RESEARCH ARTICLE

Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study

Donna R. Rivera[1], Solange Peters[2], Orestis A. Panagiotou[3], Dimpy P. Shah[4], Nicole M. Kuderer[5], Chih-Yuan Hsu[6], Samuel M. Rubinstein[7], Brendan J. Lee[7], Toni K. Choueiri[8], Gilberto de Lima Lopes Jr.[9], Petros Grivas[10,11], Corrie A. Painter[12], Brian I. Rini[7], Michael A. Thompson[13], Jonathan Arcobello[14], Ziad Bakouny[8], Deborah B. Doroshow[15,16], Pamela C. Egan[17], Dimitrios Farmakiotis[18], Leslie A. Fecher[19], Christopher R. Friese[20], Matthew D. Galsky[15,16], Sanjay Goel[21], Shilpa Gupta[22], Thorvardur R. Halfdanarson[23], Balazs Halmos[21], Jessica E. Hawley[24], Ali Raza Khaki[10], Christopher A. Lemmon[22], Sanjay Mishra[25], Adam J. Olszewski[17], Nathan A. Pennell[22], Matthew M. Puc[26], Sanjay G. Revankar[14], Lidia Schapira[27], Andrew Schmidt[8], Gary K. Schwartz[24], Sumit A. Shah[27], Julie T. Wu[27], Zhuoer Xie[23], Albert C. Yeh[10], Huili Zhu[15], Yu Shyr[6], Gary H. Lyman[11], and Jeremy L. Warner[7,28] on behalf of the COVID-19 and Cancer Consortium

ABSTRACT Among 2,186 U.S. adults with invasive cancer and laboratory-confirmed SARS-CoV-2 infection, we examined the association of COVID-19 treatments with 30-day all-cause mortality and factors associated with treatment. Logistic regression with multiple adjustments (e.g., comorbidities, cancer status, baseline COVID-19 severity) was performed. Hydroxychloroquine with any other drug was associated with increased mortality versus treatment with any COVID-19 treatment other than hydroxychloroquine or untreated controls; this association was not present with hydroxychloroquine alone. Remdesivir had numerically reduced mortality versus untreated controls that did not reach statistical significance. Baseline COVID-19 severity was strongly associated with receipt of any treatment. Black patients were approximately half as likely to receive remdesivir as white patients. Although observational studies can be limited by potential unmeasured confounding, our findings add to the emerging understanding of patterns of care for patients with cancer and COVID-19 and support evaluation of emerging treatments through inclusive prospective controlled trials.

SIGNIFICANCE: Evaluating the potential role of COVID-19 treatments in patients with cancer in a large observational study, there was no statistically significant 30-day all-cause mortality benefit with hydroxychloroquine or high-dose corticosteroids alone or in combination; remdesivir showed potential benefit. Treatment receipt reflects clinical decision-making and suggests disparities in medication access.

INTRODUCTION

With the onset of the World Health Organization (WHO)–designated global COVID-19 pandemic, a crucial need emerged to discover or repurpose safe and effective treatments to mitigate the severity and mortality of the disease. This need is particularly apparent for patients with cancer, in whom COVID-19 can have serious consequences. In a very large observational study, patients with cancer appear to be at increased risk of COVID-19 mortality, independent of any specific treatment received for COVID-19 (1). The initial study of COVID-19 and Cancer Consortium (CCC19) data found that 30-day all-cause mortality was 13% among patients with active or prior cancer and confirmed SARS-CoV-2 infection (2). This analysis suggested increased 30-day all-cause mortality among patients receiving the combination of hydroxychloroquine plus azithromycin. Other factors associated with increased mortality included age, male sex, former smoking status, number of comorbidities, Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or higher, and active cancer.

Currently, there is not yet peer-reviewed published evidence from randomized clinical trials (RCT) evaluating new potential therapies or preventive strategies that demonstrate

[1]Division of Cancer Control and Population Sciences, NCI, Rockville, Maryland. [2]Department of Oncology, University of Lausanne, Lausanne, Switzerland. [3]Department of Health Services, Policy and Practice, Brown University, Providence, Rhode Island. [4]Department of Population Health Sciences, Mays Cancer Center, UT Health San Antonio MD Anderson, San Antonio, Texas. [5]Advanced Cancer Research Group, LLC, Kirkland, Washington. [6]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee. [7]Deparment of Medicine, Division of Hematology and Oncology, Vanderbilt University Medical Center, Nashville, Tennessee. [8]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. [9]Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida. [10]Department of Medicine, Division of Oncology, University of Washington, Seattle, Washington. [11]Fred Hutchinson Cancer Research Center, Seattle, Washington. [12]Count Me In, Cambridge, Massachusetts. [13]Advocate Aurora Health, Milwaukee, Wisconsin. [14]Karmanos Cancer Institute, Detroit, Michigan. [15]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York. [16]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York. [17]Department of Medicine, Division of Hematology/Oncology, The Warren Alpert Medical School of Brown University, Providence, Rhode Island. [18]Department of Medicine, Division of Infectious Diseases, The Warren Alpert Medical School of Brown University, Providence, Rhode Island. [19]Department of Internal Medicine, Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan. [20]School of Nursing, University of Michigan, Ann Arbor, Michigan. [21]Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York. [22]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, Ohio. [23]Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota. [24]Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, New York. [25]Vanderbilt-Ingram Cancer Center, Nashville, Tennessee. [26]Department of Surgery, Section of Thoracic Surgery, Virtua Health, Marlton, New Jersey. [27]Department of Medicine, Division of Oncology, Stanford University, Palo Alto, California. [28]Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee.

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D.R. Rivera, S. Peters, Y. Shyr, G.H. Lyman, and J.L. Warner contributed equally to this article.

Corresponding Author: Jeremy L. Warner, Vanderbilt University Medical Center, 2220 Pierce Avenue, PRB 777, Nashville, TN 37232. Phone: 615-322-5464. E-mail: jeremy.warner@vumc.org

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a significant improvement in mortality outcomes in patients with COVID-19 and cancer. Given the historical challenges of clinical trial accrual, in particular for patients with cancer, the pace of the pandemic is outpacing the rate of prospective evidence generation, making observational data of great importance. In a large promising randomized study evaluating multiple treatment options, the UK RECOVERY trial, cancer is not included as a specific measured comorbidity in preliminary reports (3).

Our previous study examined risk factors associated with 30-day all-cause mortality, including the receipt of hydroxychloroquine alone or in combination with azithromycin, although only partial adjustment was possible due to limited numbers of events. This association could be influenced by confounding factors, that is, patient or clinical characteristics that could be associated with both COVID-19 treatment receipt and mortality. This follow-up study aims to identify factors associated with the receipt of COVID-19 treatments and to analyze their potential impact on 30-day all-cause mortality among patients with active or prior cancer and SARS-CoV-2 infection after a robust adjustment for additional baseline factors. Our hypotheses were that hydroxychloroquine (primary hypothesis) and other plausible anti–COVID-19 medications, namely remdesivir, tocilizumab, and high-dose corticosteroids (secondary hypotheses), are correlated with mortality in patients with cancer who are diagnosed with COVID-19 after adjustment for potential confounding. We also conducted a secondary analysis of patient factors associated with receipt of any anti–COVID-19 treatment, the combination of hydroxychloroquine plus azithromycin, and remdesivir.

