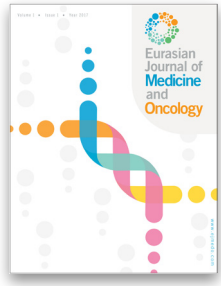
EJMO

DOI: 10.14744/ejmo.2017.63835
EJMO 2018;2(2):61-64



Research Article

The Association of Globulin Level with Treatment Response and Overall Survival in Patients with Multiple Myeloma

Rafet Eren,[1] Ozlem Ozdemir,[2] Ceyda Aslan,[1] Mehmet Hilmi Dogu,[1] Sermin Altindal,[1] Osman Yokus,[1] Elif Suyani[1]

[1]Department of Hematology, University of Health Sciences, Istanbul Training and Research Hospital, Istanbul, Turkey
[2]Department of Internal Medicine, University of Health Sciences, Istanbul Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: An increased globulin level, along with a decreased albumin level, is one of the hallmarks of multiple myeloma (MM). Albumin level has been included in the risk assessment of patients with MM; however, there are insufficient data on the prognostic value of globulin level. The aim of this study was to determine the association of globulin level at diagnosis with the treatment response and overall survival (OS) in patients with MM.

Methods: This study was a retrospective analysis of 30 patients who were diagnosed with MM, followed up, and had their globulin level recorded at the time of diagnosis at the University of Health Sciences Istanbul Training and Research Hospital Department of Hematology between June 2013 and August 2016.

Results: The median age of the patients was 61 years (range: 34-71 years). Eleven patients were female (36.6%) and 19 were male (63.4%). The median globulin level was 4.98 g/dL (range: 2.3-11.6 g/dL), and the cut-off value was 4.9 g/dL, according to the median. The patients were divided into 2 groups: >4.9 g/dL and <4.9 g/dL. Fifteen patients (50%) had a globulin value <4.9 g/dL, whereas 15 (50%) had a globulin value of >4.9 g/dL. The groups were comparable in terms of gender, age, Durie-Salmon stages, kappa/lambda ratios, creatinine value, beta-2 microglobulin level, lactate dehydrogenase level, OS, and treatment response rates ($p>0.05$). The globulin level was not significantly associated with treatment response or OS ($p>0.05$).

Conclusion: This study is the first to investigate the role of globulin in patients with MM. An increased globulin level during the course of MM is not a concern for clinicians, as it does not appear to negatively affect treatment response or OS.

Keywords: Globulin, hyperviscosity, multiple myeloma

Cite This Article: *Eren R, Ozdemir O, Aslan C, Dogu M, Altindal S, Yokus O, Suyani E. The Association of Globulin Level with Treatment Response and Overall Survival in Patients with Multiple Myeloma. EJMO. 2018; 2(2): 61-64*

Multiple myeloma (MM), a clonal malignant neoplasm of plasma cells, constitutes 1% of all cancers and 10% of hematological cancers.[1, 2] Although MM is still an incurable disease, the overall survival (OS) of the patients has apparently improved, owing to the improvements in treatment strategies over the last years.[1-3] The risk assessment, which comprises tumor burden and disease biology, is the fundamental step in estimating the prognosis and subsequently choosing the treatment modality.[1-3] While Durie–Salmon and International Staging Systems are the conventional systems that provide information on the tumor burden,[1, 3, 4] the disease biology is best established by the identification of the molecular subtype and the presence of cytogenetic abnormalities.[1-3, 5] The revised International Staging System (ISS), which has been recently used for risk determination, appears to be more favorable, as it relies on the combination of both tumor burden and disease biology.[1]

Address for correspondence: Elif Suyani, MD. Istanbul Egitim ve Arastirma Hastanesi Hematoloji Bolumu, Saglik Bilimleri Bolumu, Istanbul, Turkey
Phone: +90 212 459 63 30 **E-mail:** elifsuyani@hotmail.com
Submitted Date: July 20, 2017 **Accepted Date:** November 27, 2017 **Available Online Date:** February 05, 2018

Increased globulin levels along with decreased albumin levels, which are attributed to the monoclonal immunglobulin (M-protein) secreted by the plasma cells, is one of the hallmarks of MM.[2] Among them, only albumin levels have been included in both the ISS and revised-ISS for risk assessment, wherein low albumin levels have been associated with a poor prognosis.[1, 4] However, there is insufficient data on the prognostic value of globulin levels, and the significance of increased globulin levels emerge as suggestive of hyperviscosity, resulting in concerns among clinicians.[6, 7]

This study aimed to determine the association of globulin levels at diagnosis with the treatment response and OS in patients with MM.

