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RESEARCH

A comprehensive analysis of bone marrow-derived cytogenetic abnormalities in multiple myeloma patients with extramedullary disease

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Abstract

Background Extramedullary disease (EMD) in multiple myeloma (MM) remains a critical clinical challenge due to its aggressive behavior and resistance to conventional therapies. While cytogenetic abnormalities are recognized contributors to MM progression, their specific roles in EMD pathogenesis—particularly in distinguishing bone marrowderived profiles between EMD and non-EMD patients—remain inadequately characterized.

Methods In this comprehensive study, we analyzed 41 published studies involving 9424 MM patients, and identified EMD in 32.2% (3038) of cases. Our aim was to elucidate the bone marrow-derived cytogenetic profiles of MM patients with EMD, comparing them to those without EMD.

Results Among EMD-MM patients, the most prevalent abnormalities were del(13q)/del RB1 (32.3%), 1q21+ (29.6%), and hyperdiploidy (26.3%). High-risk cytogenetic abnormalities were led by 1q21+ (29.6%), del(17p)/del p53 (14.4%), and t(4;14) (13.6%). Notably, 1q21+ was the most frequent aberration in the EM-E subgroup, accounting for 32.2% of cases. Comparative analyses revealed significantly higher frequencies of del(17p)/del p53 and del(13q)/del RB1 in EMD patients compared to non-EMD patients, along with a slightly higher frequency of 1q21+. Conversely, EMD patients exhibited lower frequencies of hyperdiploidy and t(11;14) promoting MM evolution. Subgroup analyses confirmed these trends and revealed a more pronounced prevalence of del(13q)/del RB1 in the EM-E subgroup.

Conclusions Our findings underscore the importance of integrating cytogenetic data into risk stratification for MM patients with EMD. These results also highlight the need for further research to elucidate the mechanisms underlying cytogenetic abnormalities in EMD and their clinical implications.

Keywords Multiple myeloma · Extramedullary disease · Cytogenetic abnormalities · Bone marrow · Comparative analysis

Introduction

Multiple myeloma (MM) is a plasma cell malignancy typically confined to tumor cells within the bone marrow (BM). However, at any stage of the disease, clonal plasma cells (PCs) may occasionally migrate to extramedullary sites, resulting in extramedullary disease (EMD) or extramedullary myeloma (EMM) (Bhutani et al. 2020). Two main types of EMD are recognized in the literature: para-skeletal or extramedullary bone-related (EM-B), referring to plasmacytomas extending from contiguous bone lesions; and extraskeletal or extramedullary-extraosseous (EM-E), involving distant soft tissue or organ infiltration due to hematogenous spread (Bhutani et al. 2020; Touzeau and Moreau 2016; Blade et al. 2011; Rosiñol et al. 2021). The presence of EMD, particularly EM-E, indicates an unfavorable prognosis

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(Blade et al. 2011; Usmani et al. 2012; Pour et al. 2014; Jagosky and Usmani 2020; Zanwar et al. 2023; Jiménez-Segura et al. 2022) and is generally categorized as high-risk or even ultra-high-risk (Rosiñol et al. 2021; Rees and Kumar 2024; Rees et al. 2024; Costa and Usmani 2020). These patients often exhibit resistance to standard therapies and are prone to early relapse or progression after treatments, including autologous stem cell transplantation (ASCT) (Gagelmann et al. 2023). Emerging therapies, such as CAR T-cell therapy and bispecific antibodies, also face challenges in managing EMD (Xu et al. 2024; Riedhammer et al. 2024; Liu et al. 2024; Li et al. 2024; Hashmi et al. 2024; Gagelmann et al. 2024). Recent studies have linked EMD to high-risk chromosomal abnormalities and complex genomic traits (Bhutani et al. 2020; Pawlyn and Morgan 2017; Manier et al. 2017). Within the BM microenvironment, genetic accumulation and clonal evolution allow better-adapted clones to dominate, facilitating the extramedullary dissemination of MM cells (Bhutani et al. 2020). This consequently promotes the progression of the disease from intramedullary myeloma to EMM, a more aggressive and treatment-resistant phenotype (Bhutani et al. 2020). Therefore, understanding the distinct cytogenetic signatures in EMD patients is crucial and warrants further investigation.

To address this gap, we conducted this comprehensive analysis of published clinical studies to clarify the BM-derived cytogenetic abnormalities observed in EMD-MM patients, specifically in comparison to non-EMD patients. Our findings may offer insights for future research on MM clonal evolution and targeted therapies for EMD.

Materials and methods

Eligible studies and their characteristics

We conducted a systematic search of PubMed until March 2025 for original articles detailing cytogenetic findings in MM patients with EMD, using the search terms ((myeloma[Title/Abstract]) OR (plasmacytoma[Title/Abstract])) AND (extramedullary[Title/Abstract]). Articles were required to be in English. We included prospective studies, retrospective studies, and case series with five or more available cases. Excluded were editorials, review articles, conference abstracts, and posters. Eligible studies reported cytogenetic aberrations in EMD-MM patients detected by fluorescence in situ hybridization (FISH) and/or conventional karyotyping. Studies focusing on the cytogenetics of MM in the general population without detailed information on the EMD subgroup, as well as studies on cell lines or animal models, were excluded. Additionally, studies exclusively examining solitary extramedullary plasmacytoma, plasma cell leukemia (PCL), special types associated with HIV or EBV, or MM comorbid with another malignancy were also excluded. Data extracted from the included articles encompassed study details, patient characteristics at MM diagnosis, onset time of EMD (classified as primary if at MM diagnosis and secondary if at MM relapse), type of EMD (classified as EM-B for extramedullary bone-related and EM-E for extramedullary-extraosseous), and cytogenetic analysis results. Both primary articles and supplemental materials were available for all included studies. Studies without publicly accessible cytogenetic data were excluded (Fig. 1).

Statistical methods

We employed the chi-square test or Fisher's exact test for comparing categorical variables. Statistical significance was determined at $p < 0.05$. Statistical analyses were performed via GraphPad Prism 10 (GraphPad Software, USA).

