Clinicopathological Correlates of CD56 Expression in Multiple Myeloma: Insights from a Cross-Sectional Study in an Indian Cohort

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ABSTRACT

Background:

Multiple myeloma (MM) is a heterogeneous plasma cell neoplasm characterized by clonal proliferation of plasma cells within the bone marrow and associated end-organ damage. CD56, also known as neural cell adhesion molecule (NCAM), is aberrantly expressed in most cases of MM and has been implicated in plasma cell adhesion, bone marrow homing, and disease dissemination. The prognostic significance of CD56 expression in MM remains incompletely understood, particularly in Indian patients.

Objectives:

To evaluate the correlation between CD56 expression and clinicopathological as well as radiological parameters in patients with multiple myeloma.

Methods:

This prospective observational study was conducted in the Department of Pathology at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana, from May 2024 to October 2025. Thirty newly diagnosed patients fulfilling International Myeloma Working Group (IMWG) criteria for MM were included using convenient sampling. Bone marrow aspiration and biopsy specimens were subjected to histopathological examination and CD56 immunohistochemistry. Clinical details, biochemical parameters, International Staging System (ISS) stage, and radiological findings were recorded. Statistical analysis was performed using SPSS software. Categorical variables were analysed using Chi-square/Fisher exact test, while continuous variables were analysed using Student's t-test or Mann-Whitney U test depending on normality distribution. A p-value <0.05 was considered statistically significant.

Results:

Among 30 patients, 23 (76.7%) were CD56 positive and 7 (23.3%) were CD56 negative. The majority of patients belonged to the 61-70-year age group with male predominance.

CD56-negative cases demonstrated relatively aggressive clinicopathological features including advanced ISS stage, elevated serum creatinine, increased B2-microglobulin, elevated LDH levels, anemia, and higher marrow plasma cell burden. Radiologically, extensive osteolytic lesions and vertebral involvement were more common in CD56-negative patients. Follow-up data available in 13 patients revealed comparatively poorer clinical response among CD56-negative cases.

Conclusion:

CD56 expression was observed in the majority of multiple myeloma cases. CD56-negative myeloma demonstrated aggressive clinicobiochemical and radiological characteristics, suggesting its potential utility as a prognostic biomarker. Evaluation of CD56 by immunohistochemistry may aid in risk stratification and prognostic assessment in resource-limited settings.

Keywords: Multiple myeloma; CD56; Immunohistochemistry; Plasma cell neoplasm; Bone marrow biopsy; Prognostic marker; Radiological correlation

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INTRODUCTION:

Multiple myeloma (MM) is a malignant plasma cell neoplasm characterized by clonal proliferation of plasma cells within the bone marrow, monoclonal immunoglobulin production, and end-organ damage manifesting as hypercalcemia, renal dysfunction, anemia, and lytic bone lesions. MM accounts for approximately 10% of hematologic malignancies and demonstrates considerable biological and clinical heterogeneity.[1,2] The disease course and prognosis vary widely among patients because of differences in tumour biology, cytogenetic abnormalities, and interactions with the bone marrow microenvironment. Therefore, identification of reliable prognostic biomarkers remains important for risk stratification and therapeutic planning. CD56, also known as neural cell adhesion molecule (NCAM), is a membrane glycoprotein involved in cell adhesion and bone marrow homing.[3,4] Although normally expressed on natural killer cells and neural tissue, CD56 is aberrantly expressed in approximately 70-80% of multiple myeloma cases.[5,6] Its expression is believed to facilitate adhesion of neoplastic plasma cells to the bone marrow stromal environment. Loss of CD56 expression has been associated in several studies with aggressive disease behaviour, extramedullary dissemination, plasma cell leukaemia, elevated lactate dehydrogenase levels, renal dysfunction, and poor prognosis.[7-10] However, published studies have demonstrated inconsistent findings, and data from Indian populations remain limited. The present study was undertaken to evaluate CD56 expression in newly diagnosed multiple myeloma patients and to correlate CD56 status with clinicopathological, hematological, biochemical, and radiological parameters.

