CANCER DIAGNOSIS & PROGNOSIS
4: 696-705 (2024) doi: 10.21873/cdp.10384

Thrombocytopenia With High C-reactive Protein in Myeloma Patients Treated With Proteasome Inhibitor and/or Immunomodulatory Drugs

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Abstract. *Background/Aim: Thrombocytopenia is a poor prognostic factor in patients with myeloma; however, the factors associated with thrombocytopenia have not been extensively discussed. This study aimed to investigate the clinical significance of thrombocytopenia, defined as 130×10^3/μl or less, in patients with newly diagnosed multiple myeloma (NDMM) treated with proteasome inhibitors and/or immunomodulatory drugs. Patients and Methods: This is a retrospective review of medical records of myeloma patients treated between 2000 and 2021. A total of 241 patients were included in this study, with a median age of 72 years. Overall survival (OS) and time to next treatment (TTNT) were assessed using Kaplan–Meier analysis and Cox regression analysis. Prognostic factors were evaluated by univariate and multivariate analyses. Results: The incidence of thrombocytopenia was 17.8%. In the median follow-up period of 46.6 months, OS and TTNT in the thrombocytopenia group were significantly shorter than those in the non-thrombocytopenia group using multivariate analysis ($p<0.001$ and $p<0.001$). C-reactive protein (CRP) level was not associated with thrombocytopenia, and high CRP predicted short OS and TTNT independently from thrombocytopenia. When the low (neither thrombocytopenia nor high CRP), intermediate (either thrombocytopenia or high CRP), and high (thrombocytopenia and high CRP) risk groups were defined, the OS and TTNT among these groups showed significant differences; the hazard ratios for survival in the high and intermediate risk groups were 7.022 and 2.598, and for TTNT, they were 4.216 and 1.887, respectively, compared to the low-risk group. Conclusion: Thrombocytopenia was associated with the activity of NDMM and predicted prognosis in NDMM. When combined with high CRP levels, thrombocytopenia serves as a new indicator of poor prognosis in these patients.*

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Key Words: Myeloma, thrombocytopenia, C-reactive protein, prognosis.

Multiple myeloma (MM) represents a heterogeneous group of plasma cell neoplasms, exhibiting variability in morphology, phenotype, molecular biology, and clinical behavior. The development of novel agents, such as proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), has improved patient prognosis over the last decade; however, MM remains incurable (1). Studies have identified numerous prognostic factors for survival, including disease stage according to the International Staging System (ISS) (2) or the Durie-Salmon staging system (3) and the detection of high-risk cytogenetic abnormalities (HRCA) using fluorescence *in situ* hybridization (FISH) (4, 5) in newly diagnosed multiple myeloma (NDMM).

Thrombocytopenia is associated with advanced-stage myeloma disease, leading to poor prognosis according to the previous article concerning the ISS criteria (2). This study underscores thrombocytopenia as a significant poor prognostic factor, second only to high beta-2-microglobulin. Nevertheless, thrombocytopenia was not considered in the ISS calculation owing to its relatively low incidence. The ISS was established prior to the availability of PIs and IMiDs

for NDMM. Prior research indicates that thrombocytopenia affects approximately 4.7-19% of patients and is a notable prognostic indicator for reduced survival times (2, 6-9). The half-life of platelets is shorter in myeloma patients than in healthy individuals (10), suggesting that thrombocytopenia might depend on myeloma disease. Additionally, myelosuppression, overconsumption, and coagulation abnormality can also be associated with thrombocytopenia. Elevated immature platelet fraction (IPF) can reflect the consumption of platelets (11). Coagulation abnormalities might be associated with thrombocytopenia caused by the monoclonal protein (M-protein) and several complications, including disseminated intravascular coagulation (DIC) (12). However, the factors related to thrombocytopenia have not been thoroughly analyzed in myeloma patients.

C-reactive protein (CRP) is a protein of the pentraxin family and is induced by inflammatory cytokines, such as interleukin (IL)-6 and IL-1, from hepatocytes (13, 14). CRP promotes myeloma cell proliferation and bone destruction (15); thus, a high CRP level predicts poor clinical outcomes in myeloma patients (16, 17). However, elevated IL-6 could induce thrombocytosis *via* stimulation of thrombopoietin (TPO) (18). Therefore, thrombocytopenia and CRP are associated with a poor prognosis in myeloma patients; however, their kinetics during inflammation – particularly the increase in IL-6 – may be opposite.

