

Coagulation Abnormalities in Patients with Multiple Myeloma: A Cross-sectional Study from a Tertiary Care Centre in Southern India

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ABSTRACT

Introduction: Multiple Myeloma (MM) is a haematologic malignancy characterised by clonal plasma cell proliferation in the bone marrow. Coagulation abnormalities are common in MM patients and can result from thrombocytopenia due to disease load, acquired platelet dysfunction, anticoagulant activity of paraproteins, acquired coagulation factor deficiency, enhanced clearance of coagulation factors by reticuloendothelial system, hyperviscosity. These result in haemorrhagic and thrombotic episodes which are associated with poor prognosis and also impact treatment decisions. Early identification of coagulation abnormalities can help in anticipating complications, guiding supportive management, and improving patient outcomes. Hence, evaluating the coagulation profile in patients with MM is important and will provide valuable insights into the association between plasma cell dyscrasia and haemostatic derangements.

Aim: To describe the coagulation profile in patients with MM diagnosed on bone marrow examination and to assess the relationship between coagulation abnormalities, bleeding manifestations, aggressive cellular morphology and disease stage.

Materials and Methods: This cross-sectional study examined 67 newly diagnosed MM patients diagnosed in Government Medical College, Kottayam, Kerala, India between July 2023 to December 2024. Clinical, radiological, and laboratory parameters were assessed, which included total blood count, Prothrombin Time (PT), Activated Partial Thromboplastin Time

(APTT), Thrombin Time (TT), and fibrinogen levels. Prolonged PT, APTT, TT and a low or elevated fibrinogen levels were considered as presence of coagulation abnormalities. The association between coagulation abnormalities and bleeding manifestations and plasmablastic morphology were evaluated using Chi-square test. The association between coagulation abnormalities and International Staging System (ISS) stage was evaluated using Fisher-Freeman-Halton exact test. A p-value <0.05 was considered statistically significant.

Results: The study population included 35 (52.2%) males, with mean age of 67 years. Bleeding manifestations were seen in 16 (23.9%) cases. Coagulation abnormalities were found in 19 (28.4%) of patients, with prolonged PT in 8 (11.9%), prolonged APTT in 10 (14.9%), and prolonged TT in 3 (4.5%). Abnormal coagulation was associated with bleeding manifestations (Chi-square test, p-value= 0.001), advanced ISS stage (Fisher-Freeman-Halton exact test, p-value<0.001), and plasmablastic morphology in bone marrow (Chi-square test, p-value=0.011).

Conclusion: Acquired coagulation abnormalities can occur in a significant proportion of newly diagnosed MM patients and can be associated with advanced ISS stage (coagulation abnormalities were most common in stage 3 patients) and plasmablastic morphology, which represents a more aggressive disease variant. Routine coagulation screening should be incorporated into the management of MM patients, especially those in advanced ISS stages or with plasmablastic morphology.

Keywords: Activated partial thromboplastin time, Bleeding, Prothrombin time

INTRODUCTION

The MM is a clonal plasma cell neoplasm primarily involving bone marrow characterised by anaemia, lytic bone lesions, renal failure. It is the second most frequent haematological malignancy and constitutes 0.94% of all newly diagnosed cases of malignancy worldwide [1]. The hallmark of the malignant plasma cells is the production of large amounts of non-functional monoclonal immunoglobulins which underlies the varied clinical manifestations in MM. One of the significant abnormalities is changes in primary and secondary haemostasis leading to haemorrhagic and thrombotic episodes, which are related to poor prognosis and decreased survival [2]. Clinically, this may present as mucosal bleeding, epistaxis, gastrointestinal haemorrhage, easy bruising, postoperative bleeding, or rarely intracranial haemorrhage. Patients with myeloma are also at increased risk of venous thromboembolism, particularly with the introduction of new therapeutic agents like proteasome inhibitors, immunomodulatory drugs like thalidomide and lenalidomide and monoclonal antibodies [3]. However often

abnormal screening tests of haemostasis are not associated with clinically significant bleeding manifestations. Several studies have identified prolongation of screening coagulation tests such PT, APTT, TT, fibrinogen levels in patients with MM. The pathogenesis of coagulopathy in MM is multifactorial. Possible mechanisms include thrombocytopenia due to disease load, acquired platelet dysfunction, anticoagulant activity of paraproteins, acquired coagulation factor deficiency, enhanced clearance of coagulation factors by reticuloendothelial system, hyperviscosity. Presence of these haemostatic changes also impact treatment decisions and use of therapeutic strategies for symptomatic control of bleeding complications or thromboembolism [3]. Evaluating the coagulation profile in patients with MM is hence important and will provide valuable insights into the association between plasma cell dyscrasia and haemostatic derangements. Besides there are very limited studies [4,5] on coagulation abnormalities in MM patients done in the Indian population. The study aimed to describe the changes in screening coagulation tests in patients with MM diagnosed at a

tertiary care centre in Southern India and to assess the association of coagulation abnormalities with disease stage.

