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ORIGINAL ARTICLE

Evaluation of the Khorana score for prediction of venous thromboembolism in patients with multiple myeloma

Kristen M. Sanfilippo MD, MPHS[1,2] | Kenneth R. Carson MD, PhD[3] | Tzu-Fei Wang MD, MPH[4] | Suhong Luo MS[1,2] | Natasha Edwin MD[5] | Nicole Kuderer MD[6] | Jesse M. Keller MPD, MPHS[1,2] | Brian F. Gage MD, MSc[1]

[1]Washington University School of Medicine in St. Louis, St. Louis, Missouri, USA

[2]St. Louis Veterans Affairs Medical Center, St. Louis, Missouri, USA

[3]Rush University Medical Center, Chicago, Illinois, USA

[4]University of Ottawa at The Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

[5]ThedaCare Regional Cancer Center, Appleton, Wisconsin, USA

[6]Advanced Cancer Research Group, Kirkland, Washington, USA

Correspondence
Kristen M. Sanfilippo, Hematology Division, Campus Box 8125, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, USA.
Email: ksanfilippo@wustl.edu

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Abstract

Background: Guidelines recommend thromboprophylaxis for patients with multiple myeloma (MM) at high risk for venous thromboembolism (VTE). However, the optimal risk prediction model for VTE in MM remains unclear. Khorana et al developed a VTE risk score (Khorana score) in ambulatory cancer patients receiving chemotherapy. We aimed to evaluate the predictive ability of the Khorana score in patients with MM.

Methods: We identified patients with MM within the Veterans Affairs health care system between 2006 and 2013. The Khorana score was calculated before treatment initiation. Using logistic regression, the relationship between risk group and VTE was assessed at 3 and 6 months. We tested model discrimination using the concordance statistic.

Results: In the cohort of 2870 patients with MM, there were 1328 at low risk (0 points), 1521 at intermediate risk (1-2 points), and 21 at high risk (≥3 points) for VTE by the Khorana score. The 6-month cumulative incidence of VTE was 5.1% (95% confidence interval [CI], 4.0%-6.4%) in low risk, 3.9% (95% CI, 3.0%-5.0%) in intermediate risk, 4.8% (95% CI, 0.3%-20.2%) in high risk. The Khorana score did not strongly discriminate between patients who did and did not develop VTEs at 3 or 6 months (concordance statistic, 0.58; 95% CI, 0.54-0.63; and 0.53, 95% CI, 0.50-0.57, respectively.

Conclusions: In conclusion, in this cohort of 2870 patients with MM, the Khorana score did not predict VTE. Our study supports the need to use myeloma-specific risk models to predict VTE risk in patients with MM.

KEYWORDS
cancer-associated thrombosis, Khorana score, multiple myeloma, risk prediction, venous thromboembolism

Essentials

- The optimal prediction model to quantify risk of thrombosis in multiple myeloma (MM) is unknown.
- We evaluated the performance of one potential model, the Khorana Score, in patients with MM.
- In our cohort of 2870 patients, the Khorana Score did predict thrombosis (concordance statistic, 0.58).
- MM-specific prediction models should be used to predict thrombosis in patients with MM.

1 | INTRODUCTION

With >100 000 Americans dying from venous thromboembolism (VTE) annually, VTE is one of the most preventable causes of death.[1,2] Patients with cancer have an increased risk of VTE.[3] This risk varies with type of malignancy, and patients with multiple myeloma (MM) have a 9-fold increased risk of VTE compared to patients without MM.[4,5] Thromboprophylaxis in patients with MM at high risk of VTE may reduce the incidence of VTE and improve patient survival.[6-8] However, identification of high-risk patients in MM has remained challenging. The Myeloma XI trial incorporated International Myeloma Working Group (IMWG) guidance to identify patients with MM at high risk of VTE and guide thromboprophylaxis.[9] Despite this risk stratification, incidence of VTE remained high, exceeding 10% at 6 months after treatment initiation. Better risk prediction models are needed.

