COVID-19 Evidence Accelerator Collaborative

Lab Meeting # 43

Thursday, October 21st, 2021, 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 43

During the 43rd Vaccines and Therapeutics Evidence Accelerator Lab meeting the group heard two presentations on results from two parallel analyses conducted by the Accelerator. First, Dr. Noelle Cocoros of the Harvard Pilgrim Healthcare Institute, presented results from the Natural History of Coagulopathy study. We then heard Dr. Amar Bhat of the Reagan-Udall Foundation for the FDA provide a brief presentation of results from the Remdesivir parallel analysis.

Natural History of Coagulopathy in COVID-19

Noelle M. Cocoros, DSc, MPH, Harvard Pilgrim Healthcare Institute
Vincent Lo Re, MD, MSCE, FISPE, Perelman School of Medicine, University of Pennsylvania

Background

- Case series of hospitalized COVID-19 patients indicated many develop arterial or venous thrombotic complications.
    - Case series were limited in that they included small numbers, evaluated hospitalized patients, and did not examine factors associated with these events.
    - Knowledge gaps: incidence, determinants, & consequences of arterial and venous thrombotic complications with COVID.
- Studies that evaluate the epidemiology of these events using real-world data (RWD) can provide evidence on their frequency & mechanisms and can inform the development/ study of interventions to reduce risk of these outcomes.

Specific Aims

- ***Aim 1 –*** Determine the 90-day incidence of arterial & venous thrombotic events (evaluated separately) with COVID-19 and risk of death within 30-days of an event.
    - **Hypothesis:** Events will occur within 90 days of COVID dx and may result in death.
- ***Aim 2 –*** Evaluate patient characteristics present prior to CVOID-19 dx as risk factors for arterial and venous thrombotic events (evaluated separately).
    - **Hypothesized risk factors:** Characteristics that promote stasis of circulation, endothelial injury, hypercoagulability will be risk factors for thrombosis.
- ***Aim 3 –*** Compare 90-day risk of arterial and venous thrombotic events (evaluated separately) between health plan members with COVID-19 and those with Influenza.
    - **Hypothesis:** Risk of thrombotic events will be higher with COVID-19 than Influenza.

Study Design & Date Source

- Retrospective cohort study
- Source: FDA's Rapid Sentinel Distributed Database
    - 4 integrated health systems (EHR + claims)
    - 2 large national insurers (claims only)
- Data points
    - Lab data (availability of lab data varied by partner and care setting)
        - COVID-19
        - Influenza
        - Clinical Labs
    - Identify thrombotic events via diagnosis codes
    - Identify pre-existing comorbidities, outpatient dispensed medications

Study Patients

Aims 1 & 2

- Patients with a COVID-19 ICD-10 diagnosis code OR positive nucleic acid test (NAAT), April 1, 2020 – October 31, 2020 (study period ends before vaccines widely available)
- 1 year or more of continuous enrollment at the time of diagnosis
- No coinfection with another respiratory virus
- All eligible health plan members selected

Aim 3

- **COVID-19 Cohort:** Patients with a COVID-19 ICD-10 diagnosis code OR positive nucleic acid test (NAAT), April 1, 2020 – October 31, 2020
- **Influenza Cohort:** Patients with an Influenza A or B ICD-10-CM diagnosis code OR positive NAAT, October 1, 2018 – April 30, 2019
- 1 year or more of continuous enrollment at the time of diagnosis
- No coinfection with another respiratory virus
- All eligible health plan members selected

Primary Outcomes: Thromboembolic Events

- **Arterial Thrombosis** – acute myocardial infarction, acute ischemic or embolic stroke
- **Venous Thromboembolism** – acute upper/lower deep venous thrombosis (DVT), acute pulmonary embolism (PE)
- Outcomes based on hospital discharge ICD-10-CM diagnosis (from any position)
    - Mapped from ICD-9-CM diagnoses validated in sentinel data
    - Mapped ICD-10-CM diagnoses underwent clinical review

Secondary Outcomes

- Primary outcomes were limited to in-patient settings, secondary outcomes expand outside inpatient care setting
- **Arterial –** ICD-10-CM diagnosis for primary outcome, angina, transient ischemic attack (TIA), peripheral arterial disease (PAD), amputation, or other cerebrovascular disease in emergency department (ED), institutional stay, OR inpatient setting.
- **Venous –** ICD-10-CM for primary outcome or thrombosis of device, implant, or graft in ED, institutional stay, OR inpatient setting.

