Received: 12 June 2020 | Accepted: 13 July 2020

DOI: 10.1111/jth.15018

ORIGINAL ARTICLE

Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19

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Funding information
National Heart, Lung, and Blood Institute, Grant/Award Number: U01HL143365

Abstract

Background: Coronavirus disease-2019 (COVID-19) is a recognized prothrombotic state. Patients hospitalized with active cancer are predisposed to thrombosis but whether active cancer further amplifies thrombotic risk with COVID-19 is not known.

Objectives: To evaluate cumulative incidences of thrombotic and hemorrhagic events in hospitalized COVID-19 patients with and without active cancer at 28 days.

Methods: A retrospective cohort analysis of consecutive adults hospitalized with COVID-19 was performed. Active cancer required cancer-directed therapy within previous 6 months. The cumulative incidences of thrombosis or hemorrhage were estimated considering death as a competing risk.

Results: Patients without cancer (n = 353) and active cancer (n = 45) were comparable in terms of age, sex, antibiotics administered, length of hospitalization, and critical care. The most common malignancies were lymphoid (17.8%), gastrointestinal (15.6%), lung (13.3%), and genitourinary (13.3%). At day 28, the cumulative incidence of thrombotic events was 18.2% (95% confidence interval [CI], 10.2%-27.9%) in the non-cancer cohort and 14.2% (95% CI, 4.7%-28.7%) in the cancer cohort. The cumulative incidence of major and fatal bleeding at day 28 was 20.8% (95% CI, 12.1%-31.0%) in the non-cancer group and 19.5% (95% CI, 5.5%-39.8%) in the cancer cohort. Three patients experienced fatal bleeds, all of whom were in the non-cancer cohort. Survival was significantly shorter in the group with active cancer ($P = .038$).

Conclusions: We observed a similarly high incidence of thrombosis and bleeding among patients admitted with COVID-19 with or without active cancer.

KEYWORDS

anticoagulation, cancer, COVID-19, hemorrhage, venous thromboembolism

Manuscript handled by: Saskia Middeldorp

Final decision: Saskia Middeldorp, 13 July 2020

1 | BACKGROUND

An ongoing global pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 4.5 million people and resulted in excess of 300 000 deaths worldwide.[1] A pattern of altered coagulation parameters accompanied by a high incidence of thrombotic phenomena characterizes severe coronavirus disease 2019 (COVID-19).[2-6] Thrombosis in patients with COVID-19 is likely triggered by direct or indirect endothelial injury and subsequent generation of thrombin.[7,8] The reported rates of thrombosis in patients hospitalized with COVID-19 ranges between 5% to 45% and appears to be influenced by the performance of imaging surveillance, disease severity, and underlying co-morbidities.[2-6,9,10]

Cancer and cancer directed therapies are similarly associated with an increased risk of venous thromboembolism and arterial thrombosis.[11,12] These risks are exacerbated by acute medical illness and immobilization associated with hospitalization; the incidence of venous thromboembolism (VTE) in hospitalized patients with cancer is considerably higher than the incidence reported in acutely ill medical patients without cancer.[13,14] Studies have demonstrated poorer outcomes with higher fatality rates in patients with active cancer and COVID-19.[15,16] Cancer diagnoses are also an established risk factor for hemorrhage on anticoagulation.[17,18] The impact of COVID-19 on the incidence of thrombosis or hemorrhage in patients with active malignancy who require hospitalization has not been reported.

Essentials

- Impact of active cancer on thrombotic and bleeding risk in COVID-19 is not known.
- Thrombohemorrhagic events in 353 hospitalized non-cancer and 45 active cancer patients were analyzed.
- Cumulative incidence of thrombosis was 18.2% in the non-cancer and 14.2% in the cancer cohorts.
- Cumulative incidence of major hemorrhage was 20.8% in non-cancer and 19.5% in cancer cohort.

2 | METHODS

A retrospective analysis was performed of consecutive patients hospitalized with a diagnosis of COVID-19 at the Beth Israel Deaconess Medical Center, Boston, MA, from March to May 2020. Approval was obtained from local institutional review board and all procedures were performed in accordance with the Declaration of Helsinki. Inclusion required patients to be at least 18 years of age and to have a positive polymerase chain reaction test for SARS CoV-2 from nasopharyngeal swab (RealTime SARS-CoV-2 assay). Eligibility to the active cancer cohort required a diagnosis of cancer requiring any treatment within the previous 6 months or a recent diagnosis of cancer (within the previous 6 months). Patients were excluded from either the control or active cancer cohorts if they had a history of cancer that did not qualify as active cancer (exclusive of localized skin cancer).

