A composite risk assessment model for venous thromboembolism

Mary Sixian Lin, MD,[a] Hilary Hayssen, MD,[a] Minerva Mayorga-Carlin, MPH,[a] Shalini Sahoo, MA,[a] Tariq Siddiqui, MS,[b] Georges Jreij, MD,[a] Brian R. Englum, MD,[a] Phuong Nguyen, PhD,[c] Yelena Yesha, PhD,[c] John David Sorkin, MD, PhD,[d,e] *and* Brajesh K. Lal, MD,[a,b] *Miami, Florida; and Baltimore, Maryland*

ABSTRACT

Objective: Venous thromboembolism (*VTE*) is a preventable cause of hospitalization-related morbidity and mortality. VTE prevention requires accurate risk stratification. Federal agencies mandated VTE risk assessment for all hospital admissions. We have shown that the widely used Caprini (30 risk factors) and Padua (11 risk factors) VTE risk-assessment models (*RAMs*) have limited predictive ability for VTE when used for all general hospital admissions. Here, we test whether combining the risk factors from all 23 available VTE RAMs improves VTE risk prediction.

Methods: We analyzed data from the first hospitalizations of 1,282,014 surgical and non-surgical patients admitted to 1298 Veterans Affairs facilities nationwide between January 2016 and December 2021. We used logistic regression to predict VTE within 90 days of admission using risk factors from all 23 available VTE RAMs. Area under the receiver operating characteristic curves (*AUC*), sensitivity, specificity, and positive (*PPV*) and negative predictive values (*NPV*) were used to quantify the predictive power of our models. The metrics were computed at two diagnostic thresholds that maximized (1) the value of sensitivity + specificity-1; and (2) PPV and were compared using McNemar's test. The Delong-Delong test was used to compare AUCs.

Results: After excluding those with missing data, 1,185,633 patients (mean age, 66 years; 93% male; and 72% White) were analyzed, of whom 33,253 (2.8%) had a VTE (deep venous thrombosis [DVT], n = 19,218, 1.6%; pulmonary embolism [PE], n = 10,190, 0.9%; PE + DVT, n = 3845, 0.3%). Our composite RAM included 102 risk factors and improved prediction of VTE compared with the Caprini RAM risk factors (AUC composite model: 0.74; AUC Caprini risk-factor model: 0.63; $P < .0001$). When the sum of sensitivity and specificity-1 was maximized, the composite model demonstrated small improvements in sensitivity, specificity and PPV; NPV was high in both models. When PPV was maximized, the PPV of the composite model was improved but remained low. The nature of the relationship between NPV and PPV precluded any further gain in PPV by sacrificing NPV and sensitivity.

Conclusions: Using a composite of 102 risk factors from all available VTE RAMs, we improved VTE prediction in a large, national cohort of >1 million general hospital admissions. However, neither model has a sensitivity or PPV that permits it to be a reliable predictor of VTE. We demonstrate the limits of currently available VTE risk prediction tools; no available RAM is ready for widespread use in the general hospital population. (J Vasc Surg Venous Lymphat Disord 2025;13:101968.)

Keywords: Deep venous thrombosis; Prevention; Risk assessment; Risk factors; Venous thromboembolism

Venous thromboembolism (VTE), comprised of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a major preventable health problem in hospitalized patients. Over one-half of all VTEs are associated with hospitalization, with PE being one of the leading preventable causes of hospital mortality.[1-3] Recent data suggest that the incidence of VTE is increasing.[2,4] Reduction in incident VTE has become a national initiative, with calls for improved screening, prevention, and treatment of VTE coming from the National Quality Forum, Joint Commission, and the Centers for Medicare and Medicare Services.[1]

Prevention of VTE is predicated on accurate and reliable assessment and stratification of risk for VTE. Several risk assessment models (RAMs) have been developed to predict VTE. Of these, the Caprini RAM is one of the most widely used models. The Caprini RAM calculates a risk score for VTE from values assigned to a list of 30 VTE risk

From the Department of Surgery, University of Maryland School of Medicine, Baltimore[a]; the Department of Surgery, Baltimore VA Medical Center, Baltimore[b]; the Department of Computer Science, University of Miami, Miami[c]; the Department of Geriatric Research, Education, and Clinical Center, Baltimore VA Medical Center, Baltimore[d]; and the Department of Medicine, University of Maryland School of Medicine, Baltimore.[e]

Presented at the Thirty-eighth Annual Meeting of the Eastern Vascular Society, Charleston, South Carolina, September 19-22, 2024.

Additional material for this article may be found online at www.jvsvenous.org.

Correspondence: Brajesh K. Lal, MD, Department of Surgery, University of Maryland 22 South Greene St Baltimore, MD 21201 (e-mail: blal@som.umaryland.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2024.101968

factors.[5,6] The risk score is then stratified into risk categories for VTE with corresponding prophylaxis recommendations.

Several studies have confirmed the ability of existing VTE RAMs to effectively predict VTE in subsets of high-risk groups such as cancer, thoracic surgery, plastic surgery, gynecology, and trauma patients.[7-13] However, few studies have evaluated their performance in the general hospitalized population, where they are now being used to risk stratify and guide decisions on VTE prophylaxis. We recently evaluated the two most commonly used RAMs, Caprini and Padua, and found that both models have limited ability to predict incident VTE when applied to the general hospital population.[14] In addition, other existing VTE RAMs offer no significant advantage over the Caprini RAM.[15,16]

Because high-risk patient subpopulations have higher event rates for VTE and stronger associations between risk factors and the outcome, models developed using these groups are biased to perform better. Unfortunately, this also results in poor performance when the same model is applied to the general population, in which the event rate for VTE is lower and there are weaker associations between risk factors and VTE. Another reason for the poor performance of existing models may be that the risk factors used may not be comprehensive enough to accurately predict VTE risk and are thus more effective in the subpopulations for which they were initially designed. Almost all existing RAMs were developed by selecting a small group of risk factors empirically, based on the individual authors' assessment of their association with VTE. The number of risk factors was generally restricted in an attempt to make them user-friendly and implementable in a clinical environment. The onset of thrombosis is complex and multifactorial, such that many factors can contribute to the overall risk for VTE. Thus, the risk factors included in each individual RAM may be too limited to accurately predict VTE risk in the general hospital population. We posited that, to better compute risk for VTE in the general population, a broader set of risk factors must be included in a risk assessment model.

