ORIGINAL ARTICLE

Predicting postdischarge hospital-associated venous thromboembolism among medical patients using a validated mortality risk score derived from common biomarkers

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Abstract

Background: Discharged medical patients are at risk for venous thromboembolism (VTE). It is difficult to identify which discharged patients would benefit from extended duration thromboprophylaxis. The Intermountain Risk Score is a prediction score derived from discrete components of the complete blood cell count and basic metabolic panel and is highly predictive of 1-year mortality. We sought to ascertain if the Intermountain Risk Score might also be predictive of 90-day postdischarge hospital-associated VTE (HA-VTE).

Methods: We applied the Intermountain Risk Score to 60 064 medical patients who survived 90 days after discharge and report predictiveness for HA-VTE. Area under the receiver operating curve analyses were performed. We then assessed whether the Intermountain Risk Score improved prediction of 2 existing VTE risk assessment models.

Results: The Intermountain Risk Score poorly predicted HA-VTE (area under the curve = 0.58; 95% confidence interval [CI], 0.56-0.60). Each clinical risk assessment model was superior to the Intermountain Risk Score (UTAH area under the curve, 0.63; Kucher area under the curve, 0.62; Intermountain Risk Score area under the curve, 0.58; $P < .001$ for each comparison). Adding the Intermountain Risk Score to these scores did not substantially improve the performance of either risk assessment model (UTAH + Intermountain Risk Score, 0.65; Kucher + Intermountain Risk Score, 0.64).

Conclusion: The Intermountain Risk Score demonstrated poor predictiveness for HA-VTE when compared to existing risk assessment models. Adding the Intermountain Risk Score to existing risk assessment models did not improve upon either risk assessment model alone to justify the added complexity.

Essentials

- Up to 75% of hospital-associated venous thrombosis (HA-VTE) occurs after medical patient discharge.
- The Intermountain Risk Score is made from lab tests, the complete blood cell count and basic metabolic panel, and predicts mortality in general.
- A risk score predictive of HA-VTE was developed from these routine labs.
- The Intermountain Risk Score did not add to clinical risk assessment models to predict 90-day HA-VTE.

1 | BACKGROUND

It is estimated that 8 million patients are hospitalized in the United States for a nonsurgical indication each year.[1] The burden of hospital-associated venous thromboembolism (HA-VTE) is great, with 70%-80% of fatal pulmonary embolism (PE) events occurring among hospitalized medically ill patients.[2] The rate of symptomatic VTE more than doubles over the first 21 days after hospital discharge,[3] and while anticoagulant prophylaxis reduces the rate of VTE during hospitalization, uncertainty exists that anticoagulants continued following hospital discharge (referred to as *extended-duration thromboprophylaxis*) is best practice. Extended-duration thromboprophylaxis may reduce VTE following hospital discharge but is burdensome and carries a risk of bleeding. Randomized clinical trials of extended-duration thromboprophylaxis have returned mixed results,[4-8] and a meta-analysis[9] has demonstrated a thin margin between the rate of reduction of postdischarge VTE and the rate of bleeding complications with recent guidelines recommending against the routine use of extended-duration thromboprophylaxis.[10] It was recently estimated that nearly 1 in 4 discharged medical patients may benefit from extended-duration thromboprophylaxis,[11] while prospective randomized controlled trials have demonstrated the challenges associated with identifying these patients. In the Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk (MARINER) trial,[7] no significant reduction in VTE was realized upon randomization of discharged patients to receive extended-duration rivaroxaban thromboprophylaxis versus placebo. The Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients With Prolonged Immobilization (EXCLAIM)[8] and Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban With Enoxaparin (MAGELLAN)[5] trials demonstrated that extended-duration thromboprophylaxis reduced postdischarge VTE upon prescription of extended-duration thromboprophylaxis using enoxaparin and rivaroxaban, respectively, but this benefit was offset by an increase in bleeding events. Similarly, patients randomized to extended duration apixaban when compared with a shorter duration of enoxaparin in the Apixaban Dosing to Optimize Protection From Thrombosis (ADOPT)[4] trial experienced an increase in bleeding rates. The mixed results from these studies may be attributable to the lack of an accurate means of best predicting those patients at highest risk for postdischarge VTE.

