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INTRODUCTION

Thrombotic disease complicates severe SARS-CoV-2 infection; severely elevated D-dimers are a feature of severe COVID-19, even in the absence of identified thrombosis. In an attempt to decrease thrombotic complications in hospitalized patients, intensified prophylactic and full-dose anticoagulation strategies have been evaluated. The role of chronic anticoagulation before SARS-CoV-2 infection on the risk for subsequent thrombosis has not been systematically studied.

METHODS

This was a retrospective single-center study. All patients with positive SARS-CoV-2 PCR testing from March 13, 2020, through May 6, 2020, at the University of Rochester Medical Center were identified. We included all patients receiving therapeutic anticoagulation for at least 1 month before COVID diagnosis. We documented the rate of thrombotic complications, type of anticoagulation, bleeding complications, and mortality.

Results:

A total of 107 SARS-CoV-2-infected patients were chronically anticoagulated before SARS-CoV-2 testing with a median age of 78. Of those, 42 required hospital admission, with 17 requiring intensive care. No patients, inpatient or outpatient, were diagnosed with a new symptomatic thrombotic complication. Three patients had minor bleeding in the hospital. Thirteen (12%) patients died (69% male).

Conclusion:

Our uncontrolled findings suggest that chronic anticoagulation at the time of infection may protect against thrombotic complications and decrease disease severity.

KEYWORDS
anticoagulation, COVID, mortality, pulmonary embolus, thrombosis
Electronic medical record (EMR) interrogation and manual chart review to identify all those using therapeutic anticoagulation before positive SARS-CoV-2 testing. We included all patients receiving therapeutic anticoagulation (warfarin, enoxaparin, direct oral anticoagulants [DOAC]) regardless of indication for at least 1 month before SARS-CoV2 diagnosis. Clinic or hospital notes, medication order dates, and/or blood work were used to verify anticoagulation use.

Using manual chart review, we collected the rate of imaging confirmed or mechanical thrombotic complications; temporal relationship of the event to SARS-CoV-2 infection and hospitalization; hospitalization/intensive care unit (ICU) admission rate and reason; type of anticoagulation used at home and in the hospital; bleeding complications; and mortality. On duplex ultrasonography, thrombosis was defined as a noncompressible vein with alteration in flow (or clear thrombus seen); on chest or head computed tomography (CT) angiography, thrombosis was defined as partial or complete obstruction to flow. Major bleeding was defined as a 2 g/dL drop in hemoglobin with clinical evidence for blood loss or the need for packed red cell transfusion.

Demographics and clinical information were also collected. Categorical variables are reported as counts and percentages. Continuous variables are reported as median with interquartile ratio.

3  |  RESULTS

3.1  |  Demographics

A total of 1984 patients with positive SARS-CoV-2 PCR were identified using the EMR. A secondary EMR search indicated that 144 patients with positive SARS-CoV-2 PCR were on therapeutic anticoagulation. After manual record review, six patients were newly anticoagulated during COVID-19 index hospitalization. Thirty-one patients were erroneously identified because of medication lists that included prophylaxis or therapeutic dosing from the current or prior hospitalization. In total, 107 SARS-CoV2 infected patients (5%) were chronically anticoagulated for at least 1 month before testing. Medical history and clinical presentation are included in Tables 1 and 2. Body mass index and history of a prior venous thromboembolism (VTE) event were evenly distributed between the inpatient and outpatient groups. The majority of patients were females with a median age of 78. At the time of data analysis, 42 patients had required hospital admission, with 17 requiring intensive care. D-dimer elevations (in 27 patients who were tested) were modest in comparison with other cohorts in the literature (Table 2).

