International Journal of Nephrology and Renovascular Disease

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ORIGINAL RESEARCH

Association of Beta-2 Microglobulin Concentrations with Frailty in Patients Undergoing Chronic Hemodialysis

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Introduction: Patients with Chronic Kidney Disease (CKD) undergoing regular hemodialysis experience various metabolic changes, including premature aging marked by increased prevalence of frailty. Beta-2 microglobulin (B2M), a uremic toxin whose concentration significantly increases in hemodialysis patients, has emerged as a potential biomarker of frailty. Previous evidence suggests potential link between B2M and frailty in older adults. However, data on its relationship with frailty in hemodialysis patients remains limited.

Purpose: To determine the relationship between B2M concentration and frailty in hemodialysis patients.

Patients and Methods: This is a cross-sectional study utilizing primary data from hemodialysis patients at Rumah Sakit Cipto Mangunkusumo (RSCM), employing a total sampling method. Beta-2 microglobulin was measured using the Enzyme-Linked Fluorescent Assay (ELFA) method. Frailty was assessed using the Frailty Index 40-item. Medical history was obtained from medical records and interviews. Chi-square tests were performed to determine the relationship between B2M and frailty. Multivariate analysis was conducted to determine variables that affect frailty.

Results: A total of 79 subjects participated in the study. The median B2M concentration was 32.8 (IQR 29.8–36.77). Higher B2M concentration showed a trend toward increased frailty prevalence (PR of 4.83, 95% CI 0.69–33.81, p = 0.113). The final multivariate analysis showed that sarcopenia (PR 5.37; 95% CI 2.88–10.04) was strongly and consistently associated with frailty prevalence.

Conclusion: Higher B2M showed a trend towards increased frailty prevalence; however, this association is not statistically significant. Sarcopenia is a significant factor influencing the prevalence of frailty in hemodialysis patients.

Keywords: beta-2 microglobulin, frailty, hemodialysis

Introduction

Chronic kidney disease (CKD) is a global health problem which is predicted to be the fifth cause of death by 2040.[1] Data on the prevalence of CKD in Indonesia is still limited. According to 2018 Riskesdas data, the prevalence of CKD in Indonesia increased by 50% from 2013 to 2018.[2] A 2023 Indonesian Renal Registry (IRR) report estimated that the number of hemodialysis patients had increased significantly, with almost 130000 patients undergoing regular dialysis, and 95% of those having stage 5 CKD. This reflects the burden of end-stage renal disease (ESRD) in the country. Recent research shows that CKD patients experience premature aging along with accompanying diseases. Premature aging refers to the accelerated biological aging processes observed in CKD patients, characterized by early onset of age-related health

Received: 30 December 2024
Accepted: 26 May 2025
Published: 10 June 2025

issues, including increased frailty, sarcopenia, reduced physiological reserve, and heightened vulnerability to stressors compared to age-matched individuals without CKD.[3,4] Recent studies show that there is an increase in the prevalence of frailty in CKD population.[5] One of the biomarkers that has recently been studied in frailty is Beta-2 Microglobulin (B2M).[6–9] Beta-2 microglobulin is also a uremic toxin which plays an important role in CKD.[10]

Beta-2 microglobulin is an amino acid which is a component of the major histocompatibility class I complex (MHC-I) molecule, found in low amounts in urine, serum and other biological fluids. More than 95% of B2M is eliminated through degradation processes in the proximal tubules of the kidney.[6] The clearance of B2M is influenced by the type of dialysis membrane and technique used. As a middle molecule, B2M is poorly removed by conventional low-flux dialysis membranes, leading to its accumulation up to sixty times the normal value in hemodialysis patients.[10] Conventional low-flux hemodialysis has limited the ability to remove B2M, leading to its accumulation over time.[10] High-flux hemodialysis (HF), hemodiafiltration (HDF) and expanded hemodialysis (HDx) have demonstrated varying degrees of B2M clearance.[11–15] A study by Vega-Vega et alindicates that HDF and HDx provide significantly better B2M clearance than HF (62% vs 73% vs 27%, respectively).[12] While HDF has been shown to be the most effective technique for B2M clearance, HDx has shown comparable efficacy by utilizing medium cutoff (MCO) membranes. The MCO dialyzer enhances permeability for large middle molecules while preserving essential proteins.[14] Online HDF (OL-HDF) requires substantial convective volumes (18–22 L/session).[11] Conversely, HDx requires lesser convective volumes, broadening its accessibility.[15]

