Original Article

Prognostic significance of thromboembolism in multiple myeloma: a systematic review and meta-analysis

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Background: This study sought to investigate the clinical characteristics and prognosis of thromboembolism in multiple myeloma (MM).

Methods: The PubMed, Embase, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI) databases were systematically searched to retrieve relevant articles from the establishment of the databases to May 2022. This meta-analysis was performed to investigate the relationship between thromboembolism and overall survival (OS), progression-free survival (PFS), event-free survival (EFS), and mortality in MM patients. The meta-analysis of the included studies was performed using Revman5.3 software after quality evaluation.

Results: A total of 9 studies from 7 articles, which included 38,047 MM patients and 6,412 cases of thromboembolism in the analysis. The levels of β2 microglobulin affected the occurrence of thromboembolism in MM patients [standard mean difference (SMD) =–0.09, 95% confidence interval (CI): –0.18 to –0.01, P=0.02]. Venous thromboembolism (VTE) predicted poorer OS [hazard ratio (HR) = 0.79, 95% CI: 0.64–0.98, P=0.03] and higher early mortality (HR =2.27, 95% CI: 1.26–4.08, P=0.006) in MM. There was no significant difference in PFS/EFS (HR =0.81, 95% CI: 0.64–1.01, P=0.06) between thrombosis/embolism and non-thrombotic embolism. Arterial thrombosis was associated with significantly higher risk of death at 5 years (HR =1.89, 95% CI: 1.33–2.69, P<0.01).

Conclusions: β2 microglobulin levels were associated with VTE in MM. MM patients with VTE were more likely to have poorer prognosis and higher mortality rate than those without VTE. MM patients with arterial thromboembolism had higher 5-year mortality rate than those without arterial thromboembolism.

Keywords: Thromboembolism; multiple myeloma (MM); prognosis

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Introduction

Multiple myeloma (MM) was a hematologic disease with the abnormal proliferation of clonal plasma cells, which occurred mostly in elderly people, and was characterized by osteytic lesions, anemia, hypercalcemia, and renal failure (1). In recent years, the overall survival (OS) of patients with MM had improved with multiple new therapies in the last two decades (2-4). Studies showed that MM patients, especially those treated with immunomodulating drugs, had high risk of thrombosis and thromboembolism (5,6).

At present, it was thought that the mechanism of thromboembolism in MM was complex. The abnormal proliferation of plasma cells and the treatment-related thrombotic risk were the main causes of the disease (7,8). Thromboembolism occurs at any stage of MM onset. The highest onset risk was within 1 year of diagnosis (9).

MM thromboembolism affects survival outcomes (10). This study sought to explore the risk factors of MM and conduct prognostic analysis of thromboembolism in MM. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-285/rc).

Methods

Literature search

The PubMed, Embase, Web of Science, Wanfang, and China National Knowledge Infrastructure (CNKI) databases were searched to retrieve relevant articles from the establishment of the databases to May 20, 2022 (the last search date). The following search terms were used: "arterial thromboembolism," "venous thromboembolism," "thrombotic," "thromboembolism," "thrombosis," and "multiple myeloma". This meta-analysis registered on the PROSPERO platform, registration number: CRD42022334811.

Inclusion and exclusion criteria

To be eligible for inclusion in the meta-analysis, the articles had to meet the following inclusion criteria: (I) study subjects with thromboembolism and MM; (II) study indicators that included prognostic indicators [i.e., OS, progression-free survival (PFS), event-free survival (EFS), and the mortality rate]; and (III) groups of patients with thromboembolism and without thromboembolism. Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) concerned comments, meetings, abstracts, or case reports; (II) repeated studies or arbitrary groupings; (III) irrelevant or insufficient data.

Highlight box

Key findings

- β2 microglobulin levels are associated with venous thromboembolism (VTE) in multiple myeloma (MM). Thromboembolic MM patients have large tumor load and poor survival prognosis.

What is known and what is new?

- Thromboembolism is one of the main complications of MM. The effect of thromboembolism on the prognosis of MM is controversial. The risk of thromboembolism in MM patients is high.
- MM patients with VTE are more likely to have poorer prognosis and higher mortality rate than without VTE.

What is the implication, and what should change now?

- MM patients with high thrombosis risk should receive anticoagulant therapy.