MATERIALS AND METHODS:

Study Design and Setting:

This prospective observational study was conducted in the Department of Pathology, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, India, from May 2024 to October 2025.

Ethical Approval:

The study was approved by institutional ethics committee (IEC approval number: IEC-3258). Written informed consent was obtained from all participants.

Sample Size and Sampling:

Thirty newly diagnosed cases of multiple myeloma fulfilling IMWG diagnostic criteria were included during the study period.[11] Convenient sampling was performed during the study period.

Inclusion Criteria:

- Newly diagnosed multiple myeloma patients
- Patients fulfilling IMWG diagnostic criteria
- Patients willing to participate

Exclusion Criteria:

- Previously treated multiple myeloma
- Inadequate bone marrow biopsy specimens
- Patients unwilling to participate
- Clinical and Laboratory Evaluation:
- Detailed clinical history and examination findings were recorded.
- Laboratory investigations included:
- Complete blood count
- Serum calcium
- Serum creatinine
- Serum albumin
- Serum lactate dehydrogenase (LDH)
- ß2-microglobulin
- Serum M-band
- Urine protein analysis

Radiological evaluation included skeletal survey and additional imaging modalities wherever indicated, including CT and MRI studies for assessment of osteolytic lesions, vertebral involvement, and pathological fractures.

Bone Marrow Examination: Bone marrow aspiration and trephine biopsy were performed in all patients. Plasma cell percentage and morphology were assessed using May-Grünwald-Giemsa and hematoxylin-eosin staining.

Immunohistochemistry: CD56 immunostaining was performed on formalin-fixed paraffin-embedded bone marrow biopsy sections using monoclonal anti-CD56 antibody (clone 123C3/1B6; in vitro diagnostics, pre diluted). Antigen retrieval was performed using heat-induced epitope retrieval method. Detection was performed using DAB chromogen system. Membranous staining in plasma cells was considered positive. Cases showing staining in ≥10% plasma cells were categorized as CD56 positive.

Statistical Analysis:

Data were entered into Microsoft Excel and analysed using SPSS version XX. Continuous variables were expressed as mean + standard deviation or median with interquartile range depending on distribution. Categorical variables were expressed as frequency and percentage. Normality was assessed using the Shapiro-Wilk test. Comparisons between groups were performed using Chi-square test/ Fisher exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables. A p-value <0.05 was considered statistically significant.

Follow-up Assessment

Available follow-up data regarding treatment response and laboratory parameters were recorded. Response assessment was based on IMWG response criteria.[12] Follow-up duration ranged from 4 to 6 months.

RESULTS:

Demographic Profile:

A total of 30 patients with newly diagnosed multiple myeloma were included. The majority of patients

belonged to the 61-70-year age group, with male predominance observed.

CD56 Expression:

CD56 positivity was observed in 23 patients (76.7%), whereas 7 patients (23.3%) were CD56 negative.

Correlation With ISS Stage:

A relatively higher proportion of CD56-negative patients belonged to advanced ISS stage compared with CD56-positive patients; however, the difference was not statistically significant.

Correlation With Bone Lesions:

Lytic bone lesions were more frequently observed in CD56-positive patients. However, statistical significance was not achieved.

Table 1. Comparison of Hematological and Biochemical Parameters According to CD56 Expression

Parameter	CD56 Positive (Mean ± SD)	CD56 Negative (Mean ± SD)	p-value
Serum Calcium (mg/dL)	11.3 ± 1.6	11.5 ± 1.4	0.74
Serum Creatinine (mg/dL)	2.7 ± 1.5	3.6 ± 3.5	0.39
β2-Microglobulin (mg/L)	4.1 ± 1.1	4.8 ± 1.3	0.18
C-Reactive Protein (mg/L)	14 ± 10	23 ± 12	0.07
M-band (g/dL)	5.1 ± 1.2	4.8 ± 1.4	0.56
Serum Albumin (g/dL)	3.2 ± 0.6	2.7 ± 0.4	0.040*
Hemoglobin (g/dL)	7.9 ± 1.2	7.5 ± 1.0	0.42
Total Leukocyte Count (/µL)	6100 ± 1800	5900 ± 2100	0.79
Platelet Count (/µL)	168000 ± 65000	150000 ± 70000	0.53

*Statistically significant ($p < 0.05$)

CD56-negative patients showed trends toward higher serum creatinine, β2-microglobulin, CRP, and lower serum albumin levels. However, only serum albumin demonstrated a statistically significant difference between the groups ($p = 0.040$).

