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ORIGINAL ARTICLE

D-dimer predicts venous thromboembolism in multiple myeloma: a nested case-control study

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Abstract

Background: Clinical risk assessment scores, such as IMPEDE VTE, can identify patients with multiple myeloma (MM) at high-risk of venous thromboembolism (VTE). Refinement of these scores, by including 1 or more biomarkers, could improve risk assessment.

Objectives: We sought to determine the association between soluble P-selectin (sP-selectin) and D-dimer with VTE in MM.

Methods: We identified 545 patients with newly diagnosed MM. Using a nested case-control design, we identified 38 cases of VTE within 6-months of MM treatment and 137 randomly selected controls. Using logistic regression, we examined the association between D-dimer and sP-selectin with VTE. We also analyzed the association after adjusting for IMPEDE VTE.

Results: Each 1-point increase in IMPEDE VTE score was associated with a 27% increase in odds of VTE (odds ratio 1.27; 95% CI 1.08-1.51; *c*-statistic 0.61; 95% CI 0.51-0.71). There was no association between sP-selectin and VTE. Each one increase in natural log of D-dimer was associated with a 44% increase in odds of VTE, so we assigned points (ranging from −2 to +2) to D-dimer values and incorporated them into IMPEDE VTE, forming *IMPEDED VTE*. There was a 30% increase in odds of VTE per each 1-point increase in IMPEDED VTE (OR 1.30; 95% CI 1.12-1.52; *c*-statistic 0.65; 95% CI 0.55-0.75).

Conclusion: Among patients with newly diagnosed MM starting chemotherapy, D-dimer was associated with increased odds of developing VTE within the subsequent 6-months. The addition of D-dimer to IMPEDE VTE—*IMPEDED VTE*—could improve prediction of VTE among patients with MM.

KEYWORDS
D-dimer, multiple myeloma, risk assessment, thromboprophylaxis, venous thromboembolism

Essentials

- Anticoagulation is effective in reducing risk of venous thromboembolism (VTE) in high-risk patients with cancer.
- Adding biomarkers to clinical risk scores (eg, IMPEDE VTE) could improve VTE risk assignment.
- In this study, high D-dimer, but not soluble P-selectin, predicted VTE in patients with multiple myeloma.
- Adding D-dimer to IMPEDE VTE—IMPEDED VTE—could improve VTE prediction in patients with myeloma.

1 | INTRODUCTION

Venous thromboembolism (VTE) causes morbidity and mortality among patients with multiple myeloma (MM) [1,2]. In patients with MM, VTE is associated with a 2-fold increase in the risk of death [1,2]. Thromboprophylaxis is a safe and effective way to prevent VTE in ambulatory patients with cancer at high risk of VTE [3,4].

Clinical risk assessment scores (IMPEDE VTE, PRISM, and SAVED scores) can identify patients with newly diagnosed MM at high risk of VTE [5–9]. These scores use clinical variables (and PRISM also includes cytogenetics). When starting MM therapy, patients with high VTE risk are recommended for thromboprophylaxis [10].

Refinement of the scores, by including 1 or more additional biomarkers, could clarify which patients are likely to benefit from thromboprophylaxis. Two biomarkers, soluble P-selectin (sP-selectin) and D-dimer, predict VTE in outpatients with cancer [11,12] and improve prediction of VTE in patients with solid tumors [13–15]. Accordingly, we hypothesized that sP-selectin and D-dimer would predict VTE in patients with MM.

2 | METHODS

2.1 | Patients and study design

We used the biobank "Tissue Acquisition for Genomic and Proteomic Analysis of Plasma Cell Dyscrasias" at Washington University in St. Louis (first patient enrolled March 31, 2005) to conduct a nested retrospective case-control study. The biorepository (maintained by R.V.) archives tissue and plasma from patients with plasma cell dyscrasias, including MM, to identify novel mutations involved in disease initiation and progression. Patients with an established or suspected diagnosis of MM were recruited after providing informed consent. To protect research personnel from unnecessary risk, patients with hepatitis B or C, human T-lymphotropic virus, or HIV were not enrolled. At study inclusion, patients underwent structured data collection. Patients are followed prospectively, and data on treatment and outcomes are collected until death, loss to follow-up, or consent withdrawal. Data are managed using Research Electronic Data Capture hosted at Washington University St. Louis [16,17].

