RESEARCH

LESS IS MORE: BETA-2 MICROGLOBULIN AS A FRAILTY MARKER IN COMMUNITY-DWELLING OLDER ADULTS

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Abstract

Background: Serum beta-2 microglobulin levels are commonly employed as prognostic and inflammatory indices, given their ease in assessment, reliability, and cost-effectiveness. Herein, we aimed to confirm the effectiveness of serum beta-2 microglobulin as a marker in geriatric patients and establish its role in frailty assessment.

Materials and Methods: This cross-sectional study included 81 participants aged>65 years. Serum beta-2 microglobulin levels were compared with erythrocyte sedimentation rate, C-reactive protein, procalcitonin, interleukin-1, interleukin-6, tumor necrosis factor Tumor Necrosis Factor-α, and vitamin D levels. To determine whether beta-2 microglobulin is an effective marker for frailty assessment, the study was divided into frail and non-frail patients, except for the acute infection group. Frailty was assessed using the Clinical Frailty Scale Version 9, and quality of life was assessed using the Quality of Life Scale Short Form-36.

Results: The mean age of the participants was 72.14±7.00 years. The frail group comprised 47.5% of the total patients. beta-2 microglobulin exhibited a strong positive correlation with C-reactive protein, Clinical Frailty Scale score, and comorbidity index, and a moderate positive correlation with Tumor Necrosis Factor-α and interleukin-6 levels. Conversely, beta-2 microglobulin and Short Form-36 exhibited a strong negative correlation. The Short Form-36 was the most effective in assessing changes in beta-2 microglobulin levels. The optimal beta-2 microglobulin cut-off value to assess frailty was 3.78 (sensitivity=75%; specificity=93.5%).

Conclusion: In the geriatric population, we detected a significant association between increased beta-2 microglobulin levels and frailty, as well as a significant relationship with decreased quality of life.

Keywords: Frailty Syndrome; Inflammation; Aged.

INTRODUCTION

Frailty is a syndrome related to a decline in physiological competence and capacity to maintain homeostasis, given the accumulation of cellular damage due to several factors over the course of a lifetime. Depending on their physiological and functional status, patients can be categorized into healthy, pre-frail, and frail groups (1). Moreover, frailty is known to be influenced by socioeconomic, psychological, and lifestyle factors such as diet, exercise, and genetic factors (2, 3). The incidence of diverse diseases is reportedly increasing with the gradual accumulation of aging-related cognitive and physical dysfunction. Therefore, frailty markedly impacts this heterogeneity, given that age-related functional changes differ among individuals. In the elderly population, frailty increases the risk of mortality, geriatric syndromes, and other negative health effects. Accordingly, the early detection of frailty can help reduce or postpone such risks. Lifestyle regulation is critical to maximally retain cognitive and physical functions and avoid frailty (3, 4). Assessing frailty levels is markedly important in geriatric patients who need to undergo rehabilitation. Scales are also commonly used to evaluate the quality of life and frailty. Frailty assessment is restricted by its complications in clinical practice, partly attributed to time-consuming testing methods. The identification of biomarkers depends on determining normal laboratory values in older individuals (5-7). Beta-2 microglobulin (B2M), a polypeptide, comprises the major histocompatibility complex class I and is encoded by a gene on chromosome 15. After initial isolation from the urine of patients with tubular proteinuria, B2M was found to be present in the serum (free form), as well as in urine and cerebrospinal fluid, after release from the cell surface or cytoplasm . Reportedly, healthy individuals exhibit relatively consistent B2M concentrations. Activation of the immune system induces the release of B2M from B and T cells into circulation (5-8).

It has been reported that B2M serum concentrations increase under various inflammatory and hematologic conditions. B2M levels have been associated with heart failure and hypertension and positively correlated with the incidence and mortality of cardiovascular diseases. Accordingly, B2M affords a considerable predictive value (8-10).

METHODS

Participants and Design

This study was carried out in Çukurova University, Department of Internal Medicine. When the power 80% confidence interval was accepted as 95% d=0.5, the number of people to be reached was found to be 84. 84 patients were included, and 3 patients were excluded from the study because they were diagnosed with myeloma. The study was completed with 81 people. In the first stage of the present study, we included 81 individuals, i.e., 52 females and 29 males. The enrolled individuals were divided into four groups: rheumatoid arthritis (RA; chronic inflammatory disease), osteoarthritis (OA; chronic non-inflammatory disease), acute infection (AI), and healthy individuals (HI). We noted no additional disorders or drug use impacting inflammatory markers in patients with OA and HI. Patients with AI exhibited urinary tract infection, cellulitis, soft tissue infection, sinusitis, and lung infection. Exclusion criteria were as follows: patients who were <65 years; patients with identified or known malignancy, stage 3 or 4 congestive heart failure, renal dysfunction, chronic liver disease, obesity (body mass index (BMI) >35 kg/m^2), and autoimmune disease; patients taking anti-inflammatory agents, antibiotics, or immunosuppressive medication. Given that AI impacts frailty, individuals with AI were excluded from the second stage of the study. The other individuals were categorized into two groups: frail and non-frail.