The primary outcomes of interest were the cumulative incidences of thrombosis or hemorrhage at day 28. Thrombotic events assessed including thrombosis of upper and lower extremity deep veins, pulmonary embolism, arterial events including ischemic stroke or peripheral arterial embolism. These events required imaging confirmation and were included as key thrombotic events. Data regarding superficial thrombophlebitis, clotting of extracorporeal circuits such as dialysis lines and extracorporeal membrane oxygenation circuits, and presumed pulmonary embolism were also collected. Bleeding was assessed according to the International Society on Thrombosis and Haemostasis definitions of major bleeding and clinically relevant non-major bleeding.[19] Data were collected by manual chart review of consecutive patients hospitalized with COVID-19 infection. Baseline data included patient demographics, comorbidities including cancer type and status, baseline medications, use of anticoagulants, antiplatelet drugs during admission, laboratory values, and primary indication for admission. For patients that were still hospitalized, data were censored on May 18, 2020. Data were also collected on length of stay and transfer to the intensive care unit (ICU) during hospitalization. Details of thrombotic or hemorrhagic events including date and anatomic location were collected. Thrombotic and hemorrhagic events were evaluated independently by two data abstractors (RP and TB) in order to confirm all outcome events. In the case of disagreement, events were adjudicated by a third investigator (JZ).

Due to the anticipated high incidence of mortality among hospitalized patients with COVID-19, estimates of the cumulative incidence of venous and thrombotic arterial events as well as hemorrhage were calculated by using competing risk analyses along with 95% confidence intervals.[20] All significance testing was two-sided with a $P < .05$ being indicative of statistical significance. Median survival was assessed by the method of Kaplan-Meier with hypothesis testing by log-rank. Data were analyzed using STATA software (Stata Corp, TX).

3 | RESULTS

A total of 398 patients met eligibility criteria including 45 patients with active cancer. The cancer and non-cancer cohorts had a similar distribution for gender, race, and comorbidities (Table 1). The most common reason for hospital admissions was for COVID-19 pneumonia, 92% (n = 325) in the non-cancer cohort and 82.2% (n = 37) in the cancer cohort. Five patients in the non-cancer cohort were admitted for neuro-psychiatric evaluation (including seizures and suicidal ideation), 5 patients for urgent surgery/trauma, and 15 for other acute medical illness in the setting of COVID-19. Three patients in the cancer cohort were admitted for inpatient chemotherapy and one each for another infection, neuropsychiatric evaluation, and pulmonary embolism. Baseline platelet count and coagulation results

TABLE 1 Baseline characteristics of active cancer and non-cancer cohorts with COVID-19

	No cancer N = 353	Active cancer N = 45
Age, year (median, IQR)	61 (49-71)	69 (59-77)
Gender		
Female	166 (47%)	23 (51%)
Race		
White	121 (34.2%)	20 (44.4%)
African American	113 (32.0%)	18 (40.0%)
Asian	20 (5.7%)	1 (2.2%)
Unknown	98 (28.1%)	6 (13.3%)
Comorbidities		
Hypertension	194 (54.9%)	26 (57.8%)
Diabetes	125 (35.4%)	16 (35.6%)
Heart disease	93 (26.3%)	9 (18.1%)
Chronic respiratory disease	72 (20.4%)	11 (24.5%)
Chronic kidney disease	51 (14.4%)	0
Liver disease	19 (5.4%)	6 (13.3%)
Laboratory (median, IQR)		
Platelet count, K/μL	210 (166-264)	168 (108-243)
Prothrombin time, seconds	13.1 (12.2-14.8)	13.7 (12.6-15.5)
APTT, seconds	31.2 (28.7-35.0)	32.9 (31.0-40.7)
D-dimer, ng/mL FEU	1011 (528-1905)	1595 (1026-6064)
Fibrinogen, mg/dL	549 (449-751)	501 (409.5-661.0)
CRP, mg/L	118.45 (55.8-205.2)	105.4 (41.1-195.1)
Ferritin, ng/mL	715 (285-1654)	773 (324-1877)
Hospitalization details		
Required intensive care during index admission	182 (51.6%)	23 (51.1%)
Required invasive ventilation	140 (39.7%)	18 (40.0%)
Still hospitalized	36 (10.2%)	4 (8.8%)
Death during hospitalization	63 (17.8%)	19 (42.2%)
Length of stay, days (median, IQR)	8 (4-16)	9 (5-15)
Anticoagulant use during hospitalization		
No anticoagulant	26 (7.4%)	3 (7.0%)
Standard prophylaxis	245 (69.4%)	24 (53.3%)
Higher dose prophylaxis	81 (22.9%)	6 (13.3%)
Therapeutic anticoagulant	129 (36.5%)	22 (48.9%)