Table 2. Comparison of Bone Marrow Findings According to CD56 Expression

Parameter	CD56 Positive (Mean ± SD)	CD56 Negative (Mean ± SD)	p-value
Bone Marrow Aspirate Plasma Cells (%)	45 ± 15	44 ± 14	0.88
Bone Marrow Biopsy Plasma Cells (%)	35 ± 12	34 ± 11	0.9

Bone marrow plasma cell percentages assessed by both aspirate and biopsy were comparable between CD56-positive and CD56-negative patients, with no statistically significant differences observed.

Table 3. Comparison of Baseline and Follow-up Parameters in Patients with Available Follow-up Data (n = 13)

Parameter	Baseline Mean ± SD	Follow-up Mean ± SD	Overall Change
Hemoglobin (g/dL)	8.15 ± 1.33	9.92 ± 1.45	Increased
Serum Creatinine (mg/dL)	2.15 ± 1.08	1.11 ± 0.39	Decreased
Serum Calcium (mg/dL)	11.17 ± 1.73	9.32 ± 0.79	Decreased
M-band (g/dL)	5.37 ± 0.98	2.18 ± 0.63	Decreased
Bone Marrow Aspirate Plasma Cells (%)	46.77 ± 18.20	3.31 ± 6.60	Decreased
Bone Marrow Biopsy Plasma Cells (%)	37.92 ± 14.70	2.92 ± 5.10	Decreased

Follow-up evaluation demonstrated improvement in hematological and biochemical parameters, characterized by increased hemoglobin levels and marked reductions in serum creatinine, calcium, M-band concentration, and bone marrow plasma cell burden.

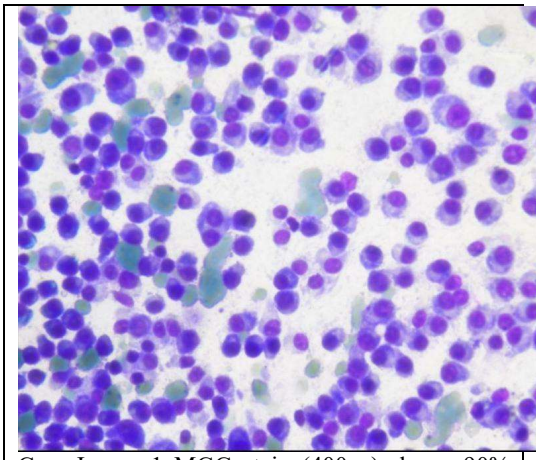
Table 4. Follow-up Changes According to CD56 Expression Status

Parameter	CD56 Positive Baseline	CD56 Positive Follow-up	CD56 Negative Baseline	CD56 Negative Follow-up
Hemoglobin (g/dL)	8.16	9.88	8.1	10.5
Serum Creatinine (mg/dL)	2.12	1.11	2.8	1.1
M-band (g/dL)	5.44	2.15	4.5	2.7
Bone Marrow Aspirate Plasma Cells (%)	47.25	3.5	41	1
Bone Marrow Biopsy Plasma Cells (%)	38.17	3.08	35	1

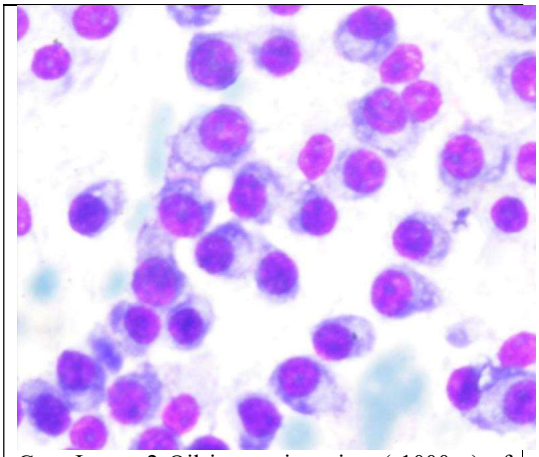
Both CD56-positive and CD56-negative patients showed substantial reductions in disease burden on follow-up, reflected by decreases in M-band levels and bone marrow plasma cell percentages, along with improvement in hemoglobin and renal function parameters. However, interpretation is limited by the small number of patients with available follow-up data.

