

# Utility of D-dimers in COVID-19 Patients Requiring Extracorporeal Membrane Oxygenation

AQSA SHAKOOR<sup>1</sup>, STACEY CHEN, JONATHAN HYDE, BRENDAN WU, BRIDGET TOY, STEPHANIE CHANG, ZACHARY KON, GRETA PIPER, AND DEANE SMITH

**A retrospective study was performed examining the trend of inflammatory markers, including D-dimers, in 29 COVID-19 patients requiring veno-venous (VV) extracorporeal membrane oxygenation (ECMO) support. We observed that COVID-19 patients with pre-cannulation D-dimer levels >3,000 ng/mL had a significantly shorter time from admission to cannulation (4.78 vs. 8.44 days,  $p = 0.049$ ) compared to those with D-dimer <3,000 ng/mL. Furthermore, patients with D-dimer >3,000 ng/mL had a trend of lower pH (7.24 vs. 7.33), higher  $p\text{CO}_2$  (61.33 vs. 50.69), and higher vasoactive inotropic score (7.23 vs. 3.97) at time of cannulation, however, these were not statistically significant. This cohort of patients also required a longer duration of ECMO support (51.44 vs. 31.25 days). However, 13 patients required at least one ECMO-circuit exchange and 16 patients did not require any exchanges. There was a consistent drop in D-dimer values after every circuit exchange, which was not observed in any of the other examined inflammatory markers, including ferritin, lactate dehydrogenase, or C-reactive protein. We propose that elevated D-dimer levels (>3,000 ng/mL) reflect increased disease severity in COVID-19, and predict a longer ECMO course. Once on ECMO, however, the D-Dimer level consistently decreased with every circuit exchange, which may reflect thrombus within the oxygenator rather than just disease severity. ASAIO Journal 2022; 68;1241–1248**

**Key Words:** ECMO, COVID-19, D-dimer, anti-coagulation

## Introduction

Extracorporeal membrane oxygenation (ECMO) offers life-saving support in the treatment of severe COVID-19 infections refractory to maximal medical therapy. Elevated D-dimer levels in COVID-19 patients are associated with both increased disease severity and in-hospital mortality.<sup>1</sup> D-dimer, a fibrin degradation product released when plasmin cleaves cross-linked fibrin, is commonly used as part of a diagnostic algorithm in detecting thrombus presence in the form of deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation, among other disease processes.

It is demonstrably higher in patients with severe COVID-19 compared to nonsevere disease.<sup>2–4</sup> Various studies have highlighted that COVID-19 nonsurvivors have an elevated D-dimer level and that D-dimer continues to increase during admission before death.<sup>3,5,6</sup>

Of interest, D-dimer levels are elevated even in severe COVID-19 patient in whom venous thromboembolism (VTE) has been ruled out by Doppler ultrasonography and computed tomography (CT) imaging.<sup>1,7</sup> These elevated levels presumably reflect a hyperfibrinolytic state and increased inflammatory burden induced by the viral infection.<sup>1</sup> Several studies have found that therapeutic anticoagulation is associated with a reduced risk of mortality, especially in COVID-19 patients requiring mechanical ventilation.<sup>8</sup> Hence, there has been a trend of D-dimer driven anticoagulation where the absolute value of D-dimers are used to determine the degree of anticoagulation.<sup>9</sup>

While there is ample evidence to suggest the presence of a prothrombotic state in COVID-19 patients with elevated D-dimers and the benefits of empiric anticoagulation, the significance of elevated D-dimer levels in a patient on ECMO support is an area of ongoing study. We hypothesize that the high D-dimer levels in COVID-19 patients requiring ECMO can partially be attributed to the ECMO circuit and may not be a true reflection of disease severity. This is because the initiation of ECMO is in itself associated with an immediate and complex inflammatory reaction, similar to that seen in systemic inflammatory response syndrome.<sup>10,11</sup> This reaction is multifactorial and a result of contact of blood to the foreign surface of the circuit,<sup>10</sup> rise of pro-inflammatory cytokines,<sup>12–15</sup> and activation of the innate immune system.<sup>16,17</sup> If this inflammatory response remains unchecked, it results in profound inflammation and secondary organ injury.<sup>10</sup> Furthermore, elevated D-dimers are associated with the presence of a thrombus burden within the oxygenator.<sup>18</sup> Hemolysis and fibrinolysis, a common phenomenon in patients on ECMO, are routinely monitored by labs such as plasma-free hemoglobin, fibrinogen, and D-dimer levels. In patients with acute respiratory distress syndrome (ARDS) requiring veno-venous (VV) ECMO, the elevation of these markers is associated with worsened outcomes secondary to thrombotic and hemorrhagic complications.<sup>19</sup>

The interplay between inflammation and coagulation in patients with severe COVID-19 parallels that of patients supported with ECMO. Hence, patients with severe COVID-19 infection requiring ECMO support pose a unique challenge with respect to how we monitor for disease severity and progression and surveillance of ECMO complications. For example, while elevated D-dimers are associated with increased COVID-19 severity, it is also not uncommon to have elevated D-dimers while supported on ECMO, which are frequently used as an early marker for oxygenator exchange.<sup>18,20</sup> Thus,

From the Department of Surgery, New York University, New York  
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Correspondence: Aqsa Shakoor, MD, Department of Surgery, New York University, 424 E 34th Street, Floor 13, New York, NY 10016.  
Email: aqsa.shakoor@gmail.com

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the objective of this study is to determine whether elevated D-dimers in COVID-19 patients on ECMO are a result of disease severity or rather, a reflection of ongoing hemolysis and fibrinolysis inherent in the ECMO circuit.