MATERIALS AND METHODS

The descriptive cross-sectional study included 67 new cases of MM diagnosed in Government Medical College, Kottayam, Kerala, India between July 2023 to December 2024. The study was approved by Institutional Ethical committee (IEC) with approval number (IEC No:174/2023).

Sample size: Sample size was calculated based on a study conducted by Gogia A et al., [4]. In their study, the proportion of prolonged aPTT, was found to be 59.2%. Using the formula. $n=pq/d^2$, $n=4 \times 59.2 \times 40.8 \div (12)^2$, sample size was found to be 67.

Inclusion criteria: All cases of newly diagnosed MM irrespective of age and sex based on the revised International Myeloma Working Group (IMWG) criteria [6] for the diagnosis of MM and related disorders were included in the study.

Exclusion criteria: Patients included patients with known bleeding disorders, liver impairment, patients on drugs affecting coagulation, recent blood or plasma transfusion were excluded from the study.

Study Procedure

Clinical, radiological and biochemical parameters were obtained from the case records. After getting informed consent, complete blood count and haemostatic parameters were assessed. For complete blood count 2 mL of blood was collected in EDTA tubes and run in MINDRAY BC 6200 5-part automated haematology analyser. Haematological parameters analysed were Haemoglobin (Males: 14-18 g/dL; Females: 12-16 g/dL), Total White Blood Cells (WBC) count (4000-11000 cells/mm³), Platelet count (1.5-4.5 lac/mm³), Erythrocyte Sedimentation Rate (ESR) (Females: 0-20 mm/hour; Males: 0-15 mm/hour). Biochemical parameters obtained from case records were S. Calcium (8.2-10.2 mg/dL), Urea (20-40 mg/dl), Creatinine (0.6-1.2 mg/dL), Uric acid (4-8 mg/dL), S.Albumin (3.5-5 g/dL), S. Globulin (2-3.5 g/dL), A/G ratio (1.1-2.5). Serum β_2 -microglobulin levels were determined by immunonephelometry using an automated nephelometric analyser Siemens BNII system. Results were expressed in mg/L. Blood collection for PT, APTT, TT and Fibrinogen concentration was done by direct venipuncture in 3.2% buffered sodium citrate in a ratio 9:1 (9 part of whole blood and one part of anticoagulant). The blood collected in sodium citrate tube was centrifuged at the rate of 3500rpm for 15 minutes in centrifuge machine to separate Platelet Poor Plasma (PPP). The PPP was then assessed in Tcoag automated haematology analyser and the readings of PT (11-14 s), APTT (25-40 s), Fibrinogen (200-400 mg/dL), TT (12-14 s) noted.

STATISTICAL ANALYSIS

Data entry, documentation and analysis were done using Statistical Package for the Social Sciences (SPSS) software, version 22.0. The association between coagulation abnormalities and bleeding manifestations and plasmablastic morphology were evaluated using Chi-square test. The association between coagulation abnormalities and ISS stage was evaluated using Fisher-Freeman-Halton exact test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 67 newly diagnosed MM patients were included in the present study. Proportion of myeloma was higher in male patients (n=35, 52.24%) with mean age of 67±5.4 years (42-79 years).

Haematologic parameters: Anaemia, leucocytosis and thrombocytopenia was seen in 51 (76.1%), 16 (23.9%) and 19 (28.4%) of patients respectively. Leukopenia was noted in 6 (9%) of patients. Thrombocytosis was noted in 6 (9%) patients. ESR was raised in 56 (83.6%) of patients while it was normal in 11 (16.4%) [Table/Fig-1].

