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Letter to the Editors-in-Chief

# Coagulopathy monitoring and anticoagulation management in COVID-19 patients on ECMO: Advantages of a heparin anti-Xa-based titration strategy

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Severe coronavirus disease 2019 (COVID-19) infection can progress rapidly to respiratory failure, with high associated mortality and prolonged mechanical ventilation [1,2]. Among COVID-19 patients with critical illness, acute respiratory distress syndrome (ARDS) develops in approximately 67–95% of cases [1,2], and extracorporeal membrane oxygenation (ECMO) has been employed across the globe to support patients with refractory hypoxemia. While the optimal time to initiate ECMO in severe COVID-19 infection remains controversial [3], the World Health Organization supports the referral of patients with refractory hypoxemia despite maximal lung protective ventilation to centers with expertise in ECMO [4] and multicenter studies have demonstrated promising outcomes [5,6] However, the unique coagulopathies associated with both severe COVID-19 infection [7] and ECMO present a clinical dilemma, as these patients are at especially high risk for both thrombosis and major bleeding, including intracranial hemorrhage [8].

We conducted a single-center, retrospective observational study in patients with confirmed COVID-19 infection who were managed with veno-venous ECMO (V—V ECMO) for refractory hypoxemic respiratory failure between April 1st and December 1st, 2020, at Thomas Jefferson University Hospital, an 883-bed academic medical center in Philadelphia, PA. The study was approved by the Thomas Jefferson University institutional review board.

All patients studied received V—V ECMO support with non-pulsatile flow via a centrifugal pump head. Patients received an intravenous unfractionated heparin (UFH) bolus of either 5000 (if weight $< 100$ kg) or 7500 units (if weight $> 100$ kg) prior to initiation of ECMO therapy. Most patients (87.1%) were cannulated using a femoral venous multistage drainage cannula, and a single stage return cannula via an internal jugular (IJ) vein, most often right. The multistage femoral venous cannulas ranged in size from 20 to 28 French, and the IJ cannulas ranged in size from 16 to 21 French.

Laboratory and clinical data were extracted from patients' electronic health records by the study investigators. The UFH anti-Xa assay was performed on ACL TOP 500 using Liquid Anti-Xa assay kit by HemosIL, which does not contain exogenous antithrombin and is thus sensitive to patient deficiencies, and was available to be run in-house for 16 h per day. The activated partial thromboplastin time (aPTT) assay was done with HemosIL SynthASil reagent. Normal aPTT range at our institution was 25–36 s, while therapeutic values for UFH by anti-Xa correlation were 58–85 s. The timing of collection for all laboratory values was recorded, such that simultaneous pairs of aPTT and UFH anti-Xa could be studied, and association with other laboratory or clinical data with the same timestamp (or within 8 h for certain labs drawn at separate times according to workflow) could be determined. Any coagulation study obtained while the patient was off UFH was excluded from analysis. Data on bleeding and thrombosis was gathered by review of clinical documentation and radiology reports. For each simultaneous pair, the goal aPTT or anti-Xa range was recorded based on the heparin order and clinical documentation. A determination of concordance was made clinically for each aPTT-anti-Xa pair. If both an aPTT and anti-Xa target were noted, those were used to determine concordance of each pair. If only an aPTT or anti-Xa goal was listed, then the therapeutic range for the other was extrapolated based on our institutional protocols. Two protocols exist at our institution for determining the intensity of UFH dosing, which are based on a clinical determination of the patient's risk of bleeding. For patients with active non-major bleeding or severe coagulopathy, the treating team employed a low-intensity protocol, while all other patients received standard intensity. The target aPTT range for standard-intensity UFH in ECMO patients at our institution is 50–65 s, and for low-intensity 45–55 s. The standard-intensity UFH anti-Xa goal in these patients is 0.3–0.5 IU/mL, and for low-intensity 0.1–0.3 IU/mL. If the goal aPTT or anti-Xa could not be determined through the medication administration record or clinical documentation, values were excluded from concordance analysis.

Deidentified data were analyzed using SPSS version 26 (IBM). Descriptive statistics are summarized, and laboratory values are expressed as mean (range) and compared using the one-way ANOVA.

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Categorical variables are expressed as numbers (%) and compared with $\chi^2$ test or Fisher's exact test. Simultaneous aPTT and anti-Xa values were plotted against each other, and $R^2$ determined using SPSS.

