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Original Research Article

Heparin-binding protein as a new biomarker for acute kidney injury related to sepsis

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ABSTRACT

Background: In emergency settings, physicians frequently encounter critically ill patients with acute kidney injury (AKI). This severe organ dysfunction leads to high morbidity and mortality, even post-discharge. To determine the association between Heparin-binding protein (HBP) and sepsis-associated AKI, facilitating early AKI prediction and intervention.
Methods: A cross-sectional prospective observational comparative study was conducted at K.P.S PG Institute of Medicine, Kanpur, from June 2023 to July 2024. Patients aged 18 years and older, suspected of sepsis, were enrolled and investigated for sepsis and AKI, along with serum heparin-binding protein.
Results: Baseline HBP levels were 5.222 (SD 3.046) in the non-AKI group and 11.979 (SD 5.972) in the AKI group. An optimum HBP cut-off >8.28 was determined. HBP levels progressively increased with AKI severity: Stage I (7.392), Stage II (10.842), and Stage III (19.623). The findings were statistically significant ($F=51.854$, $p<0.001$).
Conclusion: Sepsis-associated AKI patients had elevated HBP levels. The baseline cut-off of 8.28 aids in AKI detection.
Keywords: Sepsis, Acute kidney injury, Early detection, Heparin-binding protein

INTRODUCTION

Sepsis is a life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection.[1] One common consequence is acute kidney injury (AKI), defined as a sudden decline in glomerular filtration rate, impairing waste elimination.[2] Sepsis and AKI frequently co-occur in critical care settings, contributing to 25-75% of global AKI cases.[3] Their epidemiology is complicated by inconsistent definitions and healthcare disparities. The pathophysiology of sepsis-associated AKI (SA-AKI) involves inflammation, complement activation, mitochondrial dysfunction, and microcirculatory disturbance.[4] The prognosis is worse than for sepsis or AKI alone and correlates with longer ICU stays and higher mortality.[5] Timely identification is vital, yet traditional biomarkers like serum creatinine lag in detecting early renal insult.[6] Novel biomarkers like HBP, released from neutrophil granules, show promise for early AKI detection.[7] HBP increases endothelial permeability, promotes inflammation, and halts the cell cycle, contributing to AKI pathogenesis.[8]

Ischemic and inflammatory mechanisms underlie SA-AKI, with maintained or increased renal blood flow contradicting earlier ischemia models.[9] Innate immune activation via Toll-like receptors exacerbates kidney injury through cytokine release.[10,11]

Aim

To study and establish heparin-binding protein as a new biomarker for acute kidney injury related to sepsis.

Objective

To determine the association of plasma HBP level with the development of sepsis-induced AKI.

METHODS

Medicine, K.P.S. Post Graduate Institute of Medicine, GSVM Medical College, Kanpur, from June 2023 to July 2024. Patients presenting to the emergency department with clinical suspicion of sepsis (as per Sepsis 3.0 guidelines) were included.

Study method

The study was conducted at Post Graduate KPS Institute of Medicine GSVM Medical College Kanpur from December 2022 to May 2022. All the patients fitting inclusion and exclusion criteria attending medicine emergency were evaluated for the study. After written informed consent, history and thorough clinical examination were done and patients were then investigated for sepsis & AKI along with serum Heparin-binding protein was measured at baseline and after 72 hours of admission.

Patients were closely monitored for the development and worsening or improvement of AKI during the hospital stay. All other parameters were recorded according to the preset working proforma and monitored over the period of hospital stay.

Inclusion criteria

Patients aged 18 years and above who exhibited signs of sepsis, such as altered body temperature (>38°C or <36°C), heart rate >90 bpm, respiratory rate >20 breaths/min or PaCO2 <32 mmHg, and abnormal white blood cell count (>12,000/mm³ or <4,000/mm³ or >10% band forms), were enrolled after providing written informed consent.

Exclusion criteria

Patients were excluded if they were under 18 or over 70 years of age, had received antibiotics within 24 hours prior to admission, or had pre-existing conditions including chronic kidney disease, hematologic malignancy, chronic infections like tuberculosis, or immunodeficiency.

Individuals on immunosuppressive or heparin therapy within the previous 3 days, as well as those requiring immediate dialysis or who expired within 24 hours, were also excluded.

Statistical analysis

Data was entered into MS Excel and analyzed using SPSS v21.0. Continuous variables were expressed as mean±SD or median (IQR), and categorical data as percentages. Intergroup differences were assessed using t-tests, ANOVA, and Chi-square tests as applicable. Pearson correlation was used to explore continuous variable associations. A p value <0.05 was considered statistically significant.

RESULTS

A total of 100 patients who were more than 18 years of age were analyzed in this study.

The distribution of ages among the study cases showed that 18 individuals (18.0%) were aged 18 to 30 years, 11 individuals (11.0%) were aged 31 to 40 years, 12 individuals (12.0%) were aged 41 to 50 years, 19 individuals (19.0%) were aged 51 to 60 years, 20 individuals (20.0%) were aged 61 to 70 years, and another 20 individuals (20.0%) were over 70 years old. The mean age was 54.11 years with a standard deviation of 18.94 years.

