

Original Article

Correlation between β 2-microglobulin level and risk of cardiovascular events and prognosis in hemodialysis patients

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Abstract: Objective: This study aims to investigate the effect of β 2-microglobulin (β 2-MG) on the occurrence of cardiovascular events (CVE) in hemodialysis patients and its relationship with prognosis. Methods: In this retrospective study, we included 102 hemodialysis patients treated at Jinan People's Hospital Affiliated with Shandong First Medical University from September 2020 to January 2023. Clinical and follow-up data were collected. Logistic regression was used to evaluate the relationship between β 2-MG and CVEs, while Cox proportional hazards regression analysis was used to assess the possible correlation between β 2-MG and prognosis. Results: CVEs occurred in 41 of the 102 patients (40.20%). Of the patients, 72 patients survived, and 30 patients died, with an average survival time of 22.47 ± 7.41 months (range: 7-38 months). Univariate analysis revealed no significant differences in age, albumin, serum soluble growth stimulating expression gene 2 protein (ST2), β 2-MG, or urea clearance index (Kt/V) between the CVE group and the non-CVE group, nor between the death and survival groups ($P > 0.05$). However, logistic regression analysis showed that elevated serum ST2 and β 2-MG levels > 30.1 mg/L were independent risk factors for CVE in hemodialysis patients ($P < 0.05$). Cox regression analysis revealed that an increase in β 2-MG level was an independent risk factor for mortality in these patients ($OR = 3.385$, $P < 0.05$). Survival analysis demonstrated a significant difference in survival among patients with different β 2-MG levels (Log-rank² = 18.230, $P < 0.001$). Conclusion: Elevated β 2-MG level is an independent risk factor for CVEs and mortality in hemodialysis patients, serving as an effective indicator for predicting the occurrence and prognosis of these outcomes.

Keywords: β 2-microglobulin, hemodialysis, cardiovascular events, risk factors, influence of prognosis, analysis of correlation

Introduction

With population aging and lifestyle changes, chronic kidney disease (CKD) has become a significant cause of increased morbidity and mortality from non-communicable diseases [1]. The global prevalence of CKD is about 11.7%-15.1%, with approximately 4.9 to 7.1 million requiring renal replacement therapy due to end-stage renal disease (ESRD) [2]. Among the available treatments for ESRD, renal transplantation offers the best survival outcome. However, due to the limited availability of organs, maintenance hemodialysis (MHD) remains the

most widely used treatment in clinical practice [3]. Both the number of ESRD and MHD patients are increasing globally. In the United States, a study of 746,557 ESRD patients revealed that 62.7% were receiving MHD, and the MHD patient population grew by 84.1% from 2000 to 2017 [4]. In Europe and worldwide, there are approximately 350,000 and 3 million MHD patients, respectively, with projections indicating this number could rise to 5.4 million by 2030. These figures do not account for patients who are unable to access MHD due to economic, technological, or other barriers [5]. These epidemiologic findings suggest that MHD imposes

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a heavy economic burden on global health care.

In recent years, advancements in blood purification technology have led to longer survival time for dialysis patients [6]. It is important to note that MHD can alleviate only some symptoms of ESRD and cannot fully replace renal function. With the extension of MHD, the incidence of ESRD-related complications, such as cardiovascular events (CVE), mineral metabolism disorders, and endocrine system disorders, also rises. These adverse events not only negatively affect the long-term prognosis of MHD patients but also significantly increase mortality rates [7-9]. CVEs are a major cause of poor treatment outcomes and prognosis in hemodialysis patients. Identifying the factors influencing CVEs in hemodialysis patients and implementing timely, targeted interventions are critical for reducing CVE risk and improving patient prognosis [10]. Serum β 2-MG, a marker of middle molecular toxins, is an important indicator of glomerular filtration function and holds significant clinical value [11]. Relevant studies have shown that β 2-MG levels are associated with sudden death, myocardial infarction, and stroke, and serves as an independent risk factor for cardiovascular diseases. However, there are few studies on β 2-MG and the prognosis of hemodialysis patients [12, 13]. The role of β 2-MG in CVEs and its relationship with patient prognosis remain unclear. Therefore, this study aims to investigate the correlation between β 2-MG levels and the risk and prognosis of CVEs in hemodialysis patients, with the goal of identifying biomarkers and therapeutic targets for the prevention and treatment of CVEs in hemodialysis patients. This may provide clinicians with valuable insight to improve cardiovascular outcomes in hemodialysis patients.

