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Risk of stroke in patients with newly diagnosed multiple myeloma: a retrospective cohort study

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Abstract

Cerebrovascular events are a common complication among patients with cancer, increasing morbidity and mortality. However, the association between multiple myeloma and cerebrovascular events remains unclear. We therefore investigated multiple myeloma patients' risk factors for stroke to devise a better stroke-prevention strategy. This study includes consecutive patients 20 years and older who were newly diagnosed with symptomatic multiple myeloma at Taipei Veterans General Hospital, a tertiary medical center, between January 1, 2002 and December 31, 2014. The primary outcome was stroke development. Patients with head injuries, brain tumors, brain parenchymal invasions, or antecedent malignancies were excluded. Hazard ratios (HRs) of stroke risk factors for multiple myeloma patients were estimated by Cox proportional regression analysis. Overall, 395 patients with a median age of 70 years were investigated. In the median follow-up period of 18 months, cerebrovascular events occurred in 16 patients, including 10 ischemic strokes and 6 hemorrhagic strokes. The 5-year estimated cumulative incidence rate was 7.45%. In the multivariate analysis, the κ light chain isotype (adjusted HR, 8.37; 95% confidence interval [CI], 1.91-39.8), previous cerebrovascular accidents (adjusted HR, 5.16; 95% CI, 1.48-17.9), and serum creatinine > 2 mg/dL (adjusted HR, 4.21; 95% CI, 1.10-16.0) were identified as independent risk factors for stroke. Subgroup analysis showed that atrial fibrillation (adjusted HR, 8.07) and previous cerebrovascular accident (adjusted HR, 4.89) are significant risk factors for ischemic stroke. Serum creatinine > 2 mg/dL (adjusted HR, 30.6) and previous cerebrovascular accident (adjusted HR, 13.9) are significant for hemorrhagic stroke. Moreover, therapeutic strategies for multiple myeloma were not associated with stroke in our study. This study demonstrates that risk of stroke increases in myeloma patients with a κ light chain isotype, previous cerebrovascular events, and renal impairment. Further prospective clinical studies to clarify the relationship between multiple myeloma and stroke are warranted.

KEYWORDS

arterial thrombosis, cerebrovascular event, κ light chain isotype, multiple myeloma, stroke

1 | INTRODUCTION

Cerebrovascular accidents are prevalent among cancer patients.[1] It has been an important cause of morbidity and mortality in patients with malignancies. The neurologic sequelae following cerebrovascular complications may affect patients' life of quality. Furthermore, the cost of acute stroke is remarkable and serious for family and health care systems.[2–4]

Venous thrombosis is a well-recognized complication among multiple myeloma (MM). The introduction of immunomodulatory drugs in MM had brought venous thromboembolism (VTE) to our attention.[5] In contrast to VTE, the incidence of stroke in MM patients was rarely reported.[6,7] In a population-based data from Sweden, the stroke incidence was higher in the MM cohort than in the comparison cohort. The hazard ratio (HR) was 1.5 at 1 year of follow-up and 1.2 at 5 years of follow-up.[6] However, risk factors for predicting stroke in MM were

not completely understood.[6,7] We therefore designed this retrospective study so as to identify the risk factors with development of stroke in MM patients.

2 | METHODS

2.1 | Study population

This is a retrospective cohort study, including patients with newly diagnosed MM at Taipei Veterans General Hospital from January 1, 2002 to December 31, 2014. Individuals with solitary plasmacytoma, smoldering myeloma, and monoclonal gammopathy of undetermined significance (MGUS) were not included in the cohort. We excluded patients who had brain parenchymal injuries, defects or invasions, or with a history of malignancy. Patients' clinical information, cytogenetics, immunophenotyping, stage, therapeutic strategies, and comorbidities were assessed for further analysis. All patients were observed until loss of follow-up, death, or June 30, 2015. This study was approved by Taipei Veterans General Hospital's Institutional Review Board (No. 2014-12-001AC).

