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Letter to the Editors-in-Chief

Discordance in activated partial thromboplastin time and anti-factor Xa levels in COVID-19 patients on heparin therapy

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1. Introduction

Abnormal coagulation parameters, including prothrombin time, D-dimer, and fibrinogen degradation products, are common in coronavirus disease 2019 (COVID-19) and are associated with poor outcomes [1,2]. Moreover, thrombotic complications are common in COVID-19 [2–5], often resulting in the use of systemic anticoagulation such as intravenous unfractionated heparin (UFH), which requires frequent monitoring and dose adjustment often guided by activated partial thromboplastin time (aPTT) levels. In addition, perturbation of the aPTT has been shown to be common in this population, with aPTT prolongation frequently associated with lupus anticoagulant and decrease in the assay seen with elevated levels of fibrinogen and factor VIII [6,7], making aPTT guided UFH dose adjustment particularly challenging in patients with COVID-19. Anti-factor Xa (anti-Xa), a functional assay that facilitates the measurement of antithrombin -catalyzed inhibition of factor Xa by UFH, is used to guide the determination of therapeutic aPTT ranges in the clinical management of UFH [8]. Previous studies in non-COVID hospitalized patients have shown moderate correlation between aPTT levels and anti-Xa levels [9–11]. Here, we examined the correlation of aPTT and anti- Xa assays in patients with COVID-19 receiving intravenous UFH.

2. Methods

Patients with COVID-19 were retrospectively identified in the electronic medical record by means of positive SARS-CoV-2 RT-PCR assay codes at the New York-Presbyterian Hospital/Columbia University Irving Medical Center between March 18, 2020 and April 25, 2020 through the institution's clinical data warehouse. This study was conducted with approval from the Institutional Review Board. A total of 88 consecutive adult patients aged 18 years and older with COVID-19 who received therapeutic intravenous UFH, and in whom aPTT and anti-Xa were simultaneously measured yielding 579 paired observations. Baseline characteristics, medications, indication for anticoagulation, laboratory parameters, and intensive care unit utilization were automatedly extracted from the electronic health record. Simultaneous anti-Xa and aPTT measurements were abstracted by manual chart review. aPTT and anti-Xa assay reagents were manufactured by Stago Diagnostica, Inc., Parsippany, New Jersey. The standard of care for monitoring heparin activity in our hospital via aPTT assay unless patient has abnormal aPTT at baseline or documented antiphospholipid syndrome, in which case anti-Xa assay is preferred. Therapeutic range for aPTT is 80 to 121 s and 0.3 to 0.7 IU/mL for anti-Xa level in our hematology lab. Results were plotted on a scatterplot (X-axis, anti-Xa; Y-axis, aPTT) and linear regression analysis was performed. The best-fit line and its correlation coefficient (R^2 value) were calculated. Each paired observation was classified as subtherapeutic, therapeutic, and supratherapeutic. Statistical analysis was performed using R version 3.5.1. This research was approved by the institutional review board of Columbia University Irving Medical Center. AG performed data analysis and all authors had access to the primary data. Original data will be made available upon request to the corresponding author.

3. Results and discussion

A total of 579 observations were obtained from 88 patients (male n = 63, 71.6%). The median number of observations per patient was 4 (interquartile range (IQR), 2–9). The median age was 63.5 years (IQR, 48–71) and the median body mass index was 29.2 kg/m^2 (IQR, 25.7–34.9). Chronic anticoagulation prior to hospitalization (warfarin, low molecular weight heparin, or direct oral anticoagulants) was prescribed to 25.0% (n = 22). Mechanical ventilation was required in 83% (n = 73) of patients, and 39.8% (n = 35) died during their hospitalization. Baseline laboratory values were notable for median platelet count 115 × 10^3/μL [IQR, 70–149], international normalized ratio (INR) 1.5 (IQR, 1.3–2.3), C-reactive protein (CRP) 243 mg/L (IQR, 190.2–277), ferritin 2602 μg/mL (IQR, 1064–4207), high sensitivity-troponin 143 ng/L (IQR, 75–293), and D-dimer 13.5 μg/mL fibrinogen equivalent units (IQR, 8.3–17.8). D-dimer value > 5 μg/mL was present in 84.1% (n = 74) of patients.

Correlation of aPTT and anti-factor Xa are represented in a scatterplot (Fig. 1). R^2 value of the linear regression model was 0.005. Frequencies of aPTT and anti-Xa observations by strata (therapeutic, subtherapeutic, and supratherapeutic) are listed in Table 1. Discordance between therapeutic level in aPTT and anti-Xa was present in 40.0% (232/579) of paired observations, including 20.7% (120/579) with subtherapeutic aPTT paired with a therapeutic anti-Xa result.