Comparative analysis by CD56 status should be interpreted cautiously if CD56-negative follow-up numbers are low.

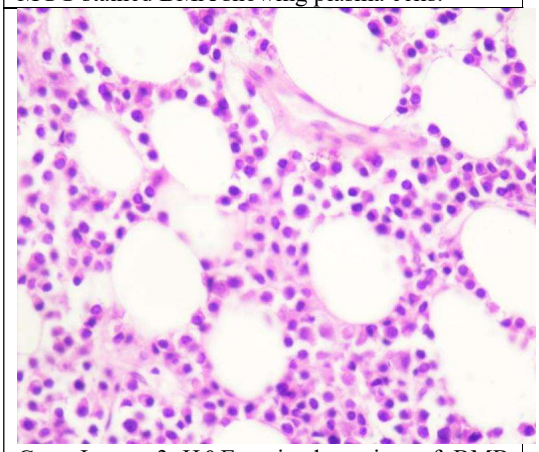
PATHOLOGY IMAGES:



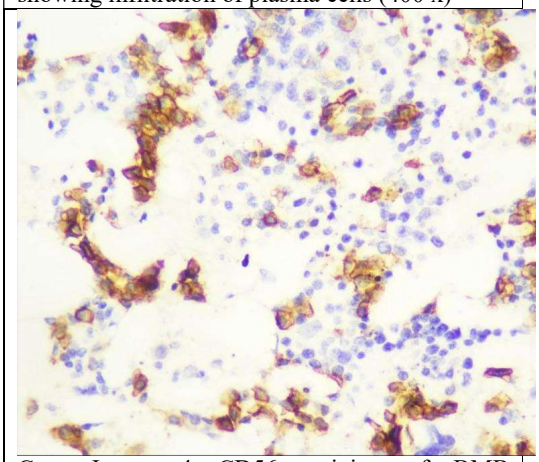
Case Image 1 MGG stain (400 x) shows 90% plasma cells in BMA



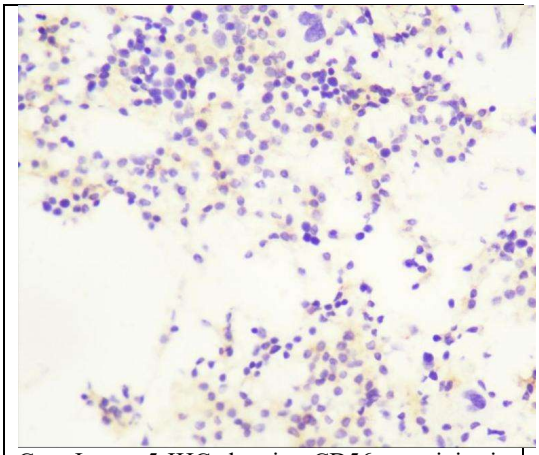
Case Image 2 Oil immersion view (1000 x) of MGG stained BMA showing plasma cells.



Case Image 3 H&E stained section of BMB showing infiltration of plasma cells (400 x)



Case Image 4 CD56 staining of BMB demonstrating distinct membranous staining of plasma cells (400 x)



Case Image 5 IHC showing CD56 negativity in neoplastic plasma cells in multiple myeloma (400 x)

DISCUSSION:

Multiple myeloma is a biologically heterogeneous plasma cell neoplasm with variable clinical behaviour and prognosis. Identification of additional prognostic biomarkers remains important in improving risk stratification. In the present study, CD56 expression was observed in 76.7% of cases, which is comparable to previously published literature reporting positivity rates ranging from 60-80%.[5,6,13] CD56-negative cases in our study demonstrated trends toward adverse clinicopathological features, including elevated serum creatinine, increased ß2-microglobulin, advanced ISS stage, and unfavourable biochemical parameters. However, most associations failed to achieve statistical significance. This may be attributable to the small sample size, unequal distribution between CD56-positive and CD56-negative groups, and limited follow-up duration.