RESULTS

The study cohort included 2,186 patients meeting the study inclusion criteria for evaluation of treatment patterns and outcomes who accrued between March 17 and June 26, 2020 (Fig. 1). Overall cohort demographic and clinical patient characteristics are shown in Fig. 2 and Supplementary Table S1, along with the characteristics of each treatment exposure group. Baseline COVID-19 severity was mild in 1,037 (47%), moderate in 876 (40%), and severe in 273 (12%). Patients received the following treatments, alone or in combination, in decreasing prevalence: hydroxychloroquine (n = 538, 25%), azithromycin (n = 485, 22%), remdesivir (n = 124, 6%), high-dose corticosteroids (n = 109, 5%), tocilizumab (n = 94, 4%), and other therapy (n = 90, 4%); no treatment was reported for 1,321 (60%) patients.

The median age of included patients was 67 years [interquartile range (IQR), 57–77], 1,078 (49%) were male, 1,115 (51%) were non-Hispanic white, and 1,011 (46%) were residents of the northeast United States. There were 1,115 (51%) patients in remission from cancer, 607 (28%) had present cancer that was stable or responding to treatment, and 239 (11%) had actively progressing cancer. Of those in remission, 149 (13%) were receiving active antineoplastic treatment. Conversely, 116 (49%) patients with progressing cancer had not received antineoplastic treatment within four weeks of COVID-19 diagnosis; 50 (43%) of these patients received some form of COVID-19 treatment. There were 749 (34%) patients with an ECOG PS of 0, 563 (26%) with ECOG PS of 1, and 352 (16%) with ECOG PS of 2 or greater. The majority of patients presented with solid tumors (n = 1,781, 81%), of which breast cancer was the most common (n = 455, 21%). Comorbidity prevalence was examined for the following conditions within the cohort: obesity (n = 705, 32%), diabetes mellitus (n = 643, 29%), hypertension (n = 1,258, 58%), pulmonary conditions (n = 471, 22%), cardiovascular conditions (n = 709, 32%), and renal conditions (n = 389, 18%). Patients received a variety of concomitant medications including aspirin or other antiplatelet agents (n = 682, 31%), anticoagulants (n = 1087, 50%), statins (n = 927, 42%), and low-dose corticosteroids (n = 184, 8%). The percentage of patients receiving anticoagulation in the treatment groups was higher, ranging from 73% to 84% (Supplementary Table S1).

Treatment Utilization

Of the 865 (40%) patients who received one or more of the exposures of interest, the most common treatment utilized was hydroxychloroquine plus azithromycin (n = 203, 23%), followed by hydroxychloroquine alone (n = 179, 21%), azithromycin alone (n = 160, 18%), remdesivir alone (n = 57, 7%), hydroxychloroquine plus azithromycin plus high-dose corticosteroids (n = 24, 3%), high-dose corticosteroids alone (n = 18, 2%), hydroxychloroquine plus tocilizumab (n = 18, 2%), and hydroxychloroquine plus azithromycin plus tocilizumab (n = 18, 2%). Various other treatment combinations were reported less frequently, with a total of 49 different treatment patterns observed (Fig. 3).

Of note, tocilizumab was rarely given alone, whereas the other treatments examined had subsets of monotherapy exposure exceeding 1%. There were differences in patterns of treatment for ever-hospitalized versus never-hospitalized patients, with no receipt of more than two agents in combination for never-hospitalized patients (Supplementary Figs. S1 and S2). Patients most frequently received remdesivir as part of a clinical trial (n = 86, 69%), whereas use of other agents was almost entirely outside the context of a specified trial.

Receipt of Therapies with Potential Anti–COVID-19 Effects

Medication utilization was examined using multivariable logistic regression (MLR) analysis to assess likelihood for receipt of treatment with (i) hydroxychloroquine plus azithromycin, (ii) remdesivir (with or without any other concomitant therapy), and (iii) any treatment of interest. Group assignments to the exposure of interest, positive controls, and negative controls are shown in Fig. 4 and Supplementary Table S2. There was no statistically significant interaction between race/ethnicity and hypertension or renal comorbidities. Goodness of fit is shown in Supplementary Table S3; all variance inflation factors (VIF) for all models were less than five. Across all treatment groups examined, baseline COVID-19 severity had the strongest association with treatment, with a stepwise increase from moderate to severe (Table 1).

In addition, the following characteristics were associated with receipt of hydroxychloroquine plus azithromycin treatment: patients in the U.S. West were less likely to receive

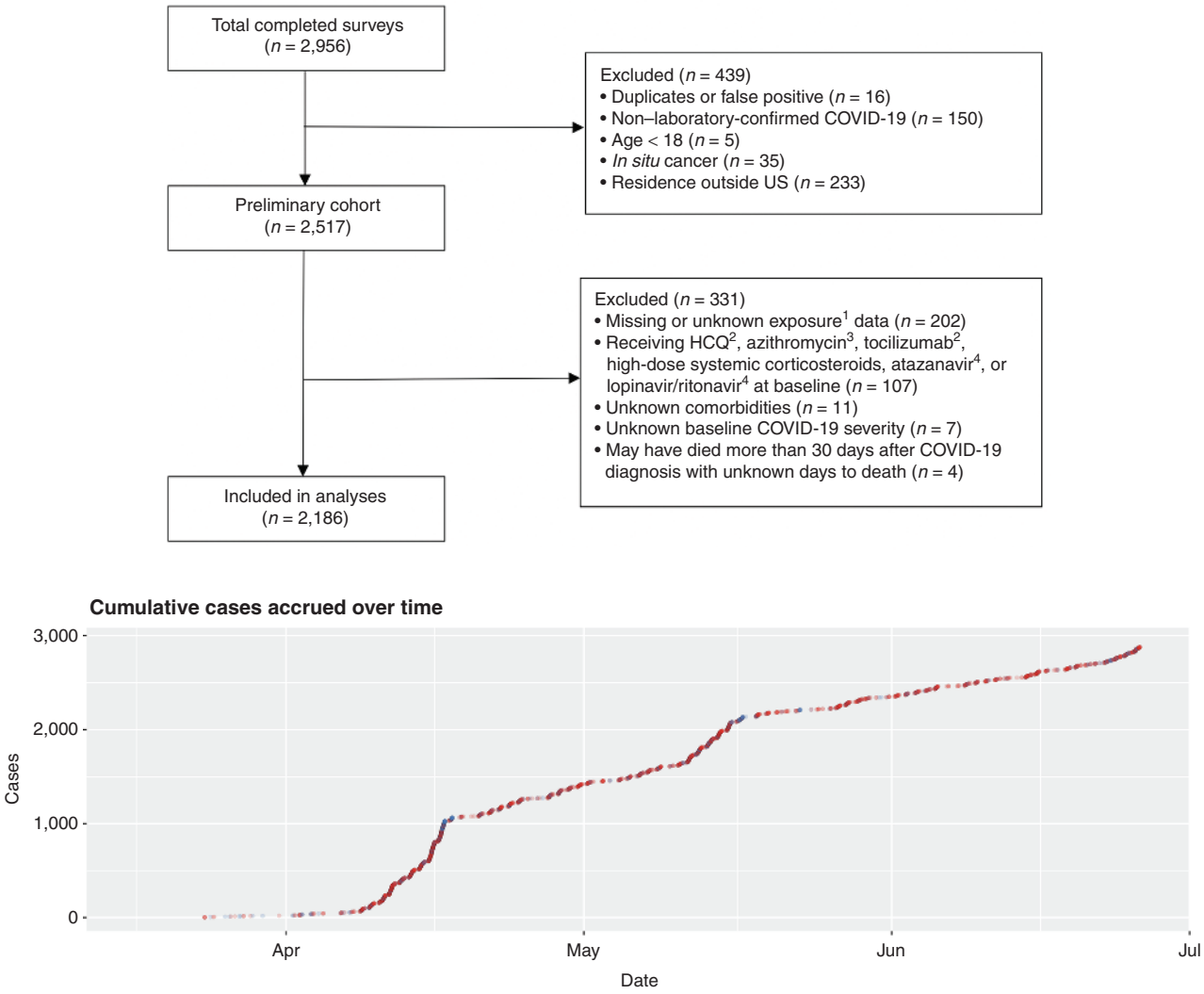

Figure 1. CONSORT diagram (top) and registry accrual (bottom) during the data collection period of March 17 to June 26, 2020. Red points represent included cases; blue points represent excluded cases. [1]Hydroxychloroquine (HCQ), azithromycin, remdesivir, high-dose systemic corticosteroids, tocilizumab, or other COVID-19 treatments; [2]Only excluded if patient has a baseline autoimmune condition; [3]Only excluded if patient has baseline chronic obstructive pulmonary disease, asthma, or HIV; [4]Only excluded if patient has baseline HIV.