Haematology	Normal	High	Low
	n (%)	n (%)	n (%)
Haemoglobin (Males: 14-18 g/dL, Females: 12-16 g/dL)	16.0 (23.9)	-	51 (76.1)
TC (4000-11000 cells/mm ³)	45 (67.2)	16 (23.9)	6 (9)
ESR (Females: 0-20 mm/hr, Males: 0-15 mm/hr)	11 (16.4)	56 (83.6)	-
Platelet count (1.5-4.5 lac/mm ³)	42 (62.7)	6 (9)	19 (28.4)

[Table/Fig-1]: Distribution of haematologic parameters.

Biochemical parameters: Hypercalcaemia was noted in 45 (67.2%) of patients. Raised urea, uric acid and creatinine were seen in 45 (67.2%), 21 (31.3%) and 51 (76.1%) of patients respectively. The Albumin: Globulin ratio (A:G) ratio was reversed in 54 (80.6%) of patients and β_2 microglobulin was raised in 89.6% of patients (n=60). M band was noted in 100% of patients [Table/Fig-2]. Regarding ISS stage, 5 cases (7.5%) was in ISS stage 1, 49 cases (73.1%) in ISS stage 2 and 13 cases (19.4%) in ISS stage 3.

Biochemical	Normal	High	Low
	n (%)	n (%)	n (%)
S. Calcium (8.2-10.2 mg/dL)	13 (19.4)	45 (67.2)	9 (13.4)
Urea (20-40 mg/dL)	22 (32.8)	45 (67.2)	-
Creatinine (0.6-1.2 mg/dL)	16 (23.9)	51 (76.1)	-
Uric acid (4-8 mg/dL)	45 (67.2)	21 (31.3)	1 (1.5)
S.Albumin (3.5-5 g/dL)	17 (25.4)	1 (1.5)	49 (73.1)
S.Globulin (2-3.5 g/dL)	17 (25.4)	50 (74.6)	-
A/G ratio (1.1-2.5)	13 (19.4)	-	54 (80.6)

[Table/Fig-2]: Distribution of biochemical parameters.

Immunofixation electrophoresis identified IgG subtype in 60 cases, IgA myeloma in three cases, IgM and light chain myeloma in two cases each. The two patients classified as IgM MM demonstrated clonal plasma cell infiltration of the bone marrow consistent with MM. There was no morphological or immunophenotypic evidence of lymphoplasmacytic lymphoma. Both cases demonstrated multiple lytic lesions in skeletal survey with abnormal renal function parameters and lacked significant lymphadenopathy or splenomegaly associated with Waldenstrom Macroglobulinemia. Accordingly, these cases were classified as IgM MM.

Bleeding manifestations were noted in 16 (23.9%) patients, which included purpura (n=6), ecchymosis (n=3), hematoma (n= 3). Two patients each had malaena and epistaxis.

Bone marrow aspirate studies showed 10-60% plasmacytosis in 63 (94%) of patients and severe plasmacytosis (>60%) in patients. Plasmablastic morphology was noted in 12 (17.9%) of 4 (6%) patients and in these cases plasmablasts constituted 5% to 10% of the nucleated cells in bone marrow.

Abnormal screening coagulation parameters were noted in 19 (28.4%) patients. The most common abnormality observed was isolated APTT prolongation in 8 (11.9%) (2 patients had both PT and APTT prolongation), Range 43.6s-50.2s) patients. Isolated PT prolongation was observed in 6 (8.9%) (2 patients had both PT and APTT prolongation), Range 15.2-19.4s) patients. Both PT and APTT were prolonged in 2 (2.9%) patients. Isolated TT prolongation was noted in 3 (4.5%, Range 18-22.5s). Fibrinogen levels were not affected in any of the patients [Table/Fig-3]. A significant association between abnormal coagulation parameters and presence of bleeding manifestation [Table/Fig-4] and presence of more than 5% plasmablastic morphology were observed [Table/Fig-5].

Association between ISS stage and abnormal coagulation was assessed using the Fisher-Freeman-Halton exact test and observed a significant association between abnormal coagulation parameters and higher ISS stage. Abnormal coagulation was more common in ISS stage III (n=11, 57.9%) compared to stage II (n=8, 42.1%), with no cases observed in stage I [Table/Fig-6].

Coagulation	Normal	Prolonged
	n (%)	n (%)
PT (11-14s)	59 (88.1)	8 (11.9)
APTT (25-40s)	57 (85.1)	10 (14.9)
TT (12-14s)	64 (95.5)	3 (4.5)
Fibrinogen (200-400 mg/dL)	67 (100)	-

[Table/Fig-3]: Distribution of coagulation parameters.