3.2  |  Thrombotic events

Approximately 2/3 of the outpatients and inpatients were chronically anticoagulated with full-dose DOAC before SARS-CoV-2 infection (as opposed to warfarin or low molecular weight heparin). None of the 65 outpatients on therapeutic anticoagulation developed a new symptomatic thrombotic event documented in our EMR after SARS-CoV-2 diagnosis. None of the 42 patients had imaging evidence for a new thrombotic event, even though six patients in the cohort had signs and symptoms triggering evaluation. Imaging evaluation included four chest CT scans and two lower extremity ultrasounds. We did not observe symptomatic thrombotic events even in the 10 inpatients anticoagulated because of a prior VTE event; such patients are generally considered to be at highest risk for developing a new VTE. Furthermore, we reviewed 12 head CT scans ordered to evaluate neurologic signs or symptoms; no ischemic strokes were identified, but concern for cerebral hemorrhage was the indication for some examinations. No patients had their anticoagulation empirically changed for a presumed new thrombotic event. One ICU patient may have had acute coronary syndrome, but because of severe chronic illness at baseline, the family elected comfort care. Two patients had continuous venovenous hemofiltration without premature filter change (premature filter thrombosis is often a marker of prothrombotic tendency). Two patients with left ventricular assist devices and two requiring intermittent hemodialysis had no device or line-related thrombosis. No patients required extracorporeal membrane oxygenation for refractory hypoxemia or shock.

3.3  |  Bleeding

Three patients in the ICU had an identified bleeding complication. One patient received a unit of blood for a thigh hematoma and another required evacuation of a thigh hematoma; both were complications of femoral venous catheterization. The third patient had a small, self-limited gastrointestinal bleed. Two patients had bleeding that prompted admission to the hospital floor (gastrointestinal bleed and cerebral hemorrhage); their emergency room visits were not related to coronavirus infectious symptoms, but they tested positive at admission.
### Table 1 Baseline characteristics

|                      | Total (n = 107) | Outpatient (n = 65) | Hospitalization Non-ICU (n = 25) | Hospitalization ICU (n = 17) |
|----------------------|-----------------|---------------------|----------------------------------|-----------------------------|
| **Age**              |                 |                     |                                  |                             |
|                      | 78 (68, 84)     | 78 (70, 87)         | 75 (69, 82)                      | 74 (65, 78)                 |
| **Sex**              |                 |                     |                                  |                             |
| Female               | 59 (55%)        | 35 (54%)            | 13 (52%)                         | 11 (65%)                    |
| **BMI**              |                 |                     |                                  |                             |
|                      | 29 (25, 34)     | 31 (26, 34)         | 28 (25, 32)                      | 29 (23, 37)                 |
| **Ethnicity**        |                 |                     |                                  |                             |
| Caucasian            | 82 (77%)        | 52 (80%)            | 21 (84%)                         | 9 (53%)                     |
| African American     | 19 (18%)        | 9 (14%)             | 3 (12%)                          | 7 (41%)                     |
| Asian                | 2 (2%)          | 2 (3%)              | 0                                | 0                           |
| Latino               | 2 (2%)          | 1 (1%)              | 0                                | 1 (6%)                      |
| **Smoking history**  |                 |                     |                                  |                             |
| Current              | 4 (4%)          | 4 (6%)              | 0                                | 0                           |
| Former               | 49 (46%)        | 27 (42%)            | 18 (72%)                         | 4 (24%)                     |
| **Anticoagulation**  |                 |                     |                                  |                             |
| DOAC                 | 71 (66%)        | 44 (68%)            | 16 (64%)                         | 11 (65%)                    |
| Warfarin             | 35 (33%)        | 21 (32%)            | 8 (32%)                          | 6 (35%)                     |
| LMWH                 | 1 (1%)          | 0                   | 1 (4%)                           | 0                           |
| **Medical history**  |                 |                     |                                  |                             |
| Atrial fibrillation  | 76 (71%)        | 41 (63%)            | 21 (84%)                         | 14 (82%)                    |
| VTE                  | 27 (25%)        | 17 (26%)            | 5 (20%)                          | 5 (29%)                     |
| Hypertension         | 76 (71%)        | 40 (61%)            | 20 (80%)                         | 16 (94%)                    |
| Diabetes             | 32 (30%)        | 14 (22%)            | 10 (40%)                         | 8 (47%)                     |
| Hypothyroid          | 28 (26%)        | 20 (31%)            | 5 (20%)                          | 3 (18%)                     |
| CKD                  | 27 (25%)        | 13 (20%)            | 9 (36%)                          | 5 (29%)                     |
| ESRD                 | 5 (5%)          | 3 (5%)              | 0                                | 2 (12%)                     |
| OSA                  | 21 (20%)        | 8 (12%)             | 7 (28%)                          | 6 (35%)                     |
| COPD                 | 15 (14%)        | 11 (17%)            | 2 (8%)                           | 2 (12%)                     |
| CAD                  | 30 (28%)        | 16 (25%)            | 8 (32%)                          | 6 (35%)                     |
| HFpEF/HFrEF          | 34 (32%)        | 18 (28%)            | 8 (32%)                          | 8 (47%)                     |
| Neurologic Impairment| 57 (53%)        | 31 (48%)            | 15 (60%)                         | 11 (65%)                    |
| Immunosuppression    | 7 (7%)          | 2 (3%)              | 2 (8%)                           | 3 (18%)                     |

