Thrombotic Events and Death Among Inpatients with COVID-19

Background

An adaptive randomized controlled trial (RCT) funded by the National Institutes of Health (NIH) is examining the most effective anti-thrombotic strategy to increase the number of organ support-free days and reduce thrombotic events and death among hospitalized adult COVID-19 patients. The RCT will stratify patients by d-dimer level and intensive care status, and while these are presumed risk factors for poor prognosis, there remains limited information on background event rates in these populations.

Objective

Among hospitalized non-pregnant adults with COVID-19, we aimed to described the number of patients with hospitalized thrombotic events or death through 28 days. We stratified each outcome by d-dimer level and record of early intensive care services.

Methods

We used electronic health record (EHR) data from the TriNetX Live™ USA Network to identify adults (age 18+ years) with positive COVID-19 antigen or PCR laboratory test results or documented COVID-19 diagnoses (ICD-10 codes: B97.29, U07.1, B34.2, B97.2, J12.81) within ±3 days of a hospitalization record. We queried 65 health care organizations' (HCOs) data from 2/20/2020 through 10/16/2020. Patients indexed on the first date they were both hospitalized and had evidence of COVID-19. To align with the RCT protocol, we excluded patients with evidence of: major bleeding, hemophilia, von Willebrand disease, heparin-induced thrombocytopenia (HIT), or tracheostomy in the 30 days prior to index; platelet count < $50x10^9$/liter or hemoglobin < 8 g/dL in the day prior through 3 days after; evidence of pregnancy in the 84 days prior; anticoagulant, thrombolytic, or antiplatelet therapy from 183 to 2 days prior; and those with a thrombotic event on the day of or day prior to index date.

We described baseline characteristics, including use of anticoagulants, antiplatelets, and thrombolytics in the first 3 days. We examined the composite outcome of death or ICD-10-CM record for hospitalized deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), or ischemic stroke (IS) through 28 days.

We conducted subgroup analyses examining outcomes by d-dimer level (elevated defined as (> 500 ng/mL for FEU; > 250 ng/mL for DDU) and a proxy indicator for early intensive care [IC] (record of the following events in the first 3 days: invasive mechanical ventilation, extracorporeal membrane oxygenation [ECMO], vasopressors, or evaluation/management CPT codes for critical care).

Results

We identified 23,580 hospitalized non-pregnant adult COVID-19 patients who met the cohort identification criteria (mean age 57 years, 49% female). Approximately 53.1% of included patients (n=12,510) initiated treatment with any anticoagulant, antiplatelet, or thrombolytic up to 3 days after COVID-19 identification. A total of 1,290 (5.5%) patients experienced a hospitalized thrombotic event or died through 28 days (compared to 17.8% among those with early IC and 3.7% of patients without early IC). Results were similar for patients regardless of d-dimer level (elevated=5.6%, normal=6.4%) among those with d-dimer laboratory results in the first 3 days (46.2%).

Limitations

We applied specific exclusion and inclusion criteria to mirror the RCT, which likely resulted in a healthier population that may differ from those explored in other studies. Specifically, because

patients presenting with a thrombotic event would not have been eligible for randomization in the RCT, these patients were excluded, potentially resulting in lower capture of this outcome. Additionally, while our composite definition of thrombotic events is comparable to the RCT, we did not include systemic arterial thromboembolism due to lack of a known validated algorithm for identification. Finally, due to the nature of EHR data, we were unable to track events occurring between or outside of the participating HCOs.

Conclusions

Death or hospitalized DVT, PE, MI, or IS in the 28 days following index was observed in 5.5% of inpatients overall and ~18% of inpatients with an indicator for early intensive care. Death or hospitalized DVT, PE, MI, or IS in the 28 days following index were similar for patients regardless of d-dimer level. Our findings for death or thrombotic events are lower than would be expected based on published literature but this difference may be attributed to several factors including the selective choice of study population and incomplete capture of inter- and outer-HCO events.