Results

Summary of eligible studies and patients

Our systematic literature search initially identified 2834 citations. After removing duplicates and screening titles and abstracts, we retrieved 465 publications for full-text review. Ultimately, 41 publications met the inclusion criteria. The details of these publications and the general characteristics of patients from the 41 eligible studies are summarized in Table 1, with additional details provided in Table S1**.** In total, 9424 MM patients were described: 3038 (32.2%) had EMD, while 6366 (67.6%) did not. The reported incidence of EMD varied between 2.5% and 33.3% (Table S1). Regarding cytogenetic detection methods, among the 41 included studies: 22 (53.6%) used FISH exclusively, 7 (17.1%) used combined FISH/karyotyping, and 12 (29.3%) did not specify the detection method. Among the EMD-MM patients, 1760 (57.9%) were diagnosed at initial presentation, 1049 (34.6%) at relapse, and in 229 cases (7.5%), the timing of EMD onset was unavailable. EMD patients were subdivided into two types based on anatomic classification: 1328 (43.7%) had only para-skeletal EMD (EM-B), 1545 (50.9%) had extra-skeletal EMD with or without concomitant EM-B (EM-E, sometimes referred to as true EMD (Weinstock and Ghobrial 2013)), and the type of EMD was unspecified in 205 cases (6.7%). Additionally, 165 patients (5.4%) had central nervous system (CNS) involvement, and 12 (0.4%) had EMD accompanied by secondary PCL. Cytogenetic information was publicly accessible for 5808 patients, representing 61.6% of the total, making these individuals candidates for further pooled analyses.

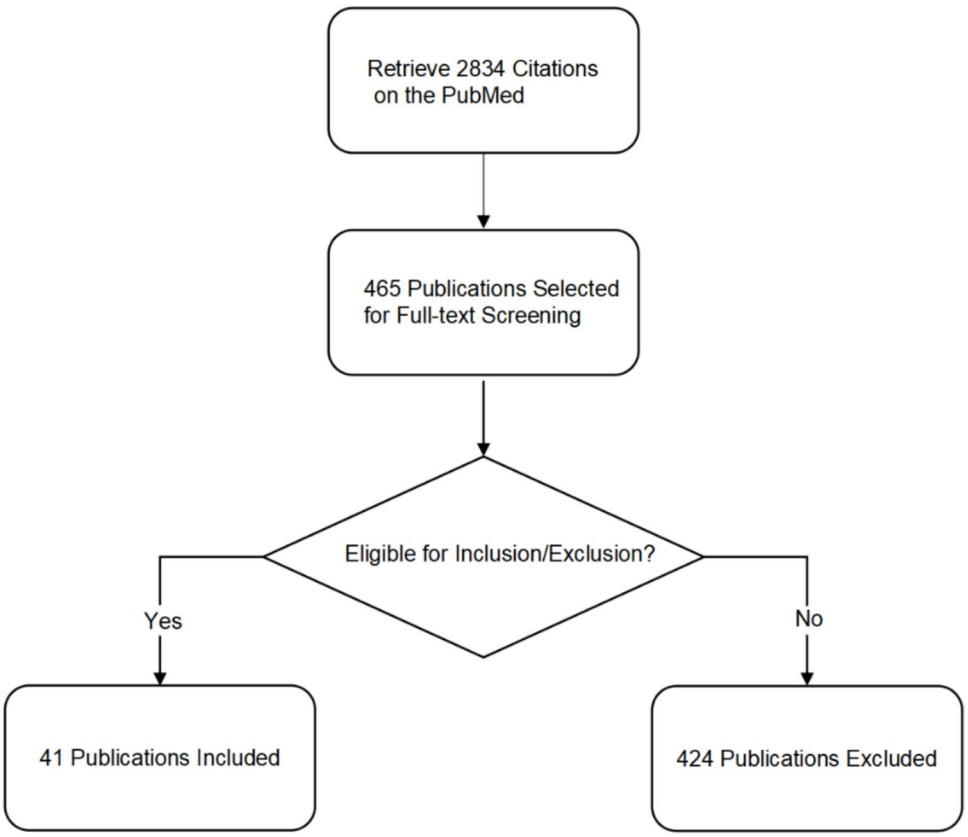

Fig. 1 Flowchart of Literature Screening Process. This figure illustrates the process of literature screening conducted for the study

Clinical characteristics of EMD-MM patients

The baseline clinical characteristics of the EMD-MM patients are summarized in Table 2, with further details for each eligible study provided in Table S2. Across 41 studies involving 3038 EMD patients, the sex distribution was 1309 men and 860 women, with 869 patients of unspecified sex. The age at diagnosis ranged from 25 to 94 years. According to the International Staging System (ISS) for MM, 1623 patients (53.4%) were classified as stage I or II, 812 (26.7%) as stage III, and 603 (19.8%) had an unknown ISS stage. For Durie-Salmon (D-S) staging, 18.6% of patients were in stage III. Regarding the Revised ISS (R-ISS), 7.1% of patients were in stage III. However, a significant number of patients had unavailable staging information, with 2290 (75.4%) lacking D-S staging and 2121 (69.8%) lacking R-ISS staging. Among patients with available data on M protein subtype, the monoclonal component of IgG, IgA, IgD, and IgM type was reported in 34.6%, 16.0%, 1.6%, and 0.2% of patients, respectively. Notably, 15.9% of patients had light chain myeloma, and 3.1% had nonsecretory myeloma. The ratio of patients with kappa to lambda light chain restriction was 1.26 (593:469).

Given the diverse nature of EMD, we specifically assessed the characteristics of primary EMD and EM-E, while secondary EMD and EM-B were excluded from the subgroup analysis for reasons detailed in the discussion section. In total, 15 studies on primary EMD and 23 studies on EM-E, encompassing 1,155 and 830 patients, respectively, were eligible for further cytogenetic analysis. The clinical characteristics of these groups are presented in Table 2 and Table S3 (for each eligible study). Among patients with primary EMD, 761 (65.9%) had EM-B, and 352 (30.5%) had EM-E. Conversely, among patients with EM-E, 256 (30.8%) had primary EMD, and 518 (62.4%) had secondary EMD. Notably, CNS involvement was rarely observed in patients with primary EMD, whereas it occurred in up to 17.1% of EM-E patients. Additionally, the incidence of IgD-type myeloma increased to 2.2% among EM-E patients.

Cytogenetic characteristics of EMD-MM patients

Due to limitations in the original data, the cytogenetic analysis of clonal plasma cells in EMD patients was based solely on BM samples collected during the initial diagnosis of MM. The incidence of various cytogenetic abnormalities in EMD patients is presented in Table 3 and Fig. 2, with further details in Tables S4 and S5.

