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Predicting Venous Thromboembolism in Multiple Myeloma: Development and Validation of the IMPEDE VTE Score

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Abstract

Background: Venous thromboembolism (VTE) is a common cause of morbidity and mortality among patients with multiple myeloma (MM). The International Myeloma Working Group (IMWG) developed guidelines recommending primary thromboprophylaxis in those identified at high-risk of VTE by the presence of risk factors. The National Comprehensive Cancer Network (NCCN) has adopted these guidelines; however, they lack validation. We sought to develop and

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Authorship Contributions:

Contribution: Kristen M. Sanfilippo, Suhong Luo, Mark Fiala, Kenneth R. Carson, Nicole M. Kuderer and Brian F. Gage. were involved in the conception and design of the study. Kristen M. Sanfilippo, Suhong Luo, Mark Fiala, Martin Schoen, and Theodore Thomas were involved in collection and assembly of the data. Suhong Luo and Mark Fiala performed data analysis. All authors were involved in interpretation of data analyses. All authors were involved in manuscript preparation.

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validate a risk prediction score for VTE in MM and to evaluate the performance of the current IMWG/NCCN guidelines.

Methods: Using 4,446 patients within the Veterans Administration Central Cancer Registry, we used time-to-event analyses to develop a risk score for VTE in patients with newly diagnosed MM starting chemotherapy. We externally validated the score using the Surveillance, Epidemiology, End Results (SEER)-Medicare database (N = 4,256).

Results: After identifying independent predictors of VTE, we combined the variables to develop the **IMPEDE VTE** score (**I**mmunomodulatory agent; Body **M**ass Index ≥ 25 kg/m^2; **P**elvic, hip or femur fracture; **E**rythropoietin stimulating agent; **D**examethasone/Doxorubicin; Asian **E**thnicity/Race; **V**TE history; **T**unneled line/central venous catheter; **E**xisting thromboprophylaxis). The score showed satisfactory discrimination in the derivation cohort, *c*-statistic = 0.66. Risk of VTE significantly increased as score increased (hazard ratio 1.20, $p = <0.0001$). Within the external validation cohort, IMPEDE VTE had a c-statistic of 0.64. For comparison, when evaluating the performance of the IMWG/NCCN guidelines, the c-statistic was 0.55.

Conclusion: In summary, the IMPEDE VTE score outperformed the current IMWG/NCCN guidelines and could be considered as the new standard risk stratification for VTE in MM.

Keywords

Venous Thromboembolism; Multiple Myeloma; Clinical Prediction Rule; Risk; Primary Prevention

Introduction:

Compared to the general population, patients with multiple myeloma (MM) have a 9-fold increased risk of venous thromboembolism (VTE).[1] Risk of VTE is even greater in MM patients treated with immunomodulatory (IMID) drugs (e.g., lenalidomide) or additional thrombogenic drugs (e.g., dexamethasone).[2–4] With treatment advances transforming MM from a fatal disease to a chronic one[5], a common cause of death in this population is VTE.[6,7] Despite the overall reduction in MM-related mortality, MM patients with VTE have a 3-fold increased risk of death at one year following MM diagnosis compared to MM patients without VTE.[8,9]

Thromboprophylaxis is a safe and effective way to prevent VTE. In a recent trial of outpatients with cancer, low-dose apixaban decreased risk of VTE (hazard ratio (HR) 0.41; 95% confidence interval (CI) 0.26–0.65) with a small increase in bleeding compared to placebo.[10,11] Two randomized trials[12,13] found thromboprophylaxis with aspirin, low-molecular-weight heparin (LMWH), or warfarin to be safe in patients with MM on IMID drugs. However, these trials excluded patients with high risk of VTE (e.g. prior history of VTE) and did not provide guidance on VTE risk stratification.[14] Overall, rates of VTE in MM remain >10%.[15]

The International Myeloma Working Group (IMWG) set forth guidelines, adopted by the National Comprehensive Cancer Network (NCCN), for the prevention of VTE in MM patients on IMID therapy[16,17]; however, these guidelines lack validation.[18] In a recent study,

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the NCCN/IMWG guidelines identified only 55% of patients who developed VTE as high-risk.[15] A validated VTE risk score predicts VTE among patients with solid tumors,[11] but not MM.[19] A risk score for VTE in MM would allow for the use of thromboprophylaxis in patients at high-risk while avoiding anticoagulant exposure in low-risk patients. Therefore, we sought to develop and validate a risk prediction score for VTE in patients with newly diagnosed MM starting therapy, as well as to evaluate the performance of the NCCN/IMWG guidelines.