2.2 | Outcome measures

We followed the American Heart Association/American Stroke Association's 2013 definition of stroke,[8] as acute neurological dysfunction with evidence of vascular infarction or hemorrhage in neuroimaging, including computed tomography and magnetic resonance. Strokes that occurred after diagnosis of MM or those concurrent with diagnosis were recorded. Transient ischemic attacks were not analyzed in this study.

2.3 | Statistical analysis

The characteristics of MM patients in this study are shown as the total number (n) and proportion (%). Categorical variables were compared between the stroke group and nonstroke group by Pearson χ^2 test. Hazard ratio and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models to test the risk factors. All risk factors with $P < .1$ in the univariate model were further included in the multivariate analysis. Therapeutic modalities and exposures of antiplatelet or anticoagulant agents were analyzed as time-dependent covariates to eliminate immortal time bias. The cumulative incidence was determined by means of Kaplan-Meier estimation. Statistical analysis was performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, North Carolina) or STATA statistical software (version 12.1; StataCorp, College Station, Texas).

3 | RESULTS

3.1 | Clinical characteristics of the study population

From January 1, 2002 to December 31, 2014, a total of 441 patients with newly diagnosed MM were identified at the Taipei Veterans General Hospital. We excluded 46 patients, including 34 with prior or concurrent malignant neoplasms, 4 with head injuries and subdural hematomas, 2 with benign brain tumors, and 6 with brain parenchymal invasions. The final cohort thus included 395 (89.6%) patients with a median follow-up of 18 months (interquartile range, 2.93-42.4 months). The median age was 70 years (interquartile range, 59-78 years), and 65.8% of the patients were male. International Staging System (ISS) stage 1, stage 2, and stage 3 were 13.8%, 37%, and 49.2%, respectively. Renal insufficiency (39.5%) was the most common comorbidity, followed by hypertension (29.1%), congestive heart failure (17.3%), and diabetes mellitus (16.4%). In our series, 26.1% of the patients had received antiplatelet treatment, and 4.6% patients had received anticoagulant treatment (Table 1).

3.2 | Stroke and multiple myeloma

Sixteen patients had cerebrovascular events. The median duration of MM to stroke was 13 months. The longest duration of MM to stroke was 84.4 months. Three patients had diagnosis of MM and stroke contemporaneously. The 5-year estimated cumulative incidence rate was 7.45% (Figure 1). Of the 16 stroke events, 10 were cerebral infarction, and 6 were intracerebral hemorrhage. No cerebral venous thrombosis was found. Twelve patients died, and 7 of the 12 patients were deceased within 30 days after stroke. Disease status of MM was evaluated in 13 patients, and 8 were active disease (Table 2).

Patients with hemorrhagic strokes had worse outcomes. Five of the 6 hemorrhagic patients died within 1 month after stroke, and the only survivor underwent craniotomy. Three hemorrhagic patients with severe thrombocytopenia (platelet count < 50 000/μL) had received both autologous hematopoietic stem cell transplantation and allogeneic hematopoietic stem cell transplantation.

Among ischemic stroke patients, 3 patients were lacunar infarction and 7 patients were large vessel infarction. Concurrent myocardial infarction and ischemic stroke developed in 1 patient. In addition, a patient with ischemic stroke had hyperviscosity syndrome in this study (Table 2, Tables S1 and S2).

3.3 | Risk factors of stroke

In the univariate Cox analysis, age ≥ 70 years, the κ light chain isotype, atrial fibrillation (Af), previous cerebrovascular accidents, serum creatinine > 2 mg/dL and ISS stage 3 were risk factors for stroke. In the multivariate Cox analysis, κ light chain isotype (adjusted HR, 8.37; 95% CI, 1.91-39.8), previous cerebrovascular accidents (adjusted HR, 5.16; 95% CI, 1.48-17.9), and serum creatinine > 2 mg/dL (adjusted HR, 4.21; 95% CI, 1.10-16.0) were shown to be independent risk factors for strokes. Age ≥ 70 years (adjusted HR, 2.95; 95% CI, 0.79-11.0), Af (adjusted HR, 2.73; 95% CI, 0.75-9.94), and ISS stage 3 (adjusted HR, 1.98; 95% CI, 0.41-9.42) were insignificant in the multivariate analysis (Table 3). We did not identify any treatment-related factors including thalidomide (HR, 0.71; 95% CI, 0.20-2.54) or antiplatelet agents (adjusted HR, 2.16; 95% CI, 0.68-6.81) (Table 4) in the multivariate analysis. We further analyzed the risk factors for stroke subtype. We found that Af (adjusted HR, 8.07; $P = .003$) and previous cerebrovascular accidents (adjusted HR, 4.89; $P = .034$) were significant risk factors for ischemic stroke (Table S2), whereas previous cerebrovascular accidents (adjusted HR, 13.9; $P = .006$) and serum