Overall, 2,278 of 3,038 (75.0%) EMD patients were eligible for cytogenetic studies. Specifically, in the primary EMD and EM-E subgroups, 1011 of 1155 (87.5%) and 597 of 830 (70.2%) patients had cytogenetic information, respectively.

Table 1 Summary of MM patients in 41 eligible studies

ID	PMID	N	Median age (range)	Gender			Cytogenetics		With EMD		Occurence of EMD			Type of EMD			EMD location	
				Male	Female	NA	n	%	−	+	Pimary	Secondary	NA	Only EM-B	EM-E with or w/o EM-B	NA	CNS involved	With sPCL
Prospective study																		
1	24,038,024	226	60.8(27.9 ~ 83.5)	115	111	0	51	22.6	171	55	0	55	0	23	32	0	2	0
2	33,512,480	18	53.5(38 ~ 66)	10	8	0	18	100.0	13	5	NA	NA	5	NA	NA	5	NA	1
3	34,314,018	97	65.0(60 ~ 70)	51	46	0	97	100.0	75	22	NA	NA	22	NA	NA	22	NA	NA
4	34,421,924	20	57.5(38 ~ 77)	12	8	0	20	100.0	13	7	0	7	0	0	7	0	NA	NA
5	34,980,210	16	58.5(48 ~ 78)	NA	NA	16	16	100.0	8	8	NA	NA	8	NA	NA	8	NA	NA
6	36,274,163	32	56(34 ~ 71)	22	10	0	23	71.9	0	32	18	14	0	9	23	0	2	0
7	39,558,020	30	62 (55–81)	5	5	0	10	33.3	0	10	0	10	0	5	5	0	1	0
Retrospective study																		
8	21,932,386	100	NA	49	51	0	39	39.0	50	50	18	32	0	0	50	0	50	0
9	22,286,070	24	56(41 ~ 79)	15	9	0	19	79.2	0	24	0	24	0	NA	24	0	5	0
10	23,000,906	5	56(46 ~ 70)	3	2	0	5	100.0	0	5	0	5	0	0	5	0	0	0
11	23,368,088	30	68(41 ~ 81)	19	10	1	17	56.7	0	30	8	21	1	11	19	0	1	1
12	24,395,149	36	58.6(31 ~ 78)	23	13	0	8	22.2	0	36	20	16	0	0	36	0	36	0
13	24,526,137	18	NA	13	5	0	18	100.0	7	11	3	8	0	0	11	0	1	0
14	25,640,025	834	58(26 ~ 86)	530	304	0	387	46.4	794	40	40	0	0	0	40	0	5	0
15	25,812,994	58	53(34 ~ 66)	34	24	0	58	100.0	0	58	NA	NA	58	38	20	0	0	0
16	25,833,301	55	52(34 ~ 66)	35	20	0	29	52.7	0	55	13	42	0	0	55	0	3	0
17	25,984,534	300	NA	NA	NA	300	175	58.3	259	41	27	14	0	8	33	0	4	0
18	26,432,667	31	64(44–82)	17	14	0	25	80.6	0	31	2	29	0	15	16	0	0	0
19	27,206,246	14	50.5(30 ~ 69)	9	5	0	9	64.3	0	14	2	12	0	0	14	0	NA	NA
20	28,770,558	114	NA	61	53	0	114	100.0	70	44	30	14	0	NA	NA	44	NA	NA
21	30,719,772	21	61(NA)	13	8	0	11	52.4	0	21	0	21	0	8	13	0	0	0
22	31,221,778	2332	NA	NA	NA	2332	1694	72.6	2065	267	267	0	0	243	12	12	NA	NA
23	31,278,209	226	62(34 ~ 87)	NA	NA	226	111	49.1	0	226	130	96	0	50	176	0	14	0
24	31,288,095	488	59(25 ~ 77)	287	201	0	488	100.0	0	488	488	0	0	374	114	0	NA	NA
25	31,334,859	127	63(27 ~ 94)	76	51	0	88	69.3	0	127	20	107	0	0	127	0	14	5
26	32,118,627	10	65(48 ~ 76)	6	4	0	5	50.0	0	10	4	6	0	0	0	10	0	0
27	32,191,818	8	56(31 ~ 65)	4	4	0	7	87.5	0	8	NA	NA	8	0	8	0	0	1
28	33,686,665	13	62(52 ~ 72)	NA	NA	13	11	84.6	0	13	3	10	0	0	13	0	13	NA
29	33,792,474	43	57(47.5 ~ 65)	25	18	0	33	76.7	0	43	NA	NA	43	0	43	0	10	2
30	34,268,123	17	63(44 ~ 74)	12	5	0	8	47.1	0	17	13	4	0	10	7	0	0	0
31	34,726,261	2326	NA	1211	1115	0	629	27.0	2092	234	0	234	0	143	71	20	NA	NA
32	35,248,783	226	61(26 ~ 85)	144	82	0	226	100.0	160	66	66	0	0	43	23	0	0	0

Table 1 (continued)

ID	PMID	N	Median age (range)	Gender			Cytogenetics		With EMD		Occurence of EMD			Type of EMD			EMD location	
				Male	Female	NA	n	%	–	+	Primary	Secondary	NA	Only EM-B	EM-E with or w/o EM-B	NA	CNS involved	With sPCL
33	36,697,375	315	69(37 ~ 94)	192	123	0	272	86.3	307	8	1	7	0	0	8	0	3	0
34	37,304,491	12	55(47 ~ 68)	7	5	0	12	100.0	7	5	5	0	0	0	5	0	1	0
35	37,421,603	299	59.7(18–89.3)	NA	NA	299	236	78.9	0	299	95	204	0	0	299	0	NA	NA
36	37,479,009	35	56(43 ~ 75)	23	12	0	25	71.4	0	35	0	35	0	11	24	0	NA	NA
37	37,568,580	17	65(49 ~ 72)	12	5	0	17	100.0	8	9	6	3	0	0	9	0	NA	NA
38	37,941,401	22	67(47 ~ 76)	13	9	0	18	81.8	0	22	3	19	0	0	22	0	NA	2
39	38,206,369	107	63(38 ~ 89)	72	35	0	92	86.0	0	107	107	0	0	79	28	0	0	0
40	39,695,462	371	NA	224	147	0	371	100.0	0	371	371	0	0	258	153	0	NA	NA
41	38,845,015	351	NA	202	149	0	316	90.0	267	84	NA	NA	84	NA	NA	84	NA	NA
Total		**9424**	**NA(25 ~ 94)**	**3546**	**2671**	**3187**	**5808**	**61.6**	**6366**	**3038**	**1760**	**1049**	**229**	**1328**	**1545**	**205**	**165**	**12**

M. male, *F.* famale, *NA* not available, *EMD* extramedullary disease, *Pri.* primary, *Sec.* secondary, *EM-B* extramedullary-bone related, *EM-E* extramedullary-extraosseous, *CNS* central nervous system, *sPCL* secondary plasma cell leukemia

Del(13q)/del RB1 and high-risk cytogenetic abnormalities (HRCA), including 1q21 +, del(17p)/del p53, and t(4;14), were prevalent among patients with EMD and its subgroups. Other cytogenetic abnormalities involving translocations of chromosome 14, such as t(11;14), t(14;16), and t(14;20), were less common.

