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ORIGINAL ARTICLE

B-Cell Maturation Antigen (CD269) as a Predictor for Response to Treatment in Multiple Myeloma Patients.

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ABSTRACT

Background: More research is going on markers for multiple myeloma (MM) to improve treatment. National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) is used for risk evaluation and treatment tailoring in MM patients. Relatively, few studies assess role of B-Cell Maturation Antigen (BCMA) in Egyptian MM. The aim of this study was to assess BCMA expression among MM patients and evaluate its prognostic significance.

Methods: Thirty-six newly diagnosed MM patients were enrolled in the study. BCMA was assessed by multicolor flow Cytometry (MFC) using BD FACS CANTO II flow cytometer. Three months following chemotherapy, patients' bone marrow (BM) was examined for evaluation of their remission status.

Results: BCMA (CD269) was expressed on malignant plasma cells of all MM cases of the studied group. There was a statistically significant difference in CD269 expression among MM groups according to the international staging system, being highest in stage II, also there was a significant difference in the expression of CD269 among MM patients by serum immunofixation being higher in the IgG type than IgA type. A highly statistically significant lower expression for CD269 was observed in MM patients who achieved remission. A significant positive correlation between CD269 Mean Fluorescence Intensity (MFI), and serum Lactate dehydrogenase (LDH) was detected. Moreover, a highly significant positive correlations between CD269 MFI, serum β2-microglobulin and CD56 MFI were observed.

Conclusion: High BCMA expression was associated with low remission rate, also it was associated with high CD56 MFI, serum LDH and serum β2-microglobulin

Keywords: MM; BCMA; MFC; Chemotherapy; Remission

INTRODUCTION

Multiple myeloma (MM) is an incurable clonal plasma cell neoplasm that starts in the bone marrow. It is the second most prevalent hematologic malignancy in adults, with a median diagnostic age of 69 years [1]. Approximately, MM is responsible for one percent of all cancers and ten percent of all blood cancers. Patients may have a considerable mortality rate with median survival of about five years [2].

Most cases of MM patients arise from monoclonal gammopathy of undetermined significance (MGUS), asymptomatic pre-malignant stage [3]. Some cases have smoldering multiple myeloma (SMM), a more advanced pre-malignant stage that is intermediately asymptomatic but can be clinically observed, the rate at which this stage advances to MM is about ten percent annually. The underlying cytogenetic type of disease and the disease load both affect this rate of advancement; patients with t(4;14), del(17p), and gain(1q) are more likely to proceed from MGUS or SMM to MM [4].

Overall MM survival has improved dramatically through the advent of hematopoietic stem cell

transplantation (HSCT) together with novel medications, such as immune checkpoint inhibitors, monoclonal antibodies, immunomodulators, and proteasome inhibitors [5]. However, MM remains incurable at this time due to the disease's non-specific clinical symptoms, and complicated bone marrow microenvironment caused by genetic instability, recurrence, and treatment resistance [6].

The choice of a suitable tumor-specific antigen is a key component of immune-based therapy. Ideally, the antigen should be expressed constantly on the MM plasma cells while having little to no expression on the normal cells. This can be difficult, particularly if subclones have been created that may give the MM cells different phenotypes [7].

The transmembrane glycoprotein known as B cell maturation antigen (BCMA), often referred to as tumor necrosis factor receptor superfamily member (17) (TNFRSF17) or CD269 that, when combined with BAFF and APRIL, is crucial for B cell differentiation and growth of malignant myeloma cells [8]. Only plasma cells and late memory cells express BCMA, non-hematopoietic organs, HSCs, and progenitor cells do not [9].

Typically, Myeloma cells exhibit increased BCMA expression than do typical plasma cells [10]. As well as a heterogeneous pattern of expression is observed in malignant plasma cells of MM patients [11]. Malignant plasma cells survival as well as proliferation is enhanced by BCMA activation and overexpression. Breakage of BCMA attached to cell surface takes place by the help of γ-secretase that allows soluble BCMA to circulate more easily [12].

The physiological function of BCMA with its restricted expression pattern on myeloma cells in both newly diagnosed and relapsed/refractory patients has made therapies like Chimeric Antigen receptor T cells (CAR T), bispecific antibodies, and Antibody Drug Conjugates (ADCs) that target it, a valuable treatment alternative for non-responding MM [13, 14]. The likelihood of treatment with anti-BCMA being incorporated into frontline therapy can't be disputed given the encouraging results of clinical trials that target BCMA.