Measurement

Frailty assessment was performed using the 36-Item Short Form Health Survey questionnaire (SF-36) for all patients and the Clinical Frailty Scale (CFS-9).

SF-36

SF-36 is a commonly used scale for assessing the quality of life; it was initially used to assess the efficacy of treatments and subsequently employed to estimate patient mortality (11). SF-36 was created specifically for examining individuals who were physically unwell. In addition, SF-36 is highly sensitive to slight changes and can assess both positive and negative characteristics associated with health conditions (12, 13). The SF-36 questionnaire comprises 36 items divided into 8 areas: physical condition, role constraints (caused by physical and emotional issues), social function, mental health, vitality (energy), pain, and general perception of health (12-14). Considering questionnaire responses, the patients marked points on a scale. Each subscale received separate scores. In addition, SF-36 assesses negative features of health. The subscale ratings range from 0 to 100, with a high score indicating good health (12-14).

The Clinical Frailty Scale (CFS)

The CFS is a measurement method that can reveal clinical frailty in the geriatric population (15, 16).

1) Very fit: People who are robust, active, energetic, and motivated. These individuals commonly exercise regularly. They are among the fittest for their age.
2) Well: People who have no severe disease symptoms but are less fit than category 1. They exercise or are very active occasionally, e.g., seasonally.
3) Managing well: People whose medical problems are well-controlled but are not regularly active beyond routine walking.
4) Living with very mild frailty: Previously named "Vulnerable." While not dependent on others for daily help, symptoms often limit activities. A common complaint is being "slowed-up" and being tired during the day.
5) Living with mild frailty: These people usually have more evident slowing and need help in higher-order instrumental activities of daily living, such as finance, transportation, heavy housework, and medication management. Typically, mild frailty progressively impairs shopping, walking outside alone, meal preparation, and housekeeping.
6) Living with moderate frailty: People need help with all outside activities and housekeeping. Indoors, these individuals often have problems with stairs, need help with bathing, and may need minimal assistance with dressing.
7) Living with severe frailty: Completely dependent on both cognitive and physical personal care. However, they seem stable and not at a high risk of death (within 6 months).
8) Living with very severe frailty: Completely dependent on personal care and approaching end of life. Typically, they could not recover even from minor illnesses.
9) Terminally ill: Approaching the end of life. This category applies to people with a life expectancy of less than 6 months, and who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death).

Scoring frailty in a patient with dementia: the degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting details of a recent event, remembering the event itself, repeating the same question/story, and social withdrawal. In moderate dementia, recent memory is markedly impaired, although the individual seems to remember their past life events well. These individuals may need to be prompted to

perform personal care. Patients with severe dementia cannot perform personal care without assistance. In very severe dementia, individuals are often bedridden, and many are virtually uncommunicative.

Laboratory measurements

Blood samples were analyzed to determine levels of glucose, blood urea nitrogen, creatinine, uric acid, Na, K, P, chloride, total protein, albumin, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol, low-density lipoprotein, triglyceride, high-density lipoprotein, hemogram, parathyroid hormone (PTH), 25-OH vitamin D, serum iron, total iron binding capacity, serum B12 and folic acid levels, B2M, ferritin, C-reactive protein (CRP), thyroid-stimulating hormone, procalcitonin (PCT), interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) levels. In addition, complete urinalysis was performed. A Beckman Coulter DXC 800 instrument was used to perform the turbidimetric method for B2M.

Statistical analysis

Parametric data are presented as the mean ± standard deviation, whereas nonparametric data are presented as the median (interquartile range (IQR)). Data analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used for the normal distribution of data. T-test, Mann-Whitney U test, binary logistic regression test, multiple linear regression test (stepwise model), and ROC analysis were used in the data analyses. A *p*-value < 0.05 was deemed as statistically significant.

Ethics

An in-depth explanation of the study was provided to all patients, and informed consent forms were obtained. This study was approved by the Çukurova University Health Sciences Research Ethics Committee and Helsinki Declaration.

