

# Multicenter point prevalence evaluation of the utilization and safety of drug therapies for COVID-19 at the onset of the pandemic timeline in the United States



Supplementary material is available with the full text of this article at [AJHP](#) online.

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**Purpose.** There are currently no FDA-approved medications for the treatment of coronavirus disease 2019 (COVID-19). At the onset of the pandemic, off-label medication use was supported by limited or no clinical data. We sought to characterize experimental COVID-19 therapies and identify safety signals during this period.

**Methods.** We conducted a noninterventional, multicenter, point prevalence study of patients hospitalized with suspected/confirmed COVID-19. Clinical and treatment characteristics within a 24-hour window were evaluated in a random sample of up to 30 patients per site. The primary objective was to describe COVID-19-targeted therapies. The secondary objective was to describe adverse drug reactions (ADRs).

**Results.** A total of 352 patients treated for COVID-19 at 15 US hospitals from April 18 to May 8, 2020, were included in the study. Most patients were treated at academic medical centers (53.4%) or community hospitals (42.6%). Sixty-seven patients (19%) were receiving drug therapy in addition to supportive care. Drug therapies used included hydroxychloroquine (69%), remdesivir (10%), and interleukin-6 antagonists (9%). Five patients (7.5%) were receiving combination therapy. The rate of use of COVID-19-directed drug therapy was higher in patients with vs patients without a history of asthma (14.9% vs 7%,  $P = 0.037$ ) and in patients enrolled in clinical trials (26.9% vs 3.2%,  $P < 0.001$ ). Among those receiving drug therapy, 8 patients (12%) experienced an ADR, and ADRs were recognized at a higher rate in patients enrolled in clinical trials (62.5% vs 22%; odds ratio, 5.9;  $P = 0.028$ ).

**Conclusion.** While we observed high rates of supportive care for patients with COVID-19, we also found that ADRs were common among patients receiving drug therapy, including those enrolled in clinical trials. Comprehensive systems are needed to identify and mitigate ADRs associated with experimental COVID-19 treatments.

**Keywords:** adverse drug reaction, COVID-19, medication safety, observational study, SARS-CoV-2, supportive care

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the global pandemic of coronavirus disease 2019 (COVID-19).<sup>1</sup> There are a few potential therapies with activity against SARS-CoV-2; yet, no agent has received Food and Drug Administration (FDA) approval for treatment of COVID-19 to date. Investigational treatments pro-

posed at the onset of the pandemic included antimicrobials, remdesivir, lopinavir/ritonavir, nitazoxanide, ivermectin, and azithromycin. Host cell modulators including hydroxychloroquine, chloroquine, and agents targeting the host immune system have also been proposed.<sup>2</sup> As more evidence has become available, postulated COVID-19 therapies have gained and lost support over

time. This dynamic has shaped therapy recommendations from government agencies, influencing the availability of hydroxychloroquine, remdesivir, and convalescent plasma via emergency use authorization (EUA) by FDA. Use of any of these agents is expected to vary across care settings and over time as new clinical evidence and safety information become available.

Many of the investigational agents lack robust evidence to support their safety in COVID-19, which may increase the potential risk of undue harm. Prior research indicates that each of these agents is associated with adverse drug reactions (ADRs), yet little is known about the safety of these agents for use in patients with COVID-19.<sup>3</sup> Data on the safety and efficacy of investigational agents currently being used for patients with COVID-19 are only beginning to emerge.<sup>4</sup> Safety concerns range from arrhythmias and QT interval prolongation with use of hydroxychloroquine and azithromycin<sup>5</sup> to intestinal perforation with use of tocilizumab.<sup>6</sup> The lack of robust evidence on the safety of COVID-19 therapies has prompted FDA to require clinicians to report serious adverse events associated with EUA remdesivir.<sup>7</sup> There is a clear need for comprehensive data on ADRs associated with drug therapies targeting COVID-19.

ADRs associated with investigational and unproven therapies targeting COVID-19 may be difficult to detect and may vary with the usage rates of supportive care. Routine monitoring for potential ADRs is encouraged by consensus guidelines, particularly as use of investigational and EUA agents continues outside of rigorously monitored clinical trials.<sup>4</sup> Multicenter point prevalence methodology may allow detection of ADR signals on a large scale and is relatively easy to implement rapidly. Although this methodology does not allow investigators to infer causation, it does supply valuable information about the landscape of current practice and may discern effects that otherwise could be missed within a single center.<sup>8,9</sup> We conducted

## KEY POINTS

- A multicenter point prevalence evaluation was conducted to characterize drug therapy among 352 patients at the onset of the COVID-19 pandemic in the United States.
- Asthma and enrollment in clinical trials were more common among patients receiving COVID-19 drug therapy as opposed to supportive care alone.
- Although drug therapy was not commonly used in COVID-19 during the study period, among patients who received drug therapy, adverse drug reactions were detected more often in the setting of clinical trials; this suggests the need for close monitoring of hospitalized patients with COVID-19.

a multicenter point prevalence study to evaluate the drug therapies used to treat COVID-19 at the onset of the pandemic in the United States. The objective of this point prevalence study was to characterize the drug therapies used in the management of COVID-19, including supportive care and combination therapies, in an attempt to identify safety signals among acutely ill hospitalized patients.

