ORIGINAL ARTICLE

Profiling HMGB1 as a Sepsis Biomarker: Insights from Comorbid Conditions and Disease Onset

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ABSTRACT

Background: High-Mobility Group Box 1 (HMGB1) is a pro-inflammatory mediator implicated in the pathophysiology of sepsis. Its role as a biomarker, particularly in patients with comorbidities, remains under investigation. The study aimed was to profile serum HMGB1 levels in sepsis patients and assess variations across comorbid conditions. **Methods:** A cross-sectional study was conducted on 105 adult sepsis patients at Dr. Soetomo General Academic Hospital. HMGB1 levels were measured via ELISA on the first day of admission. Statistical analysis was performed using SPSS version 26.0.**Results:** Most patients were over 60 years old, with diabetes mellitus (75.2%) and chronic kidney disease (CKD, 31.4%) as common comorbidities. The median HMGB1 level was 28.49 ng/mL (range, 3.76–258.51 ng/mL). Patients with CKD had significantly higher HMGB1 levels (70.47 ng/mL) than those without CKD (30.59 ng/mL; p = 0.020). No significant difference was found between diabetic and non-diabetic patients (p = 0.095). Elevated HMGB1 levels were also observed in cases with HIV and prolonged sepsis onset.**Conclusion:** HMGB1 levels varied according to comorbidity and disease onset, with CKD exhibiting a significant association. These findings support HMGB1's potential as a dynamic biomarker in sepsis.

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INTRODUCTION

Sepsis is a life-threatening condition characterized by organ dysfunction resulting from a dysregulated host response to infection (1). Despite advances in early diagnosis and supportive care, sepsis remains a major contributor to morbidity and mortality among critically ill patients (2).

One of the key molecules involved in the pathophysiology of sepsis is High-Mobility Group Box 1 (HMGB1), a nuclear protein that plays critical roles both intracellularly and extracellularly. When released into the extracellular space, HMGB1 functions as an alarmin or damage-associated molecular pattern (DAMP), amplifying the inflammatory response by interacting with receptors such as the receptor for advanced glycation end-products (RAGE), Toll-like receptor 2 (TLR2), and Toll-like receptor 4 (TLR4) (3,4).

Procalcitonin is currently the most widely used biomarker for diagnosing sepsis. However, emerging evidence suggests that other molecules, including Resolvin D2 and Heat Shock Protein 10 (HSP10), may also serve as potential biomarkers (5,6). Notably, HMGB1 has gained attention as a promising indicator for assessing sepsis severity, offering potential value in clinical decision-making (7).

In Indonesia, the burden of sepsis is substantial. A single-center report from 2013 to 2016 documented 14,076 cases of sepsis with a mortality rate of 58.3%. These figures underscore the urgent need for improved diagnostic and prognostic tools in the management of

sepsis (8). This study aimed to characterize the profile of HMGB1 levels in patients diagnosed with sepsis at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

This study employed a descriptive observational approach with a cross-sectional design to examine serum HMGB1 levels in sepsis patients on the first day of hospital admission. The study population comprised adult patients (≥18 years, based on WHO criteria) who were admitted to the internal medicine inpatient ward of Dr. Soetomo General Academic Hospital, Surabaya, with a clinical diagnosis of suspected sepsis, as defined by the Sepsis-3 criteria.

Inclusion criteria were as follows: male or female patients aged ≥18 years, diagnosed with sepsis based on a SOFA score ≥2, willing to provide informed consent, referred or non-referred from other healthcare facilities, and presenting with sepsis onset within two weeks prior to hospital admission. Total sampling was conducted between 8 June and 28 August 2023. Data collected included age, gender, HMGB1 levels, SOFA score, sepsis onset, comorbidities, and referral status.

Blood samples for HMGB1 analysis were obtained following informed consent. A total of 3 mL of venous blood was collected into gel clot activator tubes and transported to the Faculty of Medicine, Universitas Airlangga. Samples were centrifuged at 3100 rpm for 15 minutes, and the resulting serum was transferred into polypropylene tubes and stored at −80°C until analysis. Serum HMGB1 concentrations were measured using the Bioenzy ELISA kit.

