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ORIGINAL ARTICLE

Biomarker derived risk scores predict venous thromboembolism and major bleeding among patients with COVID-19

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Abstract

Background: Venous thromboembolism (VTE) risk is increased in patients with COVID-19 infection. Understanding which patients are likely to develop VTE may inform pharmacologic VTE prophylaxis decision making. The hospital-associated venous thromboembolism–Intermountain Risk Score (HA-VTE IMRS) and the hospital-associated major bleeding–Intermountain Risk Score (HA-MB IMRS) are risk scores predictive of VTE and bleeding that were derived from only patient age and data found in the complete blood count (CBC) and basic metabolic panel (BMP).

Objectives: We assessed the HA-VTE IMRS and HA-MB IMRS for predictiveness of 90-day VTE and major bleeding, respectively, among patients diagnosed with COVID-19, and further investigated if adding D-dimer improved these predictions. We also reported 30-day outcomes.

Patients/Methods: We identified 5047 sequential patients with a laboratory confirmed diagnosis of COVID-19 and a CBC and BMP between 2 days before and 7 days following the diagnosis of COVID-19 from March 12, 2020, to February 28, 2021. We calculated the HA-VTE IMRS and the HA-MB IMRS for all patients. We assessed the added predictiveness of D-dimer obtained within 48 hours of the COVID test.

Results: The HA-VTE IMRS yielded a c-statistic of 0.70 for predicting 90-day VTE and adding D-dimer improved the c-statistic to 0.764 with the corollary sensitivity/specificity/positive/negative predictive values of 49.4%/75.7%/6.7%/97.7% and 58.8%/76.2%/10.9%/97.4%, respectively. Among hospitalized and ambulatory patients separately, the HA-VTE IMRS performed similarly. The HA-MB IMRS predictiveness for 90-day major bleeding yielded a c-statistic of 0.64.

Conclusion: The HA-VTE IMRS and HA-MB IMRS predict 90- and 30-day VTE and major bleeding among COVID-19 patients. Adding D-dimer improved the predictiveness of the HA-VTE IMRS for VTE.

KEYWORDS
biomarker, bleeding, risk score, thrombosis, venous thromboembolism

Essentials

- Which patients with COVID will get venous thromboembolism (VTE) or major bleeding is not known.
- We assessed two risk scores derived from only biomarkers to predict VTE and bleeding.
- Ninety-day VTE and major bleeding was predicted by each risk score, respectively.
- Adding D-dimer to the VTE risk score improved predictiveness.

1 | BACKGROUND

Physicians in China reported pulmonary embolism complicating COVID-19 in up to 40% of patients,[1,2] and since these initial reports, subsequent observations suggest that clinical thrombosis occurs more frequently among patients with COVID than among patients with typical viral pneumonia or acute respiratory distress syndrome.[3–6] Even with pharmacologic VTE prophylaxis, VTE has been reported in 30%–38% of hospitalized patients with COVID-19.[6–8] Emerging evidence suggests that empiric use of therapeutically dosed (rather than prophylactically dosed) anticoagulation may have a greater protective effect among some populations[9] but not others.[10] The mechanisms of the prothrombotic effect of COVID-19, sometimes referred to as COVID-associated coagulopathy, are still being elucidated.[11] Hypothesized mechanisms include the effect of neutrophil extracellular traps,[12,13] transient presence of lupus anticoagulants,[14,15] and perhaps an H1N1-like distress leukocyte adhesion to the vein walls that produce inflammatory molecules.[16] A novel aspect of COVID-19 is the association of D-dimer to illness severity,[17] and this biomarker has been proposed as predictive of VTE.[18–20] Pharmacologic VTE prophylaxis, even at low doses, is associated with a risk of bleeding, and given aggressive prophylaxis regimens used in patients with COVID-19, the risk of bleeding must be taken into account to optimize patient outcomes.[21,22] Therefore, it would be ideal to apply pharmacologic VTE prophylaxis to only those patients with COVID-19 most likely to have a favorable risk : benefit balance. Accurately predicting the risk of COVID-associated VTE and major bleeding could inform patient candidacy for prophylaxis.

We recently reported the performance of the hospital-associated venous thromboembolism–Intermountain Risk Score (HA-VTE IMRS) and the hospital-associated major bleeding–Intermountain Risk Score (HA-MB IMRS) to predict 90-day VTE and major bleeding following medical hospitalization.[23] The HA-VTE IMRS is calculated with variables from routine laboratory testing—the predictive quintiles of the red blood cell distribution width (RDW), white blood cell count, platelet count, blood urea nitrogen, glucose, sodium, and age. The HA-MB IMRS is calculated from the predictive quintiles of the RDW, red blood cell count and mean platelet volume, creatinine, sodium, and age. The area under the receiver operating characteristic curve (AUC) of the HA-VTE IMRS for predictiveness of 90-day VTE was 0.6 and that of the HA-MB IMRS was 0.64 in the original validation sets, respectively. Because of the inflammatory nature of COVID-19 and its effects on the complete blood count (CBC) and basic metabolic panel (BMP), we hypothesized that these risk scores might be predictive for the outcomes of VTE and bleeding among patients with COVID-19. Because D-dimer has been reported as possibly predictive of morbidity, mortality, and thrombosis among patients with COVID-19, we wished to understand if D-dimer when added to the IMRS would be additively predictive of thrombosis and major bleeding and thus improve the performance of the scores.

