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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

Prognostic value of B-cell maturation antigen, CD56 expression and neutrophil lymphocyte ratio in patients with multiple myeloma

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Abstract

Introduction: B-cell maturation antigen (BCMA) plays a critical role in regulating B-cell proliferation and differentiation into plasma cells. CD56 is involved in the adhesion of myeloma cells to the bone marrow matrix.Thus, lack of CD56 expression is associated with a higher incidence of extramedullary disease. An elevated neutrophil-lymphocyte ratio (NLR) has been recognized as a poor prognostic factor in various hematological malignancies.

The aim of this study was to evaluate the role of BCMA, CD56 and NLR as novel prognostic markers in multiple myeloma (MM).

Material and methods: The study included 80 subjects, 40 MM patients, and 40 normal healthy age- and sex-matched controls. BCMA was analyzed by enzyme-linked immune sorbent assay. Flow cytometry was used for the determination of CD56 expression. NLR was calculated from the complete blood count differential count. All patients received six cycles of bortezomib, cyclophosphamide and dexamethasone (VCD). Treatment outcome was assessed and progression-free survival (PFS) was estimated using Kaplan-Meier survival analysis.

Results: Patients who achieved complete remission showed lower BCMAlevels, positive CD56 expression, and lower NLR. Moreover, higher BCMA levels and CD56 negative expression were significantly associated with shorter PFS.

Conclusions: Our study emphasizes the importance of BCMA, CD56 and NLR to predict the clinical outcome in MM patients. This could help in better risk stratification and tailored clinical management of MM patients.

Key words: BCMA, CD56, neutrophil-lymphocyte ratio, myeloma

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Introduction

Multiple myeloma (MM) is a hematological malignant disease characterized by monoclonal plasma cell proliferation. This disease can lead to a variety of clinical complications, including high calcium levels, renal failure, anemia, bone lesions, and opportunistic infections. Several new therapeutic agents for MM patients have resulted in a significant improvement in their median overall survival (OS). However, the relapse rate is still high, and the prognosis for MM is also highly variable [1, 2].

The International Staging System (ISS), a prognostic model based on beta$_2$-microglobulin (β2M) and albumin, was one of the first attempts to stratify MM patients. Although this system is simple and reproducible, it fails to account for the tumor-associated immune microenvironment,

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which is important in disease pathogenesis and progression [3, 4]. Furthermore, monoclonal protein (M-protein) is currently being used in clinical settingsto track the progression of the disease [5]. Serum-free light chain (SFLC) has recently beenused to predict treatment outcomes [6, 7].

Furthermore, the therapeutic options for MM have been expanded to include immune-based approaches. Unfortunately, the methods for evaluating the disease status of MM patients have not kept up with this expanding profile. As a consequence, developing moreeffective and consistent methods to characterize and monitor these patients is becoming increasingly important [3].

B-cell maturation antigen (BCMA) has been associated with B-cell malignancies. It is shed from the plasma cell surface membrane via γ-secretase–mediated cleavage, resulting in a soluble form (sBCMA). This is essential in the regulation of B-cell proliferation and differentiation into plasma cells [8].

CD56 is involved in myeloma cell adhesion to the bone marrow (BM) matrix. The lack of CD56 expression on myeloma cells reduces their adherence to the cell-matrix and is linked to an increased risk of extramedullary disease, renal insufficiency, and plasma cell leukemia [9, 10].

Inflammation markers are particularly intriguing. They are presumed to indirectly reflectthe status of the BM microenvironment, and induce cancer cell proliferation and even drug resistance in myeloma cells [11]. An elevated neutrophil-lymphocyte ratio (NLR) has been identified as a poor prognostic factor in a variety of solid cancers and hematological malignancies [12].

The main objective of this study was to investigate the role of BCMA, CD56, and NLR as novel prognostic markers in MM.

Material and methods

This study included 80 subjects: 40 MM patients admitted to the Medical Research Institute (MRI) hematology department and 40 healthy normal age- and sex-matched controls. The International Myeloma Working Group (IMWG) diagnostic criteria were used to make the MM diagnosis [13].

All patients were subjected to the following:

- a thorough history was taken, and a clinical examination performed;
- complete blood count (CBC); NLR was calculated from the differential count ofthe CBC;
- laboratory investigations: creatinine, lactate dehydrogenase (LDH), β2M, albumin,serum protein electrophoresis, and immunofixation;
- radiological examination for the evaluation of osteolytic bone lesions;
- BM examination for morphological assessment and BM plasma cell percentage [14].