We developed a new composite RAM designed to predict VTE risk within 90 days of hospital admission using 102 risk factors taken from all 23 currently available VTE RAMs. We compared the predictive ability of our composite VTE RAM with a model using the Caprini risk factors. Comparison metrics included the area under the receiver-operating characteristic curve (AUC), sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) of each RAM. We hypothesized that our composite RAM would demonstrate improved predictive ability compared with the Caprini model risk factors in an unselected general hospital population.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter retrospective cohort study of >1 million hospitalized patients
- **Key Findings:** We developed a new composite risk assessment model (RAM) for venous thromboembolism (VTE) using 102 risk factors taken from the 23 currently available VTE RAMs. We improved VTE prediction compared with the Caprini RAM risk factors; however, neither the Caprini risk factors nor our composite model is an effective predictor of VTE.
- **Take Home Message:** Combining risk factors used in the 23 currently available VTE risk assessment models does not offer a clinically useful stratification tool; no available RAM is ready for widespread use in the general hospital population.

METHODS

Study design, setting, and participants. We conducted a multicenter retrospective cohort study using data obtained from the Veterans Affairs Informatics and Computing Infrastructure (VINCI). VINCI is a repository that stores all data entered in the electronic medical record used at all Veterans Affairs (VA) health care facilities in the nation. We obtained data from all 1298 VA medical facilities nationwide on the first admission and 90-day follow-up of all patients aged 18 and older, between January 2016 to December 2021. We excluded individuals diagnosed with a VTE on admission or within 90 days prior to admission to focus on incident VTE associated with hospitalization. The protocol was approved by the Institutional Review Board of the University of Maryland and the Baltimore VA Research and Development Committee.

Variable definitions. The primary outcome measure was VTE diagnosed within 90 days of admission. VTE was defined using the International Classification of Diseases (ICD-10) codes that were diagnostic for DVT, PE, or DVT with PE (Supplementary Table I, online only). The 102 independent variables used in the composite model were selected from an aggregate list of variables taken from all 23 existing VTE RAMs.[6,17-38] Data describing each admitted patients' status in relation to the 102 independent variables was obtained from ICD-10 codes, Current Procedural Terminology (CPT) codes, demographic data, clinical and nursing orders, laboratory data, medications, and operating room data stored in VINCI. Surgical patients were defined as those who had undergone a surgical procedure during hospital admission regardless of the service they were admitted to, and medical patients were defined as those who had not. A total of 123 different risk factors were identified in the 23 RAMs (Supplementary Table II, online only). Of the 123 variables, 102 were used in the composite model. Among the 21 variables that were excluded from the analysis, primary reasons for exclusion included: (1) an excessive number of patients were missing values for the variable,

such that the total number of patients able to be included in the study would be severely limited; (2) there was overlap with already included variables; and (3) the variables were poorly defined. All 1,185,633 patients in our cohort had available data for all 102 variables. The complete list of variables used in the model are provided in Supplementary Table II (online only).

Statistical methods. To compare demographic and clinical characteristics of the study cohort, we used the Pearson χ^2 test (categorical variables) and the Student *t*-test (continuous variables). To generate the composite model, 102 independent variables from the 23 RAMs were used as the predictor variables in a logistic regression where the outcome was the development of a VTE within 90 days of hospital admission. To generate the model using the Caprini risk factors for comparison, the Caprini risk factors were used as predictor variables in a logistic regression to predict VTE within 90 days of hospital admission. Because we used only traditional statistical modeling techniques via logistic regression in this analysis, the entire study cohort was used to both develop and run our models. The predictive power of our composite RAM and the Caprini risk factor model was quantified using AUC, sensitivity, specificity, PPV, and NPV. The AUCs of our composite RAM and the Caprini risk factor model were compared using the Delong-Delong test.[39] The sensitivity, specificity, PPV, and NPV of the two models were compared using McNemar's test.[40] Given the large size of the study cohort, a P value of $< .001$ was selected as the threshold for statistical significance. Analyses were performed using SAS version 8.3 (SAS Institute Inc).

We graphed the relationship between PPV, sensitivity, and NPV of both models to facilitate selection of the optimal cut-point (value separating VTE predicted to occur vs VTE predicted not to occur). Using the graphs for each model, we identified two distinct cut-points and calculated the sensitivity, specificity, PPV, and NPV at the two cut-points. The first cut-point maximized the value of sensitivity + specificity − 1, otherwise known as Youden's J index[41]; the second maximized the PPV. Two distinct cut-points were chosen to allow for two clinical interpretations of the composite RAM. Utilization of the first approach, in which sensitivity and specificity are given equal weight, results in a test with maximum ability to differentiate between groups. This is because the metric of the sum of sensitivity and specificity − 1 approaches its maximum value of 1 as the error in prediction (false negatives and false positives) approaches zero. This cut-point selection method is suitable if the RAM is used as a screening test for VTE, where the aim is to properly predict as many incident VTEs as possible. The second cut-point, a diagnostic threshold maximizing PPV, is useful if the priority is to minimize those who are unnecessarily treated with VTE prophylaxis. The cut-points under each approach were generated using predicted probability values obtained from the logistic regression function in SAS. For the first approach, the predicted probability corresponding to the maximum value of sensitivity + specificity − 1 was selected as the cut-point; for the second approach, the predicted probability corresponding to the maximum PPV was selected as the cut-point.

