COVID-19 Evidence Accelerator Collaborative

Lab Meeting # 26

Thursday, January 21, 2021 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 26

Therapeutics lab meeting 26 introduced the Accelerator's ongoing parallel analyses addressing various questions related to COVID-19. First, Jeff Allen of Friends of Cancer Research, gave an overview on how parallel analyses helped answer questions in the context of cancer and how this work was foundational to the Accelerators' ongoing analyses. Next, we heard from Valerie Smith of Duke University, and then from Noelle Cocoros from Harvard Pilgrim Health Care Institute, the Sentinel System Operations Center, about two ongoing parallel analysis question sets – one exploring the use of remdesivir among hospitalized COVID-19 patients, and the other focused on illustrating the natural history of coagulopathy. After a short discussion about the benefits and shortcomings of a parallel analysis, we heard from three colleagues at Yale University who created hospital capacity model to help hospital administrators plan for surges in admissions amid COVID-19. The meeting closed with this week's data visualization of the week.

Overview of the Parallel Analysis Process

Amy Abernethy, Food and Drug Administration
Jeff Allen, Friends of Cancer Research

***Friends'* aNSCLC Parallel Analysis: Immunotherapy (IO) Treated advanced non-small-cell lung cancer (aNSCLC)**

- Using different approaches, different data sources, and parameters, each group used their dataset to answer the same question, then came together to observe where their results aligned and diverged.
- Typically, measures like disease progression/survival are readily available in clinical trial data. When looking at EMR/EHR data, it is not so straightforward.
    - Part of the parallel analysis work aimed to identify definitions from EMR/EHR that may correlate with the more traditional outcome measures reported in clinical trials. (e.g., How does the time a patient stays on their treatment observed in real world data correlate with overall survival observed in clinical trials?)
    - Despite the heterogeneity of the real-world datasets used in the parallel analysis, the variability in outcomes (OS and TTD) observed was within a similar range as the variability observed across the clinical trials.
- The group used a similar observational approach to compare the performance of IO in aNSCLC to a different treatment option in the same setting.

    - In the clinical trial results, the PD-(L)1 therapy outperformed chemotherapy.
    - When observing the real-world endpoints, there was a few results:
        - Overall Survival at 12 months by Treatment
            - Wide range of variability in survival observed across datasets could be owed to lack of follow-up time, patient cross over, missing data, etc.
        - Fraction of Patients Who Have Not Started Next Treatment by 12-months
            - More consistency observed here
        - Fraction of Patients Who Have Not Discontinued Treatment at 12-months
            - More consistency observed here
- This work raised the question: when consistency is observed across multiple datasets, could it be of greater or comparable value to the results from one clinical trial?

Lessons Learned

- Understanding differences across the datasets help to understand replication in results, as well as convergence and divergence of observations.
- When considering how to apply the real-world data approach to get rapid answers in the context COVID-19, we utilized lessons learned from *Friends'* parallel analysis work.
    - Replication in real-world datasets, interpreting convergence and divergence of results.

Remdesivir Parallel Analysis Question Set: Aim 1 Results*

Valerie Smith, Duke University

*These results are preliminary and include high-level overarching trends seen across partners. Any percentages presented are approximate or ranges, summarizing the preliminary numbers seen across varying partners' reports

Aim 1: Characterize use of remdesivir among hospitalized patients with COVID-19 after implementation of EUA

1. What are the characteristics of the hospitalizations where remdesivir is being administered?
2. What are the characteristics of hospitals administering remdesivir?
3. Among hospitalized patients, what are the treatment patterns associated with remdesivir including concomitant medication?
4. Among hospitalized patients, how has remdesivir prescribing changed overtime?
5. Among hospitalized patients, what are the clinical characteristics of patients getting remdesivir?
6. Among hospitalized patients, what are the baseline sociodemographic and comorbidities of patients getting remdesivir?

Data Used: Includes data from 8 hospital systems, health data companies, etc. with COVID-19 patient populations between 1,712 and 118,238.

