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The CoVID-TE risk assessment model for venous thromboembolism in hospitalized patients with cancer and COVID-19

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Background: Hospitalized patients with COVID-19 have increased risks of venous (VTE) and arterial thromboembolism (ATE). Active cancer diagnosis and treatment are well-known risk factors; however, a risk assessment model (RAM) for VTE in patients with both cancer and COVID-19 is lacking.

Objectives: To assess the incidence of and risk factors for thrombosis in hospitalized patients with cancer and COVID-19.

Methods: Among patients with cancer in the COVID-19 and Cancer Consortium registry (CCC19) cohort study, we assessed the incidence of VTE and ATE within 90 days of COVID-19–associated hospitalization. A multivariable logistic regression model specifically for VTE was built using a priori determined clinical risk factors. A simplified RAM was derived and internally validated using bootstrap.

Results: From March 17, 2020 to November 30, 2020, 2804 hospitalized patients were analyzed. The incidence of VTE and ATE was 7.6% and 3.9%, respectively. The incidence of VTE, but not ATE, was higher in patients receiving recent anti-cancer therapy. A simplified RAM for VTE was derived and named CoVID-TE (Cancer subtype high to very-high risk by original Khorana score +1, VTE history +2, ICU admission +2, D-dimer elevation +1, recent systemic anti-cancer Therapy +1, and non-Hispanic Ethnicity +1). The RAM stratified patients into two cohorts (low-risk, 0–2 points, n = 1423 vs. high-risk, 3+ points, n = 1034) where VTE occurred in 4.1% low-risk and 11.3% high-risk patients (c statistic 0.67, 95% confidence interval 0.63–0.71). The RAM performed similarly well in subgroups of patients not on anticoagulant prior to admission and moderately ill patients not requiring direct ICU admission.

Conclusions: Hospitalized patients with cancer and COVID-19 have elevated thrombotic risks. The CoVID-TE RAM for VTE prediction may help real-time data-driven decisions in this vulnerable population.

Keywords: clinical decision rules, COVID-19, SARS-CoV-2, thrombosis, venous thromboembolism
INTRODUCTION

Numerous studies have demonstrated a complex interplay between inflammation and coagulation associated with COVID-19 that results in an increased risk of venous thromboembolism (VTE) and arterial thrombotic events (ATE).1-4 Specifically, the exact incidence of VTE associated with COVID-19 is debated and has ranged from as low as 1% in the general wards to as high as 69% in intensive care units (ICUs) in published reports, depending on the diagnostic approach used and whether screening was performed.5,6 The link between coagulopathy and COVID-19 has led to an international collaborative effort of randomized controlled studies designed to investigate the use of anticoagulant therapy to prevent complications associated with COVID-19 among hospitalized medical inpatients, of which the interim unpublished results were recently released.7

Both cancer and anti-cancer therapies are well-known risk factors for thrombotic events.8,9 While many risk factors have been identified for VTE in patients with cancer, advanced disease as well as certain cancer types such as neoplasms of the pancreas, esophagus, and stomach carry the highest risk.10,11 Moreover, patients with cancer have a higher incidence of VTE compared to acutely ill medical patients without cancer.12,13 Despite being a well-known phenomenon for thrombosis, cancer diagnosis and anti-cancer therapy have not yet been identified as a strong risk factor for COVID-19-associated thrombosis and the exact thrombotic risk in hospitalized patients with both cancer and COVID-19 remains unknown. In addition, patients with cancer not only have a higher risk of VTE but also have a higher risk of bleeding on anticoagulation compared to patients without cancer.14,15 A better understanding of the epidemiology and risk factors of thrombosis in patients with cancer and COVID-19 will also help researchers, clinicians, and policymakers to place results from the before-mentioned randomized controlled trials in a relevant context and help discuss appropriate thromboprophylaxis in more vulnerable patients.