## Patients and methods

**Study design.** We conducted a noninterventional, multicenter, retrospective, point prevalence study of the health records of hospitalized patients with COVID-19. While data collection was performed retrospectively, patients were identified prospectively at each site on the basis of daily monitoring and institutional guidelines. The study was reviewed by each participating organization's individual institutional review board and found to be exempt.

A waiver of informed consent and HIPAA (Health Insurance Portability and Accountability Act) authorization was completed at each site.

Patients were eligible for inclusion if they were hospitalized as inpatients and (1) had a positive SARS-CoV-2 test or (2) had a clinical diagnosis of COVID-19 based on a physician's diagnosis. No limitations were placed on time from diagnosis to inclusion. We did not extract information on protected status, with the exception of pediatric status; protected elements not evaluated in this study included dates of symptom onset and/or duration of hospitalization prior to evaluation. Patients were excluded if they were initially treated for COVID-19 but an alternative diagnosis was made (ie, COVID-19 was ruled out) prior to evaluation of their records for survey inclusion.

**Data elements.** The point prevalence survey was circulated on April 18, 2020 to 15 hospitals across the United States. Each site was asked to select a random sample of up to 30 patients and to complete data collection by May 8, 2020. Any hospitalized patient meeting inclusion criteria was eligible. Data were manually extracted from an electronic health record (EHR) system and entered into a standardized electronic survey form. Assigned study members performed data collection on any singular date that fell within the aforementioned study period. Data extraction from EHR systems was limited to data collected during the 24 hours prior to the index date of review, and no patient identifiers were collected. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools (Vanderbilt University, Nashville, TN) hosted at Northwestern University. REDCap is a secure, web-based software platform designed to support data capture for research studies.<sup>10,11</sup> Data validation was coordinated by the principal investigator and the respective site coordinators. Data elements collected included facility demographics, total number of hospital and intensive care unit (ICU)

beds prior to the pandemic, US census region, patient populations served, facility type (eg, academic, community, inpatient rehabilitation), and active clinical trial site status. Given the noninterventional nature of the study, all patients were managed at each site according to each center’s standard of care and guidelines for the management of COVID-19.

In addition to whether patients were receiving supportive care or drug therapies targeting SARS-CoV-2, we collected basic patient demographic information and vital status (eg, age, sex, comorbidities, oxygen requirement, and ICU status). Data were abstracted from EHR systems—Epic (Epic Systems Corporation, Verona, WI) or Cerner (Cerner Corporation, Kansas City, MO)—by infectious diseases and antimicrobial stewardship pharmacists at each site. For each patient included, no follow-up or longitudinal outcomes were ascertained. Pediatric patients were eligible for inclusion.

Reported cumulative COVID-19 cases and attributable deaths in the United States, as reported by the Centers for Disease Control and

