OBJECTIVES: The presence of spontaneous echo contrast on ultrasoundography is a predisposition to increased thromboembolic risk. The purpose of this study was to assess for the prevalence and consequences of spontaneous echo contrast on point-of-care vascular ultrasound in coronavirus disease 2019.

DESIGN, SETTING AND PATIENTS: This was a retrospective cohort study of 39 adult patients admitted to the ICU with a confirmed coronavirus disease 2019 diagnosis at a large tertiary-care academic medical center. Patients were included if they had undergone a vascular ultrasound examination during their ICU admission. Overall, 48 venous ultrasound studies among the 39 patients were reviewed in blinded fashion by two reviewers for the presence of venous spontaneous echo contrast, and charts were analyzed for laboratory data and outcomes.

MEASUREMENTS AND MAIN RESULTS: Spontaneous echo contrast correlated with serum viscosity (mean values of 2.64, 2.54, and 2.04 cP for dense spontaneous echo contrast, spontaneous echo contrast, and no spontaneous echo contrast, respectively, with a p value of 0.0056 for spontaneous echo contrast compared with negative spontaneous echo contrast) and hyperfibrinogenemia (mean values of 726.6, 668.5, and 566.6 mg/dL for dense spontaneous echo contrast, positive spontaneous echo contrast, and negative spontaneous echo contrast, respectively, with a p value of 0.0045 for dense spontaneous echo contrast compared with negative spontaneous echo contrast). About 36% of patients with dense spontaneous echo contrast and 33% of individuals with positive spontaneous echo contrast experienced significant clotting events compared with 17% of those with negative spontaneous echo contrast. A total of 19% of patients with spontaneous echo contrast suffered a cardiac arrest following a major clotting event, and there were no cardiac arrests from clotting events in the negative spontaneous echo contrast group. There was no association with the presence of spontaneous echo contrast and right or left cardiac function or other laboratory values such as D-dimer, external thromboelastometry - maximum lysis, platelet counts, C-reactive protein, or interleukin-6.

CONCLUSIONS: Point-of-care venous ultrasonography is easily performed and reliably interpreted for visualization of spontaneous echo contrast. The presence of spontaneous echo contrast in patients with coronavirus disease 2019 is associated with hyperviscosity and increased rates of thrombotic events and complications.

KEY WORDS: coronavirus disease 2019; fibrinogen; point of care; thrombosis; ultrasonography; viscosity
The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) can cause significant multiple organ dysfunction. COVID-19 has been associated with significant hypercoagulable manifestations and high rates of thrombotic complications that are linked to higher morbidity and mortality (1–4). Given this, healthcare systems have implemented various protocols in an attempt to identify patients at risk for the development of thrombotic complications. Many of these protocols rely on laboratory markers such as the d-dimer. Elevated d-dimer values are routinely used for the diagnosis of venous thromboembolism in clinical practice. However, d-dimer values may also be elevated due to a variety of other etiologies such as proinflammatory states, acute aortic dissection, pregnancy, and advanced age (1, 5).

Recently, institutions have also begun to assess whether the presence of hyperviscosity in SARS-CoV-2 infected patients is associated with the development of vascular thrombosis; this has been of particular interest given the high rates of clotting in COVID-19 patients despite ongoing therapeutic anticoagulation (6). Serum viscosity laboratory tests may not, however, be readily available in all hospital systems. Furthermore, when serum viscosity is markedly elevated, the sample may clot and break the viscometer, thus inhibiting adequate readings, a phenomenon that has been observed in several cases in our practice. Therefore, other techniques are needed to improve our ability to identify at-risk patients.

Evaluation for the presence of spontaneous echo contrast (SEC) on point-of-care ultrasound examination is a promising strategy and may provide a useful alternative to the laboratory measurements. Ultrasound technology has been used successfully to identify patients with active thromboses and those at risk for clotting events. Historically, the presence of SEC on an ultrasonographic study indicates decreased blood flow velocity and rheological alterations that may serve as a surrogate marker for coagulopathy. On ultrasonographic B-mode imaging, SEC is generated by backscattering from macromolecules such as fibrinogen giving an appearance of swirling blood flow or smoke. Clinically, SEC presence has been noted in patients with depressed cardiac output rendering them at risk for left ventricular (LV) thrombus formation, deep veins in cancer patients making them at risk for the development of deep venous thrombosis (DVT), internal jugular veins with notably increased risk for ischemic stroke, and in the left atrial appendage of patients with atrial fibrillation indicating an increased risk for thromboembolism (7–11).