Bortezomib, cyclophosphamide, and dexamethasone were given to all patients over the course of six treatment cycles in a 28-day cycle [15]: bortezomib: 1.3 mg/m^2 intravenously on days 1, 8, 15, and 22; cyclophosphamide: 300 mg/m^2 orally on days 1, 8, 15, and 22; and dexamethasone: 40 mg orally on days 1, 8, 15, and 22. After six cycles, patients' treatment responses were assessed. The Kaplan-Meier survival analysis was used to evaluate progression-free survival (PFS). The local ethics committee at Alexandria University's Medical Research Institute approved this study. Before collecting samples and after a brief explanation of the research objectives, both patients and controls provided informed consent.

BCMA quantification using an enzyme--linked immune-sorbent assay

The sandwich enzyme-linked immune-sorbent assay (ELISA) technology was used. Well plates were pre-coated with anti-BCMA antibodies. Anti-BCMA antibodies conjugated with biotinwere used as detection antibodies.After drawing peripheral blood samples, the samples werecentrifuged for 20 minutes and serum samples were separated. The standards, test samples, and biotin-conjugated detection antibody were added to the wells, and the wells were washed with wash buffer. After that, the acidic stop solution was added, and a yellow product was produced. The quantity of BCMA captured in the sample was proportional to the density of the yellow color. The absorbance was measured in a microplate reader at 450 nm, and the concentration of BCMA was calculated [5].

Flow cytometry-based immunofluorescence for identification of BM mononuclear cells as well as estimation of CD56 expression

For plasma cell identification, the cells were labeled with a panel of fluorochrome-linked monoclonal antibodies. CD138 (PE), CD38 (FITC), CD56 (FITC), CD27 (PE), CD19 (FITC), Anti-human cytoplasmic kappa light chain (PE), and Antihuman cytoplasmic lambda light chain (FITC) were used as monoclonal antibodies. The cutoff point for positivity was established at 20% of the gated cells [10].

Statistical analysis of data

Two-tailed tests were used for all statistical analyses. *P*-values less than 0.05 were considered significant. A receiver operating characteristic (ROC) was used to assess a test's prognostic accuracy. The larger the area under the curve (AUC), i.e. closer to one, the better the test's performance. The cutoff point was determined using the Youden index. Sensitivity,specificity, positive predictive value (PPV), and negative predictive value (NPV) were identified at this cutoff point.

Results

The age of MM patients ranged from 40 to 75 years, with a median of 56. There were 23 males (57.5%) and 17 females (42.5%). According to the ISS staging system, 12.5% of MM patients were classified as stage I, 70% as stage II, and 17.5% as stage III. According to radiological findings, 67.5% of MM patients had lytic bone lesions.

The absolute neutrophilic count of MM patients had a mean of 5.97 ± 4.57. The absolute lymphocytic count had a mean of 2.99 ± 1.83. Table I illustrates the distribution of the studied MM patients based on the laboratory investigations.

At the end of the induction with six cycles of bortezomib, cyclophosphamide and dexamethasone (VCD), 12 (30%) patients had complete remission (CR), 22 (55%) had very good partial remission (VGPR) or partial remission (PR), and six (15%) had an unfavorable outcome in the form of progressive disease (PD) or stable disease (SD).

All patients were followed up for 5–12 months before the treatment response was reassessed; CR was observed in 14 (35%) patients, VGPR or PR in 18 (45%) patients, six (15%) of the patients showed either PD or SD, and two (5%) of the patients relapsed.

There was no statistically significant difference between the patient and control groups in terms of age (p = 0.3) or gender (p = 0.82), though there was a statistically significant difference in the level of hemoglobin (Hb) (p <0.001), calcium (p <0.001), creatinine (p <0.001), and LDH (p <0.001).

The patient group had statistically higher levels of BCMA, with a median of 15.6 (11.26–20.15) compared to the control group with a median of 2.68 (1.29–6.89) (p <0.001).

NLR was statistically higher in MM patients, with a median of 2.16 (0.20–5.50), compared to 1.24 (1.09–2.40) in the control group (p <0.005). Figure 1 demonstrates a ROC curve to assess NLR's prognostic performance in MM patients. At a cut-off value of 2.31 for NLR, sensitivity was 85.71%, specificity was 84.85%, PPV was 54.5%, and NPVwas 96.6%. The AUC was set at 0.820.