The current study has two aims. First, we aim to estimate the 90-day incidence of VTE and ATE for patients with COVID-19 and cancer requiring hospitalization, stratified by ICU status and active cancer status. Second, we aim to derive a simple risk assessment model (RAM) specifically for VTE at the time of hospital admission.

METHODS

Study design

The COVID-19 and Cancer Consortium registry (CCC19; NCT04354701) is an ongoing multi-center effort to assess the clinical-pathologic factors and disease course among patients with COVID-19 and either a current or previous diagnosis of cancer. Details of the original study design and data capture have been reported previously and are available publicly.16-18 Briefly, data were captured at baseline around the time of COVID-19 diagnosis and then at 30 days, 90 days, and 180 days after diagnosis. Centralized data management is coordinated through REDCap at Vanderbilt University. Given the de-identified nature of the data collected, this study has been exempted from institutional review board (IRB) review at Vanderbilt University.

Outcome definitions

The primary outcomes included VTE as defined by pulmonary embolism (PE), deep vein thrombosis (DVT), or thrombosis not otherwise specified (NOS); and ATE as defined by myocardial infarction (MI) or ischemic stroke (CVA). Secondary outcomes included frequency of PE and/or DVT (excluding thrombosis NOS), PE only, or CVA only. All thrombotic complications were captured as binary “yes/no” responses through retrospective chart review. The exact definition (imaging vs. clinical diagnosis, proximal vs. distal, symptomatic vs. incidental) was left to the discretion of individual sites. Notably, superficial venous thrombosis (SVT) was captured separately and was not included in any of the above definitions.

Prognostic risk factors

Members of the thrombosis research working group within the CCC19 defined important prognostic risk factors for VTE in hospitalized medical patients with both cancer and COVID-19 using previously published data from general medical inpatients,20 patients with cancer,10 and patients with COVID-199 (Table S1 in supporting
information). Specifically, the following clinical variables were chosen a priori at the time of admission as potentially important covariates based on plausibility and literature: age at COVID-19 diagnosis, sex, race/ethnicity, morbid obesity with body mass index (BMI) ≥35, history of VTE, cancer type VTE risk according to the original Khorana Score, cancer status (active vs. previous), any recent anti-cancer systemic therapy within prior 3 months, antplatelet medication prior to admission, anticoagulant medication prior to admission, or severe COVID-19 disease requiring direct ICU admission. Additional laboratory values at the time of admission were included in an exploratory analysis: white blood cell count, hemoglobin, platelet count, and D-dimer. Of note, we chose pre-admission anticoagulant use instead of post-admission prophylaxis/therapeutic use to enable the calculation of risk factors at the time of admission.

2.5 Statistical methods

The cumulative incidence of VTE and ATE within 90 days after COVID-19-associated admission was determined by the number of reported VTE or ATE events from data forms within 13 weeks of follow-up divided by the number of total available patients that met the inclusion and exclusion criteria. The primary and secondary outcomes were further estimated in pre-specified subgroups (ICU vs. wards, recent systemic therapy vs. none). The incidence trend was also plotted over quarterly intervals for the year 2020. As neither thrombotic nor mortality events had associated time stamps to protect patient identity, we did not perform competing risk analyses.

To derive a prognostic RAM for VTE, we built a multivariable logistic regression model to assess the association between 90-day VTE outcomes and baseline covariates. We included all pre-specified clinical covariates in a single model. With the exception of age, all other covariates were categorical. Age was explored both as a continuous linear variable and cubic splines. Additionally, interaction between age and other covariates was checked using the likelihood ratio test. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for VTE and PE were estimated from the models. The relative strengths of each predictor within the model were assessed using the model chi-square statistic. Multiple imputation through 10 iterations with additive regression, bootstrapping, and predictive mean matching was used to impute missing/unknown data for all clinical variables with <5% missingness in the primary analysis or laboratory variables with <10% missingness in the sensitivity analysis.