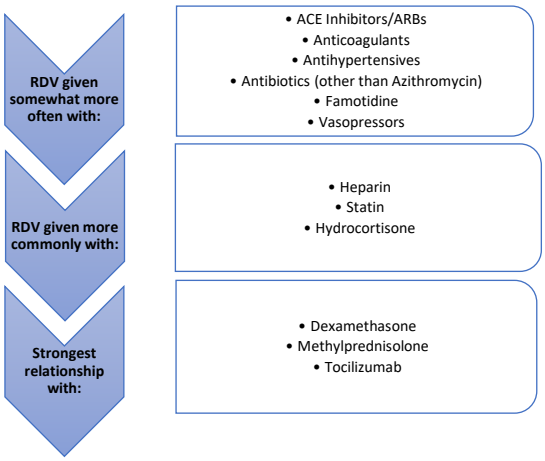
- Data included includes representation of all regions of the U.S. – representation varies by partner

Results*

- **Q1. Characteristics of hospitalizations when remdesivir is being administered**
    - Most commonly administered in a standard in patient care setting (~80% of use in most datasets vs. ~20% of use in ICUs)
    - The majority of hospitalized patients were not given remdesivir (8-35% across groups)

- **Q2. Characteristics of hospitals administering remdesivir**
    - 70-100% of hospitals administered remdesivir (not all partners reported this information)
    - Remdesivir was somewhat more often provided in hospitals with more beds
    - Some data partners reported urban hospitals were more likely to administer remdesivir, others reported no noticeable differences.

- **Q3. Treatment patterns associated with remdesivir (RDV) including use of concomitant medications**



    - No information yet available on sequencing of these medications; however, slightly more than half of patients who received RDV did so within the first day of hospitalization.

- **Q4. Remdesivir prescribing overtime among hospitalized patients**
    - Prescribing of RDV slowly increased over time and somewhat leveled off in Summer 2020
- **Q5. Clinical characteristics of patients getting remdesivir**
    - The majority of patients did not have a fever at hospitalization (< 10%, whether receiving remdesivir or not)
    - No noticeable differences in blood pressure between patients receiving remdesivir and those not
    - Among patients getting Remdesivir:
        - O2 saturation <= 93, but still administered to patients with O2 > 93
        - >90% required supplemental oxygen
        - Patients with higher respiratory rate received remdesivir more commonly
        - Patients with neutrophil-lymphocyte ratio (NLR) > 5 or lymphocytes <10% received remdesivir slightly more frequently
        - Patients with higher Ferritin levels received remdesivir more commonly
        - Patients with poorer liver function (AST>40 U/L or ALT>40 U/L) received remdesivir more frequently
        - Patients receiving remdesivir had somewhat higher lactate dehydrogenase levels (median ~380 compared to ~300)

- **Q6. Baseline sociodemographic and comorbidities of hospitalized patients getting remdesivir**
    - No significant patterns in use by age, but almost no pediatric use reported by partners
    - Hospitalized males received slightly greater proportions of remdesivir (about 2-5 percentage points more) than hospitalized females
    - Black patients received remdesivir at lower proportions (1-5 percentage points) than white patients
    - Hospitalized Hispanic patients received remdesivir between 7 percentage points less and 11 percentage points more (variation by data partner) than non-Hispanic patients (no systematic trend observed)
    - Currently compiling comorbidity data

Limitations

- Not all data elements discussed were available from all partners & these results are only preliminary.
- Results presented were descriptive trends, not predictors that cause remdesivir to be give more/less often. Additional analysis is needed to understand these relationships.

Next Steps

- Refine data elements needed to complete aim 1:
    - targeted limiting medication assessment to those most relevant to COVID-19 outcomes
    - focus only on outcomes during the *first* hospitalization for COVID-19
- Standardize medication definitions
    - Different hospitals/systems use different definitions/codes for medications, we will work to standardize these.
- Work with data partners based on revised protocol to finalize aim 1 results
- More clinical input to better understand clinical importance of observed trends
- Analysis to formally assess predictors of remdesivir use, accounting for major factors that influence use simultaneously (aim 2)

Descriptive Assessment of Coagulopathy Among COVID-19 Patients – Feasibility Data from the Sentinel System

Noelle Cocoros, Harvard Pilgrim Health Care Institute

Aim 1: Determine incidence of arterial and venous thromboembolic events (evaluated separately) with COVID-19 and its consequences.