Abbreviations: COVID-19, coronavirus disease 19; CRP, c-reactive protein; IQR, interquartile range.

were also similar in the two cohorts. A similar percentage of patients with or without cancer received antivirals (73.3% and 73.4%, respectively), steroids (11.1% and 8.2%), or convalescent plasma (13.0% and 13.3%). The median length of hospitalization was 8 days for the non-cancer cohort and 9 days with active cancer (Wilcoxon rank sum $P = .48$). At time of data extraction, 9.6% patients were still hospitalized. Among 129 patients that received therapeutic anticoagulation during hospitalization in the non-cancer cohort COVID coagulopathy was the most common indication (n = 99, 76.7%), followed by atrial fibrillation (n = 24, 18.6%) and prior VTE (n = 10, 7.8%). Twenty-two patients in the cancer cohort received therapeutic anticoagulation during hospitalization; indications were COVID coagulopathy (n = 14, 63.6), prior VTE (n = 6, 27.3%), and atrial fibrillation (n = 2, 9.1%).

There were 45 patients in the cohort with active cancer. There was not a predominant malignancy diagnoses in the cohort (Table 2). The highest percentages were lymphoid (17.8%), gastrointestinal (15.6%), lung (13.3%), and genitourinary (13.3%) cancers. Among the non-hematologic malignancies, two thirds (18 of 30) received therapy for locally advanced or metastatic disease.

TABLE 2 Distribution of cancer types among hospitalized patients with COVID-19

Site of cancer	
Primary brain	2 (4.4%)
Head and neck	1 (2.2%)
Breast	2 (4.4%)
Lung	6 (13.3%)
Gastrointestinal	7 (15.6%)
Gynecologic malignancy	4 (8.8%)
Genitourinary	6 (13.3%)
Thyroid	2 (4.4%)
Sarcoma	1 (2.2%)
Myeloid malignancy	4 (8.9%)
Lymphoid malignancy	8 (17.8%)
Myeloproliferative neoplasm	4 (6.7%)
Plasma cell dyscrasia	3 (6.7%)
Metastatic or advanced (non-hematologic malignancy)	18/30 (64.3%)

Abbreviations: COVID-19, coronavirus disease 19.

3.1 | Cumulative incidence of thrombotic events

There were 28 thrombotic events in the non-cancer cohort including 3 arterial events, and 5 (including one ischemic stroke) in the cancer cohort. In the non-cancer cohort, the cumulative incidence of all thrombotic events at day 28 was 18.2% (95% confidence interval [CI], 10.2%-27.9%), as shown in Figure 1A. By comparison, the cumulative incidence of thrombosis at day 28 among the cancer group was 14.2% (95% CI, 4.7%-28.7%). A majority of thrombotic events recorded were proximal lower extremity deep vein thrombosis (DVT, n = 10), pulmonary embolism (n = 8), and ischemic strokes (n = 10; Table 3). When analyzing key thrombotic events (lower extremity or upper extremity DVT, pulmonary embolism, or arterial events), the cumulative incidence of thrombosis at day 28 in the non-cancer cohort was 10.2% (95% CI, 5.7%-16.2%) and in the cancer cohort was 14.2% (95% CI, 4.7%-28.7%, Figure 1B).

Of the six upper extremity thrombotic events in the study population (all in the non-cancer cohort) five were line related. Three events were categorized as presumed pulmonary embolism; this was based on clear documentation by the treating physicians based on unexplained tachycardia and an acute change in mechanical ventilatory parameters. Two of these patients received systemic thrombolysis with subsequent change in ventilation to perfusion ratio. In the cancer cohort, 2 of the 5 recorded thrombotic events occurred on full dose anticoagulation compared with 8 of 29 in the non-cancer cohort (Fisher's exact $P = .62$). In the cancer cohort the median baseline D-dimer was higher among the patients who developed thrombosis compared to those who did not (11 085 versus 1466 ng/mL, $P = .01$). In the non-cancer cohort, the baseline D-dimer values did not distinguish thrombotic risk (1015 versus 1004 ng/mL, respectively, $P = .70$).