However, information regarding the level of BCMA expression is lacking among Egyptian MM patients. This study is a cohort type aimed at assessing the significance of CD269 among MM patients, evaluate its role as a predictor for response to therapy, and correlate between its expression and other prognostic factors using multicolor flow Cytometry (MFC).

METHODS

The study was done at Zagazig University Hospitals' Clinical Pathology Department in accordance with the declaration of Helsinki's ethical guidelines, with approval from the institutional review board (IRB) of Zagazig University (ZU-IRB# 9031), and written informed consent provided by all participating patients. Thirty-six newly diagnosed MM patients admitted to Medical Oncology Department and Clinical Hematology Unit were enrolled, during the period December 2021 and December 2022. The sample size was estimated using Epi Info program 6 (Atlanta, Ga, USA).

The study's inclusion criteria comprise consent to enroll, de novo cases prior to chemotherapy and without any existing cancers. Exclusion criteria encompass known or treated myeloma patients, presence of other malignancies, finally refusal to participate in the study.

Following a comprehensive history and clinical examination, the patients underwent standard laboratory tests, such as Complete Blood Count (CBC) by Sysmex Xn (Sysmex, Japan), liver and kidney function tests, serum lactate dehydrogenase (LDH) and β2-microglobulin via Cobas 6000 auto analyzer (Roche Diagnostics, Germany), serum and urine protein electrophoresis and serum immunofixation using Sebia mini cap flex piercing capillary electrophoresis (ULTRAVISION, France), assessment of serum free light chain using Cobas 501 auto-analyzer (Roche Diagnostics, Germany), BM aspiration and evaluation , multicolor flow Cytometry for diagnosis of MM and for assessment of CD269 using BD FACS CANTO II (Becton Dickinson, USA) . Radiological investigations (for any osteolytic lesions and renal impairment) were done for the patients.

MM immunophenotypic analysis

Processing was done on bone marrow samples using the Stain Lyse Wash method. Fifty microliters of BM sample were added to fluorochrome-conjugated monoclonal antibodies against CD19, CD20, CD38, CD45, CD56, CD117 and CD138. Monoclonal antibody against CD269 was involved (Fluorescein-conjugated Antibody/ Catalog Number: FAB193F R&D SYSTEMS a biotechne brand, USA). Surface staining was performed after incubation in the darkness for 25 min at room temperature. Next, erythrocyte-lysing was performed by adding freshly prepared 1 ml of BD FACS lysing buffer solution (Becton Dickinson

(BD) San Josè, California, USA) diluted 1:10 in distilled water and incubation for 10 min at room temperature. Then, the cells were washed with phosphate-buffered saline (PBS) to remove excess antibody and debris

Finally, the acquisition was performed on an 8-colors, 3-lasers BD FACS CANTO II instrument (Becton Dickinson, USA) within 2 hours of staining. Set-up of the instrument, compensation and quality control were done as per the manufacturer's protocol. Post-acquisition analysis was performed using Diva software (Becton Dickinson, USA).

Assessment of plasma cells CD269 expression

Briefly, a bivariate dot-plot of forward scatter area (FSC-A) Vs height (FSC-H) was used to eliminate doublets from the data set. Debris and non-viable cells were removed by blotting side scatter area (SSC-A) Vs FSC-A. Gating of plasma cells (PCs) was done using CD38 Vs SSC-A. Identification of PCs was done via the co-expression of CD138 and CD38. Moreover, the differentiation between malignant and normal PCs was dependent on the different expressions of CD45, CD56, CD117, CD19 and CD20. Evaluation of BCMA expression in myeloma cells was done by blotting CD269 against CD38 and its intensity of expression was assessed using the mean fluorescence intensity (MFI). T cells served as the internal negative control for the expression of CD269.

Treatment plan and follow-up

According to National Cancer Comprehensive Network 2022, Primary therapy is as follow: If the patient with renal impairment (VCD); Velcade sc 2.5, cyclophosphamide 300 & dexamethasone 400 [mg/kg at $D_{1, 8, 15, 21}$]. If without renal impairment (VRD); Velcade 2.5 mg/kg sc $D_{1,8,15,21}$, Revlimide 25mg/kg D_1-D_{21} then off one week, dexamethasone 400 mg/kg $D_{1,8,15,21}$ & Zolendronic acid 4mg for three months then reevaluation. If the patient is in CR, the therapy is continued for another 3 months, then re-evaluation if the patient is still in CR, prepare the patient for BM transplantation. In our research, follow-up of the patients was done for three months from starting therapy.