The Khorana score, a validated risk prediction model developed primarily in patients with solid tumors and lymphoma, identifies ambulatory patients with cancer at high risk of VTE.[10] Recently, two randomized controlled trials, AVERT and CASSINI, showed that prophylactic doses of direct oral anticoagulants (DOACs) reduced the risk of VTE in ambulatory patients with cancer at intermediate to high risk for VTE as determined by a Khorana score of ≥2, without a significant increase in the risk of major bleeding.[11-13] However, patients with MM were underrepresented in the derivation cohort for the Khorana score. Although CASSINI excluded patients with MM, the AVERT trial did include patients with MM as a "high-risk" cancer assigned 1 point.[12,13] Therefore, there is a need to quantify the VTE risk discrimination of the Khorana score in patients with MM. Here, we aimed to assess the discrimination of the Khorana score in patients with MM using a large cohort of US veterans.

2 | METHODS

We identified patients with newly diagnosed MM treated in the Veterans Affairs (VA) health care system between June 29, 2006, and December 31, 2013, using the International Classification of Diseases (ICD) O3 code 9732/3 within the VA Central Cancer Registry, and followed the cohort through December 31, 2014. To exclude patients with monoclonal gammopathy of undetermined significance, solitary plasmacytoma, and/or smoldering myeloma, we excluded patients who did not receive treatment within 6 months of MM diagnosis. Based on a sample size of 2870 patients, the power to reject the null hypothesis (ie, a concordance [c]-statistic of 0.50) was 96%. Prior to cohort assembly, the St. Louis VA Medical Center and Washington University School of Medicine institutional review boards approved this study.

We obtained data using the VA Informatics and Computing Infrastructure platform. Using height and weight assessed within 1 month of diagnosis, body mass index (BMI) was calculated. Hemoglobin (HGB), white blood cell (WBC) count, and platelet (PLT) count were obtained before treatment initiation but within 2 months of MM diagnosis. When height, weight, HGB, WBC count, or PLT count were not available electronically, the missing variables were abstracted manually from unstructured medical records, and if not available the patient was excluded. The primary outcome was the first episode of VTE that occurred within 6-months of MM-treatment initiation. Using a previously validated algorithm that combined ICD-9 diagnostic codes with prescription for anticoagulation or placement of an inferior vena cava filter, we identified VTE.[14] All VTEs were manually validated through chart abstraction. Patients who developed VTE between MM diagnosis and start of chemotherapy were excluded, as the Khorana score was developed for patients starting chemotherapy. Using the Pharmacy Benefits Management database, data were obtained on medication utilization, including antineoplastic therapy, aspirin, warfarin, and low-molecular-weight heparin (LMWH). Given that dexamethasone is sometimes started before chemotherapy, patients were considered dexamethasone users if they received a prescription between MM diagnosis and chemotherapy start date. Since the VA often prescribes more than a month's supply per prescription of aspirin, patients were considered aspirin users if they received a prescription within 90 days before MM diagnosis up to chemotherapy start date. For anticoagulant therapy, patients were considered users if they received a prescription within 30 days before MM diagnosis up to the start of chemotherapy.

We calculated the Khorana score as developed by assigning 1 point for the following variables: PLT ≥ 350 000/μL, HGB < 10 g/dL and/or use of erythropoiesis-stimulating agents (ESAs), WBC > 11 000/μL, and BMI ≥ 35 kg/m^2.[10] Patients with 0 points were classified as low risk, 1 to 2 points as intermediate-risk, and ≥3 points as high risk for VTE.[10] Logistic regression was used to quantify the odds ratio between the Khorana risk group and the incidence of VTE at 3 and 6 months following MM diagnosis while adjusting for the use of aspirin and anticoagulant therapy (warfarin or LMWH). We quantified model discrimination using the area under the c-statistic with a range of 0.5 (no discriminative ability) to 1.0 (perfect discriminative ability). Using 200 bootstrapped samples, 95% confidence intervals (CIs) for each c-statistic were generated. We assessed the association between risk score and development of VTE within 6 months after start of chemotherapy using a competing

risk model to adjust for the competing risk of non-VTE death.[15] A sensitivity analysis adjusting for putative thrombotic risk factors present at the time of initiation of chemotherapy (lenalidomide; thalidomide; history of VTE prior to MM diagnosis; and prescription of aspirin, warfarin, or LMWH) was performed. All medications were analyzed as time-varying variables.

