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Impact of COVID-19 on monitoring of therapeutic unfractionated heparin

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Highlights

- Anti-Xa and aPTT are prone to monitoring inaccuracies in patients with COVID-19 and severe illness.
- Unexpected thrombosis or bleeding that does not correlate with anti-Xa or aPTT levels may indicate level inaccuracies
- More research is needed on the monitoring assay to optimize UFH dose titration in COVID-19 patients

Patients with coronavirus disease 2019 (COVID-19) appear to be at high risk for thrombotic disease in both venous and arterial circulations due to excessive inflammation, platelet activation, endothelial dysfunction, and immobility [1]. Klok and colleagues reported that over 30% of COVID-19 patients admitted to the intensive care unit (ICU) developed a thrombotic complication even while receiving standard doses of thromboprophylaxis [2].

A number of hemostasis parameters have been identified in these patients with COVID-19. Disease severity has been associated with prolongation of the prothrombin time (PT) and international normalized ratio (INR) and thrombin time (TT) and variably by a trend toward shortened activated partial thromboplastin time (aPTT) [1]. Elevations in D-dimer have been associated with higher mortality [3, 4]. These changes in hemostatic parameters may indicate some form of coagulopathy that may predispose patients to thrombotic events.

Tang et al. [4] reported that anticoagulant therapy was associated with better prognosis in severe COVID-19 patients. In this study, 449 patients with severe COVID-19 were enrolled, with 99 patients receiving heparin for 7 days or longer. The majority of patients received low molecular weight heparin at a prophylaxis dose. No difference in 28-day mortality was reported between heparin users and nonusers (30.3% vs 29.7%; $p = 0.910$). However, 28-day mortality rates were lower among patients receiving heparin that had a sepsis-induced coagulopathy (SIC) score ≥ 4 (40. vs 62.9%, $p = 0.029$) or D-dimer > sixfold of upper limit of normal (32.7% vs 52.4%; $p = 0.017$).

These findings have prompted some providers to empirically initiate unfractionated heparin (UFH) infusions in high-risk COVID-19 patients. Others have opted to wait until after diagnosis of a thrombus is made to initiate therapeutic anticoagulation. Irrespective of indication to initiate anticoagulation, monitoring and adjustment of heparin infusions to reach a therapeutic range is critical. The aforementioned study by Tang et al. did not specify monitoring parameters for patients in the study who received UFH. Several factors may impact commonly used monitoring parameters for heparin in this patient population.

Most institutions in the United States utilize antifactor Xa (anti-Xa) or aPTT to monitor therapeutic range of UFH [5]. The presence of antiphospholipid antibodies in critically ill patients with COVID-19 was reported by Zhang et al. [6]. Antiphospholipid antibodies have been shown to falsely elevate anti-Xa [5]. Due to cytokine release syndrome or propofol use, many critically ill patients with COVID-19 also develop hypertriglyceridemia, which has also been shown to falsely increase anti-Xa levels [7]. Thus, anti-Xa monitoring could lead to inappropriately low heparin dosing in patients with COVID-19, putting them at higher risk for thrombotic complications (Fig. 1).

On the other hand, aPTT measurements may be affected by COVID-19 as well. High fibrinogen levels have been found to falsely decrease aPTT measurements. Elevated fibrinogen levels are common in critically ill COVID-19 patients [8]. It is unknown whether these changes are a direct effect of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or a consequence of cytokine storm that precipitates systemic inflammatory response syndrome (SIRS) as has

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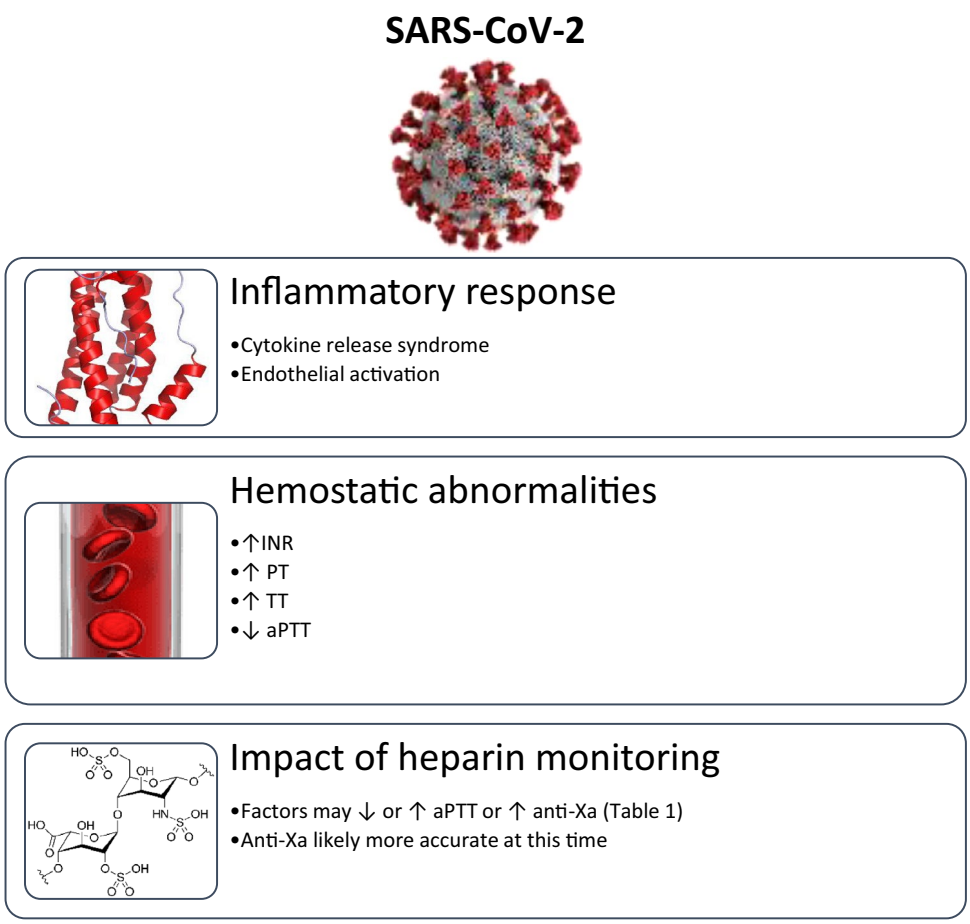

Fig. 1 Abnormalities of coagulation parameters and recommendation for heparin monitoring

Table 1 Select factors associated with alterations in coagulation parameters

	aPTT	Anti-Xa
Elevated fibrinogen	↓	–
Hypertriglyceridemia	–	↑
Antiphospholipid antibodies	↑	↑
Elevated factor FVIII	↓	–

been described with other viral diseases [9–11]. Exclusively using aPTT to monitor heparin in COVID-19 patients could result in over-dosing of heparin and bleeding complications (Table 1).

Anti-Xa and aPTT monitoring are both prone to monitoring inaccuracies in patients with severe illness and COVID-19. Monitoring of UFH by Anti-Xa has been shown to result in more predictable heparin response than aPTT. Thus for institutions that utilize Anti-Xa monitoring for UFH, monitoring should remain the same until more evidence emerges. Institutions should be vigilant to monitor for thrombotic and bleeding complications in patients with severe COVID-19 infection that are receiving UFH. Unexpected thrombosis or bleeding that does not correlate with documented Anti-Xa or aPTT levels may indicate that these levels are inaccurate. In some instances, target Anti-Xa or aPTT ranges may even need to be adjusted. More research needs to be done to determine the optimal assay to optimize UFH dose titration in these patients.

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