Del(13q)/del RB1 consistently emerged as the most common abnormality in both overall EMD and primary EMD, with incidence rates of 32.3% (444/1376) and 32.6% (115/353), respectively. The prevalence of del(13q)/del RB1 was followed by the three most frequent HRCAs: 1q21 +, del(17p)/del p53, and t(4;14). In all EMD cases, the incidence rates for these abnormalities were 29.6%, 14.4%, and 13.6%, respectively, whereas in primary EMD, the rates were 17.5%, 17.3%, and 15.7%, respectively. Within the EM-E subgroup, 1q21 + stood out as the most frequent abnormality, present in 141 of 438 cases (32.2%). This was followed by del(13q)/del RB1 in 167 of 528 cases (31.6%), del(17p)/del p53 in 93 of 585 cases (15.9%), and t(4;14) in 83 of 579 cases (14.3%). Additionally, hyperdiploidy was observed in 98 of 372 (26.3%) overall EMD patients, 22 of 101 (21.8%) with primary EMD, and 70 of 292 (24.0%) with EM-E.

Cytogenetic comparison between EMD-MM and non-EMD patients

To ensure a fair comparison, we selected studies that provided cytogenetic data specifically for both EMD-MM and non-EMD patients. The identified cytogenetic abnormalities and associated clinical features are detailed in Tables 4 and 5 and Fig. 3.

Among the 41 studies on EMD, 15 met the criteria for comparison, encompassing a total of 943 EMD-MM patients and 6,052 non-EMD patients. Cytogenetic data were available for 57.9% (546/943) of EMD patients and 53.7% (3,250/6,052) of non-EMD patients. Our analysis revealed that EMD patients exhibited significantly higher frequencies of del(17p)/del p53 (19.4% vs. 14.5%, $p = 0.004$) and del(13q)/del RB1 (52.7% vs. 45.4%, $p = 0.032$). There was also a tendency toward a higher occurrence of 1q21 + in EMD patients (44.7% vs. 39.6%, $p = 0.1050$). Conversely, EMD patients had significantly lower incidences of hyperdiploidy (25.0% vs. 41.2%, $p = 0.020$) and t(11;14) (11.4% vs. 17.7%, $p = 0.023$) compared to non-EMD patients. No significant differences were observed in the frequencies of t(4;14) and t(14;16) between the two groups. Details of all eligible studies are provided in Table S6.

Similar comparative analyses were conducted for subgroups of patients with primary EMD or EM-E. Among the six selected studies from the aforementioned 15, 69.7% (304/436) of primary EMD patients and 67.3% (2241/3,330) of non-EMD patients had comparable cytogenetic data.

Table 2 Baseline clinical characteristics of EMD-MM patients

Clinical characteristics	Overall EMD (N = 3038, 41 eligible studies)		Primary EMD (N = 1155, 15 eligible studies)		EM-E (N = 830, 23 eligible studies)	
Age, years, median(range)	NA(25 ~ 94)		NA(25 ~ 89)		NA(26 ~ 94)	
	n	%	n	%	n	%
Gender						
Male	1309	43.1	485	42.0	319	38.4
Female	860	28.3	305	26.4	198	23.9
NA	869	28.6	365	31.6	313	37.7
DS stage						
I ~ II	183	6.0	61	5.3	20	2.4
III	565	18.6	220	19.0	114	13.7
NA	2290	75.4	874	75.7	696	83.9
ISS stage						
I ~ II	1623	53.4	664	57.5	371	44.7
III	812	26.7	263	22.8	228	27.5
NA	603	19.8	228	19.7	228	27.5
R-ISS stage						
I ~ II	702	23.1	224	19.4	142	17.1
III	215	7.1	53	4.6	89	10.7
NA	2121	69.8	878	76.0	596	71.8
M protein subtype						
IgG	1050	34.6	430	37.2	322	38.8
IgA	485	16.0	183	15.8	156	18.8
IgD	49	1.6	7	0.6	18	2.2
IgE	0	0.0	0	0.0	0	0.0
IgM	5	0.2	2	0.2	3	0.4
Light chain only	484	15.9	214	18.5	160	19.3
Non-secretory	94	3.1	30	2.6	12	1.4
NA	871	28.7	289	25.0	159	19.2
Light chain restriction						
KAP	593	19.5	185	16.0	319	38.4
LAM	469	15.4	171	14.8	226	27.2
Non-secretory	94	3.1	30	2.6	12	1.4
NA	1882	61.9	769	66.6	273	32.9
Occurence of EMD						
Primary	1760	57.9	1155	100.0	256	30.8
Secondary	1049	34.5	0	0.0	518	62.4
NA	229	7.5	0	0.0	56	6.7
Type of EMD						
Only EM-B	1328	43.7	761	65.9	0	0.0
EM-E with or w/o EM-B	1545	50.9	352	30.5	830	100.0
NA	205	6.7	42	3.6	0	0.0
EMD location						
With CNS involvement	165	5.4	14	1.2	142	17.1
With sPCL	12	0.4	0	0.0	11	1.3

NA not available, *EMD* extramedullary disease, *EM-B* extramedullary-bone related, *EM-E* extramedullary-extraosseous, *DS* Durie-Salmon, *ISS* International Staging System, *R-ISS* revised ISS, *CNS* central nervous system, *sPCL* secondary plasma cell leukemia