Materials and methods

Case selection

The study included 102 patients undergoing hemodialysis at Jinan People's Hospital Affiliated with Shandong First Medical University, from September 2020 to January 2023. Inclusion criteria: (1) Diagnosis of stage 5 chronic kidney disease; (2) Stable patients receiving regular hemodialysis for at least 4 months at our hospital's dialysis center; (3) Age over 18

years; (4) Availability of complete clinical data for the study. Exclusion criteria: (1) History of severe trauma or surgery within the past 3 months; (2) Presence of malignant tumors; (3) Patients with hematological diseases; (4) Patients with mental illness. This study was reviewed and approved by the Institutional Review Board of Jinan People's Hospital Affiliated to Shandong First Medical University.

Methods for the detection of β 2-MG

Serum β 2-MG levels were measured using an Olympus AU2700 automatic biochemical analyzer by nephelometry. β 2-MG is filtered through the glomerulus and degraded in the proximal tubules through a macrophage-dependent pathway. The normal β 2-MG level in healthy individuals is 1-3 mg/L. In patients with negligible glomerular filtration due to hemodialysis, β 2-MG level can reach 20-50 mg/L or even higher.

Data collection and outcome measurement

(1) Main outcome measures included the occurrence of CVE, overall survival (OS) and mortality after follow-up. CVEs were defined as hospitalization events resulting from acute myocardial infarction, congestive heart failure, transient ischemic attack, stroke, percutaneous coronary intervention, peripheral arteriosclerosis, and cardiovascular death, as recorded in the clinical medical records [14]. The patients were subsequently followed up after discharge, with the endpoint being either death or the end of the follow-up period (January 2024).

(2) Secondary indicators encompassed general clinical data (age, sex, body mass index (BMI), dialysis time, systolic blood pressure, alcohol consumption history, smoking history, primary etiology), and laboratory indicators (serum soluble growth stimulating expression gene 2 protein (ST2), β 2-MG, hemoglobin, serum creatinine, albumin (ALB), urea clearance index (Kt/V), and C-reactive protein (CRP)).

Statistical methods

Data were processed using SPSS 27.0 statistical software. Count data were expressed as n (%) and analyzed using the chi-square test. Measured data were expressed as the mean and standard deviation and analyzed using Student's t-test. Logistic regression was used

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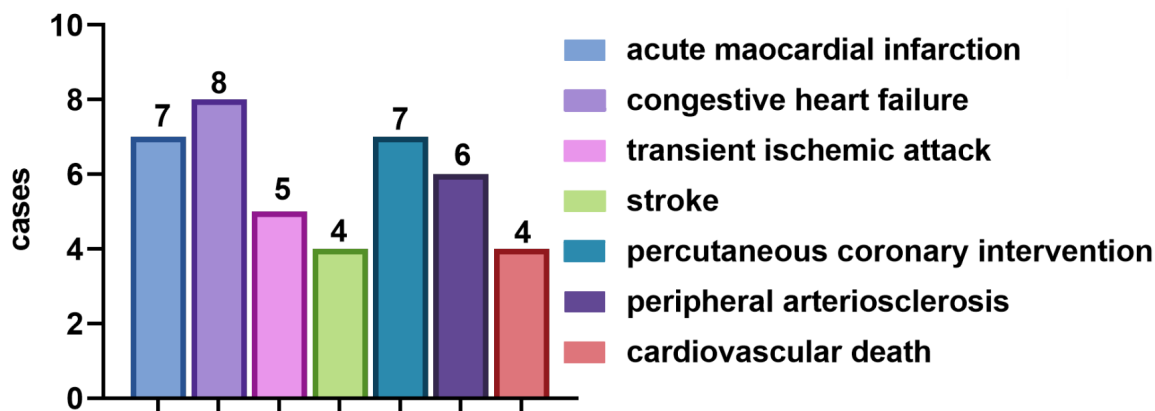