Data analysis was performed using SPSS version 26.0. A p-value <0.05 was considered statistically significant. Descriptive statistics were presented as mean, median, standard deviation, and range for numerical variables, while categorical variables were summarized as frequencies and percentages. Comparative analyses were conducted using the Mann–Whitney U test and Kruskal–Wallis's test, as appropriate.

Ethical Clearance

The study received ethical approval from the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, under approval number 0673/KEPK/V/2023.

RESULTS

A total of 105 sepsis patients were analyzed, most of whom were over 60 years old and had comorbidities such as hypertension (32.4%) and chronic kidney disease (31.4%). The median SOFA score was 5, indicating moderate to severe organ dysfunction, and the majority were referred from other facilities (81%), with sepsis onset predominantly within the first 3–4 days. Pneumonia was the most common source of infection (44.8%), with average levels of HMGB1

Table I: General Characteristics of the Sepsis Patients

Characteristics	n (%)	Mean ± SD	Median (Min – Max)
Gender		-	-
Male	49 (46.7%)		
Female	56 (53.3%)		
Age (years old)		58.54 ± 14.19	60 (19 – 86)
18 – 30	4 (3.8%)		
31 – 40	9 (8.6%)		
41 – 50	14 (13.3%)		
51 – 60	27 (25.7%)		
>60	51 (48.6%)		
Comorbidity			
Diabetes mellitus	79 (75.2%)	-	-
Chronic kidney disease (CKD)			
Stage 2	1 (1%)		
Stage 3	3 (2.9%)		
Stage 4	16 (15.2%)		
Stage 5	33 (31.4%)		
Final stage of dialysis	4 (3.8%)		
Malignancy	1 (1%)		
HIV	1 (1%)		
Hypertension	34 (32.4%)		
SOFA score		5.19 ± 2.55	5 (2 – 13)
2–3	28 (26.7%)		
4–5	36 (34.4%)		
6–7	22 (21%)		
8–9	13 (12.4%)		
10–11	3 (2.9%)		
12–13	3 (2.9%)		
Sepsis Onset (days)		3.88 ± 2.046	3 (1 – 10)
1 – 2	25 (23.8%)		
3 – 4	51 (48.6%)		
5 – 6	15 (14.3%)		
7 – 8	10 (9.5%)		
9 – 10	4 (3.8%)		
Referral			
Yes	85 (81%)		
No	20 (19%)		
Source of Infection			
Pneumonia	47 (44.8%)		
Ulcer	24 (22.9%)		
Urinary Tract Infection (UTI)	12 (11.4%)		
Pneumonia + ulcer	9 (8.6%)		
Pneumonia + UTI	4 (3.8%)		
Ulcer + UTI	2 (1.9%)		
Pneumonia + ulcer + UTI	5 (4.8%)		
Cholecystitis	2 (1.9%)		
HMGB1		46.49 ± 46.94	
Procalcitonin		13.03 ± 21.34	

and procalcitonin at 58.54 ng/mL and 5.19 ng/mL, respectively. HMGB1 levels varied across demographic and clinical characteristics, with no substantial difference between sexes. The highest median HMGB1 levels were observed in the 31–40 age group, while the lowest were in patients aged 18–30. Comorbidities such as diabetes and CKD showed modest variation, with final-stage CKD patients on dialysis having the highest median level. Exceptionally high HMGB1 was noted in patients with HIV. HMGB1 levels also fluctuated across SOFA scores and sepsis onset, with the highest median found in patients presenting on days 5–6. The infection source influenced HMGB1 variation, with the lowest levels observed in cholecystitis and the highest in mixed infections involving pneumonia, ulcer, and UTI (Tables I and II).

