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The role of CD319, CD117, CD28, CD49e, CD56, and CD44 expression as diagnostic and prognostic markers in multiple myeloma

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Abstract:

BACKGROUND: Multiple myeloma (MM) is a plasma cell disorder characterized by the infiltration of clonal plasma cells in the bone marrow and the detection of a monoclonal immunoglobulin in serum and/or urine. Renal failure, anemia, hypercalcemia, and the presence of bone lesions are the hallmarks of the disease.

OBJECTIVES: The study aimed to evaluate the clinical, hematological, radiological, and immunophenotypic features of MM patients and to identify prognostic factors influencing survival outcomes.

MATERIALS AND METHODS: This cohort study included 77 newly diagnosed, untreated MM patients. Their clinical presentation, laboratory data, imaging results, and the expression of flow cytometry markers were analyzed in correlation with the 1-year overall survival (OS).

RESULTS: The mean age was 59.29 ± 12.1 years, bone pain was the most common symptom (81.8%), and anemia was observed in 87% of patients. Radiologically, lytic lesions were present in 70.1% of cases, with 33.8% having pathological fractures. Flow cytometry revealed universal expression of CD319 (100%) and high expression of CD56 (98.7%). CD117 positivity was significantly associated with shorter OS (P = 0.029), and CD28 showed a tendency toward poorer prognosis (P = 0.054). Other markers, such as CD44 and CD49e, did not show significant prognostic associations.

CONCLUSIONS: MM may manifest at an earlier age in specific populations. The most significant features were anemia, bone lesions, and renal dysfunction. Lower hemoglobin levels, higher blood urea and serum creatinine, along with a lower glomerular filtration rate, hyperuricemia, and hypoalbuminemia, contribute to poorer outcomes, as the expression of CD117 has an inverse prognostic outcome.

Keywords:

CD117, CD28, CD44, CD49e, flow cytometry, multiple myeloma

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Introduction

Multiple myeloma (MM) is a neoplastic disorder characterized by the clonal expansion of plasma cells within the bone marrow (BM) microenvironment, the presence of monoclonal protein (M-protein) in the blood or urine, and resultant organ failure.[1] It is the second-most prevalent hematologic malignancy after non-Hodgkin lymphoma, with an incidence rate of around 7.8 per 100,000 people per year in the UK that rises with age, and about 4 per 100,000 people in the US that has been constant for decades.[2,3] It exhibits a higher prevalence in men relative to women and is observed to be twice as prevalent in African Americans compared to Caucasians.[4] The diagnostic criteria required the presence of > 10% clonal BM plasma cells based on cytomorphology or biopsy-proven plasmacytoma, along with

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one or more myeloma-defining events as outlined by the International Myeloma Working Group (IMWG).[5] Multiparametric flow cytometry is regarded as the gold standard for diagnosing and monitoring MM.[6] Current treatment strategies of MM involve induction with triplet regimens, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) in eligible patients, and subsequent consolidation and maintenance therapy. Initial treatment selection is guided by transplant eligibility, cytogenetic risk, and patient comorbidities such as renal dysfunction or neuropathy.[7]

For standard-risk patients, the VRd regimen (bortezomib, lenalidomide, and dexamethasone) remains the standard first-line therapy; VCd (bortezomib, cyclophosphamide, and dexamethasone) for patients at higher risk for lenalidomide-related complications.[8] Transplant-eligible patients typically receive four cycles of induction followed by ASCT, whereas transplant-ineligible individuals undergo 12–18 months of therapy, often followed by lenalidomide maintenance.[9] In elderly or frail patients, especially those ≥75 years, the Rd regimen (lenalidomide and dexamethasone) offers a suitable alternative.[10] Maintenance therapy is recommended after ASCT and also for patients who have completed 8–12 cycles of initial treatment without undergoing ASCT. Lenalidomide is the standard maintenance option for most MM patients.[11,12]

Materials and Methods

This prospective cohort study included 77 newly diagnosed, untreated MM patients. All patients were interviewed and asked about their name, age, career, address, past medical history, other malignant diseases, prior chemotherapy, and their complaints. The clinical features, bone lesions, blood urea, serum creatinine, serum calcium, serum protein electrophoresis, immunofixation electrophoresis, and erythrocyte sedimentation rate were retrieved from the patients' medical records at the time of diagnosis. The diagnosis of MM was established according to IMWG criteria.[13]

Twenty-two age- and sex-matched healthy individuals with normal complete blood counts (CBC) and C-reactive protein were enrolled in this study as a control group.

