Increased Incidence of Thrombosis in a Cohort of Cancer Patients with COVID-19

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\textbf{Keywords}  
Thrombosis · Thromboembolism · Arterial thrombosis · Coronavirus disease · Cancer

\textbf{Abstract}  
\textbf{Background:} Increased rates of thromboembolism (TE) have been reported in patients with COVID-19, even without prior predisposition to thrombosis. Cancer patients are already predisposed to a hypercoagulable state. This study was designed to assess the TE incidence in COVID-19+ patients with active cancer and its impact on survival.  
\textbf{Methods:} Data from cancer patients with documented COVID-19 during the dates March 15th–April 10th, 2020, were retrospectively reviewed. Active cancer was defined as disease treated within the past year. Diagnosis and evaluation of thrombosis were done at the clinicians’ discretion. All imaging studies’ reports within 30 days of the COVID-19 positive test were reviewed for identification of new arterial and/or venous TE. Patients were followed for 30 days from the date of COVID-19+ test for development of TE, hospital length of stay (LOS), and mortality.  
\textbf{Results:} Of 90 patients, 11 (12.2\%) were found to have 13 new TE within 30 days of COVID-19+ test: 8 (8.9\%) arterial and 5 (5.6\%) venous. Arterial TE was primarily new strokes and/or microvascular cerebral disease (7) with 1 splenic infarct. Venous TE was superficial (1) and deep (3) venous thromboses with 1 pulmonary embolism. Peak d-dimer (DD) values were numerically higher in the TE group versus those with no TE, median peak DD, 7.7 versus 3.2 μg/mL, \( p = 0.25 \). Kidney disease was more frequent among patients with TE (72.7\%) versus those without TE (31.6\%), \( p = 0.02 \). Prophylactic or therapeutic anticoagulation (AC) in the inpatient setting was more common among those without TE, any AC, TE versus no TE, 9.1\% versus 79.0\%, \( p < 0.0001 \). Only 1 patient on enoxaparin prophylaxis developed TE. Mortality was higher in the TE group than in those without TE (hazard ratio: 2.6; 95\% CI [1.2–5.6], \( p = 0.009 \)). Cancer type, presence of metastases, administration of prior chemotherapy, patient setting (inpatient, intensive care unit, outpatient, emergency department visit), LOS, and ventilation did not correlate with increased incidence of TE.  
\textbf{Conclusion:} Cancer patients with COVID-19 have high overall TE rates with a significant incidence of arterial events. TE was associated with worse survival outcomes.
Introduction

Cancer and the accompanying treatments are well-established risk factors for development of arterial (ATE) and, more frequently, venous thromboembolism (VTE) [1]. Cancer increases the risk of thromboembolism (TE) over 4-fold that of the general population and, for patients receiving active chemotherapy, the risk is up to 6.5 times greater [2, 3]. For patients actively receiving outpatient chemotherapy, the monthly incidence of VTE has been reported to be 0.8%, which is further increased in those requiring hospitalization [4]. Advanced stages of cancer and the initial period following diagnosis have also been associated with increased TE rates. In addition to the increased morbidity, thromboembolic events are also a leading cause of mortality in this population [5].

Severe acute respiratory syndrome coronavirus-2 induced disease (COVID-19) first emerged in December 2020 and was soon declared a pandemic by the World Health Organization (WHO) [6]. As of January 2021, >160 million people have been infected worldwide with COVID-19-related mortality reported globally as 2.07% [6]. Although the disease primarily presents with respiratory symptoms, increased thrombosis rates have been observed. A recent meta-analysis reported a 21% VTE rate and a 2% ATE rate in the overall COVID-19 infected population [7]. Patients with COVID-19 and thrombosis have increased mortality over COVID+ patients without thrombosis [7].

The impact of thrombosis on survival has not, to date, been thoroughly investigated in COVID-19+ cancer patients. A recent retrospective study noted a higher mortality in COVID-19+ patients with active cancer versus a COVID-19+ noncancer group [8]. Thrombosis rates were increased in both groups relatively to general population, but TE rates were actually lower in the cancer group than in those without cancer: 14.2% (95% CI: 4.7%, 28.7%) versus 18.2% (95% CI: 10.2%, 27.9%) [8]. However, survival was significantly decreased in the cancer group and may have been an interfering risk in this study. There were no data on whether patients with COVID-19 and cancer who developed TE had a worse survival than those who did not develop TE.

