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Assessment of Serum Beta 2-Microglobulin Levels in Crimean-Congo Hemorrhagic Fever Patients: Implications for Immune Activation and Disease Pathogenesis

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ABSTRACT

Crimean-Congo Hemorrhagic Fever (CCHF) presents a spectrum of clinical manifestations, ranging from asymptomatic cases to severe, life-threatening conditions. Despite extensive research on CCHF pathogenesis, comprehensive understanding remains elusive. Our investigation focused on assessing serum beta 2-microglobulin (β2M) levels in CCHF patients, aiming to elucidate its potential as an immune activation marker and its involvement in disease pathogenesis. The study enrolled 45 CCHF patients and 45 healthy volunteers as a control group. Serum β2M levels were quantified using the immunoturbidimetric analysis method. The patient group was divided into two groups, mild and moderate-severe, using scoring systems. The mean β2M values for the control, mild, and moderate-severe patient groups were 2.27±0.50, 4.37±1.29, and 5.82±2.62 mg/L, respectively ($p<0.001$). Positive correlations were noted between β2M concentrations and markers such as BUN, creatinine, uric acid, creatine kinase, and aPTT ($p<0.001$, $r=0.684$; $p<0.001$, $r=0.602$; $p=0.003$, $r=0.439$; $p=0.008$, $r=0.392$; $p=0.019$, $r=0.348$, respectively). Conversely, negative correlations were observed with total protein, albumin, and platelet count ($p=0.021$, $r=-0.342$; $p=0.003$, $r=-0.434$; $p=0.048$, $r=-0.296$, respectively). The findings suggest a prominent inflammatory response in CCHF, indicated by elevated β2M levels, implying its potential role in the molecular mechanisms of the disease.

Keywords: Beta 2-microglobulin, Hemorrhagic fever virus, Crimean-Congo, Patient acuity, Viral zoonoses.

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Introduction

Crimean-Congo Hemorrhagic Fever (CCHF) is a viral zoonotic disease primarily transmitted by ticks, with a clinical spectrum ranging from mild infection to severe illness or even death [1]. The causative agent of CCHF is the CCHF virus, a single-stranded RNA virus belonging to the Orthonairovirus genus of the Nairoviridae family [2]. The disease can be transmitted through tick contact, exposure to the blood or body fluids of an infected animal, or a CCHF patient [3]. The disease is clinically characterized by sudden-onset fever, headache, muscle pain, fatigue, erythema on the face and body, conjunctivitis, petechiae, mucosal bleeding, and, in the advanced stage, multiple organ dysfunction and intraparenchymal hemorrhages. In severe cases, the mortality rate varies between 5-30%, depending on the geographical region and the quality of healthcare services [4].

Although the pathogenesis of the disease is not fully understood, complex molecular mechanisms between the virus and host cells are thought to be responsible for the pathogenesis of CCHF [5]. The main elements mediating this relationship are endothelial and immune cells. The release of cytokines results in increased vascular permeability, vasodilation, multiple organ failure, and shock [6]. Hemorrhage, which is among the important clinical findings of the disease, increases vascular permeability [7]. In addition, viral antigens on endothelial cells indicate that the endothelium is the main target. Activation of endothelial cells plays a critical role in initiating inflammatory reactions, such as the organization of the immune response to infection and increased vascular permeability [8]. Endothelial damage also contributes to the activation of the intrinsic coagulation cascade. Endothelial cells can be activated directly by the virus or indirectly by host-derived mediators induced by the virus [9].

Beta 2-microglobulin (β2M), a component of the lymphocyte HLA complex, is a low molecular weight protein that serves as the light chain of class 1 MHC antigens. It is found in nearly all body fluids and on the surface of nucleated cells. β2M is an indicator of immune activation and proximal tubular function. It increases in conditions associated with high cell turnover and/or immune activation. Conditions accompanied by inflammation such as inflammatory bowel diseases, Crohn's disease, hepatitis, autoimmune diseases, multiple myeloma, chronic kidney failure, lymphoproliferative diseases, myeloproliferative diseases, myelodysplastic diseases, amyloidosis, breast cancer, hepatoma,

hyperthyroidism, vasculitis, tumor necrosis factor, and certain drugs lead to an increase in β2M levels [10].