- Hypothesis: Events will occur within 90 days and may result in death.

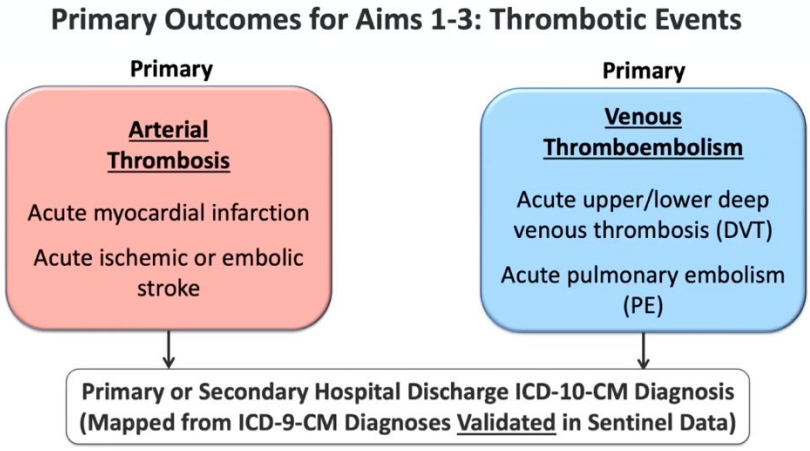
Aim 2: Evaluate patient characteristics present at COVID-19 diagnosis as risk factors for arterial and venous thromboembolic events (evaluated separately).

- Hypothesis: Characteristics that promote endothelial injury, stasis of circulation, and hypercoagulability will be risk factors for thromboembolism.

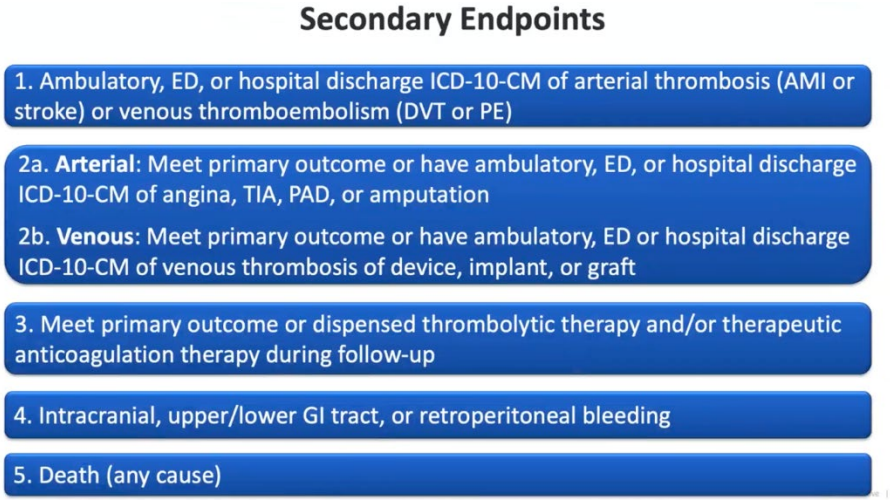
Aim 3: Compare risk of arterial and venous thromboembolic events (evaluated separately) between health plan members with COVID-19 and those with influenza.

- Hypothesis: Risk of thromboembolic events will be higher with COVID-19 than influenza.

