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Effect of Serum Beta 2-Microglobulin Levels on Functional Prognosis in Stroke Patients: A Preliminary Study

İnmeli Hastalarda Serum Beta 2-Mikroglobulin Düzeylerinin Fonksiyonel Prognoza Etkisi: Bir Ön Çalışma

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ABSTRACT Objective: Beta 2-microglobulin (β2M) levels are used to predict prognosis in stroke. To date, there are no studies linking β2M to physical recovery following stroke. The aim of this study was to evaluate the relationship between β2M levels, functionality, activities of daily living(ADLs), morbidity and mortality of patients with stroke. **Material and Methods:** Sixty six ischemic and 11 hemorrhagic stroke patients were recruited to the study. All patients received neurorehabilitation and followed up for 3 months. Functionality and ADLs were assessed using the Brunnstrom Stages of Stroke Recovery (BSSR) and Barthel index(BI). **Results:** There was no significant difference in β2M levels in those with ischemic versus hemorrhagic stroke (p=0.681). When the patients were divided into higher (>1.86 mg/l) and lower (≤1.86 mg/l) serum β2M level groups, 59 (89.4%) patients with ischemic stroke and 10 (90.9%) patients with hemorrhagic stroke had high levels of β2M. In both stroke groups, BSSR and BI values were lower in those with high β2M levels versus those with lower β2M levels. Three months after rehabilitation, two of the patients with ischemic stroke (3.4%) and 1 (11.1%) with hemorrhagic stroke had experienced new cerebrovascular events, three of the patients with ischemic stroke (5.1%) had died. All were in the β2M>1.86 mg/l group. **Conclusion:** Higher β2M levels appear to be associated with poorer functional status, ADLs, stroke recurrence, and death, regardless of stroke etiology. Closer follow-up of stroke patients with higher β2M levels may be important in preventing stroke recurrence and death and therefore in obtaining better functional outcome.

Keywords: Stroke; beta 2-microglobulin; activity of dailiy living; rehabilitation

ÖZET Amaç: Beta 2-mikroglobulin(β2M) seviyeleri inmede prognozu tahmin etmek için kullanılır. Bugüne kadar, β2M'nin inme sonrası fiziksel iyileşme ile ilişkisini araştıran hiçbir çalışma yoktur. Bu çalışmanın amacı inmeli hastaların β2M düzeyleri ile fonksiyonellik, günlük yaşam aktiviteleri(GYA), morbidite ve mortalite arasındaki ilişkiyi değerlendirmektir. **Gereç ve Yöntem:** Altmış altı iskemik ve 11 hemorajik inme hastası çalışmaya dahil edildi. Tüm hastalar nörorehabilitasyon programı aldı ve 3 ay boyunca takip edildi. Hastaların motor fonksiyonları Brunnstrom inme iyileşme evrelemesi ve GYA Barthel indeksi (BI) kullanılarak değerlendirildi. **Bulgular:** İskemik ve hemorajik inmeli hastalarda β2M düzeylerinde anlamlı bir fark yoktu(p=0.681). Hastalar yüksek(>1,86 mg/l) ve düşük(≤1,86 mg/l) β2M gruplarına ayrıldığında, iskemik inmeli 59 (%89,4) hasta ve hemorajik inmeli 10 (%90,9) hastada yüksek β2M seviyeleri vardı. . Her iki inme grubunda da Brunnstrom inme iyileşme evrelemesi ve BI değerleri yüksek β2M grubunda genellikle daha düşüktü. Rehabilitasyondan üç ay sonra, iskemik inmeli hastalardan ikisi (%3,4), hemorajik inmeli hastalardan 1'i (%11,1) yeni serebrovasküler olay geçirirken, iskemik inmeli hastalardan üçü (%5,1) ölmüştür. Mortalite ve morbidite gelişen hastaların hepsi β2M>1.86 mg/l grubundaydı. **Sonuç:** Daha yüksek β2M seviyeleri, inme etiyolojisinden bağımsız olarak kötü fonksiyonel durum ve GYA, inme rekürrensi ve mortalite ile ilişkili görünmektedir. Daha yüksek β2M seviyeleri olan inme hastalarının daha yakın takibi, inme nüksünü ve ölümü önlemede ve dolayısıyla daha iyi fonksiyonel sonuç elde etmede önemli olabilir.