The apparent paradox between hospitalized medical patients being disproportionately burdened by postdischarge HA-VTE and the "negative" clinical trials of extended-duration thromboprophylaxis may represent a limitation in the ability to identify a population of patients that would most benefit from chemoprophylaxis. Risk assessment models have been developed and variably validated to identify hospitalized medical patients at risk for VTE.[12-21] However, these risk assessment models may not be precise enough to identify patients who would experience net benefit from extended-duration thromboprophylaxis.[4,5] Efforts have been made to enhance the predictive accuracy of risk assessment models such as with the addition of biomarkers, like D-dimer testing[6,7] but with limited success.

The Intermountain Risk Score is a mortality risk prediction tool derived in a general medical population.[22] The score has been further refined and validated among outpatient, inpatient, cardiovascular, trauma, and other medical populations.[23-26] Additional outcomes predicted by variations of the Intermountain Risk Score (IMRS) include heart failure,[23] dementia,[27] chronic cardiopulmonary disease,[28] and stroke.[27,29] Likewise, the longitudinal predictive value of the IMRS has been demonstrated with serial measurements at baseline and at 1 year of follow-up and shown to be independently prognostic for mortality and heart failure among initially hospitalized patients.[30]

It is unknown if the IMRS may represent a novel tool to identify hospitalized medical patients at risk for the development of HA-VTE that may be candidates for extended-duration thromboprophylaxis. For this reason, we sought to test the predictive characteristics of the IMRS for 90-day postdischarge VTE (hereafter, HA-VTE) among hospitalized medical patients and determine the ability of the IMRS score to improve the performance of 2 existing clinical VTE risk assessment models.

2 | METHODS

2.1 | Study design and patient population

This retrospective cohort study analyzed patients including those from the Intermountain Healthcare Venous Thromboembolism Reduction

Initiative 1 (VRI-1) and VRI-2. These studies were part of a multifaceted health care quality improvement initiative and included all hospitalized medical patient admissions at 2 urban and 3 community Utah hospitals dating as we formerly described.[31,32] For this study, we considered eligible those patients from both studies and patients from 2 additional community hospitals who were hospitalized for >24 hours, discharged alive, did not have VTE detected on admission or during inpatient stay, had a complete blood cell count (CBC) and basic metabolic panel (BMP) obtained, and survived to 90 days from January 2010 through December 2014. We defined the presence of VTE within 90 days using natural language processing interrogation of the electronic medical record. We defined VTE as deep vein thrombosis (DVT) of the lower extremities or pulmonary embolism (excluding upper extremity and unusual site thrombosis) as we have formerly described.[33] Specifically, compared with manual chart review, natural language processing had a sensitivity of 92%, specificity of 99%, and positive predictive value of 97% to identify DVT, and sensitivity of 100%, specificity of 98%, and positive predictive value of 89% to identify pulmonary embolism (PE). Patient demographics are summarized in Table 1.

2.2 | IMRS and laboratory testing

As previously described,[22] the IMRS is a sex-specific, linear combination of weighted risk coefficients corresponding to observed values of the CBC elements (hematocrit, white blood cell count, platelet count, mean corpuscular volume, mean corpuscular hemoglobin concentration, red cell distribution width, mean platelet volume), BMP elements (sodium, potassium, bicarbonate, calcium, glucose, creatinine), and age. Risk scores using the weightings for the 1-year mortality version of the IMRS were calculated using both the patient labs available on admission (first labs) and the patient's last available labs prior to discharge (last labs). The first IMRS derived and reported is that 1-year mortality IMRS upon which we compare the performance of the UTAH and Kucher scores. We elect to present the performance of the IMRS based on the last labs, as we believed that they would be more representative of the patient condition at the time of discharge (and because we observed no meaningful difference in the performance of the IMRS when comparing it was derived using first and last labs of hospitalization).