We reported outcomes classifying patients as belonging to one of the following groups. “Ambulatory” patients included all patients seen in the emergency department or receiving COVID-19 testing at a remote/drive-through site never admitted to a hospital. “Hospitalized” patients were those admitted to a hospital and further divided into those with any intensive care unit (ICU) admission at any time during hospitalization (“ICU”), or those cared for exclusively on the medical wards (“medical ward”).

2 | METHODS

2.1 | Study design and patient population

We interrogated the Intermountain Healthcare electronic medical record for laboratory-confirmed cases of COVID-19 between March 12, 2020, and February 28, 2021, in patients independent from our original study derivation/validation set. We identified all cases that had a CBC and BMP within 2 days before and 7 days following the time stamp result of the positive COVID-19 test to permit calculation of a HA-VTE IMRS and HA-MB IMRS with the labs most proximate in time to the COVID-19 test. We identified the subset of patients who required hospitalization as those patients with an inpatient encounter within 2 days before and 7 days following the time stamp result of the positive COVID-19 test (ward patient), and the subset with any ICU admission (ICU patient).

While a recent presentation from the Predictive and Diagnostic Variables Scientific Subcommittee at the ISTH 2021 Congress described little evidence for biomarkers being predictive of VTE among patients with COVID-19,[24] D-dimer has been suggested as being predictive of VTE among patients with COVID-19.[7,18,24] Therefore, we investigated for incremental predictiveness of adding D-dimer to the

HA-VTE IMRS. The D-dimer (STA-R Evolution; Stago, Parsippany, NJ, USA) nearest in time during the study window ascertained as part of clinical care was collected. A D-dimer value <0.5 μg/ml is considered normal. D-dimer was first stratified into quintiles. Because the initial results suggested the greatest predictiveness of the HA-VTE IMRS existed among those patients with a D-dimer in the 0.5–1 μg/mL and 1–2 μg/mL quintiles, further analysis was conducted that combined those patients with D-dimer into three categories: D-dimer <0.5 μg/mL, 0.5–2.0 μg/mL, and >2.0 μg/mL.

The primary thrombosis-related outcome is the predictiveness of the HA-VTE IMRS for 90-day VTE, and the primary bleeding-related outcome is the predictiveness of the HA-MB IMRS for 90-day major bleeding. The outcome of 90-day VTE was defined as any deep vein thrombosis (DVT) of the lower extremities or pulmonary embolism (PE) identified upon electronic health record (EHR) interrogation via natural language processing using a method that we first described in 2010,[25] have validated in comparison with manual chart review,[26] and have implemented to report VTE as an outcome in multiple studies since.[27,28] Major bleeding was defined using the criteria by Schulman.[29] This was ascertained by interrogation of the EHR for an International Classification of Diseases (ICD), Ninth and Tenth Revisions code representative of bleeding into a critical space including the spinal cord, brain, eye, retroperitoneum, or pericardium; or clinically overt bleeding and in the same encounter a transfusion of ≥2 units of packed red blood cells during the 90-day follow-up period as we formerly reported.[23] No dedicated funding existed for this work. The study proposal was reviewed, and a waiver of oversight was provided by the institutional review board. All work was performed with the principles stated in the Declaration of Helsinki.

2.2 | Statistical analysis of the HA-VTE IMRS and the HA-MB IMRS

For the HA-VTE IMRS and the HA-MB IMRS, we computed the AUC to generate this common measure of predictive accuracy for binary outcomes. We characterized patients as being at low and high risk based on a threshold for HA-VTE IMRS where the risk of VTE exceeded 2% (HA-VTE IMRS ≥7) and for HA-HB IMRS where the risk of bleeding was >1% (HA-MB IMRS ≥9) derived from our former work.[23] Cox regression was used to evaluate the association of each risk score with study outcomes and to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Baseline was defined as the time stamp of COVID-19 laboratory results, and censoring occurred for nonevent patients at the time of death or at 90 days after baseline. Further analyses added D-dimer to the Cox models with each risk score.[30] The predicted risk from Cox regression of models with a risk score and D-dimer entered in the model was used to calculate the AUC for the combination of the risk score and D-dimer. Analyses used SPSS version 26.0 (IBM, Armonk, NY, USA) or R version 4.1.3 and the survival package (R Foundation for Statistical Computing, Vienna, Austria).[31,32]

3 | RESULTS

During the study period, 113,692 patients had a COVID-19 positive test at Intermountain Healthcare (ambulatory patients included 105,615 from "drive-through" testing and 7625 tested in the emergency department and 452 hospitalized patients). Among all patients who tested positive for COVID-19, 5047 had CBC and BMP data between 2 days before and 7 days following the COVID-19 test. This subset constituted the study population, which was 50.2% women with a mean age of 53.5 ± 20.9 years; demographics are reported in Table 1. We report outcomes among ambulatory patients ($n = 3179$), and hospitalized patients (n = 1868; divided into medical ward patients [$n = 1071$] and ICU patients [$n = 797$]).

Overall, 172 VTE events were recorded, including 92 PEs and 80 DVTs with death occurring in 18.5% of patients with PE and 6.5% of those with DVT. Among all patients with COVID-19, the HA-VTE IMRS AUC was 0.701 (95% CI, 0.66–0.74) for predicting 90-day VTE. The rate of VTE in the high-risk group compared with that of the low-risk group defined by the threshold of a HA-VTE IMRS ≥7 was 6.7% versus 2.3% (Figure 1), with a resulting HR of 3.12 (95% CI, 2.31–4.21). AUC is a measure of predictiveness of a risk score and therefore is useful for comparing models without bias that may come from the choice of variable cutoff value used. However, to report risk prediction, model performance in the clinical context of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) cutoff values must be selected. The HA-VTE among all patients had a sensitivity, specificity, PPV and NPV of 49.4% (42.0–56.8) / 75.7% (74.5–76.9) / 6.7% (5.4–8.2) / 97.7% (97.2–98.1).