Table 3 Cytogenetic characteristics of EMD-MM patients

Cytogenetic characteristics	Overall EMD			Primary EMD			EM-E		
	(N = 3038, 41 eligible studies)			(N = 1155, 15 eligible studies)			(N = 830, 23 eligible studies)		
Cytogenetics available, %(n)	75.0 (2278)			87.5 (1011)			70.2 (597)		
	n	available	%	n	available	%	n	available	%
Cytogenetics abnormalities									
Hyperdiploidy	98	372	26.3	22	101	21.8	70	292	24.0
t(4;14)	305	2237	13.6	158	1005	15.7	83	579	14.3
t(14;16)	78	1980	3.9	39	972	4.0	33	469	7.0
t(14;20)	13	877	1.5	12	565	2.1	7	391	1.8
t(11;14)	135	1339	10.1	34	344	9.9	55	557	9.9
del(17p)/del p53	321	2234	14.4	174	1006	17.3	93	585	15.9
1q21 +	498	1684	29.6	142	813	17.5	141	438	32.2
del13q/del RB1	444	1376	32.3	115	353	32.6	167	528	31.6

EMD extramedullary disease, *EM-E* extramedullary-extraosseous

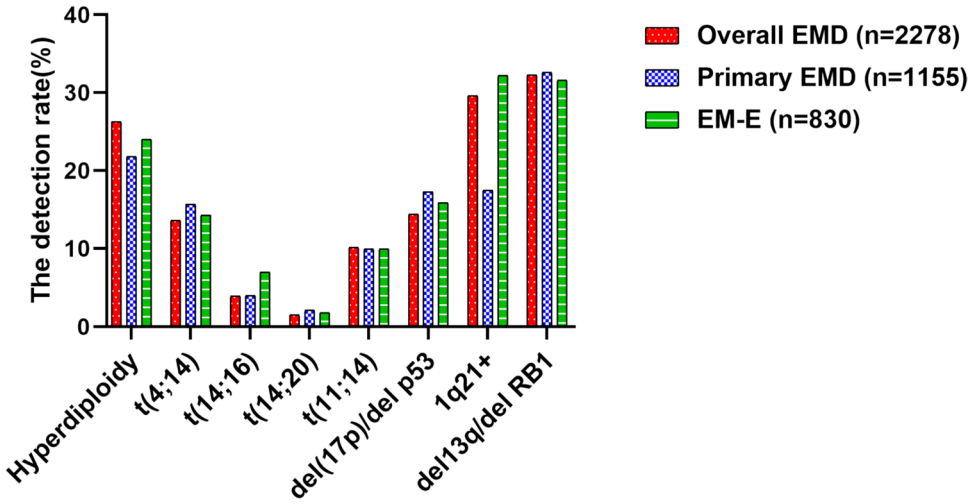

Fig. 2 Bone Marrow Cytogenetic Profiles in EMD Patients at MM Diagnosis. This figure illustrates the distribution of cytogenetic abnormalities in bone marrow samples from EMD patients at the time of MM diagnosis. *EMD* extramedullary disease, *EM-E* extramedullary-extraosseous

Compared to non-EMD patients, those with primary EMD showed a significantly higher prevalence of del(17p)/del p53 (20.1% vs. 13.3%, p = 0.0017) and a lower rate of t(11;14) (9.7% vs. 18.5%, p = 0.0121). Primary EMD patients also exhibited a slightly higher incidence of 1q21 + compared to non-EMD patients (37.0% vs. 34.4%, p = 0.5954). However, there were no significant differences in the frequencies of del(13q)/del RB1, t(4;14), or t(14;16) between primary EMD and non-EMD groups. Notably, hyperdiploidy could not be evaluated in this subgroup. Comprehensive details of each eligible study are presented in Table S7.

For the EM-E subgroup, six additional comparative studies were selected from the 15 related studies. Overall, 73 of 131 (55.7%) EM-E patients and 550 of 1,131 (48.6%) non-EMD patients were included. This subgroup also showed a significantly higher incidence of del(17p)/del p53 (21.7% vs. 12.5%, p = 0.0366) and a lower occurrence of t(11;14) (10.9% vs. 21.8%, p = 0.0366). Additionally, EM-E patients tended to have higher rates of del(13q)/del RB1 (54.4% vs. 46.7%, p = 0.3208) and t(14;16) (12.0% vs. 5.0%, p = 0.0989), and a lower occurrence of t(4;14) (13.3% vs. 18.4%, p = 0.2469). No significant differences were observed in the incidence of 1q21 + and hyperdiploidy. Detailed information for each eligible study is provided in Table S8.

Discussion

Despite significant advancements in therapeutic modalities, the prognosis for EMD-MM patients, particularly those with EM-E, remains poor. Cytogenetic aberrations contribute to myeloma evolution and EMD pathogenesis (Bhutani et al. 2020; Pawlyn and Morgan 2017), yet common abnormalities such as del(13q), 1q21 +, del(17p), and t(4;14) are also