This retrospective study aimed to investigate the clinical significance of thrombocytopenia and CRP, as well as factors related to thrombocytopenia in patients with NDMM treated with PI and/or IMiDs.

Patients and Methods

We conducted a retrospective review of medical records of myeloma patients treated at the Jikei University Hospital and the Jikei University Kashiwa Hospital between January 2000 and March 2021, with follow-up until December 2023. The primary endpoint was the overall survival (OS). The secondary endpoints were the time to the next treatment (TTNT), treatment response, and factors associated with thrombocytopenia. OS was calculated from the date of diagnosis until death from any cause or the last follow-up, whereas TTNT was computed from the initiation of chemotherapy until the start of the next treatment or death. The study was approved by the independent ethics committee/institutional review board of our institution [33-147 (10762)].

Patients. Patients older than 20 years with newly diagnosed MM who had received PI and/or IMiDs as initial chemotherapy were included. MM was diagnosed according to the International Myeloma Working Group (19). Patients with monoclonal gammopathy of undetermined significance, smoldering MM, and primary plasma cell leukemia were excluded.

Treatment and response assessment. Patients who received PI and/or IMiDs containing standard chemotherapies were included in this study. The actual regimens were: bortezomib plus dexamethasone; bortezomib, melphalan plus prednisone; cyclophosphamide, bortezomib plus dexamethasone; lenalidomide plus dexamethasone; bortezomib, lenalidomide, and dexamethasone; daratumumab, bortezomib, melphalan plus prednisone; and daratumumab, lenalidomide, and dexamethasone. Patients who underwent high-dose melphalan followed by up-front autologous stem cell transplantation (ASCT) were also included in this study. Disease response was assessed according to the International Myeloma Working Group criteria (20).

Prognostic factors. Prognostic factors were collected from laboratory data and bone surveys using computed tomography at diagnosis. Thrombocytopenia was defined as a platelet count of 130×10^3/μl or less, according to a previous report on the ISS (2). The cutoffs for IPF, nuclear cell count (NCC), and plasma cell in bone marrow percent (BMPC) were defined as 5%, 100×10^3/μl, and 30%, respectively. Coagulation abnormality was defined as 10 μg/ml or more of fibrin/fibrinogen degradation product, 150 mg/dl or less of fibrinogen, or 1.25 or higher of prothrombin time ratio according to the criteria of diagnosis for DIC (21). Anemia, hypercalcemia, and renal dysfunction were defined according to the CRAB criteria (22). The cutoff values for age and performance status (PS) were 70 and 2 years, respectively. The cutoff value for CRP was 0.3 mg/dl, which is the upper normal limit. The cutoff value of lactate dehydrogenase (LDH) was 300 IU/l according to the R-ISS criteria (4). HRCA was defined as t(4;14), t(14;16), del17p, or 1q21 gain/ amplification according to FISH (5). Chemotherapies were categorized into two groups: PI- and IMiD-containing therapies. Patients treated with bortezomib, lenalidomide plus dexamethasone (BLD) regimen were categorized into the PI and IMiDs groups.

Statistical analysis. Fisher's exact test was used to compare various parameters. Actuarial survival analysis was performed using the Kaplan–Meier method, and the resultant curves were compared using the log-rank test. Multivariate analysis for survival was conducted using Cox regression analysis. All reported *p*-values are two-sided, and *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) (23), which is a modified version of R Commander that incorporates frequently used biostatistical functions.

Results

Patients and thrombocytopenia. A total of 241 patients were included in this study, with a median age of 72 years (range=38-96 years). Forty-three patients (17.8%) experienced thrombocytopenia. The platelet counts in the thrombo-cytopenia group ranged between $2.0\text{-}12.8\times10^3$/μl. The distribution of patients with PS 0-1 and 2-4 were 104 and 76, respectively, with PS data unknown for 61 patients. The number of patients treated with PI, IMiDs, and combined PI and IMiDs therapy were 205, 89, and 54, respectively. Sixty-three patients underwent up-front ASCT. Patients with thrombocytopenia exhibited significantly higher frequencies of anemia, elevated LDH, increased IPF percentages, high BMPC, reduced megakaryocyte percentages,

Table I. *Patient characteristics*.