3.2 | Cumulative incidence of hemorrhagic events

Of 73 total hemorrhagic events in the non-cancer cohort there were 32 major (including 2 fatal) hemorrhages; in the cancer cohort there were 7 major hemorrhages of 13 total bleeding events. Accordingly, the cumulative incidence of major hemorrhage at day 28 in the non-cancer group was 20.8% (95% CI, 12.1%-31.0%) and 19.5% (95% CI, 5.5%-39.8%) in patients with active cancer (Figure 2B). The cumulative incidence of both clinically relevant non-major hemorrhage combined with major hemorrhage was 35.1% (95% CI, 24.3%-46.0%) in the non-cancer cohort and 43.5% (95% CI, 9.4%-44.7%) in the active cancer cohort (Figure 2A). Approximately one quarter (26.5%) of all bleeds were related to procedures. Of 45 major bleeding events recorded in the total cohort, the most common site was upper gastrointestinal (n = 14, 31.1%), followed by intracranial (n = 9, 20%), muco-cutaneous (n = 8, 17.8%), intramuscular (n = 6, 13.3%), and lower gastrointestinal (n = 5, 11.1%). Among the 7 major hemorrhages in the cancer cohort, 3 occurred on full-dose anticoagulation compared with 22 of the 42 major hemorrhages in the non-cancer cohort (Fisher's exact $P = .68$).

Three patients experienced fatal bleeds, all of whom were in the non-cancer cohort. Two patients had cirrhosis and were not on anticoagulants at the time of the bleed; one was intracranial with parenchymal and subarachnoid involvement. The other patient developed an abdominal wall hematoma following a paracentesis. The third patient with a fatal bleed was on therapeutic unfractionated heparin complicated by intracranial hemorrhage with cerebellar tonsillar herniation.

3.3 | Overall survival

One fifth (20.6%) of the study population died during the hospitalization. Overall survival for patients with cancer was significantly shorter for patients with active cancer compared with the non-cancer cohort (Log-rank $P = .038$, Figure 3). Accordingly, the median survival for those with active cancer was 30 days (95% CI, 8.3-51.7 days) whereas the median survival for the non-cancer group was not reached.

4 | DISCUSSION

Cancer is an established risk factor for thrombosis and hemorrhage during hospitalization but whether COVID-19 further amplifies these risks is not known. We confirmed a high rate of thrombosis among hospitalized patients with COVID-19 with a cumulative incidence of 18% at 28 days among those without cancer and 14% among those with cancer. Major hemorrhage was also frequent (occurring in one in five hospitalized patients with COVID-19) but the cumulative incidences at day 28 were comparable for patients with or without active cancer.