Table 4 Clinical comparison in patients with EMD vs without EMD

Characteristics	15 comparing studies		6 comparing studies		6 comparing studies	
	overall EMD (N = 943)	without EMD (N = 6052)	with primay EMD (N = 436)	without EMD (N = 3330)	with EM-E (N = 131)	without EMD (N = 1131)
Age, years, median(range)	NA(26 ~ 82)	NA(26 ~ 86)	NA(26 ~ 81)	NA(26 ~ 86)	NA(26 ~ 82)	NA(26 ~ 86)
Gender,%(*n*)						
Male	38.4 (362)	32.4 (1960)	25.5 (111)	18.9 (631)	62.6 (82)	48.2 (545)
Female	26.6(251)	26.3 (1589)	13.3 (58)	11.3 (375)	37.4 (49)	28.9 (327)
NA	35.0 (330)	41.4 (2503)	61.2 (267)	69.8 (2324)	0.0 (0)	22.9 (259)
DS stage,%(*n*)						
I	4.1 (39)	7.4 (446)	2.8 (12)	1.9 (62)	3.3 (4)	4.0 (45)
II	8.0 (75)	9.3 (563)	3.7 (16)	3.5 (116)	10.7 (14)	8.7 (98)
III	36.8 (347)	35.3 (2138)	30.7 (134)	24.7 (822)	58.0 (76)	62.0 (701)
NA	51.1 (482)	48.0 (2905)	62.8 (274)	70.0 (2330)	28.2 (37)	25.4 (287)
ISS stage,%(*n*)						
I	29.9 (282)	25.0 (1512)	39.2 (171)	25.4 (845)	24.4 (32)	10.8 (122)
II	25.2 (238)	28.3 (1713)	30.5 (133)	31.7 (1057)	22.9 (30)	21.0 (237)
III	19.9(188)	26.0 (1576)	21.1 (92)	25.5 (850)	22.9 (30)	24.5 (277)
NA	24.9(235)	20.7 (1251)	9.2 (40)	17.4 (578)	29.8 (39)	43.8 (495)
R-ISS stage,%(*n*)						
I	4.0 (38)	4.9 (294)	8.7 (38)	8.8 (294)	0.0 (0)	0.0 (0)
II	13.3 (125)	18.7 (1132)	28.7 (125)	34.0 (1132)	0.0 (0)	0.0 (0)
III	3.0 (28)	3.6 (215)	3.9 (17)	5.2 (173)	0.0 (0)	0.0 (0)
NA	79.7 (752)	72.9 (4411)	58.7 (256)	52.0 (1731)	100.0 (131)	100.0 (1131)
M protein subtype,%(*n*)						
IgG	25.6 (241)	29.3 (1772)	20.4 (89)	14.0 (464)	24.4 (32)	34.2 (387)
IgA	11.6 (109)	11.4 (689)	6.2 (27)	7.2 (239)	13.7 (18)	17.1 (193)
IgD	0.5 (5)	0.5 (28)	0.9 (4)	0.8 (25)	3.1 (4)	1.9 (21)
IgE	0	0	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
IgM	0.2 (2)	0.1 (6)	0.0 (0)	0.2 (5)	0.8 (1)	0.4 (4)
Light chain only	8.2 (77)	8.5 (512)	8.5 (37)	6.3 (211)	9.2 (12)	14.0 (158)
Non-secretory	1.4 (13)	1.1 (69)	0.7 (3)	1.0 (32)	1.5 (2)	2.3 (26)
NA	52.6 (496)	49.2 (2976)	63.3 (276)	70.7 (2354)	47.3 (62)	30.2 (342)
Light chain restriction,%(*n*)						
KAP	23.3 (220)	29.8 (1806)	15.6 (68)	14.8 (492)	19.1 (25)	35.5 (402)
LAM	18.0 (170)	20.9 (1265)	15.1 (66)	14.5 (483)	15.3 (20)	33.4 (378)
Non-secretory	1.4 (13)	1.1 (69)	0.7 (3)	1.0 (32)	1.5 (2)	2.3 (26)
NA	57.3 (540)	48.1 (2912)	68.6 (299)	69.8 (2323)	64.1 (84)	28.7 (325)

NA not available, *EMD* extramedullary disease, *EM-E* extramedullary-extraosseous, *DS* Durie-Salmon, *ISS* International Staging System, R-ISS revised ISS

frequently observed in non-EMD MM (Jagosky and Usmani 2020; Hagen et al. 2022; McAvera et al. 2023). The specific cytogenetic profiles that distinguish EMD and their precise roles in EMM pathogenesis are not yet fully understood. Our comprehensive study sheds new light on this issue.

By aggregating publicly available data from 41 eligible studies published before March 2025, we analyzed the BM-derived cytogenetic profiles of 2278 out of 3038 (75.0%) EMD-MM patients. To ensure a more rigorous comparison, we specifically selected studies that included cytogenetic data for both EMD and non-EMD patients. Our analysis of 2278 EMD patients from 41 studies revealed that EMD is characterized by higher frequencies of del(17p) and 1q21 +, along with lower rates of hyperdiploidy and t(11;14), compared to non-EMD MM. These findings suggest potential associations between specific cytogenetic abnormalities and extramedullary progression, warranting further investigation.

First, copy number abnormalities have been established as the most prevalent cytogenetic aberrations in EMD.

Table 5 Cytogenetic comparison in patients with EMD vs without EMD

Characteristics	15 comparing studies		*p* value	6 comparing studies		*p* value	6 comparing studies		*p* value
	Overall EMD (N = 943)	Without EMD (N = 6052)		with primay EMD (N = 436)	without EMD (N = 3330)		With EM-E (N = 131)	Without EMD (N = 1131)	
Cytogenetics									
Available cytogenetics, % (n)	57.9(546)	53.7(3250)		69.7 (304)	67.3 (2241)		55.7 (73)	48.6 (550)	
Cytogenetic abnormalities, % (n/available)									
Hyperdiploidy	25.0 (14/56)	41.2 (178/432)	0.020*	NA	NA	NA	18.2 (2/11)	14.3 (1/7)	> 0.9999
t(4;14)	14.2 (78/551)	15.2 (460/3029)	0.5340	13.9 (44/317)	14.8 (320/2169)	0.7341	13.3 (13/98)	18.4 (90/488)	0.2469
t(14;16)	3.8(17/451)	4.6 (126/2715)	0.4090	4.2 (12/285)	4.1 (85/2066)	0.8745	12.0 (6/50)	5.0 (19/377)	0.0989
t(14;20)	NA	NA	NA	NA	NA	NA	NA	NA	NA
t(11;14)	11.4 (25/220)	17.7 (167/946)	0.023*	9.7 (14/145)	18.5 (105/568)	0.0121*	10.9 (7/64)	21.8 (85/390)	0.0451*
del(17p)/del p53	19.4 (102/527)	14.5 (427/2945)	0.004**	20.1 (63/313)	13.3 (279/2104)	0.0017**	21.7 (18/83)	12.5 (53/425)	0.0366*
1q21 +	44.7 (135/302)	39.6 (523/1320)	0.1050	37.0 (44/119)	34.4 (176/511)	0.5954	46.3 (25/54)	43.5 (157/361)	0.7691
del13q/del RB1	52.7 (135/256)	45.4 (522/1151)	0.032*	43.5 (64/147)	42.1 (244/580)	0.7795	54.4 (31/57)	46.7 (182/390)	0.3208

NA not available, *EMD* extramedullary disease, *EM-E* extramedullary-extraosseous. *, $p < 0.05$; **, $p < 0.005$

Specifically, hyperdiploidy, a recognized initiating genetic event in MM development (Pawlyn and Morgan 2017; Hagen et al. 2022), stands out for its significantly lower incidence in EMD patients than in non-EMD patients. However, our understanding of hyperdiploidy within the EMD subgroup remains limited due to the scarcity of available cases. In contrast, secondary genetic events associated with MM progression, including del(13q)/del RB1, 1q21 +, and del(17p)/del p53 (Bhutani et al. 2020; Pawlyn and Morgan 2017; Hagen et al. 2022), consistently show higher prevalence in EMD patients. This cytogenetic distinction suggests that the selective accumulation of secondary genetic alterations may contribute to increased genomic instability and more aggressive clinical manifestations in EMD. Details are provided below.