### 3.4 Mortality

During this period, 13 patients (12%) died (69% male, Table 2). In 10/13 deaths, the surrogate decision makers elected to limit or stop life-sustaining interventions because of severe underlying medical conditions. The other three deaths were unrelated to SARS-CoV-2 (eg, new aggressive cancer diagnosis).

### 4 Discussion

Our single-center uncontrolled findings suggest that chronic anticoagulation use at the time of positive SARS-CoV-2 testing may protect from the increased risk of thrombotic disease observed in other cohorts of hospitalized patients. Despite being elderly with comorbidities requiring anticoagulation, 61% of our patients did not require hospitalization as of the database closure. These patients were at high risk for new thrombosis (prior thrombosis, obesity, obstructive sleep apnea, and indwelling devices/lines), but we did not observe any new thrombotic events. For the inpatient group, the median D-dimer level was also lower in comparison to other reported hospitalized cohorts, especially given the advanced age of our cohort.

The risk of thrombotic disease in association with SARS-CoV-2 initially appears to be highest in critically ill patients and has been reported in multiple hospitals and countries. Poyiadi et al recently showed that the majority of pulmonary emboli in their study occurred in non-ICU patients. Interestingly, thrombotic complications have emerged despite the usual prophylactic dosing of anticoagulation, which has led some investigators to advocate for therapeutic intensity prophylactic anticoagulation in hospitalized patients. The thrombotic process may start before hospitalization because...
Lodigiani et al found 50% of VTE occurred within 24 hours of admission. If subclinical microthrombi have already developed through neutrophil extracellular traps formed to limit viral spread, then prophylactic anticoagulation is likely insufficient. Microthrombi may then evolve to clinical events if not effectively treated with therapeutic anticoagulation.