2.3 | Validated clinical VTE risk scores

We chose 2 VTE risk assessment models, the UTAH[17] and Kucher[20] scores from among several developed to aid in quantifying the risk of hospital-acquired VTE.[3,12,17,19-21,34-36] We compared the predictive performance of the UTAH[17] and Kucher[20] risk assessment models with the IMRS individually and assessed the effect of combining the IMRS with each risk assessment model to measure their combined ability to predict HA-VTE. The UTAH score is a 4-element risk assessment model that incorporates the 4 risk factors of previous VTE, a cancer diagnosis, immobility (defined as an order in the patient's chart for bedrest), and a peripherally inserted central venous

TABLE 1 All discharged medical patients that survived to 90 d

Variable	N = 60 064
Patient characteristics (at the time of discharge)	
Age, y, mean (SD)	61 (19)
Female, n (%)	33 270 (55)
Congestive heart failure, n (%)	15 682 (26)
Diabetes, n (%)	16 396 (27)
Current tobacco use, n (%)	16 897 (28)
Infection, n (%)	17 329 (29)
PICC, n (%)	4610 (7.7)
Sepsis, n (%)	12 792 (21)
Central venous catheter, n (%)	5306 (8.8)
Major bleed, n (%)	723 (1.2)
Received prophylaxis,[a] n (%)	44 048 (73)
Had contraindication for prophylaxis,[b] n (%)	1754 (2.9)
APACHE II, mean (SD)	12 (6)
Charlson, mean (SD)	4 (3)
Duration of hospitalization, d, median (IQR)	2.9 (1.9-4.7)
VTE risk factors, n (%)	
Cancer	6152 (10)
Prior VTE	9929 (17)
Hypercoagulable state [c]	3151 (5.2)
Surgery	6375 (11)
Immobility (defined as an order for bedrest)	14 033 (23)
Obesity	14 480 (24)
HRT	2009 (3.3)

APACHE II, Acute Physiology and Chronic Health Evaluation II; HRT, hormone replacement therapy; IQR, interquartile range; PICC, peripherally inserted central catheter; SD, standard deviation; VTE, venous thromboembolism.

[a] Any chemoprophylaxis during hospitalization.

[b] As identified by the hospitalist.

[c]Defined as the presence of a heritible or acquired thrombophilia identified upon electronic medical record interrogation

catheterization line. Each risk factor is worth 1 point, and any value >0 indicates being at risk. The Kucher score incorporates 8 common risk factors that are weighted according to a point scale, with any value ≥4 indicating increased risk (Table 2).

2.4 | Statistical considerations

For the IMRS, UTAH, and Kucher scores, we computed the area under the receiver operating characteristic curve. We compared the area under the curve for the outcome of 90-day postdischarge VTE for the various scores using bootstrap methods and controlled for multiple comparisons using the false discovery rate. We also calculated the area under the curve for the IMRS plus the UTAH and Kucher scores (separately) and compared these results to the results of each score alone (Table 3). Finally, to aid in the visualization of the

relationship between the IMRS and probability of 90-day postdischarge VTE, a logistic regression was fit (adjusting for relevant covariates from Table 1 using backwards selection) and an effect plot for the IMRS was generated (Figure 3). All analyses were performed using R version 3.5.1.[37]

3 | RESULTS

Among the 60 064 patients that survived to 90 days, 55% were female and the mean age of the cohort was 61 ± 19 years. Among all

TABLE 2 Risk factors for risk assessment model

	UTAH Score[a]	Kucher Score[a]	Components of the Intermountain Risk Score
Prior VTE	1	3	Hematocrit, white blood cell count
Cancer	1	3	Platelet count, mean platelet volume
Immobility	1	1	Mean corpuscular volume
PICC/central line	1	N/A	Mean corpuscular hemoglobin concentration
Thrombophilia		3	Red cell distribution width
Surgery within 1 mo		2	Sodium, potassium
BMI > 30		1	Bicarbonate, glucose
Hormone Replacement or oral contraceptives		1	Calcium, creatinine
Age > 70 y		1	Age

BMI, body mass index; N/A, not applicable; PICC, peripherally inserted central catheter; VTE, venous thromboembolism.