## Methods

### Study Design and Parameters

This is a single-center, retrospective study performed with institutional review board (IRB) approval (New York University Langone Health IRB# S20-00611). Inclusion criteria included adults aged 18 years or older with reverse transcriptase-polymerase chain reaction confirmed COVID-19 infection with severe hypoxemia defined by the arterial partial pressure of oxygen-to-fraction of inspired oxygen ratio (P/F ratio) of less than 150 mm Hg or a pH less than 7.23 with a partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>) exceeding 60 mm Hg, refractory to conventional medical therapy. Exclusion criteria included patients older than 65 years of age, undergoing active cardiopulmonary resuscitation, those with confirmed neurologic injury, known malignancy with poor prognosis, and multisystem organ failure with the exception of acute kidney injury during the current hospitalization.<sup>21</sup>

Patients' demographics, baseline characteristics, and laboratory data, including pre-cannulation sequential organ failure assessment score (SOFA), vasoactive inotropic score (VIS), maximum pre-cannulation ventilator support and arterial blood gas were collected. Postcannulation daily values were collected for creatinine, liver function tests, hemoglobin, white blood cell count, platelets, fibrinogen, anti-factor Xa, and partial thromboplastin time (aPTT). Daily inflammatory markers collected included C-reactive protein (CRP), D-dimer, erythrocyte sedimentation rate, ferritin, lactate dehydrogenase level (LDH), and pro-calcitonin.

Therapeutic anticoagulation was initiated for all patients on extracorporeal support with a continuous heparin drip with a goal anti-factor Xa level greater than 0.15 IU/mL and a partial thromboplastin time of less than 70 seconds. All data were collected retrospectively from the review of patients' electronic medical records. Given the retrospective nature of this study, patient consent was waived.

### Outcomes

The primary outcome of the study was to identify the trend of inflammatory markers, specifically D-dimer, and post-circuit exchange. Secondary outcomes included comparing the incidence of complications in COVID-19 patients on ECMO who had precannulation D-dimer <3,000 ng/mL versus those who had D-dimer >3,000 ng/mL.

Complications on ECMO were adopted from the extracorporeal life support organization (ELSO) guidelines. Bleeding complication was defined as any bleed requiring ≥3 units of packed red blood cells (pRBCs) in 24 hours. Pulmonary complications included pneumothorax or pulmonary hemorrhage requiring ≥3 units of pRBCs. The renal complication was defined as a newly acquired serum creatinine level of ≥1.5 or requiring renal replacement therapy. Stroke was defined by the presence of clinical change in exam or imaging changes on CT scan. Infection on ECMO was defined as positive respiratory, urine, blood, or wound cultures. Thrombotic complications included DVT or PE.

### Statistical Analysis

Descriptive statistics were calculated for all study variables. Patients were stratified into two groups: precannulation D-dimer <3,000 ng/mL and D-dimer >3,000 ng/mL. Categorical variables were compared using the  $\chi^2$  test and continuous variables were compared using a two-sample Student's *t*-test. Additionally, the same statistical methodology was used to compare demographics, pre-ECMO characteristics, complications, and blood product requirements between patients with and without circuit exchange using independent two-sample Student's *t*-tests for continuous variables and the  $\chi^2$  test for categorical variables. Inflammatory marker levels for patients before and after circuit exchanges were compared using paired samples *t*-tests. Data were reported as mean ± standard error of mean. All *t*-tests were two-tailed, and a *p* < 0.05 was considered statistically significant. All analyses were performed with SPSS 26.0 (IBM, Armonk, NY). All figures were created with Microsoft Excel (Microsoft, Redmond, WA).

## Results

### Patient Characteristics

A total of 30 consecutive patients with respiratory failure secondary to severe COVID-19 infection were supported with VV ECMO between March 2020 and April 2020. One patient expired immediately after cannulation and is excluded from the analysis. Overall survival to discharge was 97% (28/29). The average age was 39 years (range of 18–65 years) (Table 1). Totally 86% of patients in this cohort were male. Significant comorbidities included obesity in 65%, diabetes in 21%, hypertension in 21%, and hyperlipidemia in 31% of patients. However, 10% of patients had preexisting asthma but none had the chronic obstructive pulmonary disease. None of the patients were active smokers or had a history of vaping. One patient (3%) was on outpatient anticoagulation.<sup>21</sup>

### Trend of Inflammatory Markers with Circuit Exchanges

The median precannulation D-dimer for the study population (*n* = 29) was 2,088 ng/mL (SEM 502). There was a consistent rise of D-dimer postcannulation for the first 72 hours of ECMO support; 2,987 ng/mL (SEM 414) on day 1 of ECMO, 4,003 ng/

**Table 1. Demographics**

Age (years), mean (SEM)	39.83 (11.70)
Sex	
Male	25 (86%)
Female	4 (14%)
Comorbidities	
Obesity	18/29 (62%)
Diabetes	6/29 (21%)
Hypertension	7/29 (24%)
Hyperlipidemia	9/29 (31%)
Coronary artery disease	0/29 (0%)
Chronic kidney disease	0/29 (0%)
Chronic liver disease	2/29 (7%)
Chronic obstructive pulmonary disease	0/29 (0%)
Asthma	3/29 (10%)
Malignancy	1/29 (3%)
Immunocompromised	2/29 (7%)
Current smoker	0/29 (0%)
Vaping history	0/29 (0%)
Outpatient anticoagulation use	1/29 (3%)

SEM, standard error of mean.

mL (SEM 690) on day 2, and 5,363 ng/mL (SEM 580) on day 3. However, beyond 72 hours, this trend did not persist. In fact, no visible trend was found in D-dimer levels during the duration of ECMO support when the average daily D-dimer value of all the patients in the cohort was graphed against the day on ECMO (Figure 1).