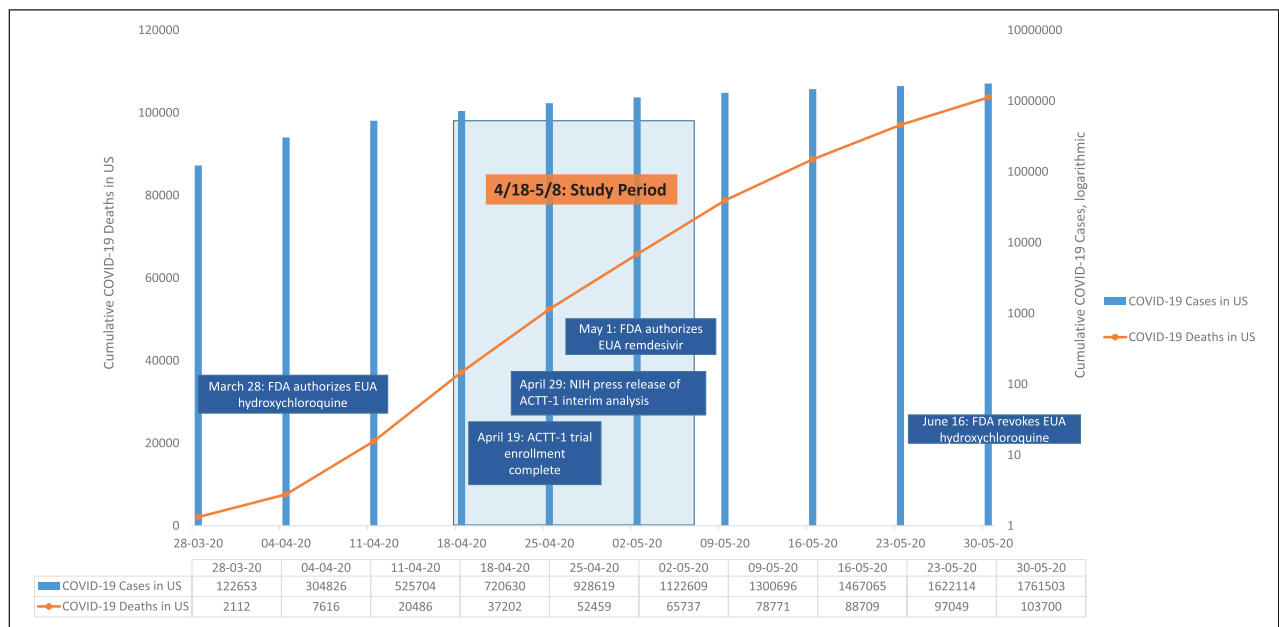
Prevention (CDC), were collected as a frame of reference for the study period. Additionally, ongoing clinical trial updates and medication availability (eg, EUA activity) are provided to describe routinely used drug therapies at the time of the study (Figure 1).<sup>12-16</sup>

**Study definitions.** For patients more than 90 years old, age was classified as “>90 years.” We evaluated the use of the following specific medications: azithromycin, hydroxychloroquine, tocilizumab or sarilumab (IL-6 antagonists), lopinavir/ritonavir, remdesivir (administered in a clinical trial or via compassionate use criteria), and other investigational agents. Clinical trial enrollment status was evaluated through review of notes within the health record. Combination therapy was considered as concurrent receipt of more than 1 agent targeting SARS-CoV-2 (eg, hydroxychloroquine plus azithromycin, hydroxychloroquine plus remdesivir). Data on requirement and degree of oxygen support within the last 24 hours was collected and classified as follows: no oxygen needed, supplemental oxygen required; low-flow oxygen (<6 L) via nasal cannula, high-flow oxygen (≥6 L) via nasal cannula, or invasive mechanical

ventilation. ICU admission status was also recorded.

ADRs were defined as any noxious and unintended occurrence (such as abnormal laboratory values) based upon existing knowledge of the adverse effect profiles of the agents evaluated as well as the existing literature on adverse events observed in patients with COVID-19 at the time of the study.<sup>17</sup> ADRs attributed to COVID-19–related therapeutic agents were collected according to clinician notes within EHR documentation. Pharmacist data collectors were instructed to assess the patients’ clinical status on the day of review as they would routinely do as part of daily clinical monitoring; the collected data were thus reflective of a real-world approach to pharmacist-provided clinical monitoring. The information evaluated, which may have varied according to reviewer practice, could include assessment of clinician notes, vital signs, and laboratory values to identify any ADRs and evaluate clinical status. We assessed the presence of new or worsening ADRs occurring concurrently with use of drug therapies for COVID-19 and observed the following reactions within the prior

**Figure 1.** Timeline of events during early months of COVID-19 pandemic in the United States. Case data are those reported by Centers for Disease Control and Prevention as of the time of writing.<sup>12-16</sup> EUA indicates emergency use authorization; FDA, Food and Drug Administration; NIH, National Institutes of Health.



24 hours: transaminitis (classified as liver enzyme elevations of 3 times or 5 times the upper limit of normal), acute kidney injury (ie, an increase in serum creatinine of 0.3 mg/L or 50%<sup>18</sup>), coagulopathy, headache, diarrhea, nausea or vomiting, prolongation of the heart rate-corrected QT interval (QTc) of >500 milliseconds (ms), new-onset arrhythmia, neutropenia, and thrombocytopenia. Severity of ADRs, aside from previously defined toxicity thresholds, was not captured given the study's point prevalence design, which provided only a 24-hour snapshot of the patients' treatment. Worsening clinical status, as documented within a physician's note, and any in-hospital mortality were also evaluated as safety endpoints.