Methods:

Assembly of Cohorts

Using International Classification of Diseases (ICD)-O3 codes 9732/3, we identified patients diagnosed with MM between September 1, 1999 and June 30, 2014 within the Veterans Administration Central Cancer Registry (VACCR) (derivation cohort). We excluded patients who did not receive chemotherapy within 6 months of MM diagnosis. We defined chemotherapy start date as the date of administration of the first chemotherapy agent. Selected chemotherapy agents included bendamustine, bortezomib, cisplatin, cyclophosphamide, doxorubicin, etoposide, lenalidomide, melphalan, and thalidomide. Chemotherapy start date for patients receiving dexamethasone monotherapy was the date of first prescription for dexamethasone. We excluded patients who received a transplant within 4 months of chemotherapy start, as these patients likely received treatment outside of the VA. We censored those who underwent transplant between 4 to 6 months at the time of transplant.

Using the VA Informatics and Computing Infrastructure platform, we obtained ICD-9 codes, Pharmacy Benefits Management (PBM) records, and laboratory data. Using ICD-9 codes, we obtained comorbidities present at the time of MM diagnosis by identifying at least two ICD-9 codes within 12 months prior to MM diagnosis. Using ICD-9 procedure codes, we defined recent surgery as cardiovascular, orthopedic, abdominal, urologic, or neurologic surgery occurring within 30 days before MM diagnosis up to start of chemotherapy. Similarly, we identified patients with a fracture of the pelvis, femur, hip within 30 days prior to MM diagnosis up to start of chemotherapy using ICD-9 codes. Using CPT codes, we identified placement of a tunneled line/central venous catheter (CVC). We recorded baseline laboratory data available from 30 days prior to MM diagnosis up to start of chemotherapy. For patients with multiple laboratory values, we selected the values closest to MM diagnosis. We assessed height and weight from 30 days prior to MM diagnosis up to the start date of chemotherapy. Similarly, if multiple height and weight data were available, we selected the value closest to MM diagnosis date. We calculated body mass index (BMI) using height and weight.[20] We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula.[21] PBM included dates of administration of all inpatient and outpatient drugs. We defined dexamethasone use as “high-dose” if total monthly dosing was greater than 160 mg; otherwise, we defined it as “low-dose” to conform to current practice patterns. However, for validating current NCCN guidelines, we defined “NCCN high-dose” as ≥ 480 mg monthly; otherwise, we defined it as “NCCN low-dose”. Using standard definitions[22,23], we classified LMWH prescriptions as

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therapeutic or prophylactic dosing. We classified all warfarin prescriptions as *therapeutic*. We manually abstracted all missing data, if unavailable we excluded those patients.

We retrospectively followed patients for 180 days after start of chemotherapy. The VA Vital Status File provided date of death from multiple sources: VA Beneficiary Identification and Records Locator Subsystem Death File, the Social Security Administration Death Master File, the Medicare Vital Status File, and the Medical SAS® Inpatient Datasets. Using ICD-9 codes, we identified cases of VTE prior to MM diagnosis and within 6 months of starting chemotherapy for MM with the requirement of the presence of at least two ICD-9 codes. We confirmed all cases of VTE with manual chart abstraction.

Using the linked Surveillance, Epidemiology, End Results (SEER)-Medicare cohort, we assembled an external validation cohort of patients with MM. Using ICD-O3 code 9732, we identified patients diagnosed with MM from January 1, 2007 to December 31, 2013. For inclusion, patients had to be Medicare eligible (≥ age 65) and continuously enrolled on Medicare parts A, B, and D starting one year prior to MM diagnosis. As with the derivation cohort, we excluded patients without treatment with chemotherapy within 6-months after MM diagnosis.

Definitions for all variables within the SEER-Medicare cohort were consistent with those used for the VACCR cohort with the following alterations. However, we did not exclude patients who received a transplant within 4 months of chemotherapy start, as unlike the VA data, this occurrence was unlikely to suggest care outside of the Medicare healthcare system. We censored those who underwent transplant between chemotherapy start date and 6 months at the time of transplant. We identified placement of a tunneled line/CVC using a combination of ICD-9, CPT and HCPCS codes. Using the National Claims History, Outpatient Medicare claims, and Part D medication files, we identified administration of all prescription medications including chemotherapy. Aspirin use was not available within this cohort. The SEER-Medicare data lacks vital sign information, thus we used ICD-9 codes to identify patients with a BMI of overweight, obese and morbidly obese. We identified VTE through use of a previously validated algorithm that used the combination of VTE-related treatment and ICD-9 code to identify VTE as manual abstraction was not possible.[24]

For baseline patient characteristics within the derivation and validation cohorts, we used the χ^2 to compare proportions, the Cochran-Mantel-Haenszel and Wilcoxon tests for categorical variables, and unpaired Student's t tests for continuous variables. Prior to cohort assembly, the St. Louis VA Medical Center and Washington University institutional review boards approved the study.