Table 1: Distribution of cases according to age.

Age (in years)	No.	%
18-30	18	18.0
31-40	11	11.0
41-50	12	12.0
51-60	19	19.0
61-70	20	20.0
>70	20	20.0
Mean±SD	54.11±18.94 year	

Table 2: Distribution of cases according to sex.

Sex	No.	%
Male	53	53.0
Female	47	47.0

Table 3: Distribution of cases according to AKI.

AKI	No.	%
Not present	9	9.0
Present	91	91.0

The gender distribution of cases found that 53% were male (53 participants) and 47% were female (47 participants) (Table 2). The occurrence of acute kidney injury (AKI) among the cases shows that it was not present in 9% (9 individuals) of the cases, while a significant majority, 91% (91 individuals), experienced AKI.

In our study, various markers were analyzed in participants with and without acute kidney injury (AKI) using an unpaired t-test. It was found that Sequential Organ Failure Assessment (SOFA) score had a mean of 5.9 (SD=3.0) in those without AKI and 7.5 (SD=2.9) in those with AKI. The t value for SOFA was -1.6 with a p value of 0.114, indicating no significant difference statistically. For heparin-binding protein (HBP) at baseline (0 hours), the

mean was 5.222 (SD=3.046) in the non-AKI group and 11.979 (SD=5.972) in the AKI group.

The t value was 3.340 with a p value of 0.001, showing a statistically significant difference. HBP at 72 hours had a mean of 3.78 (SD=1.53) in those without AKI and 5.41 (SD=3.46) in those with AKI. The t value was -2.60 with a p value of 0.018, indicating a statistically significant difference. C-reactive protein (CRP) levels at 0 hours had a mean of 44.52 (SD=35.67) in the non-AKI group and 76.38 (SD=49.93) in the AKI group. The t value was -2.45 with a p value of 0.031, showing a statistically significant difference. C-reactive protein (CRP) levels at 72 hours had a mean of 38.21 (SD = 28.24) in the non-AKI group and 68.32 (SD=41.22) in the AKI group. The t value was -2.71 with a p value of 0.022, showing a statistically significant difference.

Procalcitonin levels had a mean of 1.287 (SD=1.053) in those without AKI and 11.137 (SD=25.053) in those with AKI. The t value was -3.717 with a p value of less than 0.001, indicating a highly significant difference. The study conducted ROC (Receiver Operating Characteristic) analysis to estimate the optimum cut-off values in detecting Acute Kidney Injury (AKI). The markers analyzed included HBP (Heparin-Binding Protein) at two time points (0 and 72 hours) (Table 5). For HBP at time 0, the area under the ROC curve (AUROC) was 0.860, with a 95% confidence interval (CI) ranging from 0.745 to 0.975, indicating excellent diagnostic accuracy. The optimum cut-off for detecting AKI was determined to be HBP0 >8.28. At this cut-off, the sensitivity was 72.5% (CI: 63.7% to 81.3%) and the specificity was 88.9% (CI: 82.7% to 95.1%). HBP at 72 hours showed a lower AUROC of 0.612 (CI: 0.464 to 0.760), reflecting moderate diagnostic accuracy. The optimum cut-off for AKI at this time point was HBP72>6.22, with a sensitivity of 33% (CI: 23.8% to 42.2%) and a perfect specificity of 100% (CI: 100.0% to 100.0%).

The analysis of variance (ANOVA) for various markers across different stages of acute kidney injury (AKI) shows the following results. The sequential organ failure assessment (SOFA) score had a mean of 5.9 with a standard deviation (SD) of 3.0 for patients with no AKI, a mean of 7.6 (SD 3.4) for Stage I, a mean of 7.7 (SD 2.7) for Stage II, and a mean of 7.1 (SD 2.9) for Stage III, with an F value of 1.0 and a p value of 0.393.

Heparin-binding protein (HBP) levels at baseline showed significant differences, with means of 5.222 (SD 3.046) for no AKI, 7.392 (SD 2.940) for Stage I, 10.842 (SD 3.411) for Stage II, and 19.623 (SD 5.421) for Stage III, yielding an F-value of 51.854 and a p-value of less than 0.001. At 72 hours, HBP levels had means of 3.78 (SD 1.53) for no AKI, 4.19 (SD 3.57) for Stage I, 5.20 (SD 3.04) for Stage II, and 7.27 (SD 3.50) for Stage III, with an F value of 4.53 and a p value of 0.005. C-reactive protein (CRP) levels at baseline were also significantly different, with means of 44.52 (SD 35.67) for no AKI, 68.39 (SD 38.33) for Stage I, 83.18 (SD 56.29) for Stage II, and 101.23 (SD 60.42) for Stage III, resulting in an f value of 2.54 and a p value of 0.030.

Table 4: Association of SOFA, HBP, and other Markers with AKI.