Beta-2 microglobulin has various biological functions and is clinically known as a marker of renal dysfunction.[6] Beta-2 microglobulin has also demonstrated good predictive utility for mortality rates, disease-specific deaths, and other outcomes in a wide range of populations in various studies.[7] Beta-2 microglobulin is known as a nonspecific biological marker of disease activity in malignancies (multiple myeloma), CKD, autoimmune diseases, and various infections. Beta-2 microglobulin is known to undergo glycosylation into amyloid fibrils and is deposited especially in joints, known as Dialysis-Related Amyloidosis (DRA). Deposition of amyloid fibrils in joints can cause joint pain and immobilization which can contribute to the frailty phenotype.[16] Beta-2 microglobulin has a role as an indicator of hemodialysis adequacy, a predictor of complications, a marker for prognosis, and a guide to therapy management in hemodialysis patients.[17] Increased B2M concentration also reflects a decrease in various physiological systems of the body that can be associated with frailty.[8] Several previous studies conducted on non-dialysis populations in France, Japan, China and Turkey showed a significant relationship to B2M as a biomarker for frailty in non-dialysis patients.[6–8,9]

B2M appears to affect vascular health through changes in metabolism and cardiac performance. High serum B2M levels have been associated with reduced levels of endothelial progenitor cells CD34+ and CD133+ that are critical for neovascularization.[18] This in turn will contribute to progressive decline in physiological reserve characteristic of frailty. Moreover, as component of MHC-I molecules, elevated B2M levels may reflect immunosenescence and chronic inflammation[19]— Both of which are important in the development of frailty. A cohort study in China found that B2M was associated with frailty phenotype and frailty index measures. For each standard deviation B2M increase, the adjusted odds ratio for frailty phenotype was 1.20, demonstrating a dose–response relationship. This suggests that B2M is an independent biomarker of the aging process across multiple physiological systems.[7]

However, despite growing evidence linking B2M to frailty in the general population, its role in patients undergoing hemodialysis remains unexplored. Given that B2M accumulates significantly in these patients, understanding this relationship is crucial. Research into the association between B2M and frailty is important for early identification of frailty and to encourage routine B2M examinations in hemodialysis patients in the future in accordance with existing recommendations.

Materials and Methods

Study Design and Participants

This study is a cross-sectional study with primary data. Patients from the hemodialysis unit at Cipto Mangunkusumo Hospital, Jakarta, Indonesia were included in the study in November 2024. Total sampling was used for the sampling method. Subjects aged ≥40 years old, undergoing hemodialysis for more than 3 months, and willing to sign the consent

form were included in the study. The exclusion criteria were those with acute hemodynamical instability, history of hospitalization within three months, hematological malignancy and the presence of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). The study is done in adherence to the principle of the Declaration of Helsinki. All participants were informed about the purpose of the study and provided written informed consent to participate in the study.

Collection of Data

General data were collected by interview and medical record. Beta-2 microglobulin was measured using the Enzyme Linked Fluorescent Assay (ELFA) method by Laboratorium Medis Prodia, blood sample taken before hemodialysis. This study already passed ethical approval from Health Research Ethics Committee Faculty of Medicine Universitas Indonesia-Cipto Mangunkusumo Hospital with registered number KET-1751/UN2.F1/ETIK/PPM.00.02/2024.

Frailty is defined as a clinical syndrome characterized by a decline in physiological reserves and a reduced ability to respond to stressors. It was assessed using the Frailty Index-40 (FI-40) questionnaire, with the following classification: frail (FI-40 score ≥0.25), pre frail (FI-40 score 0.08–0.25) and fit/robust (FI-40 score <0.08). Nutritional status was assessed using the Subjective Global Assessment (SGA), a clinical tool assessing nutritional risk based on patient history and physical examination. Patients categorized as SGA-A (well-nourished) were defined as having a good nutritional status. Comorbidities were assessed using Charlson Comorbidity Index (CCI). Sarcopenia was assessed using SARC-F questionnaire.

Statistical Analysis

Research data analysis was carried out electronically using STATA software version 17.0 and SPSS software version 24.0. Statistical methods were selected based on data characteristics and distribution. Given the non-normal distribution of Beta-2 microglobulin, a categorical approach using receiver operating characteristic (ROC) curve was adopted. High concentration of B2M divided further into high and very high concentration with specified cutoff point from ROC Curve in subgroup analysis.