hydroxychloroquine plus azithromycin [adjusted odds ratio (aOR), 0.34; 95% confidence interval (CI): 0.17–0.69] as were patients with cardiovascular conditions (aOR, 0.68; 95% CI: 0.48–0.98). Patients with renal conditions were more likely to receive hydroxychloroquine plus azithromycin (aOR, 1.56; 95% CI: 1.09–2.23).

The following additional characteristics were associated with a decreased likelihood of receiving remdesivir: non-Hispanic Black patients versus non-Hispanic white patients (aOR, 0.56; 95% CI: 0.31–1.00; Supplementary Table S4); renal comorbidities (aOR, 0.32; 95% CI: 0.16–0.61); and ECOG PS of 2+ (aOR, 0.47; 95% CI: 0.24–0.90). Patients residing in the U.S. West were more likely to receive remdesivir (aOR, 1.85; 95% CI: 1.09–3.15). Increasing age was numerically associated with a decreased likelihood of remdesivir treatment, although this did not reach statistical significance (aOR, 0.87; 95% CI: 0.74–1.03).

The following additional characteristics were associated with increased likelihood of receipt of any treatment: male sex (aOR, 1.28; 95% CI: 1.04–1.56), obesity (aOR, 1.44; 95% CI: 1.16–1.80), presence of pulmonary comorbidities (aOR, 1.41; 95% CI: 1.10–1.80), and presence of hypertension (aOR, 1.28; 95% CI: 1.02–1.60). Patients with cardiovascular comorbidities were less likely to receive any treatment (aOR, 0.77; 95% CI: 0.61–0.98), as were patients with ECOG PS of 2+ (aOR, 0.72; 95% CI: 0.52–1.00), and those residing in the U.S. West (aOR, 0.63; 95% CI: 0.45–0.87).

Primary Outcome

At the time of this analysis, median follow-up for the included patients was 30 days (IQR, 10.5–42 days). Of the 357 (16%) patients who were deceased at the time of data lock, 329 (92%) died within 30 days, yielding a primary outcome rate of 15%. Goodness of fit is shown in Supplementary Table S3; all VIFs for all models were less than five.

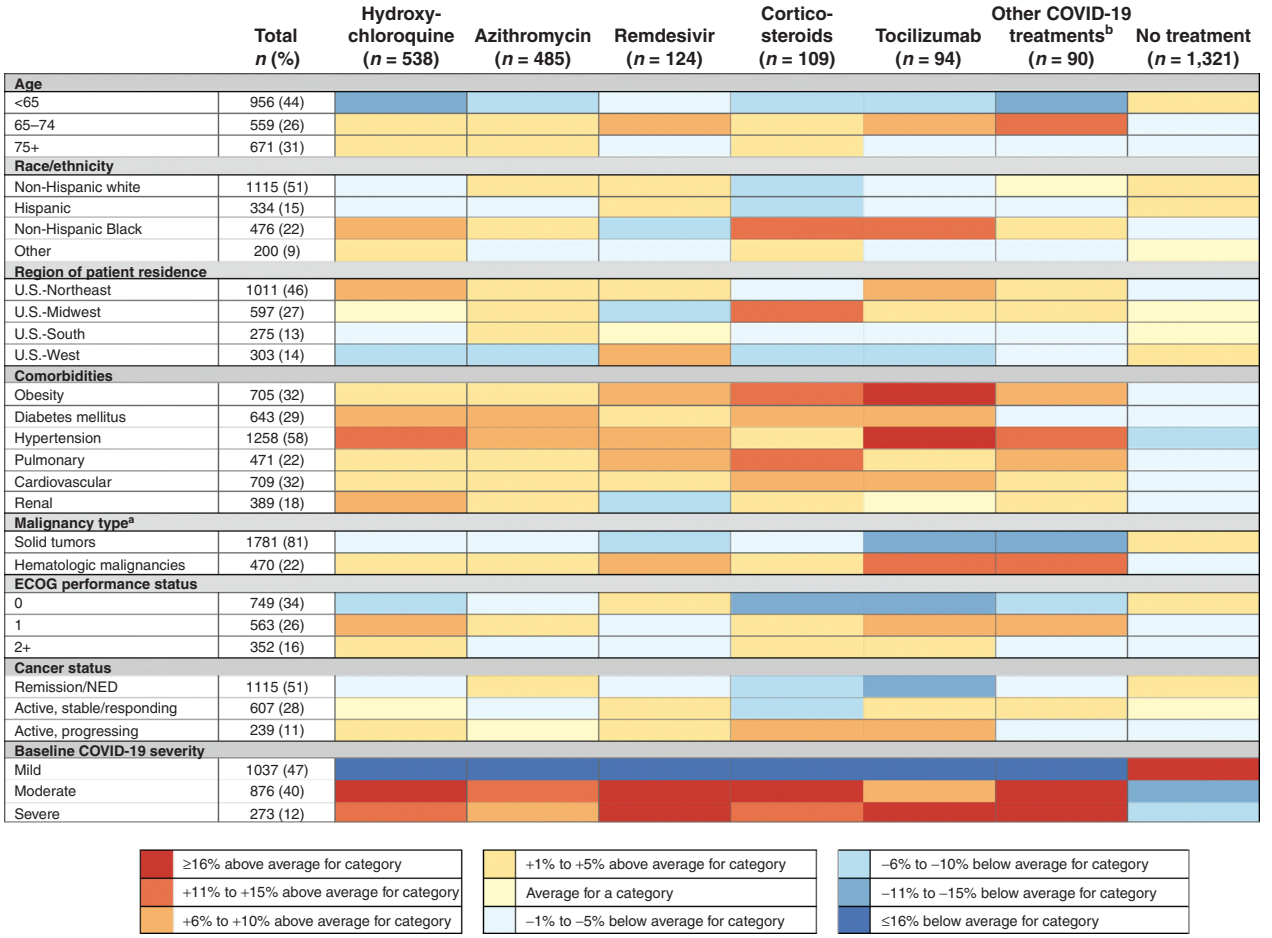

Figure 2. Heat map of selected clinical factors stratified by treatment exposures. Coloration depicts the absolute departure from the average for that category; for example, patients with obesity were overrepresented in the tocilizumab exposure group by more than 16% of the average level of obesity in the total population (51% vs. 32%); patients with renal comorbidities were underrepresented in the remdesivir exposure group by 6% to 10% below the average level of renal comorbidities in the total population (9% vs. 18%). [a]Percentages add up to more than 100 because some patients had multiple malignancies; [b]Includes patients enrolled in blinded randomized controlled trials, e.g., of remdesivir vs. placebo. NED, no evidence of disease.