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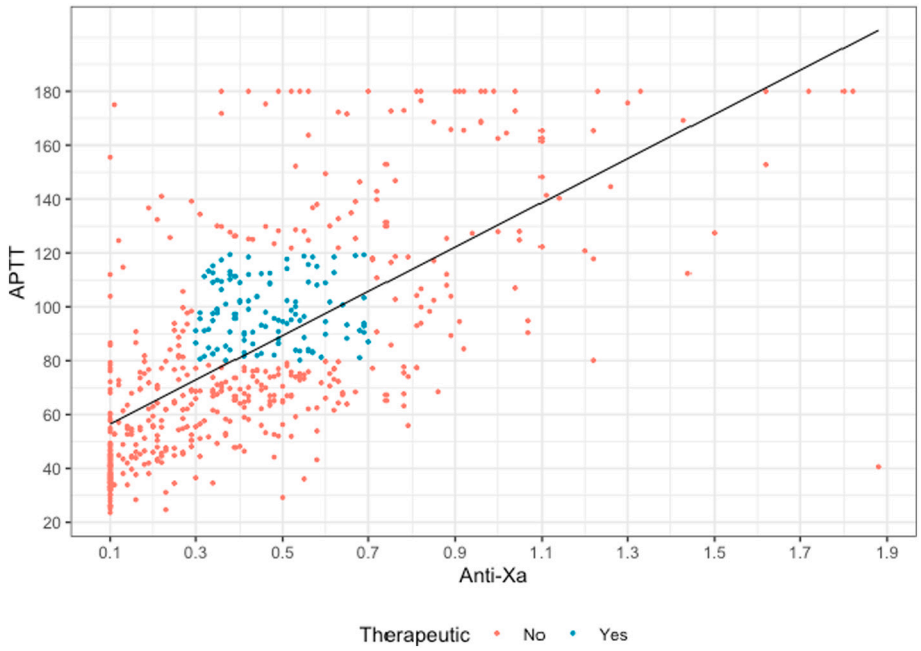

Fig. 1. Correlation of activated partial thromboplastin time (aPTT) and anti-factor Xa (anti-Xa) paired observations. Blue = results within the therapeutic range for both assays. Red = subtherapeutic or supratherapeutic results for ≥1 assay. Regression equation $y = 84.98 - 0.62x$. $R^2 = 0.005$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Paired activated partial thromboplastin time (aPTT) and anti-factor Xa (anti-Xa) observations stratified by therapeutic, subtherapeutic, and supratherapeutic levels. Concordant strata bolded.

		aPTT			Total
		Subtherapeutic	Therapeutic	Supratherapeutic	
anti-Xa	Subtherapeutic	**180 (31.1%)**	22 (3.8%)	8 (1.4%)	210 (36.3%)
	Therapeutic	120 (20.7%)	**115 (19.9%)**	37 (6.4%)	272 (47%)
	Supratherapeutic	15 (2.6%)	30 (5.2%)	**52 (9.0%)**	97 (16.8%)
Total		315 (54.4%)	167 (28.8%)	97 (16.8%)	579 (100%)

There were 120 paired observations for which there was concomitant fibrinogen drawn within 24 h. Among these 120 observations, 27 (22.5%) observations had a subtherapeutic aPTT and a therapeutic or supratherapeutic anti-Xa. The median fibrinogen in this group was 577 mg/dL, as compared with the median fibrinogen in the remaining group which was 598 mg/dL. In total, 28.8% (167/579) of aPTT values were within therapeutic range, compared with 47.0% (272/579) of values for the anti-Xa assay.

Our study included high-acuity patients, a large majority of whom had abnormal baseline coagulation parameters, elevated inflammatory biomarkers, and elevated cardiac biomarkers, and required admission to the intensive care unit. Linear regression modeling in this patient population reveals poor correlation between the aPTT and anti-Xa levels in patients treated with intravenous UFH. Historical comparison with non-COVID-19 patients receiving intravenous UFH has shown moderate correlation between these two assays ($R^2 = 0.46$ reported by Byun et al.) [9–11], suggesting diminished aPTT reliability in COVID-19 patients, in particular. Discordance between the therapeutic strata of the two assays suggests that the aPTT underestimated heparin activity compared with anti-Xa assay in a majority of discordant observations. Previous data have shown high fibrinogen associated with apparent heparin resistance; though in this study the aPTT appears refractory to the degree of heparin activity demonstrated by the anti-Xa assay, this correlation was not found in our data. Importantly, corresponding fibrinogen levels were drawn within 24 h and not necessarily concomitantly with aPTT and anti-Xa, which limit this evaluation.

Additional limitations to this study include the retrospective nature and its potential to introduce bias. Patients with both aPTT and anti-Xa collected while receiving intravenous heparin may be more likely to have had baseline abnormalities in the aPTT predisposing them poor correlation with anti-Xa. Typical confounders of the aPTT including factor VIII and lupus anticoagulant were not systematically collected, thus evaluation of their impact on the current findings is limited. Though correlation of anti-Xa and aPTT in non-COVID patients is referenced from prior literature, systematic comparison of anti-Xa and aPTT values from the same laboratory in non-COVID subjects were not available for comparison in this study.

In conclusion, our study suggests that there is poor correlation of anti-Xa and aPTT in patients with COVID-19 receiving intravenous UFH, and aPTT alone may be an unreliable measure of heparin activity. COVID-19 patients have a complex coagulopathy, with dysregulated components that can either shorten or prolong the aPTT, reducing its reliability. Additional research may prospectively explore the utility of measuring fibrinogen, Factor VIII activity and lupus anticoagulant in conjunction with the aPTT and anti-Xa in order to more accurately assess heparin activity to guide therapeutic anticoagulation in COVID-19 patients.

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Declaration of competing interest

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