Hemodialysis vintage was divided into <5 years and ≥5 years. Hemodialysis adequacy was defined as Kt/V ≥ 1.8. The Charlson Comorbidity Index (CCI) was classified as normal-intermediate (<5 points) and severe (≥5 points).

Chi-square analysis tests were performed to determine the relationship between B2M and frailty, while Poisson regression was used to assess associations and identify independent predictors of frailty. Potential confounders such as gender, age, Charlson Comorbidity Index (CCI), sarcopenia, and dialysis adequacy (Kt/V) were incorporated into multivariate analyses to control for their influence on frailty outcomes.

Results

A total of 79 subjects participated in the study. Of the 100 individuals who met the inclusion criteria, 18 were excluded due to a history of hospital admission within the preceding three months, 2 were excluded due to malignancies, and 1 was excluded due to SLE. The details of the hemodialysis technique used are provided in Table 1. The median B2M concentration was 32.8 mg/L (IQR 29.8–36.77), with an uneven data distribution for B2M and age. The prevalence of frailty was 25.3%. Table 2 presents the baseline characteristic of the study population.

To determine the optimal cutoff point for B2M concentration, ROC curve analysis was performed, identifying a threshold of 28.72 mg/L with 95% sensitivity and 25.4% specificity. Chi-square analysis, assessing the association between B2M concentration and frailty is presented in Table 3.

To further explore the biological gradient, B2M concentration was categorized into three groups. The ROC curve of B2M concentration is presented in Figure 1. The high and very high B2M category was further subdivided into high and very high concentration, using specified cutoff of 36.91 mg/L determined by ROC curve analysis (Figure 2) with 42.1 sensitivity and 75% specificity. The results of the chi-squre analysis are shown in Table 4.

Additionally, we performed bivariate analysis to assess the influence of confounding variables to show their influence to frailty output. Results are shown in Table 5.

Table 1 Hemodialysis Parameters

Parameter	Value
Blood flow (mL/min)	200–250 (Refer to Table 2)
Dialysate flow (mL/min)	500
Therapy duration (hours)	5
Dialysis adequacy (Kt/V)	Refer to Table 2
Dialysis machine	B-Braun Dialog+
Type of vascular access	Hemodialysis catheter (41) Arteriovenous fistula (38)
Dialysis membrane	Diacap® Pro (α polysulfone pro membrane)

Table 2 Baseline Characteristic of Subjects

Characteristics	Subjects (n = 79)
Sex, n (%)	
Male	44 (55.7)
Female	35 (44.3)
Menopause status, n (%) (n = 35)	26 (74.3)
Duration of Menopause, median (IQR) years	10 (4.75–15)
Age, mean (SD)	57.14 (9.58)
Age, n (%)	
< 60 years	46 (58.2)
≥ 60 years	33 (41.8)
Educational Status, n (%)	
Low	4 (5.1)
Intermediate	40 (50.6)
High	35 (44.3)
Occupational Status, n (%)	
Not Working	51 (64.6)
Actively Working	28 (35,4)
Weight, median (IQR)	61 (54.5–67.5)
Height, mean (SD)	160.15 (8.43)
Body Mass Index (BMI), median (IQR)	23.53 (21.54–26.75)
Blood Pressure, mean (SD)	
Systolic	139.59 (26.02)
Diastolic	79.38 (14.59)
Hemodialysis vintage (years), median (IQR)	5 (2.5–10)
Hemodialysis vintage, n (%)	
< 5 years	37 (46.8)
≥ 5 years	42 (53.2)
Hemodialysis frequency / week, n (%)	
2 Times	76 (96.2)
3 Times	3 (3.8)
Hemodialysis Adequacy (Kt/V), median (IQR)	2 (1.84–2.16)
Hemodialysis Adequacy (Kt/V), n (%)	
Adequate	64 (81)
Inadequate	15 (19)

(*Continued*)

Table 2 (Continued).