In this context, the primary aim of this study was to assess for the association between the presence of SEC on bedside vascular ultrasound with hyperviscosity and development of thrombotic complications in COVID-19 patients admitted to the ICU.

**MATERIALS AND METHODS**

**Study Population**

This was a retrospective cohort study of 39 adult patients admitted to the ICU with a diagnosis of COVID-19 between March and May 2020. The study was performed at three hospitals from a large urban academic medical center. The ICUs involved in the study were dedicated exclusively to the care of COVID-19 patients. Patients were included if they were over the age of 18, admitted to the ICU, had vascular ultrasound studies available for review, and had a confirmed diagnosis of COVID-19. Patients who tested negative for SARS-CoV-2 or who did not have saved ultrasound studies for review were excluded. This study was approved by the institutional review board of Emory University.

**Clinical and Laboratory Assessment**

Chart review was performed for all of the patients who had venous ultrasound studies available for assessment. Patient data, including sociodemographic information, clinical data, and laboratory data, were obtained from the electronic medical record (EMR; Cerner Millenium EMR, Kansas City, MO). Laboratory data used for analysis included platelet counts, fibrinogen, external thromboelastometry - maximum lysis (EXTEM-ML), d-dimer, C-reactive protein (CRP), interleukin-6 (IL-6) level, and serum viscosity when available. Laboratory data were noted at the time of venous ultrasound study as well as maximum levels during the patient’s ICU admission. Sociodemographic characteristics such as age and sex were included. Mortality, patients’ length of hospital admission, requirements for vasopressors, renal replacement therapy for acute kidney injury, thrombotic events, and mechanical ventilation and length of intubation were also included in the analysis.
Furthermore, the amount of positive end-expiratory pressure and \( \text{Pao}_2 \) to \( \text{FiO}_2 \) (P/F) ratios was calculated for the day the venous ultrasound was performed.

**Sonographic Protocol**

To minimize the exposure risks to technicians, formal venous duplex studies were being deferred, as point-of-care venous ultrasound studies were already routinely performed on these patients, and video clips and images were saved for radiologist review as needed. All ultrasound studies were performed by critical care physicians with experience in point-of-care ultrasound. Sonographic examinations were performed with a high-frequency, linear transducer. In order to achieve uniformity, at the start of the pandemic, our institution implemented protocols detailing performance and reporting of point of care venous ultrasound studies. Images and video clips were saved for all vascular examinations. The ultrasound examination included imaging of deep venous structures including the internal jugular and femoral veins, and the sapheno-femoral junction.

All ultrasound studies were analyzed independently by two reviewers considered experts in point-of-care ultrasound. The reviewers were blinded to clinical information and judged the presence or absence of SEC from all participants using B-mode movie files and still images. Reviewers labeled studies as positive if there was echogenicity of the blood flow that was minimal or transiently present within the venous lumen at optimal gain settings (Video 1, http://links.lww.com/CCX/A470). Studies were considered to have dense SEC if there was a dense swirling pattern throughout the cardiac cycle or presence of intense echogenicity within the venous lumen (Video 2, http://links.lww.com/CCX/A471). Studies were labeled as having no SEC when there was no visible swirling material or there was a lack of blood flow echogenicity within the vessel (Video 3, http://links.lww.com/CCX/A472). Disagreement between the reviewers was subject to a third-party evaluation for the final assessment of the presence of venous SEC in general and denser SEC specifically.

**Statistical Analysis**

Interrater variability was measured using kappa Cohen statistics to evaluate correlation and agreement between the two point of care ultrasound (POCUS) reviewers for identifying SEC. Means and standard deviation of all laboratory data were calculated for patients with SEC and without SEC with an additional subgroup analysis for patients with notably dense SEC. The comparison of means between these groups was calculated by a \( t \) test. Operating characteristics comprised of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and odds ratios (ORs) were evaluated. Differences or correlations with \( p < 0.05 \) were considered to be statistically significant. Statistical analyses were performed using the GraphPad Software (San Diego, CA).