TABLE 1 Characteristics of patients with multiple myeloma (N = 395)

Characteristics	Total[a] N = 395 n (%)	Stroke N = 16 n (%)	No-Stroke N = 379 n (%)	*P* Value
Median age, y (IQR)	70 (59-78)	77 (67-82)	70 (59-78)	
≥70	208 (52.7)	12 (75.0)	196 (51.7)	.068
<70	187 (47.3)	4 (25.0)	183 (48.3)	
Sex				
Male	260 (65.8)	10 (62.5)	250 (66.0)	.792
Female	135 (34.2)	6 (37.5)	129 (34.0)	
Pathologic fractures	162 (41.9)	5 (31.3)	157 (42.3)	.380
Immunophenotype				
IgG	206 (52.8)	11 (68.8)	195 (52.1)	.597
IgA	112 (28.7)	3 (18.8)	109 (29.1)	
LC	69 (17.7)	2 (12.5)	67 (17.9)	
IgD	1 (0.3)	0 (0.0)	1 (0.3)	
IgM	2 (0.5)	0 (0.0)	2 (0.5)	
Light chain types				
κ	195 (50.1)	14 (87.5)	181 (48.5)	.002
λ	194 (49.9)	2 (12.5)	192 (51.5)	
Durie-Salmon stages				
1	114 (28.9)	3 (18.8)	111 (29.4)	.607
2	93 (23.6)	5 (31.3)	88 (23.3)	
3	187 (47.5)	8 (50.0)	179 (47.4)	
ISS stages				
1 + 2	199 (50.8)	3 (20.0)	196 (52.0)	.015
3	193 (49.2)	12 (80.0)	181 (48.0)	
ISS stages				
1	54 (13.8)	2 (13.3)	52 (13.8)	.032
2	145 (37.0)	1 (6.7)	144 (38.2)	
3	193 (49.2)	12 (80.0)	181 (48.0)	
Comorbidities				
Coronary artery disease	40 (10.1)	1 (6.3)	39 (10.3)	1.000
Hypertension	113 (29.1)	5 (31.3)	108 (29.0)	.786
Af	40 (10.2)	5 (31.3)	35 (9.3)	.016
CHF	67 (17.2)	4 (25.0)	63 (16.9)	.328
Perivascular disease	14 (3.6)	1 (6.3)	13 (3.5)	.445
Pulmonary disease	52 (13.4)	1 (6.3)	51 (13.7)	.706
Diabetes mellitus	64 (16.3)	4 (25.0)	60 (16.0)	.306
Chronic kidney disease	155 (39.5)	10 (62.5)	146 (38.8)	.155
Antiplatelet agents	103 (26.1)	7 (43.8)	96 (25.3)	.141
Aspirin	77 (19.5)	7 (43.8)	70 (18.5)	.021
Clopidogrel	22 (5.6)	2 (12.5)	20 (5.3)	.222
Cilostazol	10 (2.5)	1 (6.3)	9 (2.4)	.342
Dipyridamole	19 (4.8)	3 (18.8)	16 (4.2)	.036
Ticlopidine	9 (2.3)	0 (0.0)	9 (2.4)	1.000
Anticoagulants	18 (4.6)	3 (18.8)	15 (4.0)	.031
Dabigatran	1 (0.3)	0 (0.0)	1 (0.3)	1.000
Rivaroxaban	2 (0.5)	0 (0.0)	2 (0.5)	1.000
Warfarin	16 (4.1)	3 (18.8)	13 (3.4)	.022
Myeloma therapeutic strategies				
HSCT	68 (17.2)	3 (18.8)	65 (17.2)	
Cytotoxic agents	203 (51.4)	9 (56.3)	194 (51.2)	.801