To create a simplified RAM, we used the strongest predictors from the multivariable model and assigned simplified integer scores based on the ratio from the division of the covariate's beta coefficient by the lowest beta coefficient. Only patients with non-missing values in all predictor categories were included in this analysis. Final risk categories were created using the sum of individual integer scores. The overall goodness-of-fit of all models was checked using the Hosmer-Lemeshow (HL) test and calibration plot. Internally validated discrimination was performed using the optimism-corrected c-statistic, for which optimism was calculated as the mean difference in c-statistic between the original and 1000 bootstrapped resamples.

Several exploratory and sensitivity analyses were performed. First, the model was tested after exclusion of patients who were already receiving anticoagulation prior to admission. Second, the model was assessed in patients not requiring ICU admission at the time of hospitalization. Third, it was expanded to explore the additive values of key laboratory values. Finally, we examined the impact of the final RAM on overall bleeding (defined as major, clinically relevant non-major, or minor bleeding without other specification) and 30-day mortality. Data analysis was performed in R 4.0.3 (R Foundation for Statistical Computing).

3 RESULTS

3.1 Cohort selection and patient characteristics

A total of 6344 patients were recorded in the CCC19 database between March 17, 2020 and November 30, 2020. After exclusion, 2804 patients with cancer and COVID-19 diagnosis who required hospitalization at diagnosis with valid thrombotic outcomes captured were included in the current study (Figure 1). Among this hospitalized cohort, 16% (n = 440) were admitted directly to the ICU and 81% (n = 2271) were initially admitted to non-ICU medical wards (3% had unknown status). The median follow-up was 42 days (interquartile range [IQR] 21–90). Unless death had occurred prior to follow-up time point assessment, approximately 83% patients had the 30-day follow-up form completed and 62% patients had the 90-day follow-up form completed.

The median age of patients was 70 (IQR 60–79) and 54% (n = 1504) were male (Table 1). Racial/ethnic breakdown revealed 48% (n = 1351) non-Hispanic White patients, 25% (n = 689) non-Hispanic Black patients, 13% (n = 368) Hispanic patients, and 12% (n = 345) other. Approximately 74% (n = 2079) had solid tumors, 48% (n = 1342) had disease in remission, and 36% (n = 1021) received systemic anti-cancer therapy within the 3 months prior to COVID-19 diagnosis. The distribution of cancer subtypes is shown in Table S2 in supporting information. Among them, 3% (n = 73) had very high-risk VTE malignancy (pancreatic, esophageal, stomach), 23% (n = 641) had high-risk VTE malignancy (lung, ovarian, kidney, bladder, testicular, lymphoma), and 75% (n = 2090) had low-risk VTE malignancy (all others). Approximately 15% (n = 429) of patients were reported to have morbid obesity. D-dimer was measured in 58% (n = 1623) of patients and a significant majority had abnormal value (n = 1376, 85%). Eleven percent of patients (n = 297) had prior history of VTE, 21% (n = 584) were taking anticoagulants, and 34% (n = 949) were taking antplatelets prior to COVID-19 diagnosis. During the COVID-19 admission, 53% (n = 1473) received anticoagulation for prophylaxis, 13% (n = 367) received anticoagulation for therapeutic reasons, 22% (n = 609) received no anticoagulation, and 13% (n = 355) had unknown status.
FIGURE 1 Patient selection for study inclusion and exclusion. This flow diagram indicates the inclusion and exclusion criteria for patient selection for the current study using the CCC19 consortium. * Some patients had unknown ICU admission status. CCC19, COVID-19 and Cancer Consortium registry; ICU, intensive care unit.

