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Letters

Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19

The novel coronavirus disease-2019 (COVID-19) has affected nearly every country worldwide. Reports note increased thromboembolic events among hospitalized patients (1,2), and there are anecdotal observations of improved outcomes with systemic anticoagulation (AC); however, the specific role of AC in disease management remains unclear (3,4). We assessed the association between administration of in-hospital AC and survival in a large cohort of hospitalized patients with COVID-19. This work was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai (#20-03271).

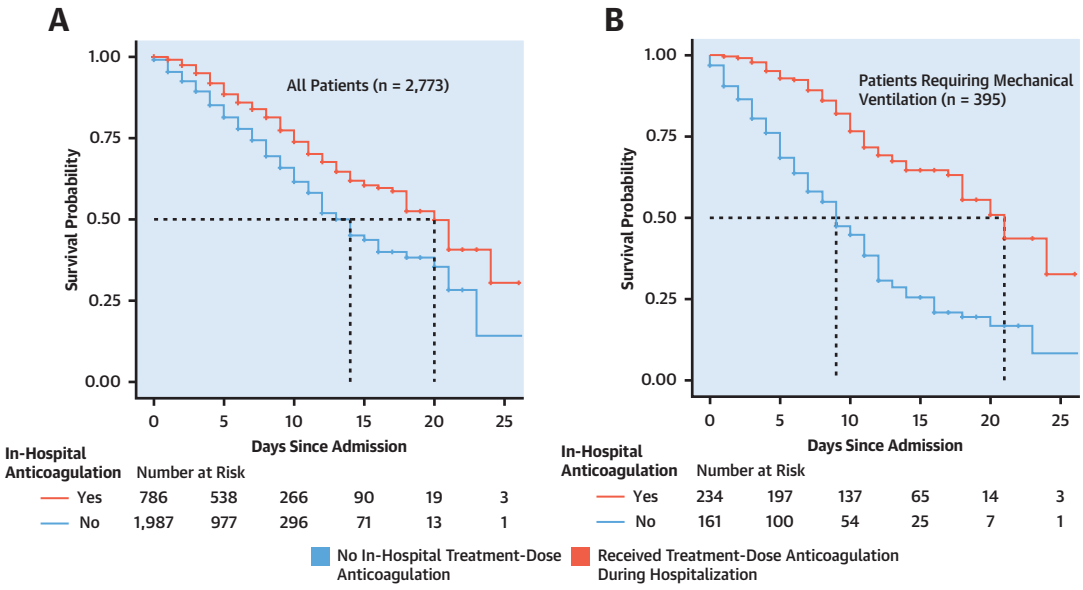
Between March 14 and April 11, 2020, 2,773 patients were hospitalized with laboratory-confirmed COVID-19 within the Mount Sinai Health System in New York City. We used a Cox proportional hazards model to evaluate the effect of treatment-dose systemic AC (including oral, subcutaneous, or intravenous forms) on in-hospital mortality. We adjusted for age, sex, ethnicity, body mass index, history of hypertension, heart failure, atrial fibrillation, type 2 diabetes, AC use prior to hospitalization, and admission date. To adjust for differential length of stay and initiation of AC treatment, AC treatment duration was used as a covariate while intubation was treated as a time-dependent variable.

Among 2,773 hospitalized patients with COVID-19, 786 (28%) received systemic treatment-dose AC during their hospital course. The median hospitalization duration was 5 days (interquartile range [IQR]: 3 to 8 days). Median time from admission to AC initiation was 2 days (IQR: 0 to 5 days). Median duration of AC treatment was 3 days (IQR: 2 to 7 days). In-hospital mortality for patients treated with AC was 22.5% with a median survival of 21 days, compared to 22.8% and median survival of 14 days in patients who did not receive treatment-dose AC (Figure 1A). Patients who received treatment-dose AC were more likely to require invasive mechanical ventilation (29.8% vs 8.1%; $p < 0.001$) as compared to those who received prophylactic dose AC or did not receive AC. Overall, we observed significantly increased baseline prothrombin time, activated partial thromboplastin time, lactate dehydrogenase, ferritin, C reactive protein, and D-dimer values among individuals who received in-hospital AC compared with those who did not. These differences were not observed, however, among mechanically ventilated patients. In patients who required mechanical ventilation ($n = 395$), in-hospital mortality was 29.1% with a median survival of 21 days for those treated with AC as compared to 62.7% with a median survival of 9 days in patients who did not receive treatment-dose AC (Figure 1B). In a multivariate proportional hazards model, longer duration of AC treatment was associated with a reduced risk of mortality (adjusted HR of 0.86 per day; 95% confidence interval: 0.82 to 0.89; $p < 0.001$).

We also explored the association of systemic treatment-dose AC administration with bleeding events. Major bleeding was defined as: 1) hemoglobin <7 g/dl and any red blood cell transfusion; 2) at least 2 U of red blood cell transfusion within 48 h; or 3) a diagnosis code for major bleeding including intracranial hemorrhage, hematemesis, melena, peptic ulcer with hemorrhage, colon, rectal, or anal hemorrhage, hematuria, ocular hemorrhage, and acute hemorrhagic gastritis. Among those who did not receive treatment-dose AC, 38 (1.9%) individuals had bleeding events, compared with 24 (3%) among those who received treatment-dose AC ($p = 0.2$). Of the 24 patients who had bleeding events on AC, 15 (63%) had bleeding events after starting AC and 9 (37%) had bleeding events before starting AC. Bleeding events were more common among intubated patients (30 of 395; 7.5%) than among non-intubated patients (32 of 2,378; 1.35%).