In infections like CMV, HIV, Epstein-Barr, and influenza A virus, β2M levels rise. This elevation during viral infections may stem from heightened production and release due to lymphocyte activation and increased turnover [11]. Notably, studies, especially in HIV cases, highlight elevated serum β2M levels as HIV targets T-lymphocytes and macrophages, intensifying turnover, and destruction [12, 13]. However, no previous study has investigated the status of β2M levels in CCHF patients.

Accordingly, this study aims to investigate serum β2M levels in CCHF patients, compare them with healthy controls, and assess their impact on the pathogenesis. This study holds significance as it pioneers the investigation of β2M in CCHF patients. Given the absence of prior research in this area, our study fills a critical knowledge gap. Understanding the role of β2M in CCHF could offer valuable insights into the disease's pathogenesis and aid in developing targeted therapeutic interventions.

Materials and Methods

Study Population

This prospective study involves 45 CCHF patients and 45 healthy volunteers without acute or chronic illnesses or medication use. Exclusion criteria for healthy volunteers included suspected clinical infection, liver disease, kidney disease, rheumatic disease, malignancy, pregnancy, or smoking. No specific criteria were applied to exclude any patients from the patient group. None of the patients had a previous acute or chronic kidney disease history. Besides, no deaths occurred in any of the patients included in the study. Demographic data, underlying chronic diseases, treatments used, and outcomes were recorded for the patients. In our study, patients were classified according to the severity score recommended by Bakır et al [15]. Thus, patients were divided into two groups: mild and moderate-severe cases, and correlations between serum β2M levels and disease severity were explored. The procedures were approved by the Ethical Committee of Sivas Cumhuriyet University, following the ethical standards established by the institution (2021-04/02). All procedures were performed by the Helsinki Declaration as revised in 2013. Informed consent was obtained from all individuals included in this study.

Sample Collection and Laboratory Analyses

Samples from the patient group were collected at the time of hospital admission. For participants in the control group, 5 mL venous blood samples were obtained in the morning after an overnight fast. Serum samples were stored at – 80 °C until analyses. β2M levels were measured by using the immune turbidimetric method (Roche Cobas 8000 c702, Germany, Manheim). Ferritin and interleukin-6 (IL-6) levels were measured using the electrochemiluminescence method (Roche Cobas 8000 e801, Germany, Manheim). Various biochemical parameters, including blood urea nitrogen (BUN), creatinine, uric acid, total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), direct bilirubin (D.bil), total bilirubin (T.bil), creatine kinase (CK) and amylase levels were measured by photometric method (Roche Cobas 8000 c702, Germany, Manheim). Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer values were measured by using a coagulation analyzer (Sysmex CS-5100, Japan). Complete blood count analyses were conducted employing a hematology analyzer (Sysmex XN-9100, Japan).

Statistical Analyses

Histogram and q-q plots were examined, and Shapiro-Wilk's test was performed to assess the data normality. To compare the differences between groups, a two-sided independent samples t-test or Mann-Whitney U test was used for continuous variables, and Pearson $\chi 2$ analysis or Fisher's exact test was used for categorical variables. Values were expressed as n(%), mean±standard deviation, or median (1st-3rd quartiles). The relationship between quantitative data was analyzed using Pearson correlation analysis. Receiver operating characteristic (ROC) analyses were used to assess the prognostic performance of the parameters to predict CCHF severity. Sensitivity, specificity, positive and negative likelihood ratio value statistics were calculated with 95% confidence intervals. Data were analyzed statistically using IBM SPSS for Windows version 23.00 software (Armonk, New York, United States of America), and GraphPad Prism version 8.3.0 (San Diego, California USA, www.graphpad.com) was used for visualization. A p-value less than 5% was considered statistically significant.