IMPEDE VTE Score Derivation

We identified candidate risk factors in myeloma through literature review and univariate analyses (Supplemental Table 1). We considered candidate predictors for entry into the multivariate model, if on univariate analysis they had a $p < 0.05$ or with a $p < 0.5$ with findings consistent with prior literature, as recommended.[25] We used the methods of Fine and Gray to model time to VTE while accounting for the competing risk of non-VTE death.[26] We entered intermittent treatments as time-varying variables, minimizing risk of immortal

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time bias and loss of information from variables that change over time.[25,27] We adjusted the model for year of diagnosis. Using a backward, stepwise approach, we retained variables in the multivariate model with a $p < 0.05$, or with a $p < 0.4$ with findings consistent with prior literature as above.[25] We derived the risk score by multiplying the parameter estimate for each variable by a common number, and rounding to the nearest integer. The risk score for each patient was the sum of integers for all predictor variables. Using risk scores, we calculated incidence rates for VTE.

We assessed discrimination by calculating Harrell's *c*-statistic.[28] We assessed the association of the prediction score and development of VTE using competing risk analysis. Using the D'Agostino modification of the Hosmer-Lemeshow test, we assessed model calibration defined as the agreement between the observed and predicted probability of VTE by IMPEDE VTE.[29] We internally validated the IMPEDE VTE score using a bootstrap procedure whereby we generated a new sample equal to the size of the cohort by randomly drawing subjects, with replacement, from the original cohort. For each of the 500 bootstrapped samples, we calculated the risk score and Harrell's *c*-statistic. Using the 500 samples, we calculated the average *c*-statistic.

IMPEDE VTE External Validation

We externally validated the IMPEDE VTE risk score using the SEER-Medicare cohort. We used the *c*-statistic to assess discrimination and competing risk analysis to quantify the association of the risk score and development of VTE.[26]

Sensitivity Analyses

In both the validation cohort, we excluded patients on therapeutic or prophylactic dose anticoagulation and then assessed the score discrimination through calculation of Harrell's *c*-statistic.

IMWG/NCCN Validation

Within the VACCR cohort, we validated the NCCN/IMWG VTE guidelines (Supplemental Table 2) for MM using a subgroup of patients receiving IMID therapy after excluding those receiving anticoagulation. As suggested by the guidelines we defined a score of 0–1 points as low-risk and ≥2 points as high-risk. In addition, we defined all patients receiving NCCN high-dose dexamethasone, doxorubicin, or multiagent chemotherapy (excluding bortezomib) in combination with IMID therapy as high-risk. To assess discrimination, we calculated Harrell's *c*-statistic.[28] We assessed the association of a high-risk score with development of VTE using competing risk analysis.[26] We carried out statistical analyses using SAS version 9.4 (SAS Institute, Cary, NC).

Results:

Patient Characteristics

The VACCR cohort contained 4,446 patients (Figure 1). The average follow up for the cohort was 5.1 months. Of the patients in the cohort, 2,837 were diagnosed after 7/½006 and thus after approval of lenalidomide. Within 6-months of starting chemotherapy, 259 patients

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(5.8%) developed VTE (Supplemental Table 3). Baseline characteristics of patients with VTE versus those without are in Table 1. In addition to the 110 patients who underwent transplant during the study period, an additional 463 proceeded to one after the study period. The SEER-Medicare cohort contained 4,256 patients. Two hundred and twenty-one patients (5.2%) developed VTE within 6-months of starting chemotherapy. Baseline patient characteristics are presented in Supplemental Table 4. A comparison of the baseline characteristics between the VACCR and SEER-Medicare cohorts is listed in Supplemental Table 5.

IMPEDE VTE Score Derivation

Supplemental Table 1 shows results of all univariate analyses. Using VACCR cohort, the final multivariate model included the following predictors after elimination: use of IMIDs; BMI ≥ 25 kg/m^2; pelvic, hip or femur fracture; use of ESAs, doxorubicin, or dexamethasone; history of VTE; presence of a tunneled line/CVC, while Asian/Pacific Islander ethnicity/race and use of thromboprophylaxis (therapeutic anticoagulation or prophylactic anticoagulation/aspirin) were protective for VTE (Table 2).

We assigned points for each variable by multiplying the parameter estimate from the Fine and Gray model by 5 and rounding the product to the nearest integer. This resulted in the acyronym and the final point assignment as listed in Table 3 (**IMPEDE VTE** score). Using the point assignments, the **IMPEDE VTE** score had a *c*-statistic of 0.66. When using the beta coefficients instead of point scores, the *c*-statistic was unchanged at 0.66.