Statistical analysis

Using SPSS program (Statistical Package for Social Science) version 24 and NCSS 12, LLC, USA, the collected data were computerized and statistically analyzed**.** Shapiro Walk test was used to determine whether the data had a normal distribution. Frequencies and relative percentages were used to illustrate the qualitative data. Quantitative data were expressed as median and range for non-normally distributed data and mean ± SD (Standard deviation) for normally distributed data. The difference between quantitative variables in two groups for non-normally distributed variables was calculated by Mann Whitney test. In order to indicate which groups were significantly different from each other, Post hoc test for multiple comparisons was done by using Dunn's Multiple Comparison Post hoc. Regarding correlation between non –normally distributed variables, Spearman's correlation test was used. Every statistical comparison was tailed. The difference is considered significant if the P-value is less than 0.05, highly significant if it is less than 0.001, and non-significant if it is greater than 0.05.

RESULTS

Thirty-six new MM cases were included, Twenty-two of them were males (61.1%). The age group less than 60 years old constituted (55.6%). According to the ISS, the most frequent one was stage I (47.2%), followed by stage II (27.2%) and lastly stage III (25%). Bence Jones protein was positive in (41.7%) of the studied group. As regards serum immunofixation, the most frequent type was IgG Kappa (36.1%), followed by IgG Lambda (27.8%), IgA Kappa (19.4%) and finally IgA Lambda (16.7%). With respect to Serum-free light chain was elevated in (33.3%) of the studied group. CD117 was positive in 25% of the patients with a good prognosis. CD269 MFI ranged from (2.11-10.28) with a median of (6.19) and CD56 MFI ranged from (1.58-8.56) with a median of (4.48). Twenty-four patients (66.7%) achieved remission during their evaluation 3 months after starting chemotherapy (Table 1).

There was a statistically significant difference in CD56 MFI among MM groups according to the international staging system, Stage: I Vs. II; P= 0.002, I Vs. III; P= 0.005, II Vs. I; P= 0.002. Also, there was a statistically significant difference in CD56 MFI among MM patients by serum immunofixation (A kappa Vs. G Lambda; P= 0.008, A Lambda Vs. G kappa; P= 0.032, A Lambda Vs. G Lambda; P= 0.002). As regards CD269, there was a statistically significant difference in CD269 MFI among MM groups according to the international staging system Stage: I Vs. II; P= 0.004, I Vs. III;

P= 0.009, II Vs. I; P= 0.005. Also, there was a statistically significant difference in CD269 MFI among MM patients by serum immunofixation (A kappa Vs. G kappa; P= 0.003, A kappa Vs. G Lambda; P= 0.002, A Lambda Vs. G kappa; P= 0.006, A Lambda Vs. G Lambda; P= 0.004). Regarding response to therapy, a highly statistically significant lower MFI for CD269 and CD56 was observed in MM patients who achieved remission ($p \leq 0.001$). (Table 2, figure 1 & figure 2)

There were significant positive correlations between CD56 MFI, serum LDH (P=0.007), and β2- microglobulin (P=0.001) and a highly statistically significant correlation between CD56 MFI and CD269 MFI (P<0.001). Additionally, there was a significant positive correlation between CD269 MFI and serum LDH (P = 0.03) and highly significant positive correlation between CD269 MFI and serum β2- macroglobulin (P <0.001). No significant correlations were found between CD269 MFI, age, total leucocytic count (TLC), hemoglobin level (Hb), platelets count, BM plasma cells, total protein, albumin, serum calcium, serum creatinine, CD38 MFI and CD138 MFI (Table 3, figure 3, & figure 4)

Table 1: Characteristics of the study population (36 patients)