We performed three additional sensitivity analyses. First, patients were categorized as high risk if their Khorana score was ≥2, similar to the AVERT and CASSINI trials.[12,13] In the second sensitivity analysis, we added 1 point to all patients for their diagnosis of MM and categorized patients as high risk with a score of ≥2 (and low risk otherwise), as in the AVERT trial.[12] Third, all patients receiving anticoagulation at the start of chemotherapy, regardless of dose, were excluded, and the association of Khorana score and VTE at 3 and 6 months was assessed using logistic regression. Analyses were performed using SAS version 9.2 software (SAS Institute, Cary, NC, USA) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

A total of 2870 patients with MM met entry criteria into the study (Figure 1). Most patients were male (97%), were of Black or White race (98%), and had a Khorana score of ≤2 (Table 1). Application of the Khorana score resulted in 1328 classified as low risk, 1521 as intermediate risk, and 21 as high risk for VTE. Within 3 months of MM diagnosis, 80 patients developed VTE with cumulative incidence as follows: 3.2% (95% CI, 2.3%-4.2%) in the low-risk group, 2.4% (95% CI, 1.8%-3.3%) in the intermediate-risk group, and 4.8% (95% CI, 0.3%-20.2%) in the high-risk group. Within 6 months of MM diagnosis, 128 patients developed VTE with cumulative incidence of 5.1% (95% CI, 4.0%-6.4%) in the low-risk group, 3.9% (95% CI, 3.0%-5.0%) in the intermediate-risk group, and 4.8% (95% CI, 0.3%-20.2%) in the high-risk group. The 6-month cumulative incidence of VTE stratified by Khorana score is listed in Table S1. Of the VTE events, 31% of patients had a pulmonary embolism, with the majority of events lower-extremity deep vein thromboses (Table 2).

There was no significant difference between the risk of VTE in the high- or intermediate-risk groups versus the low-risk group at 3 or 6 months (Table 3). The c-statistics were 0.58 (95% CI, 0.54-0.63) for 3 months and 0.53 (95% CI, 0.50-0.57) for 6 months. After excluding patients taking anticoagulants at the start of chemotherapy, results remained unchanged (Table 3), with c-statistics of 0.57 at 3 months and 0.56 at 6 months.

After adjusting for putative VTE risk factors, including chemotherapy, VTE history, aspirin, or anticoagulants, a competing risk analysis found no increased risk for VTE with increasing Khorana score (adjusted hazard ratio [aHR], 0.82 per 1-point increase; 95% CI, 0.63-1.08, $P = .17$). In the competing risk model, use of thalidomide or lenalidomide ($P = .02$) and dexamethasone (high dose, $P = <.001$) predicted VTE (Table 4). A second competing risk model found no significant association between VTE and individual variables (ie, PLT count, WBC count, HGB and/or use of ESAs, and BMI) of the Khorana score (Table 2, Supporting Information Appendix). That model had a significant interaction: patients receiving thalidomide or lenalidomide without anticoagulant therapy had twice the risk of VTE (aHR, 1.94; 95% CI, 1.30-2.90), but in patients taking lenalidomide or thalidomide, anticoagulants prevented VTE (aHR, 0.36; 95% CI, 0.16-0.81) (Table S2).

