Thrombosis-Related Loss of Arterial Lines in the First Wave of COVID-19 and Non–COVID-19 Intensive Care Unit Patients

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BACKGROUND: Patients with coronavirus disease 2019 (COVID-19) can present with severe respiratory distress requiring intensive care unit (ICU)–level care. Such care often requires placement of an arterial line for monitoring of pulmonary disease progression, hemodynamics, and laboratory tests. During the first wave of the COVID-19 pandemic in March 2020, experienced physicians anecdotally reported multiple attempts, decreased insertion durations, and greater need for replacement of arterial lines in patients with COVID-19 due to persistent thrombosis. Because invasive procedures in patients with COVID-19 may increase the risk for caregiver infection, better defining difficulties in maintaining arterial lines in COVID-19 patients is important. We sought to explore the association between COVID-19 infection and arterial line thrombosis in critically ill patients.

METHODS: In this primary exploratory analysis, a multivariable Fine-Gray subdistribution hazard model was used to retrospectively estimate the association between critically ill COVID-19 (versus sepsis/acute respiratory distress syndrome [ARDS]) patients and the risk of arterial line removal for thrombosis (with arterial line removal for any other reason treated as a competing risk). As a sensitivity analysis, we compared the number of arterial line clots per 1000 arterial line days between critically ill COVID-19 and sepsis/ARDS patients using multivariable negative binomial regression.

RESULTS: We retrospectively identified 119 patients and 200 arterial line insertions in patients with COVID-19 and 54 patients and 68 arterial line insertions with non–COVID ARDS. Using a Fine-Gray subdistribution hazard model, we found the adjusted subdistribution hazard ratio (95% confidence interval [CI]) for arterial line clot to be 2.18 (1.06–4.46) for arterial lines placed in COVID-19 patients versus non–COVID-19 sepsis/ARDS patients (P = .034). Patients with COVID-19 had 36.3 arterial line clots per 1000 arterial line days compared to 19.1 arterial line clots per 1000 arterial line days in patients without COVID-19 (adjusted incidence rate ratio [IRR] [95% CI], 1.78 [0.94–3.39]; P = .078).

CONCLUSIONS: Our study suggests that arterial line complications due to thrombosis are more likely in COVID-19 patients and supports the need for further research on the association between COVID-19 and arterial line thrombosis in critically ill patients.

KEY POINTS

- Question: Is there an increased subdistribution hazard of arterial line-associated thrombosis and subsequent arterial line dysfunction in intensive care unit (ICU) patients with COVID-19 compared to ICU patients with non–COVID-19–related sepsis/ARDS?
- Findings: An increased subdistribution hazard of arterial line dysfunction requiring replacement due to thrombosis was detected in COVID-19 patients in our study compared to non–COVID-19 sepsis/ARDS patients in our primary analysis, but this finding was not robust to a sensitivity analysis estimating the incidence rate ratio of arterial line-associated thrombosis.
- Meaning: Larger prospective studies are warranted regarding whether ICU patients with COVID-19 have a greater subdistribution hazard of arterial line dysfunction due to thrombosis.
Arterial lines are commonly used in the intensive care unit (ICU) and may require replacement in the setting of thrombosis or malfunction. A 2014 Cochrane review found that most arterial lines fail after 36 to 158 hours with failure defined as pressure waveform dampening or catheter clotting. During the March–June 2020 wave of the COVID-19 pandemic, anecdotal observations suggested that arterial line replacements due to failure were more frequent in patients with COVID-19 than in non–COVID-19 ICU patients. In addition, senior clinicians in our hospital noted that arterial lines were more difficult to place and required a greater number of attempts than a typical ICU patient despite initial blood return and ultrasound confirmation of needle position. These repeated attempts led to clinicians spending long periods of time in patient rooms placing arterial lines and/or troubleshooting dysfunctional lines increasing their exposure to the SARS-COV-2 virus.