CBC was conducted utilizing the automated hematology analyzer (Sysmex XN-350, Japan), followed by a blood film examination. BM smears were evaluated for plasma cell percentage, and the BM biopsy sections were assessed for the pattern of plasma cell infiltration.

BM aspirate samples for flow cytometric analysis were processed within 12 h, using an ammonium chloride-based bulk lysis/pre-lysis protocol, following the manufacturer's instructions.[14] Flow cytometric analyses were performed utilizing BD FACSCanto™ II Flow Cytometer and kits (Becton Dickinson and Co., BD Biosciences, San Jose, USA), using CD19, CD45, CD56, CD38, CD138, CyIgκ, and CyIgλ to confirm clonality, and CD28, CD56, CD117, CD44, CD49e, and CD319 as prognostic markers.

For the identification of plasma cells, at least 100,000 cells were counted; cells were considered positive for a marker when more than 20% of the myeloma cells expressed that marker. Data acquisition and analysis were performed using FACS Diva v9 Software (BD Bioscience, USA). Clonal plasma cells were characterized by abnormal antigen expression (CD19-, CD45- or low, and CD56+) and light chain restriction.

Patients aged 65 or younger received 4 cycles of induction therapy (VRd or VCd according to the presence or absence of renal impairment). Those who achieved complete remission, if eligible, underwent ASCT with high-dose chemotherapy (melphalan), and after 3 months of the transplant, the patients received 2 cycles of consolidation therapy with VRd or VCd, then they were continued on lenalidomide as maintenance therapy. Patients who were aged more than 65 or those who were transplant ineligible, they received induction therapy (Dara-VRd, Dara-VCd, VRd or VCd depending on drug availability and access) for 12–18 months, followed by maintenance therapy with lenalidomide. The OS was determined after 1 year.

Research approval was granted by the Research Ethics Committee at the College of Medicine, University of Baghdad (Issue Patho182 on December 14, 2022) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corporation, Armonk, New York, United States) and Microsoft Office Excel 2021. Data were presented as mean ± standard deviation, and median with interquartile range for quantitative variables and as numbers and percentages for qualitative variables. The normality test revealed that the data were not normally distributed; therefore, the Mann–Whitney *U*-test was used to assess the difference between the two groups. The Spearman rank correlation test was used to test the correlations between different variables. The Chi-square test was used to analyze the relationships within the qualitative data. $P < 0.05$ was considered statistically significant.

Results

Among the 77 MM patients enrolled in this study, the mean age was 59.29 ± 12.1 years, with a range of

31–87 years and a median of 60. Patients aged 60 years or younger were 43 (55.84%), and those aged more than 60 years were 34 (44.15%).

Through a period of 1 year, 20 patients (26%) had died, whereas 57 of them (74%) achieved complete remission and underwent ASCT [Figure 1]. There was no association between the patient's outcome and age ($P = 0.302$).

The study comprised 46 males (59.7%) and 31 females (40.3%), resulting in a male-to-female ratio of 1.5:1 [Figure 2].

Clinical presentation of patients

At presentation, 63 patients (81.8%) had bone pain, which is the most frequent presentation, 48 (62.3%) had back pain, 58 (75.3%) presented with pallor, 12 (15.6%) had plasmacytoma, and only 4 patients (5.2%) had hepatosplenomegaly [Figure 3].

Radiological findings revealed by plain X-ray, computed tomography (CT) scan, and magnetic resonance imaging of skull, vertebral column, pelvis and extremities demonstrated that 69 of patients (89.6%) had bone lesions; 54 patients (70.1%) had lytic lesions and 26 (33.8%) had pathological fracture, 22 (28.6%) had vertebral compression, and 21 (27.3%) patients had osteoporosis [Figure 4]. Only 8 (10.4%) of the patients did not have any bone lesions.