	Thrombo-cytopenia (n=43)	Non-thrombo-cytopenia (n=198)	*p*-Value
Age median 72 year (range=38-96 years)			
>70 years	23	112	0.737
≤70 years	20	86	
Sex			
Male	26	96	0.180
Female	17	102	
Performance status			
0, 1	15	89	0.363
2, 3, 4	14	62	
Missing	14	47	
Type of monoclonal protein			
IgG	16	96	0.238
Non-IgG	27	102	
Anemia			
Yes	38	124	0.001
No	5	74	
Bone disease			
Yes	26	120	0.252
No	14	48	
Missing	3	30	
Hypercalcemia			
Yes	7	35	0.999
No	36	162	
eGFR			
≤40 ml/min	12	56	0.175
>40 ml/min	27	136	
Missing	4	6	
Serum CRP			
≥UNL	13	78	0.301
<UNL	30	120	
Serum LDH			
≥300 U/l	10	15	0.005
<300 U/l	33	183	
Immature platelet fraction			
≥5%	11	8	<0.001
<5%	31	185	
Missing	1	5	
Nuclear cell count			
≥100×10^3/μl	7	41	0.087
<100×10^3/μl	28	142	
Missing	8	15	
Plasma cell percent			
≥30%	18	64	0.037
<30%	15	109	
Missing	10	25	
Megakaryocyte count			
≥50/μl	2	26	0.044
<50/μl	33	157	
Missing	8	15	
Coagulation abnormality			
Yes	21	53	0.014
No	21	141	
Missing	1	4	
ISS			
Stage 1 or 2	19	128	0.024
Stage 3	21	55	
Missing	3	15	
High risk cytogenetic abnormality			
Yes	9	32	0.411
No	13	80	
Missing	21	86	
R-ISS			
Stage 1 Or 2	20	101	0.139
Stage 3	7	13	
Missing	16	84	

eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; ISS: international staging system; UNL: upper normal limit.

coagulation disorders, and ISS stage 3 compared to those without thrombocytopenia. No significant association was found between thrombocytopenia and other factors. The characteristics of patients in the thrombocytopenia and non-thrombocytopenia groups are depicted in Table I.

Response and survival concerning thrombocytopenia. The overall response rate (ORR), very good partial response rate (VGPRR), and complete response rate (CRR) were 76.3%, 35.7%, and 19.1% in all patients, respectively. There was no significant relationship between thrombocytopenia and treatment response. The ORR between patients with and without thrombocytopenia was 69.8% and 79.0% (p=0.277), the VGPRR between patients with and without thrombocytopenia was 41.8% and 40.0% (p=0.864), and the CRR between patients with and without thrombocytopenia was 14.0% and 21.5% (p=0.301), respectively.

The median follow-up period for survival was 46.6 months (range=0.6-145.3 months). The 3-year OS rate in the patients with thrombocytopenia was significantly lower than that in those without [49.1% and 77.3%, respectively; hazard ratio (HR)=2.363; 95% confidence interval (CI)=1.510-3.699; p<0.001; Figure 1A]. Older age, poor PS, anemia, bone disease, high CRP, ISS stage 3, coagulation abnormality, ASCT, and achievement of complete response (CR) were identified as prognostic factors for OS using univariate analysis. In the multivariate analysis, thrombocytopenia was a significant prognostic factor for short OS (HR=2.216; 95%CI=1.386-3.542; p<0.001). The 3-year TTNT rate in patients with thrombocytopenia was significantly lower than