Therefore, we sought to quantify the thrombosis events in a real-world study of COVID-19 patients with active cancer during the beginning of the COVID-19 surge at a major tertiary hospital center in New York. Our objectives were to (1) report the incidence of thrombosis in patients with active cancer and COVID-19; (2) compare the impact of thrombosis on mortality; (3) identify potential risk factors that led to increased thrombosis in this already predisposed population; and (4) investigate any potential benefit of pre-emptive anticoagulation (AC).

Methods

Study Population

A cohort study was conducted in adult patients with active cancer and established COVID-19 infection at Montefiore Healthcare System hospitals who were admitted from March 15, 2020, through April 10, 2020. Active cancer was defined as disease that had been treated within the past year; patients with cancer off treatment for >1 year were excluded from the analyses. Demographic, laboratory, radiographic, and clinical data were extracted from the electronic medical record and hospital databases. The study was reviewed and approved by the Montefiore-Einstein Institutional Review Board.

Identification of COVID-19 Infection

COVID-19 infection was established with in-house laboratory testing using the polymerase chain reaction test for severe acute respiratory syndrome coronavirus-2 from nasopharyngeal swab (RealTime SARS-CoV-2 assay).

Identification of Thrombosis

All imaging studies in the cohort were reviewed for identification of new ATE or VTE. The population of the study was not subject to any routine imaging hospital protocols. Imaging studies were ordered at the clinicians’ discretion and were solely based on clinical suspicion. Imaging studies were evaluated even if initially ordered for other purposes. Patients with identified atherosclerosis and no TE were classified into the “no thrombosis” group. Prior TE re-identified in imaging was disregarded. Microvascular thrombosis was defined as radiologic report of evidence of white matter ischemic disease in the computed tomography (CT) of the head or magnetic resonance imaging of the brain. Because shedding of viral particles may have occurred before positive testing and has been reported to still occur as long as 2 months in immunocompromised and cancer patients, we extended the timeframe of our TE identification to 30 days before and 30 days after the initial COVID-19+ test [9–12]. The reported (if any) D-dimer (DD) values were checked throughout the study period, and the peak values were noted.

Anticoagulation

Propylactic and therapeutic AC data were collected. Institution guidelines recommended that patients admitted with COVID-19 infection and DD level >3 μg/mL or rapid increase of DD be started on therapeutic AC, but the initiation and dosing of AC in the inpatient setting was ultimately at the clinicians’ discretion. Propylactic AC was either enoxaparin subcutaneously (SQ) 30 mg or 40 mg once daily, unfractionated heparin SQ 5,000 units 2 or 3 times per day, or apixaban 2.5 mg twice daily in patients not meeting >1 of the following criteria: age >80 years, serum creatinine ≥1.5 mg/dL, and weight <60 kilograms (kg). Therapeutic AC was either enoxaparin SQ 1 mg/kg twice daily or 1.5 mg/kg once daily, continuous heparin infusion (IV), apixaban 5 mg (with or without 10 mg loading) or 2.5 mg twice daily for patients meeting
≥2 out of the 3 above criteria, rivaroxaban, or dabigatran. Patients were classified under the respective groups, that is, therapeutic AC versus prophylactic AC versus no AC, based on the AC dose administration before the development of any new TE.

Statistical Methods

Patients were categorized into 2 mutually exclusive groups, thrombosis and no thrombosis, based on the identification of new TE within 30 days of COVID+ test. Descriptive statistics were used to summarize demographic and clinical characteristics. Categorical variables were compared using the χ² tests and continuous variables were compared using Mann-Whitney rank-sum tests between relevant groups. Competing risk analysis was done in R using package “cmprsk.” The Kaplan-Meier function was used to assess survival between the 2 groups. Logistic regression was used to define the risk of death. All significance testing was 2-sided with a \( p < 0.05 \) being indicative of statistical significance. Statistical analyses were performed with IBM SPSS Statistics for Macintosh, Version 27.0 (Armonk, NY, USA).

Results

During the study period, 218 patients with cancer and COVID-19 infection were identified. One hundred and twenty-eight of these patients were excluded because they did not satisfy the active cancer diagnosis. The study cohort consisted of 90 active cancer patients.