The mean of the hemoglobin (Hb) concentration was 9.5 ± 2.49 g/dL, with 67 patients (87%) being anemic (Hb < 13.0 /dL for males, and <12 g/dL for females), those with Hb level <10 g/dL were 46 patients (59.4%).

At presentation, the mean white blood cells (WBC) count was 6.87 ± 3.2 × 10^9/L. Among the 77 patients, 11 (14.3%) had leukopenia (WBC count <4 × 10^9/L), 56 (72.7%) had normal WBC count (4–10 × 10^9/L), and 10 (13%) had leukocytosis (WBC count >10 × 10^9/L).

Patients presented with neutropenia (absolute neutrophil count [ANC] <2 × 10^9/L) were 14 (18.2%), whereas 11 (14.3%) presented with neutrophilia (ANC >7 × 10^9/L), and 52 (67.5%) patients had normal ANC (2–7 × 10^9/L). Patients presented with lymphopenia (absolute lymphocyte count [ALC] <1 × 10^9/L) were 10 (13%), 5 (6.5%) had lymphocytosis (ALC >3.5 × 10^9/L), and 62 (80.5%) patients had normal ALC (1–3.5 × 10^9/L).

The mean platelet (Plt) count was 230 ± 98.6 × 10^9/L. Among the 77 patients, thrombocytopenia was reported in 16 (20.8%) patients with Plt < 150 × 10^9/L, and 7 (9.1%) with Plt <100 × 10^9/L, whereas 5 (6.5%) had thrombocytosis (Plt > 410 × 10^9/L), and 56 (72.7%) had normal Plt.

There was a significant statistical difference in Hb levels between deceased and living patients, with a $P = 0.006$. For the other hematological parameters (WBC, ANC, ALC, and Plt), the differences between deceased and living patients were not statistically significant with P values of 0.290, 0.290, 0.170, and 0.180, respectively [Table 1].

The mean blood urea was 50.9 ± 28.4 mg/dL, with 40 patients (51.9%) having increased blood urea, whereas the mean serum creatinine was 1.3 ± 0.9 mg/dL with 31 (40.3%) patients had increased serum creatinine (>1.18 mg/dL), and those with serum creatinine (>2 mg/dL) were 11 (14.3%). Thirty-five patients (45.5%) had chronic renal failure with an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m^2; 24 (31.2%) patients presented with Stage III chronic kidney disease (CKD), 9 (11.7%) patients presented with Stage IV, and 2 (2.6%) patients presented with Stage V CKD.

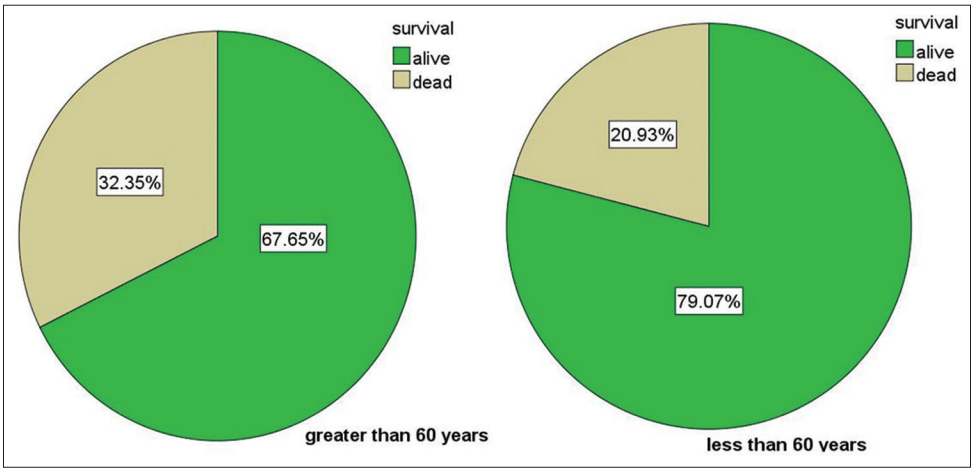

Figure 1: The distribution of patients according to their outcome

The means of serum uric acid, calcium, total protein, and albumin were 5.9 ± 2.1 mg/dL, 9.1 ± 1.4 mg/dL, 97.9 ± 15.6 g/L, and 33.8 ± 5.4 g/L, respectively. Hyperuricemia, hypercalcemia, hypocalcemia, hyperproteinemia, and hypoalbuminemia were encountered in 18 (23.4%), 16 (20.8%), 24 (31.2%), 71 (92.2%), and 46 (59.7%) patients, respectively.

