Estimating real-world outcomes under a rapidly evolving treatment paradigm: Dexamethasone and mortality among US hospitalized COVID-19 patients

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Introduction

- The novelty of COVID-19 created a demand to evaluate safety and effectiveness of treatments
- Systemic corticosteroids became a treatment option for patients hospitalized with COVID-19 because they may modulate inflammation-mediated lung injury to reduce progression to respiratory failure and death
- In July 2020, results from the United Kingdom RECOVERY trial were published
  - Patients hospitalized with COVID-19 were randomized to receive dexamethasone versus 'usual care,' and followed 28 days post-randomization to evaluate mortality or assumed to remain alive if discharged before 28 days
  - Reported a mortality reduction for patients with dexamethasone use receiving invasive mechanical ventilation (IMV) that was attenuated for those receiving supplemental oxygen (O2), and a potential mortality risk increase for patients receiving neither IMV nor O2 (rate ratio, 95% CI; IMV: 0.64, 0.51-0.81; O2: 0.82, 0.72-0.94; neither: 1.19, 0.91- 1.55)

Materials and Methods

Process objective: Establish a system for rapid-cycle evaluation of RWD, using best practice scientific and operational methods, as applied to relevant and meaningful clinical research questions to advance the understanding of COVID-19

USE CASE METHODS

Rationale: At the time when the RECOVERY results were initially published (July 2020), dexamethasone had not yet been evaluated in routine care, which made it a good use case to evaluate our process objective

Objective: Estimate the 28-day inpatient mortality risk for patients hospitalized in the US with confirmed COVID-19 associated with dexamethasone initiation versus patients who had not yet initiated a corticosteroid of interest (CSI; dexamethasone, methylprednisolone, prednisone, or hydrocortisone)

Study cohort

Underlying population: Patients from HealthVerity Chargemaster + Claims hospitalized April 2020 - March 2021 with confirmed COVID-19 (ICD-10 U07.1 or positive SARS-CoV-2 NAAT laboratory test)

Exact-matched cohort: Dexamethasone initiators ≤21 days of admission and a random selection of patients who had not yet initiated any corticosteroid of interest, 1:1 direct matched on dexamethasone initiation date, age, sex, days since admission, baseline comorbidity score, and COVID-19 severity on treatment index

Exclusions:
- no medical activity during baseline
- CSI use during the 90-day washout
- missing age, sex, or region on the hospital admission
- any record of a COVID-19 vaccine prior to hospital admission

Mortality outcome: Inpatient Chargemaster claims with a discharge status of 'expired' evaluated over follow-up from 1 day after treatment until one of the following
- IT (initial-treatment): discharge or a maximum of 28 days
- AT (as-treated): additionally censored non-CSI patients upon CSI initiation

Statistical analyses
- After the exact matching, patients were 1:1 nearest-neighbor propensity score matched (±0.01 caliper) without replacement
- Pre-specified diagnostic criteria (e.g., all absolute standardized differences (ASDs) between comparison groups ≤ 0.1 to confirm covariate balance) were satisfied prior to unmasking the treatment-specific outcomes and executing the inferential analyses
- Cox proportional hazards models with cluster-robust variance estimation to report Kaplan-Meier curves, hazard ratios, and 95% CIs overall and within each subgroup according to respiratory requirements
- 8 sensitivity analyses planned a priori + 4 post hoc
- Analyses were conducted using both the Aetion Evidence Platform® (2021) and R (v4.0.3)

Results and Discussion

Descriptive and Diagnostic Results
- After 1:1 PS-matching, there were 804 pairs with IMV, 8,008 pairs with O2/NIV, and 5,293 pairs with neither
- Covariate balance confirmed via ASDs ≤ 0.10 for pre-specified variables
- More than half of the non-CSI patients receiving IMV (66.5%) and O2 (63.3%) initiated a CSI within 1 week of their matched index date; nearly half initiated on the day after matched index, and were unable to contribute follow-up to the AT analysis (**Figure 1**)

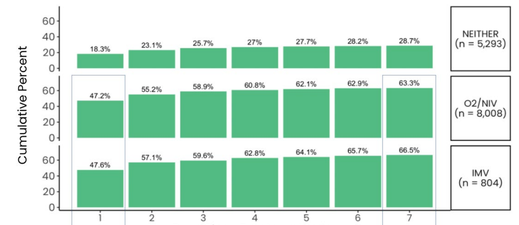

Figure 1. Initiation of a CSI among patients matched as a non-CSI referent over the first week of the study period