In total 13 patients (44.8%) required at least one ECMO-circuit exchange, whereas 16 patients (55.2%) did not require any circuit exchange. The median pre-ECMO D-dimer in the circuit exchange group was 2,088 ng/mL (SEM 853) and 1,974 ng/mL (SEM 615) in the no-exchange group. In the circuit exchange group, there was a consistent drop in D-dimer values after every exchange. Figure 2 depicts the mean D-dimer value pre- and post- each circuit exchange. There was a statistically significant decrease on D-dimer after the 1st, 3rd, and 4th exchanges (5,351–3,317 ng/mL,  $p = 0.024$ ; 5,289–2,297 ng/mL,  $p = 0.015$ ; and 7,852–3,838 ng/mL,  $p = 0.027$ ). There was one patient who required more than 6 circuit exchanges; hence, a  $p$ -value could not be calculated.

This consistent drop in D-dimer value postcircuit exchange was not replicated in any other inflammatory markers. There was no significant difference in mean CRP values pre- and post-circuit exchange (Figure 3). Ferritin levels (Figure 4) also varied pre- and post-exchange with circuit exchange number 6 demonstrating a rise in post-exchange levels (1,267–1,446 ng/mL,  $p = 0.037$ ). LDH levels (Figure 5) also fluctuated post-exchange, dropping significantly after the 1st and 5th exchange (600–522 U/L,  $p = 0.0001$  and 781–660 U/L,  $p = 0.023$ ) but rising after 4th exchange (354 to 407 U/L,  $p = 0.046$ ).

*Pre-ECMO Characteristics in Patients with Pre-Cannulation D-dimer levels <3,000 versus >3,000*

25 patients had a precannulation D-dimer level measured; 16 patients had D-dimer <3,000 ng/mL and 9 patients had D-dimer >3,000 ng/mL (Table 2). Both groups of patients had a similar time from admission to intubation and from intubation to cannulation. However, patients with pre-ECMO

D-dimer levels >3,000 ng/mL had significantly shorter time from admission to cannulation (4.78 vs. 8.44 days,  $p = 0.049$ ). This group also required a longer duration of ECMO support (51.44 vs. 31.25 days,  $p = 0.247$ ). There was no difference in ventilator settings at the time of cannulation with respect to the tidal volumes, positive end-expiratory pressure (PEEP), peak inspiratory pressure, driving pressure, and compliance or precannulation P/F ratio. D-dimer >3,000 ng/mL cohort had lower pH (7.24 vs. 7.33,  $p = 0.060$ ), higher  $pCO_2$  (61.33 vs. 50.69,  $p = 0.155$ ), and higher VIS (7.23 vs. 3.97,  $p = 0.377$ ) at time of cannulation, however, these were not statistically significant.

*Rate of Complications and Blood Product Requirements*

Patients in the D-dimer sub-cohorts had similar anti-coagulation profiles as measured by daily anti-Xa and aPTT levels. The daily fibrinogen levels also did not differ between patients with D-dimer <3,000 vs. >3,000 ng/mL groups. As can be seen in Table 3, patients with precannulation D-dimer levels >3,000 ng/mL were observed to have more pulmonary complications (44% vs. 25%,  $p = 0.317$ ) which included pneumothorax (44% vs. 19%,  $p = 0.170$ ) and hemothorax (11% vs. 6%,  $p = 0.667$ ), albeit these were not statistically significant. The D-dimer <3,000 ng/mL group had a higher rate of bleeding, neurologic, infectious, shock liver, renal, and thrombotic complications (i.e. DVT, PE, or heparin induced thrombocytopenia and thrombosis [HITT]). The difference in the rate of these complications, however, was not statistically significant. There were two neurologic complications in this study, which included a right frontal stroke and a transient ischemic attack treated with tissue plasminogen activator, although this patient did not have any evidence of ischemic or hemorrhagic stroke on imaging.

The D-dimer >3,000 ng/mL group required more circuit exchanges (2 vs. 1.44,  $p = 0.611$ ) and more transfusions of pRBCs (4,808 vs. 3,599,  $p = 0.480$ ) and cryoprecipitate (1,315 vs. 1,216,  $p = 0.280$ ), whereas the D-dimer <3,000 ng/mL group had