### TABLE 2 Clinical presentation and outcomes

| Positive COVID-19 testing | Total (n = 107) | Outpatient (n = 65) | Hospitalization Non-ICU (n = 25) | Hospitalization ICU (n = 17) |
|---------------------------|-----------------|---------------------|----------------------------------|-----------------------------|
| Before admission\(^a\)    |                 |                     |                                  |                             |
| 1-6 days                  | 10 (24%)        | 7 (28%)             | 3 (18%)                          |                             |
| >7 days                   | 9 (21%)         | 6 (24%)             | 3 (18%)                          |                             |
| Day of admission          | 20 (48%)        | 10 (40%)            | 10 (59%)                         |                             |
| Hospital acquired         | 3 (7%)          | 2 (8%)              | 1 (5%)                           |                             |
| Clinical presentation\(^b\) |                |                     |                                  |                             |
| Acute kidney injury CVVH  | 10 (24%)        | 4 (16%)             | 6 (35%)                          | 2 (12%)                     |
| Hypoxia                   | 26 (62%)        | 9 (36%)             | 17 (100%)                        |                             |
| Intubation                | 11 (26%)        | 0                   | 11 (65%)                         |                             |
| Shock                     | 4 (10%)         | 0                   | 4 (24%)                          |                             |
| Bleeding                  | 2 (5%)          | 2 (8%)              | 0                                |                             |
| Flu-like illness          | 10 (9%)         | 10 (40%)            | 0                                |                             |
| Hospital acquired         |                |                     |                                  |                             |
| Clinical presentation\(^b\) |                |                     |                                  |                             |
| Acute kidney injury CVVH  | 10 (24%)        | 4 (16%)             | 6 (35%)                          | 2 (12%)                     |
| Hypoxia                   | 26 (62%)        | 9 (36%)             | 17 (100%)                        |                             |
| Intubation                | 11 (26%)        | 0                   | 11 (65%)                         |                             |
| Shock                     | 4 (10%)         | 0                   | 4 (24%)                          |                             |
| Bleeding                  | 2 (5%)          | 2 (8%)              | 0                                |                             |
| Flu-like illness          | 10 (9%)         | 10 (40%)            | 0                                |                             |
| Hospital anticoagulation\(^c\) |            |                     |                                  |                             |
| Home DOAC                 | 21 (50%)        | 14 (52%)            | 7 (41%)                          |                             |
| Warfarin                  | 7 (17%)         | 6 (28%)             | 1 (6%)                           |                             |
| Full-dose enoxaparin      | 9 (21%)         | 3 (12%)             | 6 (35%)                          |                             |
| Continuous heparin        | 2 (5%)          | 0                   | 2 (12%)                          |                             |
| Heparin prophylaxis       | 1 (2%)          | 0                   | 1 (6%)                           |                             |
| None                      | 2 (5%)          | 2 (8%)              | 0                                |                             |
| Admission values          |                |                     |                                  |                             |
| NT-pro BNP (pg/mL)        | N = 18          | N = 6               | N = 12                           |                             |
|                          | 930 (155, 7612) | 584 (98, 4626)      | 930 (370, 12 449)                |                             |
| WBC (thousands/µL)        | N = 63          | N = 21              | N = 25                           | N = 17                       |
|                          | 6800 (4900, 9000) | 6800 (4450, 8700)  | 6000 (4600, 8300)                | 8700 (5700, 11 400)         |
| Absolute lymphocytes      | N = 63          | N = 21              | N = 25                           | N = 17                       |
| (thousands/µL)            | 1200 (625, 1675) | 1600 (800, 1900)   | 1100 (600, 1500)                 | 1000 (650, 1500)            |
| Platelets (thousands/µL)  | N = 63          | N = 21              | N = 25                           | N = 17                       |
|                          | 203 (151, 297)  | 203 (151, 301)      | 220 (154, 282)                   | 200 (141, 330)              |
| INR\(^c\)                | N = 26          | N = 13              | N = 7                            | N = 6                        |
|                          | 2 (1.7, 3.55)   | 2.8 (1.9, 3.8)      | 3.1 (1.3, 4.4)                   | 4.4 (2.3, 5.9)              |
| APTT (s)                 | N = 16          | N = 6               | N = 10                           | N = 10                       |
|                          | 35.2 (28, 40)   | 37 (31, 48)         | 45 (38, 49)                      |                             |
| Ferritin (ng/mL)          | N = 28          | N = 13              | N = 15                           | N = 12                       |
|                          | 467 (206, 849)  | 33 (192, 562)       | 839 (207, 2209)                  |                             |
| D-dimer (µg/mL)\(^d\)    | N = 27          | N = 5               | N = 10                           | N = 12                       |
|                          | 0.63 (0.42, 1.4)| 0.22 (0.22, 0.87)   | 0.78 (0.6, 1.3)                  | 0.63 (0.48, 1.64)           |
| CRP (mg/L)                | N = 29          | N = 14              | N = 15                           | N = 17                       |
|                          | 92 (30, 155)    | 53 (25, 138)        | 127 (48, 168)                    |                             |
| Creatinine (mg/dL)        | N = 60          | N = 18              | N = 25                           | N = 17                       |
|                          | 1 (0.73, 1.35)  | 1.03 (0.75, 1.31)   | 0.92 (0.70, 1.32)                | 0.95 (0.7, 1.9)             |
| Procalcitonin (ng/mL)     | N = 19          | N = 9               | N = 10                           | N = 10                       |
|                          | 0.29 (0.1, 0.80)| 0.26 (0.06, 0.65)   | 0.34 (0.13, 0.87)                |                             |