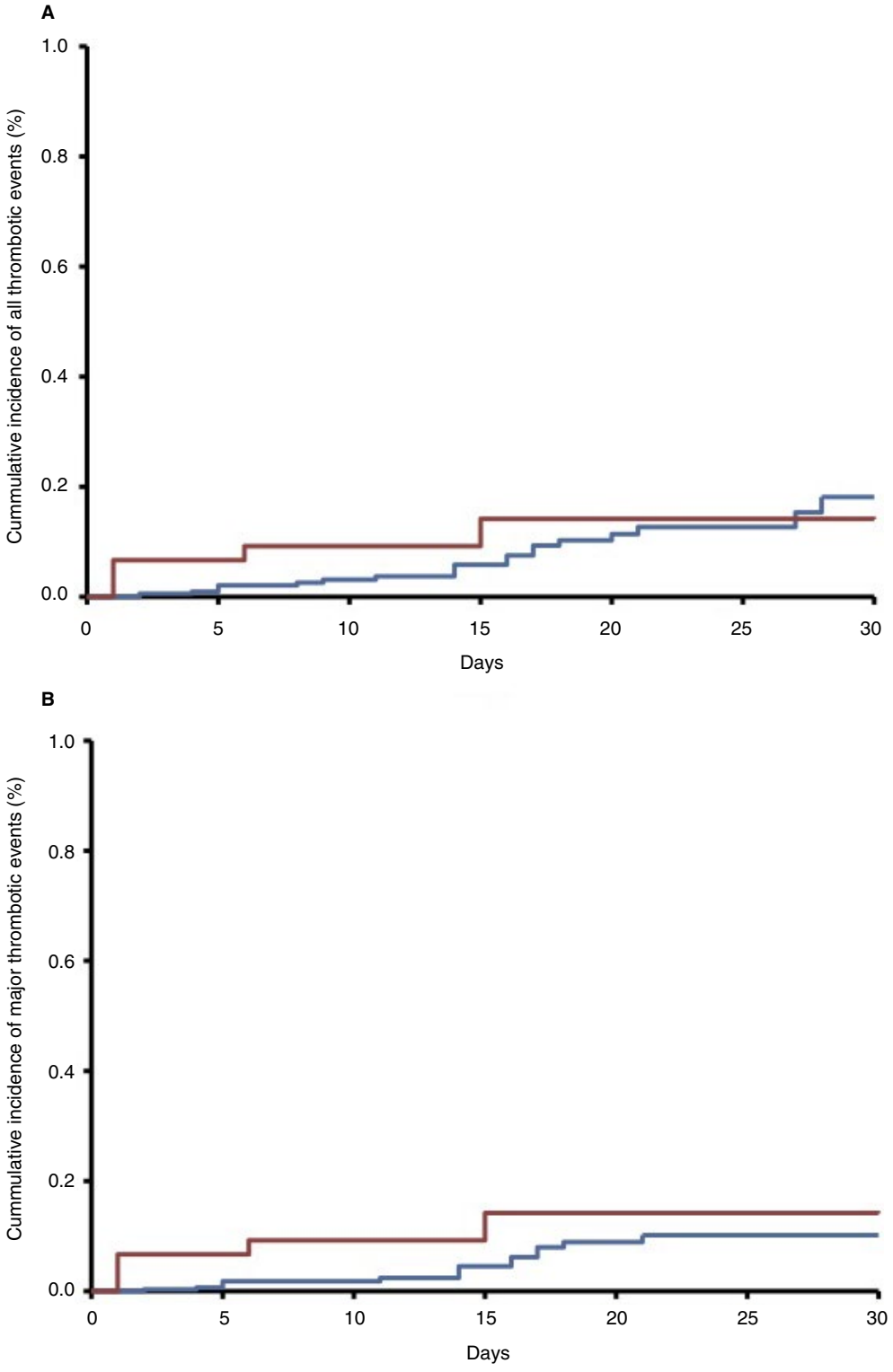

FIGURE 1 Cumulative incidence of thrombosis. A, Cumulative incidence of all thrombotic events with death as a competing risk. B, Cumulative incidence of major thrombosis, including pulmonary embolism, proximal deep vein thrombosis, upper extremity thrombosis, and arterial events. Red depicts events in active cancer cohort and blue the cohort without cancer

The incidence of hospital-related thrombosis for patients with cancer ranges from 2% to 22%, with higher rates reported in prospective trials utilizing routine screening for VTE.[21-24] Somewhat unexpectedly, we did not observe an increased incidence of thrombosis among COVID-19 patients with cancer relative to those without cancer. This could reflect the overwhelming thrombo-inflammatory state of active COVID-19 overshadowing a more modest hypercoagulable state of active cancer. The underlying pathophysiology of

TABLE 3 Location and details of thrombotic and hemorrhagic events

	No cancer N = 353	Active cancer N = 45
Thrombosis (N, %)		
Venous events		
Distal lower extremity DVT	1 (3.2%)	
Proximal lower extremity DVT	7 (22.6%)	1 (20%)
Upper extremity DVT	6 (19.4%)	
Pulmonary embolism	4 (12.9%)	3 (60%)
Presumed PE	3 (9.7%)	
Thrombosis of extracorporeal circuit	2 (6.5%)	
Superficial thrombophlebitis	2 (6.5%)	
Arterial events		
Ischemic stroke	2 (6.5%)	1 (20%)
Other arterial	1 (3.2%)	
Hemorrhage: (N, %)		
Minor hemorrhage	10 (13.1%)	3 (23.1%)
Clinically relevant non-major hemorrhage	25 (32.9%)	3 (23.1%)
Upper gastrointestinal	6 (24.0%)	2 (66.7%)
Lower gastrointestinal	6 (24.0%)	
Muco-cutaneous	12 (48.0%)	1 (33.3%)
Other	3 (12.0%)	
Major hemorrhage	38 (50.0%)	7 (53.8%)
Intracranial	7 (18.4%)	2 (28.6%)
Upper gastrointestinal	12 (31.6%)	2 (28.6%)[a]
Lower gastrointestinal	5 (13.2%)	
Retroperitoneal	2 (5.3%)	
Muco-cutaneous	6 (15.8%)	2 (28.6%)[a]
Intramuscular	5 (13.2%)	1 (14.3%)
Other	5 (13.2%)	1 (14.3%)
Fatal hemorrhage	3 (3.9%)	

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.

