age groups. The mean age of the study cases was 53.2±19.3 years (Table 1).

Table 1: Distribution of cases according to age.

Age (years)	No.	%
18-30	24	21.2
31-40	11	9.7
41-50	12	10.6
51-60	22	19.5
61-70	23	20.4
>70	21	18.6
Mean±SD	53.2±19.3	

The distribution of cases by sex is nearly equal, with 56 males (49.6%) and 57 females (50.4%). This balance ensures the study findings are representative of both genders.

On admission, 69.9% (79 individuals) did not have OD, while 30.1% (34 individuals) did. Within 72 hours, those without OD decreased to 56.6% (64 individuals), and those

with OD increased to 43.4% (49 individuals), indicating a rise in OD occurrence within the first 72 hours (Table 2).

Table 2: Cases are distributed according to OD status.

OD	No.	%
On admission		
No	79	69.9
Yes	34	30.1
In 72 hours		
No	64	56.6
Yes	49	43.4

The infection status distribution showed 54 confirmed infections (47.8%), 20 probable infections (17.7%), 11 viral infections (9.7%), 4 probable but unconfirmed infections (3.5%), and 24 cases with no infection detected (21.2%) (Table 3).

Table 3: Distribution of cases according to groups.

Group	No.	%
Infection	54	47.8
Probable infection	20	17.7
Virus	11	9.7
Probable not infection	4	3.5
No infection	24	21.2

The study examined age distribution across different infection groups. In the infection group, 46.3% were aged 51-70 years, with a mean age of 53 years (SD±18.3). The Probable Infection group had 30% aged 51-60, 25% over 70, and a mean age of 55.1 years (SD±18.9). The virus group had 36.4% aged 61-70, no cases over 70, and a mean age of 52.3 years (SD±14.0). The probable not infection group had 50% over 70 and a mean age of 62 years (SD±26.0). The no infection group had 29.2% aged 18-30 and a mean age of 51.1 years (SD±23.5) (Table 4).

Males were predominant in the virus (63.6%) and no infection (62.5%) groups, whereas females were more prevalent in the infection (57.4%) and probable infection (55.0%) groups (Table 5).

The study found no significant association between patient complaints (altered sensorium, fever, abdominal pain, nausea/vomiting, and cough/sputum) and infection status, except for shortness of breath, which was significantly associated with infection (Chi-square=12.24, p value=0.016). Other complaints had p values above 0.3, indicating no significant associations (Table 6).

The study analysed vital signs across different infection groups, finding no significant differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), respiratory rate (RR), and temperature. Oxygen saturation (SpO_2) showed borderline significance (p=0.061). Overall, vital signs did not vary significantly among the groups based on ANOVA results (Table 7).

Biochemical and hematological parameters, including random blood sugar (p=0.142), SOFA score (p=0.531), pH (p=0.680), PaO_2/FiO_2 ratio (p=0.073), hemoglobin (p=0.226), total leukocyte count (p=0.161), platelet count (p=0.286), serum sodium (p=0.870), serum potassium (p=0.201), serum urea (p=0.722), serum creatinine (p=0.935), serum bilirubin (p=0.373), serum protein (p=0.414), CRP (p=0.666), and procalcitonin (p=0.766) did not differ significantly among the groups, except for serum albumin (p=0.017), which showed a significant difference (Table 8).

The levels of HBP were measured at baseline and at 72 hours. At baseline, the mean HBP level was 11.28 ng/ml with a standard deviation of 5.57. After 72 hours, the mean HBP level decreased to 5.68 ng/ml with a standard deviation of 3.39, indicating a significant reduction in HBP levels over time (Table 9).