One possibility explaining the observed increased failure rate of arterial lines in COVID-19 ICU patients is a hypercoagulable state that drives increased rates of arterial thrombosis. Existing evidence finds an increased incidence of thromboembolic events in patients with COVID-19, and in particular those who require ICU care. Although the mechanisms underlying this hypercoagulable state are incompletely understood, the inflammatory and hypercoagulable state caused by COVID-19, characterized by elevated coagulation parameters, may play a role. Although the increased incidence of venous and arterial thromboembolic events has been well documented in patients with COVID-19, data on thrombosis of arterial lines are mostly confined to case reports and case series. The primary aim of this exploratory study was to test the hypothesis that arterial line dysfunction and thrombosis are associated with COVID-19 infection in critically ill patients. Our primary analysis targeted the subdistribution hazard (primary analysis) and incidence rate (sensitivity analysis) of arterial line dysfunction requiring replacement due to thrombosis in patients with COVID-19 infection versus those with sepsis/ARDS. Our exploratory secondary aims were to examine potential associations between different anticoagulation strategies, the subdistribution hazard of arterial line-associated thrombosis, and the incidence rate of arterial lines placed, time to arterial line removal for any reason, odds of removal for clot, and the number of arterial line insertion attempts in COVID-19 patients.

METHODS
We performed a retrospective cohort study of all patients with COVID-19 in the ICU at Brigham and Women’s Hospital (BWH) or its affiliates (Brigham and Women’s Faulkner Hospital and North Shore Medical Center) who were monitored with an arterial line at any time during the first wave of the COVID-19 pandemic (March 2020 and May 2020). Eligible patients were identified by searching the electronic health record (EHR) for an arterial line billing code from March 2020 to May 2020. The study was approved by the Institutional review board (IRB) and the requirement for written informed consent was waived by the IRB. SARS-COV-2 infection was determined by positive reverse-transcription polymerase chain reaction on nasopharyngeal or endotracheal samples. Comparison patients without COVID-19 were identified through the registry of critical illness (RoCI), a collated database and biorepository of ICU patients at BWH. Patients from the RoCI database were included in reverse chronological order starting March 2018 and included if their ICU diagnosis was sepsis or ARDS and if they had an arterial line placed during their ICU course. RoCI patients were included from March 2018 to May 2020. Patients included in the control group from the first COVID-19 wave tested negative for SARS-CoV-2 by PCR. Arterial lines were placed primarily using 20-gauge Becton-Dickinson Incite Autoguard Winged Catheters and occasionally the Arrow Radial Artery Catheterization Set. A guidewire was not routinely used. All lines were placed using Brigham and Women’s standardized procedures. The radial artery was the preferred and most commonly cannulated site. See Supplemental Digital Content 1, Supplemental Material 1, http://links.lww.com/AA/E42 for specific details on arterial line insertion and management.
Data extracted from the EHR included vital status, age on ICU admission, date of birth, and body mass index (BMI). Data collated by manual extraction included date of ICU admission and SARS-CoV-2 infection, history of clotting disorder, history of hypercoagulability, the presence of deep vein thrombosis (DVT) or pulmonary embolism (PE), and renal replacement therapy (RRT) during admission. For each patient, information about every unique arterial line was recorded, including anatomic location, the number of insertion attempts, D-Dimer at time of placement, duration of line (in days) inclusive of placement date, reason for line removal, and D-dimer at removal. The reason for removal of each arterial line was reviewed. The reason for removal was defined as thrombosis if thrombosis was seen on ultrasound, dampening of the arterial line waveform occurred, or resistance to manual flushing or blood withdrawal difficulties was experienced. We also recorded data on anticoagulant use before admission and indication, agent and intensity of anticoagulation while admitted, and any thrombotic events. For the analysis, the individual arterial lines were stratified based on the highest dose of anticoagulation.

Anticoagulant regimens were defined as standard prophylaxis, intermediate prophylaxis, and treatment dosing. Standard prophylactic dosing was defined as enoxaparin 40 mg daily (or 30 mg adjusted for renal impairment) or heparin 5000 units (U) every (Q) 8 hours (h) (for average weight patients). For obese patients defined as ≥120 kg or BMI ≥35, enoxaparin 40 mg twice daily (BID), enoxaparin 0.5 mg/kg daily (max dose 100 mg daily), or heparin 7500 U Q 8 hours was recommended. For low body weight <50 kg patients, enoxaparin 30 mg daily or heparin 5000 U BID to three times daily (TID) was recommended. Intermediate prophylactic anticoagulation included enoxaparin 40 mg BID and heparin 7500 U TID (average weight patients). For obese patients, enoxaparin 0.5 mg/kg BID (max dose 100 mg BID) or heparin 10,000 U TID was recommended. For low body weight patients, enoxaparin 30 mg BID or heparin 7500 U TID was recommended. Therapeutic anticoagulation was defined as enoxaparin 1 mg/kg BID, heparin infusion (targeting aPTT 1.5–2× baseline), apixaban 5 mg BID or 10 mg BID, rivaroxaban 15 mg or 20 mg daily, and warfarin (international normalized ratio [INR] goal >2.0). Apixaban 2.5 mg BID was considered prophylactic, unless age, weight, and renal function called for reduction of dosing in which case it was considered therapeutic. Notably, the institutions included in this study implemented intermediate-dose thrombosis prophylaxis for COVID-19 ICU patients (1.5–2× the standard anticoagulant dose) midway through the study period on April 24, 2020.