RESULTS

Study cohort

A total of 1,282,014 unique patients were admitted to VA medical facilities between January 1, 2016, and December 1, 2021 (Supplementary Fig, online only). A total of 29,554 patients were excluded due to either a diagnosis of a VTE at the time of admission (n = 17,474) or a diagnosis of VTE up to 90 days prior to admission (n = 12,080). A total of 54,198 patients were excluded for extreme variable values, including body mass index (BMI) <15 or >60 kg/m^2 (n = 49,857), hospital length of stay greater than 60 days (n = 3456), duration of surgery greater than 10 hours (n = 847), and age less than 18 years (n = 38). Finally, to perform a complete case analysis, 12,629 patients were excluded due to missing values for variables used in the composite model. Following all exclusions (n = 96,381; 7.5%), the final study cohort consisted of 1,185,633 patients. This cohort was used to generate and compare the composite and Caprini risk factor models.

Demographics

The average age of the cohort was 65.8 years (Table I). The average age was higher among patients who developed a VTE compared with those who did not (68.1 vs 65.7 years; $P < .0001$). Approximately 93% of the cohort was male, and 72.1% were white. A higher proportion of patients who developed a VTE were Black (24.6%) compared with those who did not develop a VTE (21%) ($P < .0001$). The average BMI of the cohort was 29.3 kg/m^2 and was similar in those who did and did not develop a VTE. Hospital length of stay was longer among those who developed a VTE (7.1 days) compared with those who did not (3.5 days; $P < .0001$). The cohort consisted of 26.7% surgical patients (n = 316,354). A greater proportion of medical patients developed VTE (n = 25,751; 2.96%) compared with surgical patients (n = 7502; 2.37%) ($P < .0001$). Those who developed a VTE had higher rates of multiple comorbidities, including hypertension, chronic heart disease, history of cancer, renal insufficiency, and respiratory disease, as well as higher rates of COVID-19 infection and prior VTE ($P < .0001$) (Table I). The mean Caprini score among those with VTE (5.4) was higher than that of those without (4.8) ($P < .0001$) (Table I). Of the total study population, 47% (n = 558,674) received pharmacologic prophylaxis within 48 hours of hospital admission (Table I). A greater

Table I. Demographic features of 1,185,633 consecutive patients' first admission between January 2016 and December 2021

	VTE (N = 33,253)	No VTE (N = 1,152,380)	Total (N = 1,185,633)[d]	*P* value[g]
Age, years[a]	68.1 (11.9)	65.7 (13.7)	65.8 (13.7)	< .0001
Sex[b]				< .0001
Female	1584 (4.8)	81,929 (7.1)	83,513 (7.0)	
Male	31,669 (95.2)	1,070,451 (92.9)	1,102,120 (93.0)	
Race[b]				< .0001
White	22,946 (69)	831,673 (72.2)	854,619 (72.1)	
Black	8193 (24.6)	242,143 (21.0)	250,336 (21.1)	
Native American or Pacific Islander	507 (1.5)	19,962 (1.7)	20,469 (1.7)	
Asian	123 (0.4)	7167 (0.6)	7290 (0.6)	
Other	1484 (4.5)	51,435 (4.5)	52,919 (4.5)	
BMI, kg/m^2[a]	29.2 (6.9)	29.3 (6.6)	29.3 (6.6)	.01
Hospital length of stay, days[a]	7.1 (8.4)	3.5 (4.7)	3.6 (4.8)	< .0001
Patient classification[b,c]				< .0001
Surgical	7502 (22.6)	308,852 (26.8)	316,354 (26.7)	
Medical	25,751 (77.4)	843,528 (73.2)	869,279 (73.3)	
Comorbidities[b]				
Hypertension	22,417 (67.4)	761,950 (66.1)	784,367 (66.2)	< .0001
Chronic heart disease	7051 (21.2)	213,170 (18.5)	220,221 (18.6)	< .0001
Diabetes	12,138 (36.5)	411,899 (35.7)	424,037 (35.8)	.004
History of cancer	11,705 (35.2)	323,155 (28.0)	334,860 (28.2)	< .0001
Renal insufficiency	1708 (5.1)	41,948 (3.6)	43,656 (3.7)	< .0001
Respiratory disease	12,599 (37.9)	355,172 (30.8)	367,771 (31.0)	< .0001
COVID-19[e]	1362 (4.1)	18,895 (1.6)	20,257 (1.7)	< .0001
History of VTE[b]	2513 (7.6)	16,831 (1.5)	19,344 (1.6)	< .0001
Caprini score[a]	5.4 (2.5)	4.8 (2.5)	4.8 (2.5)	< .0001
Pharmacologic prophylaxis[f]	15,332 (46.1)	543,342 (47.2)	558,674 (47.1)	.0002

BMI, Body mass index; *VTE*, venous thromboembolism.
[a]Data are presented as mean (standard deviation).
[b]Data are presented as number (%).
[c]Surgical patient defined as those who had undergone surgery during admission, medical patient defined as all others.
[d]Total cohort following exclusion of those with VTE diagnosed on or within 90 days of admission, those with extreme BMI (<15 kg/m^2 or >60 kg/m^2), very long hospitalization (>60 days), and for those undergoing surgery, long duration of surgery (>10 hours).
[e]Diagnosis of COVID-19 infection on admission.
[f]Use of pharmacologic prophylaxis within 48 hours of admission.
[g]*P* values computed using Pearson χ^2 or Student *t*-test.

proportion of medical patients (n = 425,096; 48.9%) received pharmacologic prophylaxis compared with surgical patients (n = 133,578; 42.2%) ($P < .0001$).