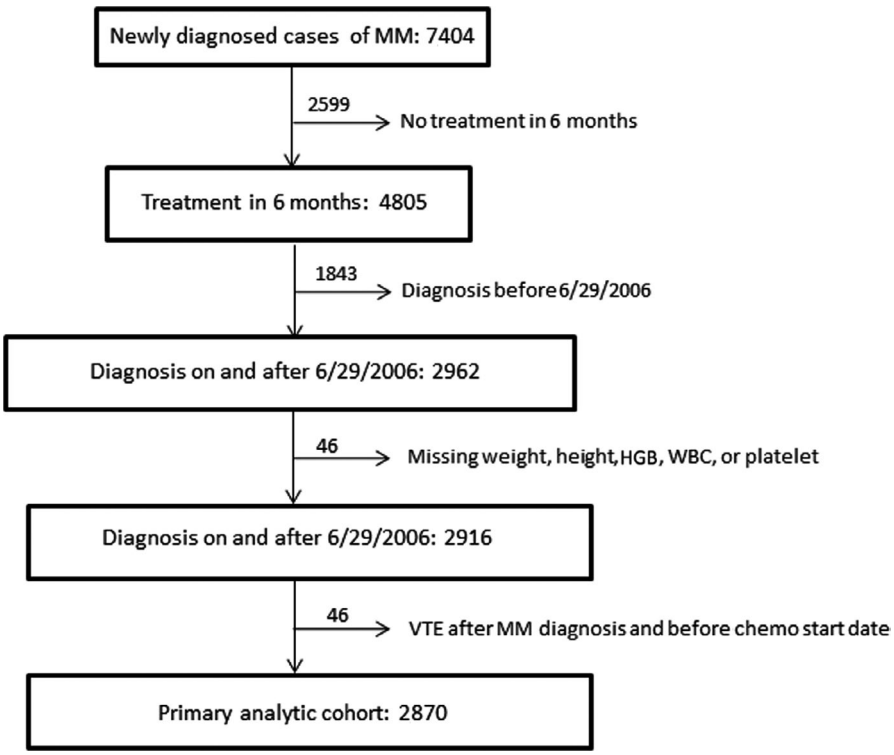

FIGURE 1 Flow diagram of patients enrolled in the cohort. HGB, hemoglobin; MM, multiple myeloma; VTE, venous thromboembolism; WBC, white blood cell count

TABLE 1 Demographic and clinical characteristics stratified by VTE in 6 months among US veterans diagnosed with multiple myeloma from 2006 to 2014

	VTE (n = 2870)		
Demographic clinical characteristics	**Yes n = 128**	**No n = 2742**	***P* value**
Age, y, mean	67.7	68.4	.44
Male, %	96.9	97.8	.50
Race, %			.16
White/Other	74.2	67.9	
Black	25.8	30.6	
Asian/Pacific Islander	0	1.5	
Body mass index, kg/m^2, %			.30
<18.5	0.8	2.2	
18.5–<25	24.2	30.2	
25–<30	43.0	37.7	
30–<35	22.7	19.1	
≥35	9.4	10.8	
Khorana score			.28
0	53.1	46.0	
1–2	46.1	53.3	
≥3	0.8	0.7	
Lenalidomide, %	22.7	19.4	.36
Thalidomide, %	20.3	16.5	.26
Melphalan, %	10.9	12.6	.58
Bortezomib, %	31.3	36.3	.25
Dexamethasone, %	78.1	69.4	.04
Aspirin, %	21.1	27.1	.13
Warfarin, %	8.6	9.5	.73
Low-molecular-weight heparin, %	4.7	4.4	.87
White blood cell > 11 × 10^9/L, %	5.5	5.7	.93
Platelet ≥ 350 × 10^9/L, %	5.5	5.5	.99
Hemoglobin < 10 g/dL, %	35.2	42.4	.11
History of VTE, %	4.7	3.0	.28
Median time to MM therapy, mo	0.79	0.76	.73

Aspirin, warfarin, and low-molecular-weight heparin use by Khorana risk group				
	Low risk n = 1328	**Intermediate risk n = 1521**	**High risk n = 21**	***P* value**
Aspirin, %	27.6	26.2	28.6	.67
Warfarin, %	10.2	8.8	9.5	.43
Low-molecular-weight heparin, %	4.4	4.5	0	.61

Abbreviations: MM, multiple myeloma; VTE, venous thromboembolism.

In the sensitivity analysis, where patients were recategorized as high risk if the Khorana score was ≥2 and low risk otherwise, there was no significant difference between the risk of VTE in the high- or low-risk group at 3 months (odds ratio [OR], 0.91; 95% CI, 0.42-2.01; *P* = .82) or 6 months (OR, 0.80; 95% CI, 0.42-1.55; *P* = .51). Findings remained unchanged when excluding patients taking anticoagulants at the start of chemotherapy. When assigning an additional 1 point for MM diagnosis, 1328 patients had a score of 1 point, while the remaining 1542 had a score of ≥2 points and no patients had a score of 0 points. There was no significant difference in risk of VTE between patients with a score of ≥2 versus 1 at 3 months (OR, 0.77; 95% CI, 0.49-1.20; *P* = .25) or 6 months (OR, 0.75; 95% CI, 0.52-1.06; *P* = .10). A competing risk analysis found no increased risk of VTE per 1-point increase in Khorana score after adding 1 point for MM diagnosis (aHR, 0.82; 95% CI, 0.63-1.08; *P* = .17), while adjusting for MM therapy and baseline aspirin or anticoagulant therapy.