Among ambulatory and hospitalized patients with COVID-19 separately, a HA-VTE IMRS was associated with an AUC of 0.70 (95% CI, 0.64, 0.76), and 0.66 (95% CI, 0.61–0.71), respectively (Figure S1). The separate HA-VTE IMRS among ambulatory and hospitalized patients had a sensitivity, specificity, PPV, and NPV of 52.48% (42.84–61.99) / 65.42% (63.18–67.61) / 7.98% (6.08–10.21) / 96.01% (94.81–97.02) and 45.07% (33.94–56.55) / 81.60% (80.21–82.93) / 5.30% (3.70–7.28) / 98.49% (97.96–98.91), respectively. Further analysis of inpatient subgroups showed that the HA-VTE IMRS predictiveness for VTE among ICU and ward patients was 0.651 (95% CI, 0.58–0.72) and 0.62 (95% CI, 0.53–0.70), respectively. We refit the Cox proportional hazards models using death as a competing risk instead of a censoring event and computed the Aalen-Johansen estimator. The results were not meaningfully different from what was found before.

At 30-day follow-up, the HA-VTE IMRS AUC was 0.70 (95% CI, 0.66–0.74). Compared with those patients for whom the HA-VTE IMRS was <7, those patients with a HA-VTE IMRS ≥7 had a HR of 3.41 (95% CI, 2.49–4.68).

D-dimer measured within 2 days before and 7 days after the COVID-19 diagnosis was available for 2407 patients, and when added to the HA-VTE IMRS improved the AUC to 0.76 (95% CI, 0.72, 0.81) for the outcome of 90-day VTE (in this patient subset, AUC was 0.67 [95% CI, 0.63–0.72] for the HA-VTE IMRS alone). Because limiting D-dimer to a time frame closest to the COVID-19 test

TABLE 1 Patients with HA-VTE IMRS within 2 days before or 7 days after a COVID-19 diagnosis

	Overall	Low-risk HA-VTE IMRS (<7)	High-risk HA-VTE IMRS (≥7)
Variable	*N* = 5047	*n* = 3779	*n* = 1268
Patient characteristics			
Age, years, mean (SD)	53.5 (20.9)	49.0 (21.3)	67.0 (12.0)*
Female, *n* (%)	2535 (50.2)	2042 (54.0)	493 (38.9)*
Race (non-White), *n* (%)	509 (10.1)	396 (10.5)	113 (8.9)
Hispanic, *n* (%)	1102 (21.8)	894 (23.7)	208 (16.4)*
Congestive heart failure, *n* (%) (*n* = 4995)	360 (7.1)	177 (4.6)	183 (14.8)*
eGFR (ml/min/1.73 m^2)	86.9 (33.2)	93.2 (30.9)	68.1 (32.8)*
Diabetes, *n* (%) (*n* = 4995)	779 (15.4)	423 (11.1)	356 (28.8)*
Current tobacco use, *n* (%)	250 (5.0)	197 (5.2)	53 (4.2)*
Infection, *n* (%)	505 (10.0)	357 (9.4)	148 (11.7)†
PICC, *n* (%)	64 (1.3)	32 (0.8)	32 (2.5)*
Sepsis, *n* (%)	409 (8.1)	211 (5.6)	198 (15.6)*
Bleed, *n* (%)	44 (0.9)	22 (0.6)	22 (1.7)*
High-flow oxygen[a] (*n* = 1868 inpatients)	306 (16.4)	133 (11.0)	173 (26.1)*
Ventilator support[b] (*n* = 1868 inpatients)	199 (10.7)	80 (6.6)	119 (17.9)*
Received chemoprophylaxis, *n* (%)	1699 (33.7)	1024 (27.1)	675 (53.2)*
Inpatient chemoprophylaxis,[c] *n* (%) (*n* = 1868)	1405 (75.2)	836 (69.4)	569 (85.7)*
Ambulatory, *n* (%) (*n* = 3179)	294 (9.2)	188 (7.3)	106 (17.5)*
Charlson Comorbidity Index, mean (SD)	1.45 (2.16)	0.99 (1.72)	2.80 (2.71)*
VTE risk factors, *n* (%)			
Cancer	280 (5.5)	156 (4.1)	124 (9.8)*
Prior VTE	348 (6.9)	203 (5.4)	145 (11.4)*
Thrombophilia[d]	123 (2.4)	75 (2.0)	48 (3.8)*
Surgery[e]	85 (1.7)	54 (1.4)	31 (2.4)†
Obesity[f]	1124 (22.3)	863 (22.8)	261 (20.6)
Estrogen hormone therapy	107 (2.1)	99 (2.6)	8 (0.6)*
Insurance, *n* (%)			
Private insurance	2396 (47.5)	2056 (54.4)	340 (26.8)*
Medicare	1728 (34.2)	942 (24.9)	786 (62.0)
Medicaid	635 (12.6)	539 (14.3)	96 (7.6)
Self-pay	200 (4.0)	182 (4.8)	18 (1.4)
Workers compensation	5 (0.1)	5 (0.1)	0 (0)
Unknown	83 (1.6)	55 (1.5)	28 (2.2)
Religious preference, *n* (%)			
Christian	2986 (59.2)	2172 (57.5)	814 (64.2)*
Other	79 (1.6)	62 (1.6)	17 (1.3)
None	1099 (21.8)	867 (22.9)	232 (18.3)
Unknown	883 (17.5)	678 (17.9)	205 (16.2)
Marital status, *n* (%)			
Married/Partnered	2756 (54.6)	2005 (53.1)	751 (59.2)*
Single	1218 (24.1)	1042 (27.6)	176 (13.9)
Divorced/Separated	489 (9.7)	331 (8.8)	158 (12.5)
Widowed	401 (7.9)	266 (7.0)	135 (10.6)
Unknown	183 (3.6)	135 (3.6)	48 (3.8)

Abbreviations: eGFR, estimated glomerular filtration rate; HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; PICC, peripherally inserted central venous catheter; SD, standard deviation; VTE, venous thromboembolism.