Data extraction and qualitative assessment

The data was independently extracted by 2 experienced researchers. The following information was extracted from each study included in the final analysis: first author, year of publication, sample size, clinical characteristic parameters (e.g., age, gender, race, globulin type, type of light chain, creatinine, calcium, β2 microglobulin, hemoglobin, and platelet), and prognostic parameters (e.g., OS, PFS, EFS, and the mortality rate). The Cochrane collaboration's tool for assessing the risk of bias was used to evaluate randomized controlled trials (RCTs), the Newcastle-Ottawa Scale (NOS) was used to assess retrospective observational studies.

Statistical analysis

The statistical analysis was performed using Review Manager (RevMan; Version 5.3. The Cochrane Collaboration). The results of the survival analysis were expressed as the risk ratio [hazard ratio (HR)], the dichotomy variables used the relative risk (RR), and the continuity variables used the standard mean difference (SMD), and the 95% confidence interval (95% CI) served as the assessed effect size. The heterogeneity of each study was quantified by the I^2 test. $P>0.1$ or $I^2<50\%$ indicated no significant heterogeneity, and the fixed-effects model was used, while the random-effects model was used for the pooled analysis.

Results

Literature search

A flow diagram of the article screening process was presented in *Figure 1*. A total of 787 studies were retrieved online. Ultimately, 9 studies in 7 articles (11-17) were included in the analysis based on screening of the titles and/or abstracts. There were 2 articles (13,17) included two studies.

Study characteristics

A total of 38,047 patients with MM were included in this study. 6,412 patients were thromboembolism, 3,152 patients

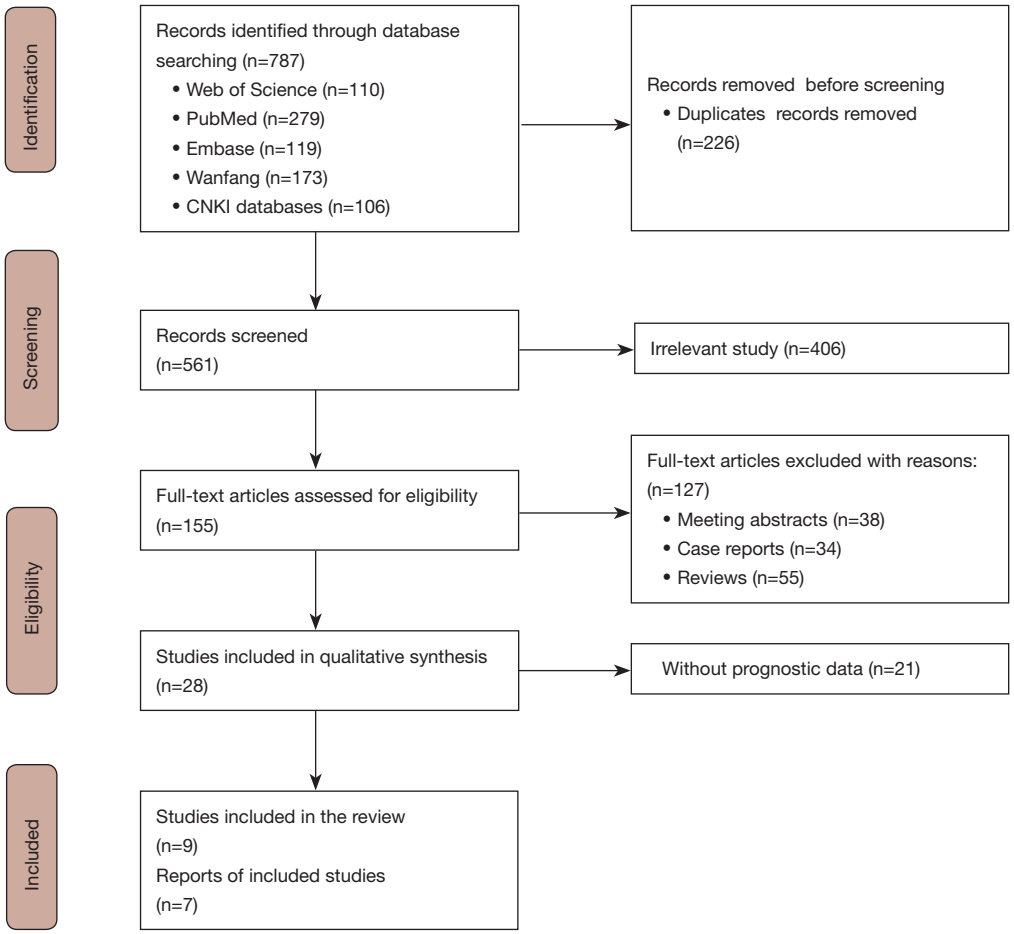

Figure 1 Flow diagram showing the article screening process.

were venous thromboembolism (VTE), and 3,404 patients were arterial thromboembolism (ATE). The quality scores of retrospective observational studies were ranging from 7 to 9, and the quality of RCT was low risk of bias. The basic characteristics of the included articles were shown in *Table 1*.