Validation and Risk of VTE according to the Clinical Prediction Score

Using the bootstrap method, we internally validated our score. The average Harrell's *c*-statistic of the samples was 0.66 (95% CI: 0.63 – 0.70). The D'Agostino modification of the Hosmer-Lemeshow test indicated good agreement between the observed and predicted probability of VTE ($p = 0.41$). Using the point assignments, Table 4 and Figure 2 show the 6-month cumulative incidence of VTE. The HR for VTE increased by 1.20 per point (95% CI: 1.15–1.24, $p = <0.0001$). Patients in the lowest risk group, IMPEDE VTE score ≤ 3, have a 6-month cumulative incidence of VTE after start of chemotherapy of 3.3% (95% CI: 2.6–4.1) while those with a score of ≥ 8 had an incidence of > 15% (95% CI: 12.1–19).

IMPEDE VTE External Validation

Within the SEER-Medicare cohort, IMPEDE VTE had a *c*-statistic of 0.64. In the validation cohort, the HR for VTE increased by 1.16 per point (95% CI: 1.11 – 1.21, $p = <0.0001$).

Sensitivity Analyses

At the time of chemotherapy start, 389 patients within the VACCR cohort was taking therapeutic or prophylactic anticoagulation. After exclusion of these patients, the IMPEDE VTE had a *c*-statistic of 0.65. Within the validation cohort, after exclusion of patients on anticoagulation, the *c*-statistic = 0.62.

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NCCN/IMWG Validation

In the VACCR cohort, 2,208 patients initiated lenalidomide or thalidomide and were not receiving anticoagulation at the start of therapy. In this population, Harrell's *c*-statistic for the NCCN/IMWG guidelines was 0.55. Risk of VTE in patients defined as high-risk (≥2 points) versus low risk (0–1 points) was 1.39 (95% CI: 1.00–1.92, *p*-value 0.05).

Discussion:

We developed a risk prediction score to quantify risk of VTE in patients with MM starting chemotherapy. Using a nationwide sample, we developed the **IMPEDE VTE** score, which comprises the following nine variables: **I**MIDs; B**M**I; **P**elvic, hip or femur fracture; use of **E**SAs, use of **D**examethasone/**D**oxorubicin; **E**thnicity/Race; **V**TE history; **T**unneled line/CVC; and **E**xisting thromboprophylaxis. The rate of VTE significantly increased as IMPEDE VTE risk score increased (HR 1.20 per point, $p = <0.0001$). The 6-month cumulative incidence of VTE for scores of ≤ 3, 4–7 and ≥8 was 3.3, 8.3 and 15.2, respectively in the derivation cohort (Figure 2, Table 4).

The IMPEDE VTE score discrimination was adequate in both the derivation cohort (*c*-statistic = 0.66) and the validation cohort (*c*-statistic = 0.64). Given availability of data in SEER-Medicare, we were unable to account for aspirin use in the validation cohort. Based off characteristics in the VACCR, as well as that observed in the United States, we estimate 19–50% of patients in the SEER-Medicare cohort were likely using aspirin.[30–32] In addition, vital signs are not reported in SEER-Medicare data, preventing calculation of BMI for identification of obesity.[33] Prior studies have shown that use of ICD-9 codes for obesity have low sensitivity.[34] We identified 479 patients (11.3%) within SEER-Medicare with an ICD-9 code for overweight, obesity or morbid obesity. Prevalence of BMI ≥ 25 kg/m^2 within the VACCR was 66.8%. In a sensitivity analysis, when we eliminated points for aspirin or BMI within the derivation cohort, the *c*-statistic decreased to 0.65. Thus, it is possible the lower c-statistic in the validation cohort reflects the unknown aspirin use and BMI in the SEER-Medicare cohort.

The discrimination (*c*–statistic) of our prediction model is in line with the performance of alternate prediction models for VTE, including in the cancer and non-cancer population.[35,36] In addition, the discrimination of the IMPEDE VTE score outperforms the current IMWG/NCCN guidelines, which had a *c*-statistic 0.55 in the VACCR cohort. These guidelines use VTE risk estimates based on expert opinion as the only available option for risk stratification.[37] Current guidelines are poorly adopted in clinical practice, with selection of thromboprophylaxis unrelated to VTE risk category.[38] Rates of VTE in MM patients starting chemotherapy remain high, exceeding 10%.[15]. Of patients who develop thrombosis, only 55% are identified as high-risk by current guidelines.[16] Hence, we developed an evidence-based risk prediction score with external validation, IMPEDE VTE score. While our score offers a significant improvement on current guidelines, given the risk of the MM population, further improvements in risk prediction would likely require incorporation of biomarkers into a model (e.g. d-dimer).