Correlation of BCMA, CD56 expression, and NLR with patient clinicolaboratory characteristics

The current study found no significant correlation between BCMA and ISS staging (p = 0.35), but CD56 negative expression was significantly associated with stage III (p <0.001).

As shown in Table II, there was also no significant association between BCMA or NLR and lytic bony lesions. All CD56 negative patients, on the other hand, did not have any lytic lesions. There was no significant correlation between BCMA, CD56 expression, or NLR and Hb, creatinine, calcium, or β2M.

Table I. Distribution of studied multiple myeloma patients according to laboratory characteristics

Patient characteristics	No. (n = 40)	[%]
Hemoglobin [g/dL]		
<10	32	80
≥10	8	20
Calcium [mg/dL]		
<11	18	45
≥11	22	55
Creatinine [mg/dL]		
<2	14	35
≥2	26	65
Lactate dehydrogenase [U/L]		
Normal	31	77.5
More than normal	9	22.5
Beta$_2$-microglobulin [mg/L]		
<3.5	12	30
≥3.5	28	70

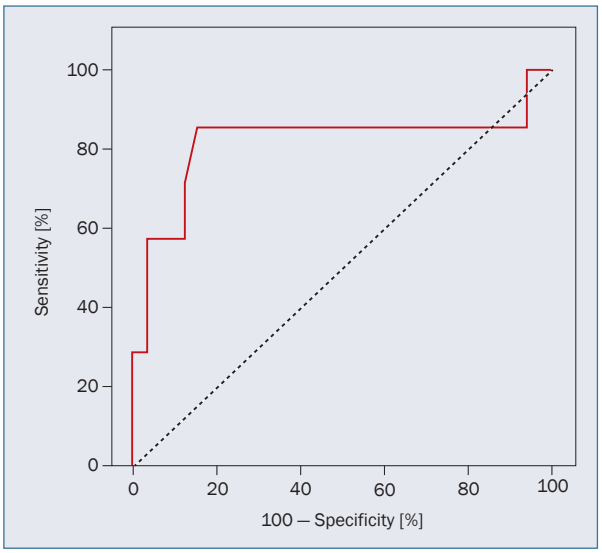

Figure 1. Receiver operating characteristic curve analysis to determine the prognostic performance of neutrophil-lymphocyte ratio

Correlation of measured parameters with BM aspirate findings and M protein

As regards BCMA, the current study showed a significant positive correlation between both the percentage of BM plasma cells and M protein level with BCMA in MM patients prior to treatment, as shown in Table III. Furthermore, there was a statisticallysignificant positive correlation between both the percentage of BM plasma cells and the M protein level with BCMA after six cycles of VCD.

Table II. Relation between B-cell maturation antigen (BCMA), CD56 expression and neutrophil-lymphocyte ratio (NLR) with clinicolaboratory characteristics of enrolled multiple myeloma patients

Parameter	Serum BCMA	CD56 expression		NLR	
	Median (range)	Negative (n = 11)	Positive (n = 29)	<2.31 (n = 28)	≥2.31 (n = 12)
Lytic bone lesions		No.	No.	No.	No.
Absent	15.97 (11.26–19.53)	11	3	9	5
Present	14.94 (11.74–20.15)	0	26	19	7
p	$^{U}p = 0.29$	$^{FE}p < 0.001$*		$^{\chi^2}p = 0.563$	
Hb [g/dL]		No.	No.	No.	No.
<10	15.56 (11.74–20.15)			21	11
≥10	16.06 (11.26–19.53)			7	1
p	$^{U}p = 0.363$	$^{\chi^2}p = 0.479$		$^{FE}p = 0.396$	
Calcium [mg/dL]		No.	No.	No.	No.
<11	15.25 (11.26–19.53)	5		13	
≥11	15.61 (12.66–20.15)	6		16	
p	$^{U}p = 0.596$	$^{\chi^2}p = 0.972$		$^{FE}p = 0.096$	
Creatinine [mg/dL]		No.	No.	No.	No.
<2	14.49 (11.26–19.53)	4		10	
≥2	15.62 (12.66–20.15)	7		19	
p	$^{U}p = 0.101$	$^{\chi^2}p = 0.911$		$^{FE}p = 0.157$	
β2M [mg/L]		No.	No.	No.	No.
<3.5	15.88 (12.66–19.53)	3		9	
≥3.5	15.25 (11.26–20.15)	8		20	
p	$^{U}p = 0.24$	$^{\chi^2}p = 0.817$		$^{FE}p = 0.651$	