Clinical characteristics of patients with VTE

To analyze the relationship between VTE and clinicopathological features, we explored the pooled estimates of the studies (*Table 2*). Age (≥65 *vs.* <65 years), gender (male *vs.* female), ECOG (Eastern Cooperative Oncology Group) scores (0–2 *vs.* 3–4), race (black *vs.* non-black), globulin type [immunoglobulin G (IgG) *vs.* non-IgG], light chain type (κ *vs.* λ), creatinine levels, calcium levels, platelet levels, and hemoglobin levels did not affect the occurrence of VTE in MM patients. However, the β2 microglobulin level affected the occurrence of VTE in MM patients. Compared to patients without thrombosis, the patients with thrombosis had a lower β2 microglobulin.

The OS of VTE in patients with MM

Among the studies, 4 examined the relationship between VTE and MM. Based on the results of the heterogeneity test (I^2=89%, P<0.01), the random-effects model was used, and the results showed that VTE was unrelated to OS in MM patients (HR =0.97, 95% CI: 0.69–1.36, P=0.85). The Shin (17) study was large source of heterogeneity, and the heterogeneity decreased after this study was excluded

Table 1 Characteristics of the studies included in the meta-analysis

First author	Year	VTE	ATE	Embolization (N)	Total	Embolization type	Outcomes	NOS scores
Kristinsson (11)	2010	777	1,751	2,384	18,627	VTE, ATE	OS	8
Zangari (12)	2007	155	0	155	668	VTE	OS, EFS	7
Bradbury (13)	2020	368	0	368	1,936	VTE	OS, PFS	–
		665	81	746	4,538	VTE, ATE	OS, PFS, mortality	
Schoen (16)	2020	327	0	327	4,446	VTE	Mortality	8
Shin (17)	2019	24	0	24	542	VTE	OS	7
		80	0	80	1,559	VTE		
Kristinsson (14)	2012	724	1,572	2,296	9,399	VTE, ATE	Mortality, OS	8
Barrett (15)	2021	32	0	32	332	VTE	Mortality	7

VTE, venous thromboembolism; ATE, arterial thromboembolism; NOS, Newcastle-Ottawa Scale; OS, overall survival; EFS, event-free survival; PFS, progression-free survival.

Table 2 Meta-analysis of the relationship between venous thromboembolism and the clinical characteristics of patients with multiple myeloma

Association	Studies	Total patients	Effect index				Heterogeneity test	
			Quantity	Model	95% CI	P	I^2 (%)	P
Age	3	1,627	RR	Random	1.33 (0.40 to 4.44)	to0.64	97	<0.01
Gender	6	42,437	RR	Random	1.13 (0.76 to 1.69)	0.54	94	<0.01
Race	3	10,659	RR	Fixed	0.89 (0.75 to 1.06)	0.21	50	0.14
ECOG score	3	6,561	RR	Fixed	1.01 (0.99 to 1.03)	0.56	0	0.79
Globulin type	2	6,267	RR	Random	1.06 (0.97 to 1.15)	0.22	57	0.13
Light-chain type	2	6,087	RR	Random	0.97 (0.81 to 1.16)	0.72	65	0.09
β2 microglobulin	3	4,893	SMD	Fixed	–0.09(–0.18 to –0.01)	0.02	0	0.81
Creatinine	2	6,226	SMD	Fixed	–0.03 (–0.10 to 0.04)	0.35	0	0.61
Calcium	2	6,215	SMD	Fixed	–0.00 (–0.07 to 0.07)	1.00	0	1.00
Platelet	3	6,625	SMD	Fixed	0.01 (–0.06 to 0.08)	0.84	0	0.52
Hemoglobin	3	6,623	SMD	Random	0.04 (–0.18 to 0.26)	0.73	84	<0.01

RR, relative risk; SMD, standard mean difference; ECOG, Eastern Cooperative Oncology Group.

(I^2=77%, P=0.01), and the MM patients with VTE were shown shorter OS (HR =0.79, 95% CI: 0.64–0.98, P=0.03; *Figure 2*) than those without VTE.