Anahtar Kelimeler: İnme; beta 2-mikroglobulin; günlük yaşam aktiviteleri; rehabilitasyon

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Stroke is one of the most common causes of disability. Given the high rates of morbidity and mortality associated with stroke, new biomarkers that identify individuals at higher risk of stroke have gained importance.[1]

Blood-based biomarkers may provide additional information on the prognosis of stroke. In the past ten years, the number of studies on prognostic blood-based biomarkers in stroke has increased 3.5 fold.[2] Furthermore, thirty four blood biomarkers have been significantly associated with physical outcomes after ischemic stroke. The biomarkers which have been found to be robust predictors of poor prognosis post-stroke, fall into four categories based on biological function of the individual biomarker: immune response [Low level of C-C motif chemokine 11 and elevated levels of C-reactive protein (CRP), interleukin-6, tumor necrosis factor alpha, osteopontin], lipids/metabolism (high glucose, cholesterol, high density lipoprotein cholesterol, and low-density lipoprotein cholesterol), neuronal function (higher levels of glutamate, and lower levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and brain-derived neurotrophic factor), and blood vessel/circulation (elevated levels fibrinogen, endostatin, fibronectin). The majority of these appear to predict physical recovery at 3 months following ischemic stroke.[3]

Beta 2-microglobulin (β2M) has been suggested as an emerging biomarker for stroke and other diseases of cardiovascular etiology.[4] Recent studies have shown that serum β2M levels are associated with an increased risk of ischemic stroke.[5] However, the effect of β2M level on functional outcome, activities of daily living (ADLs), morbidity and mortality of patients with stroke is unknown.

The aim of this study was to investigate the relationship between serum β2M levels and ability to perform ADLs, functional independence, morbidity and mortality in patients with ischemic and hemorrhagic stroke.

MATERIAL AND METHODS

STUDY DESIGN

Seventy seven patients with a history of first- time stroke admitted to the physical medicine and rehabilitation (PMR) clinic for inpatient rehabilitation between May 2019 and December 2020 were enrolled in the study.

Inclusion criteria were 1) Age 18-75 years 2) Diagnosis of stroke of vascular origin confirmed by computed tomography and/or magnetic resonance imaging. Exclusion criteria included: 1) Chronic renal failure; 2) Hematological malignancy, such as multiple myeloma; 3) Diabetic nephropathy.

Demographic details of all those included in the study were recorded. Details of stroke episode and stroke related motor dysfunction were recorded. Renal function tests (creatinin and glomerular filtration rate), CRP and serum β2M levels were recorded in all patients on admission to the rehabilitation unit. Laboratory biochemical testing was performed using the Abbott Architect c series analyzers (Abbott Diagnostics, IL, USA). Serum creatinin concentrations were measured using the modified Jaffé method; CRP and serum β2M levels were determined using the immunoturbidimetric method. The analytical coefficient of variations of tests during the study period were <3.0% for creatinin and CRP levels and <4.0% for β2M levels.

All patients received a conventional neurorehabilitation program for five days of the week for four weeks totalling twenty sessions as inpatients. Each session lasted two hours and included proprioceptive neuromuscular facilitation and neurodevelopmental facilitation techniques, range of motion, progressive resistance and strengthening exercises, balance-coordination, ambulation training and occupational therapy.

OUTCOME MEASURES

All patients were assessed by the same PMR specialist before and after treatment. The outcome measures included the change in plegic hand, upper and lower extremity motor function evaluated using the Brunnstrom Stages of Stroke Recovery (BSSR) and functional disability evaluated using the Barthel Index (BI).

The Brunnstrom stages of motor recovery is a six-stage evaluation tool which is used to evaluate motor recovery of the plegic upper extremity, hand,

and lower extremity. The higher the BSSR, the better the patient's motor function.[6]

Functional disability was assessed using the BI. The 10-item form of the BI consists of 10 common ADLs such as bathing, grooming and dressing. The items are scored according to the patient's level of independence in peforming the ADLs. A total score (minimum 0, maximum 100) is obtained by summing up points for each of the items, with higher scores representing better ADLs.[7]

Three months after discharge from the rehabilitation unit, the patients/next of kin were contacted and questioned regarding new cerebrovascular events or patient death post discharge.