The study population included 31 patients with confirmed COVID-19 infection treated with V—V ECMO for refractory hypoxemia. Table 1 summarizes their baseline characteristics. The mean age of patients was 53 years (range 32–66) and 9/31 (29%) were female.

Clinical outcomes are summarized in Table 1. Mean time on ECMO was 22.3 days (range 1–90). At the time of data censoring, 18/31 (58.1%) patients were alive, including 14 (45.2%) who were discharged, 1 (3.2%) who remained hospitalized following decannulation, and 3 (9.7%) who remained on ECMO. Among the 13 patients who died, 9 (29.0%) died on ECMO and the other 4 (12.9%) died of multi-organ failure at a mean of 15.0 days (range 8–22) following decannulation. No patients developed lower extremity deep vein thrombosis or pulmonary embolism (PE) while on ECMO, but one patient was found to have a non-occlusive, age-indeterminate portal vein thrombus and another splenic infarcts of indeterminate age. One patient developed a small segmental PE 11 days after decannulation. 8 patients (25.8%) required continuous hemodialysis for renal failure. 10 patients (32.2%) required ECMO oxygenator exchange due to clots forming and decreasing oxygenator efficiency. 25 patients (80.6%) had any bleeding while on ECMO, and 15 patients (48.4%) had major bleeding as defined by the Extracorporeal Life Support Organization [9], including a total of 29 discrete events. Two patients had small parenchymal intracranial hemorrhages without evidence of focal neurologic symptoms. No patients died of hemorrhagic or thrombotic complications. Patients with major bleeding had similar mean platelet counts immediately prior to the episode as the whole study population (125 B/L prior to major bleeding vs 134 B/L for all values), and the platelet count was normal (140–400 B/L) in 13/29 (44.8%) of the episodes.

**Table 1**
Baseline characteristics and clinical outcomes among COVID-19 patients on V—V ECMO.

| | Patients ($N = 31$) |
|---|---|
| Patient population | |
| Mean age (range) – years | 53 (32–66) |
| Sex – no. (%) | |
| Male | 22 (71.0) |
| Female | 9 (29.0) |
| Race – no. (%) | |
| Black/African-American | 10 (32.3) |
| White/Caucasian | 10 (32.3) |
| Hispanic/Latino | 7 (22.6) |
| Asian | 2 (6.5) |
| Other | 2 (6.5) |
| Mean body mass index (range) – $kg/m^2$ | 32.0 (21.5–47.6) |
| Therapies received – no. (%) | |
| Dexamethasone | 16 (51.6) |
| Tocilizumab | 15 (48.4) |
| Remdesivir | 14 (45.2) |
| Convalescent plasma | 9 (29.0) |
| Mean days mechanical ventilation pre-ECMO (range) | 4 (0–15) |
| Clinical outcomes | |
| Mean time on ECMO (range) – days | 22.3 (1–90) |
| Venous thromboembolism on ECMO - no. (%) | |
| Lower extremity deep vein thrombosis | 0 |
| Pulmonary embolism | 0 |
| Portal vein thrombus (age-indeterminate) | 1 (3.2) |
| Arterial thrombosis - no. (%) | |
| Cerebrovascular accident | 0 |
| Splenic infarct (age indeterminate) | 1 (3.2) |
| Major bleeding - no. patients (%) | 15 (48.4) |
| Major bleeding events – no. | 29 |
| Oropharynx/Nasopharynx | 8 |
| Gastrointestinal | 5 |
| Pulmonary | 4 |
| Intracranial | 2 |
| ECMO cannula | 2 |
| Non-ECMO indwelling catheter | 2 |
| Hemothorax | 2 |
| Retroperitoneal | 1 |
| Other (pericardial, gynecologic, multiple sites) | 3 |
| Acute renal failure requiring hemodialysis – no (%) | 8 (25.8) |
| Clinical outcome – no. (%) | |
| Died, on ECMO | 9 (29.0) |
| Died, after decannulation | 4 (12.9) |
| Alive, remains on ECMO | 3 (9.7) |
| Alive, decannulated but hospitalized | 1 (3.2) |
| Alive, discharged | 14 (45.2) |
| Mean time decannulation to outcomes (range) - days | |
| Died | 15.0 (8–22) |
| Discharged | 28.4 (6–69) |