*Statistically significant at $p \leq 0.05$; *p* – *p* value for association between different categories; U – Mann Whitney test; FE – Fisher Exact test; χ^2 – Chi square test; Hb – hemoglobin; β2M – beta$_2$-microglobulin

Table III. Correlation between B-cell maturation antigen (BCMA) with BMA plasma cells and M protein before and after treatment

Serum BCMA before treatment		
	r_s	*p*
BMA plasma cells [%] before treatment	0.413	0.008*
M protein before treatment	0.325	0.041*
Serum BCMA after treatment		
	r_s	*p*
BMA plasma cells [%] after treatment	0.756	<0.001*
M protein after treatment	0.704	<0.001*

*Statistically significant at $p \leq 0.05$; r_s – Spearman coefficient

Correlation between studied parameters and treatment response

As shown in Table IV, the treatment response was assessed in terms of BCMA, NLR, and CD56 expression in all MM patients.

Our study revealed that patients in CR had significantly lower serum BCMA levels, with a mean of 4.33 ± 2.96. Notably, the median serum BCMA level in CR patients (3.76 ng/mL) was very close to the level in healthy subjects (2.68 ng/mL). Patients who had VGPR or PR had relatively higher levels of serum BCMA than did those who had CR, with a mean of 8.17 ± 1.62. On the other hand, BCMA levels were significantly higher in MM patients with PD/SD, with a mean of 16.26 ± 0.92, and

Table IV. Relation between B-cell maturation antigen (BCMA), CD56 expression and neutrophil-lymphocyte ratio (NLR) with treatment response

Treatment response	Serum BCMA	CD56 expression		NLR	
	Median (range)	Negative (n = 11)	Positive (n = 29)	<2.31 n = 28)	≥2.31 (n = 12)
CR	3.76 (1.10–8.94)	2	12	13	1
VGPR/PR	8.48 (5.68–10.97)	4	14	11	7
PD/SD	16.05 (15.16–17.7)	5	3	4	4
Relapse	18.38 (16.41–20.34)				
p	^{H}p <0.001*	^{MC}p = 0.042*		^{MC}p = 0.047*	

*Statistically significant at $p \leq 0.05$; CR — complete remission; VGPR — very good partial remission; PR — partial remission; PD — progressive disease; SD — stable disease; *p* — *p* value for association between different categories; H — Kruskal-Wallis test; MC — Monte Carlo

even higher in patients who relapsed, with a mean of 18.38 ± 2.78.

Our study found that the CD56 positive group had a significantly better response rate than the CD56 negative group when it came to CD56 expression. CR was observed in 41.4% of the CD56 positive patients, VGPR/PR in 48.3%, and poor responses (PD/SD/relapse) in 10.3%. CR was observed in only 18.2% of CD56 negative patients, VGPR/PR in 36.4%, and poor response (PD/SD/relapse) in 45.4%.

Our study revealed that the NLR <2.31 patient group had a significantly higher response rate than the NLR ≥2.31 patient group. CR was observed in 46.4% of the NLR <2.31 patient group, VGPR/PR in 39.3%, and PD/SD/relapse in 14.3%. CR was observed in only 8.3% of the NLR ≥2.31 patient group, VGPR/PR in 58.3%, and poor response (PD/SD/relapse) in 33.3%.

Survival analysis

To determine the impact of studied parameters on survival, the components of potential predictive factors were evaluated in univariate analysis. Age over 60 years, male sex, high LDH, β2M >3.5 mg/L, creatinine >2 mg/dL, Hb 10 g/dL, calcium >11 mg/dL, ISS stage III, high levels of BCMA, CD56 negativity, and high NLR were among these parameters. All variables with p <0.05 in univariate analysis were included in the multivariate logistic regression model.

As shown in Figure 2, Kaplan-Meier survival analysis for CD56 revealed that patientswith negative CD56 expression had a significantly shorter PFS time than those with positive CD56 expression (8.43 vs. 11.82 months). In univariate analysis, CD56 negative expression was found to be significantly associated with PFS [hazard ratio (HR) = 5.417, 95% confidence interval (CI): 1.290–22.751, p = 0.021].