RESULTS

In the present study, patients who participated in the first phase had a mean age of 76.3±7.5 years, with 29 (35.6%) males and 52 (64.2%) females (min 65, max 99). The participants were divided into four main groups: patients with AI (22 patients, 27.2%), OA (20 patients, 24.7%), RM (20 patients, 24.7%), and HI (19 males, 23.4%). We detected no statistically significant difference between groups regarding the average age (p=0.008).

The mean B2M level of all groups was 3.8±1.3 mg/L (1.24-7.9 mg/L). We then analyzed the distribution of B2M levels across groups. The mean B2M levels were 4.68±1.29, 2.64±0.93, 4.37±1.05, and 3.53±0.90 mg/L in the AI, HI, RA, and OA groups, respectively.

The mean B2M levels of examined groups differed significantly (p = 0.0001). We noted that B2M levels were elevated during inflammatory conditions, such as AI and RA, when compared with those in HI, RA, and OA groups. We detected that differences between B2M levels in the AI and HI groups were statistically significant (p=0.0001). We also found a statistically significant difference between the RA and OA groups based on B2M levels (p =0.007).

In the AI group, CRP showed a 51% positive correlation with the B2M level. In other words, when B2M increases, the CRP value also increases. Similarly, we noted a positive association with CFS; in the AI group, we recorded an inverse correlation (66%) between the B2M level and the SF-36 quality of life scale. Accordingly, the average SF-36 score or the patient's quality of life decreases with increasing B2M levels.

In the second step (main part) of the study, the mean age of participants, except for the AI group, was 72.14±7.00 years (min: 65 years; max: 95 years). Among these patients, 30.5% (n = 18) were male and 69.5% (n = 41) were female. The frail group comprised 47.5% of the total patients.

Levels of B2M, sedimentation, CRP, PCT, IL-1, IL-6, and TNF-α, as well as the Charlson comorbidity index scores, were significantly elevated when compared with inflammatory indicators; however, quality of life and SF-36 scale scores were found to be significantly reduced (Table 1).

The logistic regression model used to estimate frailty was significant, with an accuracy rate of 94.9% and a predictive factor of 88.3%. Living with frailty (risk category CFS ≥ 4) was the dependent variable in the model, whereas B2M level, SF-36 score, age, and comorbidity index were independent variables. The risk of frailty increased by 1.61 times for every 0.476-unit decrease in the SF-36 score and by 13.9 times for every 2.6-unit increase in B2M levels, respectively (Table 2).

Considering the application of B2M levels for frailty screening or diagnostic testing, the ROC analysis revealed that the area under the curve (0.916) was a robust diagnostic tool (Table 3).

The optimal cutoff B2M value to assess frailty was 3.78, with a sensitivity of 75% and a specificity of 93.5%. Based on this cutoff value, the positive/false positive ratio was 11.53, or approximately one patient was misdiagnosed among every 12 patients. The false-negative/negative ratio value was 0.26, suggesting that for every five negatives, one false-negative patient was diagnosed (Table 4).

We assessed correlations between B2M and inflammatory markers and quality of life scale scores. Herein, we detected a robust positive correlation between B2M levels and CRP, CFS frailty score, and

Table 1. Comparison of parameters according to the frailty group

	Non-frail (n:31)	**Frail (n:28)**	**p**
Sex M/F (n)	12/19	6/22	
Parameters	X±S.D or Median (IQR)	X±S.D. or Median (IQR)	
CFS	2.06±0.81	4.57±0.63	<0.001
Age	67(10)	73(10)	0.125
B2-microglobulin	2.73(1.35)	4.17 (1.18)	<0.001
Sedimentation*	13.06±5.88	46.43±26.95	<0.001
CRP	0.24 (0.30)	1.82 (4.65)	<0.001
Procalcitonin	0.06 (0.08)	0.80 (1.04)	<0.001
Vitamin D*	20.72±11.27	18.15 (13.90)	0.512
IL-1	12.10 (28.70)	22.60 (43.90)	0.013
IL-6	32.70 (36.40)	190.40 (295.6)	<0.001
TNF-α	6.10 (7.3)	8.25 (2.33)	0.016
SF-36*	83.17±5.95	65.38±8.14	<0.001
BMI*	29.87±3.43	29.17±3.49	0.446
Comorbidty index	3(2)	5.5(2)	<0.001

Patients with acute infection are excluded. *Normally distributed

Table 2. B2-Microglobulin frailty estimation using B2M logistic regression analysis

	B	p	O.R.	95% C.I.for EXP(B)	
				Lower	Upper
Beta2-microglobulin	2.63	0.045	13.98	1.06	184.37
SF-36	-0.476	0.022	0.621	0.41	0.93
Age	-0.197	0.116	0.821	0.64	1.05
Comorbidity index	0.585	0.538	1.795	0.27	11.58

In this model, patients with acute infections are not included.