[a]Defined as administration of high-flow oxygen anytime during hospitalization.

[b]Defined as any ventilator support during the hospitalization.

[c]Defined as a pharmacologic thromboprophylaxis (prevention dose and/or treatment dose anticoagulants) administered ≥50% of hospitalized days upon electronic medical administration record electronic interrogation.

[d]A heritable or acquired thrombophilia recorded in the laboratory results of the electronic health record.

[e]Defined as surgery with general anesthesia lasting >1 hour within the preceding 30 days.

[f]Body mass index ≥30.

*$p < 0.001$ for the comparison of high-risk versus low-risk HA-VTE IMRS.

†$p \leq 0.05$ and $p \geq 0.001$.

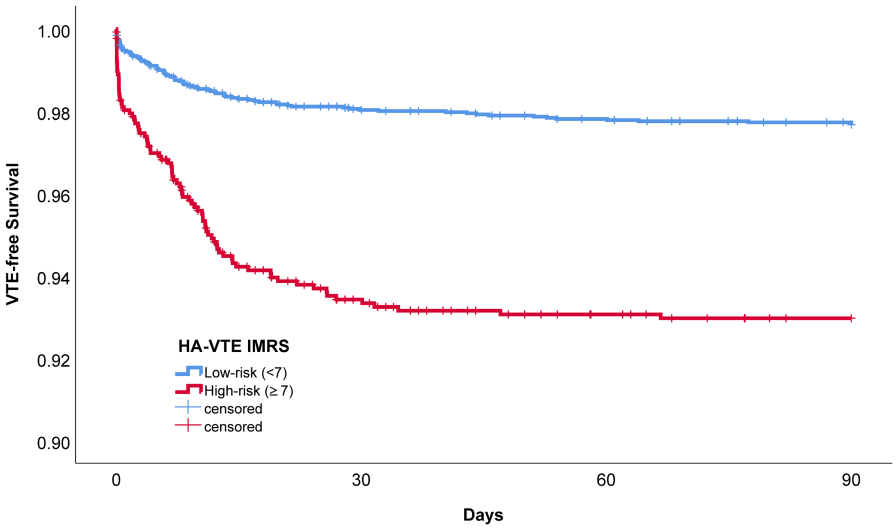


FIGURE 1 Kaplan–Meier survival curve for 90-day VTE based on the HA-VTE IMRS using the threshold of ≥7 for high risk and <7 for low risk of VTE ($p < 0.001$). Abbreviations: HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; VTE, venous thromboembolism

permits exploring the predictiveness of D-dimer for VTE by diminishing the likelihood that the D-dimer was obtained for diagnostic purposes, we performed sensitivity analyses for VTE that included only D-dimer results that were obtained ±24 hours of COVID-19 diagnosis and limited eligible candidates to those with VTE occurring >1 day after COVID-19 diagnosis ($n = 1638$; VTE events: $n = 55$). For 90-day VTE, the HA-VTE IMRS alone resulted an AUC of 0.67 (95% CI, 0.60–0.74) and 0.72 (95% CI, 0.65–0.79) with the HA-VTE IMRS and D-dimer combined. When using D-dimer values from ±24 hours of COVID-19 diagnosis and limiting VTE to only those occurring >7 days after COVID-19 diagnosis and including nonevent patients with >7-day follow-up ($n = 1550$; VTE events: $n = 35$), the AUCs were 0.69 (95% CI, 0.61–0.77) for HA-VTE IMRS alone and 0.72 (95% CI, 0.65–0.79) with both HA-VTE IMRS and D-dimer in the model. These data are found in Table S5. Since D-dimer and the IMRS are on different scales, they were combined in a single logistic regression model, and the cutoffs were then used on the predicted log-odds from this model. Combining D-dimer and the HA-VTE IMRS using a log-odds cutoff of 0.18 identified about 25% of patients as being at high risk for VTE and resulted in a sensitivity of 58.8%, a specificity of 76.2%, and a PPV and NPV of 10.9% and 97.4%; respectively. Table S4 includes the operating characteristics for the HA-VTE IMRS ± D-dimer at various selected cut points.

Preliminary analyses of D-dimer prediction by quintiles led to condensed D-dimer categories of <0.5, 0.5–2.0, and >2.0 μg/ml (Figure 2) that included 27%, 54%, and 19% of patients, respectively. These analyses showed that the HA-VTE IMRS best discriminated VTE risk among patients with a D-dimer of 0.5–2.0 μg/ml (Figure 2B). In that group, the VTE rate with the HA-VTE IMRS ≥7 was 5.2% (21/403) versus <7: 2.2% (20/893) (Table 2). In contrast, the risk score was not additively predictive for VTE risk among those patients with a D-dimer <0.5 μg/ml (Figure 2A) or a D-dimer >2.0 μg/ml (Figure 2C).