Results

Out of the CCHF patients included in the study, 10 (22%) were female, while 20 (44%) of the control group were female. There were 31 patients with a severity score of 0-4 (mild) and 14 patients with a score of 5 and above (moderate-severe) for determining the severity of CCHF disease. While there was no significant difference between the groups in terms of gender ($p=0.068$), the mean age of moderate-severe patients was higher, and this difference was statistically significant ($p<0.001$). The basic characteristics of the study population are shown in Table 1. Serum β2M concentrations were higher in moderate-severe cases ($p<0.001$). The β2M concentration values for the control, mild, and moderate-severe patient groups were found to be 2.27±0.5, 4.37±1.29, and 5.82±2.62 mg/L, respectively. Positive correlations were observed between serum β2M and BUN ($p<0.001$, $r=0.684$), creatinine ($p<0.001$, $r=0.602$), uric acid ($p=0.003$, $r=0.439$), creatine kinase ($p=0.008$, $r=0.392$), and aPTT ($p=0.019$, $r=0.348$). On the other hand, negative correlations were found between serum β2M concentrations and total protein ($p=0.021$, $r=-0.342$), albumin ($p=0.003$, $r=-0.434$), and platelet count ($p=0.048$, $r=-0.296$) (Figure 1).

Table 1. Baseline characteristics of the study population

Variable	Healthy Cases (n=45)	CCHF Patients		*p* values
		Mild (n=31)	Moderate-Severe (n=14)	
Gender, female (%)	20 (44%)	6 (%19)	4 (%29)	0.068
Age (years)	38±10[a]	43 ± 16[a]	65 ± 10[b]	<0.001
β2M (mg/L)	2.27±0.5[a]	4.37 ± 1.29[b]	5.82 ± 2.62[c]	<0.001
IL-6 (ng/L)		11.2 (5.3-30.4)	20.4 (13.2-138)	0.021
Ferritin (µg/L)		1180 (475-5274)	16275 (5566-22926)	<0.001
BUN (mg/dL)		13.0 (9.9-18.2)	15.5 (11.7-22.0)	0.108
Creatinine (mg/dL)		0.81±0.18	0.91±0.23	0.147
Uric acid (mg/dL)		3.94±1.26	5.39±1.85	0.004
Total protein (g/L)		63.2±4.7	60.5±5.6	0.103
Albumin (g/L)		38±3.2	34.2±4.2	0.002
Amylase (U/L)		65 (45-81)	107 (72-191)	0.001
ALP (U/L)		68 (107-106)	128 (85-165)	0.004
AST (U/L)		78 (40-163)	216 (150-315)	0.001
ALT (U/L)		63 (34-101)	96 (67-173)	0.019
LDH (U/L)		370 (289-573)	581 (472-759)	0.002
CK (U/L)		206 (131-380)	561 (445-866)	0.048
GGT (U/L)		42 (21-92)	121 (75-272)	<0.001
T.bil (mg/dL)		0.43 (0.29-0.57)	0.69 (0.57-1.24)	0.001
D.bil (mg/dL)		0.15 (0.1-0.2)	0.42 (0.21-0.65)	<0.001
PT (sec)		11.7 (11.1-12.2)	11.5 (11.0-12.5)	0.912
INR		1.03 (0.97-1.07)	1.02 (0.96-1.10)	0.922
aPTT (sec)		26.3±4.6	29.7±6.5	0.048
Fibrinogen (mg/dL)		288±75	300±118	0.676
D-dimer (mg/L FEU)		1.88 (1.08-2.87)	3.44 (1.45-29.1)	0.033
WBC (10^9/L)		2.66 (2.08-4.87)	2.6 (1.95-2.91)	0.477
Hemoglobin (g/dL)		13.9±1.7	12.6±2.1	0.028
Platelet (10^9/L)		101 (39-126)	39 (34-64)	0.011

Results are expressed as n (%), mean±standard deviation, or median (1st-3rd quartiles). Different superscripts in the same row indicate a statistically significant difference between groups. Significant p-values are shown in bold. CCHF, Crimean-Congo hemorrhagic fever; β2M, beta 2-microglobulin; IL-6, Interleukin-6; BUN, Blood Urea Nitrogen; ALP, Alkaline phosphatase; AST, Aspartate transaminase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; CK, Creatine kinase; GGT, Gama-glutamyl transferase; T.bil and D.bil, Total and Direct bilirubin; PT, Prothrombin time; INR, International normalization ratio; aPTT, Activated partial thromboplastin time; WBC, white blood count.