Hydroxychloroquine

Propensity score matching (PSM) was undertaken to improve covariate balance and comparability between the comparator groups within the cohort as compared to the model with unmatched controls (Supplementary Table S5; Supplementary Fig. S3). As shown in Table 2, patients receiving hydroxychloroquine plus any other therapy had a statistically significant increased risk of 30-day all-cause mortality compared with positive controls in matched and unmatched models (PSM aOR, 1.99; 95% CI: 1.29–3.08; unmatched aOR, 1.93; 95% CI: 1.27–2.94). Hydroxychloroquine treatment alone was not associated with increased risk (PSM aOR, 1.03; 95% CI: 0.62–1.73; unmatched aOR, 0.98; 95% CI: 0.59–1.62). Compared with negative controls, results are similar with an increased risk among those receiving hydroxychloroquine plus any other therapy (PSM aOR, 2.15; 95% CI: 1.51–3.06; unmatched aOR, 2.50; 95% CI: 1.74–3.59), with no increased risk for hydroxychloroquine alone. In addition, mortality associated with hydroxychloroquine exposure was modeled excluding severe cases. With this exclusion, there was an increased magnitude of the effect on the primary outcome for patients receiving hydroxychloroquine plus any other therapy versus positive controls (aOR, 2.58; 95% CI: 1.53–4.33) and negative controls (aOR, 3.86; 95% CI: 2.50–5.98). When the analysis was restricted to patients with active cancer, the findings were similarly increased (Table 2). Additional statistical methods including logistic regression with elastic-net and horseshoe regularization were conducted to ensure robustness and yielded similar results (Supplementary Tables S6 and S7). The Average Causal Mediation Effects (ACME) 95% CI showed that the mediation effect of baseline COVID-19 severity was not significantly different from zero and the proportion of the ACME in the total effect was quite small, that is, 4% (Supplementary Table S8).

Remdesivir

Remdesivir alone was associated with decreased 30-day all-cause mortality in comparison with positive controls (aOR, 0.41; 95% CI: 0.17–0.99) and was numerically associated with a decreased likelihood of mortality in comparison with negative controls, although this did not reach statistical significance (aOR, 0.76; 95% CI: 0.31–1.85; Table 3).

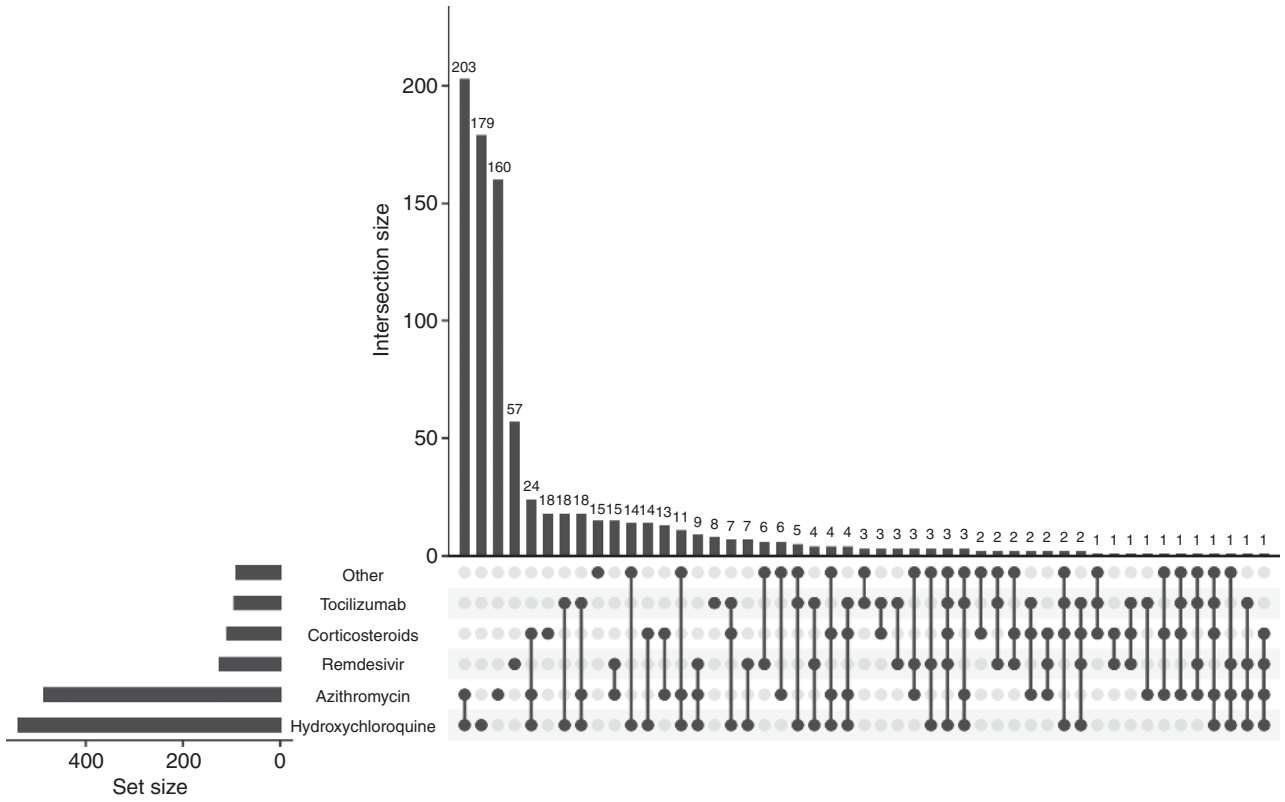

Figure 3. UpSet plot of treatment exposures. There are a total of 865 treatment exposures observed across 49 different patterns.

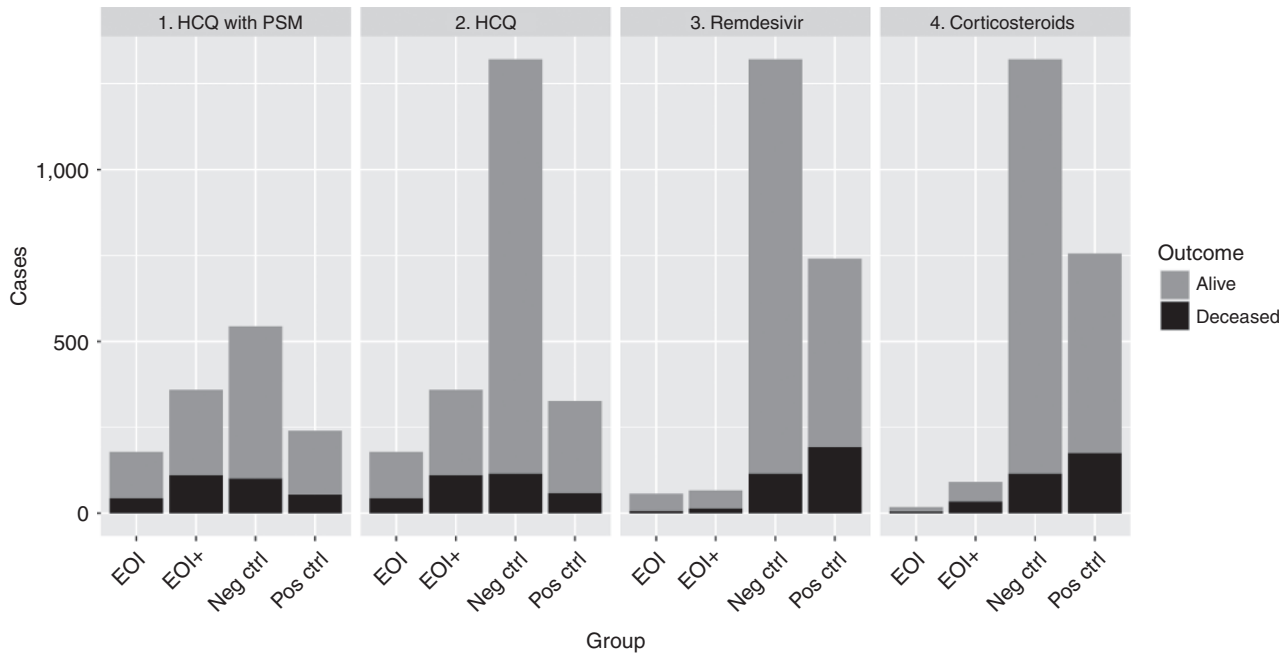

Figure 4. Distribution of matched and unmatched cohorts stratified by exposure of interest (EOI). Negative controls are patients who did not have any reported COVID-19 treatment; positive controls are patients who had a treatment reported that did not include the EOI. EOI+, EOI with any other exposure; HCQ, hydroxychloroquine.