**Statistical analysis.** Continuous data were analyzed using Student's *t* test or Wilcoxon rank-sum test, and categorical data were analyzed using  $\chi^2$  or Fisher's exact test, as appropriate. Missing data were treated as missing. All statistical analyses were performed using Intercooled Stata version 14.2 (StataCorp LLP, College Station, TX). Statistical significance was set at an  $\alpha$  of <0.05. Univariate logistic regression was used to estimate the odds ratio (OR) for harm only when the event rate exceeded 10% for the outcome (eg, any ADR).

## Results

**Demographics.** A total of 352 patients admitted to 15 hospitals across the United States between April 18 and May 8, 2020, were included. A timeline of select available evidence, EUA guidance, and reported US COVID-19 cases and deaths is outlined in [Figure 1](#) to provide context of when this study was performed in relation to the rapid trajectory of the pandemic's growth throughout the United States along with the ever-evolving pharmacotherapy recommendations.<sup>14-18</sup> Patient and facility demographics are summarized and stratified according to receipt of only supportive care vs COVID-19-directed therapy in [Table 1](#). Patients were primarily treated at academic medical

centers (53.4%), followed by community hospitals (42.6%), and a minority were treated at rehabilitation hospitals (4%). The majority of patients in our study were treated in the Midwest region (81%), with 10 states represented throughout the country. Over 97% of patients were confirmed to have had COVID-19 on the basis of diagnostic testing, with 98% of specimens collected via nasopharyngeal swab and a minority collected via bronchoalveolar lavage. The mean (SD) age of patients was 61.9 (16.1) years. Fifty-two percent of patients were males. The mean (SD) body weight and body mass index (BMI) were 89 (29) kg and 31.8 (11.3) kg/m<sup>2</sup>, respectively. Over 95% of patients were adults, and 4.5% were pediatric or neonatal patients. The majority of patients (81%) had received supportive care only (including supplemental oxygen and/or other nonpharmacological support) at the time of evaluation.

**Supportive care vs COVID-19-directed therapy.** A total of 67 patients had received COVID-19-directed drug therapy. The most commonly used COVID-19-directed drug therapies were hydroxychloroquine (69% of patients), remdesivir (10%), and IL-6 antagonists (9%). A total of 51 of the 67 patients (76%) treated with COVID-19-directed therapies required supplemental oxygen. Patients with a history of asthma were significantly more likely to have received COVID-19 drug therapy than supportive care only (14.9% vs 7%,  $P = 0.037$ ). Those patients who had other pulmonary comorbidities, including COPD, were numerically but not significantly more likely to have received drug therapy. Patients were significantly more likely to have received COVID-19-directed drug therapy if they were enrolled in a clinical trial (26.9% vs 3.2%,  $P < 0.001$ ).

**Frequency of ADRs in patients receiving monotherapy vs combination COVID-19-directed therapy.** Among patients who had received COVID-19 therapy, a total of 8 patients (12%) experienced any ADR, 5 of which (7.5%) were observed among patients who had received combination

treatment. A summary of the types and frequencies of ADRs with combination and single-agent COVID-19-directed therapy is provided in [Table 2](#). All 5 of the patients who had received combination therapy were given hydroxychloroquine in addition to another agent directed at SARS-CoV-2, including azithromycin ( $n = 2$ ), an IL-6 antagonist ( $n = 2$ ), or some other investigational agent ( $n = 1$ ). Patients who had received combination therapy were numerically more likely than those who received monotherapy to experience any ADR (20% vs 11.3%,  $P = 0.56$ ), though this difference was not statistically significant. Patients who had received monotherapy or combination therapy did not differ significantly with respect to any specific ADR evaluated ([Table 2](#)); however, numerically more patients experienced diarrhea if they had received combination therapy (20% vs 4.8%,  $P = 0.27$ ). Patients with a history of chronic kidney disease (CKD) were numerically more likely to have had any ADR detected (37.5% vs 10.2%;  $P = 0.068$ ). Likewise, patients enrolled in any clinical trial were significantly more likely to have had any ADR detected than patients who were not enrolled in a clinical trial (62.5% vs 22%; OR, 5.9;  $P = 0.028$ ). Agents observed to have been used as part of ongoing clinical trials at respective sites included remdesivir and hydroxychloroquine with or without azithromycin ([eAppendix](#)).