**RESULTS**

Thirty-nine patients with a mean age of 59.4 years were included in the study. Twenty-two (56%) were male and seventeen (44%) were female (Table 1). Overall, 14 of 39 patients (36%) died of which four of 14 (29%) suffered a cardiac arrest from a fatal clotting event. Ten patients (26%) experienced significant thrombotic events. These events were confirmed by either imaging studies or autopsy reports and ranged from DVT to visible thrombus in the extracorporeal membrane oxygenation circuit or cardiac arrest from massive pulmonary embolism. Of these, eight patients were on therapeutic anticoagulation with either enoxaparin, heparin, apixaban, or argatroban, and two patients were on prophylactic doses of enoxaparin.

There was an almost perfect agreement between the two reviewers for identifying SEC with 91% agreement and a kappa coefficient of 0.806. Overall, there were 48 venous ultrasound studies analyzed among the 39 patients. About 26 of these studies across 21 patients were positive for SEC (54%), and of these, 11 patients (23% of overall scans, 42% of those with positive SEC) were noted to have dense SEC. About 22 of 48 scans (46%) were negative for SEC, with 18 of the 39 patients having ultrasound studies negative for SEC.

The grade of SEC correlated with serum viscosity and fibrinogen levels. The mean viscosity levels obtained within 48 hours of the ultrasound study of patients with dense SEC, SEC, and negative SEC were 2.64, 2.54, and 2.04, respectively (Fig. 1). The difference in these values was statistically significant (\( p \) value of 0.05 for dense SEC vs negative SEC with area under the receiver operating characteristic...
The average fibrinogen levels were 726.6, 668.5, and 566.6 mg/dL for dense SEC, SEC, and negative SEC, respectively (Fig. 2). The difference in these values was also statistically significant for dense SEC versus negative SEC (p value of 0.045) with a trend for increased levels with SEC versus negative SEC (p value of 0.077). There was no statistical difference between the groups and levels of CRP, IL-6, EXTEM-ML, platelets, or d-dimer. There was also no difference in the vasoactive ionotrope score, rates of new renal replacement therapy for acute kidney injury, or P/F ratios between the groups (Table 2).

About four of 11 individuals (36%) with dense SEC experienced significant clotting events, seven of 21 (33%) with positive SEC experienced clotting events, and three of 18 patients (17%) with negative SEC experienced clotting events. Furthermore, 18.1% of patients with dense SEC and 19% of patients with SEC experienced cardiac arrest following a major clotting event. There were no cardiac arrests from a clotting event in the negative SEC group. There was no overall difference in mortality rates between the positive SEC (38%) and the negative SEC group (39%).

The sensitivity for SEC for clotting events was 0.7 with a specificity of 0.52, PPV of 33%, NPV of 83%,