Characteristics	Subjects (n = 79)
CCI score, median (IQR)	5 (3–6)
CCI Category, n (%)	
Low-intermediate (CCI < 5) Severe (CCI ≥ 5)	38 (48.1) 41 (51.9)
Comorbidities, n (%)	
Hypertension	79 (100)
Heart Disease	9 (11.4)
Diabetes Mellitus	31 (39.2)
Stroke	6 (7.6)
Liver Disease	13 (16.5)
Dyslipidemia	25 (31.6)
Nutritional Status, n (%)	
Good	79 (100)
SARC-F Score, median (IQR)	1 (0–3)
Sarcopenia, n (%)	
Normal Sarcopenia	67 (84.8) 12 (15.2)
Frailty, n (%)	
Non-frail Frail	59 (74.7) 20 (25.3)
Beta-2 Microglobulin, median (IQR) (mg/L)	32.8 (29.8–36.77)

Notes: Beta-2 microglobulin concentration divided into low and high with cut-off point specified from ROC Curve (Figure 1).

Table 3 Bivariate Analysis of B2M and Frailty

		Frailty		Total, n (%)	p value	PR (CI 95%)
		Frail, n (%)	Non Frail, n (%)			
B2M	High	19 (30.16)	44 (69.84)	63 (100)	0.113	4,83 (0.69–33.81)
	Low	1 (6.25)	15 (93.75)	16 (100)		
	Total	20 (25.3)	59 (74.7)	79 (100)		

We carried out a multivariate test to identify variables related to the prevalence of frailty among the independent variables and confounding variables studied. The Poisson Regression Test was carried out using backward regression on independent variables and confounding variables with a p value <0.25 in bivariate analysis (gender, comorbidities (CCI), sarcopenia, and B2M concentration) until all variables were found to be factors associated with the incidence of frailty in

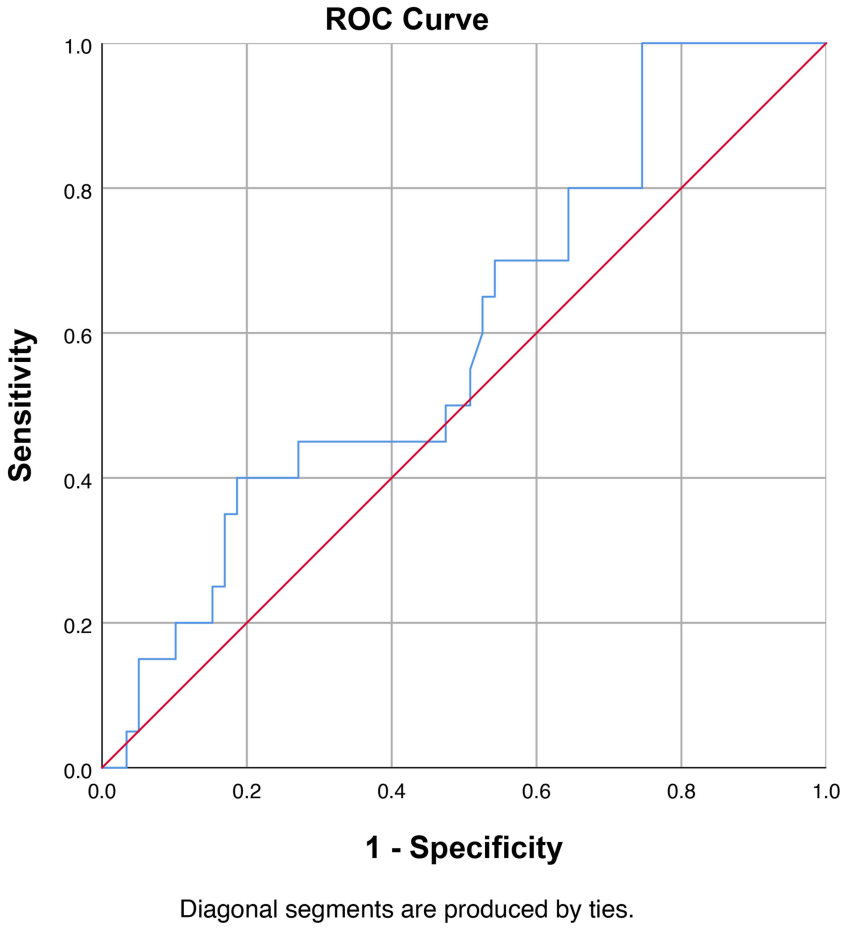

Figure 1 ROC Curve of B2M Concentration.

this study with the final model variables having $p < 0.05$. The following are the variables found to be factors associated with the incidence of frailty along with the p value and prevalence ratio (PR) with a 95% confidence interval presented in Table 6.