Del(13q)/del RB1 emerged as the most commnon cytogenetic aberration in both the entire EMD cohort (32.3%) and primary EMD subgroup (32.6%). Notably, the incidence was significantly higher in overall EMD patients compared to non-EMD patients (52.7% vs. 45.4%, $p = 0.032$), suggesting a potential role in extramedullary progression. However, this association was not maintained in primary EMD or EM-E subgroup analyses, highlighting the biological heterogeneity among EMD subtypes. These findings underscore the need for comprehensive molecular profiling to elucidate the distinct pathogenic mechanisms of del(13q) across EMD variants and its potential interplay with co-occurring genetic lesions.

Our study revealed a marked prevalence of 1q21 + across EMD subtypes: 29.6% in overall EMD, 17.5% in primary EMD, and 32.2% in EM-E cases. Although the 1q21 + incidence trended higher in EMD than non-EMD cohorts, the lack of statistical significance precludes direct causality. Notably, recent evidence positions 1q21 + as an independent prognostic marker in EMD-MM and a predictor of secondary EM-E (Zanwar et al. 2023; Gao et al. 2024; Chen et al. 2022). Jelinek et al. identified 1q21 + in 86% (12/14) of EM-E tumor specimens using FISH and/or whole-exome sequencing (WES), with 79% showing concurrent MAPK pathway alterations (Jelinek et al. 2024). They demonstrated that 1q21 + combined with KRAS mutations at diagnosis significantly increases the risk of EMM progression (Jelinek et al. 2024). Mechanistically, 1q21 + reflects chromosomal instability, dysregulated gene expression, and epigenetic alterations, often coexisting with high-risk cytogenetic abnormalities to promote progression and therapeutic resistance (Schmidt et al. 2021). Clinically, it associates with aggressive phenotypes, including elevated tumor burden, osteolysis, and poor survival (Schmidt et al. 2021). However, the role of 1q21 + as a contributor versus bystander in genomic instability remains debated (Schmidt et al. 2021). In addition, controversy persists regarding 1q21 + copy number

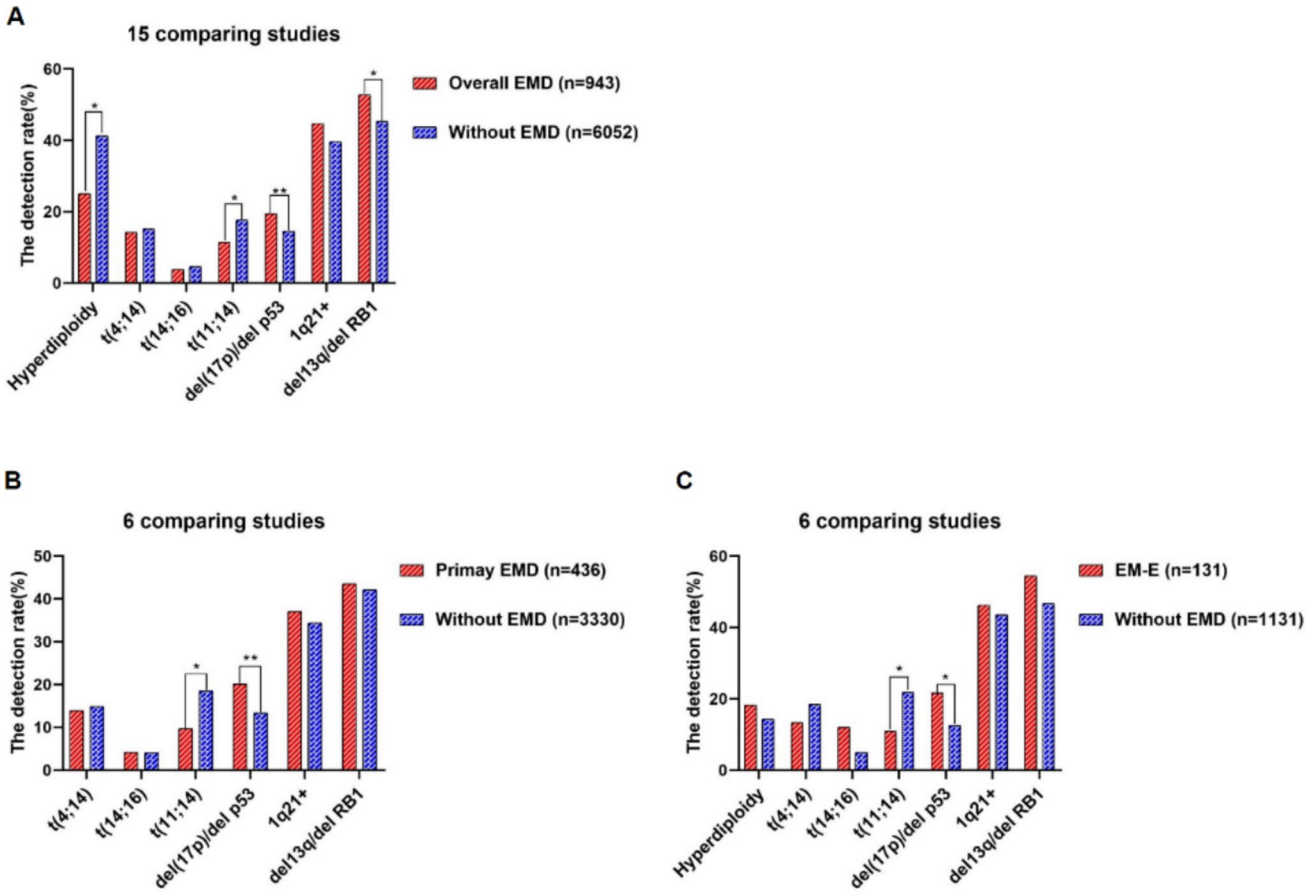

Fig. 3 Comparative analysis of cytogenetic profiles in multiple myeloma patients with different EMD manifestations. **A** Pooled data from 15 clinical studies comparing cytogenetic characteristics between patients with overall EMD manifestations and without EMD controls. **B** Subgroup analysis of 6 studies evaluating primary EMD presentations versus without EMD cases. **C** Focused comparison from 6 studies examining EM-E patients against without EMD counterparts. *EMD* extramedullary disease. *, $p < 0.05$; **, $p < 0.005$

variations (gain, 3 copies vs. amplification, ≥ 4 copies) and their prognostic implications (You et al. 2022; Locher et al. 2020). While some studies suggest amplification portends worse outcomes (You et al. 2022; Pasvolsky et al. 2024), others report no significant differences (Wang et al. 2023; Li et al. 2019). Regrettably, copy-number stratification was absent in all analyzed cohorts, underscoring the need for standardized methodologies to characterize 1q21 + CNVs (e.g., distinguishing gains from amplifications) to clarify their impact on EMD.