The PFS/EFS of VTE in patients with MM

Among the studies, 3 showed that MM patients with VTE was unrelated to poorer PFS/EFS than those without VTE (HR =0.81, 95% CI: 0.64–1.01, P=0.06), and the heterogeneity was high (I^2=86%, P<0.01) by using random-effects model (*Figure 3*).

The mortality of VTE in patients with MM

Among the studies, 3 showed that MM patients with VTE had higher early mortality rate than those without VTE (HR =2.27, 95% CI: 1.26–4.08, P=0.006), and the heterogeneity (I^2=94%, P<0.01) were analyzed by random-effects model

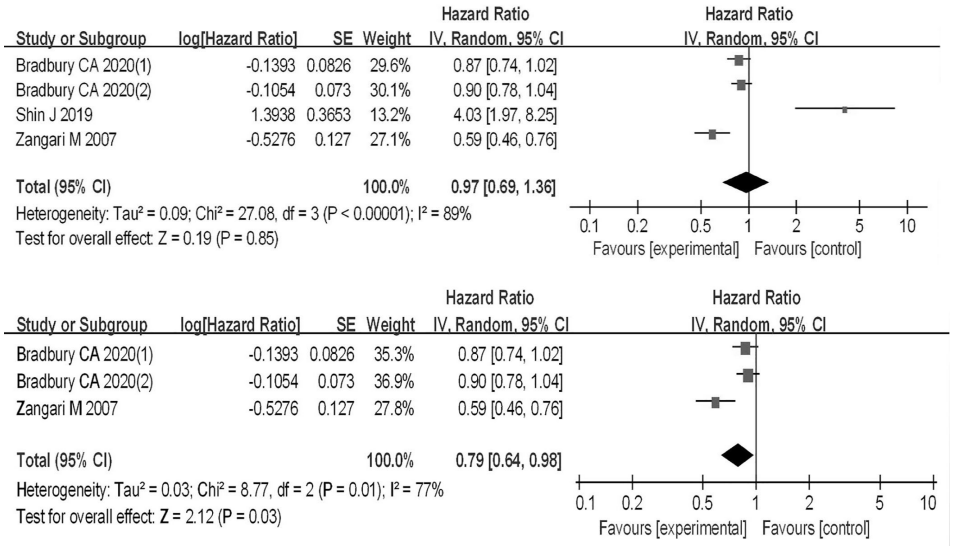

Figure 2 Overall survival of venous thromboembolism *vs.* without venous thromboembolism in multiple myeloma. SE, standard error.

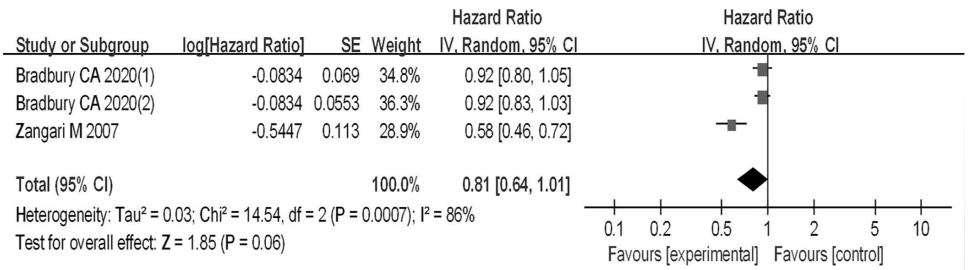

Figure 3 Progression-free survival/event-free survival of venous thromboembolism *vs.* without venous thromboembolism in multiple myeloma.

(*Figure 4*).

Effect of ATE on mortality from MM

Among the studies, 2 showed that MM patients with ATE had higher 5-year mortality rate than those without ATE (HR =1.89, 95% CI: 1.33–2.69, P<0.01), and the heterogeneity (I^2=79%, P=0.03) was used random-effects model for statistical analysis (*Figure 5*).

Publication bias

According to the Cochrane handbook, when >9 studies were included in a meta-analysis, funnel plots should be used to detect publication bias. As only 7 articles were included in our meta-analysis, we did not construct funnel plots.