**Frequency of COVID-19-directed therapy and ADRs among patients requiring oxygen therapy.** Among all patients included in the study ( $n = 352$ ), 66.5% ( $n = 234$ ) required supplemental oxygen for severe COVID-19. Of these 234 patients who required supplemental oxygen, 55.6% ( $n = 230$ ) were hospitalized on a medical floor or ward and required less than 6 L of oxygen via nasal cannula, while 44.4% ( $n = 104$ ) were treated in an intensive care setting, with 93.3% ( $n = 97$ ) requiring 6 L or more of oxygen via nasal cannula as well as noninvasive or invasive mechanical ventilation. Looking only at patients who received any COVID-19-related treatment ( $n = 67$ ), 76.1%



**Table 1.** Patient Demographics and Facility Characteristics, Overall and by Type of COVID-19 Treatment<sup>a</sup>

	Total	Drug Therapy	Supportive Care Alone	P Value
<b>Facility-Level Data (n = 352 Patients)</b>				
Census region				0.001
Midwest	285 (81)	50 (74.6)	235 (82.5)	
Northeast	21 (6)	0	21 (7.4)	
South	16 (4.5)	8 (11.9)	8 (2.8)	
West	30 (8.5)	9 (13.4)	21 (7.4)	
Facility type				0.089
Academic medical center	188 (53.4)	33 (49.3)	155 (54.4)	
Community hospital	150 (42.6)	34 (50.7)	116 (40.7)	
Rehabilitation center	14 (4)	0	14 (4.9)	
Pediatric population served				0.31
No. patients	239 (67.9)	42 (62.7)	197 (69.1)	
Neonatal population served				0.67
No. patients	285 (81)	53 (79.1)	232 (81.4)	
No. of facility beds				0.94
100-250	117 (33.2)	20 (29.9)	97 (34)	
251-500	77 (21.9)	16 (23.9)	61 (21.4)	
501-750	51 (14.5)	9 (13.4)	42 (14.7)	
751-1,000	52 (14.8)	10 (14.9)	42 (14.7)	
>1,000	55 (15.6)	12 (17.9)	43 (15.1)	
No. of ICU beds				0.007
0	14 (4)	0	14 (4.9)	
1-10	30 (8.5)	1 (1.5)	29 (10.2)	
10-25	73 (20.7)	19 (28.4)	54 (18.9)	
26-50	47 (13.4)	14 (20.9)	33 (11.6)	
>100	188 (53.4)	33 (49.3)	155 (54.4)	
<b>Patient-Level Data (n = 352)</b>				
Age, mean (SD), y	61.9 (16.1)	61.8 (15.3)	61.9 (16.4)	0.97
Weight, mean (SD), kg	89 (29.2)	84.5 (20.7)	90.1 (30.8)	0.16
Height, mean (SD), cm	167.5 (12.3)	166.6 (9.5)	167.7 (12.9)	0.51
BMI, mean (SD), kg/m <sup>2</sup>	31.8 (11.3)	30.5 (7.2)	32.1 (12.1)	0.29
Confirmed COVID-19 by test				0.54
No. patients	343 (97.4)	66 (98.5)	277 (97.2)	
Nasopharyngeal specimen				0.98
No. patients	336 (95.5)	64 (95.5)	272 (95.4)	
Sex <sup>b</sup>				0.8
Female	168 (47.9)	33 (49.3)	135 (47.5)	
Male	183 (52.1)	34 (50.7)	149 (52.5)	

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**Table 1.** Patient Demographics and Facility Characteristics, Overall and by Type of COVID-19 Treatment<sup>a</sup>

	Total	Drug Therapy	Supportive Care Alone	P Value
Population by age group				
Neonate	15 (4.3)	2 (3)	13 (4.6)	0.57
Adult (≥18 y)	337 (95.7)	65 (97)	272 (95.4)	0.5
Advanced age (>90 y) <sup>c</sup>	14 (4)	2 (3)	12 (4.2)	0.64
Any comorbidity				
Asthma	30 (8.5)	10 (14.9)	20 (7)	0.037
COPD	33 (9.4)	9 (13.4)	24 (8.4)	0.21
Heart failure	62 (17.6)	10 (14.9)	52 (18.2)	0.52
Hypertension	203 (57.7)	33 (49.3)	170 (59.6)	0.12
History of CKD	62 (17.6)	9 (13.4)	53 (18.6)	0.32
Diabetes	156 (44.3)	25 (37.3)	131 (46.0)	0.2
Obesity	113 (32.1)	21 (31.3)	92 (32.3)	0.88
History of CVA	35 (9.9)	8 (11.9)	27 (9.5)	0.54
History of chronic lung disease	8 (2.3)	1 (1.5)	7 (2.5)	0.63
Cancer	27 (7.7)	4 (6)	23 (8.1)	0.56
Solid organ or hematologic transplant	10 (2.8)	2 (3)	8 (2.8)	0.94
Hyperlipidemia	51 (14.5)	8 (11.9)	43 (15.1)	0.51
Atrial fibrillation	22 (6.3)	2 (3)	20 (7.0)	0.22
Level of acuity				
ICU admission	104 (29.5)	20 (29.9)	84 (29.5)	0.95
Required oxygen	234 (66.5)	51 (76.1)	183 (64.2)	0.06
Clinical trial enrollment <sup>d</sup>	27 (7.7)	18 (26.9)	9 (3.2)	<0.001

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ICU, intensive care unit.