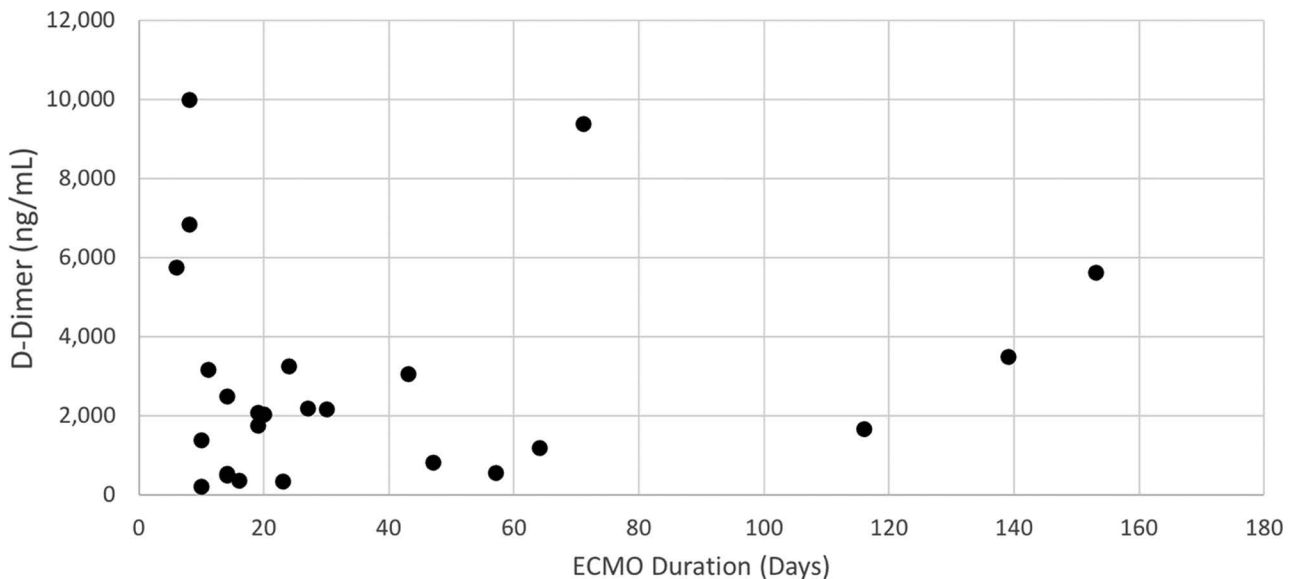
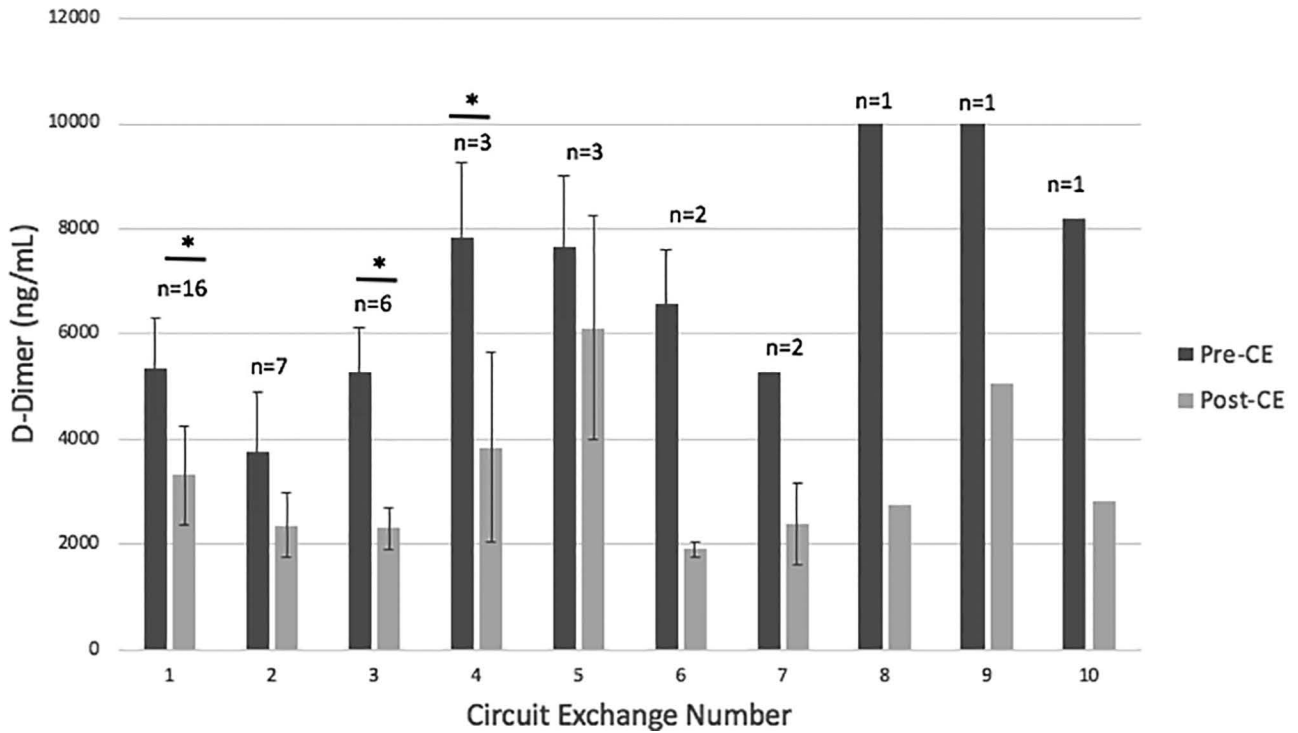


Figure 1. Trend of D-dimer during duration of ECMO support. ECMO, extracorporeal membrane oxygenation.