Although limited by its observational nature, unobserved confounding, unknown indication for AC, lack of metrics to further classify illness severity in the mechanically ventilated subgroup, and indication bias, our findings suggest that systemic treatment-dose AC may be associated with improved outcomes

FIGURE 1 Kaplan-Meier Curve for Hospitalized Patients With COVID-19 and Those Mechanically Ventilated



Kaplan-Meier curve for hospitalized patients with COVID-19 **(A)** and those mechanically ventilated **(B)**. **Colors** indicate treatment-dose anticoagulation. Patients hospitalized at time of data-freeze or discharged within the study period were right-censored. COVID-19 = novel coronavirus disease-2019.

among patients hospitalized with COVID-19. The potential benefits of systemic AC, however, need to be weighed against the risk of bleeding and therefore should be individualized. The association of in-hospital AC and mechanical ventilation likely reflects reservation of treatment-dose AC for more severe clinical presentations. Interestingly, there was an association with AC and improved survival after adjusting for mechanical ventilation.

These data, derived from a large United States cohort, provide clinical insights for consideration in the management of patients hospitalized with COVID-19. Prospective randomized trials are needed to determine whether systemic AC confers a survival benefit in hospitalized patients with COVID-19.

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Acute Myocardial Injury at Hospital Admission Is Associated With All-Cause Mortality in COVID-19

The outbreak of coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has now become a global pandemic. SARS-CoV-2 uses angiotensin-converting enzyme (ACE) 2 as the receptor for entry into host cells. The virus can attack organs with high ACE2 expression such as the heart, kidney, and gastrointestinal tract, in addition to the lungs. Acute myocardial injury is common among patients with COVID-19, and fulminant myocarditis and even sudden cardiac death are not rare. Recent studies found that patients with myocardial injury in hospitalization had a significantly higher in-hospital mortality rate than did those without myocardial injury (1,2). However, it is still unclear whether myocardial injury at the time of admission indicating early cardiac involvement is also a risk factor for mortality in COVID-19.

To study the association between acute myocardial injury at admission and all-cause mortality risk in COVID-19, we conducted a retrospective single-center cohort study among adult inpatients (age >18 years) in the Central Hospital of Wuhan, a COVID-designated hospital in Wuhan, China. All patients had been diagnosed with COVID-19 by both nucleic acid testing and chest computed tomography scanning. Patients who died or were discharged between January 28 and March 16, 2020 were included in our study. According to the Chinese management guideline for COVID-19 (version 7.0) (3), the discharge criteria are that patients have no fever for at least 3 days, have significant relief of respiratory symptoms and improvement on chest computed tomography, and have a negative SARS-CoV-2 laboratory test result twice in succession. Acute myocardial injury is defined as elevation of troponin I above the 99th percentile upper reference limit (4). This study was approved by the Research Ethics Commission of the Central Hospital of Wuhan, and was conducted in accordance with the Declaration of Helsinki.

A total of 179 patients were enrolled, and 176 (116 survivors, 60 nonsurvivors) with troponin I tests at admission were included in the current study. Median age was 67 years (interquartile range: 57 to 73 years), and 57.39% of the patients were men. The most common comorbidities were hypertension (n = 87 [49.43%]), diabetes (n = 47 [26.70%]), hyperlipidemia (n = 30 [17.05%]), coronary heart disease (n = 25 [14.20%]), and cerebrovascular disease (n = 24 [13.64%]). No patients had myocardial infarction or heart failure within 1 month before admission. Compared with survivors, nonsurvivors were older; had a higher proportion of comorbidities, including hypertension, cerebrovascular disease, and pulmonary diseases; had worse disease severity status; and had a higher proportion of acute myocardial injury on admission (58.33% vs. 12.07%). Among the 60 nonsurvivors, 25 (41.67%) with myocardial injury at admission died of circulatory failure or both respiratory failure and circulatory failure. Kaplan-Meier curves showed that acute myocardial injury at admission increased the risk of death in patients with COVID-19 (**Figure 1**). We included 169 patients in multivariable binary logistic regression models. After adjusting for sex, age, fever, severity status, comorbidities, background use of ACE inhibitors or angiotensin II receptor blockers, pulse, fasting plasma glucose, creatinine, white blood cell count, neutrophil count, platelet count, albumin, and glucocorticoid treatment, the regression models showed that acute myocardial injury significantly increased the death risk (crude odds ratio: 10.20; 95% confidence interval: 4.78 to 21.78; $p < 0.0001$; adjusted odds ratio: 6.93; 95% confidence interval: 1.83 to 26.22; $p = 0.0044$). The stratified analyses also showed that the results of the aforementioned associations remained robust according to baseline characteristics.

In summary, our cohort study demonstrated that acute myocardial injury at admission was associated with a higher risk of all-cause mortality in patients with COVID-19, which highlighted the importance of closely monitoring changes of myocardial enzymes, cardiac rhythm, and cardiac functions, and thus providing timely interventions, especially when