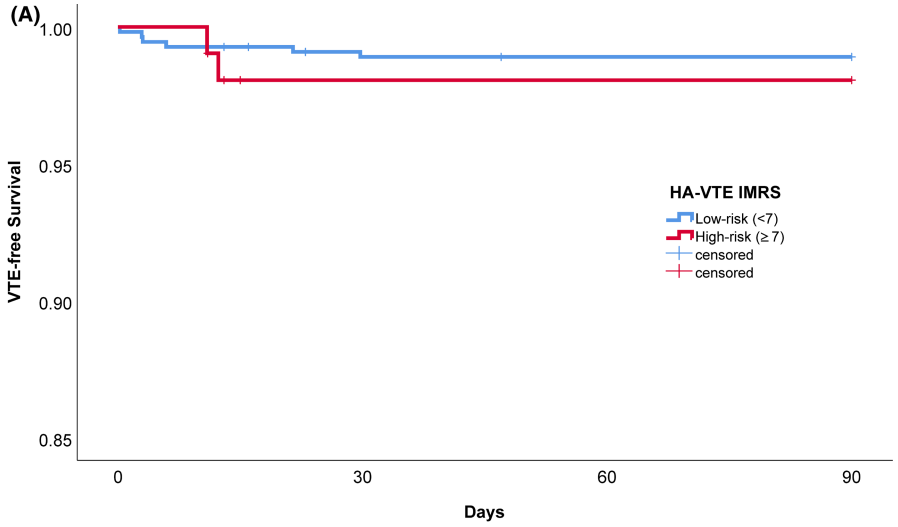
Among all patients with COVID-19, a HA-MB IMRS ≥9 yielded an AUC of 0.64 (95% CI, 0.57–0.71). The rate of major bleeding in the high-risk group defined by the threshold of a HA-MB IMRS ≥9 compared with that of the low-risk group was 2.3% versus 1.0% (Figure 3); HR, 2.23 (Table 2). Among separated hospitalized and ambulatory patients with COVID-19, a HA-MB IMRS ≥9 was associated with an AUC of 0.615 (95% CI, 0.52–0.71) and 0.63 (95% CI, 0.52–0.73), respectively (Figure S1). The addition of D-dimer to HA-MB IMRS showed in Cox regression that D-dimer was not associated (HR, 1.1; $p = 0.20$) with major bleeding in all patients with COVID-19 and yielded an AUC of 0.57 (95% CI, 0.50–0.64). Figure 4 presents that receiver operating characteristic curves for the predictiveness of the HA-VTE IMRS, the HA-VTE IMRS + D-dimer, and the HA-MB IMRS for the outcomes of VTE and major bleeding, respectively. At 30-day follow-up, HA-MB IMRS had an AUC of 0.63 (95% CI, 0.55–0.71) and, for values ≥9, had an HR of 2.22 (95% CI, 1.33–3.70).

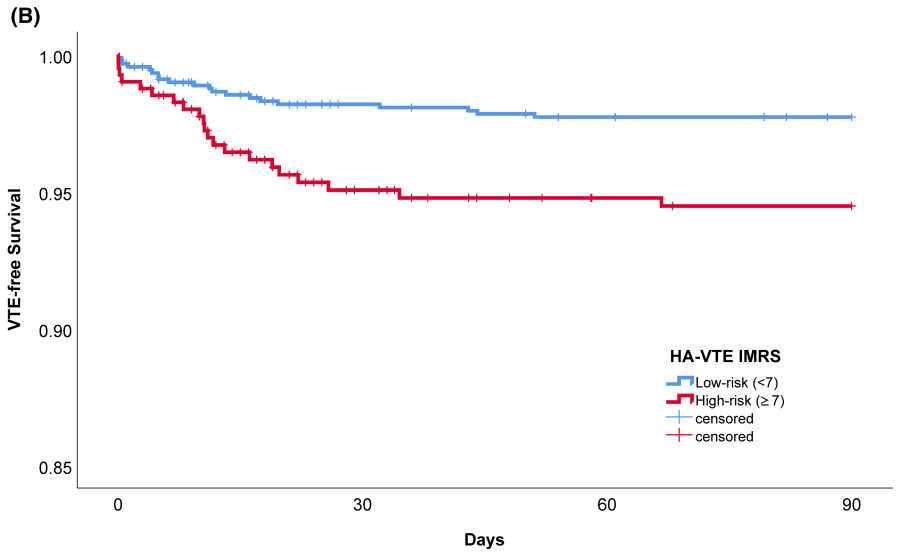
In Table 3, the predicted outcome rates of VTE and major bleeding are presented among individuals stratified at high or low risk based upon the HA-VTE IMRS and HA-MB IMRS, respectively. Similar data are provided in Table S2 for the individual scores and outcomes, and Table S3 for substrata defined by D-dimer level.

4 | DISCUSSION

The HA-VTE IMRS and the HA-MB IMRS were predictive of 90-day and 30-day VTE and major bleeding, respectively, in patients with COVID-19. Incorporating D-dimer further improved the performance of the HA-VTE IMRS. Because these scores are derived from routinely available coded data—patient age and elements of the CBC and BMP—they can be determined in most patients with COVID-19 without the need for additional clinical history or testing. Score calculation should be able to be readily automated within most EHR systems.

