

Research Article**Diagnostic and Prognostic Value of Bone Marrow Morphology in Multiple Myeloma: A Cross-Sectional Analysis****Dr. Fatima Nizami¹, Dr MH Shariff², Dr Rajesh Krishna³,**¹3rd Year PG, Department of Pathology, Yenepoya Medical College (Deemed to be University) Mangalore, India.³Professor, Department of Pathology, Yenepoya medical College (Deemed to be University) Mangalore, India.⁴Consultant Hematologist, Department of Pathology, Yenepoya medical College (Deemed to be University) Mangalore, India.

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Corresponding Author: Dr. Fatima Nizami, 3rd year PG, Department of Pathology, Yenepoya Medical College (Deemed to be University) Mangalore, India.**Email:** fatimanizami541@gmail.com**ABSTRACT**

Background: Multiple myeloma (MM) is a malignant plasma-cell disorder characterized by clonal proliferation within the bone marrow, resulting in anemia, renal impairment, hypercalcemia, and bone destruction. Morphological assessment of bone marrow remains a cornerstone in the diagnosis and prognostic evaluation of MM, particularly in settings with limited access to advanced molecular techniques. **Aim:** To evaluate the diagnostic and prognostic value of bone marrow morphology in patients with multiple myeloma. **Methods:** A cross-sectional study was conducted on 26 confirmed cases of MM at a tertiary care hospital. Bone marrow aspirate smears and trephine biopsy sections were examined for plasma-cell morphology, infiltration percentage, and architectural growth pattern. Histological staging was done based on plasma-cell proportion. Data were analyzed using descriptive statistics and Chi-square test to assess associations between morphological parameters and histological stage. **Results:** Anemia was observed in all patients (100%), renal dysfunction in 65.4%, and hypercalcemia in 30.8%. The mean hemoglobin was 7.8 ± 1.9 g/dL and mean ESR 69.4 ± 39.4 mm/h. Bone marrow aspirates revealed plasma-cell infiltration exceeding 40% in 57.7% of cases, with mature morphology predominating (46.2%), followed by intermediate (30.7%) and immature forms (23.1%). Trephine biopsy showed interstitial growth in 57.7%, nodular in 23.1%, and packed/diffuse pattern in 19.2%. A strong correlation was found between histological stage and both plasma-cell morphology ($p=0.002$) and growth pattern ($p=0.001$), indicating their prognostic significance. **Conclusion:** Bone marrow morphology provides valuable diagnostic and prognostic information in multiple myeloma. The shift from interstitial to packed/diffuse infiltration and from mature to immature plasma-cell morphology parallels disease advancement, making histological and cytological assessment essential in prognostication and management.

Keywords: Multiple Myeloma, Bone Marrow Morphology, Plasma Cell, Histological Stage, Prognosis.

INTRODUCTION

Multiple myeloma (MM) is a malignant clonal disorder of plasma cells characterized by their accumulation within the bone marrow, excessive secretion of monoclonal immunoglobulins or light chains, and associated organ dysfunction. It constitutes approximately 10% of all hematopoietic neoplasms and about 1% of all cancers, with a higher prevalence among males and the elderly population, typically diagnosed in the sixth to seventh decade of life.^[1]

The pathophysiology of MM involves complex interactions between malignant plasma cells and the bone marrow microenvironment, mediated through cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and vascular endothelial growth factor (VEGF), which promote proliferation, inhibit apoptosis, and stimulate osteoclast activity leading to lytic bone lesions.^[2]

Clinically, MM presents with bone pain, anemia, renal insufficiency, hypercalcemia, and recurrent infections-the hallmark CRAB features (Calcium elevation, Renal failure, Anemia, and Bone lesions). The diagnosis is established using the International Myeloma Working Group (IMWG) criteria, which require $\geq 10\%$ clonal plasma cells in bone marrow or a biopsy-proven plasmacytoma along with at least one myeloma-defining event such as organ damage or specific biomarkers (e.g., free light chain ratio ≥ 100 or $> 60\%$ plasma cells in marrow).^[3]

Bone marrow examination remains a cornerstone in the diagnostic and prognostic evaluation of MM. Aspirate smears and trephine biopsies provide crucial information on plasma cell percentage, maturation, morphology, and the pattern of marrow infiltration-all of which correlate strongly with disease burden and prognosis. Huang P *et al.* (2025)^[4] proposed a histological grading and staging system based on plasma cell morphology and infiltration patterns: interstitial, nodular, and packed (diffuse). The interstitial pattern is often seen in early disease with better prognosis, while nodular and packed patterns are associated with aggressive disease and poorer outcomes. Similarly, immature or plasmablastic morphology indicates higher tumor activity and worse survival, whereas mature plasma cells correlate with a relatively indolent course.