Points to calculate the component factors of the risk scores (note that the fourth column is the Intermountain Risk Score independent of the UTAH and Kucher Scores).

[a]UTAH Score > 0 is at risk; Kucher score ≥ 4 is at risk.

patients the 90-day postdischarge VTE rate was 1.9% (1125/60 064). Postdischarge chemoprophylaxis was not routinely prescribed for any patients in this study. The IMRS was significantly higher (P <.001) in patients with HA-VTE than those without HA-VTE (14.2 [standard deviation 3.9] vs 13.0 [standard deviation 4.2]), and the results did not substantively differ when the IMRS was calculated on first or last labs of admission (data not shown). However, the IMRS was poorly predictive of VTE with an area under the curve of 0.58 (95% confidence interval [CI], 0.56-0.60). The area under the curve for the UTAH (0.63; 95% CI, 0.61-0.64) and Kucher (0.62; 95% CI, 0.60-0.64) scores were significantly higher than the area under the curve of the IMRS (P < .001 for both; Table 3, Figure 1).

Combining the IMRS with either the UTAH score or the Kucher score significantly improved on the performance of the IMRS alone for HA-VTE (P < .001 for both). The combination of the IMRS with
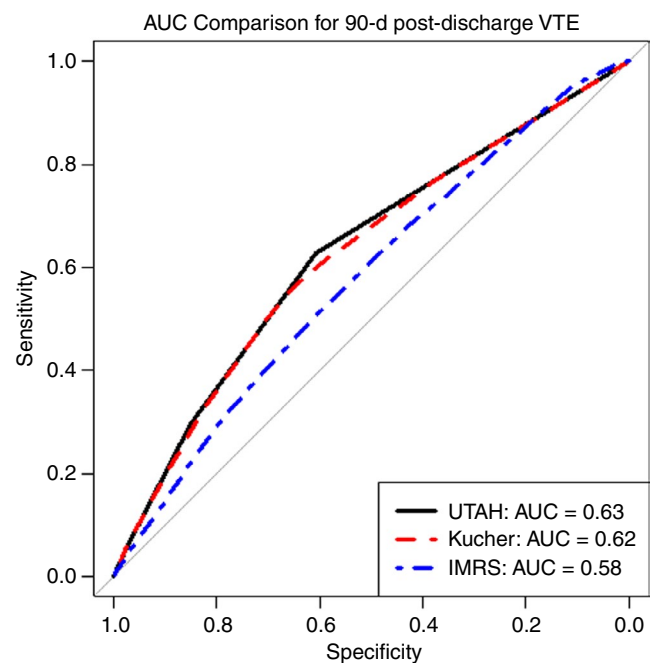

FIGURE 1 Area under the receiver operating characteristic curve for the Intermountain Risk Score and the clinical risk assessment models. AUC, area under the receiver operating characteristic curve; IMRS, Intermountain Risk Score; VTE, venous thromboembolism

TABLE 3 VTE risk score comparison

	AUC for combined score (95% CI)	AUC for single score (95% CI)	P value
IMRS + UTAH vs IMRS alone	0.65 (0.64-0.67)	0.58 (0.56-0.60)	**<.001**
IMRS + Kucher vs IMRS alone	0.64 (0.62-0.66)	0.58 (0.56-0.60)	<.001
IMRS + UTAH versus UTAH alone	0.65 (0.64-0.67)	0.63 (0.61-0.64)	.04
IMRS + Kucher vs Kucher alone	0.64 (0.62-0.66)	0.62 (0.61-0.64)	.16

AUC, area under the receiver operating characteristic curve; CI, confidence interval; IMRS, Intermountain Risk Score; VTE, venous thromboembolism.