Discussion

Previous studies that examined the relationship between B2M and frailty have primarily focused on elderly community-dwelling, non-dialysis populations, highlighting the need for research specifically targeting chronic hemodialysis patients, in whom B2M levels are notably elevated and may have distinct clinical implications.

Our study found B2M concentrations ranging from 7.13 to 49.32 mg/L, with a median of 32.81 mg/L (IQR 29.8–36.7). Participants had a mean age of 57.14 years and a median BMI of 23.53. The median hemodialysis vintage was 5 years, with 42% undergoing dialysis for more than 5 years. Bivariate analysis showed a non-significant trend ($p = 0.113$) suggesting higher B2M concentrations may increase frailty prevalence. Subgroup analysis indicated that elevated B2M levels were associated with up to a 6.73-fold increase in frailty. Multivariate analysis identified sarcopenia as the primary risk factor, increasing frailty prevalence 5.37 times (95% CI 2.88–10.04; $p < 0.001$).

Our B2M concentration range is in accordance with Traut et al which showed a mean B2M of 42.14 (SD 14) mg/L in subjects undergoing high flux hemodialysis.[20] Another study by Jeloka et al also showed a B2M concentration of 25.1 (SD 2.13) mg/L in patients undergoing high-flux hemodialysis. The study had a mean age of 44 (SD 16.45) years.[21] Another study by Topciu-Shufta et al in patients undergoing high-flux hemodialysis also showed only a slightly different results with a mean B2M concentration of 19.84 (SD 2.23) mg/L. The study was conducted on subjects aged 24–65 years who had undergone routine HD for at least six months. This study excluded subjects with malignancies, infections,

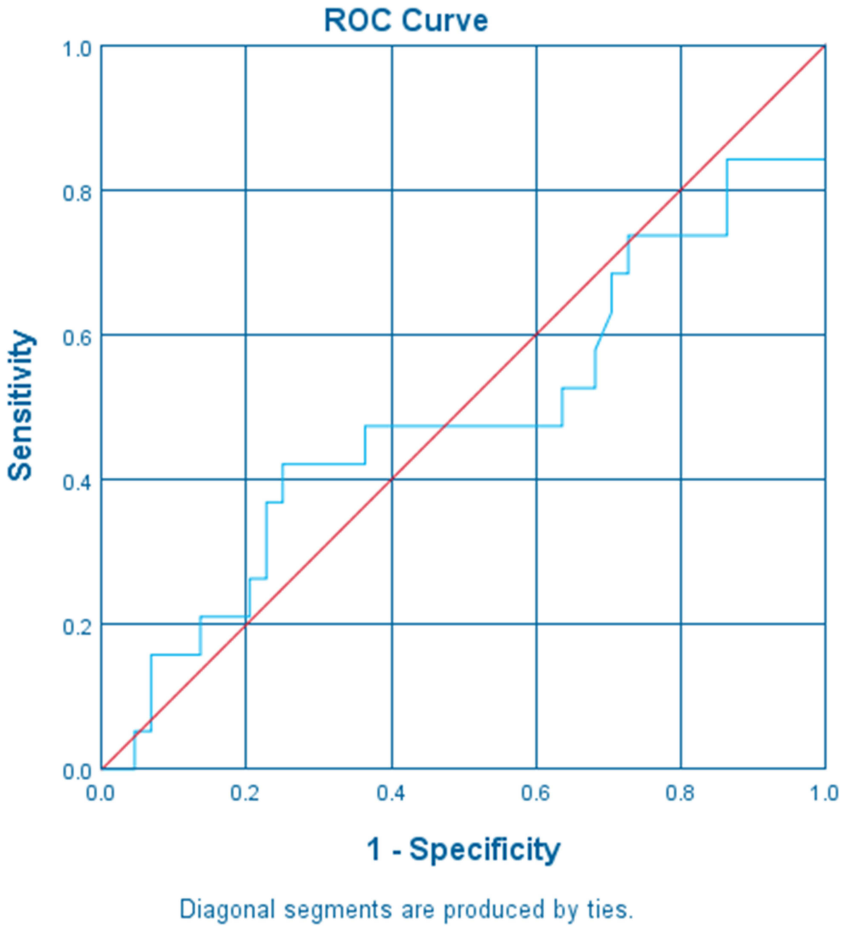

Figure 2 ROC Curve of High B2M Concentration.