Despite major advances in imaging and molecular testing (including fluorescence in situ hybridization and gene expression profiling), morphological assessment remains indispensable. It not only confirms diagnosis but also provides prognostic stratification, particularly in resource-limited settings where cytogenetic and molecular facilities may not be routinely available. The combination of histological stage, growth pattern, and plasma cell maturity can help predict treatment response and overall survival.^[5]

Aim

To evaluate the diagnostic and prognostic value of bone marrow morphology in patients with multiple myeloma.

Objectives

1. To describe and classify plasma cell morphology in bone marrow aspiration smears of multiple myeloma patients.
2. To categorize the growth pattern of plasma cells in bone marrow biopsy samples.

3. To correlate plasma cell morphology and growth patterns with histological staging of multiple myeloma.

MATERIALS AND METHODOLOGY

Source of Data: The present study was conducted in the Department of Pathology, Yenepoya Medical College, Mangaluru. Data were obtained from bone marrow aspirate and trephine biopsy samples of patients clinically diagnosed as multiple myeloma and referred for hematopathological evaluation.

Study Design: A descriptive, cross-sectional analytical study.

Study Location: Department of Pathology, Yenepoya Medical College, Mangaluru, Karnataka.

Study Duration: From November 2023 to December 2024.

Sample Size: 26 patients clinically diagnosed and confirmed as multiple myeloma.

Inclusion Criteria:

- All cases clinically suspected and diagnosed as multiple myeloma with adequate bone marrow aspirate and trephine biopsy samples.

Exclusion Criteria:

- Inadequate bone marrow aspirate smears or trephine biopsies.
- Cases with inadequate aspirate but adequate biopsy (and vice versa) were excluded to maintain uniformity.

Procedure and Methodology: Bone marrow aspiration and biopsy were performed in a single sitting under aseptic precautions using a Jamshidi needle under local anesthesia. Aspirate smears were prepared, air-dried, and stained with Leishman stain. Trephine biopsy specimens were fixed in 10% neutral buffered formalin, decalcified in nitric acid, processed, embedded in paraffin, sectioned, and stained with Hematoxylin and Eosin (H&E).

Bone marrow aspirates were assessed for cellularity, percentage of plasma cells (200-cell differential count), and morphological features according to the modified Bartl grading system:

Grade 1 (Mature): >70% mature plasma cells.

Grade 2 (Intermediate): <50% with nuclear atypia.

Grade 3 (Immature): >50% with cytologic atypia and prominent nucleoli.

Biopsy sections were evaluated for cellularity, plasma cell percentage, and infiltration pattern (interstitial, nodular, packed/diffuse) as per Wallington-Beddoe CT *et al.* (2021)[6] Histological staging was classified as:

Stage I: <20% plasma cells

Stage II: 20-50% plasma cells

Stage III: >50% plasma cells

Sample Processing: All slides were reviewed under low, high, and oil immersion magnifications to assess the distribution and morphology of plasma cells. Representative images were documented for reference.

Statistical Methods: Data were entered into Microsoft Excel and analyzed using SPSS version 25.0 (IBM Corp., Chicago, IL). Quantitative data were expressed as mean $\pm$ SD, and categorical variables as frequencies and percentages. Associations between histological stage and bone marrow findings (growth pattern, plasma cell morphology, and hypercellularity) were analyzed using the Chi-square test. A *p*-value <0.05 was considered statistically significant.

Data Collection: Patient demographic details, clinical features, laboratory parameters (hemoglobin, serum calcium, creatinine, M-band, etc.), and bone marrow findings were recorded from pathology registers and case files while maintaining patient confidentiality.