As UFH monitoring practice evolved with more experience, various mechanisms for titrating UFH were employed at different time points, with an eventual shift to using UFH anti-Xa as the primary means for titrating the UFH infusion. Overall, the anti-Xa was used to titrate UFH in 84.0% of instances of a coagulation lab being drawn while on UFH. Among labs for which a therapeutic goal could be determined, only 41.4% of aPTT values were in the therapeutic range, compared to 59.8% of anti-Xa values ($P < .001$). We observed a trend toward lower mean weight-based UFH dose when the anti-Xa was being used for titration compared to aPTT (12.9 vs 13.3 units/kg/h, $P = .514$). There were also significantly fewer UFH dose changes as a percentage of coagulation studies drawn when the anti-Xa was in use (33.5% vs 44.2%, $P = .009$). Among the 29 major bleeding events, 4 (13.8%) occurred while patients had been off UFH for at least 24 h, 2 (6.9%) occurred in a patient treated briefly with argatroban for suspected heparin-induced thrombocytopenia (HIT), 3 (10.3%) occurred while the aPTT was being used to titrate UFH, and 20 (69.0%) occurred while the anti-Xa was in use.

Overall, correlation between aPTT and anti-Xa was weak, with $R^2$ of 0.430 among the 746 pairs of simultaneous aPTT and anti-Xa (Fig. 1a). In cases in which concordance could be clinically determined, aPTT and anti-Xa were discordant in 49.5% of cases (Fig. 1b). When discordant, the aPTT was more often shortened out of proportion to the anti-Xa (30.4% of cases, compared to 19.1% when relatively prolonged, $P < .001$). This stands in contrast to other reported data on discordant aPTT-anti-Xa pairs in patients receiving mechanical circulatory support, in which the aPTT was more often prolonged relative to anti-Xa [10]. The high rate of discordant aPTT-anti-Xa pairs suggests that other non-heparin factors are likely affecting the aPTT. Severe COVID-19 infection has been marked in some studies by high levels of pro-inflammatory cytokines and endothelial cell activation, the results of which include marked elevations in factor VIII, vWF, and fibrinogen [11–14] that may contribute to a shortened aPTT relative to anti-Xa. Conversely, other conditions associated with COVID-19 infection such as antiphospholipid antibodies, disseminated intravascular coagulation (DIC), and acquired vitamin K deficiency may prolong the aPTT. In support of these hypotheses, we observed significantly greater mean PT as the aPTT lengthened out of proportion to the anti-Xa (one-way ANOVA; $P < .001$), as well as significantly greater mean platelet count ($P = .011$) and trends toward progressively greater mean C-reactive protein ($P = .216$) and fibrinogen ($P = .646$) as the aPTT shortened relative to anti-Xa (Fig. 1c–f). No other measured coagulation labs demonstrated a relationship with changes in the aPTT relative to anti-Xa. DIC, as measured by a score of $\geq 5$ on the ISTH overt-DIC score [15] was found in 7/31 (22.6%) patients. Only one patient had testing for a lupus anticoagulant, which was uninterpretable to due UFH interference. Last, 16 (51.6%) patients underwent testing for heparin-induced thrombocytopenia with anti-heparin-platelet factor 4 ELISA assay, and all tests were negative.

In conclusion, our study reports on clinical outcomes and the unique coagulopathy in COVID-19 patients receiving V—V ECMO and suggests that it may be an effective therapy for specific patients with refractory hypoxemia from COVID-19 infection. We also describe a pattern of labile aPTTs and discordance between the aPTT and UFH anti-Xa while on UFH, which may be mediated by changes in levels of procoagulant factors and markers of inflammation. These results have important implications both for selecting a reliable test on which to base UFH