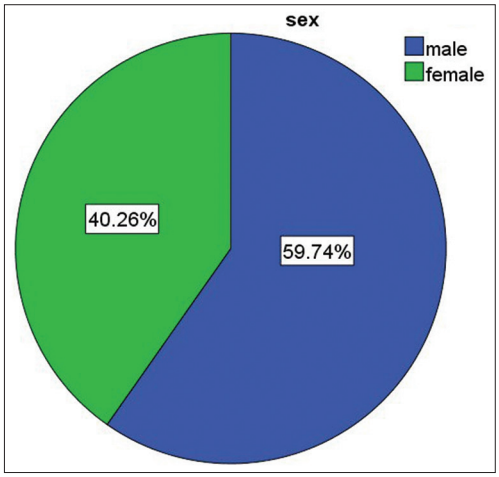

Figure 2: The sex distribution of multiple myeloma patients

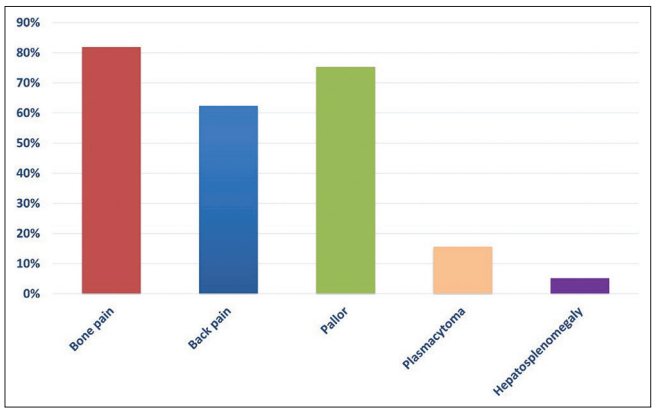

Figure 3: The clinical presentation of multiple myeloma patients

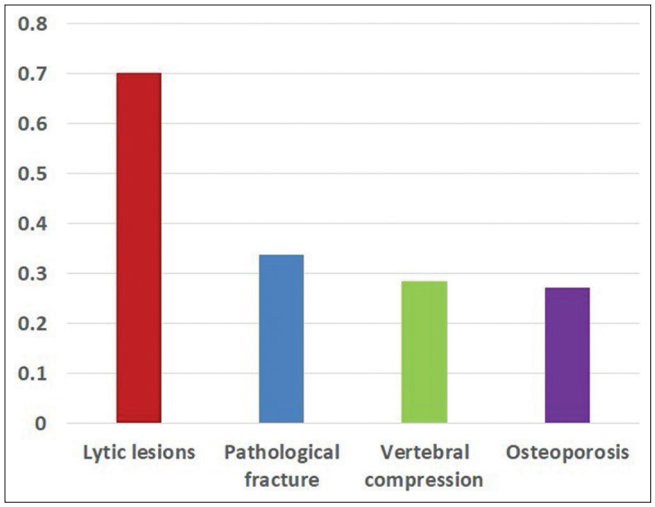

Figure 4: The radiological findings in multiple myeloma patients

The differences in blood urea, serum creatinine, eGFR, serum uric acid, and serum albumin levels between deceased and living patients were statistically significant with *P* values of 0.002, 0.002, 0.001, 0.012, and 0.0001, respectively. In contrast, the differences in serum calcium and total serum protein levels were not statistically significant [Table 2].

Regarding the flow cytometric markers expression, the highest was CD319 showing positive expression in all cases (77, 100%), followed by CD56 (76, 98.7%), CD44 (72, 93.5%), CD49e (58, 75.3%), CD28 (51, 66.2%), and the least expressed marker was CD117 (50, 64.9%) as illustrated in Figure 5.