### TABLE 1.
Descriptive Statistics of Patients (n = 39)

| Clinical Characteristics | Negative SEC (n = 18) | SEC (n = 21) | Dense SEC (n = 11) | Total (n = 39) |
|--------------------------|----------------------|-------------|------------------|---------------|
| Patient variable         |                      |             |                  |               |
| Age (yr), mean (sd)      | 59 (9.6)             | 59.8 (18.5) | 54.1 (12.3)      | 59.4 (14.9)   |
| Gender, n (%)            |                      |             |                  |               |
| Male                     | 11 (61.1)            | 11 (52.3)   | 6 (54.5)         | 22 (56.4)     |
| Female                   | 7 (38.9)             | 10 (47.6)   | 5 (45.5)         | 17 (43.6)     |
| Clinical outcome, mean (sd) |                  |             |                  |               |
| Hospital length of stay  | 34.6 (19.6), n = 18  | 23.0 (10.3), n = 21 | 19.6 (8.2), n = 11 | 28.4 (16.2) |
| Outcome, n (%)           |                      |             |                  |               |
| Discharged               | 13 (72.2)            | 12 (57.1)   | 9 (81.8)         | 25 (64.1)     |
| Died                     | 5 (27.8)             | 9 (42.9)    | 2 (18.2)         | 14 (35.9)     |
| Placed on comfort measures or admitted to hospice | 3 (60.0) | 4 (44.4) | 0 (0.0) | 7 (50.0) |
| Cardiac arrest secondary to catastrophic clotting event | 0 (0.0) | 4 (44.4) | 2 (100) | 4 (28.6) |
| Ventricular tachycardia arrest | 1 (20.0) | 0 (0.0) | 0 (0.0) | 1 (7.1) |
| Refractory shock         | 1 (20.0)             | 1 (11.1)    | 0 (0.0)          | 2 (14.3)      |
| Clotting events, n (%)   |                      |             |                  |               |
| No clotting events       | 15 (83.3)            | 14 (66.7)   | 7 (63.6)         | 29 (74.4)     |
| Significant clotting event | 3 (16.7)           | 7 (33.3)    | 4 (36.4)         | 10 (25.6)     |
| Rates of new renal replacement therapy for acute kidney injury | 8 (50.0), n = 16 | 6 (28.6), n = 21 | 4 (36.0), n = 11 | 14 (37.8), n = 37 |

SEC= spontaneous echo contrast.
+likelihood ratio (LR) of 1.46, and an OR of 2.5 (Table 3). Sensitivity decreased to 0.57 for clotting events for dense SEC; however, specificity increased to 0.68, and there was a +LR of 1.78 and an OR of 2.86. Comparatively, d-dimer elevation more than 3,000 ng/mL had a sensitivity of 0.7, specificity of 0.24, and an OR 0.74 for clotting events. With d-dimer elevation to over 5,000 ng/mL, specificity was 0.28 with an OR of 0.91. Combining dense SEC with a d-dimer greater than 5,000 ng/mL had a specificity of 0.97, a +LR of 6.67, and an OR of 7 for clotting events. Seven of the 10 patients had d-dimer maximal elevation or substantial increase in d-dimer levels the day of the clotting event or in the days following the clotting event. Conversely, of the seven patients with SEC who experienced pathologic clotting, six cases of SEC were evident prior to the event.

**DISCUSSION**

Previous evidence suggests there is an association between SEC and decreased blood flow velocity and increased thrombotic risk in various patient populations (7–11). However, there are no data available regarding the significance of SEC presence in patients infected with SARS-CoV-2. In this study, we show a correlation between SEC and increased rates of clotting events in patients with confirmed diagnosis of COVID-19. Patients with SEC had clotting events twice as often as those patients who were negative for SEC. In addition, dense SEC had even slightly higher rates of pathologic clotting, and all of the patients who had a catastrophic clotting event had SEC present on venous ultrasound, almost all of which were present prior to the cardiac arrest. Furthermore, only three out of the 21 patients with SEC had depressed cardiac function, and multiple patients without SEC had severely depressed LV or right ventricular function on echocardiography. This suggests the presence of SEC in this patient population is not attributable to reduced cardiac function.

Additionally, as the included studies were not performed by POCUS experts, our work supports the feasibility of critical care practitioner performed point-of-care ultrasonography in identifying SEC presence. There was
also excellent interrater agreement with image interpretation for the presence of both SEC and notably dense SEC. This makes venous ultrasound evaluation for SEC easily implementable for multiple levels of POCUS users.

There was also a correlation that was statistically significant between SEC and fibrinogen levels. SEC did not show a similar correlation to other inflammatory markers such as CRP and IL-6, making it less likely SEC is observed simply in the cases of a hyperinflammatory state alone. SEC also correlated with serum viscosity levels in addition to hyperfibrinogenemia and clotting events, suggesting that these facets may be interlinked. Interestingly, one patient was scanned before and after plasmapheresis, and the SEC was notably diminished