Markers	AKI				Unpaired t-test		Effect size
	Not present		Present				
	Mean	SD	Mean	SD	T value	P value	
SOFA	5.9	3.0	7.5	2.9	-1.6	0.114	0.554
HBP AT 0	5.222	3.046	11.979	5.972	-3.340	0.001	1.425
HBP AT 72	3.78	1.53	5.41	3.46	-2.60	0.018	0.610
CRP AT 0	44.52	35.67	76.38	49.93	-2.45	0.031	0.734
CRP AT 72	38.21	28.24	68.32	41.22	-2.71	0.022	0.512
Procalcitonin	1.287	1.053	11.137	25.053	-3.717	<0.001	0.556

Table 5: ROC analysis to estimate optimum cut-off and comparative efficiency of markers for detecting AKI.

Marker	Parameter	Value	95% CI lower	95% CI upper
HBP AT 0	AUROC	0.860	0.745	0.975
	Optimum cut-off for AKI	HBP0 > 8.28		
	Sensitivity	72.5	63.7	81.3
	Specificity	88.9	82.7	95.1
HBP AT 72	AUROC	0.612	0.464	0.760
	Optimum cut-off for AKI	HBP72 > 6.22		
	Sensitivity	33	23.8	42.2
	Specificity	100	100.0	100.0

Table 6: Association of SOFA, HBP, and other markers with stages of AKI.

Markers	Stages of AKI								ANOVA	
	No AKI		Stage I		Stage II		Stage III			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F value	P value
SOFA	5.9	3.0	7.6	3.4	7.7	2.7	7.1	2.9	1.0	0.393
HBP AT 0	5.222	3.046	7.392	2.940	10.842	3.411	19.623	5.421	51.854	<0.001
HBP AT 72	3.78	1.53	4.19	3.57	5.20	3.04	7.27	3.50	4.53	0.005
CRP AT 0	44.52	35.67	58.17	34.20	77.93	51.44	94.85	56.83	3.60	0.016
CRP AT 72	38.21	28.24	68.39	38.33	83.18	56.29	101.23	60.42	2.54	0.030
Procalcitonin	1.287	1.053	9.435	23.449	9.734	21.966	15.893	32.234	0.832	0.479

C-reactive protein (CRP) levels at 72 hours were also significantly different, with means of 38.21 (SD 28.24) for no AKI, 58.17 (SD 34.20) for Stage I, 77.93 (SD 51.44) for Stage II, and 94.85 (SD 56.83) for Stage III, resulting in an f value of 3.60 and a p-value of 0.016. Procalcitonin levels had means of 1.287 (SD 1.053) for no AKI, 9.435 (SD 23.449) for Stage I, 9.734 (SD 21.966) for Stage II, and 15.893 (SD 32.234) for Stage III, with an F value of 0.832 and a p value of 0.479.

DISCUSSION

Our study demonstrated a significant association between elevated serum HBP levels and the presence and severity of AKI in patients with sepsis. The baseline HBP value was significantly higher in the AKI group (mean 11.979) compared to the non-AKI group (mean 5.222), with a statistically significant difference (p=0.001). Moreover, HBP levels showed a graded increase with AKI stage, affirming its utility in predicting severity. This finding is comparable to that of Pajenda et al who observed elevated plasma HBP in AKI patients, suggesting its diagnostic value with a different cut-off.[12]

Findings are consistent with emerging literature on the role of heparin-binding protein (HBP) as an early biomarker in sepsis and its complications, particularly acute kidney injury (AKI). Johansson et al, demonstrated that elevated HBP levels at presentation in the emergency department were associated with progression to severe sepsis and subsequent organ dysfunction, underscoring its predictive value. This is corroborated by Sunden-Cullberg et al who reported a strong correlation.[13,14]

Bentzer et al provided mechanistic insights, revealing that HBP contributes to vascular leakage by inducing endothelial cytoskeletal rearrangements, a central process in the pathogenesis of sepsis-induced AKI. Linder et al further confirmed the diagnostic utility of HBP in the context of severe infections, though their study focused on meningitis. Importantly, Krag et al highlighted HBP's diagnostic superiority over traditional inflammatory markers such as CRP and procalcitonin.[15-17] Together, these findings support the potential integration of HBP into early diagnostic protocols for septic AKI, where timely recognition is crucial for intervention and prognosis.

Fisher et al also demonstrated significantly raised HBP levels in patients with sepsis-induced AKI, supporting its role as a causative biomarker. Their study identified HBP's potential in identifying patients requiring renal replacement therapy.[18] In our cohort, CRP and procalcitonin also correlated with AKI presence, but HBP had superior diagnostic performance (AUROC=0.860). This supports HBP as a more specific early biomarker compared to traditional inflammatory markers. Our findings reinforce that HBP can serve both as a diagnostic and prognostic marker in sepsis-induced AKI, enabling early intervention and improving outcomes.

The limitation of this study lies in its single-center nature and limited sample size (n=100), which may limit generalizability to broader populations. Furthermore, the study did not assess long-term renal outcomes post-discharge.

CONCLUSION

Heparin-binding protein levels are significantly elevated in patients with sepsis-associated AKI. An HBP threshold >8.28 at baseline effectively predicts AKI. Levels also correspond with AKI stage severity, suggesting HBP's potential as both a diagnostic and staging tool.

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