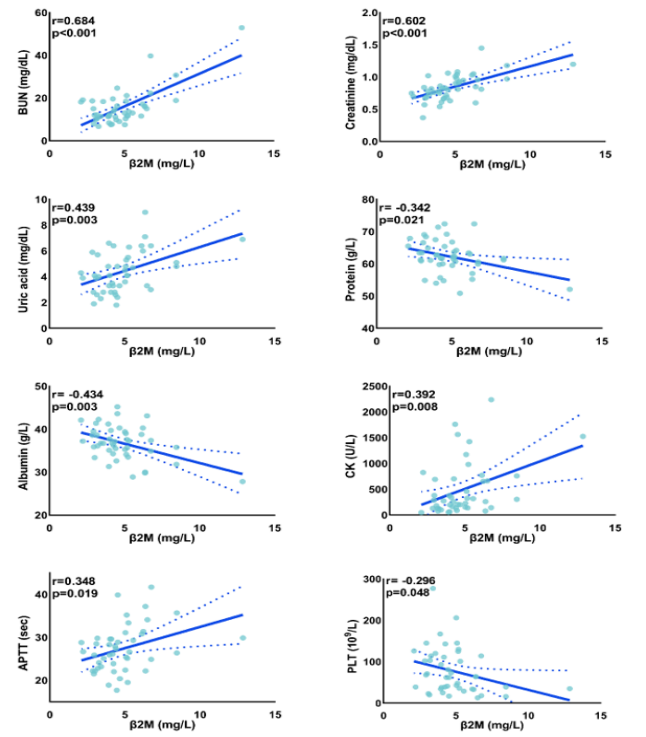

Figure 1. Pearson correlation analysis of β2M levels and laboratory parameters in patients with Crimean-Congo hemorrhagic fever. Linear lines with 95% confidence intervals are given.

