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Adoption and Deadoption of Medications to Treat Hospitalized Patients With COVID-19

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OBJECTIVES: The COVID-19 pandemic was characterized by rapidly evolving evidence regarding the efficacy of different therapies, as well as rapidly evolving health policies in response to that evidence. Data on adoption and deadoption are essential as we learn from this pandemic and prepare for future public health emergencies.

DESIGN: We conducted an observational cohort study in which we determined patterns in the use of multiple medications to treat COVID-19: remdesivir, hydroxychloroquine, IV corticosteroids, tocilizumab, heparin-based anticoagulants, and ivermectin. We analyzed changes both overall and within subgroups of critically ill versus Noncritically ill patients.

SETTING: Data from Optum's deidentified Claims-Clinical Dataset, which contains multicenter electronic health record data from U.S. hospitals.

PATIENTS: Adults hospitalized with COVID-19 from January 2020 to June 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Of 141,533 eligible patients, 34,515 (24.4%) required admission to an ICU, 14,754 (10.4%) required mechanical ventilation, and 18,998 (13.4%) died during their hospitalization. Averaged over the entire time period, corticosteroid use was most common (47.0%), followed by remdesivir (33.2%), anticoagulants (19.3%), hydroxychloroquine (7.3%), and tocilizumab (3.4%). Usage patterns varied substantially across treatments. For example, hydroxychloroquine use peaked in March 2020 and leveled off to near zero by June 2020, whereas the use of remdesivir, corticosteroids, and tocilizumab all increased following press releases announcing positive results of large international trials. Ivermectin use increased slightly over the study period but was extremely rare overall (0.4%).

CONCLUSIONS: During the COVID-19 pandemic, medication treatment patterns evolved reliably in response to emerging evidence and changes in policy. These findings may inform efforts to promote optimal adoption and deadoption of treatments for acute care conditions.

KEY WORDS: COVID-19; health policy; public health

The rapid pace and profound impact of the pandemic of novel COVID-19 forced healthcare professionals to make critical treatment decisions in the absence of high-quality evidence. In some cases, this meant applying lessons learned from historical patients with viral pneumonia, whereas at other times, there were explicit calls to deviate from known evidence-based practices (1, 2). In the context of early case reports, rapidly published observational studies, press releases with preliminary trial results, and communication from public leaders, many patients received off-label treatment with a number of different medications (3, 4). Ultimately, randomized trials published later in the pandemic showed some of these medications to be beneficial, but others to be ineffective and potentially harmful (5–9). Although early reports

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suggest variation in medication utilization (3), we lack a population-level understanding of how the use of these medications evolved over the first years of the pandemic.

Understanding how providers treated patients with COVID-19 will allow us to better prepare for the next pandemic, when we again will likely need to promote the optimal management of patients with a novel pathogen in the face of uncertain and rapidly changing evidence. If providers failed to adopt treatments in response to supportive evidence or failed to deadopt treatments in response to nonsupportive evidence, this would provide incentive to enhance strategies to support use of evidence-based practice during future public health emergencies. Similarly, if there was widespread adoption of potentially harmful medications in the absence of robust evidence, future efforts may need to focus on reducing early uptake until more is known about the risks and benefits of certain drugs.

We, therefore, sought to determine use patterns for key medications for COVID-19. We focused on six medications: remdesivir, hydroxychloroquine, IV corticosteroids, tocilizumab, therapeutic anticoagulation, and ivermectin. We leveraged a large, nationally representative dataset to characterize changes over time in medication use for patients hospitalized with COVID-19, as well as differences in use patterns based on illness severity.

MATERIALS AND METHODS

Overview of Study Design and Data Source

We conducted a longitudinal study of patients admitted to the hospital in the United States with COVID-19 from January 1, 2020, to June 30, 2021. We characterized changes in the use of each medication over time. We used the Optum's deidentified Integrated Claims-Clinical Dataset, which includes deidentified data derived from the electronic health records (EHRs) of a nationally representative, all-payer group of patients across approximately 760 hospitals, representing all census regions of the United States. Key data elements included diagnosis and procedure codes, patient location, and date- and time-stamped data on laboratory testing, vital signs, and medication administration records. This dataset allowed us to capture a cohort of laboratory-confirmed COVID-19 (4), along with details of medication use and measures of illness severity not available in traditional administrative datasets.