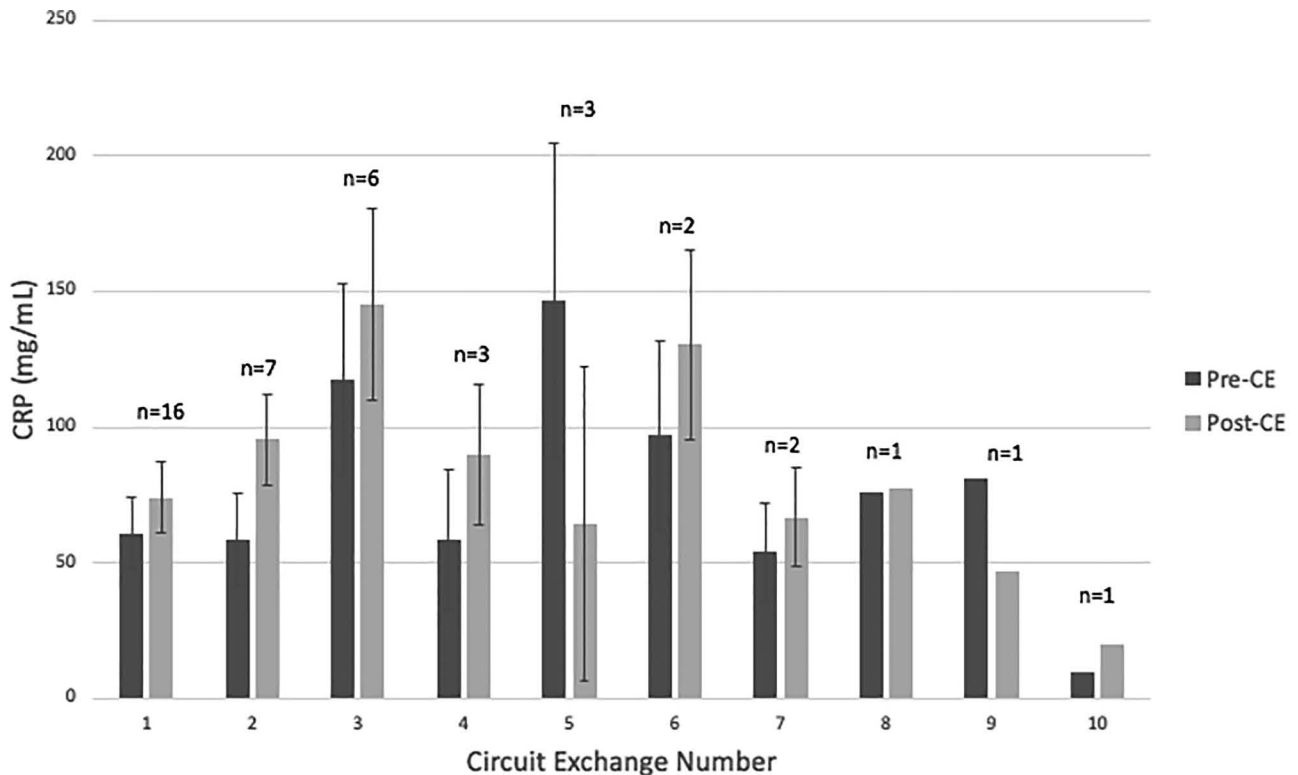


**Figure 2.** Trend of D-dimer pre- and post-ECMO circuit exchanges. ECMO, extracorporeal membrane oxygenation.

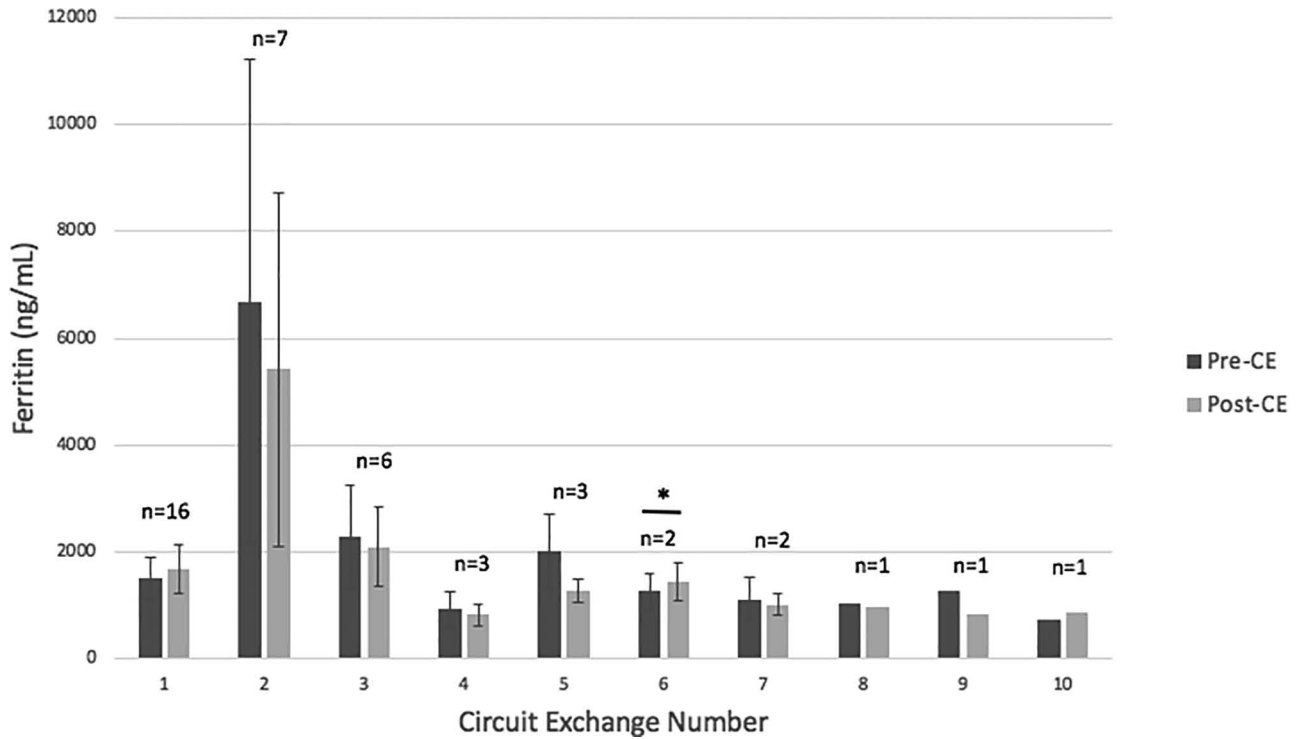
higher fresh frozen plasma (413 vs. 339,  $p = 0.844$ ) and platelets (448 vs. 131,  $p = 0.280$ ) transfusion requirements. There was no statistical difference in survival to discharge between the two groups (94% vs. 100%,  $p = 0.444$ ). These complications are listed in Table 2.