Primary (Per-Protocol) Mortality Results
- Increased mortality risk suggested for patients receiving O2/NIV (IT HR, 95% CI 1.32, 1.21-1.45) and no discernible difference among those receiving IMV (1.02, 0.89-1.18), which was directionally inconsistent with the RECOVERY trial (**Figure 2**)
- Increased mortality risk suggested for patients with neither IMV nor O2 (IT HR, 95% CI 1.79, 1.50-2.13) that appeared early and increased over the 28-day follow-up, which was directionally consistent with the RECOVERY trial (**Figure 2**)

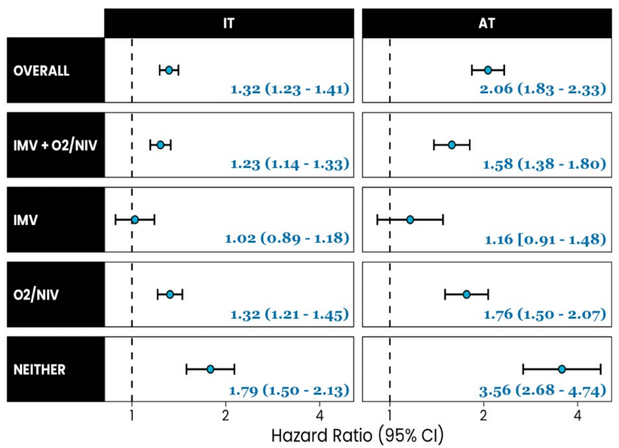

Figure 2. Primary (per-protocol) mortality hazard ratios (HRs) and 95% Confidence Intervals (CI) for dexamethasone initiation versus non-CSI

Planned Sensitivity and Post-Hoc Results
- When post hoc analyses restricted follow-up in the IMV subgroup, IT-HRs were 0.81 [0.63-1.05] at 7 days and 0.95 [0.80-1.14] at 14 days. (**Figure 3**)
- Post hoc IPCW and planned sensitivity analyses yielded generally robust HRs within the CIs of the primary analyses (data not displayed).

Process Learnings
- Although this study followed good research practices (e.g., identifying fit-for-purpose data, sensitivity analyses to evaluate the robustness of findings), several methodological and process learnings arose from this study that may be used to inform future comparative studies.
- The interpretability of IMV findings was challenging because most patients selected as a matched non-CSI referent eventually initiated dexamethasone
  - The 28-day mortality estimate compared patients who initiated dexamethasone earlier to a referent group of patients who largely initiated dexamethasone later
  - The early apparent benefit (i.e., observed in post hoc analyses at day 7) was no longer apparent by day 28

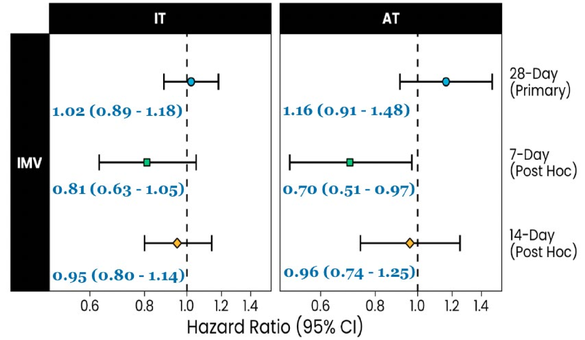

Figure 3. Post hoc mortality hazard ratios (HRs) and 95% Confidence Intervals (CI) in patients receiving IMV for dexamethasone initiation versus non-CSI, restricting 28-day follow-up to 7 and 14 days

Conclusions

- Our 28-day use case findings did not align with those from the RECOVERY trial, likely due to substantial use of corticosteroids in hospitalized COVID-19 patients during our study period
- A phased study approach with pre-specified study design contingencies may increase the interpretability of findings (e.g., additional exploration of treatment utilization and censoring), especially when the treatment paradigm is rapidly evolving

Disclosures: This paper reflects the views of the authors and should not be construed to represent FDA's views or policies. EMG, IJE, SEV, ARW, DL, AB, JAR, and NMG are employees of Aetion, Inc., with stock options or existing equity. NMG also owns stock in Pfizer Inc.