OBSERVATION AND RESULTS

Table 1: Diagnostic & prognostic profile at presentation (n=26)

Variable	Mean $\pm$ SD or n (%)	95% CI
Hemoglobin (g/dL)	7.8 $\pm$ 1.9	7.03 to 8.57
ESR (mm/h)	69.4 $\pm$ 39.4	53.48 to 85.32
TLC (/cumm)	7437.7 $\pm$ 3118.4	6177.9 to 8697.5
Platelet count ($\times 10^5$ /cumm)	1.5 $\pm$ 1.0	1.10 to 1.90
Serum creatinine (mg/dL)	2.8 $\pm$ 2.7	1.71 to 3.89
Raised creatinine (>1.1 mg/dL)	17 (65.4%)	46.22% to 80.59%
Serum calcium (mg/dL)	9.9 $\pm$ 2.3	8.97 to 10.83
Hypercalcemia (>10.2 mg/dL)	8 (30.8%)	16.50% to 49.99%
Any anemia	26 (100%)	-
Rouleaux formation (PS)	16 (61.5%)	42.53% to 77.57%
M-band present (SPEP)	21 (80.8%)	62.12% to 91.49%

The baseline hematological and biochemical profile of the 26 patients with multiple myeloma revealed marked anemia as a universal finding (100%), with a mean hemoglobin of 7.8 $\pm$ 1.9 g/dL (95% CI 7.03-8.57). The mean erythrocyte sedimentation rate (ESR) was markedly elevated at 69.4 $\pm$ 39.4 mm/h (95% CI 53.48-85.32), reflecting increased rouleaux formation secondary to high plasma protein levels. The total leukocyte count (TLC) averaged 7437.7 $\pm$ 3118.4 /cumm (95% CI 6177.9-8697.5), indicating preserved leukopoiesis in most patients. Platelet counts were mildly reduced, with a mean of 1.5 $\pm$ 1.0 $\times 10^5$ /cumm (95% CI 1.10-1.90), suggestive of marrow crowding due to plasma-cell infiltration.

Renal dysfunction was common, with 65.4% of patients exhibiting raised serum creatinine (> 1.1 mg/dL) and a mean level of 2.8 $\pm$ 2.7 mg/dL (95% CI 1.71-3.89), consistent with myeloma-related nephropathy. Mean serum calcium was 9.9 $\pm$ 2.3 mg/dL (95% CI 8.97-10.83), and hypercalcemia was observed in 30.8% of patients, indicating active bone resorption. Peripheral smear findings showed rouleaux formation in 61.5%, correlating with elevated ESR. Serum protein electrophoresis demonstrated the presence of M-band in 80.8% of cases, establishing monoclonal gammopathy as the predominant laboratory hallmark.

Table 2: Plasma-cell burden and cytomorphology on bone marrow aspiration (n=26)

Feature	n (%)	95% CI
Plasma cell percentage		
11-20%	2 (7.7%)	2.14% to 24.14%
21-30%	3 (11.5%)	4.00% to 28.98%
31-40%	4 (15.4%)	6.15% to 33.53%
41-50%	6 (23.1%)	11.03% to 42.05%
51-60%	3 (11.5%)	4.00% to 28.98%
61-70%	2 (7.7%)	2.14% to 24.14%

>70%	6 (23.1%)	11.03% to 42.05%
Plasma-cell morphology (overall)		
Mature	12 (46.2%)	28.76% to 64.54%
Intermediate	8 (30.7%)	16.50% to 49.99%
Immature	6 (23.1%)	11.03% to 42.05%
Cytoplasmic abnormalities		
Multinucleated cells	25 (96.1%)	-
Flame cells	3 (11.5%)	4.00% to 28.98%
Morula cells	3 (11.5%)	4.00% to 28.98%

Bone marrow aspirate evaluation showed variable plasma-cell infiltration ranging from 11% to > 70%. The largest subset (23.1%) demonstrated heavy marrow involvement (> 70%), followed by equal proportions (23.1%) between 41-50%. Moderate infiltration (31-60%) was seen in 38.4% of patients, while only a small fraction (7.7-11.5%) exhibited minimal infiltration ($\leq 30\%$). Morphologically, mature plasma cells predominated (46.2%, 95% CI 28.76-64.54), whereas intermediate forms accounted for 30.7%, and immature forms for 23.1%, indicating a heterogeneous population reflecting different stages of disease aggressiveness. Cytoplasmic abnormalities were frequent-multinucleation was observed in 96.1% of smears, a classic dysplastic feature. Flame cells and morula (Mott) cells were identified in 11.5% each, denoting active immunoglobulin synthesis.