Figure 1. Occurrence of cardiovascular events.

to analyze factors related to CVEs in patients on hemodialysis. The Cox proportional hazards regression model was used to identify factors related to mortality in hemodialysis patients. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive value of β 2-MG for CVEs and patient prognosis. Kaplan-Meier survival analysis was employed to explore survival differences in hemodialysis patients with different β 2-MG levels. $P < 0.05$ indicated a significant difference.

Results

Occurrence of cardiovascular events

CVEs occurred in 41/102 patients (40.20%), including acute myocardial infarction ($n=7$), congestive heart failure ($n=8$), transient ischemic attack ($n=5$), stroke ($n=4$), percutaneous coronary intervention ($n=7$), peripheral arteriosclerosis ($n=6$), and cardiovascular death ($n=4$) (Figure 1).

Univariate analysis of factors influencing cardiovascular events in hemodialysis patients

Univariate analysis revealed significant differences in age, ALB, serum soluble ST2, β 2-MG, and Kt/V between the CVE and the non-CVE groups ($P < 0.05$), as shown in Table 1.

Multivariate logistic regression analysis of factors influencing CVEs in hemodialysis patients

Significant single-factor variables were included in a multivariate analysis, with the variable assignment detailed in Table 2. Logistic regression analysis showed that elevated β 2-MG lev-

els were an independent risk factor for CVE in hemodialysis patients ($P < 0.05$), as shown in Figure 2.

Predictive value of β 2-MG for the occurrence of CVEs in hemodialysis patients

Receiver operating characteristic (ROC) analysis was used to evaluate the predictive value of β 2-MG for the occurrence of CVE in hemodialysis patients. The results showed that the area under the curve (AUC) for β 2-MG in diagnosing CVE in hemodialysis patients was 0.712 ($P < 0.001$), with a cut-off value of 30.1 mg/L, as shown in Figure 3.

Survival of hemodialysis patients during follow-up

The follow-up period lasted until January 2024. Of the 102 patients included in the study, 72 survived, and 30 died. The average survival time was (22.47 ± 7.41) months (range 7-38 months), and the 3-year overall survival rate was 72.55% (74/102).

Univariate analysis of prognostic factors in hemodialysis patients

Univariate analysis revealed significant differences between survivors and non-survivors regarding age, ALB, serum soluble ST2, β 2-MG, and Kt/V ($P < 0.05$) (Table 3).

Cox proportional hazards regression analysis of factors influencing the prognosis of patients on hemodialysis

Significant single-factor variables were included in a Cox proportional hazards regression

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Table 1. Univariate analysis of CVE in patients on hemodialysis

Index	CVE (n=41)	Non-CVE (n=61)	χ^2/t	P
Age (years)	61.17±14.83	55.03±13.48	2.166	0.033
Sex			0.001	0.971
Men	23 (56.10)	34 (55.74)		
Women	18 (43.90)	27 (44.26)		
BMI (kg/m ²)	23.74±3.56	23.31±2.84	0.682	0.497
Dialysis time			3.561	0.059
≥2 years	36 (87.80)	44 (72.13)		
<2 years	5 (12.20)	17 (27.87)		
History of drinking			0.276	0.600
Yes	12 (29.27)	15 (24.59)		
No	29(70.73)	46 (75.41)		
History of smoking			0.740	0.390
Yes	14 (34.15)	16 (26.23)		
No	27 (65.85)	45 (73.77)		
Primary disease			3.342	0.342
Chronic glomerulonephritis	17 (41.46)	35 (57.38)		
Hypertensive renal injury	12 (29.27)	14 (22.95)		
Diabetic nephropathy	9 (21.95)	7 (11.48)		
Other	3 (7.32)	5 (8.19)		
Serum soluble ST2			5.330	0.021
Increase	25 (60.98)	23 (37.70)		
Decrease	16 (39.02)	38 (62.30)		
Hb (g/L)	97.12±24.59	101.62±24.37	0.911	0.364
β2-MG (mg/L)	29.92±6.69	25.11±5.99	3.788	<0.001
Scr (μmol/L)	967.20±85.92	948.95±83.96	1.066	0.289
Albumin (g/L)	30.95±7.94	37.31±9.02	3.661	<0.001
Kt/V	1.43±0.23	1.60±0.21	3.898	<0.001
CRP (mg/L)	20.20±5.61	19.70±6.12	0.410	0.683