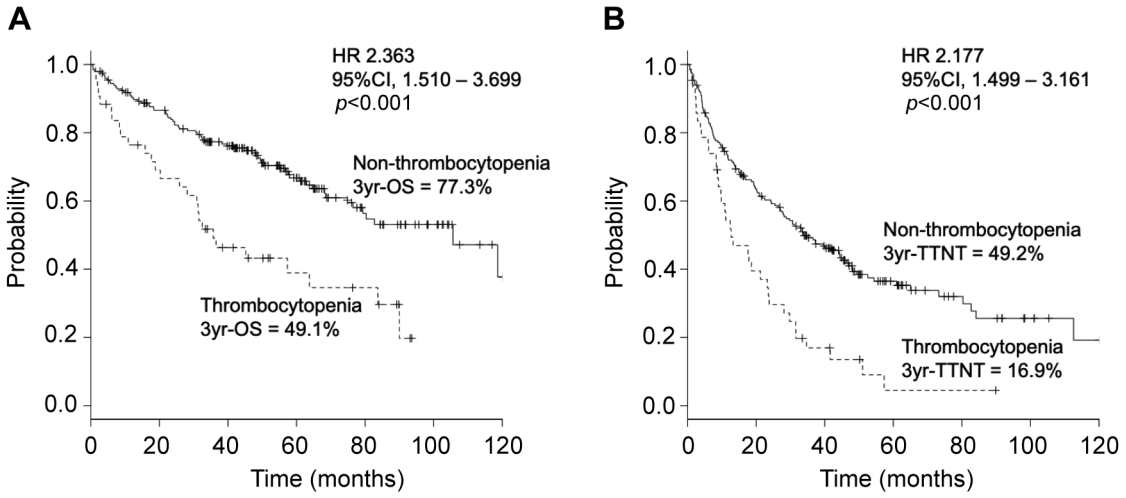

Figure 1. *Overall survival (OS) and time to next treatment (TTNT) between patients with and without thrombocytopenia. The median follow-up period for survival was 46.6 months (range=0.6-145.3 months). The 3-year OS (A) and TTNT rates (B) in the patients with thrombocytopenia were significantly lower than those without thrombocytopenia. HR: Hazard ratio; CI: confidential interval.*

that in patients without thrombocytopenia (16.9% and 49.2%, respectively; HR=2.177; 95%CI=1.499-3.161; $p<0.001$; Figure 1B). Male sex, poor PS, anemia, hypercalcemia, high CRP, high BMPC, coagulation abnormality, ISS stage 3, IMiDs-containing first-line treatment, ASCT, and achievement of CR were identified as prognostic factors for TTNT using univariate analyses. In the multivariate analysis, thrombocytopenia was identified as a significantly poor prognostic factor for TTNT (HR=1.984; 95%CI=1.315-2.994; $p<0.001$). CR was associated with longer OS and TTNT in the non-thrombocytopenia group, significantly ($p<0.001$ and <0.001), whereas no significant differences in OS and TTNT were observed between CR and non-CR patients within the thrombocytopenia group ($p=0.803$ and 0.269). High CRP levels also predicted short OS (HR=2.543; 95%CI=1.615-4.006; $p<0.001$) and TTNT (HR=1.842; 95%CI=1.291-2.630; $p<0.001$) using the multivariate analysis. Summaries of the univariate and multivariate analyses for OS and TTNT are shown in Table II.

Prognostic value of thrombocytopenia combined with high CRP. Thrombocytopenia and high CRP were poor prognostic factors for OS and TTNT, whereas there was no significant association between thrombocytopenia and CRP ($p=0.301$). Therefore, we divided all patients into four groups using platelets and CRP. Compared to the non-thrombocytopenia with low CRP group, the OS was significantly shorter in the thrombocytopenia with high CRP (HR=7.022; 95%CI=3.503-14.08; $p<0.001$), thrombocytopenia with low CRP (HR=2.686; 95%CI=1.463-4.933; $p=0.001$), and non-thrombocytopenia with high CRP groups (HR=2.562; 95%CI=1.589-4.133; $p<0.001$; Figure 2A). Similarly, the TTNT was significantly shorter in the thrombocytopenia with high CRP (HR=4.230; 95%CI=2.264-7.904; $p<0.001$), thrombocytopenia with low CRP (HR=2.334; 95%CI=1.466-3.718; $p<0.001$), and non-thrombocytopenia with high CRP groups (HR=1.741; 95%CI=1.217-2.491; $p=0.002$; Figure 2B). Finally, we categorized all patients into three risk groups: low-risk (neither thrombocytopenia nor high CRP), intermediate-risk (either thrombocytopenia or high CRP), and high-risk (thrombocytopenia and high CRP). The 3-year OS rates for the low, intermediate, and high-risk groups were 87.7% (reference), 60.4% (HR=2.598; 95%CI=1.664-4.056; $p<0.001$), and 30.8% (HR=7.022; 95%CI=3.503-14.08; $p<0.001$; Figure 2C), respectively. The 3-year TTNT rates for these groups were 59.4% (reference), 29.8% (HR=1.887; 95%CI=1.359-2.619; $p<0.001$), and 8.4% (HR=4.216; 95%CI=2.257-7.877]; $p<0.001$; Figure 2D), respectively.