Abnormal coagulation			Bleeding manifestations		Total
			Present	Absent	
	Present	Frequency	10	9	19
		Percentage	52.6%	47.4%	100.0%
	Absent	Frequency	6	42	48
		Percentage	12.5%	87.5%	100.0%
Total		Frequency	16	51	67
		Percentage	23.9%	76.1%	100.0%

[Table/Fig-4]: Association between coagulation abnormalities and bleeding manifestations.

Chi-square value- 12.06; p-value=0.001; There is significant association between abnormal coagulation and bleeding manifestations

Cell morphology- Abnormal coagulation			Abnormal coagulation		Total
			Present	Absent	
	Plasmacytic	Frequency	12	43	55
		Percentage	21.8%	78.2%	100.0%
	Plasmablastic	Frequency	7	5	12
		Percentage	58.3%	41.7%	100.0%
Total		Frequency	19	48	67
		Percentage	28.4%	71.6%	100.0%

[Table/Fig-5]: Association between coagulation abnormalities and plasma cell morphology.

Chi-square- 6.46, p-value=0.011; There is a significant association between abnormal coagulation and cell morphology

Abnormal coagulation			ISS stage			Total
			1	2	3	
	Present	Frequency	0	8	11	19
		Percentage	0.0%	42.1%	57.9%	100.0%
	Absent	Frequency	5	41	2	48
		Percentage	10.4%	85.4%	4.2%	100.0%
Total		Frequency	5	49	13	67
		Percentage	7.5%	73.1%	19.4%	100.0%

[Table/Fig-6]: Association between coagulation abnormalities and ISS stage.
Fisher-freeman-halton exact test; $p \approx 0.00002$; There is a significant association between the ISS stage and coagulation abnormalities

DISCUSSION

This study evaluated the haematological and haemostatic abnormalities in 67 newly diagnosed patients of MM. Anaemia were noted in 76.1% of patients. In the study by Gogia A et al., anaemia was identified in all their patients [4]. Liu L et al., identified anaemia in 84.4% of patients and it correlated with advanced disease stage and worse clinical outcomes [7]. Thrombocytopenia was noted in 16 (23.9%) patients while thrombocytosis was seen in 6 (9%) patients. Kuang C et al., observed thrombocytopenia in 30.4% and thrombocytosis in 7.9 % of newly diagnosed MM patients [8].

Abnormal screening coagulation parameters were noted in 19 (28.4%) patients. The most common abnormality observed was isolated APTT prolongation in 8 (11.9%) patients. Isolated PT prolongation was observed in 6 (8.9%) patients. Both PT and APTT were prolonged in 2 (2.9%) patients. Fibrinogen levels were not affected in any of the patients. Study by Gogia A et al., also found isolated prolonged APTT as the most frequent abnormal screening coagulation test [4]. In their study, prolonged PT, APTT and TT were observed in 14

(48.3%), 20 (69%) and 10 (34.5%) patients, respectively. Huang H et al., retrospectively analysed 101 newly diagnosed MM patients and found prolonged PT and APTT in 8.9% and 5% patients, respectively [9]. In their study prolonged TT was the most frequent abnormality found in 77% of patients. Geng C et al., found isolated prolonged PT as the most frequent abnormality observed in 22.3% patients [2]. In their study both PT and APTT were prolonged in 17.5% patients and isolated APTT was prolonged in 3.5% patients. Their results also demonstrated that prolonged PT or APTT is an independent poor prognostic factor in newly diagnosed MM patients. Pandey S et al., also found isolated prolonged PT (25%) as the most frequent abnormality in patients with MM and other plasma cell disorders [5].

Plasma fibrinogen levels were not affected in any of the patients in the present study. This was in contrast to other studies which have shown both elevated and reduced levels of fibrinogen [4,10]. Fibrinogen is a glycoprotein produced by liver which also acts as an acute phase reactant. Elevated fibrinogen levels in myeloma can result from production of proinflammatory cytokines like IL6 while decreased functional levels could be due to paraprotein interference causing dysfibrinogenemia. Hu M et al., observed minimal increase in fibrinogen levels in myeloma patients compared to healthy individuals but it did not show statistically significant elevation with progression of disease [10]. In the study by Gogia A et al., 34.5% and 37.9% patients showed elevated and decreased fibrinogen levels, respectively [4]. Studies have shown association between elevated fibrinogen levels and reduced overall survival in solid tumours and haematologic malignancies [11,12]. A reduced Albumin Fibrinogen Ratio (AFR) has been found to be associated with increased thrombotic risks and reduced survival in newly diagnosed MM patients [13,14].