- **All-Cause Mortality** – death from any cause, among those with an Arterial Thrombotic Event (ATE) or Venous Thrombotic Event (VTE) (evaluated separately)

Data Analysis

Aim 1

- Described the characteristics of COVID-19 cohort
- Absolute risk and incidence rates of outcomes within 90-days of diagnosis:
    - By arterial and venous events
    - Stratified by:
        - age, sex, setting of diagnosis (ambulatory, hospital)
        - disease severity at diagnosis, prior cardiovascular disease (CVD) history, prior VTE history
        - baseline anticoagulant use, antiplatelet use
- Absolute risk and incidence rate of death within 30-days of primary outcome

Aim 2

- Multivariable Cox regression: adjusted HRs (95% CIs) of events associated with predictors

Aim 3

- Compare characteristics between COVID-19 and Influenza cohorts
- Weighted Cox regression accounting for propensity score: adjusted HRs (95% CIs) of outcomes in persons with COVID-19 vs. Influenza
    - Stratified by setting of diagnosis, prior thromboembolism history

Aim 1 Results

Rates of Primary Arterial Thrombotic Events and Primary Venous Thromboembolism Events in COVID-19

- Absolute risk for ATE in the overall population = 2.8%
- Absolute risk for VTE in the overall population = 1.8%
- Increased risk for ATE & VTE with increased age
- Elevated risk for ATE & VTE in males compared to females
- Lower risk for ATE & VTE among outpatients, elevated risk for ATE & VTE higher among patients admitted to ICU or ventilated during their stay:
    - 18.7% vs. 1.1% for outpatients (ATE)
    - 10.8% vs. .8% for outpatients (VTE)

Incidence Rates of Events Overtime (April 2020 – October 2020)

- Overtime, the incidence of inpatient events of interest (primary ATEs and VTEs) decreased as clinicians got a better understanding of how to treat/ manage the disease.

Aim 2 Results

Risk Factors for Primary ATEs and VTEs in COVID-19

- Adjusted HRs – even with other factors in the model, with increased age comes increased risk for ATEs and VTEs, risk plateaus at 75+, risk no longer keeps increasing with age after 75
- Increased risk of ATEs and VTEs for males, pregnant women, alcohol/tobacco use,
- Increased risk of ATEs for patients with chronic kidney disease, hypertension, diabetes
- Increased risk of VTEs for patients with hypertension, heart failure, thrombocytosis

- History of anticoagulant use is slightly protective from ATEs
- Statin use and anticoagulant use slightly protective from VTEs

Aim 3 Results

COVID-19 and Influenza Cohorts Before and After Propensity Score Adjustment

- COVID-19 Cohort (n=240,826), Influenza Cohort (n=127,117)
    - Slightly older COVID cohort, slightly more women in the Influenza cohort
    - Slightly more prior health service utilization (mean number of ambulatory encounters, mean number of inpatient hospital encounters) among COVID-19 cohort compared to Influenza cohort
    - Care setting at index – important difference between where COVID and Influenza were diagnosed
        - Influenza typically diagnosed in outpatient care setting (6.5% were hospital inpatient)
        - COVID-19 tended to be diagnosed at hospital prior to admission (12.5% hospital inpatient)
    - Higher prevalence of asthma and COPD, more corticosteroid use in Influenza cohort
    - Higher prevalence of chronic kidney disease, chronic liver disease, diabetes, heart failure, etc. in COVID-19 cohort
- Characteristics more balanced after propensity score adjustment

Risk of Inpatient ATEs and VTEs in COVID-19 vs. 2018-19 Influenza, by Index Care Setting

- Index identified in all care settings (primary cohorts)
    - Higher risk for ATEs in COVID-19 cohort (1.09 (1.03-1.16))
    - Higher risk for VTEs in COVID-19 cohort (1.89 (1.73-2.07))
- Index identified in ambulatory setting
    - Higher risk for ATEs in COVID-19 cohort (1.6 (1.44-1.78))
    - Higher risk for VTEs in COVID-19 cohort (2.92 (2.5-3.41))
- Index identified in inpatient setting
    - ATEs Null result (.99 (.93-1.06))
        - Influenza patients who are hospitalized typically have severe disease, could help explain null result
    - Higher risk for VTEs in COVID-19 cohort (1.62 (1.45-1.80))

Risk of Secondary ATEs & VTEs, and Death in COVID-19 vs. 2018-19 Influenza

- Expanded definition of ATE/care settings
- Similar result to primary endpoint – increased risk for ATE in COVID-19 cohort (1.08 (1.05-1.12)
- Risk for mortality also increased among those with an inpatient ATE in the COVID cohort compared to the Influenza cohort (3.42 (2.72-4.32))
- Risk of VTE and Death higher in COVID-19 cohort compared to Influenza cohort
    - HR 95% CI = 1.88 (1.72-2.04) for VTE
    - 3.18 (2.15-4.71) for mortality among those with an inpatient VTE
- Risk elevated more among those without history of VTE

Limitations

- **Selection Bias** – variation in COVID-19 testing by geographical area, calendar time, and disease severity.
    - Testing limitations are why we also used testing codes, not just test results.
- **Misclassification** – lack of validation of ICD-10 diagnoses for thromboembolic events.
    - Chart reviews going well, indicating events of interest were accurately identified.
- **Uncontrolled Confounding –** Incomplete data on race, calculated propensity scores in primary cohorts only.
- **Generalizability –** Asses COVID-19 April – October 2020; single influenza season only.