strokes, and a history of heart attacks.[22] The Dialysis Outcomes and Practice Patterns Study (DOPPS) study which conducted research on hemodialysis patients aged over 18 years in Europe and Japan also showed B2M concentrations in subjects undergoing HD with high-flux dialyzer of 1.7 (SD 0.4) mg/dL to 3.8 (SD 0.9) mg/dL. The results of this study are still in accordance with the findings of the DOPPS study with a median of 3.28 mg/dL.[23]

This study shows that high B2M concentrations have a tendency to increase the prevalence of frailty (PR 4.82) but this relationship is not statistically significant (95% CI 0.69–33.81; p = 0.113). Biological mechanisms, particularly chronic inflammation, oxidative stress and muscle degradation, may explain the observed association between high B2M and frailty. B2M is a pro-inflammatory molecule that accumulates in renal failure and is associated with oxidative

Table 4 Subgroup Analysis of B2M and Frailty

		Frailty		Total, n (%)	p value	PR (CI 95%)
		Frail, n (%)	Non Frail, n (%)			
B2M	Low	1 (6.25)	15 (93.75)	16 (100)	Reff	Reff
	High	11 (25)	33 (75)	44 (100)	0.170	4 (0.55–28.91)
	Very High	8 (42.1)	11 (58.9)	19 (100)	0.059	6.73 (0.93–48.90)
Total		20 (25.3)	59 (74.7)	79 (100)		

https://doi.org/10.2147/IJNRD.S513968

Table 5 Bivariate Analysis of Confounding Variables and Frailty

Variable	Frail (n = 20)	Non-Frail (n = 59)	PR (CI 95%)	p value
Sex, n (%)				
Male	8 (18.18)	36 (81.82)	1.89 (0.86–4.12)	0.112*
Female	12 (48)	23 (52)		
Age, mean (SD)	60.45 (9.95)	56.02 (9.27)	N/A	0.074**
Age, n (%)				
< 60 years	10 (21.74)	36 (78.26)	1.39 (0.65–2.98)	0.391*
≥ 60 years	10 (30.3)	23 (69.7)		
Hemodialysis vintage (years), median (IQR)	4,25 (1.25–7.5)	5 (2.5–12)	N/A	0.267***
Hemodialysis vintage, n (%)				
< 5 years	11 (29.73)	26 (70.27)	0.72 (0.33–1.55)	0.403*
≥ 5 years	9 (21.43)	33 (78.57)		
Hemodialysis Adequacy, median (IQR)	2.08 (1.79–2.29)	1.98 (1.84–2.13)	N/A	0.420***
Hemodialysis Adequacy, n (%)				
Adequate	15 (23.44)	49 (76.56)	0.7 (0.3–1.64)	0.415*
Not Adequate	5 (33.33)	10 (66.67)		
Nutritional Status, n (%)	20 (25.31)	59 (74.69)	N/A	N/A
Good				
CCI score, median (IQR)	5 (5–6.75)	4 (3–6)	N/A	0.01***
CCI Score, n (%)				
Low-Intermediate (CCI < 5)	4 (10.52)	34 (89.48)	3.71 (1.35–10.17)	0.011*
Severe (CCI ≥ 5)	16 (39.02)	25 (60.98)		
SARC-F Score, median (IQR)	3.5 (2.25–4.75)	1 (0–1)	N/A	<0.001***
Sarcopenia Status, n (%)				
Normal	10 (14.92)	57 (85.08)	5.58 (2.98–10.47)	<0.001*
Sarcopenia	10 (83.33)	2 (16.67)		

Notes: *Chi square; **Independent *T* test; ***Mann–Whitney test.

Table 6 Multivariate Analysis Result

Variables	PR (CI 95%)	p value
First Model		
Sex	1.44 (0.71–2.89)	0.311
CCI Score	2.47 (0.88–6.92)	0.085
Sarcopenia	3.66 (1.76–7.63)	0.001
B2M	4.78 (0.95–23.93)	0.057
Final Model		
Sarcopenia	5.37 (2.88–10.04)	<0.001
B2M	4.40 (0.82–23.59)	0.083

stress.[24] Chronic inflammation leads to muscle breakdown, reduced physical function, and increased vulnerability to stressors. Moreover, high B2M levels have been linked to sarcopenia, a key characteristic of frailty. Some studies suggest that B2M may modulate IGF-1 signaling, a critical pathway for muscle maintenance.