**Discussion**

D-dimer is an important predictor of disease severity in COVID-19 patients. Early data from Wuhan, China demonstrates that higher D-dimer levels at admission is an



**Figure 3.** Trend of CRP pre- and post-ECMO circuit exchanges. CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation.



**Figure 4.** Trend of ferritin pre- and post-ECMO circuit exchanges. ECMO, extracorporeal membrane oxygenation.

independent predictor of mortality.<sup>6</sup> D-dimer level has also been shown to differentiate patients with moderate from severe disease<sup>22</sup> and dynamic changes in D-dimer during the course of the disease are associated with poor outcomes.<sup>23</sup> Data from this study further support these observations. While not statistically significant, there was a trend of lower pH, higher pCO<sub>2</sub>, and higher VIS in patients with precannulation D-dimer >3,000 ng/mL. These patients also had a statistically significant shorter time from hospital admission to ECMO cannulation (4.78 days vs. 8.44 days, *p* = 0.049).

The hypercoagulable state suggested by higher D-dimer levels is supported by postmortem studies in COVID-19 patients which revealed prominent PE, microthrombi in alveolar capillaries, thrombotic microangiopathy, and DVTs.<sup>24,25</sup> Furthermore, observational studies show that higher D-dimer levels are associated with greater probability of PE.<sup>26,27</sup> Hence, using D-dimer levels as a guide to anticoagulation has gained support among the academic community.

While there is ample evidence to support the use of D-dimers as a marker of hypercoagulability and the use of systemic anticoagulation in a patient with severe COVID-19 infection,

**Table 2. Pre-Extracorporeal Membrane Oxygenation Characteristics**

	D-dimer <3,000 (n = 16) Mean (SEM)	D-dimer >3,000 (n = 9) Mean (SEM)	<i>p</i> -value
Time from admission to intubation, days	5.31 (1.24)	2.33 (1.04)	0.119
Time from intubation to cannulation, days	3.13 (0.38)	2.44 (0.71)	0.359
Time from admission to cannulation, days	8.44 (1.20)	4.78 (0.95)	0.049
ECMO Duration, days	31.25 (6.99)	51.44 (19.23)	0.247
Pre-ECMO ventilator settings			
Tidal volume, mL	455.40 (23.79)	424.11 (29.79)	0.424
PEEP, mm Hg	14.07 (0.69)	13.67 (1.20)	0.758
PIP, mm Hg	30.58 (1.32)	30.13 (1.27)	0.816
Driving pressure, mm Hg	16.58 (1.73)	16.25 (1.37)	0.891
Compliance, mm Hg	34.93 (7.45)	25.96 (1.65)	0.348
Pre-ECMO blood gas			
pH	7.33 (0.02)	7.24 (0.04)	0.060
PCO <sub>2</sub>	50.69 (3.79)	61.33 (6.97)	0.155
PO <sub>2</sub>	88.44 (7.81)	91.56 (8.75)	0.803
Lactate	1.61 (0.12)	1.82 (0.22)	0.366
Pre-ECMO P/F ratio	88.86 (6.04)	96.99 (12.23)	0.562
SOFA score at cannulation	3.06 (0.32)	2.89 (0.42)	0.748
VIS at cannulation	3.97 (1.44)	7.23 (4.15)	0.377

ECMO, extracorporeal membrane oxygenation; PEEP, positive-end expiratory pressure; PIP, peak inspiratory pressure; P/F, PaO<sub>2</sub> to FiO<sub>2</sub> ratio; SOFA, sequential organ failure; VIS, vasoactive-inotropic score.

this proinflammatory marker should be interpreted with caution in the COVID-19 patient requiring ECMO support. This is partly because the presence of an ECMO circuit may result in elevated D-dimer levels. Dornia et al.<sup>18</sup> demonstrated that elevated D-dimers reflect thrombus burden within the oxygenator and revealed that there was a consistent drop in D-dimer level within 48 hours of an oxygenator exchange. Hence, using absolute values of D-dimers as indicators for anticoagulation oversimplifies the complex interplay of the disease process and inflammatory state caused by the presence of the circuit. The primary outcome of this study was to delineate the trend of D-dimer levels in COVID-19 patients on ECMO in an effort to ascertain whether it is a useful clinical marker for disease severity or hypercoagulable state. Similar to Dornia et al.,<sup>18</sup> we found a consistent drop in D-dimer values after every circuit exchange. These findings are also similar to those of Bemtgen et al.,<sup>28</sup> who found that D-dimer levels before thrombotic events were significantly higher in the COVID-19 group compared to the non-COVID group (35.2 vs. 15.8,  $p = 0.005$ ) but that postcircuit exchange D-dimers consistently dropped in both groups; the COVID-19 group from 35.2 to 12.78 and the non-COVID-19 group from 15.8 to 10.<sup>28</sup>

The steady drop in D-dimer levels after every circuit exchange was not replicated in any of the other inflammatory markers that we studied, including CRP, ferritin, or LDH. In fact, there was a rise in some of these markers after circuit exchange. These persistently elevated values before and after exchange support that the patients remain in a pro-inflammatory state, likely secondary to their underlying infection. However, the decrease in D-dimer levels after every oxygenator exchange suggests that the elevated levels may be attributed to the presence of thrombus within the circuit. This drop in D-dimer with circuit exchange also argues against using D-dimer levels to guide anticoagulation in patients on ECMO.