Table 2. ROC Analysis Results for Variables in Predicting CCHF Severity

Variable	Cut-off value	AUC	Sensitivity	Specificity	LR(+)	LR(-)
Age (years)	>50	0.88	1.00 (0.77-1.00)	0.68 (0.49-0.83)	3.10 (1.9-5.2)	0
β2M (mg/L)	>5.09	0.7	0.64 (0.35-0.87)	0.77 (0.59-0.90)	2.85 (1.3-6.1)	0.46 (0.2-1.0)
IL-6 (ng/L)	>13.5	0.72	0.79 (0.49-0.95)	0.61 (0.42-0.78)	2.03 (1.2-3.4)	0.35 (0.1-1.0)
Ferritin (µg/L)	>3959	0.84	0.93 (0.66-1.00)	0.71 (0.52-0.86)	3.20 (1.8-5.7)	0.1 (0.02-0.7)
Uric acid (mg/dL)	>4.8	0.75	0.64 (0.35-0.87)	0.84 (0.66-0.95)	3.99 (1.6-9.7)	0.43 (0.2-0.9)
Albumin (g/L)	≤34.1	0.76	0.64 (0.35-0.87)	0.97 (0.83-1.00)	19.9 (2.8-143)	0.37 (0.2-0.7)
Amylase (U/L)	>98	0.81	0.64 (0.35-0.87)	0.94 (0.79-0.99)	9.96 (2.5-40.3)	0.38 (0.2-0.8)
ALP (U/L)	>74	0.77	0.93 (0.66-1.00)	0.61 (0.42-0.78)	2.40 (1.5-3.8)	0.12 (0.02-0.8)
ALT (U/L)	>84	0.72	0.71 (0.42-0.92)	0.71 (0.52-0.86)	2.46 (1.3-4.7)	0.40 (0.2-0.9)
AST (U/L)	>130	0.82	0.79 (0.49-0.95)	0.74 (0.55-0.88)	3.04 (1.6-5.9)	0.29 (0.1-0.8)
LDH (U/L)	>390	0.8	1.00 (0.77-1.00)	0.58 (0.39-0.76)	2.38 (1.6-3.6)	0
CK (U/L)	>343	0.69	0.64 (0.35-0.87)	0.74 (0.55-0.88)	2.49 (1.2-5.1)	0.48 (0.2-1.0)
GGT (U/L)	>101	0.83	0.71 (0.42-0.92)	0.84 (0.66-0.95)	4.43 (1.9-10.6)	0.34 (0.1-0.8)
T.bil (mg/dL)	>0.57	0.82	0.79 (0.49-0.95)	0.77 (0.59-0.90)	3.48 (1.7-7.1)	0.28 (0.10-0.8)
D.bil (mg/dL)	>0.3	0.85	0.71 (0.42-0.92)	0.87 (0.70-0.96)	5.54 (2.1-14.6)	0.33 (0.1-0.8)
aPTT (sec)	>29.3	0.68	0.57 (0.29-0.82)	0.81 (0.63-0.93)	2.95 (1.3-6.9)	0.53 (0.3-1.0)
D-dimer (mg/L FEU)	>2.4	0.7	0.64 (0.35-0.87)	0.74 (0.55-0.88)	2.49 (1.2-5.1)	0.48 (0.2-1.0)
Hemoglobin (g/dL)	≤12.1	0.69	0.50 (0.23-0.77)	0.87 (0.70-0.96)	3.87 (1.4-11.1)	0.57 (0.3-1.0)
Platelet (10^9/L)	≤81	0.74	1.00 (0.77-1.00)	0.55 (0.36-0.73)	2.21 (1.5-3.3)	0

Results are expressed with 95% confidence intervals. CCHF, Crimean-Congo hemorrhagic fever; AUC, Area under the curve; LR, Likelihood ratio; β2M, beta 2-microglobulin; IL-6, Interleukin-6; ALP, Alkaline phosphatase; AST, Aspartate transaminase; ALT, Alanine aminotransferase; LDH, Lactate dehydrogenase; CK, Creatine kinase; Gama-glutamyl transferase; T.bil and D.bil, Total and Direct bilirubin; aPTT, Activated partial thromboplastin time.

ROC analyses were conducted to assess parameters capable of predicting the severity of CCHF. Table 2 presents the Area under the Curve (AUC), sensitivity, specificity, and likelihood ratios for the respective tests. Notably, sensitivities of 100% were observed for cut-off values of age >50 years, LDH >390 U/L, and platelet count <81 *10^9/L. Regarding β2M, a sensitivity of 64% and specificity at 77% was determined for a cut-off value >5.09 mg/L, corresponding to an AUC value of 0.697. ROC curve graphs for age, ferritin, AST, GGT, and direct bilirubin with the highest AUC values are depicted in Figure 2.

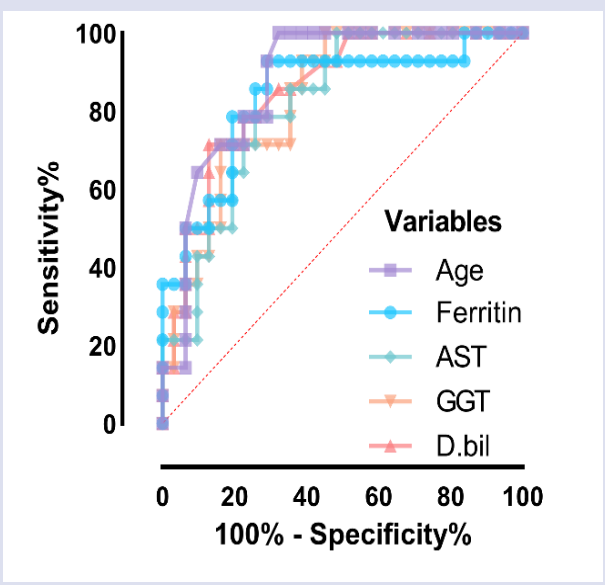

Figure 2. ROC graphs for Variables in Predicting CCHF Severity. According to the data in Table 2, the five variables with the highest AUC values are shown in the graph. AST, Aspartate transaminase; GGT, Gama-glutamyl transferase; D.bil, Direct bilirubin.