The results of this study were not in accordance with Annweiler et al which showed a relationship between B2M levels and frailty in 43 inpatients aged 70 years or more. The group of research subjects with increased B2M concentrations had a higher frailty rate than the normal group (96.2% vs 66.7%; p = 0.012). The mean age in that study was much higher at 83.1 (SD 7.2) years. There were no exclusion criteria in this study, but it was explained that there were no subjects with a history of multiple myeloma.[8] Another study conducted by Kim et al showed that the risk

of frailty is increased by 2.5 times if the B2M level reaches 1.9–2.1 mg/L, doubles if the B2M level is ≥2.2 mg/L. In this study, it was found that female who had higher B2M levels have a higher likelihood of being frail. This study had a higher mean subject age of 78.4 (SD 2.7) years. There are no exclusion criteria in this study, comorbidity is not one of the variables assessed in this study.[6] Another study by Liu et al also showed that there was a significant relationship between B2M concentration and frailty, both in terms of phenotype and accumulated deficits. Serum B2M concentration ≥2.2 mg/L had a higher prevalence of frailty with adjusted OR 1.68 (95% CI 1.04–2.71; p = 0.034) for phenotypic frailty and 1.51 (95% CI 1.01–2.27; p = 0.044) for frailty in accumulated deficits. The study had a mean age of 75.3 (SD 3.9) years. There were no exclusion criteria in this study, and comorbidity was not one of the variables assessed.[7] A subsequent study by Bayram et al also showed that there was a relationship between B2M concentration and frailty (p < 0.001) with OR 13.98 (95% CI 1.06–184.37). The study had a mean age of 76.3 (SD 7.5) years. This study excluded multiple myeloma but did not exclude other malignancies.[9] All four community studies conducted in older subjects with no exclusion of hospital admission and comorbidities (malignancies and SLE) compared to this study.

The association between B2M concentration was not statistically significant related to frailty, possibly because the B2M data in this study had an uneven distribution (Shapiro–Wilk normality test p < 0.001). The ROC curve shows an AUC of 0.599 (95% CI 0.460–0.738) which illustrates that the existing model has a poor ability to differentiate between high and low concentrations. The optimal cutoff point (28.72 mg/L) was far below the median value in this study (32.8 mg/L) and below the 25th percentile (29.8 mg/L). However, the cutoff point chosen is not much different from recommendations from existing literature. Clinical guidelines from the Japanese Society for Dialysis Therapy (JSDT) recommend that dialysis conditions achieve B2M concentrations below 30 mg/L to reduce mortality rates.[25] The proportion of B2M concentration between high and low can also influence the results of this study. This study divided subjects into 2 B2M concentration groups where 63 subjects were in the high B2M concentration group, while only 16 subjects were in the low B2M concentration group. This unbalanced number of subjects can also affect the results of statistical analysis. Apart from the difference in the number of subjects between the two B2M concentration groups, the number of frailty subjects in the two groups also had quite a difference. Only one subject in the low B2M concentration group (6.25%) suffered from frailty compared to 30.16% in the high B2M concentration group. This indeed supports the literature which shows that frailty occurs at high B2M concentrations.

Apart from the B2M concentration results, this research also has design differences from previous studies. The sample size in this study was 79 subjects, more than the study by Annweiler et al (43 subjects),[8] similar to the study of Bayram et al (81 subjects),[9] but differs greatly from the study by Kim et al (1191 subjects)[6] and Liu et al (1663 subjects).[7] This study also excluded conditions that were proven theoretically to increase B2M concentrations such as history of hospitalization in the last three months, malignant diseases, and SLE, whereas previous studies did not consider these conditions in their research subject selection methods. Comorbidity was also not a variable studied in previous studies. The age of research subjects can also influence study results. Age is known to be a factor that is closely related to the occurrence of frailty. This study had a mean age of 57.14 (SD 9.58) years, whereas previous studies had a mean age of 75.3 to 83.1 years.[6–9]

The results of the bivariate subgroup analysis of the B2M concentration variable with three categories of frailty showed that high B2M concentrations increased the prevalence of frailty by 4 times and very high B2M concentrations further increased the prevalence of frailty by 6.73 times. However, the increase in prevalence at both high and very high B2M concentrations was not statistically significant. The results from this subgroup showed biological gradient and further explained that B2M has a high potential causal relationship with the prevalence of frailty.