TABLE 2.
Laboratory and Clinical Characteristics per Venous Ultrasound Study, Stratified by Point of Care Ultrasound Findings (n = 48)*

| Variable (Reference Range) | Negative SEC (n = 22) | SEC (n = 26) | Dense SEC (n = 11) | p (95% CI) |
|----------------------------|-----------------------|-------------|------------------|------------|
| Serum viscosity (1.4–1.8 Cp) | 2.0 (0.2), n = 12     | 2.5 (0.6), n = 18 | 2.6 (0.7), n = 8 | 0.006      |
| Fibrinogen (200–400 mg/dL) | 567 (169), n = 22     | 669 (211), n = 24 | 727 (214), n = 11 | 0.077, 0.045, |
| CRP (< 10 mg/L)            | 166.8 (109.0), n = 22 | 173.0 (109.7), n = 22 | 238.4 (137.9), n = 11 | 0.852, 0.045, |
| IL-6 (< 1.8 pg/mL)         | 26.6 (27.2), n = 6    | 52.3 (82.5), n = 11 | 60.6 (96.4), n = 5 | 0.363, 0.483, |
| External thromboelastometry - maximum lysis (cutoff) | 4.50 (1.9), n = 4 | 5.0 (3.0), n = 12 | 5.8 (3.9), n = 5 | 0.708, 0.491, |
| Platelets (150–450 1,000 platelets/μL) | 294.2 (96.4), n = 22 | 264.3 (129.0), n = 26 | 253.9 (148.2), n = 11 | 0.364, 0.426, |
| d-dimer (< 250 ng/mL)      | 8,563 (15,634), n = 22 | 7,598 (16,153), n = 25 | 8,077 (17,740), n = 11 | 0.836, 0.939, |
| Vasoactive Inotrope Score  | 39.6 (64.3), n = 19   | 52.8 (88.8), n = 21 | 38.1 (61.3), n = 11 | 0.592, 0.949, |
| Pao2 to Fio2 ratio         | 182.0 (83.3), n = 19  | 142.9 (61.7), n = 22 | 144.2 (57.0), n = 9 | 0.102, 0.175, |
| Positive end-expiratory pressure | 9.5 (3.2), n = 9 | 13.0 (4.2), n = 21 | 13.1 (4.1), n = 19 | 0.005, 0.037, |
| Rates of reduced cardiac function (includes mild, moderate, or severe RV or LV dysfunction) | 2 (16.7%), n = 12 | 3 (20.0%), n = 15 | 2 (22.2%), n = 9 | 0.832, 0.767, |

SEC = spontaneous echo contrast.
*All statistics calculated using two-tailed unpaired t test with Welch correction, where appropriate.
+Bolded value: p < 0.05.
following plasma exchange, going from dense to regular and from being present in nearly all of the venous system to only one deep vein out of the five evaluated sites. Additionally, three patients were scanned following multiple rounds of plasma exchange who were negative for SEC. None of the patients who underwent plasmapheresis developed a clotting event.

In addition, the sensitivity for SEC was the same as for d-dimer elevation over 3,000 ng/mL, which is the cutoff used at our institution for expanding anticoagulation administration regardless of known clotting. The specificity was also higher than this d-dimer threshold. This suggests that visualization of SEC alone could demonstrate a prothrombotic risk and indicate the need for increasing or changing anticoagulation agents. Furthermore, the combination of SEC and a d-dimer level greater than 5,000 ng/mL had a specificity of 0.97 and an OR of 7 for clot development, suggesting that this combined finding should significantly heighten clinical suspicion for hypercoagulopathy and prompt consideration for anticoagulation adjustment. d-dimer elevation tended to lag in our cohort of patients and occur the day of or following clotting events. Conversely, SEC more often preceded episodes of thrombosis. This information has the potential to be critically useful, particularly in these patients who may develop life-threatening clotting events at any point during their hospital course regardless of their current anticoagulation regimen.

Based on the data of this study, patients with COVID-19 had a roughly one in four chance of experiencing a thrombotic event throughout their admission. The combination of SEC and d-dimer elevation increases this a priori identification of patients with clotting events to roughly 70%. The addition of ultrasound examination to the laboratory findings increases the potential likelihood for identifying thromboses, although it is important to note that a sizeable number of patients may be exposed to anticoagulation and potential bleeding risks in the absence of thrombotic disease. Thus, despite the higher risk for thrombosis and pathologic clotting, risks and benefits of empiric anticoagulation should continue to be weighed in patients with COVID-19.