CD56 is a neural cell adhesion molecule involved in plasma cell adhesion to bone marrow stromal cells. Loss of CD56 expression may impair marrow homing and facilitate extramedullary dissemination and leukemic spread. Previous studies have demonstrated an association between CD56 negativity and plasma cell leukaemia, extramedullary disease, plasmablastic morphology, and adverse prognosis. Koumpis et al. reported correlations between CD56 negativity and elevated LDH, ß2-microglobulin levels, and advanced ISS stage.[8] Similarly, Sahara et al. demonstrated poorer survival outcomes in CD56-negative multiple myeloma patients.[9] However, several studies including those by Mathew et al. and Kraj et al. did not identify CD56 as an independent prognostic marker.[13,14] The variability among published studies may be related to differences in patient populations, treatment protocols, immunohistochemical methodology, positivity cutoffs, and sample size.

LIMITATIONS:

The present study had several limitations:

- Single-center design
- Small sample size
- Unequal distribution of CD56-positive and CD56-negative groups
- Limited follow-up duration
- Inability to perform survival analysis
- Lack of cytogenetic and molecular correlation

CONCLUSION:

CD56 expression was observed in the majority of multiple myeloma cases in the present study. CD56-negative multiple myeloma showed trends toward adverse clinicopathological and biochemical parameters, although statistical significance was not achieved in most comparisons. The findings suggest a possible association between CD56 negativity and aggressive disease biology. Larger multicentric studies with longer follow-up and incorporation of cytogenetic analysis are required to better define the prognostic significance of CD56 expression in multiple myeloma.

REFERENCES:

1. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024;99(4):797-820.
2. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.
3. Kashid A, Sharma H, Kamal A, Kashwani R, Kumari A. Insights into peripheral giant cell granuloma: A case study analysis [Internet]. J Orofac Health Sci. 2024 [cited 2026 Jul 17];11(2):82-85. Available from: https://doi.org/10.18231/j.johs.2024.018
4. Harrison TR, Fauci AS, Kasper DL, et al. Harrison's Principles of Internal Medicine. 22nd ed. New York: McGraw-Hill; 2022.
5. Ceran F, Sözeri E, Unal A, et al. The clinical significance of CD56 expression in patients with multiple myeloma. Hematology. 2017;22(3):157-163.
6. Kraj M, Pogłód R, Kopeć-Szlęzak J, et al. Flow cytometric immunophenotypic characteristics of plasma cell leukemia and multiple myeloma. Leuk Res. 2011;35(1):33-38.
7. Cerny J, Fadare O, Hutchinson L, Wang SA. Expression of CD56 in multiple myeloma and extramedullary plasmacytoma. Clin Lymphoma Myeloma. 2008;8(4):249-252.
8. Koumpis E, Katodritou E, Gastari V, et al. CD56 expression in multiple myeloma: association with poor prognostic markers and disease aggressiveness. Clin Lymphoma Myeloma Leuk. 2013;13(3):221-226.
9. Sahara N, Takeshita A, Ono T, et al. Clinicopathological significance of CD56 expression in multiple myeloma. Br J Haematol. 2002;117(4):882-886.
10. Zhang L, Tai YT, Ho M, et al. Regulatory roles of CD56 in multiple myeloma progression and

prognosis: a meta-analysis. Oncotarget. 2017;8(21):34001-34010.
11. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538-e548.
12. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.
13. Mathew P, Ahmann GJ, Witzig TE, et al. Clinicopathological significance of CD56 expression in multiple myeloma. Leuk Lymphoma. 1995;20(1-2):131-137.
14. Kumar SK, Callander NS, Hillengass J, et al. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. J Natl Compr Canc Netw. 2024;22(5):e247012.