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Thromboprophylaxis is safe and effective in patients with cancer at high-risk of VTE. In the AVERT trial, the rate of major bleeding was 4.2% with no bleeding in to critical organs noted.[10] In AVERT, 6-month rates of VTE in patients with a Khorana score ≥ 2 was >10%. Patients with an IMPEDE VTE score ≥8 had a similar 6-month incidence. In the CASSINI trial, the rate of major bleeding during prophylaxis with rivaroxaban in high-risk cancer patients was low at 2.0%.[39] When considered together, there was a significant reduction in risk of symptomatic VTE in patients with cancer and high-risk of VTE receiving prophylaxis versus placebo (relative risk (RR) 0.58; 95% CI 0.35–0.94).[40] In addition, there was no significant increase in risk of major bleeding compared to placebo (RR 1.96; 95% CI 0.88–4.33). Similarly, prescribing prophylaxis in MM who have a high-risk of VTE risk could reduce morbidity and mortality. Two prior trials assessed thromboprophylaxis in MM with major bleeding rates < 1%.[12,13] However, these trials excluded patients with history of VTE, and lacked power to quantify the benefit of thromboprophylaxis. No formal VTE risk assessment was conducted in either trial but they demonstrated that thromboprophylaxis was safe in this population. Our risk score allows provider-based VTE risk assessment. Given the continued high rate of VTE in MM,[15] future thromboprophylaxis trials should incorporate a formal risk assessment score for VTE such as IMPEDE VTE.

In our model, patients with a score of ≤ 3 had a 6-month cumulative incidence of VTE of 3.3% (upper limit of confidence bounds = 4.1%). Based on risk-benefit, avoidance of thromboprophylaxis in this population might be an acceptable strategy. Conversely, patients with scores of ≥ 8 had 6-month cumulative rates of VTE that exceeded 15% and could be considered for thromboprophylaxis (lower limit of confidence bounds = 12.1%). For example, low-dose apixaban reduced the rate of VTE from 10.2% to 4.2% in a recent trial of high-risk cancer patients.[10]

Several variables associated with VTE-risk in alternate populations, were not significant predictors in our analysis. Age and male gender, in contrast to prior studies[41], were not associated with risk of VTE in our population. This finding was similar to prior MM studies.[13,14,42] In addition, surgery has been associated with a high risk of post-operative VTE.[41] However, we found no increased risk of VTE in after recent surgery. We suspect that the variable for recent fracture fully adjusted for the increase risk of VTE after hip fracture repair. Of the 89 patients who had a fracture, 56 subsequently underwent surgery within 30 days. Our model includes treatments that may have decreased in utilization since the start of the study period (e.g. high-dose dexamethasone and doxorubicin). However, the NCCN guidelines list the option to use doxorubicin in combination therapy for upfront treatment of MM. In addition, while the derivation cohort includes patients diagnosed back to 1999, the validation cohort demonstrates performance in a modern patient population diagnosed after approval of modern therapy (e.g. lenalidomide). Last, some studies have suggested a possible protective effect of bortezomib for VTE in MM.[43,44] However, several large, phase III randomized trials found no significant association between bortezomib assignment and VTE.[45–47] Thus, given the inconsistent association of bortezomib with VTE in MM and its insignificant association in the derivation dataset, we did not force bortezomib into the model.

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We took several steps to improve the validity of the IMPEDE VTE score. We used a large, nationwide cohort with individual patient data. We manually confirmed all VTE events. Third, we validated it externally. Fourth, we studied two real-world populations. Fifth, we used readily available clinical variables to assess VTE risk. Sixth, we avoided developing a model based exclusively on stepwise selection, which can lead to a loss of predictive information.[48,49] Instead, we used a liberal p value ($p = 0.4$) to include variables that predicted VTE in previous studies, as recommended[25,50]. We included tunneled line/CVC in our model as presence significantly increased risk of VTE (p = 0.04). Of the events that occurred in our cohort, 6.2% (n=16) were classified as line-associated upper extremity deep vein thrombosis. A recent post-hoc analysis of the CASSINI trial suggested a reduction in risk of line-associated VTE with thromboprophylaxis.[51] Lastly, to increase generalizability, we included patients already taking thromboprophylaxis. Half of American adults use aspirin regularly.[30] Accounting for the potential protective effect[52] of aspirin improves VTE prediction. In addition, patients may be on anticoagulation at the start of chemotherapy for alternate indications (e.g. atrial fibrillation, prior VTE). Given our model, providers will still be able to risk assess this population and provide patient education regarding risk. A subgroup analysis excluding this population in the validation cohort found the model still discriminated risk with a c-statisic of 0.62.

