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Patients with myeloproliferative neoplasms and COVID-19 have increased rates of arterial thrombosis

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Abstract

Background: Both coronavirus disease-2019 (COVID-19) and myeloproliferative neoplasms (MPNs) are associated with systemic inflammation and risk of thrombosis. Risk of thrombosis in patients with COVID with and without MPNs has not been extensively studied.

Methods: Retrospective cohort study of 44 patients with MPNs and 1114 patients without MPNs positive for SARS-COV-2. Outcomes were arterial thrombosis (AT), venous thromboembolism (VTE), bleeding, and death. Time-to-event analysis was performed using competing risk regression model and Cox proportional hazards.

Results: AT occurred more frequently in patients with MPN (7% vs. 1%, p = 0.03). Rates of VTE (7% vs. 5%, p = 0.73), bleeding (7% vs. 2%, p = 0.06), and death (9% vs. 6%, p = 0.32) were similar. MPN patients were older and had more cardiovascular comorbidities. After time-to-event competing-risk regression adjusting for age, MPN patients had higher risk of AT (subdivision hazards ratio 3.95, 95% CI 1.09–14.39) but not VTE, bleeding, or death.

Conclusions: Among patients with COVID-19, MPN patients had higher risk of arterial thrombosis but not VTE, bleeding, and death compared with non-MPN patients. Larger studies are needed to confirm our findings given the limited sample size.

KEYWORDS
arterial thrombosis, coronavirus, COVID-19, myeloproliferative neoplasms

Gabriela Hobbs and Gregory Piazza are mentored and contributed equally to the manuscript.

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1 | INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an inflammatory, multisystem infectious disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-COV-2) and has been associated with increased risk of thrombosis, particularly among critically ill patients.1 The myeloproliferative neoplasms (MPNs) are a heterogeneous group of stem cell neoplasms and include the Philadelphia chromosome-negative (Ph-negative) MPNs, polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF).2 MPNs commonly have activating mutations that cause downstream activation of the JAK-STAT signaling pathway, leading to an inflammatory state associated with thrombosis.3,4 Patients with MPNs have an increased risk of arterial and venous thrombotic complications.5,6 Cytoreduction therapy (e.g., phlebotomy, hydroxyurea, ruxolitinib) is initiated in patients with MPNs to reduce blood counts and decrease the risk of thrombosis.7,8 Additionally, aspirin is often used in patients with MPNs to prevent thrombotic complications. Given the increased propensity of thrombosis and prognostic significance of thrombosis in both COVID-19 and MPNs, defining the risk of thrombotic complications in this patient population is clinically relevant. In one retrospective cohort study, patients with Ph-negative MPNs who were hospitalized for COVID-19 had high rates of thrombosis (8.6% all thrombosis, 1.9% arterial thrombosis, 7.4% venous thrombosis).9 However, no studies have directly compared short-term risk of thrombosis in hospitalized patients with COVID-19 and MPN with the general population of patients with COVID-19. Using the multicenter observational cohort registry, CORONA-VTE,1 we assessed the risk of thrombosis in patients with and without MPN.

2 | METHODS

2.1 | Study design

This study was a retrospective observational cohort study using data gathered through the electronic health record within the Massachusetts General Brigham integrated health network. The study was approved by our institutional review board, which waived the requirement of informed consent.

2.2 | Study population

Two separate cohorts were included in this study, patients with COVID-19 with and without MPN, which included patients from the CORONA-VTE registry. Patients with MPN included 44 consecutive subjects who were 18 years or older, met World Health Organization diagnostic criteria for MPNs2 (ET, PV, PMF), and tested positive for SARS-COV-2 infection based on polymerase chain reaction testing from March 1, 2020, to January 1, 2021. The COVID-19 cohort included 1114 consecutive patients 18 years or older who tested positive for SARS-COV-2 as described by CORONA-VTE study from March 13, 2020, to April 3, 2020, but did not have a diagnosis of MPN.3 Care was taken to ensure that the MPN and non-MPN cohorts were mutually exclusive.

2.3 | Data collection

Data collection for the cohort of patients without MPN has been previously described.1 In brief, patients for the cohort without MPN were identified using a silent computerized decision support program embedded as a Best Practice Advisory within the electronic health record (EPIC, version 2015; Epic Systems). Patient data were manually entered by trained and experienced team of research assistants, nurse, and physician using the Research Electronic Data Capture (REDCap) tool hosted at Brigham and Women’s Hospital.10 For the MPN cohort, patients were identified using the same silent computerized decision support program as the cohort without MPN. Data were gathered electronically through the EPIC Best Practice Advisory and manually entered by a physician (O.L.) and managed using REDCap. Patient demographics, comorbidities, and baseline characteristics were recorded, including age, sex, race, and ethnicity. MPN-specific data were also gathered, including baseline laboratory values within 3 months before COVID-19 diagnosis, MPN type, driver mutations if known, and treatment of MPN within 3 months before COVID-19 diagnosis.