<sup>a</sup>All data are number (percentage) of patients unless specified otherwise.

<sup>b</sup>*n* = 351.

<sup>c</sup>Patients of advanced age were considered as a subset of the adult group.

<sup>d</sup>Enrolled patients could have received or not received drug therapy at the time of evaluation.

(*n* = 51) required any form of supplemental oxygen for severe disease. The requirement for supplemental oxygen secondary to severe COVID-19 was numerically more common among patients who were receiving combination COVID-19-directed therapy vs monotherapy (77.4% [48 of 62] vs 60% [3 of 5], *P* = 0.59). A summary of adverse effects according to oxygen requirement status is presented in Table 3. Patients who did not require oxygen for nonsevere COVID-19 were numerically more likely to experience any ADR within the prior 24 hours (25% vs 7.8%, *P* = 0.085). These patients were also numerically more likely to

experience QTc prolongation within the prior 24 hours (12.5% vs 0%, *P* = 0.054). On the other hand, patients who required supplemental oxygen were significantly more likely to have clinically worsened in the prior 24 hours (31.4% vs 0%, *P* = 0.008). The number of deaths was not significantly higher among patients who required supplemental oxygen than among those who did not (*P* = 0.57).

## Discussion

This multicenter point prevalence study found that between April 18 and May 8, 2020, drug therapy for COVID-19

was relatively uncommon across academic, community, and rehabilitation hospitals during a typical day. The majority of patients were receiving supportive care (81%), and a total of 66.5% required supplemental oxygen. Only 67 patients (19%) had received COVID-19-directed drug therapy, and a minority of those patients (*n* = 5) had received combination treatment with more than 1 agent targeting SARS-CoV-2. Nevertheless, we still were able to identify ADRs in 12% of patients who were receiving drug therapy. While a point prevalence approach is not comprehensive and causality cannot be

**Table 2.** Frequency and Type of Adverse Drug Reactions According to Combination COVID-19 Directed Therapy<sup>a</sup>

Drug therapy modality	Monotherapy	Combination Therapy	Total <sup>b</sup>
Patients receiving any drug therapy (n=67)	62 (100)	5 (100)	67 (100)
Any ADR in last 24 hrs (n=8) <sup>c</sup>	7 (11.3)	1 (20)	8 (11.9)
AKI (n=2)	2 (3.2)	0	2 (3)
Diarrhea (n=4)	3 (4.8)	1 (20)	4 (6)
Prolonged QTc > 500 ms (n=2)	2 (3.2)	0	2 (3)
Thrombocytopenia (n=3)	3 (4.8)	0	3 (4.5)
ADR led to therapy discontinuation (n=1)	1 (14.3)	0	1 (12.5)
Clinically worsened in previous 24 hrs (n=16)	15 (24.2)	1 (20)	16 (23.9)
Mortality in previous 24 hrs (n=1)	1 (1.6)	0	1 (1.5)

Abbreviations: ADR, adverse drug reaction; AKI, acute kidney injury; QTc, heart rate-corrected QT interval.

<sup>a</sup>All data are number (percentage) of patients; all percentages are column percentages.

<sup>b</sup>P > 0.05 for all comparisons.

<sup>c</sup>Patients may have experienced more than 1 ADR.

**Table 3.** Frequency of Adverse Drug Reactions According to Supplemental Oxygen Requirement<sup>a</sup>

Supplemental Oxygen Required:	Oxygen = No	Oxygen = Yes	Total	P Value
Patients receiving any drug therapy (n=67)	16 (100)	51 (100)	67 (100)	
Any ADR in last 24 hrs (n=8) <sup>b</sup>	4 (25)	4 (7.8)	8 (11.9)	0.085
AKI (n=2)	1 (6.3)	1 (2)	2 (3)	0.42
Diarrhea (n=4)	1 (6.3)	3 (5.9)	4 (6)	>0.99
Prolonged QTc > 500 ms (n=2)	2 (12.5)	0	2 (3)	0.054
Thrombocytopenia (n=3)	0	3 (5.9)	3 (4.5)	>0.99
ADR led to therapy discontinuation (n=1)	1 (25)	0	1 (12.5)	>0.99
Clinically worsened in last 24 hrs (n=16)	0	16 (31.4)	16 (23.9)	0.008
Mortality in last 24 hrs (n=1)	0	1 (2)	1 (1.5)	>0.99

Abbreviations: ADR, adverse drug reaction; AKI, acute kidney injury; QTc, heart rate-corrected QT interval.