Methods

This study included a retrospective analysis of 30 patients who were diagnosed with MM, followed-up, and had their globulin levels recorded at the time of diagnosis at the Department of Hematology, University of Health Sciences, Istanbul Training and Research Hospital between June 2013 and August 2016. The data related to the gender; age; Durie-Salmon stage; presence of lytic lesion; type of M-protein; kappa/lambda ratio; hemoglobin, calcium, creatinine, β2-microglobulin, lactate dehydrogenase (LDH), total protein, albumin, and globulin levels; treatment response; and OS were recorded from database of the hematology department. The diagnosis, risk stratification, and treatment response after induction chemotherapy were evaluated according to the Durie–Salmon criteria and International Myeloma Study Group criteria.[8, 9] The cutoff value for globulin was determined as 4.9 g/dl according to the median globulin level. The study protocol was approved by the local Ethical Committee.

Statistical Analysis

Statistical analysis was performed using the SPSS program. Data were represented as numbers and percentage or median and range, as appropriate. The chi-square and Fisher's exact tests were used for evaluating categorical values, and the Mann-Whitney U test was used for evaluating continuous values in the patient groups. All p values were two-sided; $p<0.05$ was considered statistically significant.

Results

This study included 30 patients who had a complete disease evaluation at diagnosis and after treatment. Patient characteristics are summarized in Table 1. The median age of the patients was 61 years (range, 34-71 years). Eleven patients were female (36.6%), and 19 (63.4%) were male. According to the Durie-Salmon stage, three patients (3%) were evaluated as stage IA, two patients (6.6%) as stage IIA, and 25 patients (83.4%) as stage IIIA. Lytic lesions were present in 25 (83.3%) patients. The M-protein type was IgG kappa in 14 (46.8%) patients, IgG lambda in four (13.4%) patients, IgA kappa in six (20%) patients, IgA lambda in two (6.6%) patients, kappa light chain in one (3.3%) patient, and lambda light chain in two (6.6%) patients; one (3.3%) patient did not have an M-protein. Free light chain ratio (kappa/lambda) was abnormal in 22 (73.3%) patients. Only one patient had symptomatic hyperviscosity with a

Table 1. Patient characteristics

Characteristics	n=30
Gender, n, (%)	
Female	11 (36.6)
Male	19 (63.4)
Age (years)	61 (34-71)
Durie–Salmon Staging, n, (%)	
Stage IA	3 (10)
Stage IIA	2 (6.6)
Stage IIIA	25 (83.4)
Lytic lesion, n, (%)	
Present	25 (83.4)
Absent	5 (16.6)
Type of M-protein, n, (%)	
IgG kappa	14 (46.8)
IgG lambda	4 (13.4)
IgA kappa	6 (20)
IgA lamda	2 (6.6)
Kappa light chain	1 (3.3)
Lambda light chain	2 (6.6)
Non secretory	1 (3.3)
Free light chain ratio, (kappa/lambda), n, (%)	
Normal	3 (10)
Abnormal	22(73.3)
Unknown	5 (16.7)
Hgb (g/dl)	10.8 (6.7-15.1)
Ca (mg/dl)	8.95 (7.60-10.40)
Creatinine (mg/dl)	0.94 (0.41-1.61)
β2-microglobulin (mg/l)	3.98 (1.9-16.6)
LDH (μ/dl)	172.5 (73-285)
Total protein (g/dl)	8.99 (5.72-13.79)
Albumin (g/dl)	3.64 (2.19-4.74)
Globulin (g/dl)	4.98 (2.30-11.60)
Overall survival (months)	16 (5-32)
Response to the induction chemotherapy, n, (%)	
CR or PR	24 (80)
<PR	6 (20)

Ca: Calcium, CR: Complete response, Hgb: Hemoglobin, Ig: Immunglobulin, LDH: Lactate dehydrogenase, PR: Partial response. Data are represented as median (range) unless otherwise specified.

