

# PERTinent new insights into venous thromboembolism risk and management in hospitalized patients with COVID-19

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The coronavirus disease 2019 (COVID-19) is a viral respiratory disease associated with coagulation dysregulation and venous thromboembolism (VTE). Various mechanisms have been postulated to explain this increased thrombotic risk. Commonly invoked is the presence of cytokine storm with significant increase in interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha and other inflammatory mediators linked to acute, multiorgan system inflammation and endothelial damage.<sup>1–3</sup> Furthermore, thrombotic microangiopathy within postmortem autopsies have also been shown in pulmonary vasculature.<sup>4</sup> Immobilization and obesity are important contributory risk factors that are of particular concern for patients suffering from severe COVID-19 disease and requiring mechanical ventilation.<sup>5</sup> Finally, associated laboratory and coagulation abnormalities include thrombocytopenia and increased D-dimer levels, and have been associated with disease severity, need for mechanical ventilation, and intensive care unit admission.<sup>6</sup>

The incidence and prevalence of VTE in COVID-19-affected patients is believed to be higher than in patients hospitalized for reasons other than COVID-19. Thrombotic event rates among patients with COVID-19 have varied widely across different global reports, often as high as 20–30%. Notably, there has not been a thorough investigation exploring differential rates of deep vein thrombosis (DVT) and pulmonary embolism (PE) among hospitalized patients with COVID-19. Furthermore, management of patients with COVID-19 and intermediate- and high-risk PE is particularly complex and is increasingly guided by pulmonary embolism response teams (PERTs) at individual centers. How the COVID-19 pandemic impacted case volume for PERTs remains largely unreported. Two recent publications in *Vascular Medicine* aimed to address these gaps in the literature.

In the first report in this issue of *Vascular Medicine*, Kollias and colleagues conducted a systematic review and meta-analysis of VTE prevalence in COVID-19.<sup>7</sup> They performed a systematic literature search of publications through September 30, 2020 and identified 47 eligible studies addressing prevalence of PE and/or DVT. Additionally,

they abstracted data individually for DVT and PE when available to explore their potential differential prevalence. The authors found that the pooled PE prevalence from 17 studies was 32% (95% CI: 25–40%) while the pooled DVT prevalence from 32 studies was 27% (95% CI: 21–34%). The pooled odds ratio for death among patients with COVID-19 and VTE was 2.1 (95% CI: 1.2–3.6). Although there was not an association between VTE and certain key risk factors, including age and sex, there was a higher prevalence with increasing d-dimer levels (prevalence ratio 1.3 per 1000 ng/mL increase; 95% CI: 1.11–1.5).

Secondly, Finn and colleagues conducted a single-center evaluation of treatment approaches, mortality, and bleeding outcomes in patients with COVID-19 who received PERT consultation.<sup>8</sup> They identified PERT consultation requests from March 1, 2020 through April 30, 2020 at a large academic tertiary care hospital in New York City. These patients were compared to historical controls from the same dates in 2019. The authors found that there was a 2.8-fold increase in PERT consultations during the COVID-19 pandemic period compared to the historical control period (74 vs 26). Notably, definitive diagnosis of PE with computed tomography was significantly lower in the COVID-19 study period than among the historical controls (58.1% vs 92.3%,  $p = 0.001$ ).

They also reported higher rates of in-hospital mortality among the PERT consulted patients during the COVID-19 period (14.9% vs 3.9%); however, this did not reach statistical significance. For the primary safety outcome, there was also a trend towards increased Global Utilization of Streptokinase and Tissue Plasminogen Activator for

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Occluded Coronary Arteries (GUSTO) moderate or severe bleeding in patients during the COVID-19 pandemic (35.1% vs 19.2%). This, however, also did not reach statistical significance. There was a higher rate of Bleeding Academic Research Consortium (BARC) minor bleeding but a similar rate of BARC major bleeding in the COVID-19 and historical cohorts, respectively (91.9% vs 57.7%,  $p < 0.0001$ ). For secondary endpoints, the authors noted a nonsignificant increase in use of systemic thrombolytic therapy during the COVID-19 period (13.5% vs 3.9%), of which seven of the 11 patients receiving thrombolysis experienced GUSTO moderate to severe bleeding. Importantly, the authors note that invasive catheter-based interventions were not attempted in any COVID-19-positive patients. In total, 45 of the 74 patients were found to be COVID-19 positive. These patients had similar rates of intensive care unit admission, increased rates of mechanical ventilation, and increased requirement of vasoactive medications. Use of systemic anticoagulation alone was significantly increased at 83.3% in the COVID-19 period, compared to 46.5% in the historical control period. There were similar rates of use of unfractionated heparin as well as enoxaparin.