TABLE 1 Demographics and baseline characteristics for hospitalized patients with cancer and COVID-19

| Characteristics                                | Total number, N | Median (IQR) | Male sex, % (N) | Race/ethnicity, % (N) | Cancer subtype, % (N) | Cancer status, % (N) | Cancer staging, % (N) | Recent systemic therapy last 3 months, % (N) |
|------------------------------------------------|-----------------|--------------|-----------------|-----------------------|----------------------|----------------------|----------------------|---------------------------------------------|
| Total number, N                                | 2804            |              |                 |                       |                      |                      |                      |                                             |
| Age in years, median (IQR)                     | 70 (60–79)      |              |                 |                       |                      |                      |                      |                                             |
| Male sex, % (N)                                | 54% (1504)      |              |                 |                       |                      |                      |                      |                                             |
| Race/ethnicity, % (N)                          |                 |              |                 |                       |                      |                      |                      |                                             |
| White                                          | 48% (1351)      |              |                 |                       |                      |                      |                      |                                             |
| Black                                          | 25% (689)       |              |                 |                       |                      |                      |                      |                                             |
| Hispanic                                       | 13% (368)       |              |                 |                       |                      |                      |                      |                                             |
| Other                                          | 12% (345)       |              |                 |                       |                      |                      |                      |                                             |
| Unknown/missing                                | 2% (51)         |              |                 |                       |                      |                      |                      |                                             |
| Cancer subtype, % (N)                          |                 |              |                 |                       |                      |                      |                      |                                             |
| Solid                                          | 74% (2079)      |              |                 |                       |                      |                      |                      |                                             |
| Hematologic                                    | 24% (676)       |              |                 |                       |                      |                      |                      |                                             |
| Other                                          | 2% (49)         |              |                 |                       |                      |                      |                      |                                             |
| Cancer status, % (N)                           |                 |              |                 |                       |                      |                      |                      |                                             |
| Remission/no evidence of disease               | 48% (1342)      |              |                 |                       |                      |                      |                      |                                             |
| Active, stable or responding                   | 26% (742)       |              |                 |                       |                      |                      |                      |                                             |
| Active, progressing or unknown                 | 23% (651)       |              |                 |                       |                      |                      |                      |                                             |
| Unknown/missing                                | 2% (69)         |              |                 |                       |                      |                      |                      |                                             |
| Cancer staging, % (N)                          |                 |              |                 |                       |                      |                      |                      |                                             |
| Localized                                      | 50% (1405)      |              |                 |                       |                      |                      |                      |                                             |
| Disseminated                                   | 29% (812)       |              |                 |                       |                      |                      |                      |                                             |
| Unknown/missing                                | 21% (587)       |              |                 |                       |                      |                      |                      |                                             |
| Recent systemic therapy last 3 months, % (N)   |                 |              |                 |                       |                      |                      |                      |                                             |
| No                                             | 61% (1717)      |              |                 |                       |                      |                      |                      |                                             |
| Yes                                            | 36% (1021)      |              |                 |                       |                      |                      |                      |                                             |

TABLE 1 (Continued)

| Characteristics                                | Hospitalized patients |
|------------------------------------------------|-----------------------|
| Unknown/missing                                | 2% (66)               |
| VTE risk by cancer subtype, % (N)              | 100% (2804)           |
| Low-risk VTE malignancy                       | 75% (2090)            |
| High-risk VTE malignancy                      | 23% (641)             |
| Very high-risk VTE malignancy                 | 3% (73)               |
| History of VTE, % (N)                         | 100% (2804)           |
| No                                            | 89% (2488)            |
| Yes                                           | 11% (297)             |
| Unknown/missing                                | 1% (19)               |
| Morbid obesity (BMI>35), % (N)                 | 100% (2804)           |
| No                                            | 84% (2359)            |
| Yes                                           | 15% (429)             |
| Unknown/missing                                | 1% (16)               |
| Anticoagulant use prior to admission, % (N)    | 100% (2804)           |
| No                                            | 76% (2136)            |
| Yes                                           | 21% (584)             |
| Unknown/missing                                | 3% (84)               |
| Antiplatelet use prior to admission, % (N)     | 100% (2804)           |
| No                                            | 63% (1761)            |
| Yes                                           | 34% (949)             |
| Unknown/missing                                | 3% (84)               |
| Direct ICU admission, % (N)                    | 100% (2804)           |
| No                                            | 81% (2271)            |
| Yes                                           | 16% (440)             |
| Unknown/missing                                | 3% (93)               |
| White blood cell (WBC), % (N)                  | 100% (2804)           |