Ninety-day Cumulative Incidence of VTE

A total of 33,253 patients developed an incident VTE within 90 days of hospital admission (Table II). Of these, 19,218 developed a DVT alone, 10,190 developed PE alone, and 3845 developed a DVT with a PE.

Evaluation of predictive ability

The predictive ability of the composite model for VTE, as measured by AUC, was higher than that of the Caprini risk factor model (Fig 1). The AUC for the composite model was 0.74, whereas the AUC of the Caprini risk factor model was 0.63 ($P < .0001$).

Relationship between test metrics

In both models (Figs 2 and 3), there was an inverse relation between PPV and NPV, and a direct relation between sensitivity and NPV. In both figures, the maximum PPV attainable from the RAM is indicated by the intersection of the horizontal dotted line with the left Y-axis. This is the point at which PPV transitions from becoming a function of NPV (each discrete value of NPV associated with a single PPV value) to having one value of NPV being associated with multiple values of PPV. The PPV at this point is the approximate maximum possible PPV of the model. In the Caprini risk factor model, the maximum PPV was approximately 0.14 (Fig 2). In the composite model, the maximum possible PPV was approximately 0.27 (Fig 3).

Table II. Ninety-day cumulative incidence of venous thromboembolism (*VTE*), pulmonary embolism (*PE*), and deep venous thrombosis (*DVT*) in 1,185,633 patients' first admission between January 2016 and December 2021

Outcome	Present, N (%)	Absent, N (%)
VTE (total)	33,253 (2.8)	1,152,380 (97.2)
DVT alone	19,218 (1.6)	1,166,415 (98.4)
PE alone	10,190 (0.9)	1,175,443 (99.1)
PE with DVT	3845 (0.3)	1,181,788 (99.7)

Predictive performance, two approaches

For each model, the sensitivity, specificity, PPV and NPV were computed using two cut-points: (1) maximizing the value of sensitivity + specificity − 1 (Youden's J index); and (2) maximizing the PPV (Table III).

Approach 1, using a cut-point that maximized Youden's index (sensitivity + specificity − 1). The sensitivity of the composite model (0.66) was higher than that of the Caprini risk factor model (0.58). The specificity of the composite model (0.69) was also higher than that of the Caprini risk factor model (0.61). The NPV of both models was very high (composite model, 0.99; Caprini risk factor model, 0.98). PPV was low for both models, but slightly higher in the composite model (0.06), compared with the Caprini risk factor model (0.04). All metrics were compared using McNemar's test and were found to be statistically significant ($P < .0001$).

Approach 2, using a cut-point that maximized PPV. The sensitivity of the composite model (0.01) was lower than that of the Caprini risk factor model (0.07). The specificity for both models was 0.99, and the NPV of both models was 0.97. The PPV of the composite model (0.27) was higher than that of the Caprini risk factor model (0.13). All metrics were also compared using McNemar's test and resulted in a significant *P* value < .0001.

DISCUSSION

Using 102 risk factors obtained from the 23 existing risk assessment models predicting incident VTE and data from a large cohort of general, unselected hospital admissions to all VA facilities across the country, we constructed a new composite RAM predicting incident 90-day VTE. The composite RAM demonstrated improvements in predictive ability for incident VTE compared with the model using Caprini risk factors. The AUC of the composite RAM was higher than that of the Caprini risk factor model.

We evaluated the sensitivity, specificity, NPV, and PPV of our models using two different cut-points—one maximizing Youden's J index, and another maximizing PPV. Compared with selecting one approach only, this permitted a more comprehensive analysis of our model, focusing on two different clinical perspectives. The cut-point derived from maximizing Youden's J index maximizes sensitivity and specificity and is relevant if the model is to be used as a screening tool. The cut-point derived from maximizing PPV is relevant if the clinical priority is to reduce individuals who are falsely diagnosed with VTE and may unnecessarily receive prophylaxis.

When the criterion of maximizing the value of Youden's J index (the sum of sensitivity and specificity − 1) was used in selecting the cut-point, all test metrics of the composite RAM (sensitivity, specific, NPV, and PPV) were improved compared with the Caprini risk factor model. However, the improvement is limited; the composite RAM demonstrates low sensitivity, specificity, and PPV, posing a significant limitation to its clinical utility. When the cut-point is selected to maximize PPV, although the specificity and NPV are high and the PPV is improved for both RAMs, the sensitivity and PPV are unacceptably low in both. Considering the graphical representation of sensitivity, PPV, and NPV for each of these RAMs (Figs 2 and 3) and the inverse relationship between PPV and sensitivity, these findings are not unexpected. Thus, although the composite RAM modestly improved PPV and sensitivity compared with the Caprini risk factor model, neither model has a PPV or sensitivity that permits it to be considered a clinically useful predictor of VTE.