These two studies bring to light a few important findings and experiences regarding VTE in patients with COVID-19. First, the pooled prevalence of DVT and PE in patients with COVID-19 appear to be significantly increased compared to patients hospitalized without COVID-19, upwards of 27–32%.<sup>9</sup> Attributed to the aforementioned microthrombotic, immunoinflammatory, and coagulation dysregulation effects, the clinical impact is quite dramatic, with nearly one-third of patients experiencing some form of VTE during their hospitalization. Apart from the respiratory impact of the coronavirus, thrombotic disease becomes a major concern in these patients. This also places particular emphasis on treatment strategies and VTE prophylaxis in this population.

With regards to treatment strategies in patients with high-risk PE for whom PERT consultation is sought, Finn and colleagues describe key initial adaptations in how care was delivered during the first wave of COVID-19 infections and hospitalizations. During the height of the pandemic, their experience suggests that fewer patients were undergoing imaging to confirm PE given infectious concerns related to COVID-19. As with many hospital systems across the world, the intent to reduce healthcare provider exposure also resulted in a modification of treatment approach as none of the COVID-19-positive patients received invasive or catheter-based therapies. Instead, they likely relied on clinical evidence from the Pulmonary Embolism Thrombolysis (PEITHO) trial, which found a reduction in the combination of death and hemodynamic decompensation at 7 days when patients were treated with systemic thrombolysis as compared to anticoagulation alone.<sup>10</sup> As a result, more critically ill patients with PE in this series received systemic fibrinolytics and a trend towards higher bleeding rates was consequently observed. This matches the findings from the PEITHO trial.

Taken together, these two reports highlight important areas for ongoing and future research. Certainly, a very active area of investigation is finding the appropriate

pharmacologic strategy for managing patients with COVID-19. Given high prevalence of VTE in patients hospitalized with COVID-19, preventative anticoagulation strategies using different intensity dosing regimens are of particular importance for further investigation. Three ongoing multicenter randomized trials (ACTIV-4a, ATTACC, REMAP-CAP) are evaluating empiric therapeutic-dose anticoagulation (vs standard VTE prophylaxis) in hospitalized patients with COVID-19 to improve clinical outcomes.<sup>11–13</sup> Another recently reported trial among critically ill patients found no benefit for intermediate-dose over standard dose prophylactic anticoagulation.<sup>14</sup> Other ongoing studies are exploring the efficacy of intermediate and low-dose anticoagulation as well as the role of adjunctive antiplatelet and combination therapies in both inpatient and outpatient settings.<sup>15</sup> As these studies begin to report their findings, a key priority is to improve VTE risk stratification methods for patients with COVID-19 so that a more personalized approach to VTE prevention can be implemented.<sup>16,17</sup>

Although another pandemic on the scale of COVID-19 is unlikely in the near future, lessons learned from 2020 can help to prepare for future management plans. For example, PERTs should consider how best to manage patients when infectious concerns limit access to diagnostic and therapeutic modalities. Though health systems are likely to reinforce their stockpiles of personal protective equipment in case of another COVID-19 surge or a new infectious outbreak, clinicians should also discuss the ethical and practical implications of selectively using diagnostic and therapeutic tests based on the perceived risk to healthcare workers versus the risk of adverse events for patients. Finally, the experience of COVID-19 highlights the importance of vascular medicine as part of multispecialty care teams, owing to the high burden of thrombotic disease observed in affected patients. There remains much to learn in order to best prevent and treat the wide range of vascular disorders related to this once-in-a-lifetime pandemic.

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