Primary Outcomes



Secondary Endpoints



Feasibility Data

- 9 Sentinel data partners populated table shells, provided by the coagulopathy working group, to help inform sample size calculations and to provide preliminary information for full study implementation focused on primary outcomes.
- Data examined by type of partner – 5 integrated delivery systems (IDS), 4 national insurer/claims data.
- Gave specific instructions and criteria to partners on how to define COVID-19 and influenza cohorts (ICD-10 codes, test results, timeframes)

COVID-19 Cohort

- **Health plan members with COVID-19, by cohort entry criteria (Jan 20 – July 31, 2020)**
    - Majority of patients were identified as having a covid-19 by diagnosis code (u07.1 or B97.29)

- **Counts of arterial thrombosis and venous thromboembolic events among health plan members with COVID-19 (Jan 20 – July 31, 2020**
    - Arterial events for claims and IDS were 3.0% and 1.7% respectively and venous events were 1.8% and 1.9% respectively.

- **Health plan members with COVID-19 and event of interest, by age (Jan 20 – July 31, 2020)**
    - Arterial and venous events increased with age.

Influenza Cohort

- **Counts of arterial thrombosis and venous thromboembolic events among health plan members with influenza (October 1, 2018 – April 30, 2019)**
    - Arterial events and venous events were less frequent in influenza cohort compared to COVID-19 cohort.

Summary

- Many Sentinel data partners were able to quickly identify cohorts and events of interest.
- Many more COVID-19 patients identified with diagnosis code than lab test, with variation by partner type.
- As we defined it, COVID-19 cohort is relatively young.
- Proportion of COVID-19 and influenza patients with an event is relatively low, with more events among older people.

Next Steps

- Full study implementation in Sentinel is underway for a more robust approach – multiple IDS partners (4) and claims partner (1) which helps to improve sample size and increases generalizability, access to additional lab data and other data elements.
- Analyses will be conducted the same across partners. All three aims implemented.

<u>Discussion on Parallel Analyses</u>

1. **Does repetition of findings among diverse Accelerators increase confidence in results?**
    a. Replication is needed to increase confidence in results. BUT repetition should be interpreted carefully.
    b. Results may be replicable across cohorts due to known errors such as bias, discrepancies in data, study design, etc.
    c. There is potential for repetition/consistency in findings to increase confidence, unless the results are consistently false.
2. **What should we do with divergent results?**
    a. Perform random effect meta-analysis across datasets and try to summarize divergent findings by accounting for the heterogeneity within each site. However, this approach may not account for residual bias.
3. **Is it helpful to explore electronic health records, claims, linked data sets, patient-generated health data?**
    a. Yes, there are elements of each which complement each other. Understanding limitations and strengths of each dataset is key for successful use/interpretation of results.

Hospital Capacity Model for COVID-19 Patients: Critical Care Capacity Planning for COVID-19

Margaret Erlendsdottir, Soheil Eshghi, & Forrest W. Crawford, Yale University

Background

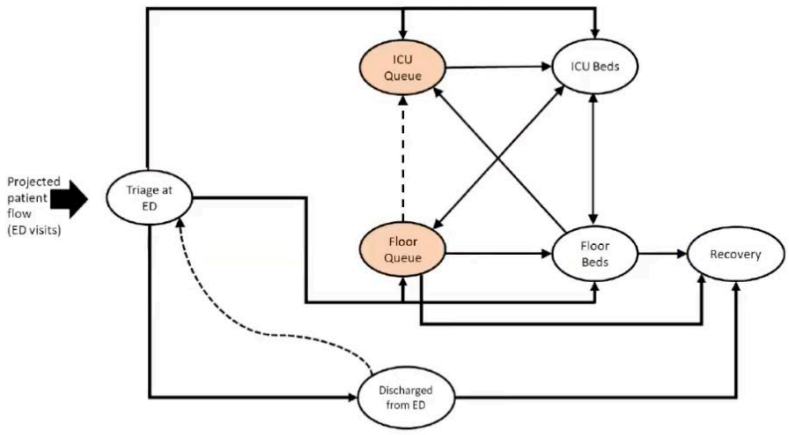
- Goal to help Yale-New Haven Hospital prepare for the surge of COVID-19 patients beginning in March 2020.
- Knowing very little about COVID-19, how many patients would need hospitalization, etc. there was a need for a pragmatic model of surge capacity: how many patients will need hospital resources on a given day?