The study has some limitations. Given the retrospective study design, we were not able to assess whether biomarkers (e.g. D-dimer) could improve score discrimination. Future research should focus on addition of these variables to IMPEDE VTE. Second, while the derivation cohort was a nationwide sample, it contained relatively few women, Asians or Pacific islanders, which may have resulted in reduced power to quantify risk of VTE in these populations. However, as with prior literature,[53] Asian ethnicity protected against VTE. In addition, a recent study looking at risk of VTE in MM found a reduction in risk associated with Asian ethnicity.[54] Aspirin is available as an over-the-counter medication, thus it is possible some Veterans received aspirin outside of the VA pharmacy and aspirin use was not known in the validation cohort. Last, in the time after the study period, the FDA has approved additional chemotherapy agents for MM (e.g. carfilzomib, ixazomib, daratumumab). However, in upfront clinical trials, these agents have not been associated with high rates of VTE.[55–57]

Summary:

In summary, we developed and validated the IMPEDE VTE score, which outperformed the risk stratification in the IMWG/NCCN guidelines. Risk assessment can help clinicians select thromboprophylaxis in high-risk patients, and avoid anticoagulants in those at low VTE risk. These data suggest that the IMPEDE VTE score could replace the risk stratification within the current guidelines for identification of patients with MM at high risk of VTE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Essentials

- Venous thromboembolism (VTE) is a cause of morbidity and mortality in multiple myeloma (MM)
- Guidelines recommend VTE prophylaxis in MM at high-risk by a risk-assessment model (NCCN/IMWG)
- The NCCN/IMWG model discriminates VTE risk poorly, c-statistic = 0.55
- IMPEDE VTE improves VTE risk-discrimination in MM and could be considered the new standard model

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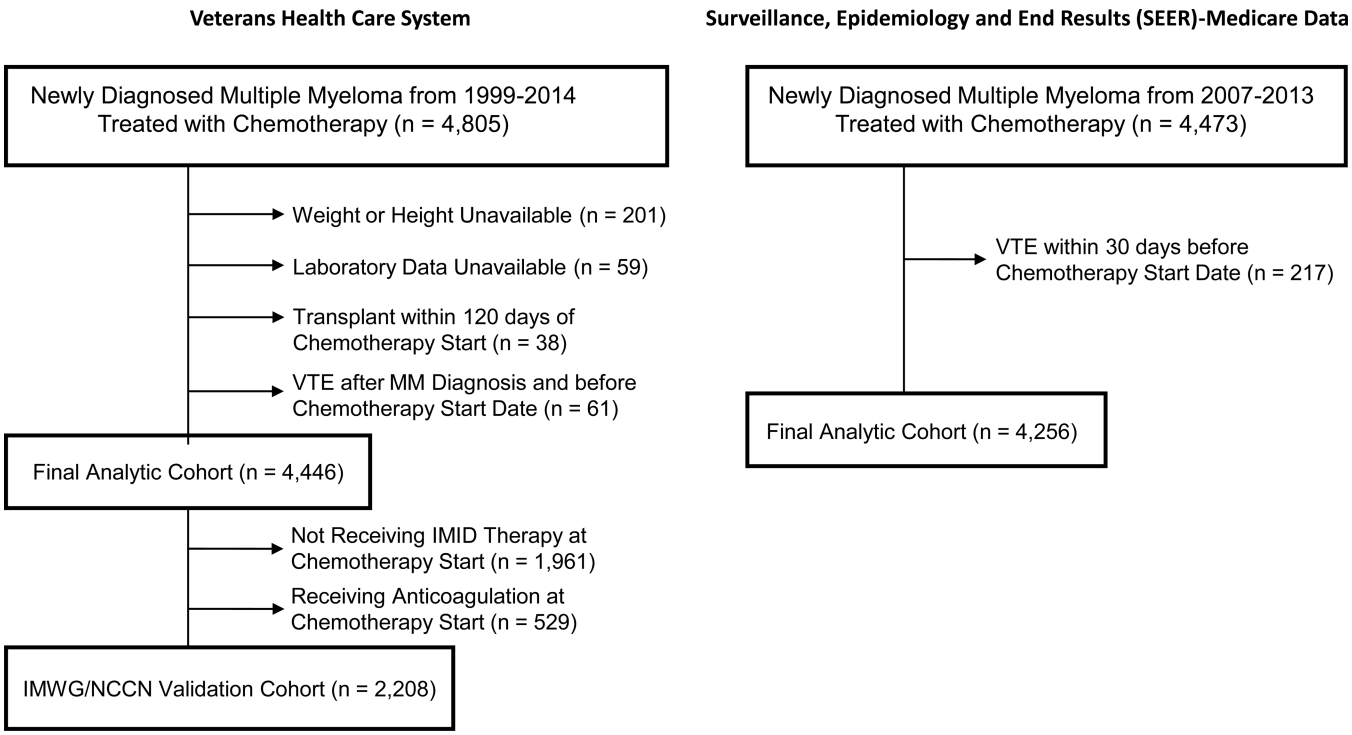

Figure 1.
Flow diagram showing selection process of patients with multiple myeloma.