Bleeding manifestations were found in 16 (23.9%) patients in the present study and the bleeding manifestations were found to be significantly associated with presence of coagulation abnormalities. All of the patients had only mucocutaneous bleeds. Though bleeding manifestations as initial presentation in myeloma is rare, there are several isolated case reports and case series describing bleeding manifestations ranging from mucocutaneous bleeds to life threatening GI, intracranial, retroperitoneal bleeds in myeloma [15-17]. These bleeding tendencies could be due to a variety of mechanisms which include thrombocytopenia due to bone marrow infiltration, paraprotein induced platelet dysfunction, Acquired Von Willibrand Syndrome (AVWS), acquired dysfibrinogenemia, acquired FIX deficiency, and acquired FX deficiency, acquired heparin like anticoagulant, hyperviscosity [18,19]. Acquired factor deficiencies could be due to adsorption of specific factors on amyloid deposits or paraproteins interacting with the coagulation protein impairing its function and resulting in bleeding symptoms. Development of clearance antibodies that bind to the non-functional domain of VWF and cause rapid clearance by the reticuloendothelial system have been proposed as a mechanism of AVWS [20]. Patients with heparin like antibody presented with unexplained prolonged TT and severe bleeding manifestations. Saadalla A et al., in their study has demonstrated that negatively charged sialic acid residues on M proteins may mimic anticoagulant properties of Heparin by interacting with antithrombin and accelerating thrombin inhibition [21].

A significant association was observed in patients with more than 5% plasmablastic morphology in bone marrow and the presence of coagulation abnormalities. Plasmablastic myeloma has been defined as a morphologic subtype of myeloma with >2% plasmablasts in bone marrow aspirate as proposed by Greipp PR et al., [22]. In the present study, plasmablastic morphology was noted in 12 cases and plasmablasts constituted 5 to 10 % of nucleated cells in the bone marrow. Studies have linked plasmablastic morphology to more aggressive disease course with frequently elevated B2 microglobulin, plasma cell labelling index, CRP, creatinine and lower albumin levels and poor prognosis with shorter event free survival and overall survival [23]. Association with coagulation abnormalities has not reported in any previous studies in literature. The significant association was

found in our study could be likely due to the aggressive biological behaviour, higher tumour burden and inflammatory cytokine milieu associated with plasmablastic myeloma.

A significant association between abnormal coagulation function and higher ISS stage of the disease (Fisher-Freeman-Halton exact test, p -value <0.001) was also observed in the present study. The ISS is based on serum β_2 -microglobulin and albumin concentration which reflects tumour burden and disease severity. Patients with advanced ISS stage generally exhibit greater plasma cell infiltration, increased inflammatory activity, renal impairment, hyperviscosity all of which contribute to abnormalities in the coagulation cascade. Hu M et al., in their study on 371 newly diagnosed MM patients and 48 normal controls similarly concluded that coagulation abnormalities in MM increases with disease stage [10]. Huang H et al., found no significant correlation between prolonged APTT and stage of myeloma while significant increase in PT was observed as stage of myeloma increased [9].

Further large scale multicentric studies involving larger patient cohorts and longitudinal follow-up are needed to better understand the pathogenesis, treatment response, and prognostic implications of haemostatic abnormalities in MM.

Limitation(s)

The single-centre design limits the generalisability of the findings to the wider Indian population. The study analysed only the screening coagulation tests in MM patients and cases with abnormal coagulation tests were not further assessed with mixing studies, factor assays or platelet function assays to characterise the cause of the abnormal screening tests.

CONCLUSION(S)

This study observed that acquired coagulation abnormalities can occur in a significant proportion of newly diagnosed MM patients and can be associated with advanced ISS stage and plasmablastic morphology, which represents a more aggressive disease variant. Routine coagulation screening should be incorporated in management of MM patients, especially those in advanced ISS stages or with plasmablastic morphology. Patients with abnormal coagulation parameters should be monitored closely for bleeding risks and treated accordingly. Early intervention for coagulation abnormalities may improve patient outcomes by preventing severe haemorrhagic complications.

Author contribution: LEL and GJ- involved in acquisition of data, analysis and interpretation of data and drafting the manuscript. PVP and VL- involved in analysis and interpretation of data and drafting the article.

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