Goals

- Construct a tool to aid hospital administrators with decision-making regarding resource allocation.
- Ensure that the tool was not dependent on population projections of infection, which could be highly variable.
- Implement the tool in a publicly accessible and easily used web application.
    - Publicly Available HERE.
- Ensure that users could interact with the tool and tailor it to the needs of their health system.

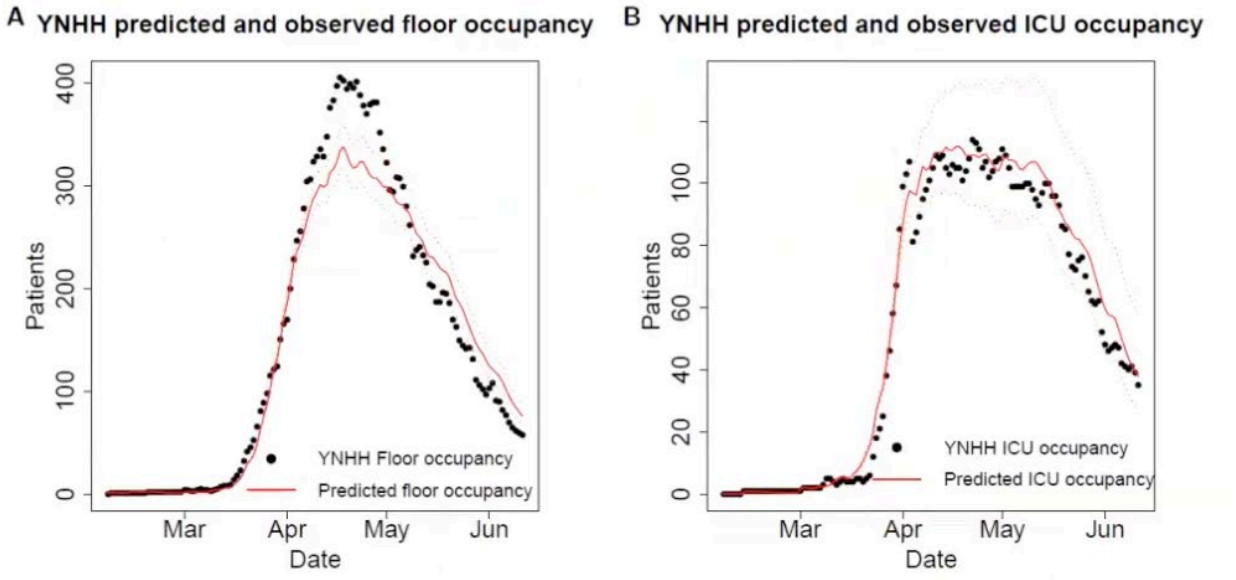
Model Structure

- Deterministic model of patient flow between the emergency department, the floor, and critical care units. Described as a system of ordinary differential equations.
- Individual-level patient trajectories were used to estimate the rates of transition between hospital departments. These rates were used to simulate dynamics of patient flow in the hospital system. We estimated the rates for three different age groups: 0-18, 19-64, 65+ years. This was due to the knowledge that different age groups require hospitalization and critical care resources at different rates.
- The solution provides estimates of expected occupancy in each compartment.



Yale New-Haven Hospital System Data

- Looked at individual patient trajectories within Yale New-Haven's hospital system including time spent on the floor, time spent in the ICU, and deaths (March – June 2020) and took census of COVID-19 patients in the hospital.
- The occupancy predicted by the hospital capacity model aligned with the occupancy that was observed.



Limitations and Future Developments

- Model is dependent on clinical management strategies which are continually evolving. The model would need to be adjusted accordingly.
- Have not taken into account ventilator capacity or repeated visits.
- What would be most helpful to decision makers as COVID-19 cases continue to surge?

Data Visualization of the Week

This tool for exploring COVID-19 data sources, tools, and other resources can be accessed online HERE.