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BRIEF REPORT

Real-World Inpatient Use of Medications Repurposed for Coronavirus Disease 2019 in United States Hospitals, March–May 2020

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We report off-label use patterns for medications repurposed for coronavirus disease 2019 (COVID-19) at 318 US hospitals. Inpatient hydroxychloroquine use declined by 80%, whereas corticosteroids and tocilizumab were initiated 2 days earlier in May versus March 2020. Two thirds of ventilated COVID-19 patients were already receiving corticosteroids during March–May 2020, resembling pre-COVID use in mechanically ventilated influenza patients.

Keywords. COVID-19; medications; repurposed; SARS-CoV-2; trends.

Early in the coronavirus disease 2019 (COVID-19) pandemic, medications approved for other diseases were expeditiously repurposed as candidate therapies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinicians across the world proposed treating patients with numerous different medications. However, the absence of robust evidence supporting these interventions prompted guidance limiting their use to randomized clinical trials (RCTs). Hydroxychloroquine and azithromycin were entered into large RCTs based on suppression of SARS-CoV-2 replication, whereas corticosteroids and the interleukin-6 receptor antagonist tocilizumab were similarly studied due to their potential for mitigating immune-mediated organ injury [1, 2]. Nonetheless, the frequency and significant morbidity of COVID-19 may have prompted clinicians to continue using these agents as usual care outside of RCTs. Contemporaneous changes in evidence, regulatory policy, and drug supplies may have also impacted the extent and timing of prescribing in hospitals. We aimed to characterize whether, how, and why utilization changed in US hospitals for key systemically administered, repurposed agents with putative anti-SARS-CoV-2 (hydroxychloroquine, azithromycin) and immunosuppressive (corticosteroids and tocilizumab) effects.

METHODS

Data Source, Study Population, and Study Design

The Premier Healthcare database (PHD), a large, all-payer administrative repository that covers approximately 20% of US hospitalizations across 48 states, was queried for initial inpatient encounters of adults (≥18 years) with diagnosis coding indicative of COVID-19 admitted to continuously reporting hospitals between March 1 and May 31, 2020. Patients discharged before availability of the COVID-19-specific diagnosis code (U07.1) were identified based on Centers for Disease Control and Prevention guidance (ie, coding for an acute lower respiratory tract illness along with other coronavirus as the cause of diseases classified elsewhere [B97.29]) (Supplement eTable 1) [3]. Each agent's usage was examined at the hospital and patient level and calculated as the proportion of encounters recording ≥1 administration. The day of drug initiation relative to hospital admission and intubation day, respectively, were compared for each drug by month. Encounters with an *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis code for influenza (J09.x, J10.x, J11.x) during the last peak influenza season between December and February 2020 were examined as a reference standard to gauge pre-COVID-19 usage.

Data Analysis

We performed multivariable logistic regression modeling to estimate the association between select covariates and the primary outcome of monthly medication usage. Generalized estimating equations accounted for within-hospital clustering and correlation. Variables were prespecified for inclusion in the multivariable model based on clinical knowledge of potential confounding over time, biologic plausibility, and completeness of data. The model was risk-adjusted for age, sex, race/ethnicity, insurance and transfer status, Elixhauser Comorbidity Index, length-of-stay, traditional prescribing indications (Supplement eTable 2), as well as acute organ failures present-on-admission. Acute organ failures were identified by crosswalking the ICD-9 adaptation of the Acute Organ Failure Score to ICD-10 using an online tool [4]. Risk-adjusted monthly usage rates for each of the 4 medications were analyzed separately for nonventilated and mechanically ventilated cohorts.

A sensitivity analysis was conducted and limited to medication initiations within 10 days of admission (see additional methods in the Supplement). Reporting of relevant study results, guidelines, and regulatory policy changes were

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superimposed on monthly trends (Supplement eTable 3). Results were visually compared for clinically meaningful differences, and tests for statistical significance were not applied owing to high sample size, as has been done previously [5]. All analyses were performed using PROC GENMOD in SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Between March and May 2020, 35 259 inpatients with COVID-19 coding were admitted to 318 hospitals, 5950 (16.9%) of whom received mechanical ventilation (Supplement eFigure 1; Supplement eTable 4). The extent to which each medication was used varied considerably across hospitals (Supplement eFigure 2); 16 164 (45.8%) of 35 259 patients received hydroxychloroquine across 302 of 318 (95.0%) hospitals, 18 164 (51.5%) received azithromycin across 311 (97.8%) hospitals, 7570 (21.5%) received corticosteroids (Supplement eTable 5) across 299 (94.0%) hospitals, and 2005 (5.7%) received tocilizumab across 188 (59.1%) hospitals.