[a]One patient with simultaneous bleed at two sites

thrombosis in COVID-19 is attributed to direct endothelial toxicity leading to in situ generation of thrombi within the pulmonary vasculature.[25] However, even if we exclude all pulmonary emboli in the cohort, the incidence of proximal upper or lower extremity deep vein thrombosis or arterial events was not appreciably higher in the cancer cohort. Given that thrombo-inflammation is the emerging basis of COVID-19 coagulopathy, it is possible that the immunosuppressive effects of active cancer and cancer directed therapies modulated the thrombo-inflammatory response. Prior reports of thrombotic events in hospitalized patients included a limited number of cancer patients with severe COVID-19, which limits extrapolation.[26,27] In a retrospective series from Italy, there were only two patients with active cancer requiring ICU-level care.[28] A study that included screening for asymptomatic DVT in hospitalized COVID patients identified two occurrences of DVT among 16 cancer patients, which was similar to the incidence observed in the non-cancer cohort.[6] Considering the shortened survival of active cancer, interpretation of these studies is potentially limited by failure to account for death as a competing risk for thrombosis.[6,28]

The recognition of increased thrombotic risk in COVID-19, despite standard thromboprophylaxis,[4,7] led to implementation of empiric intermediate and therapeutic anticoagulation regimens.[29,30] A recent report suggests that the hemorrhage is fairly common among hospitalized patients with COVID-19. Among 400 patients hospitalized with COVID-19, the overall rate of hemorrhagic events was 4.8% with 2.3% rate of major hemorrhage.[31] The rates of hemorrhage in our cohort were substantively higher but approximately 60% received anticoagulants above the standard prophylactic dosing as compared to 11% in the prior report.[31]

Patients with cancer appear predisposed to severe COVID-19, likely due to a constellation of factors including advanced age and an immunocompromised state due to underlying disease or its therapy.[32,33] A nationwide analysis of data from 2007 cases of COVID-19 from 575 hospitals across China showed that patients with cancer had a significantly higher likelihood of requiring mechanical ventilation and shortened survival (hazard ratio 3.56, 95% CI 1.65-7.69).[34] In 218 patients from a single health system in New York City, the case fatality rate was found to be 28% in cancer, which was double the rate of a matched cohort from the same system without cancer.[15] We similarly observed that the survival of hospitalized patients with COVID-19 was significantly worse for patients with active cancer compared to patients without cancer.

Given the burgeoning pandemic and its implications on health care, including cancer care, observational data can provide rapid and vital evidence but there are inherent limitations. Due to the retrospective nature of the study, underestimation of thrombotic event rates is likely, in part due to the complexities of obtaining cross-sectional imaging in patients with tenuous respiratory status or receiving mechanical ventilation. However, a similar percentage of patients in the two cohorts were treated in the intensive care unit or required mechanical ventilation, thereby suggesting that this bias was unlikely to be imbalanced. We also recognize that there is limited power in the current study to definitively conclude that there is not a modest increase in rates of thrombosis or hemorrhage in the cancer group. And finally, we acknowledge that thrombotic and bleeding risks are not uniform across cancer sites, stage, or treatment. The cohort of cancer patients in the study were varied including 40% with hematologic malignancies, which may not be representative of other studies focused on cancer thrombosis; this cautions for care in interpretation and generalization of results although all but four of these patients carried