Outcomes were arterial thrombosis, venous thromboembolism (VTE), all-cause mortality, and ISTH major and clinically relevant nonmajor bleeding at 90days and were ascertained using standard definitions (Appendix S1).1,11 Arterial thrombosis included myocardial infarction, ischemic stroke, or transient ischemic attack; systemic embolism; and major adverse limb events. Systematic screening protocol for VTE was not in place during our study. Outcomes for the MPN cohort were initially adjudicated by a physician (O.L.) using the same definitions and criteria as the non-MPN cohort. These events were then confirmed by the same blinded CORONA-VTE cardiology clinical end-point committee that adjudicated the non-MPN cohort events. The CORONA-VTE end-point committee consisted of three board-certified cardiovascular medicine specialists, as previously described.1

Essentials

- Myeloproliferative neoplasm (MPN) are associated with inflammation and risk of clotting.
- COVID-19 is also associated with increased clotting and inflammation.
- Our study aimed to compare incidence of clotting and death in patients with COVID-19 with MPN.
- Our study suggests that patients with MPN and COVID-19 are at higher risk of arterial clotting.
2.4 | Statistical analysis

Continuous and categorical variables were compared using non-parametric Mann–Whitney test and Fisher exact test, respectively. A two-tailed p value of <0.05 was considered significant. Time-to-event analysis modeling risk of any thrombosis, arterial thrombosis, VTE, bleeding, and death in patients with and without MPN, adjusting for age at COVID-19 diagnosis, was performed using Cox proportional hazards regression and subdistribution hazards ratio (SHR) estimated using competing risk regression (Fine and Gray’s method with death as competing risk). Statistical analysis was performed using STATA version 15 (STATA Corporation), GraphPad Prism 9 (GraphPad, Inc.), and Microsoft Excel 360 (Microsoft Corp.).

3 | RESULTS

3.1 | Characteristics and outcomes of patients with and without MPN

There were 44 patients from the MPN cohort (from March 1, 2020, to January 1, 2021) and 1114 in the non-MPN cohort (from March 13, 2020, to April 3, 2020). Of the 44 patients in the MPN cohort, 17 (39%) had ET, 23 (52%) had PV, and four (9%) had PMF. A mutation in the JAK2 gene was present in 31 (70%) of patients with MPN. Cytoreduction before COVID-19 was used in 34 (77%) of all MPN, 13 (57%) of PV, 14 (82%) of ET, and two (50%) of PMF patients. The median age at MPN diagnosis was 61 years (interquartile range [IQR] 47, 71) for all MPN, 68 years (IQR 47, 78) for PV, 59 years (IQR 43, 70) for ET, and 60 years (57, 62) for PMF patients. The median time from MPN diagnosis to COVID-19 was 6 years (IQR 3, 10) for all MPN, 68 years (IQR 47, 78) for PV, 59 years (IQR 43, 70) for ET, and 60 years (57, 62) for PMF patients. The median time from MPN diagnosis to COVID-19 was 6 years (IQR 3, 10) for all MPN, 4 years (IQR 3, 9) for PV, 7 years (IQR 3, 12) for ET, and 2 years (IQR 1, 4) for PMF patients (Table S1).

Patients with MPN were significantly older than patients without MPN (median age 64 years vs. 50 years), more likely to be White (89% vs. 72%), and had leaner body mass index (median 26 vs. 28; Table 1). Patients with MPN had similar proportion of patients requiring hospital admission and intensive care admission compared with patients without MPN. There was no difference in corticosteroid use (14% vs. 7%) in patients with MPN compared with those without MPN. Patients with MPN had higher rates of remdesivir prescription (16% vs. 4%). Patients with MPN had higher rates of cardiovascular comorbidities including heart failure (14% vs. 4%), atrial fibrillation (14% vs. 5%), hypertension (59% vs. 36%), former or current smoking (57% vs. 34%), and atherosclerotic disease (39% vs. 12%).

Patients with MPN were more likely to be receiving baseline anticoagulation (18% vs. 4%) and aspirin (77% vs. 3%) compared with those without MPN. However, among patients requiring hospital admission, patients with MPN were less likely to receive in-hospital anticoagulation (72% vs. 95%). Patients with MPN also had lower median hematocrit (31% vs. 41%), estimated glomerular filtration rate (42 vs. 78), and have platelet counts less than 100 K/μl (22% vs. 72%), and were more likely to be White (89% vs. 72%), and have leaner body mass index (median 26 vs. 28; Table 1).