Patients

We included patients admitted to the hospital age 18 or older, with either an *International Classification of Diseases,* 10th Edition (ICD-10) code for COVID-19 or a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction test. In the event of multiple hospitalizations meeting these criteria for a given patient, we included only the first hospitalization, since most treatments were focused on the initial phases of illness with COVID-19.

Variables

We identified whether each patient was treated with one of six therapies during the hospital stay: remdesivir, hydroxychloroquine, IV corticosteroids (hydrocortisone, dexamethasone, or methylprednisolone), tocilizumab, heparin-based anticoagulation (enoxaparin at a dose over 40 mg or heparin via IV route), and ivermectin. We identified mechanical ventilation using ICD-10 codes and ICU admission using ICU-specific location codes in the data. Due to deidentification procedures, the dataset did not contain a variable for inhospital mortality, so we used a separate "month of death" variable to define mortality, assigning deaths to the hospitalization if the discharge disposition was not specified, and the death occurred in the same month as the date of discharge. Other variables included month of hospital admission, age, sex, race, ethnicity, region, insurance status, and chronic comorbidities defined in the manner of Elixhauser et al (10). In our analysis of anticoagulation, we also identified and excluded patients with a diagnosis of deep venous thrombosis or pulmonary embolism because we were interested in examining empiric anticoagulation rather than anticoagulation for diagnosed venous thromboembolic disease.

Analysis

To describe the demographic and clinical characteristics of the cohort, we used standard summary statistics.

To characterize differences in treatment patterns by drug over time, we used logistic regression models in which the dependent variable was an indicator for treatment with the drug of interest, and the independent variable was a categorical variable for month of hospital admission. We performed this separately for each of the six treatments. We used the margins from these models to graphically display treatment patterns over time.

To assess differences in treatment by illness severity at hospital admission, we restricted the analysis to medications from the first two calendar days from admission, both because many treatments were approved primarily for use early in the course of illness and to reduce the likelihood that observed medications were used in response to new diagnoses or complications of inpatient treatment. We defined critical illness based on the presence of either mechanical ventilation or ICU admission, since due to hospital capacity constraints, we suspected that some mechanically ventilated patients were managed outside of ICUs. We did not examine the development of critical illness later in a hospital stay, given the difficulty in unpacking the heterogeneous drivers and consequences of late deterioration. We then created logistic regression models with an indicator for critical illness interacted with month of hospital admission. These models estimate differences in treatment based on whether the patient was critically ill, as well as whether changes in treatment over time differed between critical and noncritical populations.

Ethics and Data Sharing

This research used a completely deidentified dataset and, therefore, was determined not to represent human subjects research by the University of Pittsburgh Human Research Protections Office. The data will not be made publicly available, pursuant to the Optum data licensing agreement. Researchers seeking to use these data must contact Optum directly.

RESULTS

Our inclusion criteria yielded 141,533 unique patients admitted for COVID-19. The vast majority (99.0%) had either a COVID-19 diagnosis code or a positive SARS-CoV-2 test and a respiratory failure diagnosis code (see **Table s1**, http://links.lww.com/CCX/B29, for codes). The majority of the cohort (76%) had a positive SARS-CoV-2 test. The distribution of patients over the course of the pandemic is displayed in **Figure 1**. Patient characteristics are summarized in **Table 1**. Individuals of Black race made up 20% of the patients. The plurality of patients (45.3%) were in the Midwest, with approximately a quarter each from the Northeast (21.3%) and South (23.8%), and relative underrepresentation from the West (6.2%). Approximately a quarter of patients (24.4%) required admission to an ICU, and a tenth (10.4%) required mechanical ventilation. The overall mortality rate was 13.4%. Averaged over the entire time period, treatment with corticosteroids was most common (47.0%), and treatment with ivermectin was least common (0.4%).