Table 2. Comparison of patients with globulin <4.9 g/dl and globulin >4.9 g/dl

	Globulin <4.9 g/dl	Globulin >4.9 g/dl	p
Gender, n, (%)			
Female	5 (33.3)	6 (40)	1.0
Male	10 (66.7)	9 (60)	
Age (years)	61 (39-70)	62 (34-71)	0.715
Durie–Salmon Staging, n, (%)			
Stage IA	1 (6.6)	2 (6.6)	
Stage IIA	1 (6.6)	1 (13.2)	0.827
Stage IIIA	13 (86.8)	12 (80.2)	
Type of M-protein, n, (%)			
IgG	6 (42.8)	12 (80)	
IgA	5 (35.8)	3 (20)	0.036
Light chain Zincir	3 (21.4)	0	
Free light chain ratio, (*kappa/lambda*), n, (%)			
Normal	2 (14.3)	1 (9)	0.688
Abnormal	12 (85.7)	10 (91)	
Hgb (g/dl)	12.9 (7.4-15.10)	10 (6.7-11.4)	0.009
Ca (mg/dl)	9.2 (8.1-10.4)	8.5 (7.6-9.7)	0.027
Creatinine (mg/dl)	0.8 (0.41-1.61)	0.96 (0.58-1.53)	0.466
β2-microglobulin (mg/l)	2.52 (1.90-7.70)	5.0 (3.01-16.6)	0.370
LDH (µ/dl)	182 (121-)		0.466
Albumin (g/dl)	4.15 (2.55-4.74)	3.2 (2.19-4.08)	0.027
Overall survival (months)	13 (8-32)	16 (5-33)	1
Response to the induction chemotherapy, n, (%)			
CR or PR	13 (54.2)	11 (45.8)	0.651
<PR	2 (33.3)	4 (66.7)	

Ca: Calcium, CR: Complete response, Hgb: Hemoglobin, Ig: Immunglobulin, LDH: Lactate dehydrogenase, PR: Partial response. Data are represented as median (range) unless otherwise specified.

globulin level of 11.4 g/dl. The patients received bortezomib based chemotherapies±vinciristine, adriablastina, and dexamethasone (VAD); 24 (80%) patients responded to the induction chemotherapy (complete response or partial response), whereas only six (20%) patients did not respond to the induction chemotherapy. The OS of the patients was 16 months (range, 5-32 months).

The median globulin level was 4.98 g/dl (range, 2.3–11.6 g/dl), and the cutoff value for globulin was determined as 4.9 according to the median globulin level. The patients were divided into two groups according to the median globulin value >4.9 g/dl and <4.9 g/dl. Fifteen (50%) patients had a globulin value <4.9 g/dl, whereas 15 (50%) had a globulin value of 4.9 g/dl. Both groups were comparable in terms of gender, age, Durie-Salmon stages, kappa/lambda ratios, creatinine value, β2-microglobulin level, LDH level, OS, and treatment response rates (p>0.05).

In the group with a globulin level >4.9 g/dl, the number of patients with IgG type proteinemia was significantly higher (p=0.036) and the median hemoglobin level was lower (p=0.009) compared with those in the group with a globulin level <4.9 g/dl. Likewise, correlation analysis revealed that the hemoglobin level was negatively correlated with the globulin level. The median albumin level was lower in the group with a globulin level >4.9 g/dl (p=0.027), whereas the median calcium level was higher in the group with a globulin level <4.9 g/dl (p=0.027) (Table 2).

The globulin level was not significantly associated with the treatment response or OS between the two groups (p>0.05).