Parameter		Value
Age (Years)		57±8
Age group	< 60 y	20 (55.6%)
	≥ 60 y	16 (44.4%)
Sex	F	14 (38.9%)
	M	22 (61.1%)
I.S.S Stage	I	17 (47.2%)
	II	10 (27.8%)
	III	9 (25.0%)
BJ	N	21 (58.3%)
	P	15 (41.7%)
SPIF	A kappa	7 (19.4%)
	A Lambda	6 (16.7%)
	G kappa	13 (36.1%)
	G Lambda	10 (27.8%)
Free light chain	Elevated k	12 (33.3%)
	Normal	24 (66.7%)
UPEP	Negative	24 (66.7%)
	Positive	12 (33.3%)
CD117	Negative	27 (75.0%)
	Positive	9 (25.0%)
TLC		2.5±0.8
Hb		8.1±1.5
PLT		72±20
BM Plasma		53±14
LDH		613±151
T.PTN		9.9 (8.0-20.0)
Alb		2.8 (1.0-3.8)
β2-microglobulin		4.0 (1.5-34.9)
Cr		5.6 (3.6-11.0)
Ca		12.0 (10.7-14.8)
CD38 MFI		16.25 (4.88-95.60)

Parameter		Value
CD138 MFI		18.62 (1.98-120.88)
CD269 MFI		6.19 (2.11-10.28)
CD56 MFI		4.48 (1.56-8.56)
Remission	No	24 (66.7%)
	Yes	12 (33.3%)

Abbreviations: F, Female; M, Male; ISS, International Staging System; BJ, Bence Jones; SPIF, Serum Protein Immunofixation; UPEP, Urine Protein Electrophoresis; TLC, Total Leucocyte count; Hb, Hemoglobin; PLT, Platelets; BM, Bone Marrow; LDH, Lactate Dehydrogenase; T.PTN, Total Protein; Alb, Albumin; Cr, Creatinine; Ca, Calcium; CD, Cluster Differentiation; MFI, Mean Fluorescence Intensity.

Table 2: CD56 MFI, and CD269 MFI levels in different study parameters

Parameters		CD56 MFI	P-value	CD269 MFI	P-value
		Median (range)		Median (range)	
Age group	< 60 y	4.41 (1.92-8.56)	0.778	6.63 (2.11-10.10)	0.912
	≥ 60 y	4.64 (1.56-6.88)		5.25 (3.01-10.28)	
Sex	F	3.58 (2.18-6.88)	0.191	4.06 (2.24-10.28)	0.18
	M	5.38 (1.56-8.56)		7.18 (2.11-10.10)	
I.S.S Stage	I	3.45 (1.56-5.78)	**0.005***	3.54 (2.16-10.28)	**0.011**$^{+}$
	II	5.83 (1.92-8.56)		8.02 (2.11-10.10)	
	III	5.67 (2.18-8.23)		7.48 (4.45-10.08)	
BJ	N	4.70 (2.16-8.56)	0.987	5.88 (2.16-10.28)	0.374
	P	4.26 (1.56-8.23)		6.50 (2.11-10.08)	
SPIF	A kappa	3.15 (2.16-5.66)	**0.0f***	3.14 (2.16-6.96)	**0.003***
	A Lambda	2.45 (1.56-5.67)		3.27 (2.11-7.48)	
	G kappa	5.11 (2.18-8.56)		7.52 (2.32-10.28)	
	G Lambda	6.01 (3.64-8.23)		7.82 (3.66-10.08)	
Free light chain	Elevated k	3.16 (1.56-6.58)	0.128	4.84 (2.32-9.86)	0.251
	Normal	4.91 (1.92-8.56)		7.12 (2.11-10.28)	
UPEP	Negative	4.51 (1.56-8.23)	0.728	5.58 (2.24-10.28)	0.728
	Positive	4.41 (1.92-8.56)		7.13 (2.11-10.10)	
CD117	Negative	4.12 (1.56-8.56)	0.59	5.88 (2.11-10.28)	0.971
	Positive	5.01 (2.21-6.58)		6.87 (2.24-9.88)	
Remission	No	5.65 (2.18-8.56)	**<0.001***	7.53 (4.25-10.28)	**<0.001***
	Yes	2.78 (1.56-4.26)		2.89 (2.11-3.66)	

Variables were expressed as Median (range) and compared using the Mann-Whitney *U* test, or Kruskal-Wallis H test., as indicated. Notes: * $P \leq 0.05$, statistically significant; ** $P < 0.001$, statically highly significant. Abbreviations: F, Female; M, Male; ISS, International Staging System; BJ, Bence Jones; SPIF, Serum Protein Immunofixation; UPEP, Urine Protein Electrophoresis; CD, Cluster Differentiation; MFI, Mean Fluorescence Intensity.

Table 3: Correlations between CD56 MFI, CD269 MFI levels, and certain studied parameters in the studied population.