(*Continues*)

TABLE 1 (Continued)

Characteristics	Total[a] N = 395 n (%)	Stroke N = 16 n (%)	No-Stroke N = 379 n (%)	*P* Value
Bortezomib	152 (38.5)	5 (31.3)	147 (38.8)	.544
Thalidomide	177 (44.8)	8 (50.0)	169 (44.6)	.670
Lenalidomide	15 (3.8)	1 (6.3)	14 (3.7)	.468

Abbreviations: Af, atrial fibrillation; CHF, congestive heart failure; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range.

[a]Including some missing values.

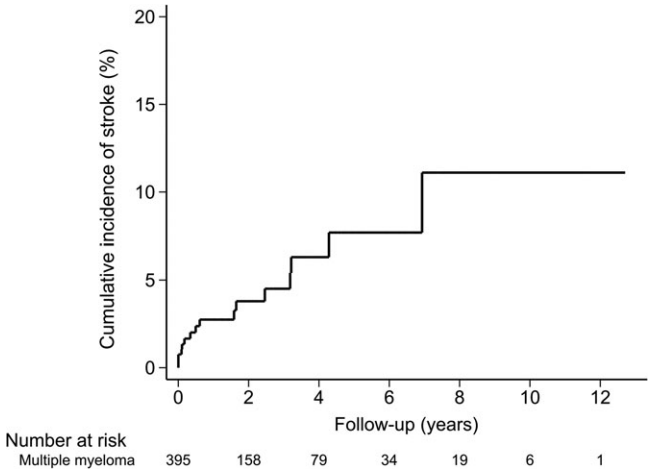

FIGURE 1 Cumulative incidence of stroke

creatinine > 2 mg/dL (adjusted HR, 30.6; *P* = .025) were significant risk factors for hemorrhagic stroke (Table S3).

4 | DISCUSSION

Several risk factors were identified in our study, including previous cerebrovascular accidents, serum creatinine > 2 mg/dL and MM with κ light chain. We found the κ light chain isotype put patients at highest risk (adjusted HR, 8.37), followed by antecedent cerebrovascular accidents (adjusted HR, 5.16) and serum creatinine > 2 mg/dL (adjusted HR, 4.21). Subgroup analysis showed that Af (adjusted HR, 8.07) and previous cerebrovascular accident (adjusted HR, 4.89) are significant risk factors for ischemic strokes. An insignificant trend showed that patients with κ light chain isotype have higher incidence of ischemic stroke (Table S2). On the other hand, significant risk factors for hemorrhagic strokes are serum creatinine > 2 mg/dL (adjusted HR, 30.6) and previous cerebrovascular accident (adjusted HR, 13.9) (Table S3).

Studies show that cancer patients have an increase of 2 to 7 times of thrombosis risk.[9] In practice, it is hard to differentiate cerebral metastasis from cerebrovascular disorders in patients with focal neurological deficits. However, Graus et al showed that nearly 15% of cancer patients had pathological evidence of cerebrovascular complications and that approximately half of them developed neurological deficits. He also demonstrated that patients with hematological malignancies had a higher proportion of hemorrhagic strokes (72% in leukemia and 36% in lymphoma).[10] Zhang et al proposed that hemorrhagic stroke in cancer patients could be attributed to disseminated intravascular coagulopathy, chemotherapy-induced thrombocytopenia, and hematological malignancies itself.[11]

Several studies have investigated epidemiology of thromboembolism in plasma cell dyscrasia. In 1 population-based study from the United States, the incidences of deep vein thrombosis among the control, MGUS, and MM were 0.9, 3.1, and 8.7 per 1000 person-years, respectively.[12] Another study using population-based data from Sweden demonstrated that MM patients had an HR of 4.1 to 7.5 for venous thrombosis, and that thrombosis is associated with an inferior prognosis in MM patients.[13] Generally, Asians and Pacific Islanders have the lowest incidence of spontaneous VTE,[14] and the risk of VTE is also relatively low in Asian patients with cancer.[15] A Taiwanese population-based study with 2657 MM patients reported a cumulative incidence of deep vein thrombosis and pulmonary embolism for MM of 1.24% and 0.41%.[9]