AUC Comparison for 90-d post-discharge VTE

IMRS + UTAH: AUC = 0.65
IMRS + Kucher: AUC = 0.64
UTAH only: AUC = 0.63
Kucher only: AUC = 0.62
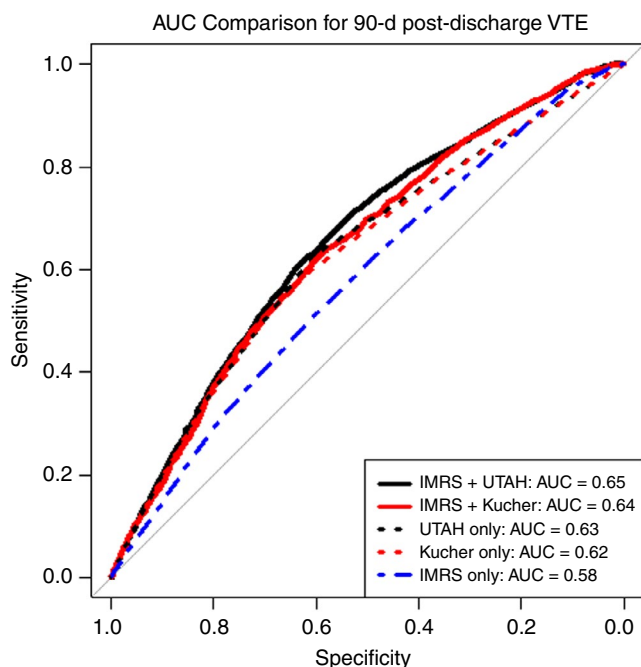IMRS only: AUC = 0.58

FIGURE 2 Area under the receiver operating characteristic curve for the Intermountain Risk Score and clinical risk assessment models alone and in combination. AUC, area under the receiver operating characteristic curve; IMRS, Intermountain Risk Score; VTE, venous thromboembolism
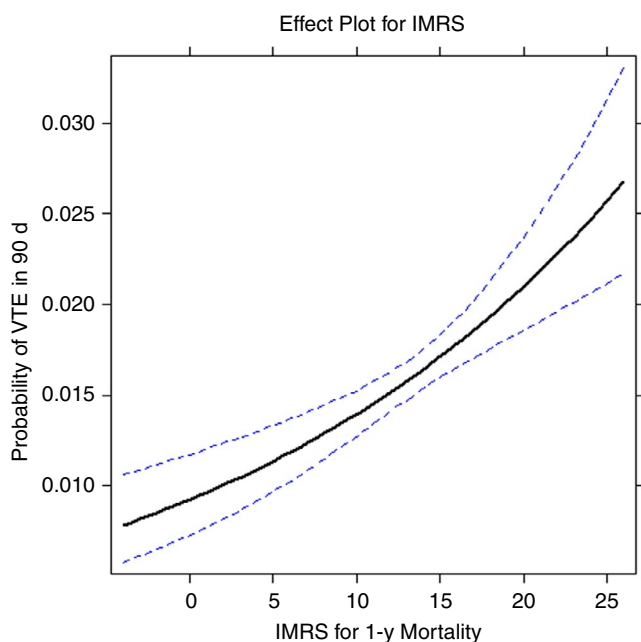
Effect Plot for IMRS

FIGURE 3 Effect plot for the Intermountain Risk Score to predict the probability of 90-day venous thromboembolism. IMRS, Intermountain Risk Score; VTE, venous thromboembolism

the UTAH score marginally improved upon the UTAH score alone (0.65 vs 0.63; $P = .04$). However, the combination of the IMRS with the Kucher score did not significantly improve upon the area under the curve derived using the Kucher score alone (0.64 vs 0.62; $P = .16$; Figure 2). The effect of the IMRS on the probability of HA-VTE,

based on a logistic regression adjusted for relevant covariates, is found in Figure 3.

4 | DISCUSSION

As a purely exploratory process given the impressive predictiveness of the IMRS for mortality among various populations it was our hypothesis that the IMRS, a highly pragmatic tool that uses inexpensive and commonly available laboratory results, might identify medical patients at high risk for HA-VTE, and would be a simple way to improve the performance of existing risk assessment models to better select patients for extended duration thromboprophylaxis. Unfortunately, the IMRS did not accomplish this goal and was found to be a poor predictor of HA-VTE. While the IMRS was significantly higher among patients with HA-VTE and upon combination with the UTAH and Kucher scores, the magnitude of these improvements is unlikely to be clinically meaningful. A similar finding for the IMRS was made previously among heart failure patients in association with hospital readmission, which led to the derivation of a separate readmission IMRS.[38]