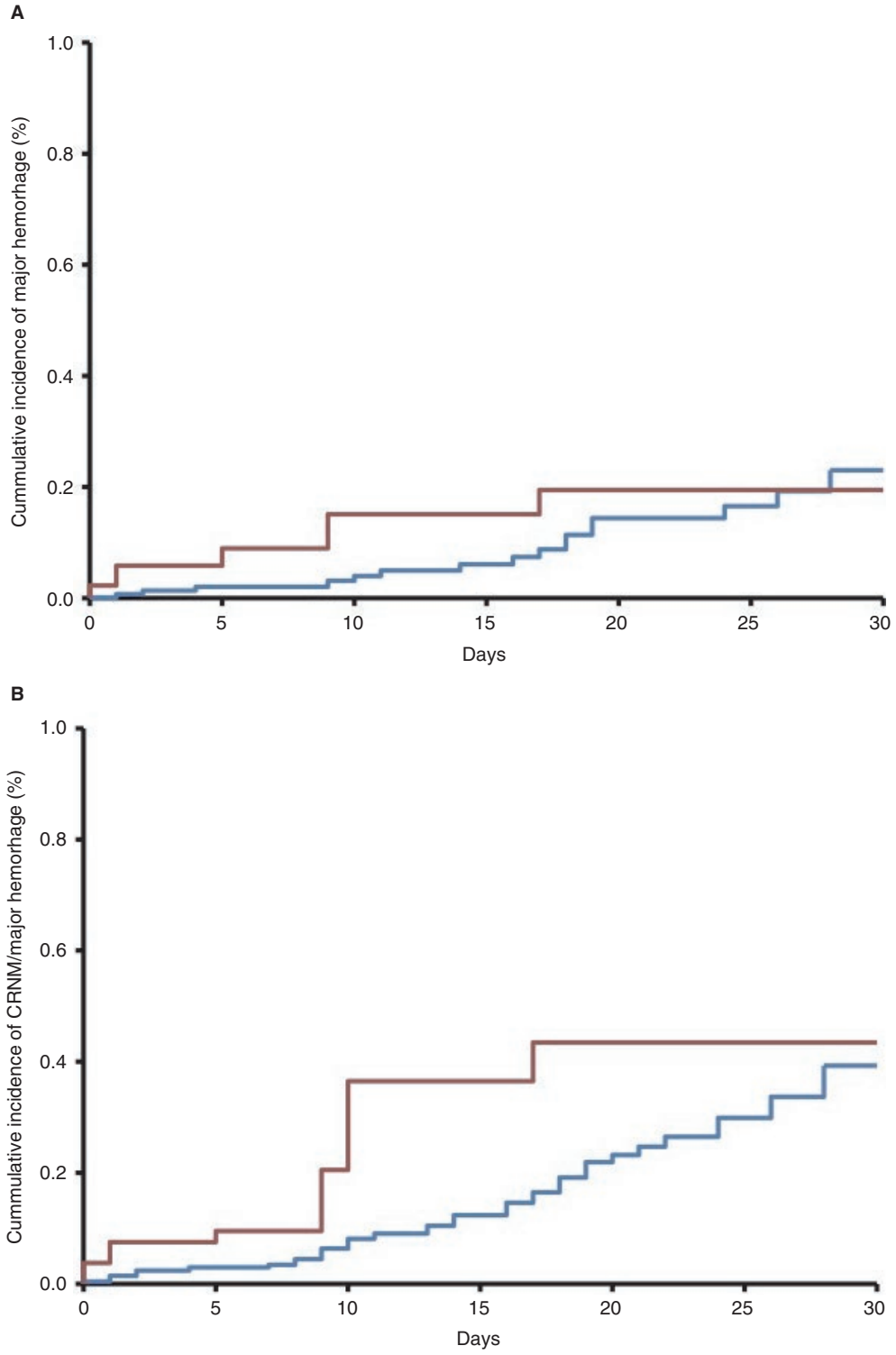

FIGURE 2 Cumulative incidence of hemorrhage. A, Cumulative incidence of major and fatal hemorrhagic events with death as a competing risk. B, Cumulative incidence of the composite of hemorrhage including major or fatal as well as clinically relevant non-major bleeding. Red depicts events in active cancer and blue patients without cancer

hematologic diagnoses associated with a high incidence of thrombosis (lymphoma, myeloma, or myeloproliferative neoplasm).[35-37] The limited size of our cohort precluded assessment of the impact of cancer-specific factors on the risks in hospitalized COVID-19 patients. However, at least among the subgroup of cancer patients with locally advanced or metastatic disease, there was no evidence of an increased incidence of thrombosis.