CVE, cardiovascular events; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; Scr, serum creatinine; ST2, growth stimulating expression gene 2; MG, microglobulin; Kt/V, urea clearance index.

Table 2. Variable assignment

Variable	Assignment
CVE occurrence	1: happened, 0: did not happen
Age	Input actual value
Albumin	Input actual value
Serum soluble ST2	1: increase, 0: decrease
β2-microglobulin	Input actual value
Kt/V	Input actual value

CVE, cardiovascular event; ST2, growth stimulating expression gene 2; Kt/V, urea clearance index.

analysis. Death during the follow-up period was coded as 1, and survival at discharge or the end of follow-up was coded as 0. The assignment of other variables is shown in **Table 2**. Cox proportional hazards regression analysis showed that elevated β2-MG level was an indepen-

dent risk factor for mortality in patients on hemodialysis (overall risk =3.385, $P<0.05$) (**Figure 4**).

Differences in survival among hemodialysis patients with different β2-MG levels

Patients were divided into two groups based on a β2-MG cut-off value of 30.1 mg/L: the high level group (β2-MG>30.1 mg/L) and the low level group (β2-MG≤30.1 mg/L). The survival outcomes of these two groups were compared. As shown in **Figure 5**, the survival of patients with different β2-MG levels was significantly different (Log-rank² =18.230, $P<0.001$).

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variable	B	SE	wald x ²		P
Age	0.774	0.520	2.217		0.136
ALB	0.008	0.471	0.000		0.986
Serum soluble ST2	1.038	0.476	4.766		0.029
β2-MG	1.586	0.525	9.114		0.003
Kt/V	0.161	0.642	0.063		0.802

Hazard Ratio(95%CI)

Figure 2. Multivariate logistic regression analysis of factors affecting CVE occurrence in patients on hemodialysis. Alb, albumin; ST2, growth stimulating expression gene 2; MG, microglobulin; Kt/V, urea clearance index.

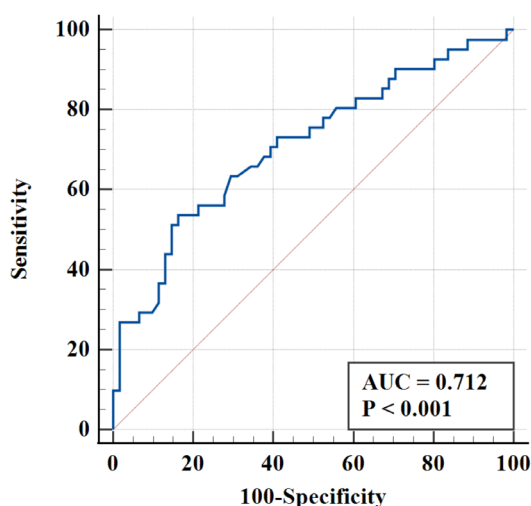


Figure 3. Predictive value of β2-microglobulin for the presence of cardiovascular events in hemodialysis patients. AUC, Area under curve.