In-hospital anticoagulation, N (%) admitted

| Treatment | MPN | Non-MPN |
|-----------|-----|---------|
| AC at baseline | 8 (18) | 47 (4) |
| Aspirin at baseline | 34 (77) | 150 (13) |
| Non-MPN malignancy | 9 (20) | 120 (11) |
| Baseline immunosuppression | 31 (70) | 91 (8) |

Laboratory results at COVID-19 diagnosis, median (IQR)

| Test | MPN | Non-MPN |
|------|-----|---------|
| WBC, k/μl | 13 (7, 22) | 6 (5, 8) |
| Hematocrit, % | 31 (22, 38) | 41 (37, 44) |
| Platelets, k/μl | 273 (117, 559) | 183 (148, 232) |
| Ferritin, mcg/L | 435 (146, 2244) | 567 (226, 966) |
| D-dimer, ng/ml | 842 (513, 1413) | 1090 (583, 3900) |
| CRP, mg/L | 58 (33, 177) | 56 (22, 129) |
| LDH, U/L | 553 (324, 791) | 290 (233, 402) |
| EGFR, ml/min/1.73m² | 42 (27, 74) | 78 (60, 96) |

Abbreviations: AC, anticoagulation; BMI, body mass index; COVID, coronavirus disease 2019; CRP, C-reactive protein; EGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; MPN, myeloproliferative neoplasm; WBC, white blood count.

Atherosclerotic disease includes coronary artery disease, previous stroke or transient ischemic attack, and peripheral arterial disease.

Includes chronic steroid use, antitumor necrosis-α inhibitor, chemotherapy, tyrosine kinase inhibitor, hydroxyurea use.
vs. 5%) at time of COVID-19 diagnosis than those without MPN. Median lactate dehydrogenase levels were higher in patients with MPN compared with patients without MPN (553 vs. 290).

Arterial thrombosis, VTE, bleeding, and all-cause death occurred in 18 patients (three MPN, 15 non-MPN), 63 patients (three MPN, 60 non-MPN), 24 patients (three MPN, 21 non-MPN), and 67 patients (four MPN, 63 non-MPN), respectively (Table 2). All arterial thrombosis and bleeding events occurred during hospitalization for COVID-19. Three bleeding events occurred in patients not receiving any in-hospital anticoagulation (two MPN patients, one non-MPN patient), 22 bleeding events occurred in patients not receiving baseline anticoagulation, and 13 bleeding events occurred in patients not receiving aspirin at baseline. One VTE event occurred in a non-MPN patient as an outpatient. Three deaths in non-MPN patients occurred after initial hospitalization for COVID-19. Rates of VTE (7% vs. 5%), ISTH major and clinically relevant nonmajor bleeding (7% vs. 2%), and all-cause mortality (9% vs. 6%) were similar between the MPN and non-MPN patients. Patients with MPN had higher rates of arterial thrombosis (7% vs. 1%) compared with patients without MPN.

### 3.2 | Time-to-event analysis

Our Cox model showed that patients with MPN did not have significantly different risk of VTE (HR 0.60, 95% CI 0.14–2.50), bleeding (HR 2.15, 95% CI 0.61–7.54), or all-cause mortality (HR 0.53, 95% CI 0.19–1.47) compared with those without MPN. Similarly, after competing risk regression modeling there were no differences in VTE (SHR 0.62, 95% CI 0.15–2.60), and bleeding (SHR 2.32, 95% CI 0.71–7.59) in patients with MPN compared with those without MPN. Although there was no significant difference in risk of arterial thrombosis in patients with MPN compared with those without MPN after Cox proportional hazards modeling (HR 3.73, 95% CI 0.98–14.14), there was an increased risk of arterial thrombosis after competing risk regression modeling (SHR 3.95, 95% CI 1.09–14.39). Cumulative incidence of arterial thrombosis, VTE, and bleeding outcomes, and Kaplan–Meier overall survival graphs are shown in Figure 1.

### 4 | DISCUSSION

Our study suggests that patients with COVID-19 and MPN have high rates of adverse events including thrombosis, bleeding, and mortality, especially in those requiring hospitalization. Additionally, compared with those without MPN, patients with MPN may be at increased risk of arterial thrombosis despite higher rates of anticoagulation and aspirin use before COVID-19 diagnosis. Of note, the cohort with MPN had high rates of pre-COVID cytoreduction therapy (77% of MPN patients), which is routinely instituted to reduce the risk of thrombosis. Despite this, the cohort with MPN remained at high risk of thrombosis when diagnosed with COVID-19.

The long-term risk of thrombosis is well known in patients with MPN, with the highest risk being within 3 months of MPN diagnosis and diminishing thereafter. Of note, the MPN patients in our cohort had a median time of 6 years between MPN and COVID-19 diagnoses. Therefore, our findings of possibly increased short-term arterial thrombotic risks in patients with established MPNs and COVID-19 are likely to be clinically meaningful. Additionally, in patients with and without MPN, most events occurred within 30 days of COVID-19 diagnosis in line with previous evidence. Further investigation is needed to characterize long-term effects of COVID-19 in patients with MPN.