Overall, the use of hydroxychloroquine and azithromycin was higher for mechanically ventilated versus nonventilated patients, respectively, but the relative difference was much greater for corticosteroids and tocilizumab. Compared with nonventilated COVID-19 patients, mechanically ventilated COVID-19 patients were 3-fold more likely to receive corticosteroids (22.0% vs 61.8%) and 6-fold more likely to received tocilizumab (3.0% vs 18.9%). The use of corticosteroids among mechanically ventilated COVID-19 patients (at 62%) was comparable to its use among pre-COVID-19, mechanically ventilated influenza patients (at 68%) (Supplement eFigure 3A and B).

Over the 3-month period, hydroxychloroquine use rate decreased by 81% and 79%, whereas azithromycin use rate decreased by 46% and 51% among nonventilated and mechanically ventilated encounters, respectively (Figure 1). On the other hand, corticosteroid use rate for COVID-19 increased among both mechanically ventilated and nonventilated patients, whereas tocilizumab use rate remained relatively stable, especially among mechanically ventilated patients. Most were initiated within the first 10 days of admission; the 10-day restriction for medication initiation in the sensitivity analysis resulted in excluding 112 (0.7%) hydroxychloroquine, 41 (0.2%) azithromycin, 628 (6.2%) corticosteroids, and 140 (6.9%) tocilizumab encounters and generated trends that were similar to those from the primary analysis (Supplement eTable6).

Overall, both corticosteroids and tocilizumab were initiated 2 hospital days earlier in May versus March 2020, respectively (Figure 2). Among mechanically ventilated patients, median initiation of hydroxychloroquine and azithromycin continued to occur on or before the intubation day over the study period. On the other hand, the median day of initiation for corticosteroids and tocilizumab among mechanically ventilated patients occurred on the day of intubation in May compared to 1 and 2 days postintubation in March 2020, respectively. It is notable that the median day to intubation remained the second hospital day across all 3 study months.

DISCUSSION

Our study offers important population-level insights into how, when, and possibly why inpatient clinicians used medications repurposed for COVID-19 and how prescribing practices changed over the first 3 months of the pandemic in the United States. Although historical, our findings tell a cautionary tale and provide key lessons for the various stakeholders in the current and in future pandemics.

Approximately half of all hospitalized COVID-19 patients received hydroxychloroquine, and most (95%) of the study hospitals prescribed the drug to at least 1 inpatient with COVID-19. Despite uncertainty of effect, initial frequent use of hydroxychloroquine by inpatient prescribers may have been catalyzed by an absence of contemporaneous effective alternatives, a US Food and Drug Administration-issued Emergency Use Authorization (EUA), institution-specific treatment policies, herd mentality, and a variety of mass-media influences [6].

However, ensuing factors likely dissuaded ongoing use. Between March and May 2020, the rate of hydroxychloroquine use among COVID-19 patients declined sharply by 80% in US hospitals. Appraisal of the initial positive study highlighted significant methodologic flaws, and multiple studies emerged showing a lack of benefit [1, 7]. A large study reporting excess deaths and arrhythmias associated with the combined use of hydroxychloroquine or chloroquine and azithromycin, although retracted, created headlines and potentially discouraged coadministration [8]. Azithromycin use may have also declined following few reported bacterial coinfections overall [9, 10]. The EUA was revoked, and the World Health Organization's hydroxychloroquine trials that had been resurrected postretraction were subsequently terminated [8]. More importantly, our study adds a key element to the hydroxychloroquine saga: inpatient clinicians were quick to change their prescribing behavior in response to emerging reports of potential harm associated with hydroxychloroquine use even before the alarm was sounded by regulatory authorities, and this speaks to their commitment to patients even at a time of extreme personal physical and emotional stress.