Between 2007 (following the Food and Drug Administration approval of lenalidomide) and 2019, 545 patients with plasma samples available at the time of MM diagnosis were enrolled. Patients were excluded if they lacked follow-up data (N = 116). Of the remaining 429 patients, 35 cases of VTE within 6 months of anti-MM treatment initiation were identified using International Classification of Disease codes. We randomly selected 140 controls (ratio of 1:4) from the remaining 394 patients. Subsequently, data were manually abstracted and reviewed for accuracy for the following variables: VTE within 6 months of anti-MM treatment initiation, history of VTE prior to MM diagnosis, first-line MM-specific chemotherapy, and VTE risk factors in MM. VTE risk factors were dexamethasone dose; presence of a central venous catheter; use of erythropoietin-stimulating agents; antithrombotic therapy; pretreatment laboratory data; and presence of a pelvic, hip, or femur fracture within 30 days prior to the start of MM therapy. All patients had pretreatment laboratory data available. Lack of documentation of a rare variable (eg, erythropoietin-stimulating agents use) was assumed to represent absence of the variable.

2.2 | Outcome definition

VTE was defined as objectively confirmed deep vein thrombosis or pulmonary embolism, including VTEs that were asymptomatic or distal. Superficial VTEs were excluded. Methods of objective confirmation of VTE diagnosis were duplex ultrasonography or venography, computed tomography angiogram, and/or ventilation/perfusion lung scan. Only VTEs that occurred within 6 months of starting MM therapy were considered.

2.3 | sP-selectin and D-dimer measurement

Venous peripheral blood was obtained by venipuncture or cannulation of an indwelling venous access device at time of MM diagnosis and prior to treatment initiation. Ten-milliliter samples were placed in sterile K2EDTA vacutainer tubes. Whole blood was separated within 1 hour of collection, and plasma aliquots were preserved at −80 °C until testing was performed. sP-selectin levels (nanograms per milliliter) were measured by Eve Technologies Corp using the Luminex 100 system (Luminex) with the MILLIPLEX Human Cardiovascular Disease Panel 2 2-Plex kit (Millipore) according to the manufacturer's protocol. D-dimer levels (micrograms per milliliter fibrinogen equivalent units [FEUs]) were measured by an immune-turbidimetric assay (STA-Liatest D-Di, Diagnostica Stago S.A.S.) on a STA-R Compact STA Satellite analyzer (Diagnostica Stago) at one of our (J.DP.) laboratories according to the manufacturer's protocol. All analyses were performed in duplicate with

results averaged. Laboratory personnel were blinded to patients' characteristics and outcomes.

2.4 | Statistical analysis

We examined the associations between sP-selectin and D-dimer with development of VTE using bivariate statistics and multivariable weighted logistic regression models. We tested if the association of each biomarker was an independent predictor of VTE by adjusting for IMPEDE VTE. In addition to being used as a continuous variable, sP-selectin and D-dimer were dichotomized based on precedent [12,14]; sP-selectin and D-dimer levels were dichotomized as elevated (75th percentile or greater) and nonelevated (<75th percentile). As D-dimer levels can increase with worsening renal function, we further adjusted for estimated glomerular filtration rate (eGFR). Based on the results of the multivariable analyses, we tested revised risk scores incorporating associated biomarkers with IMPEDE VTE and compared models using the *c*-statistic. The goodness of fit of models was assessed using the Hosmer-Lemeshow test. Analyses were conducted using R Statistical Software (R Foundation for Statistical Computing) and RStudio (RStudio, PBC) [18,19].

3 | RESULTS

3.1 | Patient characteristics

We studied 175 patients. Using manual data abstraction as the gold standard, we identified 38 cases with VTE within the first 6 months of therapy, 3 of which were not captured on the initial screening based on International Classification of Disease, 10th Revision codes, and 137 randomly identified controls. The median time from chemotherapy initiation to VTE was 51 days (range, 4-193 days). The most common VTE event was proximal lower extremity deep vein thrombosis (n = 13), followed by pulmonary embolism (n = 10) (Table 1).

TABLE 1 Distribution of venous thromboembolism within the first 6-months of multiple myeloma treatment.

Venous thromboembolism classification	No. of patients
Pulmonary embolism	10
Pulmonary embolism and lower extremity deep vein thrombosis	3
Lower extremity deep vein thrombosis	
Distal	9
Proximal	13
Upper extremity deep vein thrombosis	
Line-associated	2
Not line-associated	1

3.2 | IMPEDE VTE

The median IMPEDE VTE score was 4 (IQR, 3-6). Patients who developed VTE were more likely to have a central venous catheter (32% vs 10%) and had higher baseline IMPEDE VTE scores (5.8 vs 4.7) (Table 2). Each 1-point increase in IMPEDE VTE score was associated with a 27% increase in odds of VTE (odds ratio [OR], 1.27; 95% CI, 1.08-1.50; $P < .001$); the model *c*-statistic was 0.61 (95% CI, 0.51-0.71). The Hosmer-Lemeshow test suggested poor model calibration ($P = .04$) (Supplementary Figure 1).