4 | DISCUSSION

The Khorana score is the most validated VTE risk prediction model for ambulatory cancer patients with solid tumors and lymphoma.[16] In this study of 2870 US veterans with MM, the Khorana score did not accurately predict VTE in patients with MM (c-statistic 0.58 at 3-months and 0.53 at 6 months). The lack of discriminative ability was corroborated in a competing risk model and after adjusting for putative factors for VTE (VTE before MM diagnosis and prescription of lenalidomide, thalidomide, dexamethasone, aspirin, or anticoagulant therapy). Sensitivity analyses recategorizing risk group (high risk ≥2 points) or adding a risk point for MM diagnosis did not change findings.

Risk factors for VTE in MM include patient-, disease-, and treatment-specific factors not included in the Khorana score. While patient-specific risk factors may be similar across different cancer types, there are MM-specific risk factors not included in the Khorana score that may account for the modest discriminative ability of the model in patients with MM. First, patients with MM have a higher prevalence of cytopenias at diagnosis compared to patients with solid tumors.[17] In our cohort, 42% of patients presented with anemia (HGB < 10 g/dL), while only 5.6% presented with leukocytosis and 5.5% with thrombocytosis. Conversely, in the derivation cohort for the Khorana score, 6.2% presented with anemia (HGB < 10 g/dL), 12.6% leukocytosis, and 22% thrombocytosis. Thus, baseline complete blood count values used in the Khorana score may not predict VTE in MM. In addition, many MM therapies are thrombogenic. Two trials combining immunomodulatory imide drugs with dexamethasone or multiagent therapy found that VTE incidence exceeded 33%.[18,19] Adjunctive therapy in MM, such as dexamethasone, is also associated with VTE.[20,21] Patients with MM frequently present with pathologic fractures (>25% in some studies), [22,23] which are associated with an increased risk of VTE.[21] These events may necessitate surgery, which further increase risk of VTE.[20] Finally, cancer type is a risk factor in the Khorana score.[10] While several cancer types are classified as high risk for VTE in the Khorana score, MM is not.[10] In summary, patients with MM can benefit from a disease-specific risk prediction model for VTE to guide thromboprophylaxis.

The IMWG guidelines provided recommendations on VTE risk assessment and thromboprophylaxis in patients with MM.[24] However, these recommendations were based on an extrapolation of prior literature and expert opinion.[25] In the Myeloma XI trial, in which IMWG criteria identified high-risk patients, 80.5% of patients received thromboprophylaxis with aspirin or LMWH.[9] However, the 6-month cumulative incidence of VTE remained high (>10%). Recently, the predictive performance of the IMWG criteria was assessed in two large cohorts.[20,21] Similar to findings in the present study, the IMWG criteria were found to have low discriminative ability with a c-statistic of 0.52 in a cohort of Surveillance, Epidemiology, and Results Program–Medicare patients and a c-statistic of 0.55 in a cohort of US veterans.[20,21] Thus, two new risk prediction models were developed specifically in patients with MM, the SAVED score and IMPEDE VTE.[20,21] Both models had greater discrimination (SAVED score c-statistic, 0.60; IMPEDE VTE c-statistic, 0.64) than the IMWG criteria on external validation. Therefore, the National Comprehensive Cancer Network 2020 guidelines for cancer-associated thrombosis recently recommended using the SAVED score or IMPEDE VTE for VTE risk

TABLE 2 Distribution of VTE events within 6 months

Pulmonary embolism	N = 20
Pulmonary embolism + lower-extremity DVT	N = 20
Lower-extremity DVT	N = 71
Proximal	N = 56
Distal	N = 10
Site not specified	N = 5
Proximal upper-extremity DVT	N = 9
Line-associated	N = 4
Incidental	N = 5
Site not specified	N = 8

Abbreviation: DVT, deep vein thrombosis.

TABLE 3 Logistic regression for the risk of VTE in relation to Khorana risk score in MM

	3-month VTE OR (95% CI)	Number of VTE in 3 months	6-month VTE OR (95% CI)	Number of VTEs in 6 months
Entire cohort (n = 2870)[a]				
Low risk (n = 1328)	Reference	42	Reference	68
Intermediate risk (n = 1522)	0.76 (0.49-1.19)	37	0.74 (0.52-1.06)	59
High risk (n = 21)	1.51 (0.20–11.51)	1	0.93 (0.12-7.06)	1
Cohort excluding patients on anticoagulants (n = 2517)[b]				
Low risk (n = 1158)	Reference	40	Reference	62
Intermediate risk (n = 1340)	0.66 (0.41-1.06)	31	0.70 (0.48-1.02)	51
High risk (n = 19)	1.54 (0.20-11.85)	1	0.98 (0.13-7.43)	1

Abbreviations: CI, confidence interval; LMWH, low-molecular-weight heparin; MM, multiple myeloma; OR, odds ratio; VTE, venous thromboembolism.