Parameter	CD56 MFI		Parameter	CD269 MFI	
	R	P- values		R	P- value
Age	-0.029	0.868	Age	-0.027	0.877
TLC	0.063	0.717	TLC	-0.023	0.893
Hb	-0.069	0.688	Hb	0.008	0.961
PLT	-0.087	0.615	PLT	-0.023	0.896
BM plasma	0.107	0.536	BM plasma	0.247	0.147
LDH	0.442	0.007*	LDH	0.363	0.03*
T.PTN	0.043	0.803	Total protein	-0.017	0.92
Alb	-0.022	0.9	Albumin	-0.027	0.877
β2-microglobulin	0.538	0.001*	β2-microglobulin	0.564	<0.001*
Cr	0.115	0.505	Cr	-0.028	0.873
Ca	0.178	0.299	Ca	0.109	0.527
CD38 MFI	-0.024	0.887	CD38 MFI	0.002	0.989
CD138 MFI	0.072	0.677	CD138 MFI	0.015	0.932
CD 269 MFI	0.86	<0.001*			

Notes: * P ≤ 0.05, statistically significant; ** P< 0.001, statically highly significant.

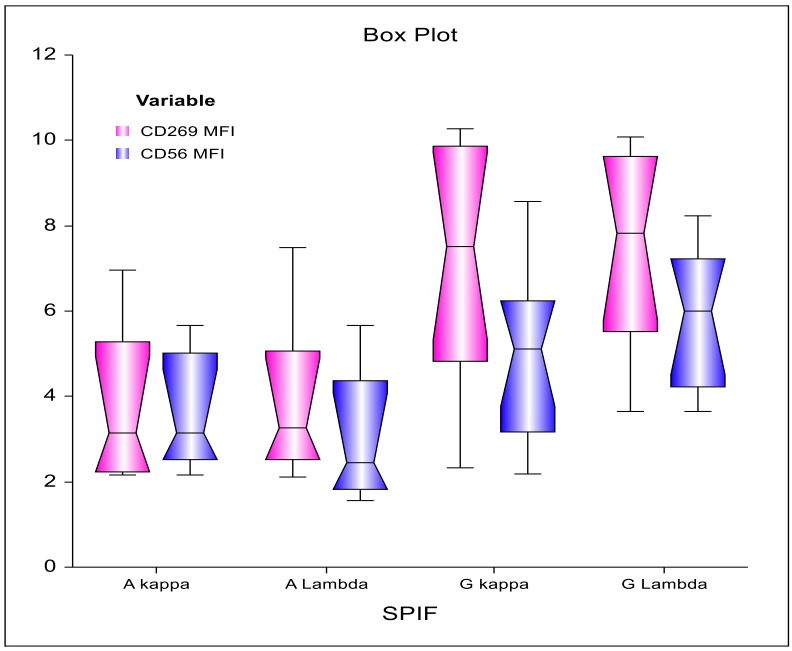

Figure 1: Box-plot diagram represents the range of CD56 MFI, and CD269 MFI levels as regard SPIF**.**