Understanding 90- and 30-day VTE risk can further identify ambulatory patients with COVID-19 and those hospitalized patients who at discharge might benefit from pharmacologic VTE prophylaxis, informed by concomitant bleeding risk estimation. To advance generalizability, our study population included all patients with a





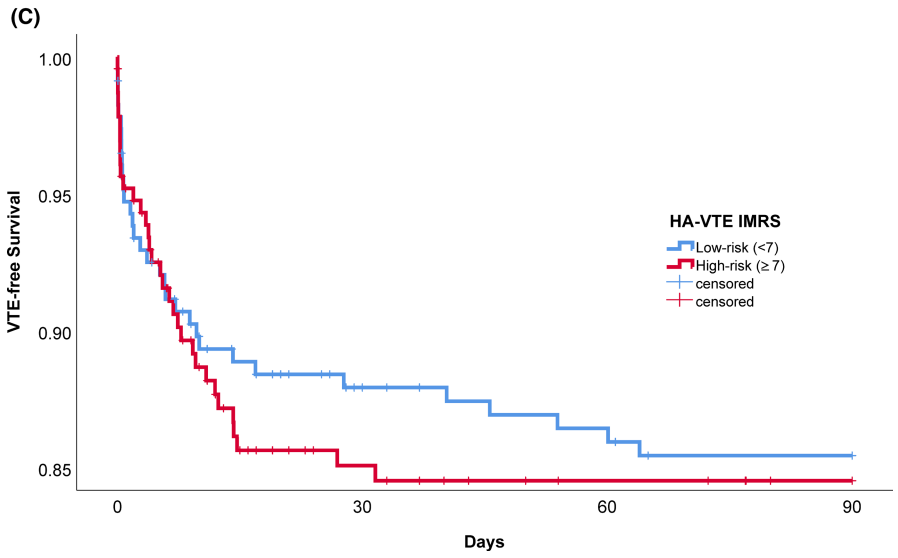


FIGURE 2 Kaplan–Meier survival curves for 90-day VTE using HA-VTE IMRS ≥7 versus <7 in subgroups of D-dimer (μg/ml): (A) <0.5 ($p = 0.47$), (B) 0.5–2.0 ($p = 0.003$), (C) >2.0 ($p = 0.75$). Abbreviations: HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; VTE, venous thromboembolism

TABLE 2 Cox regression modeling of HA-VTE IMRS for VTE and HA-MB IMRS for major bleeding with and without D-dimer

Outcome/Variable	Hazard Ratio	95% CI	Events	Sample size
Venous thromboembolism				
HA-VTE IMRS				
<7	1.0	(referent)	87	3779
≥7	3.12	2.31–4.21	85	1268
D-Dimer subgroups				
<0.5 μg/ml				
HA-VTE IMRS < 7	1.0	(referent)	6	549
HA-VTE IMRS ≥ 7	1.78	0.36–8.82	2	104
0.5–2.0 μg/ml				
HA-VTE IMRS < 7	1.0	(referent)	20	893
HA-VTE IMRS ≥ 7	2.46	1.33–4.54	21	403
>2.0 μg/ml				
HA-VTE IMRS < 7	1.0	(referent)	32	228
HA-VTE IMRS ≥ 7	1.08	0.67–1.76	33	230
Joint modeling for VTE (patients with a D-dimer measurement: $n = 2407$)				
Univariable				
HA-VTE IMRS < 7	1.0	(referent)	58	1670
HA-VTE IMRS ≥ 7	2.34	1.62–3.37	56	737
Multivariable				
HA-VTE IMRS < 7	1.0	(referent)	58	1670
HA-VTE IMRS ≥ 7	1.51	1.03–2.20	56	737
D-dimer				
<0.5 μg/ml	1.0	(referent)	8	653
0.5–2.0 μg/ml	2.49	1.17–5.33	41	1296
>2.0 μg/ml	11.66	5.52–24.61	65	458
Major Bleeding				
HA-MB IMRS				
<9	1.0	(referent)	40	3811
≥9	2.23	1.38–3.62	28	1236

Abbreviations: CI, confidence interval; HA-MB IMRS, hospital-associated major bleeding–Intermountain Risk Score; HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; VTE, venous thromboembolism.

positive COVID-19 test and a qualifying CBC and BMP, regardless of hospitalization status. However, we reported the performance of the risk scores among (i) ambulatory patients and (ii) hospitalized patients which were subdivided into (iia) medical ward and (iib) ICU patients. The HA-VTE IMRS and the HA-MB IMRS were calculated for each subgroup.

The pragmatic implications of VTE risk mitigation among hospitalized versus ambulatory patients differs, and we were especially encouraged by the performance of the HA-VTE IMRS among ambulatory patients. This is a patient population that does not routinely receive pharmacologic VTE prophylaxis, and for which it has been suggested to be futile.[33] Yet it is likely that a subset of ambulatory patients is at risk for VTE, and emerging evidence suggests that pharmacologic VTE prophylaxis may further mitigate the composite outcome of thrombosis and vascular death,[34] at least following hospital discharge. Identifying these patients represents an unmet need. Our study was not designed to predict risk for VTE and bleeding and inform thromboprophylaxis decision making during hospitalization.

Overall D-dimer improved the HA-VTE IMRS predictiveness AUC for VTE from 0.701 to 0.764. Furthermore, we observed that D-dimer permitted an incremental benefit in stratifying risk for thrombosis among patients with a D-dimer of 0.5–2 μg/ml, which represented 54% of the study cohort. In that subset of patients, the HA-VTE IMRS significantly discriminated risk for 90-day VTE as demonstrated in Figure 2B. These findings suggest that among patients with COVID-19, should a D-dimer be obtained, then the greatest predictiveness exists among those patients with a D-dimer of 0.5–2.0 μg/ml. While the risk threshold for prescribing pharmacologic VTE prophylaxis among patients with COVID-19 is unknown, if the HA-VTE IMRS can discriminate between those patients with a