Discussion

The incidence of thrombocytopenia in this study was 17.8%, consistent with previous studies (2, 6-9). Thrombocytopenia was associated with poor prognosis in patients with NDMM treated with PI and/or IMiDs, similar to previous studies (2, 6, 7). Thrombocytopenia was not associated with the NCC but BMPC and high IPF, suggesting that thrombocytopenia might reflect not myelosuppression but the activity of myeloma disease and consumption of platelets. Thrombocytopenia and high CRP independently predicted short OS and TTNT in patients with NDMM, and a new prognostic factor was developed using thrombocytopenia and high CRP.

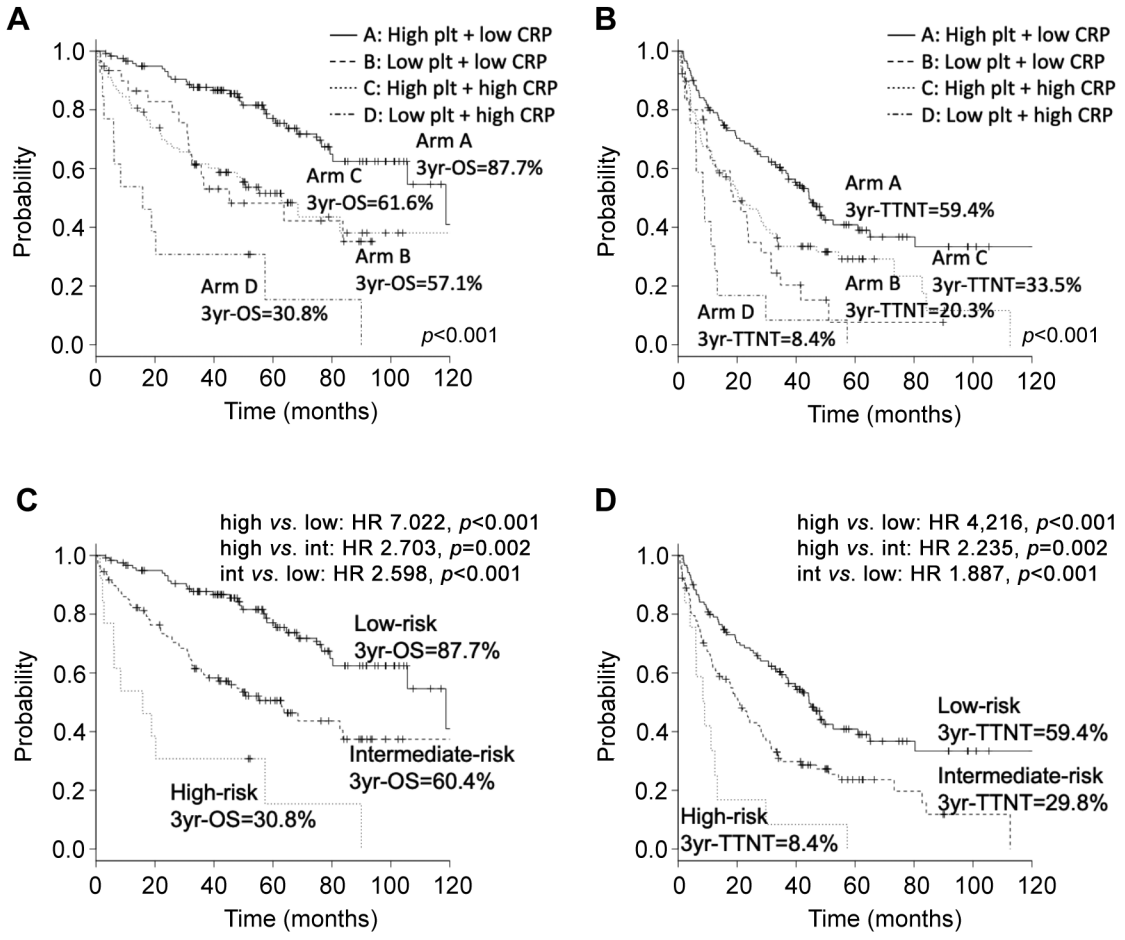

Figure 2. *Overall survival (OS) and time to next treatment (TTNT) among the thrombocytopenia with and without coagulation abnormality and the non-thrombocytopenia groups. The 3-year OS (A) and TTNT (B) among the non-thrombocytopenia with low C-reactive protein (CRP), thrombocytopenia with high CRP, non-thrombocytopenia with low CRP, and thrombocytopenia with high CRP groups were significantly different. In a new prognostic model using thrombocytopenia and CRP, the 3-year OS (C) and TTNT (D) among the high, intermediate, and low-risk groups were also significantly different. plt: Platelet; HR: hazard ratio; int: intermediate; CI: confidential interval.*