Table 3. The area under the curve for B2-microglobulin

Area	S.E.	p	95% Confidence Interval	
			Lower Bound	Upper Bound
0.916	0.037	<0.001	0.845	0.988

Table 4. Cutoff value for B2-microglobulin

Cut-off	Sensitivity	Specificity	Youden index	LR(+)	LR(-)
3.785	%75	%93.5	0.685	11.53	0.26

comorbidity index; a moderate positive correlation was observed with TNF-α and IL-6; a strong negative correlation was found with the SF-36 score.

Multiple linear regression was used to predict the association between B2M and sedimentation, IL-1, IL-6, TNF-α, CRP, PCT, vitamin D, BMI, comorbidity index, and SF-36. Notably, SF-36, comorbidity index, TNF-α, and CRP levels significantly contributed to the model. A stepwise approach was used for this model. The model described 83% of the changes in the B2M, and the most relevant factor related to changes in B2M levels was SF-36 (53.3%), followed by comorbidity index (7.2%), TNF-α (6%), and CRP (2.6%). For every unit increase in SF-36 score, B2-microglobulin decreased by 0.030 units (Table 5).

DISCUSSION

B2M has been confirmed as a significant mortality marker in geriatric individuals and has prognostic and predictive value, particularly in inflammatory conditions (17, 18). Herein, we determined whether B2M should be used as a marker for frailty assessment, as it involves an easy blood test that is relatively simple to perform (19) and can be used by physicians for routine measurement. Few studies have investigated the association between serum

Table 5. Predicting B2 microglobulin using the multiple linear regression model

Model	Unstandardized Coefficients		p	Collinearity Statistics	
	B	Std. Error		Tolerance	VIF
(Constant)	4.050	1.215	0.002		
SF-36	-0.030	.013	0.022	0.398	2.511
Comorbidity index	0.293	.074	<0.001	0.446	2.244
TNF-α	0.055	.019	0.005	0.934	1.070
CRP	0.051	.024	0.040	0.828	1.208

B2M levels and age and found that serum B2M levels increase with age. For instance, one study has reported that healthy adults with an average age of 40 to 86 years old exhibit elevated serum B2M levels with progressive aging. Similar findings have been reported in other studies (20-23). Additionally, B2M in the older Chinese population can reportedly affect both the frailty phenotype and index. Moreover, B2M was shown to be independently associated with baseline frailty in older adults (19, 24). The findings of the present study are consistent with a few previously reported studies, indicating that B2M levels increase with age. Serum B2M levels in the first stage of our study were higher in two groups, the RA and AI groups, and were likely related to inflammation. Based on these findings and minimal accumulated literature, B2M may be an elevated acute-phase marker during acute infectious conditions. In HI, excluding those with inflammatory and infectious disorders, increased serum B2M levels were unrelated to inflammatory conditions. As a notable feature of our study, we excluded participants with renal dysfunction, cancer, and AI, as these conditions would impact plasma B2M measurements. During the second and most important stage, the remaining participants were divided into two groups to represent frail and non-frail individuals, and the effect of B2M levels was examined based on frailty. We performed in-depth laboratory assessments and conducted two different assessment scales (CFS and SF-36). Comparing variables, the levels of B2M, CRP, IL-1, IL-6, TNF-α, sedimentation, PCT, and comorbidity index were significantly elevated in the frail group, whereas the SF-36 scores were significantly reduced. On analyzing B2M levels, we observed that this frailty marker was unrelated to other variables, and the optimal cutoff value for B2M to assess frailty was 3.78. Plasma B2M levels can be used to assess the degree of frailty in geriatric patients and, consequently, the need to establish essential medical care.

In the present study, frailty in a subset of the Turkish population was assessed using CFS, a validated test. To the best of our knowledge, this study is the first to develop a logistic regression model for estimating frailty and performing ROC analysis to determine whether B2M could be utilized as a marker for frailty assessment. In conclusion, B2M may be an important marker for predicting the risk of frailty in geriatric patients. A limitation of our study was its single-center, cross-sectional nature. Accordingly, large-scale, prospective, observational studies are required.

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