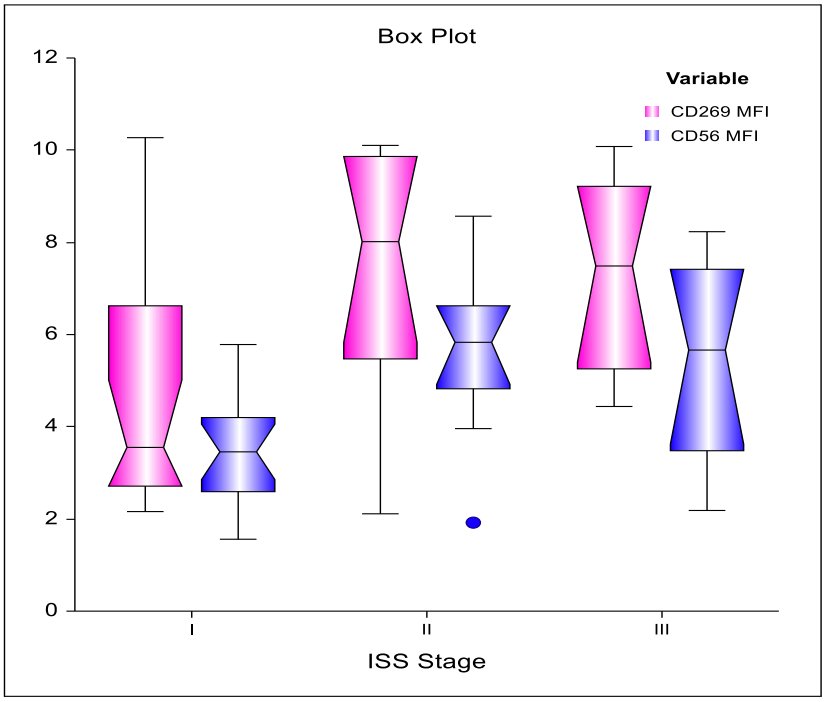

Figure 2: Box-plot diagram represents the range of CD56 MFI, and CD269 MFI levels as regard ISS.

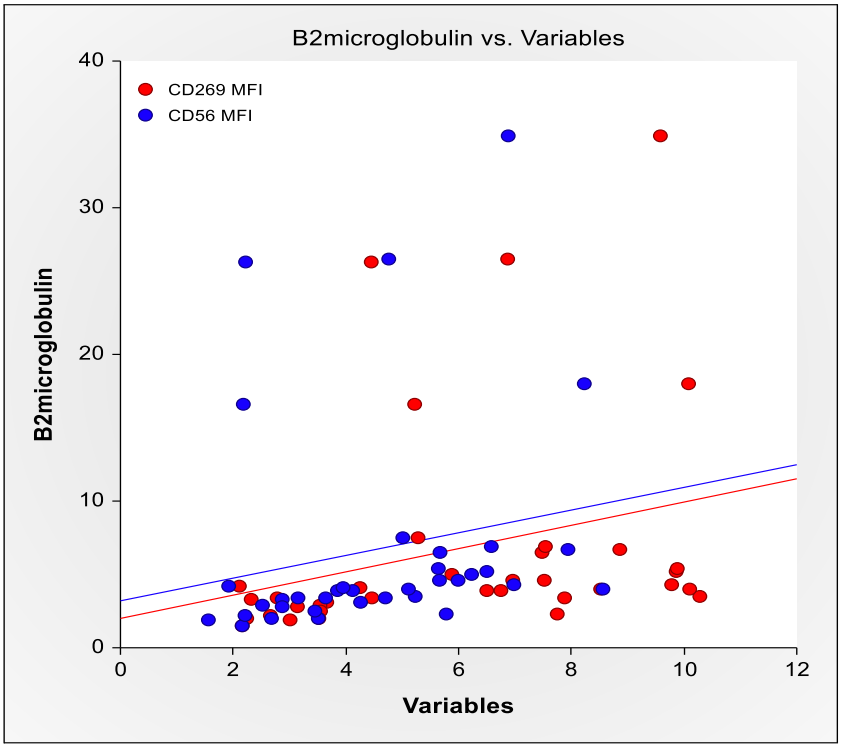

Figure 3: Correlations between CD56 MFI, CD269 MFI levels and β2-microglobulin in the studied population.

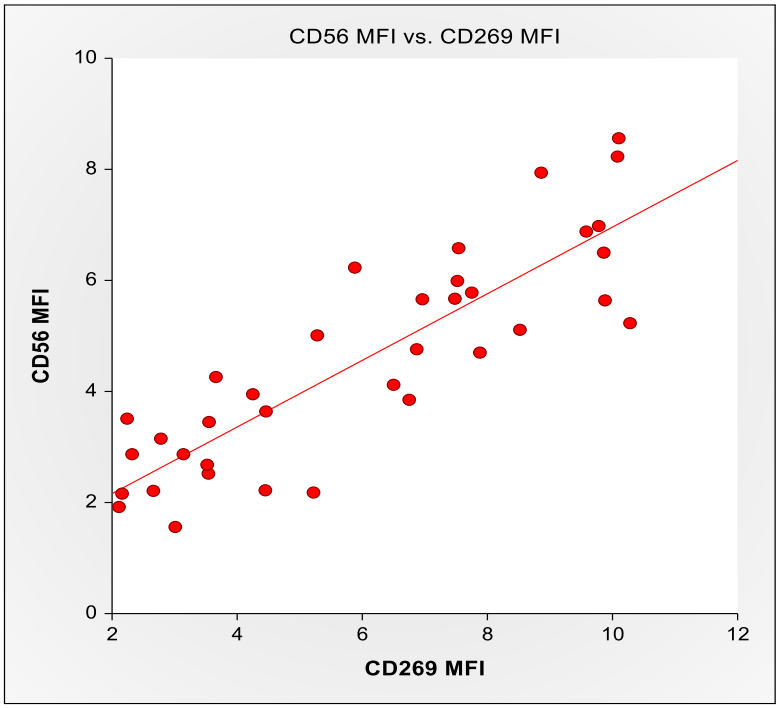

Figure 4: Correlations between CD56 MFI, and CD269 MFI levels in the studied population.