The prothrombotic state of a COVID-19 patient on ECMO is well documented.<sup>2,29</sup> We observed DVT in 48% (14/29) of patients, HIT in 3% (1/29), and no PEs. It is important to note, that we did not routinely surveil patients for DVT and PEs during their ECMO course. Imaging studies were only obtained if there was clinical suspicion so the actual number of prothrombotic complications is likely higher. Determining the baseline hypercoagulable state in COVID-19 patients is essential in the management of these patients not only to guide anticoagulation but as a means to prevent thromboembolic complications. While D-dimer is the commonly used hypercoagulability marker in these patients, it is nonspecific. We demonstrate in this article that elevated D-dimer levels may, in part, be a result of the ECMO circuit but it may also be from existing VTE, sepsis, or a hyperinflammatory state.<sup>30,31</sup> In COVID-19 patients receiving ECMO therapy, fibrinogen was demonstrated to be a more useful marker of hypercoagulability based on its positive correlation to thromboelastography maximum amplitude.<sup>31</sup> In our study, we did not observe a significant difference in the daily fibrinogen concentrations between the <3,000 and >3,000 ng/mL D-dimer cohorts. This finding is important in that the higher disease severity as evidenced by worse precannulation blood gases, more pulmonary complications, and a longer ECMO course observed in the >3,000 ng/mL D-dimer cohort likely reflects severe intrinsic COVID-19 disease rather than complications acquired from a profoundly hypercoagulable state. While we argue, that D-dimer levels may be superficially

elevated because of the ECMO circuit, the elevated D-dimer levels nevertheless remain useful markers to trend throughout the disease course. This is especially true as dynamic changes in D-dimer are associated with worse outcomes and may help anticipate the clinical course and help guide the management of patients.<sup>23</sup>

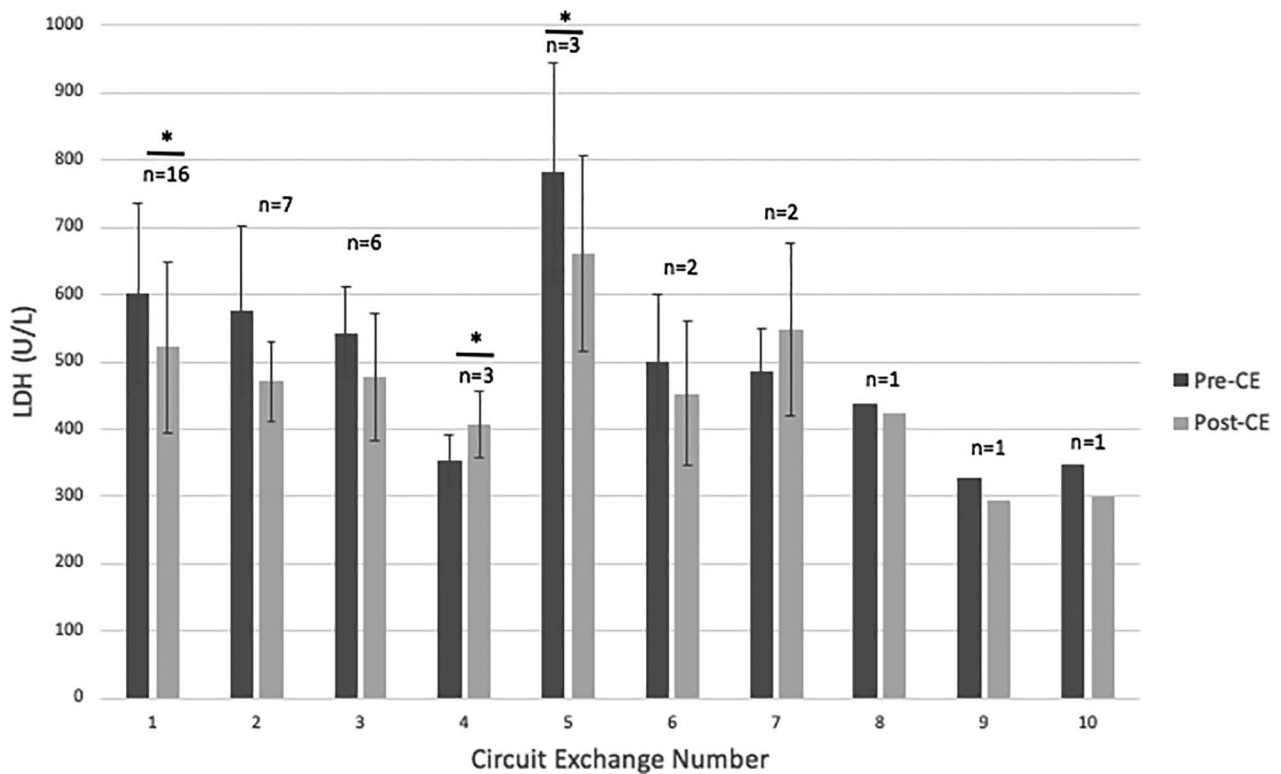
Despite the high risk of thrombotic complications, it is also worth considering that bleeding complications in the COVID-19 patient requiring ECMO support can be severe, with the most fatal being an intracranial hemorrhage (ICH). Even before the COVID-19 pandemic, ICH was a known complication in patients with profound respiratory failure requiring VV ECMO. The ELSO registry reported a rate of ICH at 3.6% (181/4,988) in non-COVID ARDS patients on VV ECMO, while the ECMO to Rescue Lung Injury in Severe ARDS study demonstrates a 2.4% (3/1124).<sup>32,33</sup> Smaller studies demonstrate an even higher risk with Arachchillage et al. observing the prevalence and incidence of ICH at ECMO initiation and duration of support in this population was 10.7% (16/149) and 5.2% (7/133), respectively.<sup>34</sup>