<sup>a</sup>All data are number (percentage) of patients; all percentages are column percentages.

<sup>b</sup>Patients may have experienced more than 1 ADR.

firmly established, our findings serve as a warning that COVID-19 drug therapies are not benign. Among patients receiving combination therapy (mostly involving hydroxychloroquine), diarrhea was more common. Our findings suggest that on a typical day more patients were receiving supportive care alone vs COVID-19 drug therapies, which may be reflective of the paucity of data supporting effective treatment at the onset of the pandemic. Notably, our point prevalence approach did not capture previous treatment, so some patients receiving only supportive care may have been previously treated with drug therapy. Enrollment in a clinical

trial and a history of asthma were associated with increased use of drug therapies targeting SARS-CoV-2.

Notably, our sample included 15 hospitals distributed throughout the United States, with high representation by facilities in the Midwest, a region underrepresented in the available COVID-19 literature.<sup>19-22</sup> Our methodology provided a new perspective on COVID-19 treatment in academic medical centers primarily located in the Midwestern United States, though comprehensive multicenter studies are needed. While not representative of all hospitals in each state, the sites

included in our study provided a relevant and representative sample of patients with COVID-19 throughout the United States early in the pandemic's course. Institution-specific data related to numbers of cases and COVID-19-related deaths were not available due to the nature of the study.

It is also important to note that our study took place before wide availability of EUA remdesivir.<sup>7</sup> Most patients in our study were receiving supportive care at the time of evaluation; however, cumulative exposure to drug therapies was not ascertained. Supportive care has been suggested

as a cautious approach to providing unproven and understudied drug therapy in an emergency situation,<sup>23,24</sup> and more data are needed to define the safety of COVID-19 drug therapies. Our finding that ADRs were relatively common among patients with COVID-19 receiving drug therapy underscores the need for close monitoring. Among those who had received drug therapy, use of therapeutic agents in COVID-19 was based on institutional prescribing protocols, local guidance, or individual clinician practice. The study protocol was observational and did not call for the use of any specific agents or dosages; however, among the dosages observed, all were consistent with available dosing guidance in preprint and published literature at the time of use, which could be expected to limit the anticipated risk of ADRs.

We found that patients who were enrolled in clinical trials were nearly 6-fold more likely to have an ADR detected, likely reflecting the careful monitoring occurring in trials. Reduced face-to-face time between clinicians and patients in an effort to reduce transmission of COVID-19 and conserve personal protective equipment might also contribute to the lower incidence of ADR reporting among patients not enrolled in clinical trials. Unfortunately, the vast majority of patients with COVID-19 do not have access to clinical trials but receive these agents nonetheless. Therefore, there is a clear need for improved ADR monitoring in patients receiving unproven therapies.

Given the timing of our study, which was relatively early in the pandemic's course throughout the United States, most COVID-19 pharmacotherapies were recommended and used on the basis of limited and sometimes conflicting evidence. As noted, various drug therapies are being evaluated in the fight against COVID-19; however, at the time of writing there was no definitive cure. While some drugs have been touted as efficacious, clinical trial findings have not mirrored these claims, and many of these potential treatments

have been plagued by safety concerns. Lopinavir/ritonavir was initially evaluated in China for its role in hospitalized adults diagnosed with severe COVID-19, but a controlled trial did not demonstrate benefits relative to standard of care in outcomes such as time to clinical improvement and mortality at 28 days.<sup>25</sup> Serious adverse events were more common in the standard care group, yet use of lopinavir/ritonavir was associated with a higher rate of gastrointestinal ADRs. Of note, there was no use of lopinavir/ritonavir in our patient sample.

Similarly, the use of hydroxychloroquine, alone or combined with azithromycin, has diminished markedly due to safety concerns and questionable efficacy.<sup>26,27</sup> Though less than 20% of patients in our study were receiving COVID-19 drug therapy, the most commonly used drug was hydroxychloroquine. Recently, results of a multinational registry analysis of over 96,000 hospitalized patients with COVID-19 who were treated with hydroxychloroquine ( $n = 3,016$ ), hydroxychloroquine plus a macrolide ( $n = 6,221$ ), chloroquine ( $n = 1,868$ ), or chloroquine plus a macrolide ( $n = 3,783$ ) were reported.<sup>27</sup> The investigators observed an increased risk of in-hospital mortality and de novo ventricular arrhythmias with use of hydroxychloroquine or chloroquine-based therapy, though these results have been called into question,<sup>28</sup> resulting in retraction of the paper. Subsequently, the World Health Organization discontinued enrollment for a clinical trial of hydroxychloroquine, as the use of hydroxychloroquine as a COVID-19 therapy appears to be futile.<sup>29</sup>