DISCUSSION

MM is a genetically complicated and heterogeneous cancer that has significant morbidity and mortality. Patients still undergo cycles of remission and relapse despite advancements in therapy, thus, treatments with distinct modes of action against novel myeloma antigens are required [15].

Due to the introduction of innovative medicine like anti-CD38 MoA, Immunomodulatory Drugs and proteasome inhibitors (PIs), MM patients' prognosis has improved dramatically over the past 20 years. Triple-class refractory myeloma, which is MM refractory to the three medication classes indicated above, had restricted therapeutic options until recently [16]. Other treatment options for this type of myeloma comprise dexamethasone plus selinexor and therapies targeting CD269 (ADC and CAR-T) [17].

In our study, we analyzed BCMA (CD269) by flow Cytometry in 36 newly diagnosed myeloma patients and its level was correlated with other prognostic factors & response to treatment. CD269 ability to detect MM cells in flow Cytometry analysis was assessed in order to determine whether it could be included in standard MM flow Cytometry panels or not.

Our results showed that CD269 was expressed on malignant plasma cells of all MM cases of the studied group, this agreed with the findings of Sriram et al. who confirmed that CD269 may be promising for developing focused treatment against MM since they discovered that malignant PCs expressed CD269 also its intensity was noticeably higher in activated plasma cells than normal plasma cells [18].

A significant statistical difference as regards CD269 MFI was evidenced among MM groups according to the international staging system being highest in stage II, followed by stage III and lastly stage I. Also, there were significant difference in the expression of CD269 and CD56 among MM patients by serum immunofixation being higher in the IgG type than IgA type. Ma et al. found that while there was no statistically significant variation for CD269 expression throughout different stages of MM, newly diagnosed IgG patients had higher expression of CD269 than those of IgA type [19].

Our results showed that patients who achieved remission 3 months follow up after starting therapy had lower CD269 MFI than patients who didn't achieve with highly statistically significant difference. Lee et al. showed that myeloma cells with increased surface BCMA expression had shorter progression-free survival (PFS) and overall survival [20]. However, Sriram et al. discovered no correlation between the levels of BCMA expression and the clinical prognosis or even early therapeutic response [18].

In our research, CD269 MFI was positively correlated with Hb level, percentage of bone marrow plasma cells, serum calcium, CD38 MFI and CD138 MFI without statistical significance, meanwhile it was negatively correlated with age, TLC, platelets, serum albumin and serum creatinine also without statistical significance. Ma et al. found that CD269 was significantly positive correlated with age and percentage of bone marrow plasma cells and significantly negative correlated with Hb level and serum albumin [19].

Our correlation result regarding CD269 MFI and serum LDH was significantly positive, also highly significant positive correlations between CD269 MFI, serum β2- microglobulin and CD56 MFI were observed. Although Ma et al. found no significant correlation between the patients' serum β2-microglobulin and bone marrow BCMA expression, but their finding demonstrated that myeloma patients with elevated BCMA had elevated serum β2- microglobulin. Additionally, they didn't observe significant relationship between the patients' serum LDH and bone marrow BCMA expression [19].

Insightful information about BCMA (CD269) was displayed, one of the tumor necrosis factor receptor superfamily that plays a critical role in the proliferation of malignant myeloma, regarding its expression in MM patients and its prognostic significance.

Limitations:

On the other hand, the current study had some shortcomings, including a small sample size, being done in a single center, a short follow–up period, and an absence of data on cytogenetic abnormalities influencing disease outcomes in MM patients.

CONCLUSIONS

High BCMA (CD269) MFI was detected among MM stage II according to ISS also in MM patients of IgG type according to SPIF. Additionally, this high expression was associated with high levels of CD56 MFI, serum LDH, and serum β2-microglobulin denoting an association between BCMA and poor outcomes in MM.

Conflict of interests

The authors declare no conflicts of interest.

Financial Disclosures

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