Discussion

Long-term hemodialysis can increase the burden on the myocardium and cardiovascular system of patients, leading to multiple organ damage. This not only worsens clinical efficacy and quality of life but may also threaten the life safety of patients [15]. Therefore, reducing the incidence of complications during hemodialysis and improving their long-term survival and prognosis have become the focus of current clinical research. In hemodialysis patients, CVEs are a common and serious complication in hemodialysis patients, with a significant negative effect on prognosis [16]. The incidence of heart

failure in hemodialysis patients exceeds 40%, and both CVEs and mortality rates are higher compared to non-dialysis patients [17]. Our analysis revealed that 40.2% of hemodialysis patients experienced CVEs, which aligns with previous studies [18]. Therefore, the risk of CVEs in hemodialysis patients should not be ignored. Understanding the factors influencing CVE in hemodialysis patients helps us to better grasp its pathogenesis and provides a scientific basis for clinical intervention.

Univariate analysis revealed significant differences in age, ALB, serum soluble ST2, β2-MG and Kt/V among hemodialysis patients with different CVEs and prognosis. Specifically, patients with CVE were older, had higher serum soluble ST2 and β2-MG levels, and lower ALB and Kt/V levels compared to those without CVE. Preliminary analysis shows that aging leads to the gradual decline in the function of organs such as blood vessels and the heart, which may lead to decreased vascular elasticity, increased blood pressure, and weakened heart function. These changes increase the risk of CVE and adversely affect patient prognosis [19]. Albumin level is an important indicator of nutritional status and dialysis adequacy in dialysis patients, and a decrease in albumin level may indicate malnutrition or inadequate dialysis [20, 21]. Serum soluble ST2 is a cardiac marker primarily secreted by cardiac fibroblasts. Previous studies have confirmed that higher serum soluble ST2 levels are associated with an increased risk of heart failure in patients [22]. The Kt/V ratio represents the effi-

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Table 3. Univariate analysis of prognosis in patients on hemodialysis

Index	Survival (n=72)	Death (n=30)	χ^2/t	P
Age (years)	55.01±13.99	63.47±13.40	2.814	0.006
Sex			0.957	0.328
Men	38 (52.78)	19 (63.33)		
Women	34 (47.22)	11 (36.67)		
BMI (kg/m ²)	23.38±3.18	23.74±3.07	0.526	0.600
Dialysis time			0.604	0.437
≥2 years	55 (76.39)	25 (83.33)		
<2 years	17 (23.61)	5 (16.67)		
History of drinking			1.028	0.311
Yes	17 (23.61)	10 (33.33)		
No	55 (76.39)	20 (66.67)		
History of smoking			3.325	0.068
Yes	25 (34.72)	5 (16.67)		
No	47 (65.28)	25 (83.33)		
Primary disease			1.267	0.737
Chronic glomerulonephritis	39 (54.17)	13 (43.33)		
Hypertensive renal injury	18 (25.00)	8 (26.67)		
Diabetic nephropathy	10 (13.89)	6 (20.00)		
Other	5 (6.94)	3 (10.00)		
Serum soluble ST2			11.777	0.001
Increase	26 (36.11)	22 (73.33)		
Decrease	46 (63.89)	8 (26.67)		
Hb (g/L)	98.88±25.52	102.07±21.85	0.599	0.550
β2-MG (mg/L)	25.58±5.90	30.56±7.22	3.635	<0.001
Scr (μmol/L)	952.68±85.41	964.93±84.15	0.663	0.509
Albumin (g/L)	35.92±8.99	31.97±8.93	2.025	0.046
Kt/V	1.58±0.21	1.42±0.25	3.283	0.001
CRP (mg/L)	20.38±5.85	18.77±5.94	1.259	0.211
Cardiovascular events			4.796	0.029
Yes	24 (33.33)	17 (56.67)		
No	48 (66.67)	13 (43.33)		



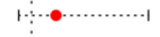

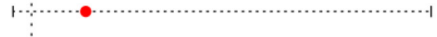

BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; Scr, serum creatinine; MG, microglobulin; Kt/V, urea clearance index.

ciency of dialysis, calculated as the clearance of urea relative to the volume of the dialyzer per unit of time [23]. Increasing the Kt/V value has been shown to reduce the risk of mortality in patients undergoing hemodialysis [24].