Discussion

Previous large retrospective cohort studies shown that patients with MM increased risks of VTE and ATE, and patients with MM had one of the highest risks for thromboembolism among those with hematologic diseases (18,19). Patients with MM had 9 times higher risk of developing thromboembolism than no MM (20). High-risk factors for venous thrombosis in MM included high viscosity, kidney disease, erythropoietin, and immunomodulatory drugs and hormones (6,21). Immunomodulating drugs could increase the incidence of venous thrombosis, the immunomodulating drug-associated VTE risk was affected by the combination of high-dose corticosteroids, and some studies shown that the incidence of VTE in patients treated with lenalidomide and dexamethasone was almost 3 times higher than that of those

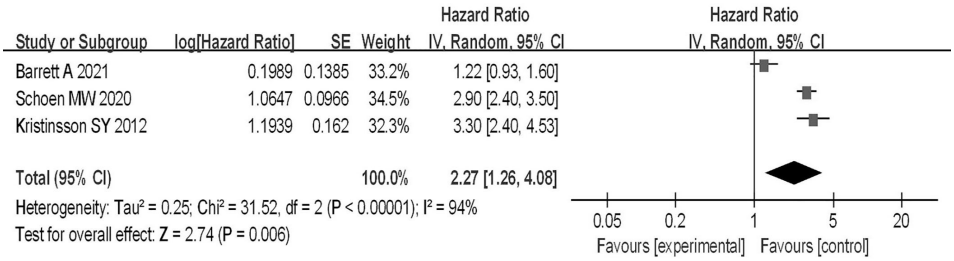

Figure 4 Early mortality of venous thromboembolism *vs.* without venous thromboembolism in multiple myeloma.

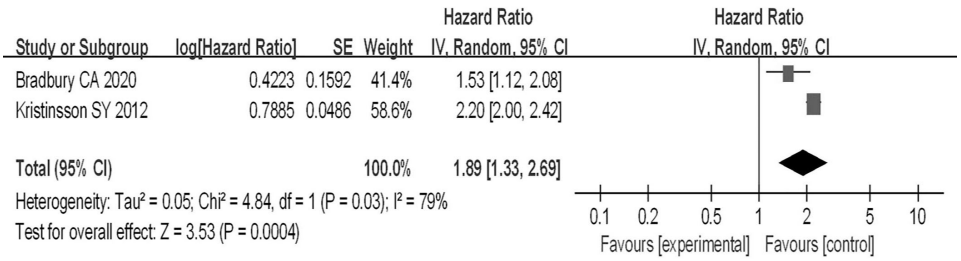

Figure 5 Five-year mortality of arterial thromboembolism *vs.* without arterial thromboembolism in multiple myeloma.

treated with dexamethasone alone (22,23). Thalidomide maintenance therapy did not increase the risk of thrombosis, but maintenance therapy with lenalidomide increased the risk of arterial and venous thrombosis (13). This study found that β2 microglobin levels were associated with the development of VTE in MM. Thus, β2 microglobulin predicted the occurrence of VTE in MM patients.

Thromboembolism was associated with shorter survival during the diagnosis and treatment of cancer patients (24). Large study shown that arterial and venous thrombosis were associated with lower survival in MM patients (14). However, the RCTs found that venous thrombosis was not associated with OS (13). A study found that 95% of VTE was diagnosed in the 1st year of MM diagnosis (12). The results of this study showed that thromboembolism was not associated with 10-year OS in MM patients regardless of the thromboembolism type (HR =1.12, 95% CI: 0.83–1.51, P=0.46).

Due to the different incidence rates of VTE and ATE, this study analyzed the effect of VTE on survival prognosis (i.e., OS) and found that patients with VTE had shorter OS (HR =0.79, 95% CI: 0.64–0.98, P=0.03) than those without VTE. No significant PFS/EFS difference was found (HR =0.81, 95% CI: 0.64–1.01, P=0.06). This study also found that MM patients with VTE had higher early mortality rate (HR =2.27, 95% CI: 1.26–4.08, P=0.006) than those without VTE. Further, the study found that the occurrence of venous thrombosis within 6–12 months had no significant effect on the survival rate of the surviving patients, which might be due to the low incidence of thromboembolism in effective patients, and the study also found that low-molecular-weight heparin had anti-tumor activity (14,25). Thus, according to the thromboembolism risk stratification, high-risk patients should be treated with low-molecular-weight heparin, warfarin, or other new anticoagulants, while low-risk patients should be treated with aspirin (26,27). Thromboembolism was serious complication of MM. This study was the first time to research the prognosis effect of thromboembolism on MM using meta-analysis. The included studies were all high quality, and the MM patients with thromboembolism had poor survival prognosis, which had important clinical significance.

The study had some limitations. First, the number of studies included in this meta-analysis was limited, but as the total number of cases exceeded 10,000, this should not have affected the characteristics of the total population. Second, the results of the survival prognosis analysis were heterogeneous. Finally, the subgroup analysis was failed to

further clarify the results due to the limited study.