(Continues)
Table 1 (Continued)

| Hospitalized patients | VTE | PE/DVT | PE | ATE | CVA |
|------------------------|-----|--------|----|-----|-----|
| Within normal limit of normal | 58% (1614) | 6.6% (186) | 4.0% (113) | 3.9% (109) | 1.6% (45) |
| Below lower limit of normal | 20% (552) | 17% (468) |
| Above higher limit of normal | 10% (173) |

Hemoglobin (Hb), % (N)

| Within normal limit of normal | 37% (1034) | 2% (45) |
| Below lower limit of normal | 55% (1552) |
| Above higher limit of normal | 6% (173) |

Platelet (Plt), % (N)

| Within normal limit of normal | 61% (1709) |
| Below lower limit of normal | 27% (757) |
| Above higher limit of normal | 4% (125) |
| Unknown/missing | 8% (213) |

D-dimer (DD), % (N)

| Within normal limit of normal | 9% (247) |
| Above higher limit of normal | 49% (1376) |
| Not tested/not available | 37% (1034) |
| Unknown/missing | 5% (147) |

Note: VTE = venous thromboembolism defined as pulmonary embolism (PE), deep vein thrombosis (DVT), or thrombosis not otherwise specified (i.e., unusual splanchnic or cerebral sinus venous thrombosis), ATE = arterial thromboembolism defined as myocardial infarction or ischemic stroke (CVA). Abbreviation: ICU, intensive care unit; IQR, interquartile range.

3.2 Incidence of VTE and ATE by illness severity and systemic therapy subgroups

Among hospitalized patients, VTE occurred in 7.6% (n = 213) patients, of which 4.0% (n = 113) were PE; ATE occurred in 3.9% (n = 109) patients, of which 1.6% (n = 45) were CVA. Most VTE and ATE events occurred within 30 days of hospitalization. The incidence remained nearly constant from the second to the fourth quarter of 2020 (Figure S1 in supporting information).

In the prespecified subgroup analysis (Table 2), the incidence of all thrombotic complications was approximately 2-fold higher among severely ill patients requiring direct ICU admission (VTE 14.1%, ATE 7.3%) compared to moderately ill patients requiring wards admission (VTE 6.3%, ATE 3.2%). The incidence of VTE but not ATE was higher among patients receiving recent anti-cancer systemic therapy (VTE 10.0%, ATE 3.1%) compared to those not receiving recent therapy (VTE 5.8%, ATE 4.0%). There was no significant interaction between the two subgroups and the risk factors appeared to be multiplicative.

3.3 Multivariable modeling of VTE and PE risk among hospitalized patients with cancer and COVID-19

Variables significantly associated with VTE (primary outcome) included recent anti-cancer systemic therapy (OR 1.58, 95% CI 1.16–2.14), VTE history (OR 1.89, 95% CI 1.21–2.95), and direct ICU admission (OR 2.62, 95% CI 1.89–3.64; Figure 2). Other non-significant but appreciable variables with notable degrees of association based on model chi-square test (Figure 3) included cancer subtype VTE risk (OR 1.37, 95% CI 0.99–1.89 for high risk vs. low risk; OR 1.74, 95% CI 0.83–3.64 for very-high risk vs. low risk) and Hispanic race/ethnicity (OR 0.64, 95% CI 0.39–1.03 for Hispanic vs. White). In the current study, Black patients represented 25% of the population but did not have an appreciably increased VTE risk compared to White patients (OR 0.99, 95% CI 0.70–1.40). The c statistic was 0.67 (bootstrapped 95% CI 0.63–0.70). The model had adequate fit as demonstrated by an HL test P-value of .48 and the appearance of the calibration plot (Figure S2 in supporting information).