Table 1: The relation of hematological parameters in multiple myeloma patients to the 1-year overall survival outcome

Parameter	Patient's outcome	*n*	Mean±SD	Median (IQR)	*P**
Hb (g/dL)	Deceased	20	8.5±2.7	8.1 (2.3)	0.006
	Living	57	9.9±2.3	9.9 (3.2)	
WBC (×10^9/L)	Deceased	20	7.8±4.1	7.1 (5.8)	0.290
	Living	57	6.5±2.8	5.9 (3.1)	
ANC (×10^9/L)	Deceased	20	5.3±3.5	5.0 (4.4)	0.054
	Living	57	3.8±2.3	3.2 (2.3)	
ALC (×10^9/L)	Deceased	20	1.8±0.9	1.8 (1.1)	0.170
	Living	57	2.0±0.9	2.0 (1.1)	
Plt (×10^9/L)	Deceased	20	202±96.1	182 (170)	0.180
	Living	57	241±98.2	237 (109)	

*Mann–Whitney *U*-test. *n*=Number of cases, SD=Standard deviation, IQR=Inter-quartile range, Hb=Hemoglobin, WBC=White blood cells, ANC=Absolute neutrophil count, ALC=Absolute lymphocyte count, Plt=Platelet count

Table 2: The association of biochemical parameters between deceased and living patients

Parameter	Patient's outcome	*n*	Mean±SD	Median (IQR)	*P**
Blood urea (mg/dL)	Deceased	20	69.6±40.2	49.5 (50.1)	0.002
	Living	57	44.3±19.4	41 (24.2)	
Serum creatinine (mg/dL)	Deceased	20	1.9±1.5	1.3 (1.3)	0.002
	Living	57	1.08±0.5	0.9 (0.6)	
eGFR (ml/min/1.73 m^2)	Deceased	20	49.3±30.4	49.8 (43)	0.001
	Living	57	85.3±61.3	81.2 (54.6)	
Serum uric acid (mg/dL)	Deceased	20	6.8±2.4	7.0 (1.1)	0.012
	Living	57	5.5±2.0	5.0 (3.0)	
Serum calcium (mg/dL)	Deceased	20	9.1±1.8	9.4 (2.1)	0.323
	Living	57	9.0±1.3	9.1 (1.1)	
Serum total protein (g/L)	Deceased	20	99.4±18.4	99.1 (20.7)	0.307
	Living	57	97.4±14.6	95 (21)	
Serum albumin (g/L)	Deceased	20	30.1±3.8	30.5 (5.6)	0.0001
	Living	57	35.1±5.4	35.6 (8.9)	

*Mann–Whitney *U*-test. *n*=Number of cases, SD=Standard deviation, IQR=Inter-quartile range, eGFR=Estimated glomerular filtration rate

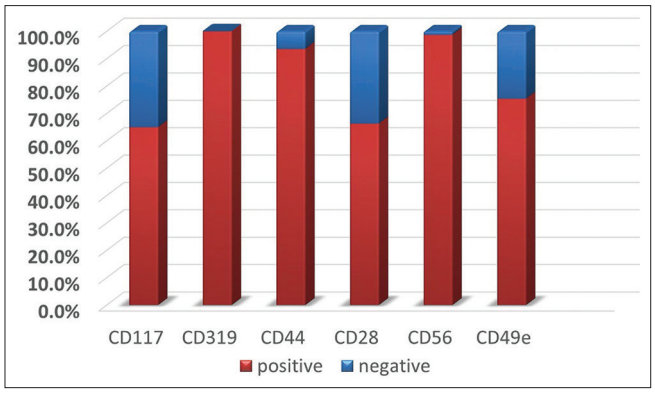

Figure 5: The expression of the flow cytometry markers used in 77 multiple myeloma patients

Assessment of CD markers expression in patients according to the one-year survival status [Table 3].

CD117 expression

34% (17/50) of patients who were positive for the marker expression died after 1 year, compared to only 11.1% (3/27) who were negative for the marker expression. The expression of CD117 showed a potential inverse prognostic impact and was associated with shorter OS, as the difference between deceased and living patients was statistically significant ($P = 0.029$).

CD28

Among patients with positive CD28 expression, 33% (17/51) died within 1 year compared to 12% (3/26) of the patients with CD28-negative expression. The difference between deceased and living patients did not reach statistical significance ($P = 0.054$).