[a]Adjusted for use of aspirin, warfarin, or LMWH.

[b]Adjusted for use of aspirin.

TABLE 4 Adjusted competing risk model of VTE in MM

	Adjusted HR	95% CI
Khorana score per 1-point increase	0.82	0.63-1.08
VTE before MM	1.89	0.80-4.45
Lenalidomide or thalidomide	1.62	1.08-2.41
Aspirin	0.75	0.50-1.12
Anticoagulation	0.67	0.36-1.25
Low-dose dexamethasone	1.52	0.97-2.37
High-dose dexamethasone	3.09	1.89-5.05

Abbreviations: CI, confidence interval; HR, hazard ratio; MM, multiple myeloma; VTE, venous thromboembolism.

prediction in patients with MM.[26] Further studies are needed to evaluate the clinical utility of incorporating these scores in the decision of thromboprophylaxis in patients with MM as well as the effect of adding biomarkers (eg, D-dimer).

The current study has several strengths and limitations. The cohort represented a large nationwide population. Patients had diverse therapy, with one-third receiving immunomodulatory agents. We were able to adjust for potential confounders including antithrombotic therapy and thrombogenic chemotherapy (ie, thalidomide, lenalidomide, and dexamethasone). Although most patients were White, over 25% of them were Black. It is possible that thrombotic events diagnosed outside of the VA health system were not captured. Also, given that the algorithm for detection of VTE required treatment or death within 30 days of ICD code for VTE, we may have missed untreated, nonfatal VTEs. In addition, we could not distinguish incidental versus symptomatic VTE. However, as staging computed tomography scans are not routinely done for the MM population, we expect that the majority of VTEs were symptomatic. Finally, given the gender distribution within the Veterans Health Administration, over 97% of our cohort was male. However, in available risk models for predicting VTE in ambulatory patients with cancer, sex was not a risk factor.[10,20,21,27,28] Still, our findings warrant validation within the female MM population. Finally, there were 21 patients in the cohort with a Khorana score of ≥3; thus, conclusions regarding this high-risk group are limited by power.

In conclusion, in this cohort of 2870 patients with MM, the Khorana score did not significantly predict VTE. While prior studies have validated the Khorana score among outpatients with solid tumor and lymphoma,[11] the score did not perform well in the MM population. Thus, our study supports the need to use myeloma-specific risk models to predict VTE risk in that population.[20,21]

RELATIONSHIP DISCLOSURE

KMS declares the following conflicts of interest: research funds from AstraZeneca and Astellas Pharma Global paid to the institution and outside the scope of the submitted work; advisory board fees from Pfizer Inc. and Bayer HealthCare Pharmaceuticals Inc. outside the scope of the submitted work; expert review for Covington & Burling LLP and Luther & Associates outside the scope of the submitted work; and travel funds from Pfizer Inc., AstraZeneca Pharmaceuticals LP, and Bayer HealthCare Pharmaceuticals Inc., all outside the scope of this study. TFW reports research funds from the ISTH outside the scope of this study; and advisory board fees from Pfizer Inc. and Servier outside the scope of this study. NMK reports personal fees from G1 Therapeutics, Invitae, Beyond Spring, Spectrum, Bristol-Myers Squibb, Janssen, and Total Health outside of the submitted work. KMS, KC, TFW, SL, NMK, JK, and BFG developed and validated the IMEPDE VTE score for prediction of VTE risk in MM. KMS and BFG helped developed the SAVED score for prediction of VTE risk in MM. All other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

KMS, KRC, SL, and BFG were involved in the conception and design of the study. KMS, SL, and JK were involved in collection and assembly of the data. SL performed all statistical analyses. All authors were involved in interpretation of data analyses. All authors were involved in manuscript preparation.

ORCID

Kristen M. Sanfilippo https://orcid.org/0000-0002-0433-7845
Tzu-Fei Wang https://orcid.org/0000-0003-2407-9000
Nicole Kuderer https://orcid.org/0000-0002-9263-8540

TWITTER

Kristen M. Sanfilippo @KSanfilippoMD
Tzu-Fei Wang @TzufeiWang
Nicole Kuderer @NicoleKuderer

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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