PFS was longer in MM patients with NLR <2.31 (11.5 months) compared to NLR ≥2.31 (10.58 months), as shown in Figure 3. However, in univariate analysis, there was no significantcorrelation between PFS and NLR (HR = 2.641, 95% CI: 0.660–10.568, p = 0.170).

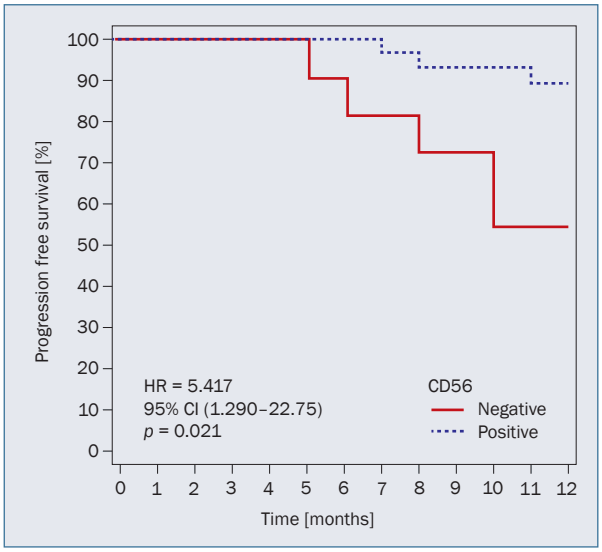

Figure 2. Kaplan-Meier survival curve for progression-free survival (PFS) with CD56. Statistical differences between curves were calculated using the log-rank test; HR — hazard ratio; CI — confidence interval

As shown in Figure 4, Kaplan-Meier survival analysis revealed that patients with high levels of BCMA had significantly shorter PFS than those with low levels of BCMA (8.43 vs. 11.82 months). In multivariate analysis, only BCMA wasfound to be an independent prognostic factor for progression-free survival (HR = 2.414, 95% CI: 1.141–5.105, p = 0.021).

Discussion

MM is a heterogeneous disease; while some patients progress rapidly despite treatment,others can remain asymptomatic for years. Our study found that both BCMA and NLR levels were significantly higher in patients compared to controls.

This finding is consistent with the results of Ghermezi et al. [5], who found that BCMA levels were higher in MM

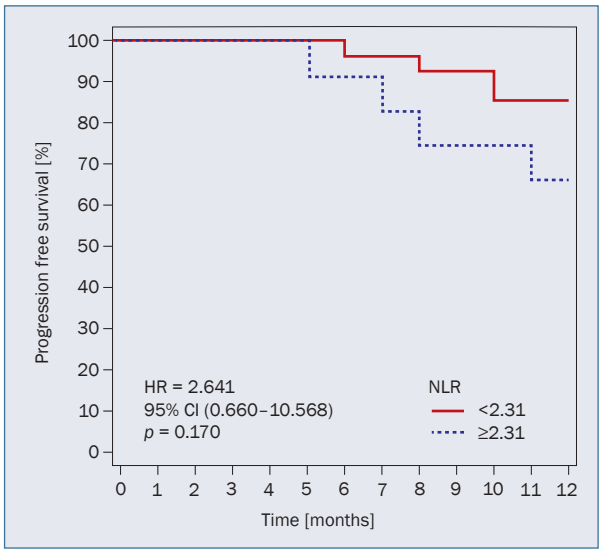

Figure 3. Kaplan-Meier survival curve for progression-free survival (PFS) with neutrophil-lymphocyte ratio (NLR). Statistical differences between curves were calculated using the log-rank test; HR — hazard ratio; CI — confidence interval