We explored using the IMRS to predict HA-VTE because it is based on ubiquitously available laboratory data and can be calculated without adding additional health care expense. Further, the data are easily integrated into computerized decision support systems (the IMRS is presently calculated automatically and displayed in our electronic medical record for every patient admitted to any of our 23 hospitals). While designed to predict mortality, the IMRS has shown surprising ability to predict outcomes in several disease states, such as heart failure,[23] dementia,[27] stroke,[29] and trauma mortality.[26] Unfortunately, this utility does not appear to extend to HA-VTE. This may be due to any one or a combination of several reasons. First, it is possible that predictiveness of the components of the CBC and BMP does not exist for the outcome of HA-VTE. However, there are several conditions for which the IMRS has shown to be predictive, as noted above. Second, because the weighting of the components of the CBC and BMP used in the IMRS are based on the outcome of 1-year mortality, these may differ when the outcome of interest is VTE. This raises the question of whether an IMRS derived specifically for the outcome of 90-day postdischarge VTE would perform better, a concept that may be worth future study.

Strengths of our study include that we have a robust data set of >60 000 discharged medical patients who survive to 90 days in which we can test our hypothesis. Likewise, we have experience in the assessment of the IMRS performance in different populations. We elected to include as our outcome VTE occurrence within the 90 days following hospital discharge (as opposed to including also patients who experienced thrombosis both during and following hospitalization). This is important given that few risk assessment models exist that have been assessed for predictiveness of postdischarge VTE at the exclusion of predicting VTE during hospitalization. A weakness of our study is that we compare our IMRS to the performance of 2 clinical risk assessment models that have

comparatively less external validation than others. However, a study comparing these risk assessment models has demonstrated that the UTAH score and Kucher score perform favorably when considered alongside the Padua and IMPROVE score risk assessment models.[39] Also, while patients from 5 hospitals contributed to our data set, all hospitals reside in the Intermountain Healthcare network, and therefore our observations do not constitute external validation of the predictiveness of the IMRS that we observed. Finally, we cannot refute the possibility that by including only patients who survived to 90 days, we omitted some patients who died from VTE within 90 days of follow-up, which would have been of interest to include. However, we believe that if this had occurred, it would be rare and would not meaningfully impact our large data set.

We observed that the IMRS formerly derived to predict 1-year mortality is a poor predictor for 90-day HA-VTE, yet predictive of other important outcomes. We have formerly analyzed these laboratory-based variables for predictiveness as a parsimonious set of predictors of other outcomes such as 30-day rehospitalization. We suggest that a next step would be to explore other weightings and combinations of the components of the IMRS to generate a 90-day postdischarge HA-VTE–specific IMRS.

In conclusion, the IMRS is poorly predictive of HA-VTE. When compared to clinical risk assessment models, the UTAH and Kucher scores have significantly greater predictive ability than the IMRS, and combining IMRS elements into these scores did not meaningfully improve the performance.

RELATIONSHIP DISCLOSURE

Dr. Woller reports grants from Bristol Meyer Squibb, grants from Pfizer, outside the submitted work; and Co-Chair, American College of Chest Physicians, Guideline writing panel, Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, Living Guideline. Dr. Woller reports grants from Bristol Meyer Squibb, grants from Pfizer, outside the submitted work; and Co-Chair, American College of Chest Physicians, Guideline writing panel, Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, Living Guideline. Dr. Stevens reports grants from Bristol Meyer Squibb, grants from Pfizer, outside the submitted work; and Co-Chair, American College of Chest Physicians, Guideline writing panel, Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-based Clinical Practice Guidelines, Living Guideline. Dr. Horne reports other from CareCentra and Alluceo, grants from GlaxosmithKline, grants from Astra-Zeneca, outside the submitted work; and PI of grants involving clinical decision tools that were funded by Intermountain Healthcare's Foundry innovation program, the Intermountain Research and Medical Foundation.

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Drs. Fazili, Lloyd, Snyder and Wilson have nothing to disclose.

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