Of the 90 patients, 11 (12.2% of the cohort) were found with a new TE during the study period, with 2 patients having 2 TEs. Figure 1 shows the cumulative incidence of thrombosis, considering death as a competing risk, during the surveillance period. Eight events (61.5%) were arterial; 7 involved the central nervous system with 1 new cerebral vascular accident and 6 newly identified microvascular disease, and 1 patient developed new acute splenic infarcts. Five events (38.5%) were venous, including 3 deep venous thrombosis events, 1 pulmonary embolism (PE), and 1 superficial venous thrombosis, which was provoked by a peripheral venous line placement. Out of the 11 patients with new TE, 7 were identified before and 4 after the date of the COVID+ test. All of the new TEs were identified in hospitalized patients; no TEs were identified in the outpatient setting or simple emergency department (ED) visits.

Table 1 shows the baseline characteristics of the cohort. The median age was 69 years, 62.2% of the population were men, and 45.6% were African Americans. Of those with thrombosis, 6 out of 11 patients with thrombosis (54.5%) were men, 54.5% were African American, and 18.2% Hispanic. Sex, race, and ethnicity were not different between the groups. Hispanics constituted 31.1% by ethnicity. Common comorbidities were identified be-

| Table 1. Baseline characteristics of the study population |
|----------------------------------|------------------|------------------|------------------|----------|
| All patients, 90 (100.0%)       | Thrombosis, 11 (12.2%) | No thrombosis, 79 (87.8%) | \( p \) value |
| Age, median (IQR)               | 69 (60–78)       | 60 (54–76)       | 71 (61–79)       | 0.76     |
| Female, N (%)                   | 34 (37.8)        | 5 (45.5)         | 29 (36.7)        | 0.74     |
| Race                            |                  |                  |                  |          |
| White, N (%)                    | 10 (11.1)        | 0 (0.0)          | 10 (12.7)        |          |
| African American, N (%)         | 41 (45.6)        | 6 (54.5)         | 35 (44.3)        | 0.23     |
| Asian, N (%)                    | 5 (5.6)          | 2 (18.2)         | 3 (3.8)          |          |
| Other/NA, N (%)                 | 34 (37.8)        | 3 (27.3)         | 31 (39.2)        |          |
| Ethnicity                       |                  |                  |                  |          |
| Hispanic, N (%)                 | 28 (31.1)        | 2 (18.2)         | 26 (32.9)        |          |
| Non-Hispanic, N (%)             | 58 (64.4)        | 8 (72.7)         | 50 (63.3)        | 0.49     |
| N/A, N (%)                      | 4 (4.4)          | 1 (9.1)          | 3 (3.8)          |          |
| Comorbidities                   |                  |                  |                  |          |
| DM, N (%)                       | 36 (40.0)        | 5 (45.5)         | 31 (39.2)        | 0.75     |
| Hypertension, N (%)             | 64 (71.1)        | 9 (81.8)         | 55 (69.6)        | 0.50     |
| Chronic lung disease, N (%)     | 23 (25.6)        | 3 (27.3)         | 20 (25.3)        | 0.99     |
| Kidney disease, N (%)           | 33 (36.7)        | 8 (72.7)         | 25 (31.6)        | 0.02     |
| Coronary artery disease, N (%)  | 13 (14.4)        | 0 (0.0)          | 13 (16.5)        | 0.35     |
| Congestive heart failure, N (%) | 14 (15.6)        | 2 (18.2)         | 12 (15.2)        | 0.68     |
| Obesity, N (%)                  | 32 (35.6)        | 3 (27.3)         | 29 (36.7)        | 0.74     |

IQR, interquartile range; DM, diabetes mellitus.
Increased Thrombosis Rates in COVID-19+ Cancer Patients

The incidence of thrombosis in patients with kidney disease was 8/33 (24.3%) while the incidence of TE in patients without kidney disease was significantly lower, at 3/57 (5.3%), \( p = 0.008 \). Conversely, patients with thrombosis were more likely to have kidney disease (72.7%) versus those without thrombosis (31.6%), \( p = 0.02 \). This was not true for other comorbidities, such as diabetes mellitus or obesity. BMI was actually decreased in patients with arterial TE, median BMI (IQR), thrombosis versus no thrombosis, 24.3 (22.3–25.9) versus 28.4 (24.9–31.8) kg/m\(^2\), \( p = 0.02 \).