Table II: HMGB1 Levels based on Characteristics of participants

Characteristics	Median (Min – Max)
Age (years old)	
18 – 30	20.604 (18.89 – 22.47)
31 – 40	44.34 (29.94 – 183.22)
41 – 50	34.79 (20.54 – 229.68)
51 – 60	31.43 (3.76 – 106.71)
>60	24.97 (8.58 – 258.51)
Comorbidity	
Absence of Diabetes mellitus	25.99 (5.77 - 183.22)
Presence of Diabetes mellitus	30.72 (3.76 - 258.5)
Absence of Chronic Kidney Disease	30.59 (8.58 - 183.22)
Chronic kidney disease (CKD)	
Stage 2	19.13 (19.13 - 19.13)
Stage 3	29.09 (18.85 - 90.80)
Stage 4	20.60 (3.76 - 137.09)
Stage 5	27.25 (5.77 - 229.68)
Final stage CKD with dialysis	70.47 (27.43 - 258.51)
Absence of Malignancy	28.48 (3.76 - 258.51)
Presence of Malignancy	38.33 (n=1)
Absence of HIV	28.48 (3.76 - 258.51)
Presence of HIV	183.22 (n=1)
Absence of Hypertension	28.47 (3.76 - 258.51)
Presence of Hypertension	28.85 (8.58 - 229.68)
SOFA score	
2–3	28.48 (16.91 – 106.71)
4–5	30.59 (8.58 – 229.68)
6–7	30.80 (10.96 – 183.22)
8–9	24.89 (8.69 – 103.72)
10–11	48.57 (3.76 – 258.51)
12–13	17.16 (5.77 – 48.80)
Sepsis Onset (days)	
1 – 2	29.09 (9.05 – 151.21)
3 – 4	28.49 (3.76 – 229.68)
5 – 6	38.01 (5.77 – 137.09)
7 – 8	23.28 (8.58 – 124.21)
9 – 10	147.77 (70.99 – 258.51)
Referral	
Yes	28.47 (3.76 – 258.51)
No	30.90 (19.13 – 229.68)
Source of Infection	
Pneumonia	29.09 (8.58 – 229.68)
Ulcer	31.21 (19.72 – 258.51)
Urinary Tract Infection (UTI)	25.36 (16.91 – 103.72)
Pneumonia + ulcer	30.41 (16.78 – 151.21)
Pneumonia + UTI	7.41 (3.76 – 24.70)
Ulcer + UTI	23.81 (19.13 – 28.49)
Pneumonia + ulcer + UTI	23.58 (15.84 – 99.98)
Cholecystitis	33.73 (18.89 – 48.57)

Note: CKD = chronic kidney disease; HIV = human immunodeficiency virus; SOFA = sequential organ failure assessment; UTI = urinary tract infection.

HMGB1 levels demonstrated notable variation across clinical severity, gender, and comorbid conditions. Although the highest mean HMGB1 concentration was observed in patients with sepsis compared to those in the severe and shock groups, the differences were not statistically significant. However, no significant difference were observed between male and female patients (Fig. 1). In contrast, analysis by comorbidity revealed that patients with chronic kidney disease had significantly lower HMGB1 levels compared to other groups (p = 0.020). Interestingly, exceptionally high HMGB1 levels were also noted in a patient with HIV and malignancy, although this finding was based on a single case (Fig. 2).

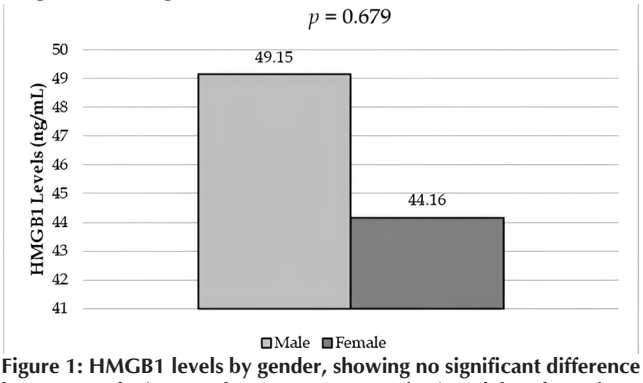

Figure 1: HMGB1 levels by gender, showing no significant difference between male (mean of 49.15 ± 51.02 ng/mL) and female patients (mean of 44.16 ± 43.39 ng/mL; p = 0.679).