CD44

The percentage of living patients with positive expression of CD44 for more than 1 year after diagnosis was 73.6%, compared to 80% for those with negative expression, with no statistical significance ($P = 0.753$). CD44 is commonly expressed in MM, but it does not appear to influence short-term survival outcomes.

CD49e

The mortality percentage among the patients with positive CD49e expression within 1 year of diagnosis was 24.1% (14/58), compared to 31.6% (6/19) with negative expression. There is no association between CD49e expression and the outcome of the patients ($P = 0.521$).

Discussion

In this study, the mean age of the participants is comparable to that reported by Ibrahim and Al-Rubaie,[15] Abdullah *et al*.,[16] and Elsabah *et al*.[17] However, Vagnoni *et al*.[18] and Gonsalves *et al*.[19] reported higher median ages for MM patients, at 72 years and 65 years, respectively. This may be attributed to geographical, socioeconomic, and demographic factors. Martínez-Cordero *et al*.[20] included patients younger than 40, with a median age of 35.14 years, and Quetzal and González[21] included a case of a 33-year-old man with MM who exhibited similar presentation characteristics to the elderly patients.

The male-to-female ratio was similar to that of Al-Ani *et al*.[22] and Abbas *et al*.[23] in Iraq and was almost similar to the result of a British study of Bird *et al*.,[24] but higher than that of Qasem *et al*.[25] in Jordan (1:1). This difference may be related to various factors, including environmental factors, hormonal influences, or genetic predisposition.

Bone pain and back pain were the most common symptoms reported, which aligns with the findings of Alwan *et al*.,[26] Baiee *et al*.,[27] and Goldschmidt *et al*.[28] However, Seesaghur *et al*.[29] found that 49.1% of patients experienced bone pain, whereas 33.7% reported back pain.

In this study, patients presented with plasmacytoma were 15.6%; this finding is close to that reported by Jiménez-Segura *et al*.[30] (19.6%) in Spain, but it is higher than Chen *et al*.[31] (9%) in China, and lower than a study by Çiftçiler *et al*.[32] (21.6%) in Turkey.

The prevalence of lytic lesions was aligned with studies conducted by Abbas *et al*.[23] (71%), Qasem *et al*.[25] (73.5%), and Yassin[33] (77.98%) but lower than Mjali *et al*.[34] study (87.18%).

Anemia in MM is a common condition in MM and can be caused by several factors. These include the infiltration of the BM by malignant plasma cells, chronic inflammation, relative deficiency of erythropoietin due to accompanying renal failure, and, later on, the myelosuppressive effects of chemotherapy.[35,36] In the current study, the Hb concentration is close to what is reported by Liu *et al*.,[36] Jalaeikhoo *et al*.,[37] and Abbas *et al*.[23]

The mean levels of blood urea and serum creatinine are in agreement with the results of Mohammed *et al*.,[38] Li *et al*.,[39] and Sultan *et al*.[40] studies. Higher levels were reported by Alwan[26] (blood urea 67.4 mg/dL, and serum creatinine 1.86 mg/dL), and Chen *et al*.[41] (serum creatinine of 1.75 mg/dL). Goldschmidt *et al*.[28] reported lower percentages of patients with high creatinine (28% with creatinine >1.2 mg/dL, and 6% with creatinine >2 mg/dL). The serum Ca level was comparable to Alwa,[26] Yassin,[33] Salih *et al*.[42] Jalaeikhoo *et al*.,[37] Mohammed *et al*.,[38] Kaçmaz *et al*.,[43] Huang *et al*.,[44] and Utsu *et al*.[45] studies. The frequency of hypercalcemia and hypocalcemia was in agreement with Elsabah *et al*.,[17]

Table 3: The association of cluster of differentiation markers expression and the patient's outcome