The 102 variables used in the composite model are all risk factors for VTE that have been included in the 23

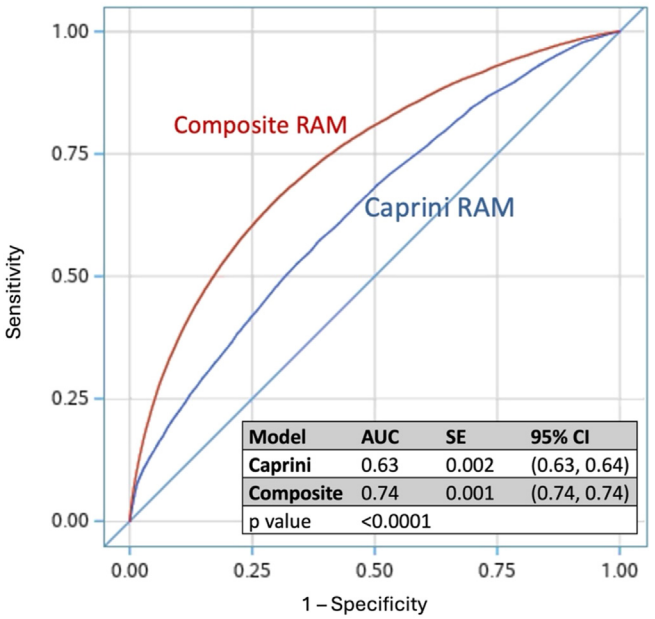

Fig 1. Receiver operating characteristic curves comparing prediction of cumulative incidence of venous thromboembolism (*VTE*) 90 days after hospital admission in 1,185,633 patients' first admission between January 2016 and December 2021. *Inset table*: Comparison of area under the receiver operating characteristic curve (*AUC*) of the Caprini risk factor model vs the composite model. *P* value generated using the Delong-Delong test. *CI*, Confidence interval; *RAM*, risk assessment model; *SE*, standard error.

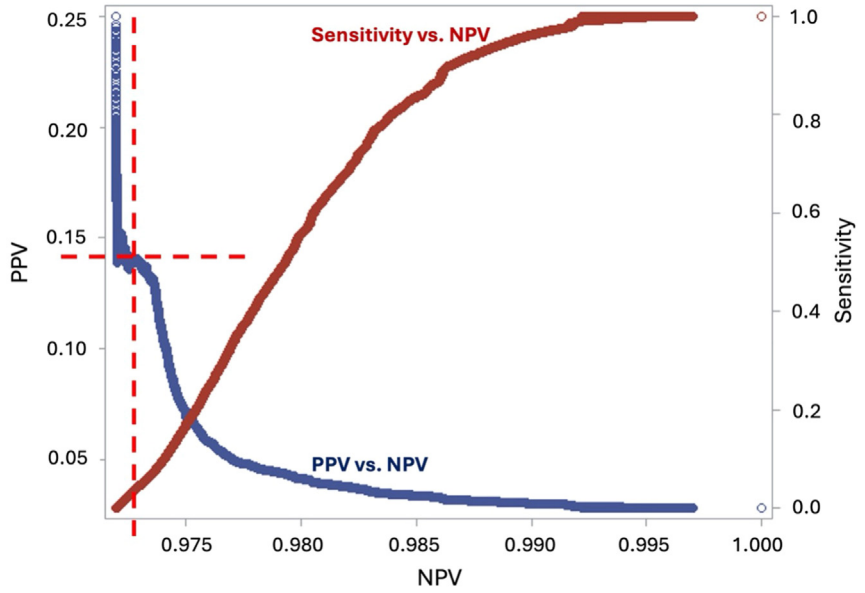

Fig 2. Relationship between sensitivity, positive predictive value (*PPV*), and negative predictive value (*NPV*) for the Caprini risk factor model. *Blue line*: PPV vs NPV; *red line*: sensitivity vs NPV. *Crossed dotted lines* indicate the maximum possible PPV from this model, ~0.14.

existing VTE RAMs, each of which has been believed to be an important risk factor for VTE by its authors. When these individual VTE RAMs are applied to the specific high-risk populations that were used to develop the RAMs, they show high predictive ability for VTE. Although this is good to know, federal agencies mandate risk stratification of the entire general hospital admission population. The current response has been to use these same RAMs that were built for high-risk populations in the general population. Our results show that these RAMs are not effective in the general population.

It may be suggested that the results of our analysis are limited by the exclusion of patients with extreme or missing variable values, as well as the exclusion of 21 of the possible total of 123 risk-factors. Of the total original cohort of 1,282,014 patients, 66,827 patients (5.2%) were

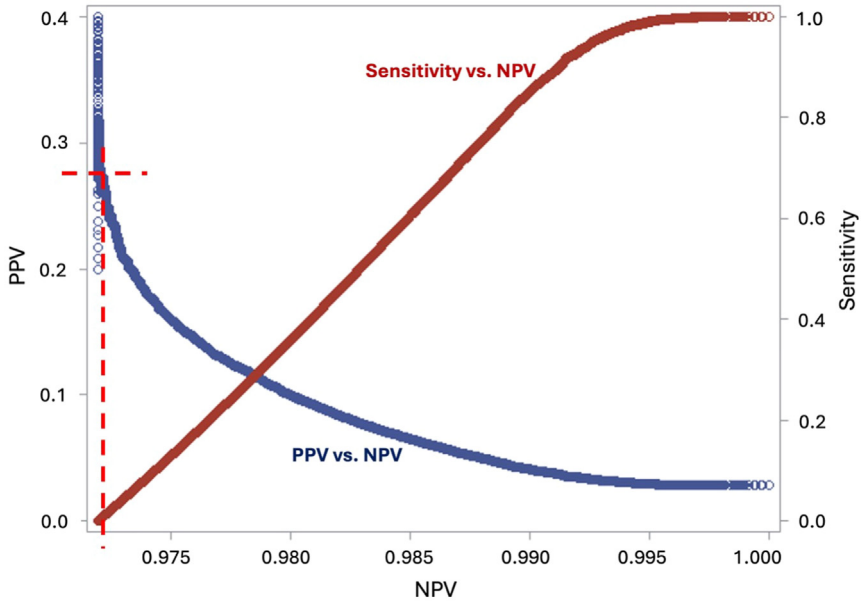

Fig 3. Relationship between sensitivity, positive predictive value (*PPV*), and negative predictive value (*NPV*) for the composite model. *Blue line*: PPV vs NPV; *red line*: sensitivity vs NPV. *Crossed dotted lines* indicate the maximum possible PPV from this model, ~0.27.