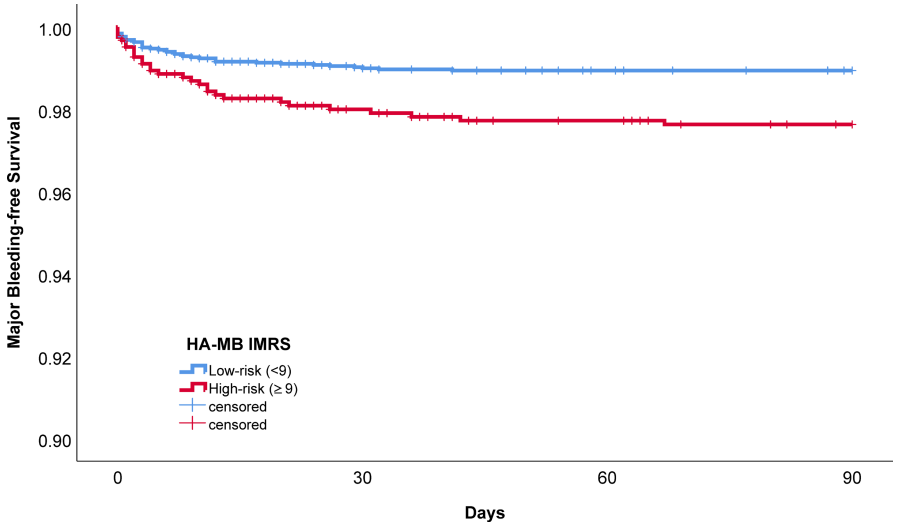


FIGURE 3 Kaplan–Meier survival curve for 90-day major bleeding based on the HA-MB IMRS using the threshold of ≥9 for high risk and <9 for low risk of major bleeding ($p < 0.001$). Abbreviations: HA-MB IMRS, hospital-associated major bleeding–Intermountain Risk Score

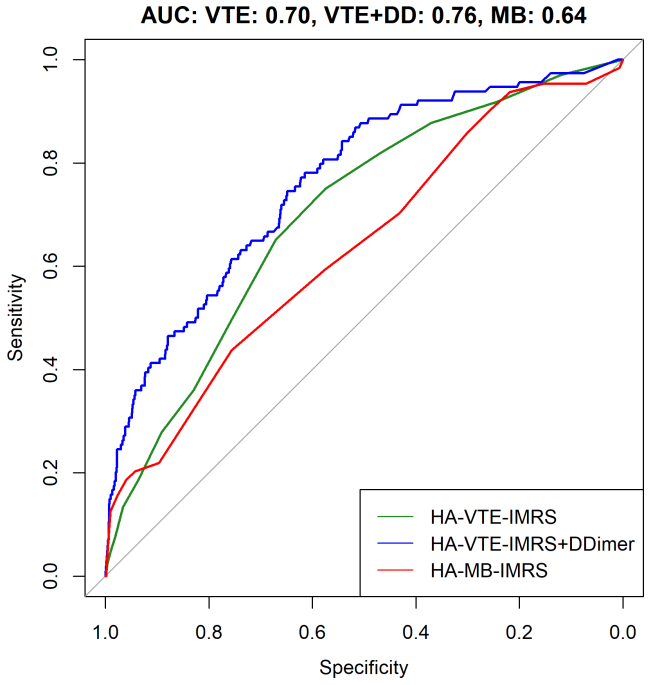


FIGURE 4 Receiver operating characteristic curves show the predictiveness of the HA-VTE IMRS (green), and HA-VTE IMRS + D-dimer (blue) for 90-day VTE; and the HA-MB IMRS (red) for major bleeding. Abbreviations: HA-MB IMRS, hospital-associated major bleeding–Intermountain Risk Score; HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; VTE, venous thromboembolism

90-day VTE risk of ≤2% versus ≥2%, that information may be useful in this decision making.

Yet, to date, uncertainty exists that pharmacologic VTE prophylaxis among ambulatory patients with COVID-19 is useful. A large, prospective, randomized control trial involving ambulatory patients with COVID-19 and evidence of inflammation was terminated prematurely when interim stopping rules suggested futility.[33] A possible explanation provided for this observation was an inability to identify the subset of ambulatory COVID-19 patients that would benefit from pharmacologic VTE prophylaxis. Our study is important because it suggests that a cohort of identifiable ambulatory and discharged medical COVID-19 patients exists for which pharmacologic VTE prophylaxis could be beneficial. Given that 89% of all VTE occurred within 4 weeks following COVID-19 diagnosis, pharmacologic VTE prophylaxis could likely be administered for a relatively short period (eg, 4 weeks), which has recently been suggested in a draft guidance statement.[35] Additionally, recent reports suggest that the prescription of reduced-dose anticoagulation among patients with COVID-19 found to be at an increased risk for VTE at the time of discharge using a standardized VTE risk assessment tool may realize a composite outcome benefit in 35-day thrombosis and major adverse vascular events.[36] Finally, implementing a risk prediction tool such as the HA-VTE IMRS may provide a way for clinical trialists to identify a study population thought to be at increased risk for thrombosis, thereby economizing enrollment efforts.

The role of biomarkers to predict major bleeding is even less well defined.[37,38] However, the HA-MB IMRS permits objective assessment of major bleeding risk in the absence of extended-duration thromboprophylaxis and identifies patients estimated to be at increased risk for bleeding, thereby excluding them from candidacy for pharmacologic prophylaxis to prevent VTE. Accounting for both thrombosis and bleeding risk optimizes the net clinical benefit of any pharmacologic prophylaxis to prevent VTE.