Markers	Patient's outcome	Positive, *n* (%)	Negative, *n* (%)	Total, *n* (%)	*P**
CD117	Deceased	17 (34)	3 (11.1)	20 (26)	0.029
	Living	33 (66)	24 (88.9)	57 (74)	
	Total	50 (100)	27 (100)	77 (100)	
CD28	Deceased	17 (33)	3 (12)	20 (26)	0.054
	Living	34 (67)	23 (88)	57 (74)	
	Total	51 (100)	26 (100)	77 (100)	
CD44	Deceased	19 (26.4)	1 (20)	20 (26)	0.753
	Living	53 (73.6)	4 (80)	57 (74)	
	Total	72 (100)	5 (100)	77 (100)	
CD49e	Deceased	14 (24.1)	6 (31.6)	20 (26)	0.521
	Living	44 (75.9)	13 (68.4)	57 (74)	
	Total	58 (100)	19 (100)	77 (100)	

*Chi-square test. CD=Cluster of differentiation

Al-Ani *et al*.,[22] Li *et al*.,[39] and Cesar *et al*.[46] However, in Malaysia, Ismail *et al*.[47] found a comparable percentage of patients with hypocalcemia (35.9%) but a higher percentage of patients with hypercalcemia (64.1%). Hussain *et al*.[48] also reported a higher incidence of hypercalcemia (33%) but a lower incidence of hypocalcemia (9%). Qian *et al*.[49] reported a lower incidence of hypercalcemia (10.9%). The difference in the levels of biochemical parameters could be attributed to several factors, including sample size, laboratory methods and techniques, the degree of renal impairment, and the stage of MM at the time of diagnosis. In addition, studies conducted in different countries or regions may have genetic, environmental, and lifestyle factors that impact the results.

Comparing the initial levels of biochemical parameters between living and deceased patients reveals statistically significant differences in blood urea and serum creatinine, indicating that renal function is a critical prognostic indicator in MM. Close monitoring and management of renal failure are crucial for improving patient outcomes.

All patients demonstrated positive expression of CD319, aligning with the findings of Soh *et al*.[50] and reported that since CD319 has a better resolution metric and brighter expression intensity than CD38 and CD138, it might be used as a substitute marker. El-Osh *et al*.[51] also demonstrated that CD319 was positive in all MM patients, and a good prognosis and a significantly better response to therapy are linked to low expression of CD319 on plasma cells, suggesting that CD319 is a significant prognostic marker in MM.

The absence of CD56 expression on myeloma cells is linked to increased peripheral blood involvement and BM infiltration. It may also result in a more aggressive course of the illness, a higher risk of developing plasma cell leukemia (PCL), and a shorter progression-free survival (PFS) and OS.[52] CD56 expression in this study was 98.7%. This level of expression is higher than what was reported in other studies, such as Skerget *et al*.[52] (71%), Rath *et al*.[53] (79.1%), and Iriyama *et al*.[54] (72%). This may be due to geographical or genetic differences, patient selection (relapsed or refractory), or patients with high-risk cytogenetics. Pan *et al*.[55] demonstrated that 74% of patients express CD56**,** and that the absence of CD56 expression was associated with a poor prognosis.

CD117 expression is expressed in 64.9% of cases; lower percentages were reported by Ismail *et al*.,[47] Pan *et al*.,[55] Chen *et al*.,[56] and Zheng *et al*.[57] (25.6%, 32%, 35.88%, and 39.1%, respectively). Although many studies have linked CD117 positivity with a favorable prognosis in MM, this study presents a contrasting prognostic indicator, showing a significant inverse association between CD117 positivity and 1-year overall survival (OS) in MM, which aligns with findings reported by Keski *et al*.[58] and Wang *et al*.[59] Several possible explanations may account for this divergence: small sample size (the total number of deceased patients = 20), demographical and biological difference (age distribution, disease stage at diagnosis, or cytogenetic abnormalities), treatment regimens, and biological heterogeneity of $CD117^+$ plasma cells (CD117 expression may reflect different biologic subtypes depending on co-expression of other markers (e. g., CD56, CD19, and CD45), or molecular mutations. Therefore, its prognostic role may not be uniform across all clinical settings.