Table 2 Incidence of venous thrombosis (VTE, PE/DVT, PE) and arterial thrombosis (ATE, CVA) in cancer patients within 90 days post-SARS-CoV-2 diagnosis and hospitalization, stratified by ICU admission & anti-cancer treatment

| ICU admission status | VTE | PE/DVT | PE | ATE | CVA |
|----------------------|-----|--------|----|-----|-----|
| Direct ICU admission (n = 440) | 14.1% (62) | 12.3% (54) | 7.5% (33) | 7.3% (32) | 2.3% (10) |
| Wards admission (n = 2271) | 6.3% (143) | 5.5% (126) | 3.3% (75) | 3.2% (72) | 1.4% (31) |

| Recent anti-cancer therapy | VTE | PE/DVT | PE | ATE | CVA |
|----------------------------|-----|--------|----|-----|-----|
| Recent systemic therapy (n = 1021) | 10.0% (102) | 8.9% (91) | 5.7% (58) | 3.1% (32) | 1.4% (14) |
| No recent therapy (n = 1717) | 5.8% (99) | 4.8% (83) | 2.6% (45) | 4.0% (69) | 1.7% (29) |

Note: VTE = venous thromboembolism defined as pulmonary embolism (PE), deep vein thrombosis (DVT), or thrombosis not otherwise specified (i.e., unusual splanchnic or cerebral sinus venous thrombosis), ATE = arterial thromboembolism defined as myocardial infarction or ischemic stroke (CVA). At baseline, 58% (1614) of the patients had a hemoglobin level within the normal limit, 20% (552) had a value below the lower limit, and 17% (468) had a value above the upper limit. For platelet count, 61% (1709) had a value within the normal range, 27% (757) had a value below the lower limit, and 4% (125) had a value above the upper limit. For D-dimer, 9% (247) had a value within the normal range, 49% (1376) had a value above the upper limit, and 37% (1034) had a value not tested/not available. The abbreviations used are BMI, body mass index; ICU, intensive care unit; IQR, interquartile range.

There are 93 patients with unknown/missing ICU admission status.

There are 66 patients with unknown/missing recent anti-cancer status.
The additional variable that reached significant association was anticoagulant use prior to admission (OR 0.40, 95% CI 0.22–0.75). The PE-specific model had similar performance as the VTE model with a discrimination c statistic of 0.69 (bootstrapped 95% CI 0.64–0.74) and an HL P-value of .13. Dedicated association testing for ATE outcomes was not performed due to the low number of events.

3.4 | Scenario and sensitivity analyses for VTE predictors

We performed several additional scenario and sensitivity analyses. In the scenarios in which we retested the clinical model after excluding patients on anticoagulants prior to admission (Table S4 in supporting
TABLE 3 Simplified risk assessment model for VTE (CoVID-TE thromboembolism score) in hospitalized patients with complete data. (a) CoVID-TE score assignment, (b) CoVID-TE risk category stratification and performance

| Risk assessment model | (a) | All hospitalized patients (n = 2457) |
|-----------------------|-----|-----------------------------------|
| **Baseline variables**                                      |  | **Risk category (N)** | **VTE % (N)** | **PE % (N)** |
| **Cancer subtype by original Khorana score** | +1 | Low-risk (0–2) | 4.1% (59) | 2.3% (33) |
| VTE history (lifetime) | +2 | 0–1 (657) | 3.6% (24) | 2.0% (13) |
| 2 (766) | 4.6% (35) | 2.6% (20) |
| **High-risk (3+)** | | 3 (529) | 8.9% (47) | 3.6% (19) |
| 4 (317) | 11.7% (37) | 6.3% (20) |
| 5+ (188) | 17.6% (33) | 9.6% (18) |
| **C statistic (95% CI)** | 0.67 (0.63–0.71) | 0.67 (0.61–0.73) |
| HL test p-value | .90 | .77 |

Note: Integer points (1 or 2 points) were assigned to each of the baseline variables listed in the table above. A final composite score ranging from 0 to 8 is created. Based on outcome distribution shown above, 0–2 point is considered low-risk and 3 or more points is considered high-risk.