Del(17p)/del p53, an established high-risk cytogenetic abnormality (HRCA) in MM, has been consistently implicated in extramedullary disease pathogenesis (Blade et al. 2011). Our comprehensive analysis confirmed its prominent frequency, second only to del(13q)/del RB1 and 1q21 +. Notably, we observed significantly higher prevalence of del(17p)/TP53 across all EMD subtypes compared to non-EMD cases, reinforcing its universal association with extramedullary progression. These findings not only validate prior reports but also highlight TP53 inactivation as a potential unifying molecular feature in EMD development, with important implications for risk stratification and therapeutic targeting.

Second, immunoglobulin heavy chain (IgH) translocations—including t(11;14), t(4;14), t(14;16), and t(14;20)—were among the less frequent cytogenetic abnormalities in EMD. Like hyperdiploidy, these translocations, particularly t(11;14), are established early oncogenic contributors in MM (Pawlyn and Morgan 2017; Hagen et al. 2022). Intriguingly, our data revealed a significantly lower prevalence of t(11;14) in EMD compared to non-EMD cases (11.4% vs. 17.7%, $p = 0.023$), a trend consistently observed across primary EMD and EM-E subgroups. This inverse association raises the possibility that t(11;14) may confer a protective effect against extramedullary progression, though the mechanistic basis remains elusive. Notably, t(11;14) is the most prevalent primary translocation in MM (Bal et al. 2022) and defines a clinically distinct disease subset characterized by cyclin D1 overexpression and BCL-2-mediated anti-apoptotic signaling (Bal et al. 2022; Fonseca et al. 2002; Paner et al. 2020;

Kleber et al. 2023; Diamantidis et al. 2022). The reduced frequency of t(11;14) in EMD suggests that its associated molecular program—while promoting intramedullary myeloma growth—may simultaneously restrict the biological adaptations required for extramedullary dissemination. Further studies are needed to dissect whether this reflects differential clonal selection pressures or cell-intrinsic limitations in migration and survival within extramedullary niches.

Other recurrent IgH translocations—t(4;14), t(14;16), and t(14;20)—were identified in EMD patients at frequencies of 13.6%, 3.9%, and 1.5%, respectively. Particularly noteworthy is the concordance between our findings and Jelinek's cohort, both revealing unexpectedly reduced t(4;14) prevalence in EM-E (14.3% and 14%, respectively) compared to the historically reported 37% frequency (Jelinek et al. 2024; Besse et al. 2016). While these rates were numerically comparable to those in non-EMD cohorts ($p > 0.05$), the biological significance of these translocations in EMD pathogenesis should not be overlooked. The similar prevalence across disease sites suggests these alterations may represent early genomic events that precede extramedullary progression. Future investigations should focus on delineating whether specific molecular interactions or microenvironmental factors modify the clinical impact of these translocations in different EMD subtypes.

This study has several limitations that warrant consideration. Our comprehensive analysis not only provided insights into the cytogenetic landscape of EMD but also highlighted several critical limitations in current EMD genetic research. These include: i) Lack of standardized reporting on detection methods; ii) Limited data on co-occurring abnormalities; iii) Few studies with longitudinal genomic assessments. First, while all included studies employed well-established cytogenetic techniques (interphase FISH with or without conventional karyotyping), critical methodological details were rarely reported. Variations in FISH probe design (including target regions and cutoff thresholds), sample processing protocols, and cell selection methods (particularly CD138 + enrichment versus bulk marrow analysis) may affect the reported prevalence of cytogenetic abnormalities (Clarke et al. 2024). Standardized reporting of these technical parameters in future studies would improve cross-study comparability and data reliability. Second, the lack of individual patient data prevented adjusted analyses of coexisting abnormalities (such as 1q21 + with del(17p)), which may act synergistically to drive extramedullary progression. Future research incorporating comprehensive clinical-genomic datasets could help elucidate these potential interactions. Third, cytogenetic assessments were typically performed at MM diagnosis using bone marrow aspirates, which may not fully capture the genomic heterogeneity of extramedullary disease. Since EMD frequently originates from minor subclones that evolve under therapeutic pressure (Pawlyn and Morgan 2017; Manier et al. 2017), longitudinal profiling of paired bone marrow and extramedullary samples—ideally using advanced techniques like single-cell sequencing—could provide crucial insights into the clonal dynamics underlying EMD development. To address these challenges, we propose several key areas for future study: (i) Prospective studies with uniform FISH protocols; (ii) Comprehensive molecular profiling of paired BM-EMD samples; (iii) Investigation of clonal evolution patterns during EMD progression.

Notably, comparative research on secondary EMD or EM-B subgroups was not conducted for two reasons. First, most studies involving secondary EMD lacked serial genomic assessments at extramedullary relapse, making it difficult to analyze the associated cytogenetic landscape given the complex evolutionary biology of EMD progression. Second, due to its significant biological overlap with conventional intramedullary disease, EM-B was considered less suitable than EM-E for identifying differential cytogenetic features of EMD. Consequently, primary EMD (not involving treatment-induced clonal evolution) and EM-E (with presumed greater genomic divergence) were prioritized for subgroup analyses in this study.

Conclusions

Cytogenetic abnormalities exhibit differential patterns between EMD and non-EMD MM patients, characterized by significantly higher frequencies of secondary genetic events (del(17p)/del p53, del(13q)/del RB1 and 1q21 +) and lower frequencies of initiating events (hyperdiploidy and t(11;14)). These findings highlight the importance of detailed genetic testing in EMD to better understand disease development and improve risk assessment.

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Author contributions J.X. and HN.Y conducted the data collection and analysis, and prepared the manuscript. YH.Z. designed and supervised the research, and prepared the manuscript. L.Z. assisted with data interpretation and provided critical suggestions. YH.Z. and L.Z. contributed equally to this work as co-corresponding authors. H.J., N.T and C.S. provided critical suggestions. All authors have reviewed and approved the final version of this manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval The study was approved by the Ethical Review Committee of West China Hospital, Sichuan University. All methods used in this study follow the principles of the Declaration of Helsinki.

Informed consent N/A.

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