The patients were divided into 2 groups (ischemic and hemorrhagic) and then ischemic and hemorrhagic groups were divided into subgroups with high serum β2M (>1.86 mg/L) levels and low serum β2M (≤1.86 mg/L) levels following which data of evaluation parameters between groups and subgroups were analyzed. The β2M cut off value was determined according to the study of Hu et al. in which 1.865 mg/L was calculated as the optimal cut-off value for discriminating between good and poor outcomes in patients with ischemic stroke with a sensitivity of 73% and a specificity of 75%.[8]

Written informed consent was obtained from all study participants at the beginning of the study. Ethical approval for the study was obtained from the Başkent University Non-interventional Clinical Research Ethics Committee (date: September 27, 2017 no: 17/181) and the study was conducted in accordance with the principles of the Helsinki Declaration.

STATISTICAL ANALYSIS

The power of the study was calculated using the Power and Sample Size Statistical Programme version 3.1.2 (Vanderbiltg University, 2015). In order to obtain a study power of 80% with a 5% Type 1 error, 65 study participants were required. Data values of continuous variables were expressed as means±standard deviations and or medians (minimum-maximum), categorical variables were expressed as numbers and percentages. Normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Intergroup comparison of the normally distributed qualitative variables was performed using the independent samples t-test. Within group analysis of normally distributed data was performed using the paired t-test. Inter-group analysis of non-normally distributed data was performed using the Mann-Whitney U test; the Wilcoxon Signed Rank test was used in within group analyses. The chi-square test was used in the comparison of categorical data. Linear relationships between variables was analyzed using the Spearman Rho correlation coefficient. Statistical analyses of data was performed using the IBM SPSS version 24 (IBM Corporation, Armonk, NY, USA). A p value of less than 0.05 was considered to be of statistical significance.

RESULTS

A total of 77 patients were recruited to the study; 66 patients had a history of ischemic stroke, and 11 patients hemorrhagic stroke. The mean age of the patients in the ischemic stroke group was 67.09±11.46 years, and 61.54±11.59 years in the hemorrhagic stroke group (p=0.143). Time since stroke was 2.30±2.34 months in the ischemic stroke group and 1.90±1.30 in the hemorrhagic stroke group (p=0.589). No statistically significant difference was found between the ischemic and hemorrhagic stroke groups in terms of gender, marital status, hemiplegic side and comorbidities (p>0.05). The patients in the hemorrhagic stroke group had a higher level of education (p=0.006) (Table 1).

There was no significant difference in serum β2M levels in those with a history of ischemic stroke versus hemorrhagic stroke (p=0.681). In all patients, creatinine and glomerular filtration rate levels were within normal parameters (Table 2).

Ischemic and hemorrhagic groups were divided into subgroups with higher serum β2M (>1.86 mg/L) and lower serum β2M (≤1.86 mg/L) levels.[8] Fifty nine of the patient with a history of ischemic stroke (89.4%) and 10 of the patients with a history of hemorrhagic stroke (90.9%) were in the higher serum β2M group. On admission to hospital, in both ischemic and hemorrhagic stroke groups, BSSR (lower

TABLE 1: Comparison of socio-demographic and clinical characteristics of ischemic and hemorrhagic stroke group patients.

Parameters	Ischemic stroke group (n=66)	Hemorrhagic stroke group (n=11)	Total (n=77)	p value
Gender (n, %)				
Female	29 (43.9)	3 (27.3)	32 (41.6)	0.345*[a]
Male	37 (56.1)	8 (72.7)	45 (58.4)	
Education (n, %)				
Illiterate	10 (15.2)	0 (0.0)	10 (13.0)	0.006*
Literate	28 (42.4)	0 (0.0)	28 (36.4)	
Middle/High school graduate	18 (27.3)	7 (63.6)	25 (32.5)	
University graduate	10 (15.2)	4 (36.4)	14 (18.2)	
Marital status (n, %)				
Married	53 (80.3)	10 (90.9)	62 (81.8)	0.678*[a]
Single	13 (19.7)	1 (9.1)	14 (18.2)	
Hemiplegic side (n, %)				
Right	26 (39.4)	4 (36.4)	30 (39.0)	0.849*
Left	40 (60.6)	7 (63.6)	47 (61.0)	
Comorbidity (n, %)				
Present	57 (86.4)	7 (63.6)	64 (83.1)	0.083*[a]
Absent	9 (13.6)	4 (36.4)	13 (16.9)	
Total	66 (100.0)	11 (100.0)	77 (100.0)	

*Chi-square test ([a]Fisher's exact test).