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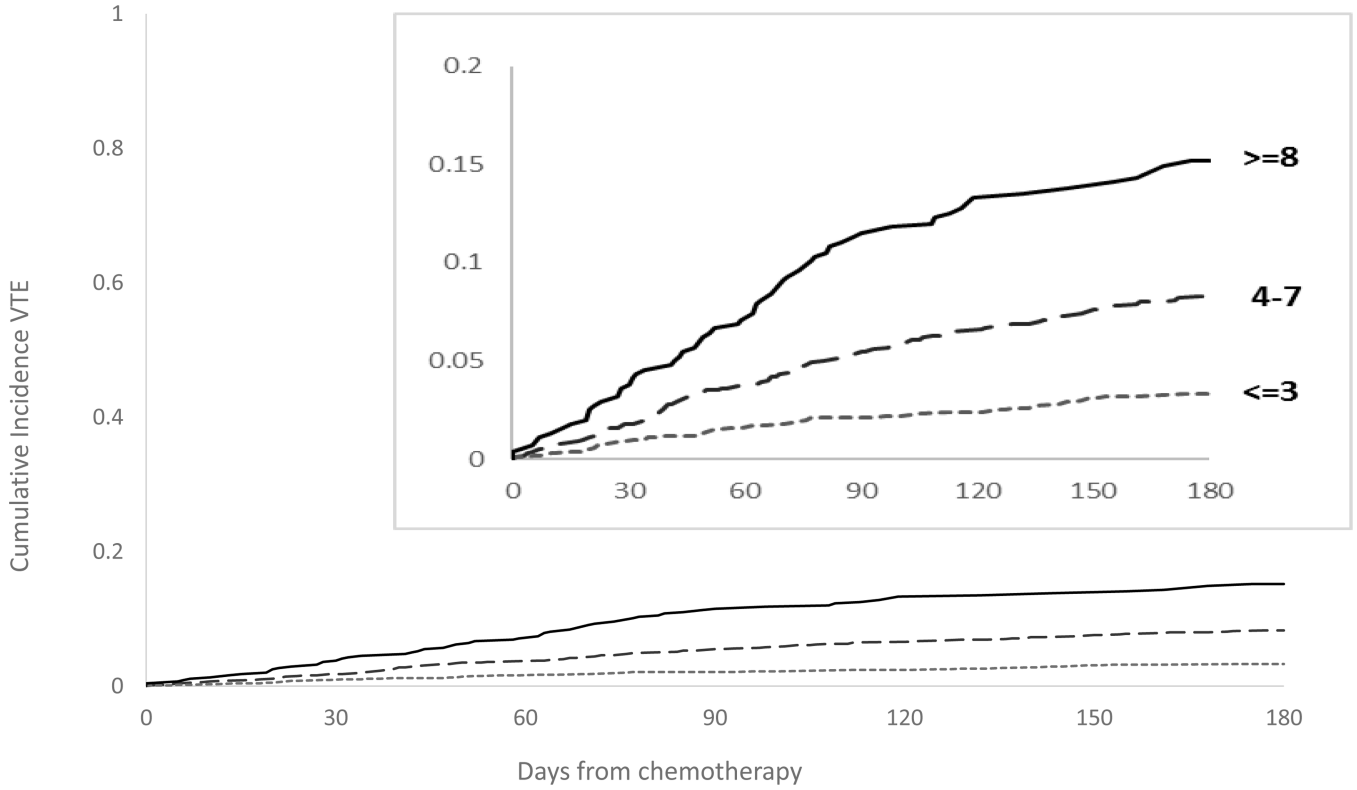

Figure 2.
6-Month Cumulative Incidence Curves of VTE according to IMPEDE VTE Score.