In contrast to venous thrombosis, the epidemiology of stroke or arterial thrombosis in MM patients has been less studied. Kristinsson et al estimated the risks of arterial thrombosis and cerebrovascular events (cerebral infarction, transient ischemic attack, and cerebral hemorrhage). Compared with matched controls, MM patients had HRs of 1.5 to 1.9 for arterial thrombosis and 1.2 to 1.5 for cerebrovascular events, and MGUS patients had HRs of 1.4 to 1.9 for arterial thrombosis and 1.1 to 1.4 for cerebrovascular events.[6] A prospective cohort study from the Netherlands reported 11 of its 195 young MM (5.6%) having developed arterial thrombosis, with 5 patients having had cerebrovascular events, including 2 transient ischemic attacks and 3 strokes.[7] In addition, a retrospective study investigating the frequency of thromboembolism in Taiwanese MM patients with thalidomide-containing therapy found that the majority in this study were refractory or relapsed myeloma patients. The results included 3 venous thromboses and 2 arterial thromboses (1 myocardial infarction and 1 anterior tibial artery thrombosis) of 144; no stroke events were reported.[16]

Several mechanisms of thrombosis were proposed, which include hyperviscosity, thalidomide therapy, being elderly, immobility, and hemostatic disorders.[5,17] It has also been reported that 2% to 6% of MM patients have symptomatic hyperviscosity,[18] with hypergammaglobulinemia being the most common etiology of both hyperviscosity and hypercoagulation. Another possible mechanism of stroke is vascular injury and the bleeding tendency caused by M protein. M protein impairs platelet function, interferes with coagulation, and increases a bleeding risk.[17] Several mechanisms behind vascular injury have been proposed. M protein may directly involve endothelial cells with endothelial injury.[19]

The positive correlation between chronic kidney disease and stroke is widely accepted.[20,21] A recent population-based study reported that lower levels of estimated glomerular filtration rate were

TABLE 2 Clinical features of patients with acute stroke

Case No.	Age/Gender	Time to Stroke (mo)	MM Type	Comorbidities	Stroke Subtype	Clinical Features
1	86/M	1.3	IgG/κ	DM, CKD, Af	Cerebral infarction	Antiplatelet agent, anticoagulant
2	75/M	Contemporaneous	IgA/κ	CKD, HTN	Cerebral infarction[a]	Hyperviscosity
3	85/F	Contemporaneous	IgG/κ	Previous CVA, CKD, Af	Cerebral infarction	Antiplatelet agent
4	52/M	20.1	IgG/κ	No known risk	ICH[a]	HSCT, severe thrombocytopenia[b]
5	62/M	2.1	LC/κ	PAD, previous CVA, DM, CKD	ICH	N/A
6	71/F	38.7	LC/λ	DM, CKD, Af	Cerebral infarction	Antiplatelet agent, anticoagulant
7	82/M	4.2	IgG/κ	CKD	ICH[a]	Antiplatelet agent
8	55/M	84.4	IgG/κ	CKD	ICH[a]	HSCT, severe thrombocytopenia[b]
9	40/F	52.2	IgA/κ	CKD	ICH[a]	HSCT, severe thrombocytopenia[b]
10	82/M	6.0	IgA/κ	Af	Cerebral infarction(lacunar infarction)	N/A
11	78/M	7.4	IgG/λ	Af, HTN	Cerebral infarction	Antiplatelet agent, anticoagulant
12	77/F	30.0	IgG/κ	HTN	Cerebral infarction	Antiplatelet agent
13	82/F	1.1	IgG/κ	DM	Cerebral infarction(lacunar infarction)	N/A
14	72/F	39.1	IgG/κ	Previous CVA, CKD, HTN	Cerebral infarction[a] (lacunar infarction)	Antiplatelet agent, severe thrombocytopenia
15	76/M	19.3	IgG/κ	Previous CVA, CKD, HTN	ICH[a]	N/A
16	86/M	Contemporaneous	IgG/κ	MI, previous CVA	Cerebral infarction	Concurrent MI and stroke

Abbreviations: Af, atrial fibrillation; CKD, chronic kidney disease; CVA, cerebrovascular accidents; DM, diabetes mellitus; HTN, hypertension; HSCT, hematopoietic stem cell transplantation; ICH, intracerebral hemorrhage; PAD, peripheral artery disease; MI, myocardial infarction; MM, multiple myeloma; N/A, not applicable.