The incidence of thrombosis was similar for both solid (12.1%) and hematologic (11.4%) malignancies; the distribution of solid or hematologic tumor types was also not associated with thrombosis (Table 2). Importantly, no patients with underlying lung, head and neck, pancreatic, neurologic, hepatobiliary, and neuroendocrine malignancies were found to have new thromboses. There was no significant difference in TE between the myeloid and non-myeloid malignancies, with the exception of acute lymphocytic leukemia (AML), where the incidence of thrombosis was higher in AML patients (100%) compared to patients without AML (80%), \( p = 0.02 \).

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\text{Table 2. Cancer types in the study population}
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| Cancer type | All patients \( (N = 90) \) | Thrombosis \( (N = 11) \) | No thrombosis \( (N = 79) \) | \( p \) value |
|-------------|-----------------------------|--------------------------|-----------------------------|--------------|
| Solid tumors, n (%) | 58 (100.0) | 7 (12.1) | 51 (87.9) | |
| Genitourinary, n (%) | 17 (100.0) | 2 (11.8) | 15 (88.2) | |
| Breast, n (%) | 6 (100.0) | 1 (16.7) | 5 (83.3) | |
| Colorectal, n (%) | 6 (100.0) | 1 (16.7) | 5 (83.3) | |
| Upper gastrointestinal tract, n (%) | 4 (100.0) | 1 (25.0) | 3 (75.0) | |
| Pancreas, n (%) | 2 (100.0) | 0 (0.0) | 2 (100.0) | |
| Neuroendocrine, n (%) | 2 (100.0) | 0 (0.0) | 2 (100.0) | |
| Gynecologic, n (%) | 3 (100.0) | 1 (33.3) | 2 (66.7) | |
| Lung, n (%) | 8 (100.0) | 0 (0.0) | 8 (100.0) | |
| Head and neck, n (%) | 4 (100.0) | 0 (0.0) | 4 (100.0) | |
| Neurologic, n (%) | 1 (100.0) | 0 (0.0) | 1 (100.0) | |
| Hepatobiliary, n (%) | 4 (100.0) | 0 (0.0) | 4 (100.0) | |
| Skin, n (%) | 1 (100.0) | 1 (100.0) | 0 (0.0) | |
| Hematologic malignancies, n (%) | 32 (100.0) | 4 (11.4) | 28 (88.6) | |
| Myeloid malignancy, n (%) | 6 (100.0) | 1 (16.7) | 5 (83.3) | |
| Myelodysplastic syndromes, n (%) | 3 (100.0) | 1 (33.3) | 2 (66.7) | |
| MPN, n (%) | 2 (100.0) | 0 (0.0) | 2 (100.0) | |
| AML, n (%) | 1 (100.0) | 0 (0.0) | 1 (100.0) | |
| Lymphoid malignancy, n (%) | 26 (100.0) | 3 (11.5) | 23 (88.5) | |
| Non-Hodgkin’s lymphoma, n (%) | 8 (100.0) | 0 (0.0) | 8 (100.0) | |
| Hodgkin’s lymphoma, n (%) | 3 (100.0) | 0 (0.0) | 3 (100.0) | |
| CLL, n (%) | 2 (100.0) | 0 (0.0) | 2 (100.0) | |
| Multiple myeloma, n (%) | 10 (100.0) | 2 (20.0) | 8 (80.0) | |
| Acute lymphocytic leukemia, n (%) | 3 (100.0) | 1 (33.3) | 2 (66.7) | |
| Metastatic cancer (solid tumors only), n (%) | 36 (100.0) | 4 (11.1) | 32 (88.9) | 0.99 |
| Chemotherapy ≤30 days, n (%) | 36 (100.0) | 3 (8.3) | 33 (91.7) | 0.52 |
| Immunotherapy ≤30 days, n (%) | 5 (100.0) | 0 (0.0) | 5 (100.0) | 0.99 |

MPN, myeloproliferative neoplasm; AML, acute myeloid leukemia.

**Fig. 1.** Cumulative incidence of thrombosis with death as competing risk.
lymphoid malignancy population within the hematologic malignancies. Among the patients with hematologic malignancies, patients with lymphoma, myeloproliferative neoplasms, acute myeloid leukemia, and chronic lymphocytic leukemia did not develop new TE. Metastatic disease, chemotherapy, or immunotherapy administration within the past 30 days did not increase the risk of thrombosis.