Discussion

In this study, significant differences were found in terms of β2M levels between patient and healthy control groups. Additionally, higher β2M levels were associated with a more severe disease course. Our study is the first to determine the associations between serum β2M levels and the course of CCHF disease.

Our study revealed that β2M levels were higher in CCHF patients than in healthy controls. β2M, a protein found in cell membranes of activated immune cells such as T and B lymphocytes and macrophages, is produced by lymphocytes under the influence of interferons and proinflammatory cytokines [14, 15]. Studies in CCHF patients have shown that cytokine storm is one of the factors that play a role in the pathogenesis and prognosis of the disease [16]. Our study found that IL-6 levels were higher in the patient group compared to healthy controls. We also found a statistically significant difference between the two groups in terms of lymphocyte levels. Accordingly, we think changes in lymphocyte levels and increased inflammation may cause elevated β2M levels in CCHF patients.

In the present study, we also determined statistically significant difference between mild and moderate-severe groups. This finding is consistent with a study in which high β2M levels were associated with poor prognosis in individuals with the Omicron variant of COVID-19 [17]. Currently, no specific pharmaceuticals or vaccines are available to combat the disease directly, so the primary therapeutic approach relies heavily on supportive measures. These include interventions such as administering fresh frozen plasma, conducting apheresis procedures, applying platelet treatments, and carefully regulating fluid-electrolyte equilibrium [18]. Given this

context, the early determination of the disease's prognosis emerges as a critical factor in guiding effective treatment strategies. Therefore, integrating the β2M assessment into prognostic evaluations presents an opportunity to refine and optimize the management of therapeutic interventions. By leveraging β2M as an indicator of disease progression and outcome prediction, clinicians may gain valuable insights that facilitate more precise and tailored approaches to patient care. This underscores the importance of proactive prognostic assessments in informing therapeutic decisions and ultimately improving patient outcomes in the absence of specific curative interventions.

β2M is considered an early and sensitive biomarker for acute kidney injury and a structural protein that regulates the immune system in the host. It directly participates in the inflammatory response and can regulate cytokine expression. β2M is implicated in the regulation of immune responses. Changes in β2M concentration can impact the activation and function of immune cells, including T lymphocytes and natural killer (NK) cells. Elevated levels of β2M have also been associated with certain viral infections and inflammatory conditions, indicating its role as a biomarker for immune activation [10, 17]. These findings indicate a progressive elevation of β2M levels with the severity of CCHF. Furthermore, our analysis revealed positive correlations between serum β2M concentrations and several markers, including BUN, creatinine, uric acid, creatine kinase, and aPTT. Conversely, negative correlations were observed with total protein, albumin, and platelet count. The positive correlations with impaired markers of kidney function and prolonged coagulation time suggest a potential association between elevated β2M and organ dysfunction in CCHF. The negative correlations with indicators of overall protein status (total protein and albumin) and platelet count suggest a potential link between increased β2M levels and compromised immune function and coagulation balance.

The study has some limitations. Firstly, no comorbidity that could affect the outcome of CCHF patients has been included in the investigation. Secondly, serum β2M levels were measured only on the first day the patients presented, and a time-dependent evaluation was not performed.

In conclusion, our study suggests that higher β2M levels in CCHF patients may indicate increased immune activation and systemic inflammation. The positive correlations with markers of organ dysfunction and negative correlations with indicators of overall health imply a potential role for β2M as a biomarker for disease severity and prognosis in CCHF.

Conflicts of Interest

There are no conflicts of interest in this work.

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