This study has several limitations, including its retrospective design and being performed at one healthcare system. The ultrasound examinations were able to be reviewed at various days during a patient’s hospitalization, so it is unclear whether timing had any significant effect on the results. As it was a retrospective analysis, it is unclear whether there was a certain concern that prompted the performance of each of the ultrasound studies such as new onset hemodynamic instability. This study has several interesting points; however, given the small size and retrospective nature, our conclusions should best serve as hypothesis generating. Additional larger prospective studies will be needed to examine the predictive capacity of SEC in the development of vascular thrombosis.

**CONCLUSIONS**

Point-of-care vascular ultrasound can be easily performed by clinicians at the bedside in the care of COVID-19 patients to identify the presence of SEC.

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**TABLE 3.**

| Variable                      | Sensitivity | Specificity | Positive Predictive Value (%) | Negative Predictive Value (%) | +LR | –LR | OR |
|-------------------------------|-------------|-------------|-------------------------------|-------------------------------|-----|-----|----|
| SEC                           | 0.70        | 0.52        | 33                            | 83                            | 1.46| 0.58| 2.5|
| Dense SEC                     | 0.57        | 0.68        | 36                            | 83                            | 1.78| 0.63| 2.86|
| d-dimer > 3,000               | 0.70        | 0.24        | 24                            | 70                            | 0.92| 1.25| 0.74|
| d-dimer > 5,000               | 0.70        | 0.28        | 70                            | 28                            | 0.97| 1.07| 0.91|
| SEC plus d-dimer > 5,000      | 0.20        | 0.97        | 67                            | 69                            | 6.67| 0.82| 7   |

LR = likelihood ratio, OR = odds ratio, SEC = spontaneous echo contrast.
This may allow treatment teams to implement therapies, as the presence of SEC in the deep venous system of COVID-19 patients is associated with hyperfibrinogenemia, hyperviscosity, and an increased risk for thrombotic complications including fatal clotting events. Identification of patients at risk for the development of such complications is of paramount importance as COVID-19 patients may develop thrombosis while already receiving therapeutic anticoagulation treatment.

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REFERENCES

1. Tang N, Bai H, Chen X, et al: Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18:1094–1099

2. Klok FA, Kruip 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. Levi M, Thachil J, Iba T, et al: Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020; 7:e438–e440

4. Wichmann D, Sperhake JP, Lütgethetmann M, et al: Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. Ann Intern Med 2020; 173:268–277

5. Adam SS, Key NS, Greenberg CS: D-dimer antigen: Current concepts and future prospects. Blood 2009; 113:2878–2887

6. Maier CL, Truong AD, Auld SC, et al: COVID-19-associated hyperviscosity: A link between inflammation and thromboophilia? Lancet 2020; 395:1758–1759

7. Jensen CT, Chahin A, Amin VD, et al: Qualitative slow blood flow in lower extremity deep veins on Doppler sonography: Quantitative assessment and preliminary evaluation of correlation with subsequent deep venous thrombosis development in a tertiary care oncology center. J Ultrasound Med 2017; 36:1867–1874

8. Yasuoka Y, Naito J, Hirooka K, et al: Right atrial spontaneous echo contrast indicates a high incidence of perfusion defects in pulmonary scintigraphy in patients with atrial fibrillation. Heart Vessels 2009; 24:32–36

9. Hsu HY, Chung CP, Chen SY, et al: Spontaneous echo contrast in internal jugular veins: A probable indicator for systemic inflammation and a prothrombotic state. Ultrasound Med Biol 2012; 38:926–932

10. Steinberg EH, Madmon L, Wesolowsky H, et al: Prognostic significance of spontaneous echo contrast in the thoracic aorta: Relation with accelerated clinical progression of coronary artery disease. J Am Coll Cardiol 1997; 30:71–75

11. Seaburg LA, Sekiguchi H: Two chronically ill patients presenting with hypoxemic respiratory failure. Chest 2016; 149:e107–e110