Temporal patterns of medication use are displayed in **Figure 2**, which also shows the dates for several key events including press releases for clinical trial results and emergency use authorizations (EUAs) from the U.S. Food and Drug Administration (FDA). Remdesivir use started rising in May 2020 contemporaneous with the FDA EUA, which was issued on May 1 (11) and the inclusion of remdesivir in National Institutes of Health (NIH) COVID-19 guidelines on May 12 (12). Hydroxychloroquine treatment was highest in March 2020 (before the FDA EUA for hydroxychloroquine was issued on March 28) but fell precipitously in the ensuing months and was near zero by the time the RECOVERY trial announced lack of benefit on June 5, and the FDA revoked the EUA on June 15 (13). IV corticosteroid use was low initially but rose significantly starting in June 2020, contemporaneous with the RECOVERY trial press release announcing a mortality benefit, which was issued on June 16, 2020 (14), and the inclusion of steroids in the NIH guidelines on June 25 (12). Tocilizumab use occurred overall infrequently, though with higher use early in the pandemic and a modest increase in adoption starting in February 2021, contemporaneous with a RECOVERY trial press release on February 11, 2021, which announced the mortality benefit of tocilizumab in severe illness (15) and the inclusion of tocilizumab in NIH guidelines on February 3 (12). Anticoagulation use also remained infrequent throughout the pandemic, without clinically meaningful changes following the January 22, 2021, announcement of benefit in moderately ill patients (16); as of June 2021, the NIH guidelines continued to interpret the evidence to be insufficient to recommend for or against anticoagulation (12). Finally,

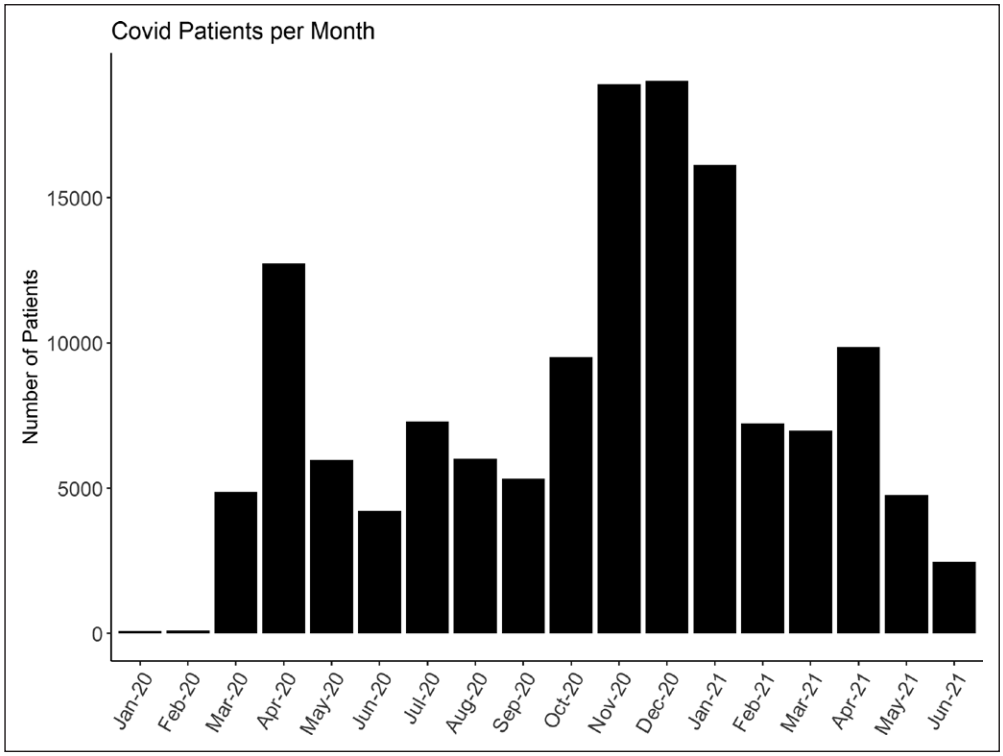

Figure 1. Number of patients with COVID-19 in the cohort by month.

ivermectin use increased slightly over the course of the pandemic, but overall use for the most part remained extremely low.

Differences in treatment of critically ill versus noncritically ill patients are displayed in **Figure 3**. For all therapies, use was more common in critically ill patients, and the patterns of adoption and deadoption were relatively similar in the two groups. The magnitude of the differences in use between critically ill and noncritically ill patients was smallest for hydroxychloroquine, which, at its peak, was given to over half of both populations.