Unlike age, ALB, serum soluble ST2, and Kt/V, β2-MG showed significant differences between hemodialysis patients with different CVEs and different prognosis. Moreover, high level of β2-MG is an independent risk factor for CVE and death in hemodialysis patients. β2-MG is an endogenous, low-molecular-weight serum protein whose levels reflect the degree of renal dysfunction in hemodialysis patients [25]. In

the normal population, the synthesis rate of β2-MG and its release from cell membranes are relatively stable. However, in hemodialysis patients, the clearance rate of β2-MG is affected by many factors, such as dialysis membrane permeability, dialysis time, and blood flow. As a result, β2-MG levels can become elevated in these patients. Elevated β2-MG levels usually indicate more severe renal impairment, which may increase the risk of CVE. Elevated β2-MG levels usually indicate more severe renal impairment, which may increase the risk of CVE. This is in line with the findings of Jin et al., who noted that hemodialysis patients with elevated β2-MG levels tend to have poorer prognoses

β2-microglobulin level in hemodialysis patients

variable	B	SE	wald x ²		P
Age	-0.191	0.470	0.165		0.684
ALB	-0.206	0.397	0.268		0.604
Serum soluble ST2	0.499	0.464	1.155		0.282
β2-MG	1.232	0.407	9.167		0.002
Kt/V	0.890	0.795	1.252		0.263
CVE	0.189	0.424	0.199		0.656

Hazard Ratio(95%CI)

Figure 4. Cox proportional hazards regression analysis of prognosis in patients undergoing hemodialysis. Alb, albumin; ST2, growth stimulating expression gene 2; MG, microglobulin; Kt/V, urea clearance index; CVE, cardiovascular events.

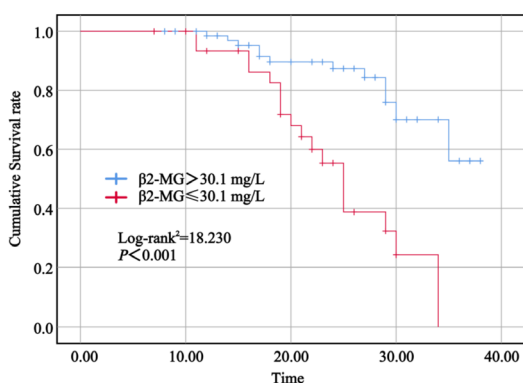


Figure 5. Survival curves of hemodialysis patients with different β2-microglobulin levels. MG, microglobulin.

and shorter survival [26]. Elevated β2-MG levels may not only impair cardiovascular function but also may damage the immune and skeletal systems, leading to a variety of complications that worsen health and quality of life. Therefore, monitoring β2-MG levels is crucial for the assessment of CVE risk and prognosis in hemodialysis patients.

However, several limitations of this study should be acknowledged. These include its retrospective design, limited sample size, data collection from a single center, and the relatively short follow-up duration. In addition, there may have been other unmeasured confounders that influenced our findings. To address these limitations, we recommend conducting a prospective, multicenter study to improve the gener-

alizability and reliability of the results. Expanding the sample size would improve the statistical power, while extending the follow-up period would provide more comprehensive understanding of the long-term effect of β2-MG levels on patient prognosis. Future studies should also consider more potential confounders, including lifestyle, genetic factors, and environmental exposures. We look forward to further studies that will address these challenges and offer stronger evidence for managing cardiovascular disease in hemodialysis patients.

Conclusion

This study used logistic regression and Cox proportional hazards regression analysis to explore the relationship between β2-MG levels and CVE in patients on hemodialysis, focusing on possible correlations with prognosis. The analysis found that elevated β2-MG level is an independent risk factor for both CVE and mortality in patients on hemodialysis. β2-MG can be used to predict the occurrence and prognosis of CVE in patients on hemodialysis.

Disclosure of conflict of interest

None.

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