Among subgroups of patients with COVID we observed a lower predictiveness of the HA-VTE IMRS among hospitalized patients (AUC = 0.659) when compared with ambulatory patients (AUC = 0.697). Most VTE events (89.5%) occurred within the 30 days following COVID-19 diagnosis. Most patients with COVID-19 do not require hospitalization, 99.6% of all COVID-19 tests performed during the study period were among ambulatory patients, and 63% of all study patients were ambulatory.

Limitations of our work include that the HA-VTE and HA-MB IMRS are not validated to the degree of other scores that have been described to predict postdischarge VTE such as the IMPROVE VTE risk score,[39] the Modified IMPROVE VTE risk score,[40] and the IMPROVEDD risk score.[41] The IMPROVE-DD RAM was recently

TABLE 3 Net clinical benefit evaluation of VTE and major bleeding event risk in quadrants of patients defined by level of risk using HA-VTE IMRS and HA-MB IMRS

A. All patients		HA-VTE IMRS—calculated VTE risk	
HA-MB IMRS—calculated MB Risk	**Event**	**Low-risk**	**High-risk**
Low-risk	VTE	2.0% (64/3268)	***5.5% (30/543)***
	MB	0.8% (25/3268)	***2.8% (15/543)***
High-risk	VTE	4.5% (23/511)	7.6% (55/725)
	MB	0.8% (4/511)	3.3% (24/725)
B. Ambulatory patients		**VTE risk**	
MB Risk	**Event**	**Low-risk**	**High-risk**
Low-risk	VTE	1.3% (30/2261)	***3.8% (11/288)***
	MB	0.6% (13/2261)	***2.4% (7/288)***
High-risk	VTE	2.9% (9/314)	6.6% (21/316)
	MB	0.3% (1/314)	2.5% (8/316)
C. Hospitalized patients		**VTE Risk**	
MB risk	**Event**	**Low-risk**	**High-risk**
Low-risk	VTE	3.4% (34/1007)	***7.5% (19/255)***
	MB	1.2% (12/1007)	***3.1% (8/255)***
High-risk	VTE	7.1% (14/197)	8.3% (34/409)
	MB	1.5% (3/197)	3.9% (16/409)

Abbreviations: HA-MB IMRS, hospital-associated major bleeding–Intermountain Risk Score; HA-VTE IMRS, hospital-associated venous thromboembolism–Intermountain Risk Score; MB, major bleeding; VTE, venous thromboembolism.

assessed for predictiveness of VTE among hospitalized medical patients with COVID-19 in a large health care system not dissimilar to ours demonstrating similar operating characteristics in predictiveness for hospital-associated VTE (IMPROVEDD AUC = 0.703[42] vs the HA-VTE IMRS + D-dimer AUC = 0.764). Our study was limited to those patients with a CBC and BMP proximate in time to the COVID-19 diagnosis. We cannot remark how these patients compare with COVID-19 patients for which a CBC and BMP were not available.

Strengths of this study include reporting VTE and bleeding risk prediction tools that can be automated and would not be reliant on manual physician data entry/chart review (eg, "history of thrombosis") or require ICD codes with inherent limitations described.[43,44] Taken together, the application of these two risk scores may aid the clinician in identifying the patient population for which the net clinical benefit would favor the intervention of pharmacologic VTE prophylaxis.

To our knowledge, ours represents the first VTE and bleeding risk scores predictive of 90- and 30-day VTE and major bleeding, respectively, among patients with COVID-19 that are derived from only patient age and laboratory tests that are part of routine clinical care. The HA-VTE IMRS predicts VTE among patients with COVID-19 regardless of patient hospitalization status. Considering an individual patient's bleeding risk estimated by the HA-MB IMRS may best identify those patients for which pharmacologic VTE prophylaxis would be considered too great a risk for bleeding. Maintaining safety ("first do no harm") is a core tenet to any proposed primary prevention intervention. An attractive characteristic of these risk scores is that EHR programming could likely occur regardless of an institution's EHR as most EHRs are capable of integrating equations with threshold parameters such as those that the HA-VTE and HA-MB IMRS require.

Future research should include the external validation of our HA-VTE and HA-MB IMRS among patients with COVID-19.[45,46] To facilitate collaboration and external validation of our work, we published the HA-VTE IMRS and HA-MB IMRS covariate quintile thresholds in a previous article[23] (https://onlinelibrary.wiley.com/doi/10.1002/rth2.12560).

In conclusion, formerly derived and validated biomarker risk scores predictive of 90-day hospital-associated VTE and major bleeding appear to be also predictive of 90- and 30-day VTE and major bleeding, respectively, among patients with COVID-19. Adding D-dimer improved predictiveness. This predictiveness exists for both ambulatory and hospitalized patients. Taken together, patients with COVID-19 for whom the net clinical benefit of pharmacologic VTE prophylaxis is favorable to reduce the burden of VTE may be identified.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept, design, drafting of manuscript: SCW, SMS, GLS, JRB, MF, and BDH. Manuscript critical review and refinement: SCW,

GLS, SMS, JFL, JRB, MF, and BDH. Statistical analysis: SCW, BDH, GLS, and JFL.

RELATIONSHIP DISCLOSURE

SCW, SMS, MF, JFL, GLS, and JRB report nothing to disclose. BDH is an inventor of clinical decision tools licensed to CareCentra and Alluceo, is principal investigator of grants funded by Intermountain Healthcare's Foundry innovation program, the Intermountain Research and Medical Foundation, CareCentra, Sysmex, GlaxoSmithKline plc., and AstraZeneca, and is a co-investigator for a grant from the Patient-Centered Outcomes Research Institute.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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