TABLE 2: Comparison of blood biochemistry values of ischemic and hemorrhagic stroke groups.

	Ischemic stroke group (n=66)	Hemorrhagic stroke group (n=11)	p value
Creatinin (μmol/L) ($\bar{X}$±SD)	0.84±0.18	0.71±0.21	0.028*
GFR (mL/min) ($\bar{X}$±SD)	82.37±17.01	97.36±21.18	0.011*
CRP (mg/L) ($\bar{X}$±SD)	11.51±14.90	21.05±28.14	0.189**
Beta 2-microglobulin (mg/L) ($\bar{X}$±SD)	3.02±1.17	2.86±0.67	0.681*

*Independent samples t-test; **Mann-Whitney U test; SD: Standard deviation; GFR: Glomerular filtration rate; CRP: C-reactive protein.

and upper extremity-hand) and BI values were generally lower in the patient group with higher β2M compared to the patient group with lower β2M. Moreover, The BI was significantly higher in ischemic stroke patients with low serum β2M both before and after treatment (p=0.003 and p=0.035 respectively) (Table 3, Table 4).

During the three month follow up period after discharge, two of the patients experienced new ischemic cerebrovascular events (3.4%) and three of the patients with ischemic stroke died (5.1%). Of the patients with a history of hemorrhagic stroke, 1 (11.1%) reported a new cerebrovascular event. All those who had developed new cerebrovascular events or had died, were in the serum β2M level >1.86 mg/L group (Table 3, Table 4).

Following treatment, there was a significant improvement in BSSR of the lower extremity and BI in those with ischemic stroke and higher serum β2M levels (p<0.001 and p=0.002 respectively). When the BSSR (all subgroups) and BI scores of ischemic and hemorrhagic stroke patients with high β2M values were compared, overall, the scores in patients with hemorrhagic stroke were lower. The difference was only significant for BSSR-lower extremity and BI pre-treatment values (p=0.021 and p=0.015, respectively).

When the linear relationship between the β2M values of the ischemic and hemorrhagic groups and evaluation parameters was examined, there was a positive, moderately correlated and statistically significant correlation between β2M values and age averages in those with ischemic stroke (p<0.001, r=0.456) (Table 5).

TABLE 3: Comparison of BSSR and BI values within and between groups according to the beta 2 ≤1.86 cut-off value in both ischemic stroke groups.

	Ischemic stroke group (n=66)		
Parameter ($\bar{X}$±SD)	**Beta 2 ≤1.86 mg/L (n=7)**	**Beta 2 >1.86 mg/L (n=59)**	**p^1**
BSSR upper pre-treatment	3.28±1.97	2.71±1.81	0.436*
BSSR upper-post-treatment	3.57±1.90	3.16±1.83	0.561*
	p^2=0.157***	p^2<0.001***	
BSSR hand-pre-treatment	3.00±2.00	2.61±1.77	0.450*
BSSR hand-post-treatment	4.14±1.21	3.05±1.47	0.573*
	p^2=0.157***	p^2<0.001***	
BSSR lower-pre-treatment	3.28±1.97	3.05±1.81	0.066*
BSSR lower-post-treatment	4.28±1.25	3.69±1.31	0.256*
	p^2=0.317***	p^2<0.001***	
BI pre-treatment	69.28±26.04	35.33±27.55	0.003**
BI post-treatment	80.00±21.21	53.72±31.38	.035**
	p^2=0.041****	p^2<0.001****	
Follow-up period [n (%)]			
-New CVA	0 (0.0)	2 (3.4)	0.832*****
-Death	0 (0.0)	3 (5.1)	

*Mann-Whitney U test; **Independent samples t-test; ***Wilcoxon signed rank test; ****Dependent samples t-test;
*****Chi-square test; p^1: Between group p values; p^2: Within group p values; BSSR: Brunnstrom Stages of Stroke Recovery; BI: Barthel Index; SD: Standart deviation; CVA: Cerebrovascular accident.