[a]Mortality within 30 days after event.

[b]Severe thrombocytopenia is defined as platelet count of less than 50 000/μL.

associated with a higher incidence of stroke among patients with chronic kidney disease.[22] Endothelial dysfunction and accelerated atherosclerosis due to hypercalcemia were proposed as the main etiologies of strokes in patients with chronic kidney disease.[22–24]

In this study, we express that the κ light chain isotype is as an independent risk factor for cerebrovascular events. Few articles have reported an association between light chain isotypes and acute stroke. Libourel et al showed that 11 of 195 untreated MM patients developed arterial thrombosis. Ten of 11 had the κ light chain isotype.[7] In addition, Foiri et al demonstrated that patients with acute stroke had increased excretion of urinary polyclonal κ light chains.[25] The excretion of urinary polyclonal κ light chains has positive correlation with the serum κ light chains level. A strong correlation with the κ light chains is also found in 2 rare MM associated diseases—type 1 cryoglobulinemia and acquired Fanconi syndrome.[26–29] A study by Trejo et al reported that 30 of its 31 patients with type 1 cryoglobulinemia had the κ light chain isotype.[28] Patients with cryoglobulinemia had vascular occlusion and hyperviscosity. In M protein–associated acquired Fanconi syndrome, the pathogenic free light chain is resistant to proteolysis and prone to crystallization. The accumulation of light chains in the lysosomal compartment of proximal renal tubular cells impairs renal function.[26,27] The precise mechanism behind risk for stroke in patients with a κ light chain isotype is largely uncertain. Endothelial injury from deposition of crystalline may increase the risk of stroke. In patients with acquired Fanconi syndrome, crystalline from light chains being deposited into endothelial cells has been reported.[30] However, our observational study includes only epidemiological results, and we have no obtainable pathological samples to assess the impact of κ light chains on vessels, which needs further research to investigate the mechanism.[28]

Nonetheless, the impact of the κ light chains was insignificant for ischemic (Table S2) and hemorrhagic stroke (Table S3). Owing to the small number of events (10 in ischemic strokes and 6 in hemorrhagic strokes) in subgroup analysis, the result should be interpreted with caution. In our study, we focus on the risk factors of stroke, including ischemic and hemorrhagic subtypes. The CI for κ light chains (adjusted HR, 8.37; 95% CI, 1.91-39.8) was wide in combined analysis. The main reason for the wide CI could be a result of the small number of events (n = 16). Therefore, a small case number is our limitation. Further, we need more patients to prove the result and analyze the difference of subtypes in strokes.

The small number of events is a major limitation in our study. The limited number of events could affect the validity; and some risk factors, such as antiplatelet agents and anticoagulation, could not be analyzed. Here, our data revealed an inconsistent result of Af. Atrial fibrillation was a significant risk factor in ischemic stroke but insignificant in all stroke. Second, potential confounding factors, such as daily blood pressure, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels, antihypertensive medication, and