Based on the results of the multivariate analysis, sarcopenia was the main risk factor that had a significant effect on frailty with an increase in prevalence of up to 5.37 times (95% CI 2.88–10.04; p < 0.001). These results demonstrate a strong and consistent association between sarcopenia and frailty. High B2M concentrations showed a tendency to increase the prevalence of frailty up to 4.4-fold (95% CI 0.82–23.59; p = 0.083), though this was not statistically significant in the final model. The relationship between sarcopenia and frailty has overlapping clinical manifestations, especially in terms of physical decline. Sarcopenia is defined as age-related loss of muscle mass leading to reduced muscle strength and physical capacity, whereas frailty is a geriatric syndrome also characterized by reduced homeostatic reserves. Some literature even states that sarcopenia is a physical phenotype of frailty.[26,27] Given the close relationship between sarcopenia and frailty,

potential biological mechanism linking B2M to frailty may involve muscle degradation and chronic inflammation. Furthermore, sarcopenia and frailty share common risk factors. The study of Sousa-Santos et al shows that these conditions often coexist with malnutrition and obesity.[28] While B2M concentrations in this study were not significantly associated with frailty, the observed tendency for higher B2M levels to correlate with increased frailty prevalence supports existing literature suggesting a potential role of B2M in muscle degradation and systemic inflammation.

The strength of this study is that we included subjects with a fairly wide age range (40 years to 79 years). The distribution of age data in this study was even, and subgroup analysis was performed on patients aged under and over 60 years, so that it could describe the relationship between age and frailty in the subject population who experienced premature aging due to their CKD. This study also carried out a subgroup analysis of B2M concentrations so that it could see the biological gradient of frailty. This study assesses frailty using the Frailty Index instrument which has the advantage of a quantitative and comprehensive approach. The Frailty Index evaluates various health deficits concluding physical, psychological and social factors. Compared to other instruments (Fried's Frail Phenotype or FRAIL score) the Frailty Index instrument has a continuous scoring system that can assess the progression of frailty over time and is an excellent instrument to use in a research setting.[29] This study covers the duration of hemodialysis starting from 1 year to more than 10 years, varying degrees of hemodialysis adequacy, and varying degrees of comorbidity. This study assesses patient comorbidity as one variable using the CCI score, so the results of this study can describe frailty in hemodialysis patients by level of comorbidity. This study is also the first study to consider factors such as history of hospitalization and comorbidities in research methods which were not taken into account in previous studies.

This study has several methodological limitations that may impact result interpretation. The cross-sectional design allows for assessing frailty prevalence in hemodialysis patients but cannot establish causality. Longitudinal studies are needed to determine whether elevated B2M levels contribute to frailty or serve as markers of existing frailty. The sample size was relatively small (n = 79), resulting in wide confidence intervals, particularly for comorbidity (CCI) and sarcopenia. Additionally, the uneven distribution of B2M concentrations, along with the presence of frail subjects in the low B2M group, may have reduced statistical power, limiting the ability to detect significant associations and could potentially increase the risk of Type 1 errors. Dichotomization may further reduce statistical power and variability, limiting the ability to detect subtle associations. The sample size calculation was based on community population data due to the lack of prior studies on B2M and frailty in hemodialysis patients, making it less than ideal.

Future research should use larger sample sizes and power calculations tailored to the hemodialysis population. Residual confounding remains a concern, as inflammatory markers, and nutritional status were not fully accounted for, particularly since all participants had good nutritional status. This limitation prevented the assessment of malnutrition's impact on B2M concentrations and frailty. Furthermore, while dialysis adequacy was considered, inflammatory biomarkers and dialysis dose were not measured, which could influence the observed associations. Lastly, this study was conducted at a single center, which may limit generalizability. Future studies should aim for multicenter designs, balanced B2M group distributions, explicit adjustments for multiple comparisons, and inclusion of inflammatory markers to provide a more comprehensive evaluation of these associations.

Conclusion

In hemodialysis patients, high B2M concentrations showed a trend toward increased frailty prevalence; however, they were not a statistically significant predictor. In contrast, sarcopenia was strongly associated with the prevalence of frailty. Given the cross-sectional design of this study, further research is needed to explore causal relationships.

Acknowledgments

The authors acknowledge the Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia, for their support and guidance throughout this research. We thank the staff of the hemodialysis unit at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, for their assistance during data collection. We are grateful to Angeline Tancherla for her contribution to the completion of this manuscript.

Disclosure

The author declares that there is no relevant or material financial interests that relate to the research described in this paper.

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