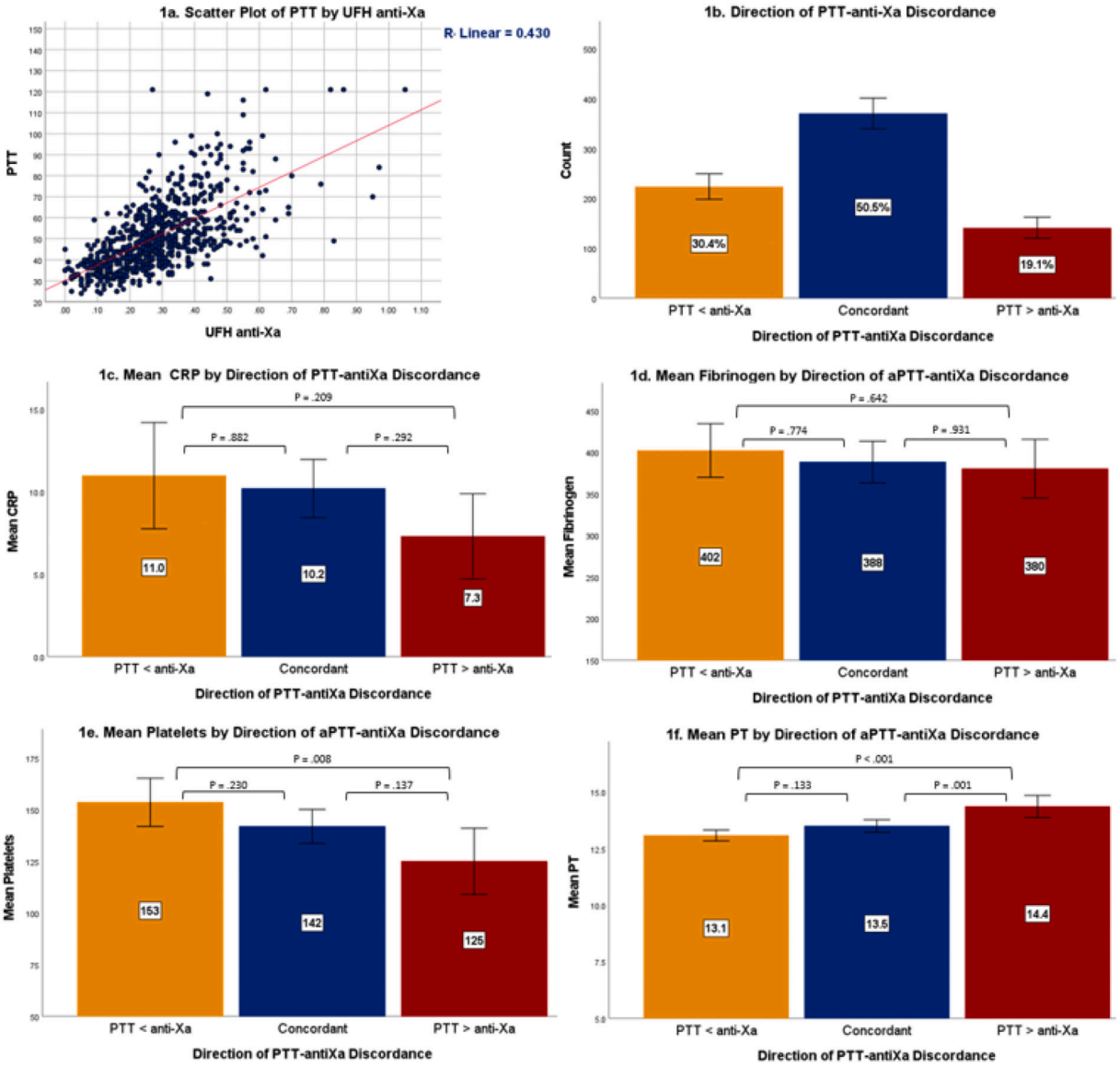


**Fig. 1.** PTT-UFH anti-Xa concordance patterns and mean values of C-reactive protein, fibrinogen, platelets, and prothrombin time, according to aPTT-anti-Xa concordance (error bars represent 95% confidence intervals; data were analyzed using one-way ANOV with *P* values derived from Tukey HSD post-hoc analysis).

titration and for monitoring patients for bleeding and thrombotic complications. In our study, the anti-Xa proved to be associated with greater likelihood of achieving therapeutic values, fewer UFH titrations, and a trend toward lower UFH doses. Overall, we observed few thrombotic complications and, while most patients had bleeding episodes while on ECMO, no patients died of hemorrhagic complications.

## Author contributions

Drs Rhoades and Al-Rawas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design*: Rhoades, Al-Rawas, Rame, McKenzie.

*Acquisition, analysis, or interpretation of data*: Rhoades, Al-Rawas, Leong, Kopenitz, Thoma, McDermott, Dovidio, Barletti.

*Drafting of the manuscript*: Rhoades, Al-Rawas, Leong, Barletti.

*Critical revision of the manuscript for important intellectual content*: Rhoades, Al-Rawas, Rame, Massey, Gong, McKenzie.

*Statistical analysis*: Rhoades.

*Administrative, technical, or material support*: Rhoades, Al-Rawas, Rame.

*Supervision*: Rhoades, Al-Rawas, Rame.

## Declaration og competing interest

Dr. Rame reported that he serves as a consultant for Novalung ECMO systems (Fresenius, Inc.). No other disclosures were reported.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.04.008.

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