Table 3: Growth pattern of plasma cells on trephine biopsy (n=26)

Growth pattern	n (%)	95% CI
Interstitial	15 (57.7%)	38.95% to 74.46%
Nodular	6 (23.1%)	11.03% to 42.05%
Packed / Diffuse	5 (19.2%)	8.51% to 37.88%

Trephine biopsy assessment revealed interstitial infiltration as the most frequent growth pattern (57.7%, 95% CI 38.95-74.46), characterized by scattered plasma-cell clusters among residual hematopoietic elements. Nodular infiltration was noted in 23.1% (95% CI 11.03-42.05), whereas packed or diffuse replacement of marrow elements by plasma cells occurred in 19.2% (95% CI 8.51-37.88). The predominance of interstitial pattern corresponds to early or moderate disease, while nodular and packed patterns reflect advanced marrow infiltration and correlate with poorer prognosis.

Table 4: Correlation of morphology & growth patterns with histological stage (n=26)

A) Growth pattern vs histological stage

Growth pattern	Stage 1	Stage 2	Stage 3	Test / P
Interstitial	2 (100.0%)	12 (92.3%)	1 (9.1%)	Chi-square, p=0.001*
Nodular	0 (0.0%)	1 (7.7%)	5 (45.5%)	
Packed / Diffuse	0 (0.0%)	0 (0.0%)	5 (100.0%)	
Total	2	13	11	

B) Plasma-cell morphology vs histological stage

Morphology	Stage 1	Stage 2	Stage 3	Test / P
Mature	0 (0.0%)	10 (76.9%)	2 (18.2%)	Chi-square, p=0.002*
Intermediate	2 (100.0%)	3 (23.1%)	3 (27.3%)	
Immature	0 (0.0%)	0 (0.0%)	6 (54.5%)	

Total	2	13	11	
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A highly significant association was found between the growth pattern and histological stage ($\chi^2 = 18.42$, $p = 0.001$). Interstitial infiltration predominated in Stage 1 (100%) and Stage 2 (92.3%) cases, whereas in Stage 3, only 9.1% retained this pattern. Conversely, packed/diffuse growth appeared exclusively in Stage 3 (100%), and nodular infiltration increased to 45.5% at this advanced stage. These findings underline that increasing histological stage parallels progressive architectural effacement of bone marrow.

Similarly, plasma-cell morphology showed a statistically significant correlation with histological stage ($\chi^2 = 15.67$, $p = 0.002$). Stage 1 marrows contained only intermediate forms (100%), Stage 2 predominantly mature cells (76.9%), and Stage 3 mainly immature forms (54.5%), accompanied by residual intermediate (27.3%) and mature (18.2%) types.

DISCUSSION

Cohort shows the classic “CRAB” signature at diagnosis, with universal anemia (100%), high ESR (mean 69.4 mm/h), frequent renal dysfunction (creatinine >1.1 mg/dL in 65.4%), hypercalcemia in 30.8%, M-band positivity in 80.8%, and rouleaux in 61.5%. The anemia rate aligns with several regional and international series-near-universal in Wallington-Beddoe CT *et al.*(2021)^[6] and very high in Firsova MV *et al.*(2020)^[7] where anemia ranged from 94-100% at presentation, while Gong YY *et al.*(2021)^[8] reported lower anemia prevalence (65%) in a cohort, underscoring geographic and referral-pattern differences.

Renal involvement in our series (65.4%) is higher than many general estimates and mirrors Biswal’s central-Indian experience (creatinine > 2 mg/dL in 63.0%), but exceeds Hussain’s 27.2%, again suggesting later presentation or heavier light-chain burden in our setting. Hypercalcemia (30.8%) sits between Hussain’s (11.3%) and Biswal’s (36.9%), and within the broad ranges reported across Indian centers. These contrasts likely reflect tumor load and bone disease at presentation and emphasize the need for early case-finding strategies. Allegra A *et al.*(2022)^[9]

M-band detection in our cohort (80.8%) matches the expected 80-90% detection by serum protein electrophoresis; Hari reports 91.3% and Hussain 70.8%, highlighting assay mix (immunofixation/light-chain testing) and the share of oligo/non-secretory myeloma as key determinants of yield. The rouleaux frequency (61.5%) is consistent with high paraprotein states and parallels series that document conspicuous peripheral-smear changes in newly diagnosed MM.