3.3 | sP-selectin

Median sP-selectin was 189 ng/mL (IQR, 140-271 ng/mL). There was no significant difference ($P = .94$) in baseline sP-selectin between patients who experienced VTE (mean, 215 ng/mL) and those who did not (mean, 217 ng/mL). Twenty-six percent of those with VTE were in the 75th percentile of sP-selectin compared to 25% of those without VTE ($P = .85$).

There was no significant association between sP-selectin and VTE using raw values (OR per 1 standard deviation increase 0.99; 95% CI, 0.69-1.36; $P = .93$) or when dichotomized at the 75th percentile (OR, 1.08; 95% CI, 0.48-2.24; $P = .84$). Controlling for IMPEDE VTE score or eGFR did not substantially change the results.

3.4 | D-dimer

The median D-dimer was 1.18 μg/mL FEU (IQR, 0.56-2.16 μg/mL FEU). Six patients were below the lower level of quantification, and 1 patient was above the upper level of quantification per the manufacturer's (STA-Liatest D-Di) assay; these patients were excluded from analysis of D-dimer as a continuous variable but were included in the analysis of ordinal variables. The upper limit of normal of this assay was 0.50 μg/mL FEU.

Twenty-nine percent of those in the 75th percentile of D-dimer (>2.1 μg/mL FEU) experienced VTE compared to 19% of those without ($P = .25$). Due to positive skewness (2.58), D-dimer was transformed using the natural log (resulting skewness, 0.22) (Supplementary Figure 2). Patients with VTE had higher D-dimer (mean, 0.34 logs) than those without (mean, 0.04 logs), but the difference was not statistically significant ($P = .11$). In univariate analyses, the OR (95% CI) of VTE was 1.31 (0.95-1.83) per each one increase in the natural log of D-dimer ($P = .11$) and 1.71 (0.82-3.42) for D-dimer in >75th percentile ($P = .14$). When adjusting for IMPEDE VTE, the adjusted OR (95% CI) of VTE was 1.44 (1.03-1.72; $P = .04$) per each one increase in the natural log of D-dimer, while the dichotomized variable was not significantly associated with VTE (adjusted OR, 1.89; 95% CI, 0.89-3.85; $P = .08$). Adjusting for eGFR did not substantially change the results for either model.

TABLE 2 Baseline characteristics according to IMPEDE VTE variable and IMPEDE VTE point system.

IMPEDE VTE variable	VTE (*n* = 38)	No VTE (*n* = 137)	Univariate *P* value	IMPEDE VTE points
Immunomodulatory drug				4
Lenalidomide	76%	77%	1.00	
Thalidomide	5%	4%	1.00	
Body mass index > 25 mg/m^2	84%	81%	.83	1
Pathologic fracture	5%	1%	.23	4
Erythropoietin-stimulating agent	0%	1%	1.00	1
Doxorubicin	0%	1%	1.00	3
Dexamethasone			.57	
High dose	40%	33%		4
Low dose	61%	67%		2
Race/ethnicity			.36	
White	79%	87%		
African American	21%	12%		
Other/Asian/Pacific Islander	0%	1%		−3
VTE prior to multiple myeloma diagnosis	5%	7%	1.00	5
Tunneled/central venous line	32%	10%	<.001	2
Existing antiplatelet/anticoagulant				
Aspirin	55%	59%	.81	−3
Anticoagulation	3%	9%	.36	−4
IMPEDE VTE score (mean)	5.8	4.7	.02	
Baseline biomarker levels				
D-dimer (mean)	2.2 μg/mL	1.8 μg/mL	.33	
sP-selectin (mean)	215.5 ng/mL	217.0 ng/mL	.94	

VTE, venous thromboembolism; sP-selectin, soluble P-selectin.

3.5 | IMPEDED VTE

We then assigned points to nontransformed D-dimer values based on the odds association of the natural log of D-dimer with VTE from the multivariable analysis. Points were assigned as follows: −2 points for a D-dimer level <0.41 μg/mL FEU, −1 point for a D-dimer level of 0.41 to <0.83 μg/mL FEU, 0 points for a D-dimer level of 0.83 to <1.70 FEU, 1 point for a D-dimer level of 1.70 to <3.31 μg/mL FEU, and 2 points for a D-dimer level ≥3.31 μg/mL FEU. The points for D-dimer were chosen to satisfy the following constraints: (1) the average IMPEDE VTE and IMPEDED VTE scores would be the same; (2) the ORs from a 1.0 μg/mL-point increase in D-dimer and a 1-point increase in IMPEDE VTE would be the same; and (3) the distance between each threshold in D-dimer would be constant (on the logarithmic scale).