Discussion

The tumor burden and disease biology markers identified at the time of diagnosis are the determinants of treatment response and OS in patients with MM.[1-3, 8] While Durie-Salmon staging includes the M-protein level in establishing tumor burden,[9] the ISS is based solely on the albumin and β2-microglobulin levels.[4] However, the association of the globulin level with treatment response and OS had not been previously investigated. In our study, we

found that increased globulin levels were associated with decreased albumin and hemoglobin levels, which indicated that increased globulin levels were a sign of high tumor burden. However, it did not negatively affect response to induction chemotherapy and OS.

Although albumin is the major protein component of blood, globulins constitute the remaining minor portion of total blood proteins that comprise numerous subsets, such as carrier proteins, enzymes, complements, and immunglobulins.[10, 11] This ratio can be altered frequently due to the enhanced production of immunglobulins and acute phase proteins during inflammatory diseases.[11] In MM, increased globulin levels due to the secretion of M-protein is often encountered[6, 10, 11] and may evoke the risk of hyperviscosity, particularly during very high globulin levels.[6] The incidence of symptomatic hyperviscosity in MM is 2%-6%.[6] Hypergammaglobulinemia augments serum viscosity leading to serious symptoms such as bleeding and ocular, neurological, and cardiovascular manifestations, all requiring urgent intervention with plasmapheresis.[6, 7, 12] The hyperviscosity develops mostly in the IgA type MM.[12, 13] The relatively low number of patients having IgA type M-protein might be the reason for diminished number of patients with hyperviscosity syndrome in our cohort.

The retrospective nature of the present study, relatively low number of patients assessed, lack of hyperviscosity measurements, and inadequate data on the risk assessment of patients are the major limitations of this study; thus, a precise evaluation of the role of globulin in the treatment response and OS in patients with MM could not be achieved. However, to the best of our knowledge, this study is the first to investigate the role of globulin in patients with MM. Consequently, increased globulin levels are not a concern for clinicians during the course of the MM because it does not appear to negatively affect the treatment response and OS. Further studies are required to elucidate the precise contribution of globulin levels in the risk assessment of patients with MM, including trials with a large number of patients.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship contributions: Concept – R.E., E.S.; Design – R.E., E.S.; Supervision – E.S.; Materials – R.E., O.O., C.A., M.H.D.; Data collection &/or processing – R.E., E.S., O.O., C.A.; Analysis and/or interpretation – R.E., E.S., O.O., C.A.; Literature search – R.E., E.S.; Writing – R.E., E.S., O.O., C.A.; Critical review – R.E., E.S., M.H.D., S.A., O.Y.

References

1. Moreau P, San Miguel J, Sonneveld P, Mateos MV, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv52–61. [CrossRef]
2. Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc 2016;91:101–19. [CrossRef]
3. Hanbali A, Hassanein M, Rasheed W, Aljurf M, Alsharif F. The Evolution of Prognostic Factors in Multiple Myeloma. Adv Hematol 2017;2017:4812637. [CrossRef]
4. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–20. [CrossRef]
5. Mikhael JR, Dingli D, Roy V, Reeder CB, Buadi FK, Hayman SR, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc 2013;88:360–76. [CrossRef]
6. Mehta J, Singhal S. Hyperviscosity syndrome in plasma cell dyscrasias. Semin Thromb Hemost 2003;29:467–71. [CrossRef]
7. Stone MJ, Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. Blood 2012;119:2205–8.
8. Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, et al. IMWG consensus on risk stratification in multiple myeloma. Leukemia 2014;28:269–77. [CrossRef]
9. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36:842–54. [CrossRef]
10. Busher JT. Serum Albumin and Globulin. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston: Butterworths; 1990. Chapter 101.
11. O'Connell TX, Horita TJ, Kasravi B. Understanding and interpreting serum protein electrophoresis. Am Fam Physician 2005;71:105–12.
12. Gertz MA, Kyle RA. Hyperviscosity syndrome. J Intensive Care Med 1995;10:128–41. [CrossRef]
13. Chandy KG, Stockley RA, Leonard RC, Crockson RA, Burnett D, MacLennan IC. Relationship between serum viscosity and intravascular IgA polymer concentration in IgA myeloma. Clin Exp Immunol 1981;46:653–61.