On marrow aspirates, we observed wide plasma-cell burdens, with heavy involvement (>70%) in 23.1%. Morphologically, mature forms predominated (46.2%), followed by intermediate (30.7%) and immature (23.1%), while multinucleation (96.1%), flame cells (11.5%), and morula/Mott cells (11.5%) were frequent dysplastic/immunoglobulin-overload signatures. Hu X *et al.*(2024)^[10] similarly documented common morphologic variants (flame, multinuclearity, morula, Dutcher bodies) with a predominance of mature plasmacytic forms and 20-50% marrow involvement in many cases. Štifter’s comparative BMA/BMB work further linked higher tumor burden and atypical/immature cytology with worse survival, reinforcing the prognostic content of what we observed on smears.

Trephine biopsies in our cohort most often showed interstitial growth (57.7%), then nodular (23.1%), and packed/diffuse (19.2%). When benchmarked, our interstitial share is higher than Di Giuliano F *et al.*(2020)^[11] (27%) and Baffour FI *et al.*(2020)^[12] (7.8%) but above Bębnowska D *et al.*(2021)^[13] 35.7%; conversely, our packed/diffuse proportion (19.2%) is lower than the

diffuse-heavy distributions in Di Giuliano F *et al.*(2020)^[11] (64%) and Baffour FI *et al.*(2020)^[12] (68.6%). These differences suggest a spectrum of disease architecture at first presentation across centers. Critically, the architectural pattern carries outcome implications; Bartl's classic work linked diffuse/packed patterns to inferior survival, a principle echoed by our stage-wise distribution.

The stage-morphology-architecture triad in our data is strongly coherent. Interstitial growth dominated Stage 1-2 (100% and 92.3%), while Stage 3 shifted to nodular (45.5%) and exclusively packed/diffuse (100% of that category). Cytologically, Stage 3 was enriched for immature forms (54.5%) whereas Stage 2 retained mature cells (76.9%); both associations were significant ($p=0.001$ and $p=0.002$). This mirrors Takakuwa T *et al.*(2020)^[14] observations that higher infiltrative burden, diffuse architecture, and atypical/immature cytology track with advanced stage and poorer survival, and it accords with broader frameworks that integrate morphology into risk stratification.

Collectively, these comparisons position our cohort as typical for symptomatic, newly diagnosed MM in South Asia-anemic, frequently with renal and skeletal involvement, and displaying marrow features that shift from interstitial/mature to packed-immature as stage advances. The concordance with multi-center literature supports the interpretive value of detailed bone-marrow morphology (aspirate + trephine) alongside electrophoretic and biochemical parameters at baseline, both for diagnosis and for early prognostic signaling. Al Saleh AS *et al.*(2020)^[15]

CONCLUSION

The present cross-sectional study comprehensively analyzed the diagnostic and prognostic significance of bone marrow aspirate and trephine biopsy findings in 26 patients. The study demonstrated that detailed evaluation of bone marrow morphology offers crucial insights into the disease burden, stage, and prognosis. The presence of anemia, renal dysfunction, and hypercalcemia remained dominant clinical features at presentation, reflecting advanced disease in most cases. Bone marrow aspirate analysis revealed a wide spectrum of plasma-cell morphology, ranging from mature to immature forms, while trephine biopsies showed progressive transition from interstitial to nodular and packed/diffuse growth patterns with increasing histological stage.

Statistical correlation between histological stage and both plasma-cell morphology ($p=0.002$) and growth pattern ($p=0.001$) was significant, indicating that architectural and cytological parameters of the bone marrow can serve as reliable prognostic indicators. These findings reaffirm the diagnostic value of bone marrow evaluation and support its continued use as a fundamental tool for staging, monitoring disease progression, and guiding therapeutic decisions in multiple myeloma, especially in resource-limited settings where molecular assays may not be routinely accessible.

LIMITATIONS OF THE STUDY

1. The study had a **limited sample size (n=26)**, which may reduce the generalizability of results and limit statistical power for subgroup analyses.
2. Being a **cross-sectional design**, the study could not assess long-term survival outcomes or post-treatment morphological changes.
3. **Selection bias** may be present, as the study included only cases with adequate aspirate and biopsy specimens, excluding suboptimal samples.

4. The absence of **cytogenetic and molecular correlation** (such as FISH or gene-expression profiling) restricts deeper prognostic stratification.
5. **Single-center design** may not fully represent regional variability in disease presentation and histopathological patterns.

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