DISCUSSION

In a study of over 140,000 hospitalized patients with COVID-19, we found variation in adoption and deadoption patterns across different medications used to treat COVID-19. Use of remdesivir, hydroxychloroquine, and corticosteroids was generally responsive to emerging evidence and U.S. drug policy. In contrast, providers were less responsive to the publication of randomized trials for anticoagulation, which appeared later in the pandemic.

These results suggest that treatment of hospitalized patients was generally responsive to changes in medical evidence and public policy over the course of the early phases of the pandemic, despite anecdotes and media reports that created concerns about widespread use of nonevidence-based therapies (17). The patterns of use for remdesivir, tocilizumab, hydroxychloroquine, and corticosteroids are instructive in both their similarities and differences. Remdesivir was developed prior to the pandemic as an antiviral agent for Ebola but was neither familiar nor readily available to U.S. clinicians at the onset of COVID-19. Indeed, supply constraints meant that even after the EUA, patients could often only receive the medication through special allocation mechanisms (18). Although widespread supply limitations for tocilizumab emerged starting in July and August 2021 (19)—after the end of our study period—it is possible that a longer observation period would have uncovered an impact of supply limits on treatment patterns. Nevertheless, its expense and potential adverse effects may have limited its adoption to some degree. In contrast, hydroxychloroquine was a widely available oral medication used to treat rheumatologic disease and as malaria prophylaxis. Experience with the drug as a relatively safe prophylactic medication in healthy outpatients may have promoted perceptions of a low risk profile in COVID-19 patients, leading to relatively liberal use based on a theoretical benefit. However, as evidence accumulated for its lack of benefit and potential harm—even in advance of the change in FDA policy—use in hospitalized patients plummeted. Corticosteroids are a class of medication with a long history, including one of uncertain evidences for benefit in severe respiratory failure and potential harm in viral pneumonia caused by influenza (20, 21). Given clinicians' general level of comfort with corticosteroids, the low use early in the pandemic is perhaps not surprising, as is the apparent response to

TABLE 1.
Patient Characteristics

	n (%); Total *n* = 141,533
Age (yr)	60.3 ± 19
Sex	
Female	69,650 (49.2)
Male	71,740 (50.7)
Unknown	143 (0.1)
Race	
White	91,121 (64.4)
Black	27,766 (19.6)
Asian	3,302 (2.3)
Other/unknown	19,344 (13.7)
Ethnicity	
Hispanic	17,174 (12.1)
Non-Hispanic	109,067 (77.1)
Other/unknown	15,292 (10.8)
Region	
Midwest	64,182 (45.3)
Northeast	30,202 (21.3)
South	33,747 (23.8)
West	8,792 (6.2)
Other/unknown	4,610 (3.3)
Insurance	
Commercial	44,131 (31.3)
Medicaid	25,902 (18.4)
Medicare	68,470 (48.6)
Other	2,503 (1.8)
Comorbidities	
Hypertension	71,321 (50.4)
Diabetes	35,130 (24.8)
Chronic lung disease	35,185 (24.9)
Obesity	45,629 (32.3)
Severity	
ICU admission	34,515 (24.4)
Mechanical ventilation	14,754 (10.4)
Mortality	18,998 (13.4)
Drug treatment	
Remdesivir	46,959 (33.2)
Hydroxychloroquine	10,328 (7.3)
Corticosteroids	66,548 (47.0)
Tocilizumab	4,847 (3.4)
Anticoagulants[a]	25,345 (19.3)[a]
Ivermectin	531 (0.4)

[a]Total *n* = 131,535 after excluding patients with pulmonary embolism and deep vein thrombosis from the denominator.

the release of the RECOVERY data, which suggested a substantial mortality benefit.

These results also highlight the challenges that remain regarding adoption of some evidence-based therapies. Specifically, in this study, anticoagulation use was relatively low even in noncritically ill patients for whom the evidence is strongest (8). Several factors could explain this finding. First, the evidence for benefit from anticoagulation in moderately ill patients emerged later in the pandemic at a time when healthcare providers were experiencing fatigue and burnout—this may have interfered with their ability to attend to and implement new practices. However, the data for anticoagulation emerged at the same time as those for tocilizumab, for which there was at least a modest change in practice, perhaps due to the perceived novelty of interleukin 6 blockade in contrast to anticoagulation. Second, although there was evidence for benefit in less severely ill patients, there was evidence for harm in critically ill patients (9); the presence of these opposing effects in different populations may have complicated efforts to promote both adoption of anticoagulation in less severely ill patients and deadoption in critically ill patients. Indeed, as of the end of the study period, empiric anticoagulation was not endorsed by NIH guidelines. Finally, the psychology of empiric anticoagulation may have inhibited adoption—whereas the reductions in organ support from initiating anticoagulation outside the ICU may not have been readily apparent to hospitalists and other non-ICU physicians, the potential for harm from bleeding complications may have felt more tangible. This may have been an example of how errors of commission weigh more heavily than errors of omission (22).