Conclusions

β2 microglobulin levels affected the occurrence of VTE in MM patients. MM patients with VTE had shorter OS and higher early mortality rate than those without VTE. MM patients with ATE had higher 5-year mortality rate than those without ATE.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-285/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-285/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004;351:1860-73.
2. Waxman AJ, Mink PJ, Devesa SS, et al. Racial disparities in incidence and outcome in multiple myeloma: a population-based study. Blood 2010;116:5501-6.
3. Turesson I, Velez R, Kristinsson SY, et al. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol 2010;28:830-4.
4. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008;111:2516-20.
5. Carrier M, Le Gal G, Tay J, et al. Rates of venous thromboembolism in multiple myeloma patients undergoing immunomodulatory therapy with thalidomide or lenalidomide: a systematic review and meta-analysis. J Thromb Haemost 2011;9:653-63.
6. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414-23.
7. Eby C. Pathogenesis and management of bleeding and thrombosis in plasma cell dyscrasias. Br J Haematol 2009;145:151-63.
8. Swan D, Rocci A, Bradbury C, et al. Venous thromboembolism in multiple myeloma - choice of prophylaxis, role of direct oral anticoagulants and special considerations. Br J Haematol 2018;183:538-56.
9. Falanga A, Marchetti M. Venous thromboembolism in the hematologic malignancies. J Clin Oncol 2009;27:4848-57.
10. Schoen MW, Luo S, Gage B, et al. Association of venous thromboembolism with increased mortality in patients with multiple myeloma. J Clin Oncol 2018;36:8051.
11. Kristinsson SY, Pfeiffer RM, Björkholm M, et al. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. Blood 2010;115:4991-8.
12. Zangari M, Barlogie B, Cavallo F, et al. Effect on survival of treatment-associated venous thromboembolism in newly diagnosed multiple myeloma patients. Blood Coagul Fibrinolysis 2007;18:595-8.
13. Bradbury CA, Craig Z, Cook G, et al. Thrombosis in patients with myeloma treated in the Myeloma IX and Myeloma XI phase 3 randomized controlled trials. Blood 2020;136:1091-104.
14. Kristinsson SY, Pfeiffer RM, Björkholm M, et al. Thrombosis is associated with inferior survival in multiple myeloma. Haematologica 2012;97:1603-7.
15. Barrett A, Quinn J, Lavin M, et al. Validation of Risk-Adapted Venous Thromboembolism Prediction in Multiple Myeloma Patients. J Clin Med 2021;10:3536.
16. Schoen MW, Carson KR, Luo S, et al. Venous thromboembolism in multiple myeloma is associated with increased mortality. Res Pract Thromb Haemost 2020;4:1203-10.

17. Shin J, Lee JJ, Kim K, et al. Venous thromboembolism in relapsed or refractory multiple myeloma patients treated with lenalidomide plus dexamethasone. Int J Hematol 2019;109:79-90.
18. Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715-22.
19. Cesarman-Maus G, Braggio E, Fonseca R. Thrombosis in multiple myeloma (MM). Hematology 2012;17 Suppl 1:S177-80.
20. Kristinsson SY, Fears TR, Gridley G, et al. Deep vein thrombosis after monoclonal gammopathy of undetermined significance and multiple myeloma. Blood 2008;112:3582-6.
21. Wang J, Park C, Arroyo-Suarez R. Venous thromboembolism in patients with multiple myeloma receiving daratumumab-based regimens: a post hoc analysis of phase 3 clinical trials. Leuk Lymphoma 2021;62:2219-26.
22. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.
23. Sørensen HT, Mellemkjaer L, Olsen JH, et al. Prognosis of cancers associated with venous thromboembolism. N Engl J Med 2000;343:1846-50.
24. Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood 2010;116:5838-41.
25. Mousa SA, Linhardt R, Francis JL, et al. Anti-metastatic effect of a non-anticoagulant low-molecular-weight heparin versus the standard low-molecular-weight heparin, enoxaparin. Thromb Haemost 2006;96:816-21.
26. Li A, Wu Q, Luo S, et al. Derivation and Validation of a Risk Assessment Model for Immunomodulatory Drug-Associated Thrombosis Among Patients With Multiple Myeloma. J Natl Compr Canc Netw 2019;17:840-7.
27. Chinese Hematology Association, Chinese Society of Hematology. Guidelines for the diagnosis and management of multiple myeloma in China (2022 revision). Chinese Journal of Internal Medicine 2022;61:480-7.

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