TABLE 4: Comparison of BSSR and BI values between and within groups according to the beta 2 ≤1.86 cut-off value in both hemorrhagic stroke groups.

	Hemorrhagic stroke group (n=11)		
Parameter ($\bar{X}$±SD)	**Beta 2 ≤1.86 mg/L**	**Beta 2 >1.86 mg/L (n=10)**	**p^1**
BSSR upper pre-treatment	3.00	2.20±1.31	-
BSSR upper-post-treatment	5.00	2.80±1.47	-
	-	p^2=0.102*	
BSSR hand-pre-treatment	3.00	2.10±1.28	-
BSSR hand-post-treatment	5.00	2.60±1.42	-
	-	p^2=0.180*	
BSSR lower-pre-treatment	3.00	1.90±1.37	-
BSSR lower post-treatment	5.00	3.00±1.41	-
	-	p^2=0.026*	
BI pre-treatment	35.00	20.00±14.52	-
BI post-treatment	90.00	37.50±37.28	-
	-	p^2=0.047**	
Follow-up period [n (%)]			
-New CVA	0 (0.0)	1 (11.1)	-
-Death	0 (0.0)	0 (0.0	

*Wilcoxon signed rank test; **Dependent samples t-test; p^1: Between group p values; p^2: Within group p values; BSSR: Brunnstrom Stages of Stroke Recovery; BI: Barthel Index; SD: Standart deviation; CVA: Cerebrovascular accident.

DISCUSSION

This study investigated the relationships between serum β2M levels and functional status and ADLs in 77 patients with stroke. Our study revealed that higher β2M levels in both ischemic and hemorhhagic stroke were associated with worse motor function and ADLs. Hence, these findings suggest that β2M can be a prognostic factor in stroke rehabilitation. In addition, higher β2M levels were associated with higher rates of morbidity and mortality. To the best of our knowledge, our study is one of the first to determine

TABLE 5: Comparison of BSSR and BI values of ischemic and hemorrhagic stroke patients with beta 2 >1.86 between groups.

	Etiology	n	$\bar{X}$±SD	p value
BSSR upper	Ischemic	59	2.71±1.81	0.772 *
Pre-treatment	Hemorrhagic	10	2.20±1.31	
BSSR upper	Ischemic	59	3.16±1.83	0.622*
Post-treatment	Hemorrhagic	10	2.80±1.47	
BSSR hand	Ischemic	59	2.61±1.77	0.662*
Pre-treatment	Hemorrhagic	10	2.10±1.28	
BSSR hand	Ischemic	59	3.05±1.81	0.658*
Post-treatment	Hemorrhagic	10	2.60±1.42	
BSSR lower	Ischemic	59	3.05±1.47	0.021*
Pre-treatment	Hemorrhagic	10	1.90±1.37	
BSSR lower	Ischemic	59	3.69±1.31	0.166*
Post-treatment	Hemorrhagic	10	3.00±1.41	
BI-Pre-treatment	Ischemic	59	35.33±27.55	0.015**
	Hemorrhagic	10	20.00±14.52	
BI-Post-treatment	Ischemic	59	53.72±31.38	0.146**
	Hemorrhagic	10	37.50±37.28	
BSSR upper mean (%)	Ischemic	59	31.24±59.41	0.789*
	Hemorrhagic	10	50.00±124.72	
BSSR hand mean (%)	Ischemic	59	29.20±54.82	0.608*
	Hemorrhagic	10	50.00±126.92	
BSSR lower mean (%)	Ischemic	59	37.76±54.98	0.181*
	Hemorrhagic	10	98.33±132.04	
BI mean (%)	Ischemic	51	71.56±97.97	0.755*
	Hemorrhagic	9	64.63±68.93	

BSSR: Brunnstrom Stages of Stroke Recovery; BI: Barthel Index; SD: Standart deviation; *Mann Whitney U test; *T Test

the effects of pre-treatment serum β2M levels on functional outcome and morbidity in stroke patients.