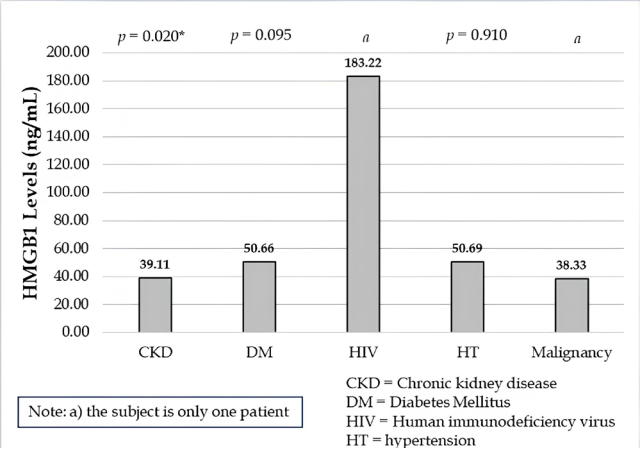

Figure 2: HMGB1 levels based on comorbidities in patients with sepsis. Several comorbidities had mean values, namely CKD (39.11 ± 39.21 ng/mL; p = 0.020), DM (50.66 ± 50.15 ng/mL; p = 0.095), and hypertension (50.69 ± 52.15 ng/mL; p = 0.910). In contrast, two other comorbidities, HIV and malignancy, did not have mean values as each was represented by only a single patient.

DISCUSSION

A total of 105 sepsis patients were included in this study, with the majority aged over 60 years. Sepsis remains a major concern among elderly populations, where advancing age is strongly associated with increased mortality risk. In terms of comorbidities, diabetes mellitus was the most prevalent condition, and pneumonia emerged as the leading source of infection (9).

Serum HMGB1 levels among participants ranged from 3.76 to 258.51 ng/mL, with a median value of 28.49 ng/mL. Patients with diabetes mellitus exhibited slightly higher median HMGB1 levels, consistent with previous findings linking HMGB1 to metabolic dysregulation. Notably, patients with end-stage chronic kidney disease (CKD) undergoing dialysis demonstrated elevated HMGB1 levels, with one case presenting a prolonged sepsis onset of 10 days. HMGB1 is known to play a critical role in the pathogenesis of kidney disease through mechanisms such as hemodynamic alterations, tubular cell apoptosis, tissue fibrosis, and inflammation (10, 11).

Patients with a sepsis onset of 9–10 days showed the highest median HMGB1 levels, supporting prior evidence that HMGB1 acts as a late-phase inflammatory mediator, with levels rising during the first week of illness (12). Additionally, pharmacologic factors may influence HMGB1 expression; for instance, atorvastatin has been shown to reduce HMGB1 levels, particularly in patients with hypertension and hyperlipidemia. This suggests that prior statin therapy may obscure the inflammatory profile in hypertensive sepsis patients (13). Elevated HMGB1 levels have also been reported in other inflammatory and vascular conditions, including rhinitis, ischemic stroke, hypertension, and heart disease (14,15).

In the context of sepsis, HMGB1 functions as a damage-associated molecular pattern (DAMP), initiating immune responses and amplifying inflammation. DAMPs are endogenous molecules released from injured or dying cells that activate the innate immune system via pattern recognition receptors (PRRs). While DAMPs contribute to host defense, they also drive pathological inflammation. Recent studies have highlighted HMGB1's pathogenic role in various inflammatory diseases (16).

Moreover, HMGB1 has been implicated in sepsis-related immunosuppression, mediating the release of inflammatory cytokines through the activation of immune cells, pyroptosis pathways, and nuclear factor-κB phosphorylation. Its elevated levels in patients with acute sepsis, compared to healthy individuals, further underscore its potential as a diagnostic and prognostic biomarker (17, 18).

This study has several limitations. First, the sample size was relatively small, suggesting that future research should be conducted with larger cohorts. Second, a cross-sectional design limits the ability to assess temporal changes and prognostic outcomes. Third, the absence of healthy controls and comparator groups restricts broader interpretation. Lastly, more robust statistical modelling is needed to strengthen the analytical depth of future studies.

CONCLUSIONS

This study highlights the diverse profile of HMGB1 levels among sepsis patients, influenced by age, comorbidities, the source of infection, and the time of disease onset. While diabetes mellitus was the most common comorbidity, chronic kidney disease showed a statistically significant association with altered HMGB1 levels, suggesting its potential role in modulating inflammatory responses. The exceptionally high HMGB1 levels observed in patients with prolonged sepsis onset and HIV infection further support HMGB1 as a dynamic biomarker reflecting disease progression and immune activation. These findings reinforce the relevance of HMGB1 in sepsis pathophysiology and underscore the need for further research to explore its prognostic and therapeutic implications in diverse clinical settings.

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