Table III. Comparison of predictive performance of the Caprini risk factor model vs composite risk assessment model (*RAM*) in 1,185,633 patients' first admission between January 2016 and December 2021

Comparison of predictive ability, composite vs Caprini risk factor RAM									
		Maximized sensitivity + specificity − 1				Maximized PPV			
RAM	AUC	Sen	Spec	NPV	PPV	Sen	Spec	NPV	PPV
Composite	0.74	0.66	0.69	0.99	0.06	0.01	0.99	0.97	0.27
Caprini risk factors	0.63	0.58	0.61	0.98	0.04	0.07	0.99	0.97	0.13
P-value	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001	< .0001

AUC, Area under the receiver operating characteristic curve; *NPV*, negative predictive value; *PPV*, positive predictive value; *Sen*, sensitivity; *Spec*, specificity.
P-value for AUC computed using Delong test, *P*-values for Sen, Spec, PPV, NPV computed using McNemar's test.

excluded for extreme or missing variable values. Although it is possible that these patients are significantly different from the remainder of the study cohort such that their inclusion would have changed the results of the analysis, this is unlikely. An analysis of the demographic characteristics of the overall study population prior to any exclusions yielded very similar results compared with the demographic characteristics seen in the analysis cohort alone. It may also be argued that incorporating the excluded risk factors could have improved the predictive ability of the model. Although this is possible, we believe that for use in a general, unselected population, the exclusion of these variables had minimal impact on the final model. This is because several of the excluded factors are highly specific to certain subpopulations—the variables of 'injury severity score' and 'serious trauma' are only relevant to those who had sustained traumatic injuries, whereas the variables for various preoperative laboratory values are only relevant to those who had undergone surgery. Other excluded risk factors, such as D-dimer and fibrinogen, are laboratory values that are not routinely collected in the general population. These markers are elevated as the result of a VTE and are collected to diagnose the presence of a VTE (ie, prevalent VTE). They are not risk factors for the development of VTE and thus should not be included in a model designed to predict incident VTE. The role of VTE RAMs is to predict incident VTE and to guide prophylactic measures to prevent incident VTE. Although 21 variables were excluded, a total of 102 risk factors were included in our composite model. This is a significant increase in the number of predictive variables compared with all existing VTE RAMs and represents the most comprehensive model in the literature. Additionally, because data for all 102 of the variables included in composite model were available for all 1,185,633 patients in our cohort consisting of patients across all VA facilities, we can conclude that these risk factors are being consistently collected. These factors would be readily available for analysis in general hospitals outside of the VA system, and appropriate for use in a RAM being developed for general hospital populations. Thus, the effect of these exclusions on the results of our analysis is likely to be minimal.

Ultimately, we demonstrate that, although the composite RAM does improve prediction, it is not the optimal solution to improve VTE prediction in the general hospital population. The studies validating the Caprini and Padua RAMs have primarily been done in highly selected subpopulations, in which the models perform well. Our results do not negate their use in these highly selected subpopulations; however, the performance of these models is poor when applied to the general population. The composite RAM reveals that the risk factors from those RAMs, even when aggregated into a single, more comprehensive model, do not generate a similarly high predictive ability when applied to an unselected general hospital population. These results raise concerns about the indiscriminate use of any of the available 23 VTE RAMs in the general hospital population outside of the high-risk categories in which the individual RAMs were tested. For the vast majority of patients that fall outside of those subpopulations, at present, we are just as likely to be correct if we make prophylaxis decisions based on clinical judgement. Although it is possible that the poor predictive ability may still be related to other unknown risk factors that are not being considered, it is more likely that the limitation in predictive ability lies with the traditional method for model development (logistic regression). These findings highlight the need for a new approach to developing a RAM that can predict incident VTE in the general hospital population.

A potential solution to the limited prediction of incident VTE by existing and composite RAMs might be to divide risk prediction into multiple, ordinal categories of progressively higher risk rather than into a binary outcome, VTE predicted to occur vs VTE predicted not to occur. However, earlier work by our group demonstrates that this approach has not been successful.[42] A review of 895 papers that cited the Caprini RAM yielded 57 that fulfilled inclusion criteria for a systematic review. In these studies, there was no standardization achieved for the actual number of categories of risk that could be defined, and

importantly, no standardization in the cutoff scores that could be used to define the categories of risk or the VTE rates reported for similar risk categories. This heterogeneity of risk categories, cut-points for risk categories, and varying fractions of patients in similar categories indicates that no categorization works for all patients. Given that we have included the collective knowledge of a diverse group of experts in our analysis using risk factors reported by 23 different groups, it appears that a new approach to constructing VTE RAMs is needed.