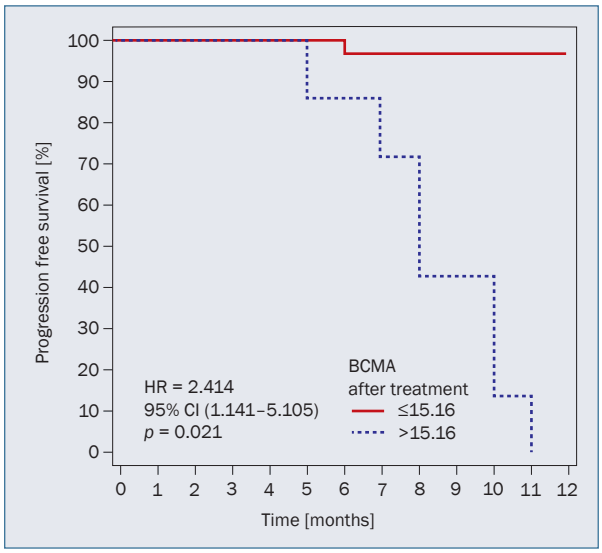

Figure 4. Kaplan-Meier survival curve for progression-free survival (PFS) with B-cell maturation antigen (BCMA). Cut-off (>15.16) was optimized according to BCMA prognostic performance using receiver operating characteristic curve analysis. Statistical differences between curves were calculated using the log-rank test; HR — hazard ratio; CI — confidence interval

patients (n = 243) than in healthy donors. Sanchez et al. [16] as well as Lee et al. [17] confirmed the same results.

In addition, Kelkitli et al. [18] reported that NLR was significantly higher in myeloma patients (n = 151) than in the control group. These results were also supported by Huaqin Zuo etal. [19] and Lihui Shi et al. [20].

The cut-off values of NLR used for prognosis in cancers have not been uniform in previously published studies. In the present study, a cut-off optimization for NLR was calculated. The cutoff point of 2.31 revealed the highest Youden value for stratification of the patients into low riskand high--risk groups. An NLR cut-off of 2 was chosen by Kelkitli et al. [18] and Romano et al. [21]. A cut-off point of 2.95 was reported by Zhou et al. [22]. A higher NLR cut-off point of 4 was chosen by Lihui Shi et al. [20]. The discrepancy in the cut-offs among these studies might be related to their different areas or to the accuracy of detecting instruments.

Next, the present study focused on the correlation between the studied parameters and differentclinicopathological parameters. There was no significant association between BCMA and ISS or lytic bone disease. Complete agreement was found between these results and those reported by Sanchez et al. [16], Lee et al. [17] and Ghermezi et al. [5] who demonstrated that BCMA is independent of MM bone disease. Also, the present study showed that CD56 negativity was significantly associated with both advanced stage and lytic lesions. These results are in line with Ceran et al. [23], who reported that the negativity of CD56 expression was dramatically associated with advanced stage. CD56 expression is considered to have a role in lytic bony lesions by leading to a decrease in osteoblast functions. Thus, the interactions between the plasma cells, stromal cells and osteoblasts result in a decrease in bone matrix production [23]. The results of our study strongly support that idea.

Furthermore, the present study explored the relationship between the studied parameters and different laboratory characteristics. There was no significant association between BCMA, CD56 expression and NLR with Hb, creatinine, calcium and β2M. For BCMA, these results were in complete agreement with Ghermezi et al. [5], Lee et al. [17] and Sanchez et al. [16]. For CD56 expression, these results were also supported by Ceran et al. [23] and Matevz Skerget et al. [10]. For NLR, similar results were reported by Zhou et al. [22] and Szudy-Szczyrek et al. [11].

The present study showed a statistically significant positive correlation between the percentage plasma cells and BCMA before and after treatment. Complete agreement was obtained between our results and those obtained by Sanchez et al. [24] and Ghermezi et al. [5]. It is also worth mentioning thatthey demonstrated a correlation between BCMA and BM findings in MM patients with nonsecretory disease.

The present study showed that there was no statistically significant difference between both CD56 expression and NLR with the BM plasma cells. For CD56 expression, Ceran et al. [23] reported no correlation between CD56 expression and BMA plasma cells. For NLR, complete agreement was found between the results of the present study and those reportedby Lihui Shi et al. [20] and Li et al. [25].

Assessment of M-protein using protein electrophoresis has been the gold standard for monitoring MM patients [26]. The present study showed a statistically significant positive correlation between M-protein level and BCMA before and after therapy. Complete agreement was found between these results and those of Ghermezi et al. [5] and Lee et al. [17]. Moreover, studies have shown that BCMA has a shorter half-life (24–36 hours) compared to IgG (21 days) and IgA (7 days), suggesting that BCMA can evaluate the effect of treatment more rapidly. This could identify when patients are not responding to their current therapy, allowing them to be changed to another therapy more rapidly [5, 24]. The present study showed that there was no statistically significant difference between both CD56 expression and NLR with M protein level. For CD56 expression, similar results were obtained by Pan et al. [27]. For NLR, complete agreement was found between these results and those reported by Romano et al. [21] and Zuo et al. [19].