Thrombocytopenia was identified as a poor prognosis factor for OS according to several studies (2, 6, 7). The HR for thrombocytopenia was 1.63 for OS in the original article based on ISS criteria, despite differing treatment strategies at that time (2). In real-world evidence from a Japanese database, thrombocytopenia with a cutoff value of $8.2\times10^3/\mu l$ was predictive of shorter OS, despite approximately a quarter of patients being treated with cytotoxic agents (24). A meta-analysis of five randomized trials revealed that thrombocytopenia, with a cutoff value of $15\times10^3/\mu l$, significantly increased the risk of mortality and severe infection in patients undergoing bortezomib-based induction therapy followed by ASCT (25). Additionally, thrombocytopenia can lead to the reduction of therapeutic doses during treatment. Continuing PIs may help achieve a deeper response by maintaining therapeutic doses while preventing adverse events (26). For patients who initially have thrombocytopenia, the dose intensity may need to be reduced more frequently due to thrombocytopenia-related adverse events (27). Therefore, the adverse effects of thrombocytopenia on survival have been increasingly reported, even after the availability of PIs and IMiDs. Our study, which included patients treated with PIs and/or IMiDs regardless of transplant eligibility, found that thrombocytopenia was an independent predictor of survival time, irrespective of age.

However, whether thrombocytopenia can also predict treatment response remains unclear. Generally, treatment response is associated with survival time; for instance, a higher response is typically linked to a longer survival time (28, 29). However, HRCA was related to the early achievement of VGPR and short survival time (30, 31). There was no significant difference in survival time between the CR and non-CR groups among patients with thrombocytopenia; however, survival time

Table II. *Univariate and multivariate analysis of time to next treatment.*

	OS					TTNT				
	Univariate		Multivariate model			Univariate		Multivariate model		
	3 year-OS (%)	*p*-Value	Hazard ratio	95%CI	*p*-Value	3 year-TTNT (%)	*p*-Value	Hazard ratio	95%CI	*p*-Value
Thrombocytopenia										
Yes	49.1%	<0.001	2.216	1.386-3.542	<0.001	16.9%	<0.001	1.984	1.315-2.994	0.001
No	77.3%		Reference			49.2%		Reference		
Age										
>70 years	67.6%	0.030	1.292	0.785-2.127	0.313	41.6%	0.541			
≤70 years	78.2%		Reference			45.9%				
Sex										
Male	70.1%	0.357				37.3%	0.030	1.332	0.947-1.873	0.100
Female	74.4%					49.8%		Reference		
Performance status										
0, 1	77.8%	0.021	Reference			53.7%	0.016	Reference		
2, 3, 4	67.3%		1.352	0.786-2.326	0.276	35.5%		1.307	0.883-1.935	0.181
Missing	68.8%					36.3%		1.188	0.773-1.826	0.433
Type of monoclonal protein										
IgG	71.4%	0.653				46.2%	0.211			
Non-IgG	73.0%					41.2%				
Anemia										
Yes	66.5%	0.013	1.618	0.950-2.757	0.077	37.8%	<0.001	1.508	0.988-2.302	0.057
No	83.9%		Reference			55.1%		Reference		
Bone disease										
Yes	69.9%	0.027	1.643	0.981-2.751	0.059	41.6%	0.285			
No	73.1%		Reference			46.3%				
Missing	81.2%		0.505	0.209-1.219	0.129	47.1%				
Hypercalcemia										
Yes	63.7%	0.100				31.3%	0.013	1.363	0.890-2.088	0.155
No	73.9%					45.8%		Reference		
eGFR										
≤40 ml/min	66.4%	0.502				43.7%	0.378			
>40 ml/min	74.5%					42.8%				
Missing	75.0%					60.0%				
Serum CRP										
≥UNL	57.1%	<0.001	2.543	1.615-4.006	<0.001	30.1%	0.002	1.842	1.291-2.630	<0.001
<UNL	81.6%		Reference			51.5%		Reference		
Serum LDH										
≥300 U/l	51.0%	0.303				28.3%	0.220			
<300 U/l	74.6%					45.2%				
Immature platelet fraction										
≥5%	57.9%	0.227				22.3%	0.180			
<5%	73.9%					45.3%				
Missing	62.5%					50.0%				
Nuclear cell count										
≥100×10^3/µl	70.9%	0.197				41.4%	0.375			
<100×10^3/µl	78.9%					52.9%				
Missing	67.8%					38.7%				
Plasma cell percent										
≥30%	69.5%	0.377				35.3%	0.027	1.191	0.817-1.737	0.363
<30%	73.8%					50.2%		Reference		
Missing	73.2%					39.8%		0.867	0.518-1.452	0.587
Megakaryocyte count										
≥50/µl	68.8%	0.843				42.6%	0.972			
<50/µl	73.2%					44.2%				
Missing	67.8%					38.7%				