Limitations. The generalizability of our findings may be limited, given the use of a study population with more males and Whites than in the general population. Although this is a constraint inherent to the use of VA data, the numbers of female (n = 83,513) and Black patients (n = 250,336) in our study were large, and the total cohort of over 1 million patients represents the largest unselected study population analyzed for VTE RAM prediction to date. In excluding those diagnosed with VTE either on admission or in the 90 days prior to admission, we relied on accuracy of documentation regarding the timing of diagnosis. Given the limitations of retrospective data, we cannot account for any patients who may have presented to the hospital with VTE but had delayed diagnoses. Additionally, due to the large size of our cohort of over 1 million patients from an administrative dataset, we relied on ICD-10 coding to define the outcome of VTE and were unable to perform image-based verification to cross-check the ICD coding. However, prior studies have confirmed that administrative databases reliably identify patients with VTE when using ICD-10 codes. One systematic review of 24 such studies showed that they have good sensitivity and specificity for identification of VTE.[43] Because our data source includes only VA records, we are unable to account for patients who may have had a diagnosis of VTE made at non-VA facilities. However, most Veterans return to the VA for continued care after acute events are diagnosed or managed at other facilities; therefore, we would have identified a new ICD-10 entry once they visited a VA clinic. We were limited by the imprecise definitions that were provided for some variables in the original RAMs. As a result, for some variables it was necessary to use our own interpretation of the original intent of those variables when operationalizing them in our models. Given limitations with our dataset, we also made slight modifications to the original variables. For example, there were two different variables from the original RAMs regarding transfusion; one was defined as transfusion of >4 units of red cells in the 72 hours prior to surgery, and the other was the transfusion of >4 units of red cells in the first 24 hours. Due to lack of available information in our data regarding timing of transfusion, we included a single transfusion variable, defined as any transfusion during admission. Other such modifications to the original variables are detailed in Supplementary Table II (online only). Finally, although this study generates a new composite RAM for VTE that is better than the Caprini RAM, this model is not suitable for clinical use, given its low sensitivity and positive predictive value. Thus, it is not suitable for use in the VA population or in the general United States population.

CONCLUSION

Using 102 risk factors obtained from all 23 available VTE RAMs, we improved prediction of incident VTE in a large, national cohort of over one million general hospital admissions. Neither the model generated using Caprini risk factors nor the new composite RAM had a sensitivity or PPV that permits them to be reliable predictors of VTE in a population of unselected, general patients admitted to the hospital. We therefore conclude against using a composite RAM with 102 risk factors. It is neither practical nor clinically effective as a predictor of VTE, and a new approach to risk stratification is needed. We demonstrate the limits of currently available VTE risk-prediction tools; no available RAM is ready for widespread use in the general hospital population. For the vast majority of patients that fall outside of the high-risk sub-populations, at present, we are just as likely to be correct if we make prophylaxis decisions based on clinical judgement.

AUTHOR CONTRIBUTIONS

Conception and design: JS, BL
Analysis and interpretation: ML, MM, SS, GJ, BE, PN, YY, JS, BL
Data collection: ML, HH, TS
Writing the article: ML, JS, BL
Critical revision of the article: ML, HH, MM, SS, TS, GJ, BE, PN, YY, JS, BL
Final approval of the article: ML, HH, MM, SS, TS, GJ, BE, PN, YY, JS, BL
Statistical analysis: ML, MM, JS
Obtained funding: BL
Overall responsibility: BL

FUNDING

This work was funded by an American Venous Forum Research Grant, Institute for Clinical & Translational Research Award 1UL1TR003098; National Institutes of Health Awards NS080168, NS097876, and AG000513; and U.S. Department of Veterans Affairs Awards HSRD C19-20-407, RRD RX000995, and CSRD CX001621 (B.K.L.); Baltimore VA Medical Center Geriatric Research, Education, and Clinical Center and National Institutes of Health P30AG28747 (J.D.S.); and the American Venous Forum Jobst Clinical Research Grant and National Institutes of Health T32 AG000262 (M.S.L.). None of the funding sources had any involvement in the study design or collection, analysis, and interpretation of data, manuscript writing, decision to submit for publication, or any other involvement in creation of this manuscript.

DISCLOSURES

None.

REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism. A public health concern. *Am J Prev Med*. 2010;38:S495–S501.
2. Neeman E, Liu V, Mishra P, et al. Trends and risk factors for venous thromboembolism among hospitalized medical patients. *JAMA Netw Open*. 2022;5:e2240373.
3. Pandor A, Tonkins M, Goodacre S, et al. Risk assessment models for VTE in hospitalised adult patients: a systematic review. *BMJ Open*. 2021;11:e045672.
4. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the worcester VTE study (1985-2009). *Am J Med*. 2014;127:829–839.e5.
5. Caprini JA, Arcelus JI, Hasty JH, Tamhane AC, Fabrega F. Clinical assessment of venous thromboembolic risk in surgical patients. *Semin Thromb Hemost*. 1991;17:304–312.
6. Cronin MA, Dengler N, Krauss ES, et al. Completion of the updated Caprini risk assessment model, 2013 version. *Clin Appl Thromb Hemost*. 2019;25:1076029619838052.
7. Hewes PD, Hachey KJ, Zhang XW, et al. Evaluation of the caprini model for venothromboembolism in esophagectomy patients. *Ann Thorac Surg*. 2015;100:2072–2078.
8. Sterbling HM, Rosen AK, Hachey KJ, et al. Caprini risk model decreases venous thromboembolism rates in thoracic surgery cancer patients. *Ann Thorac Surg*. 2018;105:879–885.
9. Hachey KJ, Hewes PD, Porter LP, et al. Caprini venous thromboembolism risk assessment permits selection for postdischarge prophylactic anticoagulation in patients with resectable lung cancer. *J Thorac Cardiovasc Surg*. 2016;151:37–44.e1.
10. Hazeltine MD, Guber RD, Buettner H, Dorfman JD. Venous thromboembolism risk stratification in trauma using the Caprini risk assessment model. *Thromb Res*. 2021;208:52–57.
11. Shi J, Ye J, Zhuang X, Cheng X, Fu R, Zhao A. Application value of Caprini risk assessment model and elevated tumor-specific D-dimer level in predicting postoperative venous thromboembolism for patients undergoing surgery of gynecologic malignancies. *J Obstet Gynaecol Res*. 2019;45:657–664.
12. Stroud W, Whitworth JM, Miklic M, et al. Validation of a venous thromboembolism risk assessment model in gynecologic oncology. *Gynecol Oncol*. 2014;134:160–163.
13. Yago H, Yamaki T, Sasaki Y, et al. Application of the caprini risk assessment model for evaluating postoperative deep vein thrombosis in patients undergoing plastic and reconstructive surgery. *Ann Vasc Surg*. 2020;65:82–89.
14. Hayssen H, Sahoo S, Englum B, et al. Evaluating the ability of caprini and Padua scores to predict venous thromboembolism in a nationwide study. *J Vasc Surg Venous Lymphat Disord*. 2023;11:457–458.
15. Darzi AJ, Repp AB, Spencer FA, et al. Risk-assessment models for VTE and bleeding in hospitalized medical patients: an overview of systematic reviews. *Blood Adv*. 2020;4:4929–4944.
16. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients: a systematic review. *Thromb Haemostasis*. 2017;117:801–808.
17. Autar R. The management of deep vein thrombosis: the Autar DVT risk assessment scale re-visited. *J Orthop Nurs*. 2003;7:114–124.
18. Rogers SO, Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg*. 2007;204:1211–1221.
19. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for VTE: the Padua prediction score. *J Thromb Haemostasis*. 2010;8:2450–2457.
20. Rothberg MB, Lindenauer PK, Lahti M, Pekow PS, Selker HP. Risk factor model to predict venous thromboembolism in hospitalized medical patients. *J Hosp Med*. 2011;6:202–209.
21. Woller SC, Stevens SM, Jones JP, et al. Derivation and validation of a simple model to identify venous thromboembolism risk in medical patients. *Am J Med*. 2011;124:947–954.e2.
22. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N Engl J Med*. 2005;352:969–977.
23. Pannucci CJ, Osborne NH, Wahl WL. Creation and validation of a simple venous thromboembolism risk scoring tool for thermally injured patients: analysis of the national burn repository. *J Burn Care Res*. 2012;33:20–25.
24. Rogers FB, Shackford SR, Horst MA, et al. Determining venous thromboembolic risk assessment for patients with trauma: the Trauma Embolic Scoring System. *J Trauma Acute Care Surg*. 2012;73:511–515.
25. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg*. 2013;217:833–842e3.
26. Greenfield LJ, Proctor MC, Rodriguez JL, Luchette FA, Cipolle MD, Cho J. Posttrauma thromboembolism prophylaxis. *J Trauma Acute Care Surg*. 1997;42:100–103.
27. Liu LP, Zheng HG, Wang DZ, et al. Risk assessment of deep-vein thrombosis after acute stroke: a prospective study using clinical factors. *CNS Neurosci Ther*. 2014;20:403–410.
28. Spyropoulos AC, Anderson FA, FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140:706–714.
29. Chopard P, Spirk D, Bounameaux H. Identifying acutely ill medical patients requiring thromboprophylaxis. *J Thromb Haemostasis*. 2006;4:915–916.
30. Pannucci CJ, Laird S, Dimick JB, Campbell DA, Henke PK. A validated risk model to predict 90-day vte events in postsurgical patients. *Chest*. 2014;145:567–573.
31. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902–4907.
32. Lecumberri R, Marqués M, Díaz-Navarlaz M, et al. Maintained effectiveness of an electronic alert system to prevent venous thromboembolism among hospitalized patients. *Thromb Haemostasis*. 2008;100:699–704.
33. de Bastos M, Barreto SM, Caiafa JS, Boguchi T, Silva JLP, Rezende SM. Derivation of a risk assessment model for hospital-acquired venous thrombosis: the NAVAL score. *J Thromb Thrombolysis*. 2016;41:628–635.
34. UK National Institute for Health and Care Excellence. NICE guideline [NG89]: venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. Accessed January 31, 2024; 2018. https://www.nice.org.uk/guidance/ng89.
35. Medrano Ortega FJ, Navarro Puerto A, Vidal Serrano S, et al. *Guía PRETEMED*. Córdoba: SADEMI; 2007.
36. Zakai NA, Callas PW, Repp AB, Cushman M. Venous thrombosis risk assessment in medical inpatients: the medical inpatients and thrombosis (MITH) study. *J Thromb Haemostasis*. 2013;11:634–641.
37. Nafee T, Gibson CM, Travis R, et al. Machine learning to predict venous thrombosis in acutely ill medical patients. *Res Pract Thromb Haemost*. 2020;4:230–237.
38. Shen C, Ge B, Liu X, Chen H, Qin Y, Shen H. Predicting the occurrence of venous thromboembolism: construction and verification of risk warning model. *BMC Cardiovasc Disord*. 2020;20:249.
39. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated ROC curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
40. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*. 1947;12:153–157.
41. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32–35.
42. Hayssen H, Cires-Drouet R, Englum B, et al. Systematic review of VTE risk categories derived from Caprini score. *J Vasc Surg Venous Lymphat Disord*. 2022;10:1401–1409.e7.
43. Liu B, Hadzi-Tosev M, Eisa K, et al. Accuracy of venous thromboembolism ICD-10 codes: a systematic review and meta-analysis. *Thrombosis Update*. 2024;14:100154.

Submitted Jun 26, 2024; accepted Sep 10, 2024.

Additional material for this article may be found online at www.jvsvenous.org.