Abbreviations: HL, Hosmer-Lemeshow test; ICU, intensive care unit; PE, pulmonary embolism; VTE, venous thromboembolism.

aCombined high and very-high risk categories based on the original Khorana score: pancreas, stomach, esophageal, lung, ovarian, kidney, bladder, testicular, lymphoma.

bSpecific cut-off could not be determined using the current dataset.

1Asian race also associated with lower risk of VTE in other studies; however, this was not specifically assessed in the current study.

4 | DISCUSSION

In this retrospective cohort study of 2804 hospitalized patients with COVID-19 and cancer, we found the 90-day VTE and ATE incidences were elevated at 7.6% (n = 213) and 3.9% (n = 109), respectively. VTE risk was higher in patients admitted to ICU and those with active cancer having received recent systemic therapy. Our newly derived VTE risk assessment model, the CoVID-TE score, incorporated six clinicopathologic factors readily available at the time of hospital admission. With a modest discrimination, the CoVID-TE score stratified patients into two different risk categories: 58% in the low-risk group (score 0–2) had an observed incidence of 4.1% for VTE and 2.3% for PE; 42% in the high-risk group (score 3+) had an incidence of 11.3% for VTE and 5.5% for PE. Patients with these thrombotic risk factors might also be at higher risk for bleeding and mortality. We believe risk stratification from the current study can provide relevant context and help with the interpretation and implementation of anticoagulant prophylaxis based on the results of ongoing randomized controlled trials for this vulnerable patient population.

While COVID-19, prolonged hospitalization, and active cancer are all well-known pro-thrombotic risk factors, the exact incidence of thrombosis in a population with all three has not been previously reported. We examined the incidence over a 90-day follow-up to match with previous studies for medical inpatient-associated thrombosis. Among general patients hospitalized with COVID-19, the reported incidence based on retrospective cohort studies varies proportional to the beta coefficients. From the original cohort of 2804 patients, 2457 had complete data capture for all the chosen baseline variables (no imputation). Variables with their associated weights included: Cancer subtype high to very-high risk by original Khorana score (pancreas, stomach, esophageal, lung, ovarian, kidney, bladder, testicular, lymphoma; +1), VTE history (hypercoagulable, ICU admission (+2), D-dimer elevated on admission (+1), Therapy (recent systemic therapy last 3 months) (+1), and Ethnicity non-Hispanic (+1; Table 3). The initial letter of each variable formed the new risk assessment model "CoVID-TE" for COVID-19–associated thromboembolism. Patients with scores 0 to 2 (n = 1423) appeared to have lower risk of VTE (4.1%) and PE (2.3%). In contrast, patients with a score of 3 or higher (n = 1034) had appreciably increased risk of VTE (11.3%) and PE (5.5%). The simplified RAM had modest discrimination with a c statistic of 0.67 (0.63–0.71) for VTE prediction and an HL test P-value of .90. In a sensitivity analysis, after excluding patients with anticoagulant use prior to COVID-19 diagnosis, the CoVID-TE RAM demonstrated similar discrimination, with a c-statistic of 0.69 (0.64–0.74) for VTE prediction (Table S7 in supporting information). Finally, we assessed overall bleeding and 30-day mortality for patients stratified by the CoVID-TE RAM (Table S8 in supporting information). Compared to patients with low risk for VTE, those classified as high risk for VTE also had higher risk for overall bleeding (10.0% vs. 4.3%) and mortality (29.3% vs. 19.5%). As the bleeding endpoint was not predefined or adjudicated, this remained an exploratory analysis.
patients with COVID-19 on the need for organ support and secondarily assessed the role of therapeutic anticoagulation among hospitalized patients with cancer and COVID-19. Due to the sample size, we were able to apply stringent selection criteria to ensure adequate follow-up and exclude patients with incomplete data capture such that multiple imputation was only performed to address missing data in variables with <5% missingness (or <10% in exploratory analyses). Our multiple sensitivity analyses showed that the findings would be replicable under different meaningful clinical scenarios. Furthermore, the CoVid-TE RAM consists of variables that are simple and readily available to providers at the time of admission with the potential to impact the care of patients with cancer and COVID-19 in a meaningful way. Limitations inherent to our non-randomized retrospective study nature include the potential for unmeasured confounding, selection bias, and underreporting of outcomes. Given that each institution had its own protocol for the prevention and diagnosis of thrombosis, this heterogeneity could have impacted the actual rates from individual sites, although the stable aggregate rates of VTE over each quarter of 2020 verified overall consistency. Furthermore, the heterogeneous use of anticoagulation before admission (21%) and the low proportion of very high-risk cancer types (3%) may limit the generalizability of the RAM. Additionally, we did not perform time-to-event or competing risks analysis due to the lack of specific timing for VTE complications. Finally, for any novel model to be clinically applicable, it needs to be tested and validated in an external cohort.