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Table 1:

Demographic and clinical characteristics at chemotherapy start stratified by VTE in 6 months (Yes vs. No) among US veterans diagnosed with MM from 1999 to2014 (N=4446)

Demographic clinical characteristics	VTE in 6 months after chemo		P-value
	Yes (n=259)	No (n=4187)	
Age (mean years)	67.2	68.5	0.048
Male (%)	253 (97.7)	4099 (97.9)	0.82
Race (%)			0.33
White	188 (72.6)	2872 (68.6)	
Black	69 (26.6)	1257 (30.0)	
Asian/Pacific Islander	2 (0.8)	58 (1.4)	
Body Mass Index (BMI) (%)			0.048
BMI < 18.5	2 (0.8)	105 (2.5)	
18.5 <= BMI < 25	70 (27)	1302 (31.1)	
25 <= BMI < 30	107 (41.3)	1612 (38.5)	
BMI >= 30	80 (30.9)	1168 (27.9)	
Hemi- or Paraplegia (%)	6 (2.3)	71 (1.7)	0.50
History of Venous Thromboembolism	13 (5.0)	97 (2.3)	<0.001
Diabetes (%)	59 (22.8)	1139 (27.2)	0.12
Diagnostic year (median)	2007	2008	0.16
Central Venous Catheter (%)	11 (4.3)	180 (4.3)	0.95
Transplant (%)	13 (5.0)	96 (2.3)	<0.001
Immunomodulatory Drug (%)	148 (57.1)	1813 (43.3)	<0.001
Dexamethasone (%)			<0.001
No use	54 (20.9)	1405 (33.6)	
Low dose	113 (43.6)	1830 (43.7)	
High dose	92 (35.5)	952 (22.7)	
Bortezomib (%)	70 (27)	1252 (29.9)	0.32
Doxorubicin (%)	37 (14.3)	301 (7.2)	<0.001
Erythropoietin (%)	78 (30.1)	1080 (25.8)	0.13
Warfarin (%)	26 (10)	578 (13.8)	0.09
Low Molecular Weight Heparin (%)			<0.001
Prophylactic	16 (6)	121 (2.9)	
Therapeutic	9 (3.5)	50 (1.2)	
Aspirin (%)	69 (26.6)	1357 (32.4)	0.05
Fracture (%)	14 (5.4)	117 (2.8)	0.02
Surgery (%)	10 (3.9)	230 (5.5)	0.25
Hemoglobin < 10g/dL OR Hematocrit < 30g/dL (%)	103 (39.8)	1670 (40.6)	0.80
Platelet ≥ 350 × 10^9/L (%)	19 (7.3)	251 (6.0)	0.39
Estimated Glomerular Filtration Rate < 30 mL/min (%)	56 (21.6)	942 (22.5)	0.73
White Blood Cell ≥ 10 × 10^9/L (%)	15 (5.8)	389 (9.3)	0.06

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Table 2:

Time-Varying Multivariate Prediction Model Derivation

	Backward Elimination	
Predictor	**β Coefficient**	***P* - Value**
Immunomodulatory Drug	0.76	<0.001
Body Mass Index ≥ 25 kg/m^2	0.22	0.11
Pelvic, Hip or Femur Fracture	0.86	<0.001
Erythropoiesis-Stimulating Agent	0.21	0.22
Doxorubicin	0.50	0.04
Dexamethasone		
High-Dose	0.86	<0.001
Low-Dose	0.48	0.01
Asian/Pacific Islander	−0.63	0.37
History of Venous Thromboembolism before MM	1.05	<0.001
Central Venous Catheter	0.46	0.04
Therapeutic Low Molecular Weight Heparin or Warfarin	−0.72	<0.001
Prophylactic Low Molecular Weight Heparin or Aspirin	−0.59	<0.001

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Table 3:

IMPEDE VTE Score

Predictor	***Acronym***	**Score**
Immunomodulatory Drug	**I**	4
Body **M**ass Index ≥ 25 kg/m^2	**M**	1
Pelvic, Hip or Femur Fracture	**P**	4
Erythropoiesis-Stimulating Agent	**E**	1
Doxorubicin	**D**	3
Dexamethasone		
High-Dose		4
Low-Dose		2
Ethnicity/Race = Asian/Pacific Islander	**E**	−3
History of **V**enous Thromboembolism before MM	**V**	5
Tunneled Line/Central Venous Catheter	**T**	2
Existing Thromboprophylaxis: Therapeutic LMWH or Warfarin	**E**	−4
Existing Thromboprophylaxis: Prophylactic LMWH or Aspirin		−3

LWMH = Low Molecular Weight Heparin

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Table 4:

6-Month Cumulative Incidence of VTE based on IMPEDE VTE Score

	Derivation Cohort (VACCR)	
Score	**VTE/No VTE in 6 months**	**6-Month Cumulative Incidence % (95% CI)**
≤ 3	67/2245	3.3 (2.6–4.1)
4–7	129/1553	8.3 (7.1–9.8)
≥8	63/389	15.2 (12.1–19)