ANOVA analysis shows that HBP levels significantly differ across diagnostic categories both at baseline and 72 hours. At baseline, HBP levels (mean±SD) were: infection 11.21±5.51, probable infection 7.37±4.41, virus 6.63±5.22, probable not infection 4.73±2.15, and no infection 4.31±3.72 (F=7.58, p<0.001). At 72 hours, levels were: infection 5.55±3.05, probable infection 4.77±2.60, virus 4.18±2.95, probable not infection 3.67±1.43, and no infection 2.16±1.14 (F=3.67, p=0.008). This indicates HBP as a potential biomarker for distinguishing infection statuses (Table 10).

Table 4: Distribution of age according to groups.

Age (years)	Infection		Probable infection		Virus		Probable not infection		No infection	
	N	%	N	%	N	%	N	%	N	%
18-30	11	20.4	4	20.0	1	9.1	1	25.0	7	29.2
31-40	6	11.1	1	5.0	2	18.2	0	0.0	2	8.3
41-50	4	7.4	3	15.0	2	18.2	0	0.0	3	12.5
51-60	10	18.5	6	30.0	2	18.2	1	25.0	3	12.5
61-70	15	27.8	1	5.0	4	36.4	0	0.0	3	12.5
>70	8	14.8	5	25.0	0	0.0	2	50.0	6	25.0
Mean±SD	53.0±18.3		55.1±18.9		52.3±14.0		62.0±26.0		51.1±23.5	

Table 5: Distribution of sex according to groups.

Sex	Infection		Probable infection		Virus		Probable not infection		No infection	
	N	%	N	%	N	%	N	%	N	%
Male	23	42.6	9	45.0	7	63.6	2	50.0	15	62.5
Female	31	57.4	11	55.0	4	36.4	2	50.0	9	37.5

Table 6: Association of complains with patient diagnosis.

Complaints	Infection		Probable infection		Virus		Probable not infection		No infection		Significance
	N	%	N	%	N	%	N	%	N	%	
Altered sensorium	10	18.5	6	30.0	4	36.4	1	25.0	7	29.2	Chi sq=2.47, p=0.650
Fever	24	44.4	8	40.0	8	72.7	1	25.0	13	54.2	Chi sq=4.69, p=0.320
Shortness of breath	31	57.4	3	15.0	6	54.5	1	25.0	9	37.5	Chi sq=12.24, p=0.016
Abdominal pain	3	5.6	4	20.0	2	18.2	1	25.0	4	16.7	Chi sq=4.72, p=0.317
Nausea/vomiting	5	9.3	2	10.0	0	0.0	0	0.0	3	12.5	Chi sq=1.90, p=0.755
Cough/sputum	10	18.5	3	15.0	0	0.0	1	25.0	4	16.7	Chi sq=2.62, p=0.623

Table 7: Association of vitals with patient diagnosis.

Vitals	Infection		Probable infection		Virus		Probable not infection		No infection		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-value	P value
SBP	89.44	21.42	98.20	13.33	87.09	12.57	103.50	18.14	88.52	28.92	1.15	0.335
DBP	58.72	10.43	62.22	10.03	57.60	6.24	63.50	4.73	59.60	13.13	0.59	0.667
PR	119.8	13.6	112.1	16.9	120.4	8.6	110.0	5.9	119.0	20.6	1.28	0.283
RR	25.2	4.2	24.2	5.6	24.1	2.9	23.5	3.8	24.8	5.5	0.36	0.839
SpO_2	86.1	7.7	90.6	5.2	86.7	10.0	92.8	2.2	83.8	11.5	2.32	0.061
Temp	100.3	1.7	99.8	1.7	99.9	2.0	100.3	1.4	99.3	2.0	1.19	0.318

Table 8: Association of biochemical and hematological parameters with patient diagnosis.