Our finding of increased arterial thrombosis in patients with MPN may reflect a common underlying pathophysiology between MPN and COVID-19, which includes a proinflammatory state, endothelial dysfunction, and platelet activation. Inflammation and the MPN phenotype may drive some of the increased risk of thrombosis in patients with COVID-19. MPNs with elevated neutrophil/lymphocyte ratio and ET phenotype are also associated with increased thrombosis. The small number of events in either group should prompt further examination in larger studies to corroborate these observations.

The potential increased risk of arterial thrombosis in patients with MPN has important clinical implications with regard to pharmacologic thromboprophylaxis and antiplatelet agents. Although prophylactic anticoagulation of hospitalized COVID-19 patients is recommended, the ideal dosing of thromboprophylaxis remains unclear. Despite intermediate- and therapeutic-dose anticoagulation not demonstrating a mortality benefit in critically ill patients with COVID-19, therapeutic anticoagulation may be beneficial in hospitalized patients not requiring intensive care unit-level care. Whether patients with MPN and a higher risk of arterial thrombosis may benefit from therapeutic or intermediate dosing of thromboprophylaxis warrants further investigation. However, despite higher rates of baseline anticoagulation use compared with patients

### TABLE 2 Patient outcomes at 90 days

| Outcomes, N (%)a  | MPN N = 44 | Non-MPN N = 1114 | p value |
|------------------|------------|------------------|---------|
| Arterial thrombosis | 3 (7) | 15 (1) | 0.03 |
| MI | 1 (2) | 14 (1) |
| Stroke | 2 (5) | 0 |
| SEE | 1 (2) | 1 (0) |
| VTE | 3 (7) | 60 (5) | 0.73 |
| DVT | 2 (5) | 28 (3) |
| PE | 1 (2) | 10 (1) |
| Catheter-associated | 1 (2) | 42 (4) |
| Bleeding | 3 (7) | 21 (2) | 0.06 |
| All-cause mortality | 4 (9) | 63 (6) | 0.32 |

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; MPN, myeloproliferative neoplasms; PE, pulmonary embolism; SEE, systemic embolic event; VTE, venous thromboembolism.

aBecause of patients having multiple events, arterial thrombosis and VTE subcategories are not mutually exclusive.
without MPN in our cohort, patients with MPN had lower rates of in-hospital anticoagulation. This may be explained by increased rates of thrombocytopenia and anemia in patients with MPN compared with those without. Additionally, the identification of other important risk factors and the development of validated clinical risk scores may help optimize thromboprophylactic strategies in patients hospitalized with COVID-19.21

Our study has limitations, including its retrospective nature and the small sample size of the MPN cohort, which limited our analysis and the use of multivariable models to control for confounding risk factors. Patients in our MPN cohort had higher rates of traditional cardiovascular and thrombotic risk factors including hypertension, atrial fibrillation, smoking, and atherosclerotic disease compared with those without MPN. Additionally, though patients from both MPN and non-MPN cohorts were obtained using similar methods and from the same health care system, the patients without MPN were diagnosed with COVID-19 earlier in the pandemic (March 2020 to April 3, 2020) than those with MPN (March 2020 to January 2021). This may have contributed to more patients in the MPN cohort being treated with remdesivir and corticosteroids.22,23 Overall mortality trends have decreased throughout the pandemic, which may be due to increased clinical experience and advances in therapy.24,25 Despite the different time interval, we do not suspect the variation to have had a major impact on the study findings or thrombotic risk over the early course of the pandemic as major variants had not yet emerged for either interval and the impact of vaccines and other antiviral therapies had yet to be realized. Additionally, our study did not capture whether cytoreduction, immunosuppression, and aspirin were continued or stopped on hospital admission in patients with MPN.

In conclusion, our study suggests that patients with MPN and COVID-19 have high rates of adverse events and are at an increased risk of arterial thrombosis compared with those without MPN. Validation in a larger cohort is needed to confirm our results.
AUTHOR CONTRIBUTIONS
O.L., G.H., G.P., and S.G. designed the research; O.L. performed statistical analysis of the results and made the figures; O.L., U.C., J.S., B.B., and C.K. performed the chart review and data extraction; O.L. drafted the first draft of the manuscript; U.C., A.B., H.A., R.K.L., R.P.R., K.G., L.B., A.F., S.G., G.P., and G.H. provided critical review of the manuscript and edits. O.L., U.C., G.H., G.P., and S.G. 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.

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**SUPPORTING INFORMATION**

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