### Statistical Analysis

The magnitude and direction of the differences in demographics, comorbidities, length of ICU stay, and death between COVID-19 ICU and sepsis/ARDS ICU patients were quantified as standardized differences. Standardized differences with magnitude ≥0.1 were taken to indicate a notable difference between groups. Demographics, comorbidities, length of ICU stay, and death were also compared between groups using 2-sample t-tests or Wilcoxon rank-sum tests for continuous variables, and χ² or Fisher exact tests for nominal categorical variables. For the primary analysis, an extension of the multivariable Fine-Gray subdistribution hazard model for clustered data (here, multiple arterial lines per patient) was used to estimate the association between arterial lines placed in COVID-19 patients versus those with non–COVID-19 sepsis/ARDS and the subdistribution hazard of arterial line removal for clot while accounting for arterial line removal for any other reason (eg, ICU discharge and patient death) as a competing risk.

As a sensitivity analysis for the primary analysis, the number of arterial line clots observed per 1000 arterial line days was compared between COVID-19 ICU and non–COVID-19 sepsis/ARDS ICU patients using multivariable negative binomial regression. A multivariable Fine-Gray subdistribution hazard model for clustered data was used to estimate the association between arterial lines placed in COVID-19 ICU patients before the anticoagulation protocol change versus COVID-19 ICU patients after the anticoagulation protocol change versus non–COVID-19 sepsis/ARDS ICU patients and the subdistribution hazard of arterial line removal for clot.

A multivariable Fine-Gray subdistribution hazard model for clustered data was also used to estimate the association of treatment versus intermediate versus prophylactic anticoagulation (defined as the maximum level while each line was in place) with the subdistribution hazard of arterial line removal for clot among lines placed in COVID-19 ICU patients during which anticoagulation did not change beyond one level (n = 164 arterial lines). The time to arterial line removal for any reason was compared between arterial lines placed in COVID-19 ICU versus non–COVID-19 sepsis/ARDS ICU patients using multivariable Cox proportional hazards regression with cluster robust standard errors. Multivariable logistic regression with cluster robust standard errors was used to estimate the association between arterial lines placed in COVID-19 ICU versus sepsis/ARDS ICU patients and the odds of clot as reason for removal. The number of arterial line insertion attempts was compared between arterial lines placed in COVID-19 ICU versus sepsis/ARDS ICU patients using multivariable
zero-truncated Poisson regression (where >5 attempts were analyzed as 5 attempts) with cluster robust standard errors. The association between COVID-19 ICU versus sepsis/ARDS ICU patients and the incidence rate of arterial line placement was estimated using multivariable zero-truncated Poisson regression. All regression models included covariates for patient age, sex, BMI, and the presence of hypercoagulable diseases excluding obesity. The proportional subdistribution hazards assumption of each Fine-Gray model was assessed using a score test based on modified weighted Schoenfeld residuals. The proportional hazards assumption of the Cox model was evaluated using a score test based on scaled Schoenfeld residuals. For the count outcome models, overdispersion was assessed via estimation of the negative binomial dispersion parameter. Count outcomes were modeled using Poisson regression when there was no evidence of overdispersion, and with negative binomial regression when overdispersion was detected. A χ² test was used to assess whether D-dimer ≥500 ng/mL (considered clinically abnormal) at insertion of the patient’s first arterial line was associated with the development of least one arterial line removal for clot among COVID-19 ICU patients. All statistical hypothesis tests were evaluated at a 2-sided alpha level of 0.05 with no correction for multiple testing given the exploratory nature of the study. Statistical analyses were performed using SAS software version 9.4 (SAS Institute) and the crrSC package implemented in R software version 4.2.0 (R Foundation for Statistical Computing).