Table 1. Factors associated with receipt of COVID-19 therapy

Characteristics	Hydroxychloroquine & azithromycin, aOR (95% CI)	Remdesivir, aOR (95% CI)	Any treatment, aOR (95% CI)
Number exposed	*N* = 203[a]	*N* = 124[b]	*N* = 865
Age[c]	0.97 (0.85–1.11)	0.87 (0.74–1.03)	0.96 (1.05–1.14)
Sex			
Male vs. female	1.30 (0.95–1.77)	1.24 (0.84–1.85)	1.28 (1.04–1.56)
Race/ethnicity			
Hispanic vs. non-Hispanic white	0.73 (0.44–1.20)	1.22 (0.71–2.11)	0.96 (0.70–1.31)
Non-Hispanic Black vs. non-Hispanic white	0.82 (0.57–1.19)	0.56 (0.31–1.00)	1.13 (0.87–1.46)
Other vs. Non-Hispanic white	0.65 (0.36–1.16)	0.56 (0.26–1.22)	1.01 (0.71–1.45)
Region of patient residence			
U.S. Midwest *vs.* U.S. Northeast	0.90 (0.63–1.31)	0.79 (0.47–1.33)	0.89 (0.70–1.14)
U.S. South *vs.* U.S. Northeast	1.34 (0.87–2.07)	1.03 (0.56–1.90)	0.84 (0.61–1.15)
U.S. West *vs.* U.S. Northeast	0.34 (0.17–0.69)	1.85 (1.09–3.15)	0.63 (0.45–0.87)
Smoking status			
Current or former smoker *vs.* never-smoker	1.06 (0.77–1.47)	0.90 (0.58–1.38)	0.99 (0.80–1.24)
Comorbidities			
Obese vs. not obese	1.07 (0.77–1.49)	1.32 (0.87–2.00)	1.44 (1.16–1.80)
Diabetes mellitus present vs. absent	1.16 (0.84–1.61)	0.84 (0.55–1.30)	0.99 (0.79–1.24)
Pulmonary comorbidities present vs. absent	1.09 (0.76–1.56)	1.53 (0.98–2.40)	1.41 (1.10–1.80)
Cardiovascular comorbidities present vs. absent	0.68 (0.48–0.98)	1.15 (0.74–1.79)	0.77 (0.61–0.98)
Renal comorbidities present vs. absent	1.56 (1.09–2.23)	0.32 (0.16–0.61)	1.02 (0.79–1.33)
Hypertension present vs. absent	1.11 (0.78–1.58)	1.31 (0.84–2.04)	1.28 (1.02–1.60)
ECOG performance status			
1 vs. 0	1.07 (0.71–1.63)	0.72 (0.43–1.21)	1.25 (0.95–1.64)
2+ vs. 0	0.77 (0.46–1.28)	0.47 (0.24–0.90)	0.72 (0.52–1.00)
Unknown vs. 0	1.10 (0.71–1.71)	1.00 (0.59–1.69)	1.10 (0.83–1.47)
Cancer status			
Active, progressing vs. remission/NED	0.94 (0.57–1.55)	1.03 (0.55–1.93)	0.99 (0.71–1.39)
Active, stable or responding vs. remission/NED	0.90 (0.62–1.32)	1.18 (0.74–1.88)	1.01 (0.79–1.29)
Unknown vs. remission/NED	0.81 (0.48–1.38)	0.72 (0.36–1.45)	0.98 (0.69–1.39)
Baseline COVID-19 severity			
Moderate vs. mild	5.68 (3.66–8.82)	9.88 (5.26–18.6)	7.53 (5.96–9.53)
Severe vs. mild	6.80 (4.07–11.4)	21.2 (10.7–42.0)	11.9 (8.60–16.5)

[a]This includes patients who received hydroxychloroquine and azithromycin without any other COVID-19 treatments.
[b]This includes patients who received remdesivir whether or not they received other COVID-19 treatments.
[c]Risk per decade.

High-Dose Corticosteroids

High-dose corticosteroids alone were numerically but not significantly associated with increased 30-day all-cause mortality versus negative controls (aOR, 2.8; 95% CI: 0.77–10.15). High-dose corticosteroids plus any other therapy was associated with increased mortality in comparison with positive and negative controls, respectively (aOR, 2.04; 95% CI: 1.19–3.49 and 3.16; 95% CI: 1.80–5.54; Table 3).

Tocilizumab

Because of insufficient numbers of independent exposures, tocilizumab exposure was reported for descriptive purposes only and not analyzed further.

Clinical and Demographic Factors

Across all of the examined treatment groups, exploratory analysis of potential factors associated with 30-day all-cause mortality showed increases in patients with increased age, increased baseline COVID-19 severity, patients with active cancer (progressing or stable/responding), and patients with an ECOG PS of 2+, similar to our initial findings. Decreased mortality was associated with residence in the U.S. Midwest region (Supplementary Table S9). Individual comorbidities were not statistically significant in these analyses, nor were sex, race/ethnicity, smoking status, and receipt of anticoagulation; however, these factors were not independently tested for formal significance.

Table 2. Evaluation of 30-day all-cause mortality associated with hydroxychloroquine exposure, as compared with positive (treated) and negative (untreated) controls using different methodological approaches

Treatment exposure	With PSM, aOR (95% CI)	Unmatched, aOR (95% CI)	Without severe cases, aOR (95% CI)[a]	HCQ, active cancer only, aOR (95% CI)[a]
HCQ alone vs. positive control	1.03 (0.62–1.73)	0.98 (0.59–1.62)	1.01 (0.55–1.85)	1.05 (0.47–2.35)
HCQ + any other exposure vs. positive control	1.99 (1.29–3.08)	1.93 (1.27–2.94)	2.58 (1.53–4.33)	2.44 (1.27–4.69)
HCQ alone vs. negative control	1.11 (0.71–1.74)	1.27 (0.80–1.99)	1.52 (0.90–2.57)	1.25 (0.61–2.57)
HCQ + any other exposure vs. negative control	2.15 (1.51–3.06)	2.50 (1.74–3.59)	3.86 (2.50–5.98)	2.91 (1.69–4.99)
Positive control vs. negative control	1.08 (0.70–1.65)	1.30 (0.87–1.94)	1.50 (0.92–2.45)	1.19 (0.64–2.24)

[a]Unmatched controls.

DISCUSSION

In this largest currently available cancer-specific observational study of treatments purported to improve COVID-19 outcomes, use of therapies was frequent and highly variant, likely due to patient, prescriber, and access factors. We did not find evidence of benefit, with the possible exception of remdesivir as compared with positive controls. Conversely, the receipt of hydroxychloroquine with other medications (most commonly azithromycin) remained associated with increased 30-day all-cause mortality, after extensive adjustment. The encouraging findings for corticosteroids in the prospective UK RECOVERY trial were not replicated in this cohort of patients with cancer. Although this study was not designed to independently examine other clinical factors associated with 30-day all-cause mortality, most of the additional covariates were consistent with our initial observations, with the notable exception of sex, which was numerically but no longer statistically associated with mortality.