Biochemical and hematological parameters	Infection		Probable infection		Virus		Probable not infection		No infection		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-value	P value
RBS	185.6	105.9	145.9	95.3	216.0	117.5	237.8	197.9	151.1	52.3	1.76	0.142
SOFA	7.9	3.0	6.9	3.2	8.5	2.2	6.0	2.4	7.9	4.3	0.80	0.531
PH	7.303	0.120	7.327	0.086	7.346	0.073	7.363	0.059	7.317	0.139	0.58	0.680
PaO_2/FiO_2	212.85	55.88	204.70	45.01	182.05	63.69	297.25	88.01	211.82	97.73	2.21	0.073
Hb	10.80	2.45	10.41	2.88	9.83	2.66	11.75	0.90	11.73	2.56	1.44	0.226
TLC	21632.4	7991.9	22963.0	12028.0	17745.5	8400.4	27825.0	14988.7	18899.2	5281.9	1.67	0.161
Platelet	1.60	1.15	9.32	33.13	1.62	1.02	1.33	0.62	1.54	1.04	1.27	0.286
S. Na	137.9	6.8	137.8	6.1	139.6	7.7	134.9	19.0	137.9	6.3	0.31	0.870
S. K	4.24	0.80	4.13	0.73	3.74	0.65	3.94	1.65	3.89	0.65	1.52	0.201
S. Urea	88.8	60.0	68.6	30.0	81.7	83.4	90.0	43.4	80.9	43.4	0.52	0.722
S. creatinine	2.65	3.39	2.20	1.25	2.21	2.00	2.30	1.27	2.87	3.14	0.20	0.935
S. billirubin	1.55	2.13	1.11	0.55	2.78	4.88	1.38	1.14	1.46	1.23	1.07	0.373
S. protein	5.87	0.82	5.97	1.01	6.29	1.17	5.48	0.88	6.07	0.53	0.99	0.414
S. albumin	3.25	0.48	3.05	0.61	2.72	0.42	2.95	0.70	3.27	0.49	3.17	0.017
CRP	75.42	44.82	69.79	57.08	47.84	58.24	22.99	14.96	12.89	8.12	0.60	0.666
Procalcitonin	12.290	27.954	7.571	17.001	5.378	3.494	2.726	3.735	1.621	2.208	0.46	0.766

Table 9: Descriptive summary of HBP level.

Heparin-binding protein level	Mean	SD
Baseline	11.28	5.57
At 72 hours	5.68	3.39

Table 10: Association of HBP level with patient diagnosis.

Heparin-binding protein (HPB) level	Infection		Probable infection		Virus		Probable not infection		No infection		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F-value	P value
Baseline	11.21	5.51	7.37	4.41	6.63	5.22	4.73	2.15	4.31	3.72	7.58	<0.001
At 72 hours	5.55	3.05	4.77	2.60	4.18	2.95	3.67	1.43	2.16	1.14	3.67	0.008

DISCUSSION

The present study entitled "Heparin binding protein as a prognostic biomarker for diagnosis of sepsis" was carried out in, KPS Post Graduate Institute of Medicine, G.S.V.M. Medical College, Kanpur from December 2022 to May 2024.

Parameters of study population

Age and sex of patients and aetiology of sepsis

Kahn et al studied 718 emergency department sepsis patients, with 194 males and 524 females, all over 18 years old.[11] In a subset of 113 patients, the average age was 53.2±19.3 years. Age distribution was as follows: 20.4% between 61-70 years, 18.6% over 70 years, 21.2% between 18-30 years, 9.7% between 31-40 years, 10.6% between 41-50 years, and 19.5% between 51-60 years. Gender distribution was nearly equal, with 49.6% males and 50.4% females.

Chief complaint related to sepsis

According to Zuo et al, there were 326 sepsis patients in total.[12] Fever was the most prevalent complaint, with 54 reports—or 47.8% of the total—being made. Breathlessness, which afflicted 50 people, or 44.2% of the participants, came next. Cough and sputum were recorded by 18 people (15.9%), and altered sensorium was observed in 28 instances (24.8%). Less often reported symptoms were nausea/vomiting (10.8%) and abdominal discomfort (14.4%), respectively.