No a priori power calculation was performed. However, per recommendation by Althouse, we calculated our power to detect a hazard ratio of 1.3 for arterial line removal due to clot for COVID-19 ICU versus sepsis/ARDS ICU observations with the study sample size and observed outcome incidence. With 200 arterial lines in COVID-19 ICU patients, 68 sepsis/ARDS ICU arterial lines, and an overall 29.5% incidence of arterial line removal for clot, we had 17% power to detect a hazard ratio of 1.3 at a 2-sided alpha level of 0.05 using a Cox proportional hazards model.

RESULTS

Patient selection and inclusion for the study are outlined in Figure 1. One hundred and nineteen patients (receiving 200 arterial lines) with COVID-19 and 54 patients with sepsis or ARDS (receiving 68 arterial lines) were included in the final analysis. Patient demographics, comorbidities, length of ICU stay, and death within 45 days of ICU admission are presented in Table 1. A significant proportion of the COVID-19 cohort met the definition for clinical ARDS.

Standardized differences between COVID and non-COVID cohorts with absolute value ≥0.1 include: history of known clotting disorder, hypercoagulable diseases (defined by thrombophilia, cancer, and history of DVT/PE/stroke) in the absence or presence of obesity, history of DVT, and RRT use. ICU length of stay was longer in the COVID-19 ICU versus sepsis/ARDS ICU group (16 [8–25] vs 12 [7–18] days; standardized difference, 0.325). The incidence of death within 45 days of ICU admission did not differ between groups (42.9% for COVID vs 44.4% for non–COVID-19 cohort).

The cause-specific cumulative incidence of arterial line removal due to clotting in COVID-19 ICU patients and sepsis/ARDS ICU patients is shown in Figure 2. A multivariable Fine-Gray model estimated an adjusted subdistribution hazard ratio (SHR) (95% confidence interval [CI]) for arterial line clot of 2.18 (1.06, 4.46) for arterial lines placed in COVID-19 versus sepsis/ARDS patients (P = .034) (Table 2). In addition, we found an 87% increase in the hazard of an arterial line

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**Figure 1.** Flow diagram of COVID-19 and non–COVID-19 sepsis/ARDS ICU patient selection. ARDS indicates acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit; RoCI, registry of critical illness database.
clot occurring in women compared to men (adjusted SHR [95% CI], 1.87 [1.15–3.05]; \( P = .012 \)) (Table 2). An increased hazard of arterial line removal for clot was also detected between lines placed in COVID-19 ICU patients before the anticoagulation protocol change (n = 143 arterial lines) versus non–COVID-19 sepsis/ARDS patients (adjusted SHR [95% CI], 2.44 [1.18–5.04]; \( P = .016 \)), but not between lines placed in COVID-19 ICU patients after the anticoagulation protocol change (n = 57 arterial lines) versus non–COVID-19 sepsis/ARDS patients (adjusted SHR [95% CI], 1.64 [0.69–3.87]; \( P = .260 \)) (Supplemental Digital Content 1, Table 1, http://links.lww.com/AA/E42).

Figure 2. Plot of cause-specific cumulative incidence of removal of arterial lines due to clot formation for COVID-19 ICU and non–COVID-19 sepsis/ARDS ICU patients. Arterial line removal for reason besides clot was treated as a competing risk. ARDS indicates acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Arterial line characteristics such as the total number of arterial lines needed for a patient during ICU stay, the number of lines removed from presumed clot, and the number of insertion attempts are shown in Table 3. The number of arterial lines placed per 1000 ICU days did not differ between COVID and non-COVID patients (91.4 vs 86.5, respectively; adjusted incidence rate ratio [IRR] [95% CI], 1.05 [0.80–1.40]; \( P = .711 \)). The median (first quartile [Q1] and third quartile [Q3]) longevity of each arterial line also did not differ between COVID and non-COVID patients (6 [3–13] days in COVID-19 ICU patients vs 6.5 [3–10] days in non-COVID patients) (adjusted hazard ratio...
Table 2. Multivariable Fine-Gray Subdistribution Hazard Models for Comparison of Time to Arterial Line Clot Between Arterial Lines Placed in COVID-19 ICU Versus Non—COVID-19 Sepsis/ARDS ICU Patients and Between Anticoagulation Levels Among Lines Placed in COVID-19 ICU Patients