Although our analysis was restricted to U.S. hospitals reporting EHR data to Optum, we observed treatment patterns similar to those reported in another recent study of COVID-19 treatment in the United States and abroad (23). The study by Prats-Uribe et al (23) examined the use of repurposed and adjuvant therapies at any time in the 30 days following the date of admission to the hospital for COVID-19, including several datasets from the United States , as well as Spain, China, and South Korea. These authors also found an early spike in hydroxychloroquine use, followed by deadoption after the publication of observational studies suggesting harm. They also found between 50% and 60% of patients treated

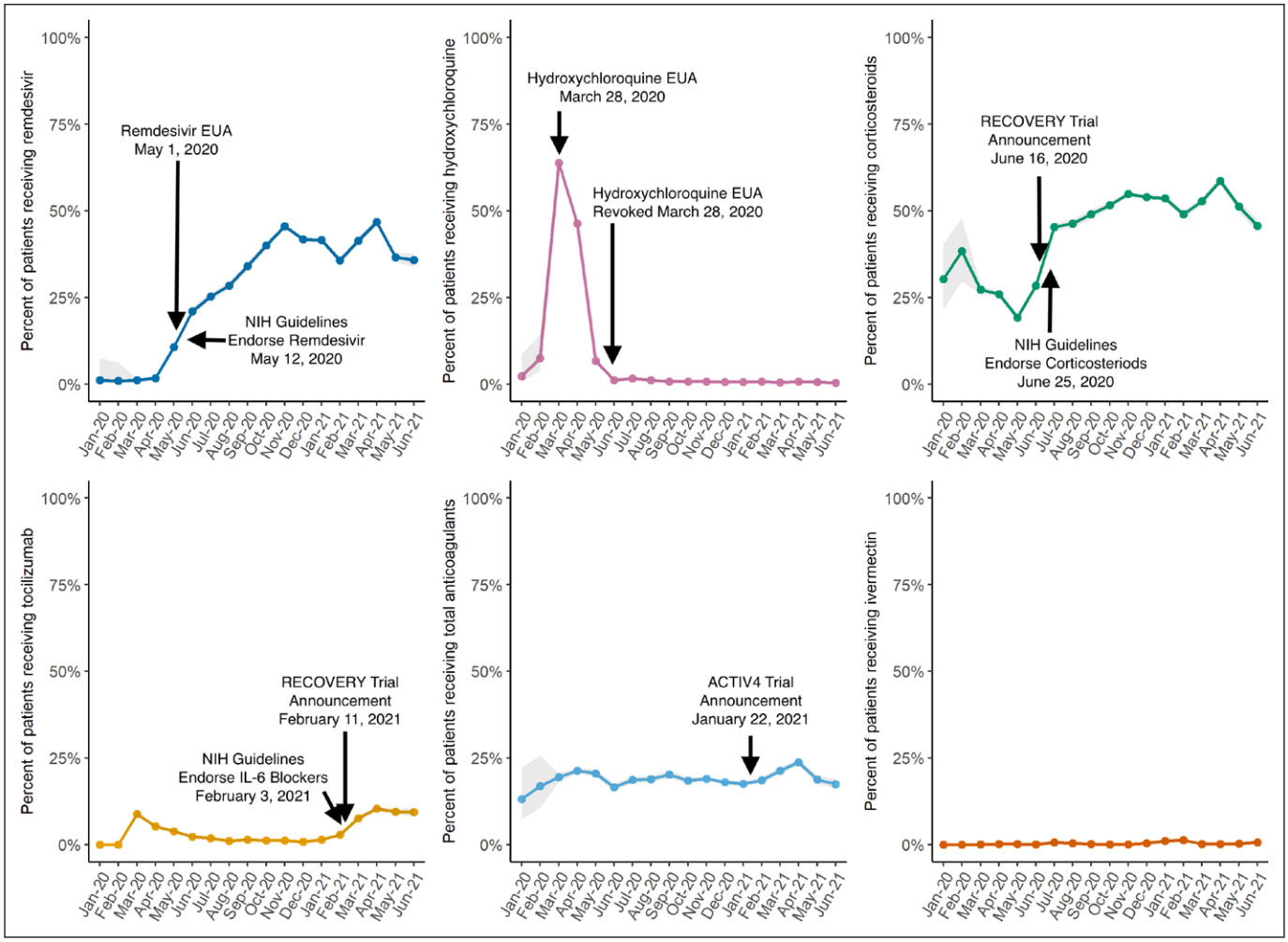

Figure 2. Patterns of medication use in the overall cohort. *Y*-axis is the percentage of patients each month treated with each medication. *X*-axis is month of hospital admission. For anticoagulants, patients with diagnosis of pulmonary embolism or deep vein thrombosis were excluded. ACTIV4 = Accelerating COVID-19 Therapeutic Interventions and Vaccines, EUA = emergency use authorization, IL-6 = interleukin 6, NIH = National Institutes of Health.

with dexamethasone—remarkably similar to the rates we observed for early treatment with corticosteroids. Despite some differences in datasets and methods, the remarkable concordance of the findings from that study and ours supports their validity and generalizability.

The patterns we observed have important implications for how we adopt new treatments for seriously ill patients. Many prior studies demonstrate that clinicians do not rapidly adopt new therapies in response to emerging evidence or new clinical guidelines, even with a variety of strategies to change practice (24, 25). In contrast to this research, we observed large, rapid shifts in some treatment practices in response to new evidence during the early phases of the pandemic. Although a full analysis of all the variables contributing to these changes is beyond the scope of this study, it is likely that major drivers included the heightened attention to potential therapies for a novel, high-impact pathogen, in concert with the widespread communication of new findings and opinions via global social media networks and the unusually large amount of public engagement given the extraordinary scope of the pandemic. It is possible that policy makers and professional societies could harness some of the drivers of practice changes during the pandemic to drive the implementation of evidence-based medicine for nonpandemic diseases.

Our findings should be interpreted in the context of several limitations. First, although we had some information on illness severity, we lacked detailed data on pulmonary physiology (e.g., oxygen flow rates), which might inform whether treatment with a particular medication at a particular time was consistent with the current guidelines. Consequently, we cannot comment on whether the absolute frequency of treatment with a