In conclusion, we investigated the incidence of venous and arterial thromboses in hospitalized patients with cancer and COVID-19 and derived a new RAM that can be calculated at the time of admission to risk stratify patients into different VTE risk groups. We anticipate that the CoVid-TE RAM, upon external validation, can serve as a real-time clinical decision support tool to assist with personalized decisions on the initiation of thromboprophylaxis in hospitalized patients with cancer and COVID-19.

**CONFLICTS OF INTEREST**

ARK (or an immediate family member) have currently or during the past 2 years owned stock or held an ownership interest in Merck, Sanofi, and BMS. ALS reports travel support from Pfizer and Astellas, outside the scope of the submitted work. BIR reports grants, personal fees, and non-financial support from Merck; grants and personal fees from BMS; grants and personal fees from Pfizer, grants and personal fees from Aveo, grants from Astra Zeneca, grants and personal fees from Genentech; personal fees from Synthorx; personal fees from 3D Medicines; personal fees from Arravive; personal fees from Surface Oncology; other from PTC Therapeutics; personal fees from Arrowhead Therapeutics, outside the scope of the submitted work. BH reports research funding to the institution from Amgen, Abbvie, Bi, Mirati, Merck, Eli-Lilly, Astra-Zeneca, BMS, Novartis, GSK, Pfizer, Advaxis, and GuardantHealth; consulting/advisory role with
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SG reports research grant support from the National Cancer Institute in support of this work; the funder had no role in the design of conduct of the study, or the decision to publish. Equity in HemOnc.org LLC, Consultant: Westat, IBM Watson Health; outside the scope of the submitted work. VK reports honoraria from Diagnostica Stago, all outside the scope of the submitted work. SG reports research grant support to her institution from AstraZeneca and Isorary, all outside the scope of submitted work. RPR reports research grant support to his institution from BMS and Janssen; Consultant/Advisory Board: BMS, Janssen, and Dova, all outside scope of submitted work. JMP reports honoraria from Radius, outside the scope of the submitted work. 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**AUTHOR CONTRIBUTIONS**

AL, NMK, GHL conceived the study. AL, NMK, YS, GHL, RPR designed the methods. AL, CYH, JLW performed the statistical analysis. AL, RPR drafted the manuscript. AL, NMK, CYH, YS, JLM, DS, VK, SS, ARK, JF, SG, RZ, ML, AD, PE, ZB, DKC, CH, IA, RM, JG, AS, BH, MAT, JMP, NAP, DRR, SP, AE, GdLL, DS, PG, ARK, BR, CAP, SM, JMC, GHL, RPR critically reviewed and edited the manuscript. SG, RZ, PE, ZB, DKC, CH, IA, RM, JG, ARK, PG, GHL collected the data and contributed >10% of study outcomes.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.