With the limited availability of RCT data to support clinical decision-making in oncology, observational studies are necessary to provide a timely understanding of real-world practice. Observational studies have a role in supporting understanding of drug utilization and real-world outcomes while awaiting prospective trials to establish the causality of these associations, complementing each other in a rapid cycle of evidence generation to meet the needs of the pandemic (4). Although observational studies have emerged rapidly to identify potential treatments for COVID-19, they have produced conflicting evidence and raised concerns over accuracy of reported associations (5, 6). Robust adjustment for potential confounding is necessary in such studies, especially confounding by disease severity, as sicker patients are more likely to receive the treatments of interest. Likewise, the results of observational studies may be confounded by lack of access to therapeutic agents due to variable health system limitations, as well as sociodemographic barriers and regional differences (7).

Functioning at record pace, the scientific community is evaluating new drugs, developing vaccine candidates, and studying drugs for repurposing because there is an imperative to meet current global health needs in the COVID-19 pandemic. The array of new and existing drugs being evaluated for therapeutic use in SARS-CoV-2 infection includes hydroxychloroquine, azithromycin, antivirals, immunomodulatory mAbs, interleukin inhibitors, cytokine blockers, histamine antagonists, corticosteroids, kinase inhibitors, and protease antagonists, among other drugs, some of which were previously studied for other emerging respiratory viruses (8). Ongoing multiarm RCTs including the WHO Solidarity trial (NCT04321616) and the UK RECOVERY trial

Table 3. Evaluation of 30-day all-cause mortality associated with additional exposures of interest, as compared with positive (treated) and negative (untreated) controls

Treatment exposure	Remdesivir, aOR (95% CI)[a]	High-dose sytemic corticosteroids, aOR (95% CI)[a]
EOI vs. positive control	0.41 (0.17–0.99)	1.81 (0.50–6.56)
EOI + any other exposure vs. positive control	0.57 (0.28–1.16)	2.04 (1.19–3.49)
EOI vs. negative control	0.76 (0.31–1.85)	2.80 (0.77–10.2)[a]
EOI + any other exposure vs. negative control	1.06 (0.51–2.18)	3.16 (1.80–5.54)
Positive control vs. negative control	1.85 (1.36–2.51)	1.55 (1.14–2.11)

Abbreviation: EOI, exposure of interest.
[a]Precision of estimation for this category is poor.

(NCT04381936) are prospectively evaluating these therapeutic strategies nationally and globally. ClinicalTrials.gov has more than 1,000 registered interventional trials for COVID-19 as of July 2020, the majority of which are actively recruiting.

Within the context of biological plausibility (9–14), our study provides an overview of treatment utilization and therapeutic outcomes among patients with cancer and COVID-19 across various potential candidate drugs of interest. In observational studies such as this, isolation of the treatment effect is complicated due to nonrandomized, non–strictly controlled conditions for treatment; however, this is a useful indicator of what occurs in real-world clinical settings. As shown in Fig. 3, the utilization of medications in this cohort is not straightforward and indicates the use of multiple drug combinations and therapeutic strategies, including intense multiagent use in some cases. Making matters more complex, the cancer population in this cohort is heterogeneous, with a variety of histologic subtypes and differing cancer statuses. This heterogeneity is reflective of real-world practice. Notably, 43% of patients with progressing cancer who were not actively receiving cancer treatment still received COVID-19 treatment.

In the secondary hypothesis-generating analysis, medication utilization in the observed population indicates concordance with clinical evaluation of patient comorbidities. Patients with increased baseline COVID-19 severity were significantly more likely to receive any treatment. The differential use of anticoagulants in the treated population further indicates the role that disease severity may have had in treatment use. Males, obese patients, and those with hypertension were more likely to receive any anti–COVID-19 therapy, likely reflecting clinical decision-making within the context of the emerging literature on COVID-19 vulnerabilities (15). Use of hydroxychloroquine plus azithromycin was less likely in patients with cardiovascular conditions, perhaps driven by awareness of the synergistic potential risk of QT prolongation and torsades de pointes (16, 17). Use of remdesivir was less likely in patients with renal impairment, a specific exclusion criteria in clinical trials and compassionate-use programs (18). Aside from remdesivir, few of the other therapies were administered as part of a formal clinical study, and no patients in this cohort received high-dose corticosteroids on trial.

The results also indicated a decreased likelihood to receive treatment with remdesivir for Black patients, adding to a growing literature of concern around disparities of outcomes in COVID-19 (19–21). Although there was no apparent interaction between race/ethnicity and hypertension or renal comorbidities in our population, the interaction analysis was relatively underpowered and does not exclude other, untested, interactions. Nevertheless, historically underrepresented populations are prone to disparities in health outcomes throughout the U.S. health care system, both within and outside the context of clinical trials (22). As the CCC19 cohort continues to grow, we will continue to carefully examine possible racial and ethnic inequities in treatment exposures and in outcomes.

Similar to our first analysis and other smaller series, the CCC19 updated cohort confirms high all-cause mortality among patients with cancer infected by the SARS-CoV-2 virus ($n = 357$, 16%), remaining significantly higher than the 2% to 7% reported in the general population (23–30). The findings from the PSM and unmatched models in this study as well as the model excluding severe cases are consistent with available published observational studies alongside clinical trial data suggesting the lack of benefit for use of hydroxychloroquine (31). In the RECOVERY trial of hospitalized patients with COVID-19, no benefit was found for hydroxychloroquine, and the arm was closed early (per press release at https://www.recoverytrial.net/results/hydroxychloroquine-results). In the same trial, dexamethasone was associated with reduced mortality in ventilated patients and patients receiving oxygen (3). Although these findings were not replicated in this cohort of patients with cancer, where corticosteroids with other COVID-19 treatments were associated with increased mortality, the limited number of patients exposed to corticosteroid monotherapy within our cohort ($n = 18$) indicates the need for additional study to improve the precision of the estimate. Nevertheless, given that patients with cancer were not explicitly defined in the RECOVERY trial, caution needs to be taken when extrapolating the results to a population of patients with cancer.

Although the association between remdesivir versus negative controls and reduction in 30-day all-cause mortality was not statistically significant, it is consistent with literature suggesting that the drug may lessen disease severity or reduce the duration of infection, similar to currently approved antivirals for other conditions. Promising results for remdesivir are shown versus positive controls and were reported in small series, including in a cohort of patients hospitalized for severe COVID-19, with clinical improvement observed in 68% of 53 patients (32, 33). More recently, the likely pivotal RCT of remdesivir was published, with a significantly faster time to improvement versus placebo ($P < 0.001$) as well as a HR for death at 14 days of 0.70 (95% CI: 0.47–1.04; ref. 34). Of note, this HR for mortality is numerically similar to our observed aOR for 30-day mortality in remdesivir versus negative control (0.76; 95% CI: 0.31–1.85. The definition of an ideal comparator group in our real-world setting is complicated, as the positive controls included patients exposed to hydroxychloroquine.

After IL6 was shown to be a potential key driver in the cytokine storm upon SARS-CoV-2 infection, tocilizumab has been used in multiple small series, with a recent retrospective study showing a reduction in risk of invasive mechanical ventilation or death in 179 treated patients among 1,351 with severe COVID-19 pneumonia (14). Because tocilizumab was not frequently used and when used was almost never given alone or without hydroxychloroquine (Fig. 3), we were unable to isolate any effect of tocilizumab. Ongoing prospective randomized trials in noncancer populations (e.g., NCT04356937, NCT04372186) and nonrandomized trials in cancer populations (NCT04370834) may help to further clarify the role of this agent.