Whereas the aforementioned agents have known limitations, other agents such as IL-6 antagonists (tocilizumab and sarilumab), IL-1 antagonists (anakinra and canakinumab), and remdesivir are gaining increased attention. Use of the IL-6 antagonist tocilizumab appeared to be beneficial in critically ill patients with severe COVID-19, with reported improvements in oxygen requirements, fever

resolution, lung imaging, and inflammatory markers.<sup>30</sup> Unfortunately, these benefits have not been reproduced in randomized, placebo-controlled trials.<sup>31</sup> Similarly, a randomized, placebo-controlled trial of sarilumab was stopped in light of study results demonstrating no significant clinical benefit and a potential risk of adverse events.<sup>32</sup> As depicted in these studies, off-label and investigational drug therapy targeting the cytokine response may increase the risk of secondary infections, gastrointestinal perforations, and hepatic toxicity.<sup>33</sup> As the full results of these studies become available, clinicians will benefit from a greater understanding of the risk of ADRs among patients receiving treatment for COVID-19.

Remdesivir has garnered considerable interest as a treatment for COVID-19 since it was granted EUA status in May 2020.<sup>7</sup> A recent randomized, placebo-controlled trial by Wang et al<sup>34</sup> did not establish significant benefit with use of remdesivir and was terminated early. Serious adverse events occurred in 18% and 26% of patients receiving remdesivir and placebo, respectively. The ACTT-1 trial was a randomized, placebo-controlled study of 1,063 hospitalized patients with COVID-19.<sup>15</sup> Preliminary results showed a shorter median time to recovery with remdesivir therapy (11 days vs 15 days). Serious adverse events occurred in 21% and 27% of patients receiving remdesivir and placebo, respectively. ADRs occurring more often with remdesivir were decreased renal function, pyrexia, and hyperglycemia.<sup>15</sup> The Gilead-sponsored SIMPLE trial comparing 5 and 10 days of remdesivir did not identify a primary efficacy difference for the regimens evaluated; however, significantly more patients treated for 10 days experienced any serious adverse event, including AKI.<sup>35</sup> We did not identify higher rates of ADRs with use of remdesivir in our study, but patients could have been receiving remdesivir under compassionate use criteria or may have been placebo recipients in the setting of a clinical trial. Based upon available evidence, patients receiving



remdesivir, particularly for more than 5 days, will require more intensive monitoring. According to available COVID-19 literature, rates of reported ADRs are relatively high, ranging from 18% to 27%, a range that exceeds the rate of observed ADRs in our study, likely due to infrequent remdesivir use among included patients.<sup>34,35</sup>

Our study had a number of limitations. First, it was a point prevalence survey and thus cause-and-effect relationships could not be discerned. Our survey data window was limited to the prior 24 hours, so it is likely that our evaluation of adverse effects was conservative. Because our ability to discern causation was limited, it is not completely clear to what extent the adverse events we found were related to COVID-19 sequelae vs drug therapies. Nevertheless, we observed numerically more adverse reactions among patients who did not require supplemental oxygen. These patients were at various points of their disease course (ie, we included anyone who was hospitalized and required treatment), so prior exposure to agents that may have led to the noted adverse effects (eg, diarrhea due to use of antibiotics) was not comprehensively assessed. Additionally, patients with less severe illness may have been able to communicate ADRs more effectively to clinicians. Our sample size was somewhat small because drug therapy was not as common early in the pandemic. Finally, as our study was conducted before drug therapy became more common, our assessment of ADRs associated with drug therapy may be conservative. More work is needed to define the time course and severity of ADRs in this population in order to improve patient safety.

Despite these limitations, strengths of our study included the representative sample of patients with COVID-19 across various geographic and demographic populations. Data from clinical trials and ADR registries are needed to more clearly define the risks of COVID-19 drug therapies.

In conclusion, we observed high rates of supportive care in more than

80% of included patients with COVID-19 in our point prevalence survey. Among patients who were receiving drug therapy, we found that as many as 12% experienced an ADR within the prior 24 hours, with the most commonly reported adverse event being diarrhea. Patients enrolled in clinical trials were over 6-fold more likely to have an ADR identified, suggesting a greater need for routine ADR monitoring in patients receiving drug therapy against COVID-19. Comprehensive systems are needed to identify and mitigate adverse effects associated with COVID-19 drug therapies.

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