Remdesivir Parallel Analysis Presentation of Aim 4 Results

Amar Bhat, PhD, Reagan-Udall Foundation for the FDA

Research Aims

- ***Aim 1 –*** Characterize use of remdesivir among hospitalized patients with COVID-19 after implementation of the emergency use authorization (EUA).
- ***Aim 2 –*** Develop and construct a propensity score model to achieve balance on observed characteristics to apply in aim 4.
- ***Aim 3 –*** Assess weighting technique assumptions and diagnostics and confirm that baseline balancing is achievable.
- ***Aim 4 –*** Assess the real-world safety and effectiveness of remdesivir among hospitalized patients with COVID-19.

Treatment Groups

- **Exposure period**: day of hospital admission + 2 days after
- **Treatment group**: patients who received Remdesivir during the exposure period.
- **Comparison group**: patients who did not receive Remdesivir during the exposure period, including those who received Remdesivir later in hospitalization.

Cohort Description

- Hospitalized COVID-19 Patients (COVID-19 diagnosis in clinical record AND/OR positive SARS-CoV-2 RNA test) from May 1, 2020, to May 1, 2021 (Dascena), October 11, 2020 (Health Catalyst), July 5, 2021 (Target RWE)
- Excluded inpatient records with:
    - Incomplete COVID-19 treatment data
    - Hospitalization greater than 14-days after the time of COVID-19 diagnosis or to evidence of clinical encounter, and/or greater than 7-days from hospitalization to COVID-19 diagnosis
    - Hospitalizations related to COVID-19 following the first hospitalization related to COVID-19
    - Age < 18 year old, or missing age/sex information
    - Mechanical ventilation, on ECMO, or died/discharged within the first 2 days after hospitalization

Sample Sizes & Dates

- **Dascena –** 7 US hospitals (May 1, 2020 – May 1, 2021), 604/650 (Patients receiving Remdesivir/ Comparison group)

- **Health Catalyst –** 16 US Health Systems (May 1, 2020 – October 11, 2020), 4627/7221
- **Target RWE –** 333 Hospitals in 40 US States (May 1, 2020 – July 5, 2021), 66837/94129

Approach

Aims 2 & 3

- Intent to Treat (ITT) approach – Patients either treated or not during exposure period, regardless of later receipt of treatment. (Goal: protect against bias that may arise from impending bad outcomes causing later remdesivir use in the comparison group).
- Inverse probability weight (IPTW) with weights constructed to estimate the average treatment effect on the treated (ATT).
- Patients were "trimmed" from the analytic sample as needed to create appropriate overlap in the propensity score distributions. (Trimming differed by partner depending on data-specific needs)
- Balance was assessed via standardized mean differences (SMDs) (SMDs <= 0.1 indicate good balance)
    - All measured & included covariates were balanced after weighting and had SMD <= 0.1 or close to this threshold.
    - Confounders differed in availability by data source so not all could be incorporated into each analysis.

Aim 4 Effectiveness & Safety Outcomes

- **In-hospital mortality** – binary indicator (0/1) of whether patient died during hospitalization
- **Ventilation during hospitalization** – binary indicator of whether patient was ventilated or on ECMO during hospitalization (patients ventilated during exposure window should have been excluded already)
- **Hospital length of stay** – number of days from hospital admission to discharge
- **Acute kidney injury (AKI)** – binary indicator (0/1) of whether the patient experienced a diagnosis code for AKI during their hospital stay. AKI defined by ICD-10-CM code N17*, N19*, R34*

Results

In-hospital mortality

- Target RWE estimated protective effect of Remdesivir – fewer patients receiving Remdesivir died of COVID-19 compared to patients not receiving Remdesivir.
- Dascena & Health Catalyst – null/ not statistically significant results

In-hospital ventilation

- Target RWE & Health Catalyst – statistically significant odds of increased in-hospital ventilation
- Dascena – estimated similar HR to Health Catalyst, but will null CI

Acute kidney injury

- Health Catalyst estimated protective effect against AKI
- Dascena & Target RWE had non-significant results
- Lingering questions about safety issues

Hospital length of stay

- Slightly longer length of stay for patients receiving Remdesivir in the hospital

Limitations

- Residual confounding
- Good weighting and balance, but some differences in covariates measured and limited ability to control for other baseline characteristics, medications, disease severity, etc.

Summary

- One analysis found significant protection against mortality (other two had null results)
- Some evidence of increased in-hospital ventilation for Remdesivir-treated patients
    - Could be residual confounding or sicker patients survive but need ventilation
- Some evidence of less AKI among Remdesivir patients
- Some evidence of decreased rates of discharge/longer length of stays
    - Due to remaining alive or length of treatment?