This study is limited by the lack of randomization and potential for selection bias, including lack of access to clinical trials or expensive therapies. Confounding by severity is a concern in this population, as patients with increased baseline severity were more likely to be treated with one or more therapies. Collider bias and channeling associated with treatment may also affect assessment of the associations

(35, 36). Although adjustments and varying methodologic techniques were applied, residual confounding may affect the results, and causality cannot be established. For example, sociodemographic factors which may adversely affect outcomes are not yet captured with fidelity in the CCC19 registry. The study is not population-based, and generalizability to other populations may be limited. Aside from hydroxychloroquine, PSM was unable to be conducted due to a relatively small number of exposures and events. Although active cancer treatments are collected in analyzable form, they are not currently sufficiently granular to determine whether certain specific treatments are associated with treatment exposure decisions and/or outcomes; this is a focus of future work. Another limitation is the lack of temporal associations due to institutional review board (IRB) restrictions on timing data collection as well as the feasibility of collecting granular data at scale, including calculation of time to event data and adjustment for COVID-19 progression, as disease severity is only able to be estimated as baseline severity. Finally, unseen trends such as temporal evolution of treatment strategies as knowledge of COVID-19 has evolved may have affected the results; these trends are also intrinsically tied into institutional treatment protocols and the geographical distribution of the infection, and future studies can evaluate this phenomenon with expanded longitudinal data capture.

CONCLUSION

Treatments utilized in patients with COVID-19 and cancer included hydroxychloroquine, azithromycin, remdesivir, high-dose corticosteroids, tocilizumab, and other therapies alone and in combination. Treatment patterns appear to be complex, especially because of the evolving use of experimental therapies and knowledge around the multisystem effects of COVID-19. With the exception of remdesivir, the majority of treatments received by our study population were administered outside the context of clinical trials. Isolation of the treatment effect is therefore challenging. This study included multiple methods to emphasize replicability of estimate validity and evaluate the primary concerns of selection bias and confounding by severity. Our findings add to the emerging understanding of nonbeneficial impact of hydroxychloroquine and suggest a potentially beneficial impact of remdesivir, while also highlighting the racial disparities in enrollment of clinical trials of potentially beneficial experimental therapies. We encourage the evaluation of these treatments in prospective RCTs, along with systematic efforts to assess and address disparities and promote health equity in current studies evaluating potentially effective anti–COVID-19 therapies.

METHODS

Data Sources and Study Population

Data were collected through the CCC19 registry, an international collaboration of cancer centers (Supplementary Appendix) and anonymous healthcare providers providing data through a comprehensive REDCap survey for patients with COVID-19 and cancer. Detailed methodology has been previously described (2, 37, 38). Only deidentified data are collected, and the study was considered exempt from IRB review (VUMC IRB#200467) and was approved by local institutional IRBs at participating sites per institutional policy, according to principles of the Declaration of Helsinki. This study is registered on ClinicalTrials.gov (NCT04354701).

Eligible cases included U.S. adult patients with current or history of invasive cancer and laboratory-confirmed SARS-CoV-2 infection with baseline forms (demographics, initial course of COVID-19 illness, and cancer details) completed between March 17 and June 26, 2020. The following exclusion criteria were then applied (CONSORT diagram; Fig. 1): (i) unknown or missing treatment exposures of interest; (ii) autoimmune conditions and taking hydroxychloroquine or tocilizumab at baseline; (iii) chronic obstructive pulmonary disease (COPD), asthma, or HIV and taking azithromycin at baseline; (iv) high-dose corticosteroids at baseline unless manual review confirmed that the high-dose corticosteroids were being given as a treatment for acute viral illness; (v) HIV and taking lopinavir/ritonavir or atazanivir at baseline; (vi) unknown baseline comorbidities; (vii) unknown baseline severity of COVID-19; and (viii) deceased patients with insufficient information to determine whether they died within the 30-day window.

Exposure and Outcome Measurement

Treatment exposures were recorded as binary for the following drugs: (i) hydroxychloroquine; (ii) azithromycin; (iii) high-dose corticosteroids (defined as receipt of ≥ 20 mg/day of prednisone dose equivalents); (iv) remdesivir; (v) tocilizumab; and (vi) other, which included chloroquine, lopinavir/ritonavir, atazanavir, baricitinib, plasma from convalescent individuals, IL inhibitors other than tocilizumab, TNFα inhibitors, and any other treatment given within the context of a clinical trial of COVID-19 treatment. Drug exposures were recorded by respondents in three locations within the REDCap survey (Supplementary Table S10), where they were asked to choose from a structured multiselect option for: (i) "Concomitant medications being taken at time of presentation with COVID-19" (concomitant_meds); (ii) "COVID-19 treatment, including preexisting drugs that were continued during the COVID-19 diagnosis" (covid_19_treatment); and (iii) "Additional COVID-19 treatment" (covid_19_treatment_fu). For the COVID-19–specific variables, they were additionally asked whether any of the selected drugs were given within the context of a clinical trial (covid_19_trial_tx and covid_19_trial_tx_fu). Additional free text entries allowed for optional detailed explanations, for example, drug dosing and indication. With the exception of high-dose systemic corticosteroids, which were manually reviewed for free text indicating short-course administrations in the context of viral illness, all medications selected on the patient demographics form were defined to be taken at baseline. Intermittent steroids being given for cancer treatment were converted into daily prednisone dose equivalents, for example, dexamethasone 20 mg weekly for 3 out of 4 weeks for multiple myeloma was calculated as 14.3 mg/day of prednisone dose equivalents.

Each exposure of interest was examined in isolation (i.e., only that drug was prescribed to a particular patient) and in combination with any of the other treatment exposures defined above. These exposed groups were then compared against two control populations: (i) positive controls, defined as patients receiving any of the defined treatments in the absence of the drug of interest; and (ii) negative controls defined as patients receiving none of the defined treatments (i.e., an unexposed, untreated control). For each drug exposure, factors associated with medication utilization were evaluated. The primary outcome was the impact of each drug of interest on 30-day all-cause mortality.

Statistical Analysis

Multivariable Logistic Regression (MLR) Model. Evaluation of medication utilization was examined using an MLR model with

baseline covariates adjustment to assess likelihood for receipt of treatment. The primary evaluation of 30-day all-cause mortality within the context of hydroxychloroquine exposure and the secondary evaluations of remdesivir and high-dose systemic corticosteroids were also conducted using MLR with baseline covariates adjustment. The aOR for treatment exposure and mortality association were modeled using the following baseline variables: age, sex, self-reported race, and ethnicity (as available in electronic medical records), region of patient residence, smoking status, obesity (body mass index greater than or equal to 30 mg/m^2), hypertension, diabetes mellitus, cardiovascular, pulmonary, and renal comorbidities, ECOG PS, cancer status, and baseline severity of COVID-19. The models for mortality association were additionally adjusted for exposure to anticoagulants or antiplatelet agents (ever/never), and the treatment exposures of interest. Tests of interaction were performed for (i) race/ethnicity and hypertension and (ii) race/ethnicity and renal comorbidities.

Cardiovascular comorbidities were defined as any of the following: coronary artery disease, congestive heart failure [including heart failure with preserved ejection fraction (HFpEF) and with reduced ejection fraction (HFrEF)], atrial fibrillation, cardiac arrhythmias not otherwise specified (NOS), peripheral vascular disease, or history of cerebrovascular accident. Pulmonary comorbidities were defined as any of the following: COPD, asthma, previous history of radiation pneumonitis, immune checkpoint inhibitor-related pneumonitis, or pulmonary disease NOS. Renal comorbidities were defined as any of the following: chronic kidney disease, end-stage renal disease with or without dialysis, and renal disease NOS. Baseline severity of COVID-19 was defined by the local investigator as mild (no hospitalization indicated); moderate (hospitalization indicated, whether or not it occurred); and severe (intensive care unit admission indicated, whether or not it occurred). With the exception of ECOG PS and cancer status, unknown values were redefined as missing. Before conducting the regression analyses, we performed multiple imputation for the missing values using additive regression, bootstrapping, and predictive mean matching.