Table II. *Continued*

Table II. *Continued*

	OS					TTNT				
	Univariate		Multivariate model			Univariate		Multivariate model		
	3 year-OS (%)	*p*-Value	Hazard ratio	95%CI	*p*-Value	3 year-TTNT (%)	*p*-Value	Hazard ratio	95%CI	*p*-Value
Coagulation abnormality										
Yes	57.9%	0.029	1.076	0.691-1.674	0.746	35.0%	0.049	0.823	0.568-1.192	0.302
No	78.4%		Reference			46.7%		Reference		
Missing	75.0%		0.795	0.103-6.130	0.826	60.0%		1.201	0.354-4.079	0.768
ISS										
Stage 1 or 2	78.6%	0.006	Reference			49.4%	0.003	Reference		
Stage 3	61.4%		1.035	0.640-1.673	0.889	33.3%		0.867	0.590-1.275	0.469
Missing	66.2%		1.203	0.567-2.553	0.631	37.5%		0.997	0.512-1.938	0.992
High risk cytogenetic abnormality										
Yes	70.7%	0.177				45.5%	0.177			
No	76.8%					48.6%				
Missing	68.8%					60.0%				
R-ISS										
Stage 1 or 2	75.3%	0.195				47.8%	0.173			
Stage 3	62.3%					37.2%				
Missing	70.4%					39.5%				
PI containing treatment										
Yes	74.1%	0.066				43.0%	0.937			
No	61.9%					48.0%				
IMiD containing treatment										
Yes	78.8%	0.325				58.0%	<0.001	0.654	0.442-0.967	0.033
No	68.3%					34.8%		Reference		
Autologous stem cell transplant										
Yes	90.2%	<0.001	0.658	0.327-1.327	0.243	64.9%	<0.001	0.808	0.517-1.264	0.351
No	65.7%		Reference			35.6%		Reference		
Treatment response										
CR	93.8%	<0.001	0.192	0.079-0.462	0.002	68.6%	<0.001	0.365	0.221-0.601	<0.001
Non-CR	66.1%		Reference			36.1%		Reference		

OS: Overall survival; TTNT: time to next treatment; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; ISS: international staging system; PI: proteasome inhibitor; IMiD: immunomodulatory drug; CR: complete response; UNL: upper normal limit.

was significantly longer in the CR group compared to the non-CR group among patients without thrombocytopenia in our cohort. Therefore, we conclude that a favorable treatment response does not always translate to extended survival time, particularly in patients with high-risk features. Consequently, attention should be given to the risk of recurrence and death in patients with thrombocytopenia, even when CR is achieved.

Pathogenesis of thrombocytopenia has not been well-analyzed, although thrombocytopenia has been identified as a poor prognostic factor for survival in patients with myeloma. The incidence of anemia in the thrombocytopenia group was significantly higher than that of the non-thrombocytopenia group in this study, suggesting that a common pathogenesis of thrombocytopenia and anemia might be present. The cause of anemia was not only attributed to myelosuppression but also to various factors, including IL-6, IL-1, tumor necrosis factor-alpha, hepcidin, and erythropoietin deficiency in myeloma patients (32-35). However, IL-6 increases platelet count *via* stimulating TPO (18); thus, elevated IL-6 might not be the common cause of anemia and thrombocytopenia. Furthermore, the half-life of platelets in the patients with myeloma was significantly shorter than that in healthy individuals (10), and the platelet count was lower in the advanced disease stages than in the non-advanced stage (2, 10, 36). In our study, thrombocytopenia was related to high BMPC and IPF percentages, whereas thrombocytopenia was not associated with the NCC. Therefore, we considered that the cause of thrombocytopenia was not myelosuppression but overconsumption of platelets by the progression of myeloma disease.