Balancing the risk of bleeding and thrombosis in patients with COVID-19 patients requiring ECMO support is challenging. In one of the largest studies to date, Barbaro et al.<sup>35</sup> examined the clinical course of 1,035 patients with COVID-19 who required ECMO support using the ELSO registry across 213 hospitals in 36 countries. The authors observed a higher risk of bleeding compared to thrombotic complications with respect to neurologic injuries; 6% risk of central nervous system (CNS) hemorrhage compared to 0.7% CNS infarcts. Mechanical complications in their study were defined as circuit exchange, pump failure, or membrane lung failure, which were reported to be at a rate of 15%, 8%, and 8%, respectively.

**Table 3. Association Between D-dimers and Complications on Extracorporeal Membrane Oxygenation**

Complications	D-dimer <3,000	D-dimer >3,000	<i>p</i> value
Bleeding	9/16 (56%)	3/9 (33%)	0.271
Neurologic	2/16 (13%)	0/9 (0%)	0.269
Infections	3/16 (19%)	0/9 (0%)	0.166
Surgery	4/16 (25%)	1/9 (11%)	0.405
Shock liver	2/16 (13%)	1/9 (11%)	0.918
Renal complications	11/16 (69%)	5/9 (56%)	0.509
AKI	6/16 (38%)	2/9 (22%)	0.618
CRRT	1/16 (6%)	2/9 (22%)	0.238
Pulmonary complications	4/16 (25%)	4/9 (44%)	0.317
Pneumothorax	3/16 (19%)	4/9 (44%)	0.170
Hemothorax	1/16 (6%)	1/9 (11%)	0.667
CPR required	2/16 (13%)	0/9 (0%)	0.269
Thrombotic complications			
DVT	9/16 (56%)	4/9 (44%)	0.571
PE	0/16 (0%)	0/9 (0%)	
HITT	1/16 (6%)	0/9 (0%)	0.444
Circuit exchange	1.44 (0.63)	2.00 (0.94)	0.611
Blood product transfusions			
Packed red blood cells, mL (SEM)	3,599 (920)	4,808 (1,544)	0.480
Fresh frozen plasma, mL (SEM)	413 (244)	339 (240)	0.844
Cryoprecipitate, mL (SEM)	1,216 (362)	1,315 (555)	0.832
Platelets, mL (SEM)	448 (210)	131 (62)	0.280
Survival to discharge	15/16 (94%)	9/9 (100%)	0.444

AKI, acute kidney injury; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; DVT, deep venous thrombosis; PE, pulmonary embolus; HITT, heparin induced thrombocytopenia and thrombosis; SEM, standard error of mean.



**Figure 5.** Trend of LDH pre- and post-ECMO circuit exchanges. ECMO, extracorporeal membrane oxygenation; LDH, lactate dehydrogenase level.

Ripoll et al.<sup>7</sup> examined the incidence of thrombotic and bleeding events in 30 COVID-19 patients on VV ECMO in whom baseline whole-body CT scans were performed on admission. 13 patients were found to have thrombotic events at the time of the baseline scan. These included nine patients with PEs, two DVTs, one splenic infarct, one liver and bowel ischemia, and one patient with combined PE and renal infarcts. Of these patients, only two developed further thrombotic complications while on ECMO; one DVT and one PE. However, five of the 13 patients developed major bleeding: four intracranial bleeds and one combined subcapsular liver and intracranial bleed. Similar to our findings, these bleeding complications occurred despite only 20% of patients being anticoagulated within the target range for more than 50% of the time. To minimize bleeding risk, it is essential that for the COVID-19 patients on ECMO support, we do not rely on D-dimer as the primary or guiding marker for anticoagulation.

Our cohort of patients had a 3% mortality which is in contrast to the larger retrospective studies, the largest of which was led by Barbaro et al.<sup>35</sup> using the ELSO registry, which had a 38% mortality.<sup>35</sup> The difference in these observed rates is in part contributed by our stringent criteria for candidacy. The average age of patients in our cohort was 39 years old and patients were required to have previously normal functional status, and lack of secondary organ injury with exception of an acute kidney injury at the time of cannulation. Furthermore, having an established ECMO program with a team of trained perfusionists, respiratory, physical, and occupational therapists, nutritionists, experienced nursing staff, and a dedicated team of cardiothoracic surgeons, pulmonologists, and intensivists cannot be underestimated in our success.

In summary, while D-dimer is a useful marker in assessing disease severity, it may be partially elevated due to the presence of the ECMO circuit. Use of anticoagulation based on absolute D-dimer levels in this patient population can result in over-anticoagulation and devastating bleeding. Hence, caution and prudent clinical judgement should be used when considering an adjustment in anticoagulation based on D-dimer values alone for a patient with severe COVID-19 on VV ECMO support.

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