Precision Analysis. The precision analysis was focused on the evaluation of 30-day all-cause mortality within the context of hydroxychloroquine exposure. It was completed using 5,000 computer simulations based on a generalized linear model (GLM). With the study sample size of 2,186 (hydroxychloroquine alone = 179, hydroxychloroquine + any other exposure = 359, negative controls = 1,321, and positive controls = 327), the largest half-width of the 95% confidence intervals of the precision ratio, that is, standard error (SE) of the estimated OR divided by estimated OR, among all-pairwise comparisons is less than 3% without multiple comparison adjustment (Supplementary Data). Therefore, it is reassured that our study has excellent precision of the reported results.

PSM Method. Because of sufficient numbers of exposures and events based on degrees of freedom, the evaluation of hydroxychloroquine utilized a PSM regression model assessing the treatment exposure and primary outcome for robustness and validation; other drug exposures were too infrequent to utilize the PSM method. Because of the multiple control and exposure groups, we considered "pseudo" propensity score matching to balance the covariate distributions in the treatment groups. Instead of directly balancing the covariate distributions in the four treatment groups, "pseudo" propensity score matching balanced the covariate distribution in two "pseudo" groups: the control unit, which consists of the negative and positive control groups, and the treated unit, which consists of hydroxychloroquine alone and with other drugs. Other pairwise matchings were limited by the overall sample size. For the matching, we adopted the nearest-neighbor method with a 1:2 ratio (treated units: control units) and 0.3 SD of the distance measure within which to draw the control units, based on the optimal balance between loss of events and the maximum mean difference between the four groups (Supplementary Fig. S4). The parameters in matching kept as many events as possible, and according to the χ^2 test results, improved the balance of the covariate distributions in the four groups. After 5-run analyses (each run: multiple imputation + matching + logistic regression analysis), the average results were reported.

Sensitivity Analyses. We conducted several sensitivity analyses to explore the robustness of the findings for the primary hypothesis of association of hydroxychloroquine exposures with 30-day all-cause mortality. First, we excluded patients with severe baseline COVID-19, as the disease course may be too advanced in these patients for any disease-modifying therapeutic activity. Second, we limited the analysis to patients with active cancer only, to evaluate the degree to which the findings might be specific to this subgroup. Third, we performed elastic-net and horseshoe regression analyses to explore whether these advanced statistical techniques provided additional insight beyond ordinary logistic regression. Fourth, we conducted a mediation analysis to determine the indirect effect of baseline COVID-19 severity.

Descriptive Statistics and Model Evaluation. We used descriptive statistics to display the baseline demographic information of the participants included in our analyses, including UpSet plots for visualizations of intersecting data (39). Goodness of fit was assessed by Harrell C-statistic (40). VIFs were computed for every covariate in each adjusted model. Statistical significance was preset as $\alpha = 0.05$. All data analyses were performed using base R 4.0.0 (R Foundation) and the R packages rms 6.0-0, MatchIt 3.0.2, Hmisc 4.4-0, glmnet 3.0-2, mediation 4.5.0, horseshoe 0.2.0, pROC 1.16.2, and UpSetR 1.4.0 (41–49).

Data and Code Sharing

The dataset analyzed for the primary and secondary hypotheses will be made immediately available upon request; requests should be sent to contact@ccc19.org. All aggregate deidentified patient data with site identifiers removed and geographical region of patient residence masked to a level no smaller than U.S. Census Divisions will be made publicly available for any purpose through the CCC19 website (https://www.ccc19.org) beginning 6 months and ending 72 months after publication of this article. These data will be displayed with an interactive graphical tool, allowing for visual analytics of the data. Individual deidentified patient data with site identifiers removed and geographic region of patient residence masked to a level no smaller than U.S. Census Divisions will be made available to researchers who provide a methodologically sound proposal, and whose proposed use of the data has been approved by an independent review committee identified for this purpose. External proposals can be submitted beginning 6 months and up to 72 months after publication of this article; the CCC19 is open to additional collaborators as well. All proposals should be directed to contact@ccc19.org; to gain access, data requestors will need to sign a data access agreement.

An abbreviated version of the data dictionary and pseudo-code to generate the derived variables used in the analysis are in Supplementary Tables S10 and S11. The full data dictionary and code used to create the derived variables and propensity score matching method are available upon request.

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Authors' Contributions

D.R. Rivera: Conceptualization, validation, investigation, methodology, writing-original draft, writing-review and editing. **S. Peters:** Conceptualization, supervision, validation, investigation, methodology, writing-original draft, writing-review and editing. **O.A. Panagiotou:** Supervision, validation, methodology, writing-review and editing. **D.P. Shah:** Methodology, writing-review and editing. **N.M. Kuderer:** Methodology, writing-review and editing. **C.-Y. Hsu:** Formal analysis, writing-review and editing. **S.M. Rubinstein:** Formal analysis, methodology, writing-review and editing. **B.J. Lee:** Data curation, writing-review and editing. **T.K. Choueiri:** Supervision, writing-review and editing. **G. de Lima Lopes:** Supervision, writing-review and editing. **P. Grivas:** Supervision, writing-review and editing. **C.A. Painter:** Supervision, writing-review and editing. **B.I. Rini:** Supervision, funding acquisition, writing-review and editing. **M.A. Thompson:** Supervision, writing-review and editing. **J. Arcobello:** Data curation, writing-review and editing. **Z. Bakouny:** Data curation, writing-review and editing. **D.B. Doroshow:** Data curation, supervision, writing-review and editing. **P.C. Egan:** Data curation, writing-review and editing. **D. Farmakiotis:** Data curation, writing-review and editing. **L.A. Fecher:** Data curation, writing-review and editing. **C.R. Friese:** Data curation, supervision, writing-review and editing. **M.D. Galsky:** Data curation, writing-review and editing. **S. Goel:** Data curation, writing-review and editing. **S. Gupta:** Data curation, supervision, writing-review and editing. **T.R. Halfdanarson:** Data curation, supervision, writing-review and editing. **B. Halmos:** Data curation, supervision, writing-review and editing. **J.E. Hawley:** Data curation, writing-review and editing. **A.R. Khaki:** Data curation, writing-review and editing. **C.A. Lemmon:** Data curation, writing-review and editing. **S. Mishra:** Project administration, writing-review and editing. **A.J. Olszewski:** Data curation, writing-review and editing. **N.A. Pennell:** Data curation, supervision, writing-review and editing. **M.M. Puc:** Data curation, supervision, writing-review and editing. **S.G. Revankar:** Data curation, supervision, writing-review and editing. **L. Schapira:** Data curation, writing-review and editing. **A. Schmidt:** Data curation, writing-review and editing. **G.K. Schwartz:** Data curation, supervision, writing-review and editing. **S.A. Shah:** Data curation, supervision, writing-review and editing. **J.T. Wu:** Data curation, writing-review and editing. **Z. Xie:** Data curation, writing-review and editing. **A.C. Yeh:** Data curation, writing-review and editing. **H. Zhu:** Data curation, writing-review and editing. **Y. Shyr:** Conceptualization, formal analysis, supervision, validation, investigation, methodology, writing-review and editing. **G. Lyman:** Conceptualization, supervision, validation, methodology, writing-original draft, writing-review and editing. **J.L. Warner:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing-original draft, writing-review and editing.

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