When combining D-dimer with IMPEDE VTE using these points, we formed *IMPEDED VTE*. There was a 30% increase in odds of VTE (OR = 1.30; 95% CI, 1.12-1.52; *P* < .001) per each 1-point increase in IMPEDED VTE (Supplementary Table). The model *c*-statistic for IMPEDED VTE was 0.65 (95% CI, 0.55-0.75), which was not statistically better (*P* = .20) than the *c*-statistic for IMPEDE VTE. The Hosmer-Lemeshow test suggested satisfactory model calibration (*P* = .63) (Supplementary Figure 3).

4 | DISCUSSION

Activation of the hemostatic system among patients with MM is common and may be associated with an increased risk for VTE [20–22]. D-dimer is a marker of coagulation, and elevations predict VTE in other populations [11,14,23]. We found that per each one increase in the natural log of D-dimer, there was a significant increase in odds of VTE in patients with newly diagnosed MM after adjusting for IMPEDE VTE (adjusted OR, 1.44; 95% CI, 1.03-1.72). Assigning points to D-dimer levels improved model discrimination (IMPEDED VTE); however, these findings were not significantly improved from IMPEDE VTE, *c*-statistic 0.65 (95% CI, 0.55-0.75) versus 0.61 (95% CI, 0.51-0.71).

sP-selectin is a cell adhesion molecule that plays a role in thrombus growth via increasing generation of fibrin and accrual of

tissue factor [24]. While prior studies found that elevated sP-selectin level is associated with increased risk of VTE in other cancer populations [12,22], we found no association between sP-selectin and risk of VTE.

In 2 cohorts of patients with mostly solid tumors, both sP-selectin and D-dimer predicted the occurrence of VTE [11,20]. Accordingly, both biomarkers improved the predictive performance of a clinical risk prediction model for VTE in that population [14]. However, only 2.2% of the prior cohorts had a diagnosis of MM [11,14]. Limited prior studies have assessed sP-selectin levels or D-dimer in patients with MM [25,26]. Our study demonstrates that elevated D-dimer level predicts VTE in patients with newly diagnosed MM, but sP-selectin does not.

We found that D-dimer alone was not sufficient to predict VTE in patients with MM. The National Comprehensive Cancer Network guidelines recommend the use of either IMPEDE VTE or SAVED clinical risk assessment scores to identify patients with newly diagnosed MM at high risk of VTE. Accordingly, adjusting for thromboprophylaxis and other factors in IMPEDE VTE provided a more accurate estimate of the association between elevated D-dimer and VTE. Assessment of both the association between D-dimer and VTE in MM as well as the gain in predictive performance of adding D-dimer to clinical prediction models, such as IMPEDED VTE, in larger cohorts is warranted based on our findings.

Our study has several strengths. First, we confirmed all VTE events. Second, we measured biomarkers in duplicate. Third, we used a commercial D-dimer assay that is readily available in clinical practice. Fourth, we included all factors in the IMPEDE VTE score [5]. Our study was not without limitations. First, the sample size was modest, so future confirmation is warranted. Second, our cohort was from a large tertiary care center, so patients with an acute VTE might have presented to their local medical center and not reported that event to their hematologist/oncologist. However, our electronic medical record is linked with most healthcare systems in the area. Similarly, absence of variables, such as medications and comorbidities, was assumed to represent true absence. Given the retrospective design of this study, it is possible that the absence instead represented missingness of data. Finally, patients referred for transplant evaluation may be healthier with fewer medical comorbidities compared to patients not referred for transplant evaluation.

In conclusion, among patients with newly diagnosed MM starting chemotherapy, D-dimer was associated with incident VTE within the subsequent 6 months. The addition of D-dimer to IMPEDE VTE, IMPEDED VTE, could improve prediction of VTE in MM. Future research is warranted.

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AUTHOR CONTRIBUTIONS

K.M.S. and B.F.G. conceived the study. K.M.S. drafted the first version of the manuscript. M.A.F. performed all analyses and drafted the methods section of the manuscript. H.T. and D.F. abstracted all data. T.G. ran all D-dimer testing. R.V. provided the cohort. J.D.P. supported all D-dimer testing. All authors reviewed the manuscript to allow for editing and approved the final version.

RELATIONSHIP DISCLOSURE

K.M.S. developed the IMPEDE venous thromboembolism score and received funds for consulting for the Health Services Advisory Group. B.F.G. developed the IMPEDE venous thromboembolism score. All other authors have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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