TABLE 3 Univariate and multivariate analysis of factors associated with stroke

	Univariate Analysis		Multivariate Analysis[a]	
Predictive Variables	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Age ≥ 70 y	4.44 (1.37-14.36)	.013	2.95 (0.79-11.04)	.109
Sex (male)	0.90 (0.33-2.47)	.832	0.76 (0.26-2.21)	.607
Light chains				
λ	Reference		Reference	
κ	7.06 (1.60-31.05)	.010	8.37 (1.91-39.89)	.005
Pathologic fractures	0.74 (0.25-2.14)	.575		
Comorbidities				
Coronary artery disease	0.70 (0.09-5.29)	.727		
Af	5.69 (1.92-16.86)	.002	2.73 (0.75-9.94)	.127
CHF	2.02 (0.65-6.28)	.224		
Perivascular disease	1.53 (0.20-11.59)	.681		
Previous cerebrovascular accidents	7.01 (2.43-20.26)	.000	5.16 (1.48-17.98)	.010
Pulmonary disease	0.51 (0.07-3.89)	.518		
Diabetes mellitus	2.25 (0.72-7.05)	.164		
Laboratory data				
WBC < 4000	1.15 (0.37-3.58)	.804		
Hemoglobin < 10 g/dL	1.07 (0.39-2.95)	.902		
Hemoglobin < 8.5 g/dL	0.97 (0.31-3.05)	.960		
Corrected serum calcium > 12 mg/dL	Do not converge	.993		
Serum creatinine > 2 mg/dL	4.31 (1.59-11.70)	.004	4.21 (1.10-16.07)	.036
ISS stage				
1 + 2	Reference			
3	5.18 (1.46-18.42)	.011	1.98 (0.41-9.42)	.393

Abbreviations: Af, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; ISS, International Staging System; WBC, white blood cells.

[a]All factors with $P < .1$ in the univariate analysis were entered in the multivariate Cox regression model.

TABLE 4 Univariate and multivariate analysis for therapeutic strategies

	Univariate Analysis		Multivariate Analysis[b]	
Treatment[a]	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
HSCT[c]	0.59 (0.16-2.10)	.413		
Cytotoxic agents	1.58 (0.57-4.38)	.378		
Bortezomib	1.87 (0.67-5.20)	.233		
Thalidomide	0.71 (0.20-2.54)	.595		
Antiplatelet agents	4.43 (1.64-11.98)	.003	2.16 (0.68-6.81)	.189
Anticoagulants	3.06 (0.39-23.90)	.287		
HSCT[c]	0.59 (0.16-2.10)	.413		
Cytotoxic agents	1.58 (0.57-4.38)	.378		

Abbreviations: CI, confidence interval; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation.

[a]Treatment was analyzed as a time-dependent covariate in the Cox regression model.

[b]All factors with $P < .1$ in Table 2 univariate analysis were entered in a multivariate Cox regression model.

[c]Time-independent covariate.

lifestyle variations, were not completely obtained for our cohort. For example, we tried to assess the impact of antiplatelet agents, but a strong interaction between antiplatelet agents and Af was attributed to a negative result. The echocardiogram is not a compulsory examination for patients with Af in our hospital. As a result, we do not have a complete record about types of Af (valvular and nonvalvular) in our patients. In Taiwan, prophylactic aspirin is not routinely given in thalidomide combination treatment because of the low incidence of VTE (2.1%).[16] In addition, mortality is a major competing risk. In our cohort, early mortality (death within 60 days after diagnosis) was around 12%.[31] Finally, prothrombotic factors were not available for this study. Von Willebrand factor and factor VIII levels and the incidence of

acquired activated protein C resistance increased in patients with advanced stages of disease.[7,32,33] Hence, larger prospective studies and molecular studies are required to validate our results.

5 | CONCLUSION

This is the first study that identified the κ light chain isotype as an independent risk factor for stroke in patients with MM. Other significant risk factors include serum creatinine level > 2 mg/dL and previous cerebrovascular events. As the life expectancy of MM patients extends, stroke prevention strategies should be considered for patients with risk factors.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

YCL and CJL were responsible for the accuracy of analysis and the integrity of the cohort. GYL and YTL contributed equally and are the first authors. GYL, YTL, YCL, and CJL designed the study. CJL and CMY performed the statistical analysis. GYL, YTL, YCL, and CJL interpreted the results. GYL and YTL drafted the manuscript. PH, TWL, JPG, YBY, LTH, CHT, TJC, and JHL made critical revisions to the manuscript. TWL, JPG, YBY, LTH, CHT, TJC, and JHL provided administrative, technical, and material support. All authors approved the final version for submission.

ABBREVIATIONS USED

CI	confidence interval
HR	hazard ratio
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
VTE	venous thromboembolism

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