Our study suggests clinicians' corticosteroid usage in COVID-19 may have been influenced by their management of mechanically ventilated influenza patients. Despite conflicting contemporaneous recommendations on corticosteroids for COVID-19 underpinned by weak evidence early on, approximately two thirds of mechanically ventilated COVID-19

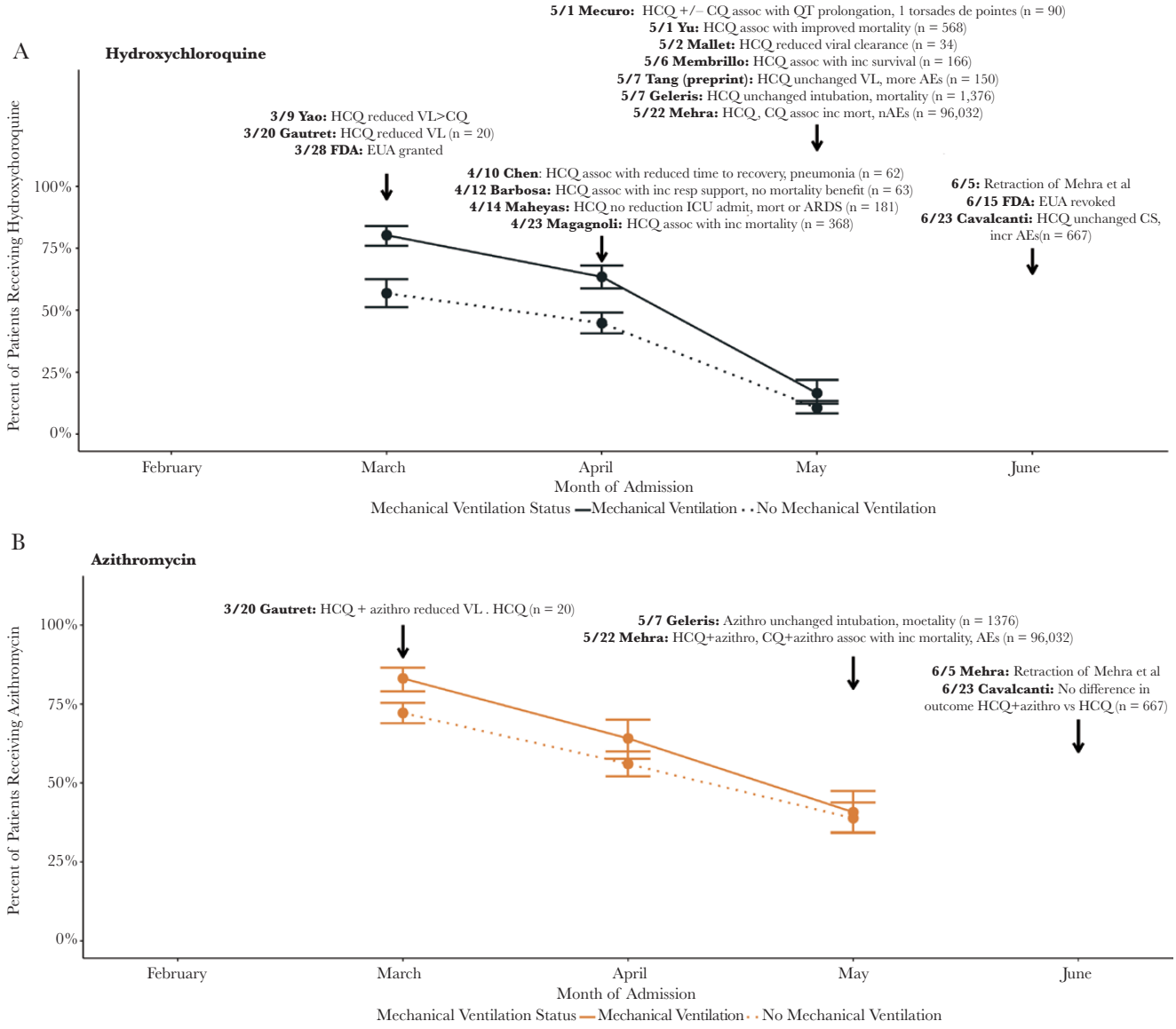

Figure 1. (A–D) Risk-adjusted monthly trends in real-world usage of 4 repurposed medications among coronavirus disease 2019 (COVID-19)-coded inpatient encounters by need for mechanical ventilation (MV). Dots represent estimates of risk-adjusted monthly use rates and bars represent 95% confidence intervals. Solid trend lines represent mechanically ventilated and dotted lines represent nonventilated COVID-19 patients, respectively. Studies/reports linked by vertical arrows are labeled by first-author last names along with date of online publication unless specified. Relevant publications/press releases/regulatory policies outside of the study period (ie, February and June 2020) are included for context where applicable. In subfigure D, a July 2, 2020 event is presented under June for space constraints. *SpO_2 ≤94% on room air, and those who require supplemental oxygen, MV, or extracorporeal membrane oxygenation. ^initial version of "living" guideline. AEs, adverse events; ARDS, acute respiratory distress syndrome; CS, clinical status; CQ, chloroquine; EUA, Emergency Use Authorization; FDA, US Food and Drug Administration; HCQ, hydroxychloroquine; HHS, US Department of Health and Human Services; ICU, intensive care unit; VL, viral load; WHO, World Health Organization.

patients were surprisingly already receiving corticosteroids [11–13]. The striking similarity in the extent to which corticosteroids were administered in mechanically ventilated COVID-19 versus influenza patients from the last peak-influenza season, respectively, is hard to ignore. In fact, the use of corticosteroids represents a key component of usual care for COVID-19 that was already in place well before the June 2020 press release reporting improved survival associated with dexamethasone among ventilated patients in the RECOVERY trial [14]. In addition, our finding of clinicians' growing penchant and earlier trigger for corticosteroids during the course of COVID-19 hospitalizations observed between March and May 2020 reinforces this notion.

Despite comparable levels of evidence at the time, tocilizumab was used considerably less frequently and in fewer hospitals compared with corticosteroids, possibly reflecting tocilizumab's