Our next interest was to determine whether BCMA, CD56 expression and NLR could play a role in the prediction of therapeutic response in MM. As regards BCMA, there was a statistically significant relation between BCMA and response to therapy. Complete agreement was found between these results and those of Sanchez et al. [16]. They concluded that patients with complete or partial response (n = 80) had lower BCMA levels than patients (n = 79) with progressive disease (median 4.06 ng/mL vs. 19.76 ng/mL, respectively). Jew et al. [26] reported that all patients who achieved CR (n = 27) showed normalization of BCMA after treatment. However, 37 out of 43 patients (86%) who achieved SD or PD did not show normalization of BCMA after treatment. They concluded that normalization of BCMA after treatment predicts a higher overall response rate.

As regards CD56 expression, the present study demonstrated that CD56 negativity showed a significant association with poor treatment response. Complete agreement was found between these results and those of Pan et al. [27] who investigated 44 MM patients who received bortezomib-based induction chemotherapy. The overall response rates were higher in the CD56-positive group compared to the CD56-negative group (70.6% vs. 30.0%).

Yoshida et al. [28] investigated the correlation between CD56 and the response to bortezomib plus dexamethasone (Bd) therapy. They classified patients as either good responders (CR + VGPR + PR) or poor responders (SD + + PD). CD56 was significantly lower in the poor responders.

Based on these studies, CD56 could be a promising candidate biomarker for predicting response to therapies involving bortezomib.

As regards NLR, the present study showed that there was a significant difference in the treatment response between NLR <2.31 and NLR ≥2.31 patient groups. Complete agreement was found between these results and those reported by Zhou et al. [22]. A meta-analysis designed by Zeng et al. [29] analyzed pooled data from eight clinical trials conducted on 1,886 MM patients. These pooled results suggested that NLR was higher in non-responders (p <0.001).

Last but not least, the present study demonstrated the relation between the studied parameters and survival. We showed that patients with high levels of BCMA had markedly shorter PFS time than those with lower levels of BCMA. In the same line, Sanchez et al [16] and Ghermezi et al. [5] reported that higher BCMA was predictive of a shorter PFS and OS. Using multivariate analysis, they proved that BCMA was an independent prognostic marker.

As regards CD56 expression, the present study demonstrated that patients with negative CD56 expression had significantly shorter PFS time than those with positive CD56 expression. Similar results were reported by Pan et al. [27] who identified that the positivity of CD56 is associated with longer survival. The estimated 2-year OS rate was higher in CD56 positive thanin CD56 negative patients (82.5% vs. 43.1%).

As regards NLR, no statistically significant relationship between survival and NLR was detected in the present study. Complete agreement was found between these results and thosereported by Zhou et al. [22], who concluded that NLR was not an independent prognostic factorfor survival in MM patients treated with bortezomib-based regimens. In the same line, Lee et al. [30] investigated the impact of NLR on survival in 176 MM patients who were ineligible for ASCT. All patients were treated with melphalan, prednisone and bortezomib. There was no significant difference in PFS between the high and low NLR groups (2-year PFS rate, 27.7 vs. 29.9%, respectively).

Conclusions

Our study demonstrated that BCMA is a novel independent marker for both monitoring and predicting outcomes for MM patients. Also, it can be easily obtained from routine blood tests, and thus widely applied in the clinic. Moreover, CD56 expression adds additional prognostic information and could be one of the leading myeloma markers in the era of novel agents. High NLR is also likely to be associated with poor response to treatment. Large-scale and long-term follow-up studies focusing on the significance of BCMA, CD56 expression and NLR in MM are recommended to conclusively define the prognostic impact of these novel markers on survival in MM patients. In general, our study emphasizes the importance of considering novel MM prognostic markers to assess the tumor burden and predict the clinical outcome. Therefore, it should help towards better risk stratification and more tailored clinical management, enhancing therapeutic successesand increasing life expectancy of MM patients.

Authors' contributions

HKS — general supervision of whole work and interpretation of data. MMAEG — supervision of collecting samples and participation in practical work, statistical data analysis and writing. OAB — supervision and participation in practical work. AAEN — supervision and participation in practical work. MSF — participation in practical work and writing.

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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