CRP predicted short OS and TTNT independently from thrombocytopenia in our study. CRP is increased by IL-6, which can induce proliferation of myeloma cells *via* secretion

from myeloma and bone marrow stromal cells (37). Recently, Jiang *et al*. reported that high CRP reduced the immune response of $CD8^+$ T-cell in myeloma patients (38), which plays a key role in extending survival time (39). Therefore, CRP can be a biomarker for prognosis in myeloma patients from the proliferative and immunological point of view. In our retrospective study, high CRP was associated with anemia (p=0.003) but was not related to thrombocytopenia. These results appear reasonable given the role of IL-6. However, unlike thrombocytosis, thrombocytopenia, consistent with prior studies, predicted clinical outcomes, suggesting a potential discrepancy in the pathogenesis of thrombocytopenia and elevated CRP when considering IL-6's role in myeloma. We hypothesized that thrombocytopenia might result from an overconsumption of platelets owing to myeloma disease activity rather than from thrombocytosis induced by IL-6. Subsequently, we developed a new prognostic model based on thrombocytopenia and elevated CRP. In this model, thrombocytopenia coupled with high CRP, classified as high-risk, likely indicates platelet overconsumption and increased IL-6 levels owing to intense myeloma disease activity. Conversely, the intermediate-risk group may exhibit either platelet overconsumption or elevated IL-6.

Study limitations. We did not evaluate several factors that contribute to thrombocytopenia and coagulation abnormality, such as TPO and IL-6. These factors play an important role in thrombocytopenia and thrombotic events in patients with myeloma, suggesting that the causes of thrombocytopenia and coagulation abnormalities could be investigated more thoroughly. Additionally, several parameters, such as bone marrow testing data, were partially lacking because this was a retrospective study using a real-world dataset. Some patients were diagnosed not by 10% or more of BMPC but by the presence of plasmacytoma in the bone marrow sample obtained *via* needle biopsy. To further our understanding, the clinical significance of thrombocytopenia and elevated CRP should be studied in future large-scale prospective trials.

Conclusion

Thrombocytopenia was observed in 17.8% of the patients with NDMM treated with PI and/or IMiDs. The thrombocytopenia group showed significantly shorter OS and TTNT compared to the non-thrombocytopenia group despite having similar treatment responses between the two groups. The pathogenesis of thrombocytopenia might be overconsumption of platelets by myeloma disease beyond thrombocytosis because of inflammatory conditions, such as high IL-6. Thrombocytopenia with high CRP predicted shorter OS and TTNT compared with the other groups, including thrombocytopenia with low CRP and non-thrombocytopenia with high CRP. However, because our sample size was small, larger-scale studies are required to further our understanding of the optimal treatment for these patients.

Conflicts of Interest

K. Suzuki received personal fees from Takeda Pharmaceutical Company, Janssen Pharmaceutical K.K., Sanofi, Bristol Myers Squibb, Ono Pharmaceutical Co., Ltd., outside the submitted work; K. Nishiwaki reports personal fees from Kyowa Hakko Kirin Co, Ltd, outside the submitted work; Dr. Yano reports grants from Kyowa Kirin, grants from Astella Pharma, grants from Chugai Pharma, grants from Mochida Pharma, grants from Lilly Pharma, grants from Takeda Pharma, grants from MDS Pharma, grants from Pfizer, grants from Dai Nippon Sumitomo Pharma, grants from Ono Pharma, outside the submitted work; the other Authors declare that they have no conflict of interest.

Authors' Contributions

Conception and design: Kazuhito Suzuki. Analysis and interpretation of data: Tadahiro Gunji, Masaharu Kawashima, Hideki Uryu, Riku Nagao, Takeshi Saito, Kaichi Nishiwaki, and Shingo Yano. Writing, review, and revision of the manuscript: Kazuhito Suzuki.

Acknowledgements

The Authors would like to thank the attending doctors and nurses at the Jikei University Hospital and the Jikei University Kashiwa Hospital. The Authors would also like to extend gratitude to the myeloma patients and their families for consenting to participate in our study.

Funding

The Authors have no direct financial interest.

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Received August 15, 2024
Revised September 6, 2024
Accepted September 9, 2024