| Parameter                              | Adjusted subdistribution-hazard ratio (95% CI) | P value |
|----------------------------------------|-----------------------------------------------|---------|
| COVID-19 ICU versus non—COVID-19 sepsis/ARDS ICU | 2.18 (1.06–4.46)                              | .034    |
| Age (per 1 y increase)                 | 1.00 (0.98–1.02)                              | .970    |
| Female versus male                     | 1.87 (1.15–3.05)                              | .012    |
| Body mass index (per 1 kg/m² increase) | 1.01 (0.97–1.04)                              | .760    |
| Hypercoagulable diseases excluding obesity | 0.93 (0.54–1.59)                            | .780    |
| Intermediate versus prophylaxis        | 0.60 (0.30–1.21)                              | .150    |
| Treatment versus prophylaxis           | 0.30 (0.13–0.72)                              | .007    |
| Treatment versus intermediate          | 0.50 (0.19–1.31)                              | .160    |
| Age (per 1 y increase)                 | 1.00 (0.98–1.03)                              | .790    |
| Female versus male                     | 1.74 (0.85–3.56)                              | .130    |
| Body mass index excluding obesity      | 0.99 (0.94–1.05)                              | .800    |
| Hypercoagulable diseases               | 1.03 (0.48–2.23)                              | .930    |

Multivariable Fine-Gray subdistribution hazard models for clustered data were used to compare the subdistribution hazard of arterial line removal for clot between (1) arterial lines placed in COVID-19 ICU versus non—COVID-19 sepsis/ARDS ICU patients and (2) maximum anticoagulation level for lines placed in COVID-19 ICU patients during which anticoagulation did not change beyond one level (n = 164 arterial lines). These Fine-Gray models accounted for arterial line removal for any reason besides clot as a competing risk, as well as the correlation between multiple arterial lines from the same patient.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

...and intermediate dose anticoagulation (adjusted SHR [95% CI], 0.50 [0.19–1.31]; P = .160) (Table 2). The length of arterial line patency and percentage of arterial lines removed for presumed clot stratified by anticoagulation strategy and COVID-19 disease status are shown in the Supplemental Digital Content 1, Table 2, http://links.lww.com/AA/E42. No association was detected between D-dimer level ≥500 ng/mL at first arterial line insertion and the development of arterial line clot in patients with COVID-19 in the ICU (P = .185).

DISCUSSION

High rates of arterial line failure have been anecdotally observed among COVID-19 ICU patients since the beginning of the pandemic. In this retrospective study, we found that COVID-19 ICU patients had an increased hazard of arterial line thrombosis (adjusted SHR [95% CI], 2.18 [1.06–4.46]) when compared with non—COVID-19 patients (P = .034), with 2.56 times the odds of arterial line removal for confirmed or clinically suspected clotting in a COVID-19 patient compared to a non—COVID-19 patient (95% CI, 1.18–5.52; P = .017). The incidence rate of arterial line clots did not differ between COVID-19 and non—COVID-19 ICU patients, although the IRR point estimate was clinically relevant (36.3 arterial clots per 1000 arterial line days versus 19.1 arterial line clots per 1000 arterial line days; adjusted IRR [95% CI], 1.78 [0.94–3.39]; P = .078). We found no evidence for a difference in the number of arterial lines placed per 1000 ICU days between the aforementioned groups (adjusted IRR [95% CI], 1.05 [0.80–1.40]; P = .711).

Although exploratory only, our data suggest a relationship between COVID-19 infection and arterial line dysfunction. Because the number of insertion attempts between patients with COVID-19 versus non—COVID-19 did not differ, procedural vascular trauma during placement was unlikely to have contributed to the increased risk of line failure from thrombosis. However, 5 COVID-19 patients required 5 or more attempts for arterial line placement compared to no patients in our non—COVID-19 ICU cohort. As both patient discomfort and the risk of caregiver infection are increased with the multiple attempts, increased difficulty with arterial line insertion is clinically relevant and hopefully will drive further investigations to understand the underlying pathophysiology and develop countermeasures. Finally, while general population data on sex-based differences in venous thromboembolism risk are mixed, prior data indicate that male sex is associated with greater arterial line patency. In our model, female sex was an independent risk factor for arterial line failure. The 1.87 adjusted SHR of arterial line clot for women in our study was higher than previously reported and should also promote...
The role of anticoagulation and its intensity in COVID-19 is still under investigation. The INSPIRATION Trial found no difference in venous or arterial events, extracorporeal membrane oxygenation (ECMO) use, or mortality at 30 days between COVID-19 patients in the ICU using an intermediate anticoagulation strategy compared to standard prophylactic anticoagulation. The National Institutes of Health (NIH) sponsored Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE (ACTIV-4a), in combination with a Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP

Table 3. Comparison of Arterial Line Characteristics Between COVID-19 ICU and Non–COVID-19 Sepsis/ARDS ICU Patients

| Characteristic                        | COVID-19 ICU | Non–COVID-19 sepsis/ARDS ICU | Adjusted effect size (95% CI) | P value |
|---------------------------------------|--------------|------------------------------|-------------------------------|---------|
| Arterial line level                   |              |                              |                               |         |
| Time to arterial line removal for any reason (d), median (Q1–Q3) | 6 (3–13)    | 6.5 (3–10)                   | 0.82 (0.62–1.09)*             | .170    |
| Clot as reason for removal, n (%)     | 68 (34.0)    | 11 (16.2)                    | 2.56 (1.18–5.52)*             | .017    |
| Number of insertion attempts, n (%)   |              |                              | 0.92 (0.60–1.42)*             | .720    |
| 1                                     | 126 (68.1)   | 42 (62.7)                    |                               |         |
| 2                                     | 33 (17.8)    | 15 (22.4)                    |                               |         |
| 3                                     | 15 (8.1)     | 6 (9)                        |                               |         |
| 4                                     | 6 (3.2)      | 4 (6)                        |                               |         |
| 5                                     | 5 (2.7)      | 0 (0)                        |                               |         |
| Group level                           |              |                              |                               |         |
| Arterial lines per 1000 ICU days      |              |                              |                               |         |
| n = 2187 ICU days                     | n = 786 ICU days |                             | 1.05 (0.80–1.40)*             | .711    |
| n = 1875 arterial line days           | n = 575 arterial line days |             |                               |         |
| 36.3                                  | 19.1         | 1.78 (0.94–3.39)*            | .078                           |         |

All comparisons were adjusted for age, sex, BMI, and hypercoagulable diseases excluding obesity.

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; Q, quartile.

*Effect size is an adjusted hazard ratio estimated with a multivariable Cox proportional hazards model using cluster robust standard errors.

Effect size is an adjusted odds ratio estimated with a multivariable logistic regression model using cluster robust standard errors.

Effect size is an adjusted incidence rate ratio estimated with a multivariable zero-truncated Poisson regression model using cluster robust standard errors. Placements with >5 attempts were analyzed as 5 attempts.

Effect size is an adjusted incidence rate ratio obtained from a multivariable zero-truncated Poisson regression model.

Effect size is an adjusted incidence rate ratio obtained from a multivariable negative binomial regression model.

Figure 3. Plot of cause-specific cumulative incidence of removal of arterial lines for clot for COVID-19 ICU patients stratified by maximum anticoagulation strategy used. Arterial line removal for reason besides clot was treated as a competing risk. COVID-19 indicates coronavirus disease 2019; ICU, intensive care unit.
CAP) and Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC), multiplatform trial, which assessed full dose anticoagulation versus standard prophylactic dose in COVID-19 ICU patients, found no benefit of therapeutic dose anticoagulation in this population. Current American Society of Hematology guidelines suggest using standard prophylactic anticoagulation over intermediate or treatment dosing for COVID-19 ICU patients. Other trials are currently investigating the optimal anticoagulation regimen for COVID-19 ICU patients.

Our data suggest that treatment dose anticoagulation compared with standard prophylaxis dose led to longer duration of functioning of arterial lines without clotting. We observed no significant difference between intermediate versus treatment dosing or intermediate versus prophylactic anticoagulation dosing on arterial line functioning. Although preserving arterial line function is not itself a compelling reason for full anticoagulation, it is a potentially relevant consideration given the risk of caregiver infection with invasive procedures.

Before the COVID-19 pandemic, data were conflicted on the benefit of heparin flushes compared to normal saline flushes in maintaining the functionality of arterial catheters. A 2020 observational cohort study found improved arterial line patency duration in COVID-19 patients when using low-dose heparinized saline, suggesting a potential benefit in this patient population. However, the effects of systemic or local anticoagulation on arterial lines have not been further tested in large, prospective studies.