(Continues)
Diagnosis of SARS-CoV-2. In Klok’s follow-up confirmation report, patients were on chronic therapeutic anticoagulation before the patients not on anticoagulation. Their report does not describe the during hospitalization had improved outcomes compared with patients treated with full-dose anticoagulation (eg, new vs residual thrombus; lobar vs segmental filling defects). In an observational report, Paranjpe et al found that 22 hospitalized SARS-CoV-2-infected patients with a thrombotic event, only one was receiving therapeutic anticoagulation. Poissy et al found that of 22 SARS-CoV-2-infected patients whose course was complicated by pulmonary embolism, only two were on chronic anticoagulation. Poyiadi et al do not comment whether their patients were on chronic therapeutic anticoagulation before the diagnosis of SARS-CoV-2. In Klok’s follow-up confirmation report, 3/17 patients chronically anticoagulated for various reasons were identified with pulmonary embolism. Importantly, that report lacks detail about the thrombotic events identified in the chronically anticoagulated patients (eg, new vs residual thrombus; lobar vs segmental filling defects). In an observational report, Paranjpe et al found that patients treated with full-dose anticoagulation during hospitalization had improved outcomes compared with patients not on anticoagulation. Their report does not describe the number of patients on chronic anticoagulation before admission.

It is possible that anticoagulation could have therapeutic benefits beyond inhibition of fibrin clot formation. Heparin neutralizes complement C5a and binds inflammatory cytokines, which may influence this respiratory illness beyond its anticoagulant effects. Heparin could even modify binding of the SARS-CoV-2 spike S1 protein to cell surface receptors, attenuating cell infection. However, only one of our patients was treated with low molecular weight heparin as an outpatient, and even during hospitalization, the majority of our patients continued their home DOAC without apparent thrombotic events. Beyond structural properties of heparins, there is extensive cross-talk between the inflammatory and coagulation cascades, and it is reasonable to speculate that attenuating Xa or thrombin signaling might modify host inflammatory responses to SARS-CoV2.

In our small and uncontrolled dataset, it is impossible to estimate whether anticoagulation had an impact on mortality. Reported mortality from observational cohorts is greatly influenced by the number and types of people tested, patient treatment preferences, and the degree to which COVID-19 pandemic undermined health care systems. Using the logistic regression model of Lodigiani et al, the expected inpatient mortality is 40% to 45% in our patient group; we observed 23.8%, and most of our deaths occurred after a decision to limit the use of life support. Our data also suggest that anticoagulation did not cause unexpected or high rates of bleeding in 107 patients with COVID-19.

There are limitations to our single-center observational study. We have no control group and make comparisons only to the published literature in this rapidly evolving field. We could have underestimated the rate of thrombosis because some of the more severely ill patients placed limitations on their care at admission. They may have had or might have developed clinically significant thrombotic disease if all life-sustaining measures had been pursued. We may have underestimated thrombosis in outpatients in the unlikely event that they had care for the initial diagnosis of SARS-CoV-2 within our system but had treatment for thrombosis in another health care system; our health care system was well under capacity during this time. It is also possible that we missed asymptomatic thrombosis in outpatients and inpatients, but inpatient clinicians were certainly sensitive to the risk for thrombosis and evaluated signs or symptoms with six negative studies. Although our inpatient cohort has a clearly different rate of thrombotic events than others reported in the literature, there are very few reports about outpatient cohorts. It seems apparent that the outpatients did not have particularly severe symptoms, which might be interesting, but we cannot deduce anything of substance without a control group.

Our single-center and uncontrolled findings suggest that chronic anticoagulation at the time of SARS-CoV-2 infection may protect against developing thrombotic disease, in contrast to other reported inpatient cohorts in which thrombosis occurred with remarkably high frequency. Of note, manual chart review was critical to the accuracy of our data, and we caution that searching the EMR (without confirmation) overestimated the size of our anticoagulated cohort by 30%. The overall severity of illness in our elderly population appears to be less than others have reported. We
speculate that anticoagulation at the time of initial infection may have limited the thrombotic and inflammatory cascades from accelerating. Randomized studies are necessary to determine whether anticoagulation at the time of diagnosis improves outcomes for this unusual respiratory virus.

CONFLICT OF INTEREST
None of the authors report any conflicts of interest related to this work.

AUTHOR CONTRIBUTIONS
All authors had substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. All authors helped with drafting the work or revising it critically for important intellectual content. All authors had final approval of the version submitted for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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