**Course of Illness in Patients with COVID-19 and Cancer with and without Thrombosis**

Table 3 details the course of illness for these patients. Seventy-three patients (81.1% of the cohort) were hospitalized due to COVID-19 at least once during the follow-up period and 8 (8.9%) visited the ED at least once while the remaining 9 patients (10%) were solely followed as outpatients. Of the hospitalized population, 7 patients (7.8% of the cohort and 9.6% of the inpatients) needed intensive care unit (ICU) level of care, whereas 21 (23.3% of the cohort) needed intubation.

DD levels were checked in 45 patients (50% of the cohort) during the study period and 37 patients (41.1% of the cohort) had levels tested during the first 36 h of admission. The peak DD value, during the total admission time and within 36 h of admission, was elevated in all patients and was not significantly higher in the thrombosis group (Table 3).

**AC Data in the Inpatient Setting**

Twelve out of the 73 inpatients (16.4%) received therapeutic AC, 38/73 (52.1%) received prophylactic AC, and the rest 23/73 (31.5%) did not receive any form of AC. Four of the 11 patients with thrombosis (36.4%) were identified with their new thromboses on the day of admission and thus were not exposed to any form of prior AC.

Nine patients (75% of patients on therapeutic AC) had been on therapeutic AC at home. Reasons for AC at home included atrial fibrillation (7 patients) and prior VTE (2 patients). The remaining 3 patients were started in-hospital. One of the 3 was initially started on prophylactic AC when admitted but was later switched to therapeutic dose because of concern for PE. Out of the patients who received solely prophylactic dose AC, enoxaparin was given as first agent in 16/38 (42.1%), subcutaneous heparin in 15/38 (39.5%), and 2.5 mg dose apixaban in 7/38 (18.4%).

Inpatients with TE were less likely to have received AC prior, any AC, TE versus no TE, 9.1% versus 79.0%, $p < 0.0001$ (Table 3). Of all 11 patients with new confirmed TE, only 1 patient received AC (prophylactic AC) prior to the thrombotic event. This patient was found to have new microvascular ischemic changes in the cerebral white matter 3 days after being found to be COVID-19+.

The other newly confirmed TE (in 10/11 patients, 90.9%) oc-
Increased Thrombosis Rates in COVID-19+ Cancer Patients

Survival

The thrombosis group was found to have significantly decreased survival within the first 30 days following the COVID-19+ test (shown in Fig. 2). Univariate analysis showed a hazard ratio of 2.6 (95% CI: 1.2–5.6, \( p = 0.0009 \)) for mortality in patients with thrombosis versus no thrombosis. Nine out of 11 patients of the thrombosis group (81.8%) and 33 out of the 79 patients without thrombosis (41.7%) expired. Of note, 7 patients with thrombosis (63.6% of the thrombosis group) expired within the first 7 days since COVID-19 diagnosis.

Discussion

Cancer is a well-known independent risk factor for TE and COVID-19 infection has also been associated with a hypercoagulable state. A recent meta-analysis of 8271 COVID-19+ patients revealed 21% VTE and 2% ATE rate [7]. While recent studies have shown that cancer is an independent risk factor for TE in patients with COVID-19 infection [13], the characteristics and impact on survival of patients with COVID-19 and active cancer have not been well described. Whether these 2 risks are synergistic or additive is unclear but with hallmarks of disease being high fibrinogen and DD levels in addition to elevated inflammatory markers, such as C-reactive protein, ferritin, and interleukin-6 [14], it may be important to determine.

There is general agreement that inpatient patients with cancer should receive thromboprophylaxis, but during the very early stages of the COVID-19 pandemic, when hospitals had doubled in capacity and death rates could be over 100/day, it was often impossible to maintain protocols. The only positive effect of this chaos was that it did allow us to analyze, and therefore, re-emphasize, the beneficial effect of AC. The analysis of the present cohort is in alignment with the recent reports, showing an increased incidence of TE at 12.2%, as compared to 0.8% of monthly TE incidence in patients with active cancer and no COVID-19 infection [3]. Interestingly, the majority of our events were arterial (8/13, 61.5%). This can be partly explained by the high number of CT scans of the head done in this cohort (total 20 CTs), which identified 7/8 ATEs, as compared to studies done to detect VTE (7 CT chest with PE protocol and 12 deep venous thrombosis studies). It is also notable that patients with cancers historically associated with increased thrombosis risk, such as pancreatic cancer and several hematologic malignancies, did not develop any TE. Although many comorbidities, such as diabetes and obesity, have been shown to independently increase the mortality risk in the COVID-19+ population [15, 16], these did not seem to further increase the risk of thrombosis. Kidney disease was significantly associated with increased TE risk, with 8/11 patients with TE (72.7%) having underlying CKD or ESRD.