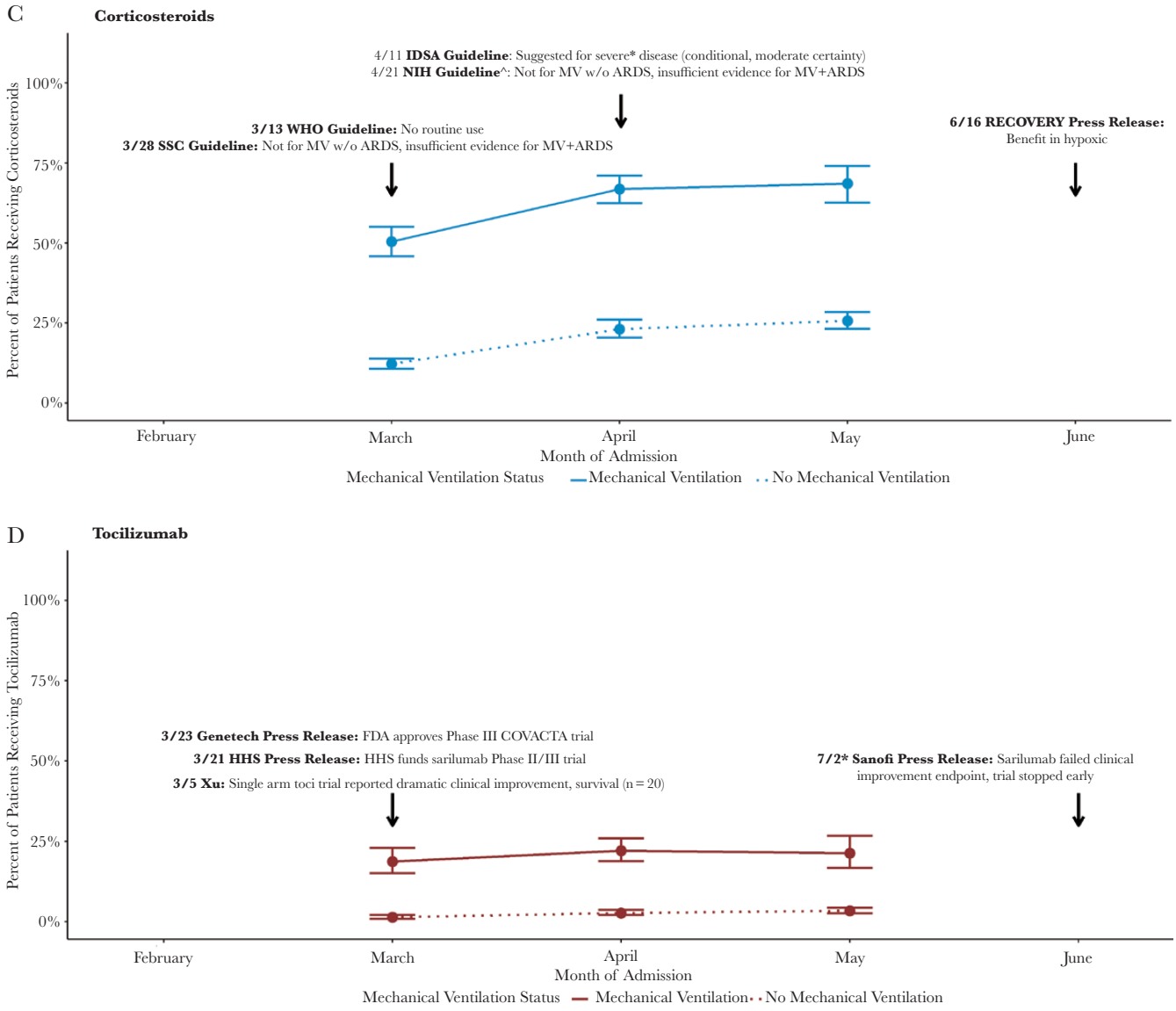

Figure 1. Continued.

greater cost, limited supply, and rationing for sicker patients, as suggested by its 6-fold greater use among mechanically ventilated patients. Despite promising signals of survival benefit of tocilizumab for COVID-19 in observational studies, RCT data remain less convincing, and the role of cytokine storm in COVID-19-mediated organ failure has been questioned [15–18]. Ongoing real-world use in COVID-19 patients will likely be contingent on whether future RCTs identify a niche for this drug.

Our study has limitations. Despite its large and all-payer nature, PHD is a convenience sample of US hospitals and may not have been nationally representative. However, the national COVID-19 landscape remains dynamic. Fewer May 2020 (versus March/April) admissions may have received discharge dispositions when hospitals submitted data. Date jumbling in the commercially leased version of PHD precludes temporal granularity beyond the month-level. However, our sensitivity analysis mitigates concern for admission month misrepresenting the month of medication initiation. We did not focus on unapproved agents because they often evade administrative data due to investigational usage or incomplete mapping early on. The uptake and accuracy of recently introduced procedure codes representing the use of remdesivir, convalescent plasma, and other newer agents will need to be closely tracked to determine whether they are reliable for pharmacoepidemiologic proposes [19].