Our study has several limitations. The small and retrospective nature limited our ability to detect small effect sizes and raises the possibility of confounders that may have affected the effect we observed. The limited sample size posed challenges to extensive, granular confounder adjustment given low prevalence comorbidities and concerns for overfitting. Rapidly evolving protocols during the first COVID wave, such as an institutional shift in April 2020 to intermediate dose prophylactic anticoagulation for all COVID-19 ICU patients, may also have confounded our results. The impact of other evolving COVID-19 therapeutics on our outcome was not assessed. Although we sought contemporaneous non–COVID-19 ICU patients, this comparator group was comprised primarily of patients hospitalized before the onset of the pandemic due to suspension of most non–COVID-19 studies at the beginning of the pandemic. Finally, our study focused only on the first COVID wave, and subsequent waves may have had different clinical characteristics. Given these limitations, our results should be interpreted as hypothesis generating.

In conclusion, patients with severe COVID-19 frequently require arterial line placement. Because of the risk of infection, minimizing provider exposure while placing, managing, and replacing arterial lines is important to reducing patient to caregiver infection. Our finding is exploratory only but suggests an increased subdistribution hazard of arterial line removal for clot in COVID-19 ICU versus non–COVID-19 sepsis/ARDS ICU patients. Treatment dose anticoagulation compared to prophylactic dose resulted in a significant decrease in the subdistribution hazard of arterial line removal for clot. Further studies should be undertaken to investigate the association of COVID-19 with arterial line thromboses and the role anticoagulation in minimizing arterial line dysfunction in patients with COVID-19.

DISCLOSURES
Name: Rebecca L. Zon, MD.
Contribution: This author helped with development of study concept, data collection, and writing contribution.
Conflicts of Interest: R. L. Zon is a consultant and stockholder for Amagma Therapeutics.
Name: Lauren E. Merz, MD, MSc.
Contribution: This author helped with data collection and writing contribution.
Conflicts of Interest: None.
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Name: Jean M. Connors, MD.
Contribution: This author helped with the development of the study concept and writing contribution.
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Name: Gyorgy Frendl, MD, PhD.
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REFERENCES

1. Robertson-Malt S, Malt GN, Farquhar V, Greer W. Heparin versus normal saline for patency of arterial lines. Cochrane Database Syst Rev. 2014;5:CD007364.
2. Klok FA, Kruij MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–147.
3. Moll M, Zon RL, Sylvester KW, et al. VTE in ICU patients with COVID-19. Chest. 2020;158:2130–2135.
4. Litjoh JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost. 2020;18:1743–1746.
5. Spieza L, Boscolo A, Poleto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120:998–1000.
6. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. Clin Chem Lab Med. 2020;58:1116–1120.
7. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136:489–500.
8. Dolinay T, Kim YS, Howrylak J, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med. 2012;185:1225–1234.
9. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399–424.
10. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Simul Computat. 2009;38:1228–1234.
11. Zhou B, Fine J, Latouche A, Labopin M. Competing risks regression for clustered data. Biostatistics. 2012;13:371–383.
12. Zhou B, Fine J, Laird G. Goodness-of-fit test for proportional subdistribution hazards model. Stat Med. 2013;32:3804–3811.
13. Althouse AD. Post hoc power: not empowering, just misleading. J Surg Res. 2021;259:A3–A6.
14. Montagnana M, Favaloro EJ, Franchini M, Guidi GC, Lippi G. The role of ethnicity, age and gender in venous thromboembolism. J Thromb Haemost. 2010;29:489–496.
15. American Association of Critical-Care Nurses. Evaluation of the effects of heparinized and nonheparinized flush solutions on the patency of arterial pressure monitoring lines: the AACN thunder project. Am J Crit Care. 1993;2:3–15.
16. Sadeghipour P, Talasaz AH, Rashidi F, et al; INSPIRATION Investigators. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. JAMA. 2021;325:1620–1630.
17. Investigators R-C, Investigators AC-a, Investigators A, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. N Engl J Med. 2021;385:777–789.
18. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021;5:872–888.
19. Maurer LR, Luckhurst CM, Hamidi A, et al. A low dose heparinized saline protocol is associated with improved duration of arterial line patency in critically ill COVID-19 patients. J Crit Care. 2020;60:253–259.