The expression of CD28 by myeloma cells in newly diagnosed individuals is a significant predictor of poor clinical outcome after high-dose chemotherapy.[60] In this study, 66.2% of newly diagnosed MM patients showed positive expression of CD28, suggesting a possible association with poorer OS. These results were comparable to those of Skerget *et al*.,[52] who demonstrated that CD28 expression was observed in 68% of MM patients with no significant association between the marker expression and OS. Malek *et al*.[61] reported that 74% of patients express the marker, which closely aligns with the findings of this study. Guo *et al*.,[62] GE *et al*.,[63] and Zhang *et al*.[64] revealed lower expressions of CD28, 19%, 26%, and 34.1%, respectively, suggesting that CD28 can serve as a prognostic factor for individuals with newly diagnosed MM. The lower values reported in other studies, along with the lack of differences in survival outcomes, may be due to geographic, ethnic, and genetic variations among patient populations. Furthermore, a 1-year follow-up duration may be insufficient to provide insight into prognosis, along with the disease's heterogeneity and clonal evolution associated with specific cytogenetic abnormalities.

Some studies have reported that increased expression of CD44 in MM patients is associated with advanced clinical stage, extramedullary myeloma, and poor survival.[62] In the current study, the high prevalence of CD44 positivity among both living and deceased patients suggests that its presence by itself is not a reliable indicator of early survival outcomes. This finding is in partial agreement with Riaz *et al*.,[65] who reported a lower incidence of CD44 expression (48.5%) but also reported no correlation between the total CD44 expression and prognosis. Guo *et al*.[62] demonstrated a 65% CD44 expression, which was associated with an adverse prognosis and a shorter PFS. Ning *et al*.[66] showed that CD44 expression on abnormal plasma cells was gradually increased (MGUS 7.9%; smoldering MM 11.2%; MM 40.2%; and PCL 81.9%), indicating that CD44 could be used as a marker to differentiate between different plasma cell diseases. The relationship between CD44 expression and patient outcomes within 1 year may not be significant due to the high baseline levels of CD44. Moreover, the limited number of CD44-negative patients could reduce the statistical power of comparisons, making CD44 less effective as a standalone prognostic marker. Furthermore, CD44 may play a more prominent role in disease progression, drug resistance, or extramedullary spread rather than directly affecting early mortality.[65,66]

Expression of CD49e is reported to identify mature plasma cells, while a lack of CD49e identifies immature plasma cells. Immature MM cells have been reported to have a higher proliferation rate, a stronger resistance to chemotherapy, a more aggressive clinical course, and a worse OS compared with mature-type MM.[67]

This study revealed that among the 75.3% of patients with positive expression of CD49e, 24.1% died within 1 year of diagnosis, while 75.9% remained alive, whereas the mortality rate among CD49e-negative patients was slightly higher (31.6%). The difference was statistically insignificant ($P = 0.521$). The findings about the expression of CD49e are comparable to what was reported by Okura *et al*.,[67] regarding the frequency of the CD49e expression in MM patients, and there was no difference in OS between the CD49e-positive and CD49e-negative patients. Iriyama *et al*.[68] investigated the association between prognosis and myeloma cell maturity. They found that the median OS in patients with mature or intermediate myeloma cell type was longer compared to immature type cells. The lack of prognostic impact with CD49e expression suggests that CD49e expression alone does not have a significant impact on short-term survival in MM. The small sample size, particularly the limited number of CD49e-negative patients, may explain the challenges in detecting subtle differences in outcomes. In addition, short follow-up periods, genetic variations, disease stages, and types of treatment all contribute to short-term outcomes. Studies that support the role of CD49e as a standalone prognostic marker for early survival are limited.

Conclusions

The patients in this study were younger than reported worldwide. The main presenting features were bone pain, with more than two-thirds of patients exhibiting lytic lesions and approximately one-third suffering from pathological fractures or vertebral compression, and lower hemoglobin levels are significantly associated with mortality. Renal dysfunction, along with a lower eGFR, hyperuricemia, and hypoalbuminemia, contributes to poorer outcomes. CD319 and CD56 show universal or near-universal expression. CD117 expression demonstrated a significant correlation with poorer 1-year survival, indicating its potential role as a prognostic marker. Other markers, such as CD44, CD49e, and B2M, are commonly expressed in MM but exhibited no significant prognostic impact during the follow-up period. Detection of anemia and renal impairment is essential in the early detection and initial assessment of MM patients. Multicenter studies with expanded follow-up periods are necessary to clarify the impact of immunophenotypic markers on overall and PFS.

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Conflicts of interest
There are no conflicts of interest.

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