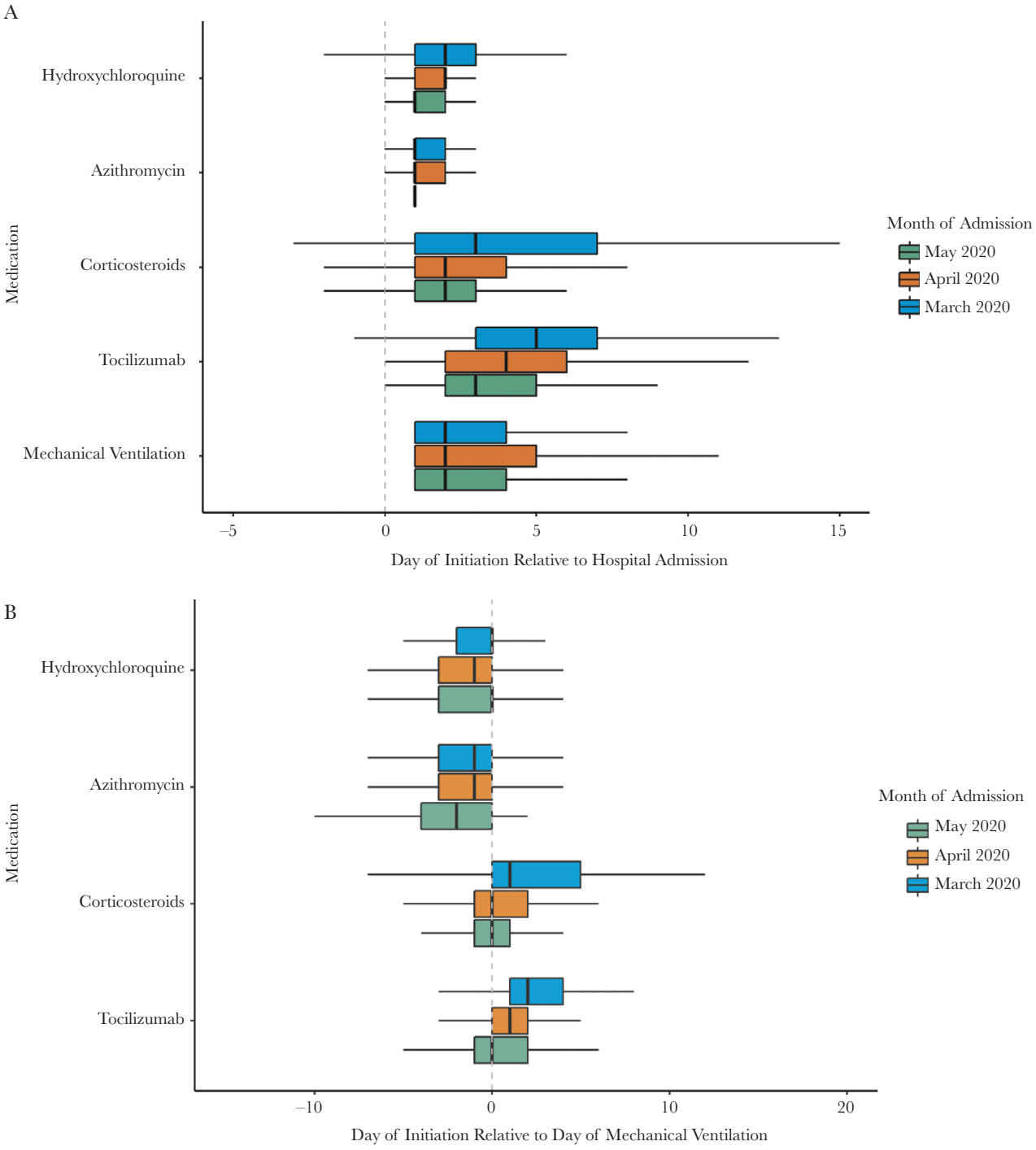

Figure 2. (A) Medication and mechanical ventilation initiation relative to hospital admission, and (B) medication initiation relative to first day of mechanical ventilation. Each colored box represents interquartile range for the given month, thick vertical black lines represent medians, think horizontal lines represent 95% confidence intervals. The vertical dashed line in (A) represents day of hospital admission and in (B) represents day of initiation of mechanical ventilation.

CONCLUSIONS

Our study suggests that in times necessitating desperate measures, usual care may be greatly influenced by suboptimal evidence, mass media, experiences from analogous and anecdotal clinical scenarios coupled with need to "do something," especially for severely ill patients. Future candidate agents may not necessarily be met with the serendipitous success achieved with pre-evidence-based adoption of corticosteroids or the early warnings signals of harm that were available for hydroxychloroquine. Variable uptake across hospitals in the use of these repurposed agents for COVID-19 is testament to the lack of a perceived standard-of-care early on. Moving

forward, the provider, guideline, and regulatory communities may need to carefully and prospectively weigh the urge for earlier real-world adoption of new and repurposed agents against not only potential direct harms, but also the risk of delaying systematic generation of more definitive evidence [20, 21]. Ongoing appraisal of real-world use of medications for COVID-19 could inform usual care arms of future RCTs and also reveal whether emerging evidence and guideline recommendations have translated to the bedside.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. S. S. K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. S. S. K. contributed to concept and design. S. S. K., S. W., C. Y. D., and J. S. contributed to acquisition, analysis, or interpretation of data. S. S. K. contributed to drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. C. Y. D. and J. S. contributed to statistical analysis. S. W. and S. S. K. contributed to administrative, technical, or material support.

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