All of the patients with COVID and TE were inpatients. This is not surprising, given the fact that inpatients were more likely to be afflicted with a severe inflammatory response, which would further exacerbate their prothrombotic state. Mean hospital length of stay was numerically higher in the thrombosis group. Admission to the intensive care unit or need of ventilation support was not associated with a higher risk of thrombosis in our cohort.

Prior studies have shown that DD levels seem to correlate well with the risk of thrombosis in COVID-19 infected patients [17]. Patients with active cancer would have been expected to have higher baseline DD and may indicate a further prothrombotic risk in the cancer population [18]. In the early days of the pandemic, our in-
stitution had implemented a DD cut-off value of 3 μg/mL or rapidly increasing DD in order to initiate empiric therapeutic rather than prophylactic AC. However, our numbers were too small to determine whether this had any effect in our cancer population. Our data suggest that any type of AC, either prophylactic or empiric therapeutic, seemed to protect against TE in our cohort. The low reported rates of inpatient thromboprophylaxis (23/73, 31.5% of hospitalized patients were not receiving AC) can at least partly be explained by the following reasons: (i) the thromboprophylaxis state was defined as any AC before the identification of any TE; in 5/23 (21.7%) TE was identified early on or at the time of admission and those patients were not receiving any AC prior; (ii) 9/23 patients (39.1%) had contraindications to AC initiation, such as gastrointestinal hemorrhage or brain metastases or were under comfort care treatment due to imminent death; (iii) due to limited inpatient capacity at the peak of the pandemic, many inpatients were being managed at the ED and were often AC was not efficiently started (4/23 patients, 17.4%); and (iv) the rest of the patients (5/23, 21.7%) were not started on AC for miscellaneous reasons, such as early discharges against medical advice or short-term admissions for chemotherapy.

**Limitations**

The present patient population was characterized by very high mortality following the COVID-19+ test; in total, 29/90 patients (32.2%) expired within 1 week of COVID-19 diagnosis, 7 from the thrombosis group (63.3% of the group), and 22 from the non-thrombosis group (27.8% of the non-TE group). Since almost one-third of the non-thrombosis group evaluated for new TE was censored early since they expired early after diagnosis, the competing mortality risk may have led to underreporting of the real TE risk. Also, because of the high risk of exposure at the time, thromboembolic events may have been underreported due to the inability to pursue the appropriate imaging tests – this is especially true for the admitted patients as compared to those in the ED, where imaging is more easily accessible. The use of thromboprophylaxis in hospitalized patients might have also contributed to lower rates of thrombosis compared to the rates in outpatients and thus underestimate the TE incidence. Finally, because several TE were diagnosed before the establishment of COVID-19 diagnosis, it is possible that the TE prompted the admission initially in some of the patients and subsequently those were screened positive for COVID-19.

**Conclusion**

Our study highlights that TE can be associated with an independent risk of mortality in cancer patients with COVID-19. Further studies are needed to confirm our results and further investigate the overall impact of TE in this patient population.

**Statement of Ethics**

The present study is in accordance with the World Medical Association Declaration of Helsinki. The Montefiore-Einstein Institutional Review Board reviewed and approved the study and waived the need for informed consent.

**Conflict of Interest Statement**

The authors do not report any conflict of interest relevant to the information in the manuscript.

**Funding Sources**

These studies were supported by Albert Einstein Cancer Center Grant (P30CA013330).

**Author Contributions**

P.D.Z. was responsible for the study design, data collection, data analysis, interpretation of the results, and drafted the initial manuscript. H.H.B. was responsible for the study design, major revisions, and final approval of the version submitted. V.M. and S.G. were responsible for data collection and revision of the manuscript.

**Data Availability Statement**

The data for the present study were extracted from the Montefiore Health Care System’s electronic medical record; thus, they are not publicly available because this would compromise the privacy of research participants. Research datasets would be available from P.D.Z. upon reasonable request.
Increased Thrombosis Rates in COVID-19+ Cancer Patients

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