In keeping with the findings of previous studies, our study showed that β2M level is associated with ischemic stroke. β2M plays an important role in the formation and development of atherosclerosis; recent studies have identified β2M as a biomarker for coronary atherosclerosis and stroke in patients with carotid atherosclerosis.[9] Inflammation has been suggested as a potential mechanism linking β2M and cerebrovascular diseases. The surfaces of lymphocytes and monocytes contain large amounts of β2M, and β2M is synthesized by lymphocytes, regulated by interferon and proinflammatory monocytic cytokines. This may explain the role of β2M in the pathophysiological process of vascular endothelial diseases.[9] An alternative explanation might be that β2M, not covalently attached to the major histocompatibility complex (MHC-I), has a tendency to be released into the systemic circulation as a result of chronic ischemia. Reperfusion damage may occur repeatedly in patients with vulnerable soft plaques, small vessel disease, or vasospasms resulting in endothelial dysfunction and inflammation.[10]

The mechanism behind high-level serum β2M after stroke is still unclear, but several pathways are thought to exist. β2M, as the light chain of MHC-I, is co-expressed with MHC-I molecules, indicating that stable expression of MHC-I at the cell surface is increased after stroke. In the damaged cerebral hemisphere, β2M increases significantly as it is necessary to stabilize the cell surface in order to express most of the MHC-I proteins.[11] Another reason for the increase in β2M levels may be that the expression of MHC-I molecules in the peripheral immune system is upregulated after stroke. Moreover, β2M can pass into the blood from damaged brain tissue due to disruption to the blood-brain barrier.[12]

In this study, we also compared the serum β2M levels between the ischemic and the hemorrhagic group and our data revealed that β2M levels were high in both groups. As previously mentioned, high β2M levels may be one trigger of the proinflammatory process resulting in vascular endothelial injury and subsequent atherosclerosis and ischemic stroke. Equally, β2M has been related to the evolution of arterial stiffness and hypertension.[13] Hypertension, in turn, is the most common cause of non-traumatic intracerebral hemorrhage resulting in hypertensive arteriopathy.[14] The relationship between type of stroke and β2M levels is a topic which requires further investigation; to the best of our knowledge there is only one previous study, which, contrary to our results, found that serum β2M levels were much higher in patients with ischemic stroke when compared to those with hemorrhagic stroke.[15]

Another finding of our study was that functional level of stroke patients with high serum β2M was poorer. MHC-I plays an important role in regulating axonal growth and cortical connections.[16] MHC-I molecules may play a dual role in the inflammatory background namely, increasing brain tissue damage and limiting neurological functional recovery by inhibiting neural plasticity.[12,17] This may explain why the functional status of stroke patients with higher β2M levels was worse.

The results of this study also showed that β2M values were high in all of the patients who developed a second stroke or died during the follow up period. This result suggests that β2M level may be related to mortality and morbidity. Indeed, Hu et al. have shown that serum β2M levels are closely associated with recurrence but not with the severity of stroke.[8] Available observational data of a systemic review and meta-analysis in 2021 has shown that there are moderate positive associations between β2M levels and cerebrovascular events, including coronary heart disease, stroke, and mortality.[4]

LIMITATIONS

The relatively low number of research subjects is an important limitation of this study. Secondly, biochemical indicators were not remeasured after rehabilitation. The findings of this study suggest that follow up of patients regarding repeat episodes of stroke and mortality should surpass three months. Finally, one of our results was that following treatment, there was a significant improvement in BSSR for the lower extremity and BI in those with ischemic stroke and higher serum β2M levels. Unfortunately we do not have an explanation for why functional recovery was better in those with ischemic stroke and higher serum β2M levels, this may have been an incidental finding. Furthermore, grouping of patients according to lesion localization, such as middle or anterior cerebral artery lesions, may yield interesting result regarding post stroke recovery due to the difference in the healing properties of the two localizations. Further studies may add clarification.

CONCLUSION

According to the findings of our study, β2M microglobulin levels were similar in hemorrhagic and ischemic stroke groups. Higher β2M levels appear to be associated with poorer functional status and ADL, stroke recurrence and mortality rate, regardless of stroke etiology. Therefore, we believe that earlier and closer follow-up of stroke patients with higher β2M levels is important in preventing stroke recurrence and mortality and obtaining better functional outcomes. As a biomarker of inflammation, β2M may have potential practical applications as a prognostic parameter for those undergoing stroke rehabilitation. Further clinical trials are needed to consolidate these findings.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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