How sepsis cases are distributed according to the state of infection

Kahn et al identified 524 sepsis patients: 18.3% confirmed infections, 16.03% probable, 7.44% viral, 45% no infection, and 13.16% likely but unconfirmed.[11] Our study found 47.8% confirmed, 17.7% probable, 9.7% viral, 3.5% likely but unconfirmed, and 21.2% no infection.

Association between the patient's infection condition and OD

Our investigation found no significant relationship between organ dysfunction (OD) and patient diagnosis at admission or within 72 hours. At admission, 25.9% had infections, 25% probable infections, 45.5% viral, 25% likely not infected, and 37.5% no infection (Chi-square=2.60, p=0.627). Within 72 hours, 38.9% had infections, 40% probable infections, 45.5% viral, 62.5% no infection (Chi-square=7.19, p=0.126). Both comparisons showed no significant correlation.

HBP level: a descriptive summary and its association with patient diagnosis

Our investigation assessed HBP levels at baseline and after 72 hours. The average baseline HBP level amongst infection group was 11.21 ng/ml (SD=5.51), dropping to 5.55 ng/ml (SD=3.05) after 72 hours. Baseline HBP levels varied significantly among patient groups (F=7.58, p≤0.01): 4.73 ng/ml (not infected), 6.63 ng/ml (virus), 11.21 ng/ml (infection), 7.37 ng/ml (probable infection), and 4.31 ng/ml (no infection). After 72 hours, HBP levels decreased in all groups with no significant differences (F=3.67, p=0.008): 4.18 ng/ml (virus), 3.67 ng/ml (probable not infected), 5.55 ng/ml (infection), 4.77 ng/ml (probable infection), and 2.16 ng/ml (no infection).

In a study by Zuo et al, infection, sepsis, septic shock, and control groups had median (IQR) HBP values of 18.0 (9.9–32.1), 24.0 (14.1–56.4), 45.7 (24.8–107.9), and 69.0 (33.8–150.9) ng/ml, respectively (p<0.001).[12] Effective distinctions between patients with and without infection or sepsis might be made with HBP.

Limitations

This study has several limitations that should be considered when interpreting the results. Firstly, it was conducted at a single tertiary care hospital, which may limit the generalizability of the findings to other settings, particularly in rural or low-resource regions. Secondly, the sample size of 113 patients may not be large enough to

detect subtle differences in HBP levels across certain subgroups or rare infection types. Additionally, the study focused on adult patients, limiting its applicability to pediatric populations. Furthermore, while HBP levels showed significant differences across diagnostic categories, other confounding factors, such as comorbidities and treatment interventions, were not fully controlled for. Finally, the study did not assess the long-term clinical outcomes, such as survival rates, which could provide further insights into the prognostic value of HBP in sepsis management.

CONCLUSION

In our study, we found that among 113 patients, there is balanced gender distribution (49.6% male, 50.4% female) and a mean age of 53.2±19.3 years, exhibited varying infection statuses: 47.8% confirmed infections, 17.7% probable, and 9.7% viral. Organ dysfunction prevalence increased from 30.1% on admission to 43.4% within 72 hours. Urine routine microscopy results indicated that a notable minority exhibited abnormalities, aligning with infection status observations where confirmed infections were predominant. Patient complaints, except for shortness of breath, did not significantly correlate with infection status. Vital signs and most biochemical parameters did not differ significantly among infection groups, except for serum albumin levels. Notably, HBP levels decreased significantly from baseline (11.28 ng/ml) to 72 hours (5.68 ng/ml), though baseline levels varied significantly across groups ($p \leq 0.001$). Notably (HBP) levels were found significantly differ across diagnostic categories both at baseline and 72 hours. Specifically, the highest HBP levels were observed in confirmed infections, which decreased over 72 hours. HBP demonstrates potential as a prognostic biomarker for diagnosing sepsis. The significant reduction in HBP levels from baseline to 72 hours suggests its utility in monitoring disease progression. Thus, HBP levels could be utilized as a valuable tool in the early identification and prognosis of sepsis, facilitating timely and appropriate clinical interventions to improve patient outcomes.

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