In a retrospective cohort study of hospitalized patients with COVID-19 we observed high rates of thrombosis and bleeding among patients with or without active cancer. Patients with active

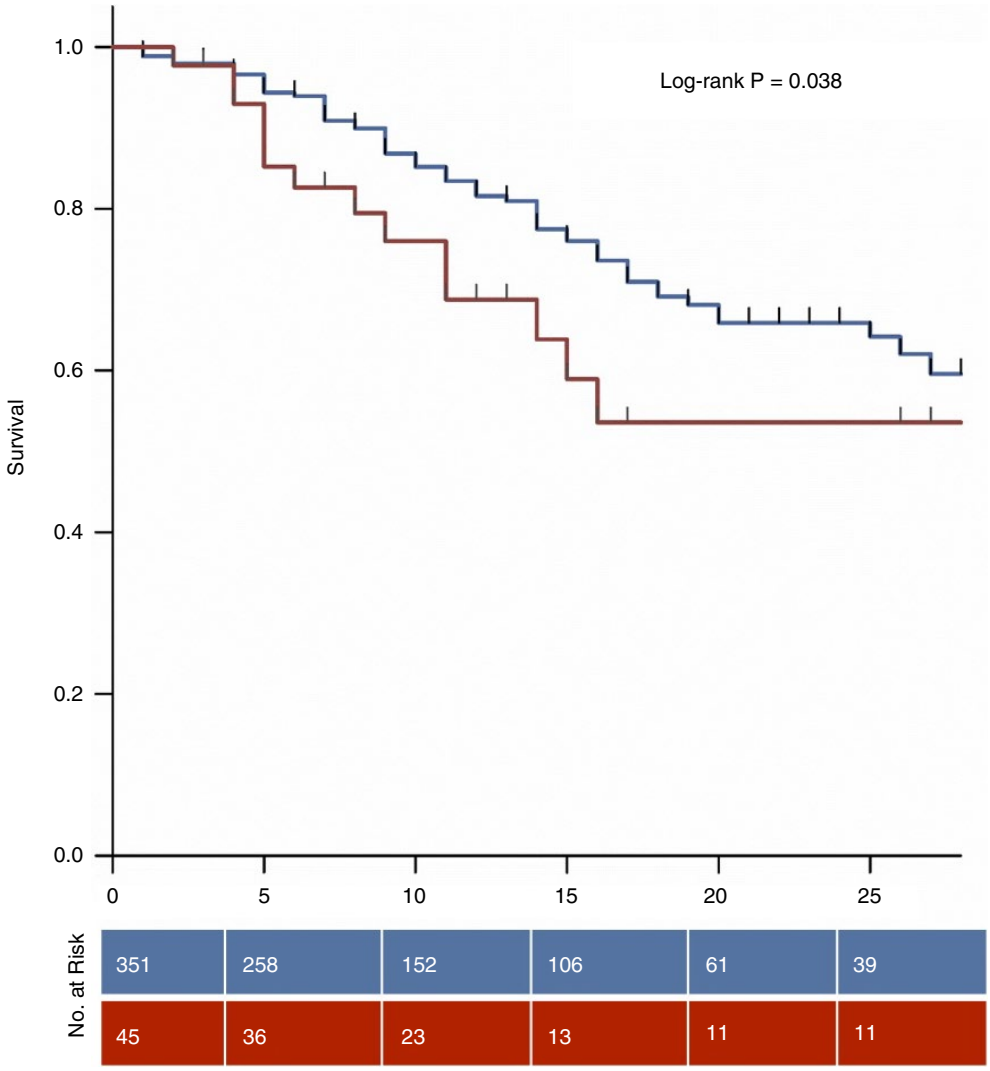

FIGURE 3 Survival comparison for patients with COVID-19 with and without active cancer. Figure shows the Kaplan-Meier survival estimates for hospitalized patients with COVID-19, with active cancer (red) and without cancer (blue)

cancer and COVID-19 had significantly worse mortality compared to those with no history of cancer. Given the precarious balance of thrombotic and bleeding risks in cancer patients, anticoagulation prophylaxis can be clinically challenging. Randomized studies are needed in order to appropriately assess the benefit and safety of thromprophylaxis regimens among hospitalized patients with COVID-19.

CONFLICTS OF INTEREST

JIZ reports research funding from Incyte and Quercegen; consultancy: Sanofi, CSL, Parexel; honoraria/advisory boards: Pfizer/BMS, Portola, Daiichi. KAB reports consultancy with Janssen. WCA is employed by DynaMed.

AUTHOR CONTRIBUTIONS

Study was designed by RP, WCA, KB, and JIZ. Data collection and analyses performed by RP, TB, MM, AK, and PB. Manuscript authored by JIZ and RP. All authors reviewed and contributed to final manuscript preparation.

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How to cite this article: Patell R, Bogue T, Bindal P, et al. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. *J Thromb Haemost*. 2020;18:2349–2357. https://doi.org/10.1111/jth.15018