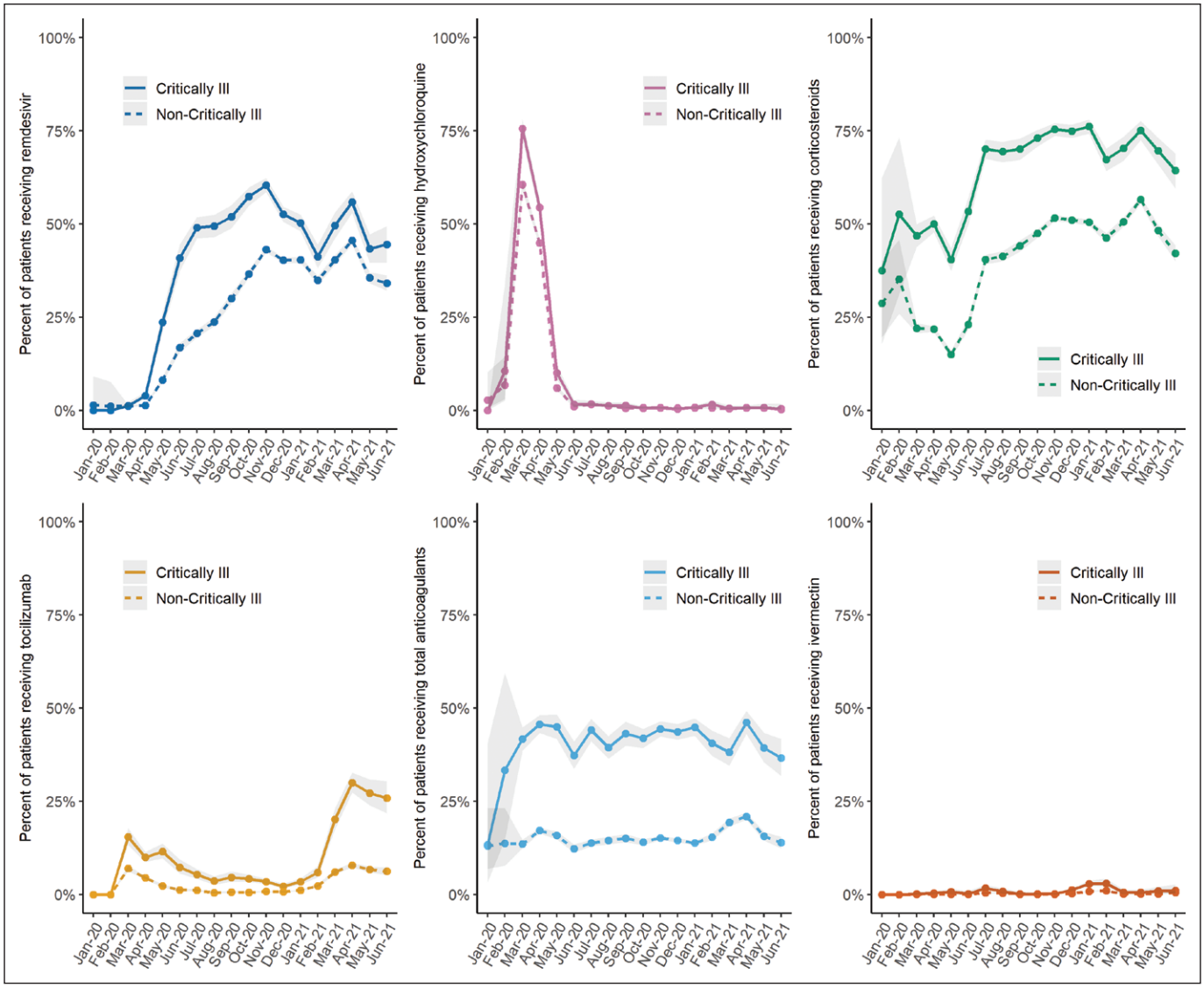

Figure 3. Patterns of medication use by disease severity. *Y*-axis is the percentage of patients each month treated with each medication. *X*-axis is the month of hospital admission. For anticoagulants, data are restricted to first two calendar days of hospital admission. Critical illness defined by either ICU admission or mechanical ventilation.

particular medication is optimal in relation to current evidence. Second, for privacy reasons, the dataset did not indicate whether a patient died in the hospital—only month of death is provided—so we could not examine differences in clinical outcomes in association with differences in treatment. However, given changing case mix and unobserved hospital and provider-level confounding, a comparative effectiveness study with these data would face significant methodologic challenges due to residual confounding (26). Third, the pandemic was characterized by not only changes in public policy but also a constantly evolving landscape of preprint publications and social media dialogue about emerging evidence. Given the near-continuous nature of these factors and the fact that they were intertwined with the announcement of clinical trial results, it was not possible to account for their separate impact on observed treatment patterns. Fourth, the racial demographics of our cohort may not match the national demographics due to underlying differences in the regional makeup of the Optum dataset. Fifth, we examined treatment early in the hospital stay to avoid the heterogeneity involved in late hospital deterioration and the fact that many treatments were endorsed primarily for early use; it is possible that treatment patterns differed among patients who deteriorated later in their hospital stays due to attempts to "do something" in response to clinical worsening. Finally, because we could not identify

individual hospitals, we could not examine how hospital-level variation in treatment drove the observed treatment patterns, how hospital-level variation contributed to disparities in treatment, and how hospital volume contributed to variation in care—all of which remain important topics for future research.

In a study of over 140,000 unique patients hospitalized with COVID-19, we found variable patterns of adoption and deadoption of medical treatments for the disease, with an apparent relationship to emerging evidence and policy.

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Dr. Barbash helped in conceptualization, methodology, project administration, writing–original draft, writing–review and editing. Dr. Minturn contributed to data curation, formal analysis, investigation, methodology, visualization, and writing–review and editing. Dr. Davis helped in investigation, methodology, and supervision writing–review and editing. Dr. Kahn contributed to conceptualization, resources, supervision, and writing–review and editing.

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