# Outcomes of COVID-19 Patients Hospitalized at Acute Care Services

## *Real-World Experience in the New York Metropolitan Area During the Early Pandemic Before Initiation of Clinical Trials*

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**Background:** As New York became the epicenter of the COVID-19 pandemic early on, clinicians were challenged to provide optimal medical and pharmaceutical care, despite the paucity of supporting literature and guidance. We sought to describe prescribing patterns and outcomes of physician response to the urgent need to treat COVID-19 patients before initiation of randomized clinical trials.

**Methods:** This was a retrospective cohort study of adult patients with COVID-19 initially admitted to acute care services during March 2020. Critically ill patients requiring intensive care unit level of care on admission were excluded.

**Results:** A total of 639 consecutive patients (supportive care, n = 247; treatment n = 392) were included in the analysis. Overall, the 28-day mortality rate was 12.2%. The mortality was 8.7% higher in the treatment group (15.6% vs 6.9% in the supportive care group, $P < 0.001$). Treatment was not protective against progression to severe disease (18.4% vs 3.6% with supportive care, $P < 0.0001$). Time to defervescence, duration of oxygen support, and hospital and intensive care unit (ICU) length of stay were also higher in the treatment group. In multivariate analysis, 60 years or older, presence of severe disease, and need for ICU admission were identified as independent predictors of 28-day mortality. There were 41 (10.5%) adverse event in the treatment group, with the majority being QT prolongation and gastrointestinal effects.

**Conclusions:** In this cohort of hospitalized patients admitted to acute care services, treatment with hydroxychloroquine, lopinavir/ritonavir or both could not be shown to improve mortality, progression to severe disease, or clinical response.

**Key Words:** COVID-19, treatment, safety, hydroxychloroquine, lopinavir ritonavir

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In December 2019, a novel coronavirus (SARS-CoV-2) detected in central China was associated with a new pneumonia syndrome (COVID-19). Over a 2-month period, this infection became classified as a pandemic, resulting in substantial morbidity and mortality worldwide. As New York became the epicenter of the pandemic early on, clinicians were challenged to provide optimal medical and pharmaceutical care, despite the paucity of supporting literature and guidance.[1]

Pharmacotherapeutic agents, such as hydroxychloroquine (HCQ) and lopinavir/ritonavir (L/R) have been previously studied in vitro for SARS-CoV and MERS-CoV.[2–5] An early study from France reported a virologic response in 26 COVID-19 patients treated with HCQ with or without azithromycin, suggesting that HCQ may lead to faster SARS-CoV-2 clearance than supportive care or observation. However, this study reported on a very small population size, had a high rate of patients lost to follow-up, and had a primary outcome that was of unclear relevance to clinical patient outcomes.[6] Nitazoxanide has activity against MERS CoV and betacoronavirus growth in mice, and in vitro activity against SARS-CoV-2.[7] Anti–interleukin-6 medications, such as tocilizumab, have been considered in COVID-19 patients with evidence of cytokine storm.[8] Finally, zinc inhibits RNA-dependent RNA polymerase and has been shown to do this in vitro against SARS-CoV. When combined with HCQ, cellular uptake is increased, making it more likely to achieve elevated intracellular concentrations.[9]

Despite the lack of published literature describing the safety and efficacy of these agents for COVID-19 in humans during the early pandemic, many of the mentioned medications were frequently used "off-label" in clinical practice. This usage has led to perceptions of efficacy that, while receiving media coverage, lacked robust evidence supporting use. Randomized clinical trials are necessary to provide support for effective treatment options during this and any future outbreaks of SARS-CoV-2 associated disease. This retrospective review describes real world experience managing the COVID-19 hospitalized population in the New York metropolitan area during the early pandemic when physician response to the urgent need for patient care took place before initiation of randomized clinical trials.

## METHODS

### Patient Population

This was a retrospective cohort study of consecutive patients aged at least 18 years with COVID-19 (confirmed by positive SARS-CoV-2 reverse-transcriptase polymerase-chain-reaction [RT-PCR] test results) from March 1, 2020, to March 31, 2020, and hospitalized with symptoms consistent of COVID-19 at New York University (NYU) Langone Health (Tisch Hospital/Kimmel Pavilion,

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NYU Brooklyn, and NYU Winthrop campuses) and Bellevue Hospital (a New York City [NYC] Health + Hospitals facility affiliated with NYU). Patients were excluded if they required an intensive care unit (ICU) level of care on admission or at the start of HCQ or L/R therapy (whichever came first), had received HCQ or L/R as home medications for other indications or for COVID-19 within the last 30 days, were enrolled in clinical trials for sarilumab versus placebo or clazakizumab versus placebo, had taken any drug not Food and Drug Administration (FDA) approved for the treatment of COVID-19 (except azithromycin) with the intent to treat COVID-19 within 30 days before admission, received less than 48 hours of HCQ or L/R during admission, or were pregnant.

## Data Collection

Electronic health records (EHR; Epic Systems, Verona WI) were reviewed to collect data on baseline demographics, medical history, characteristics of the disease, laboratory values, and treatment used. QTc value changes were documented based on scanned electrocardiograms in the EHR, while consideration of "QT prolongation" as an adverse event (ADE) was based on physician documentation. Medication characteristics that were collected included dose, frequency, and duration of therapy. The presence of SARS-COV-2 was determined by RT-PCR of nasopharyngeal or oropharyngeal samples collected on swabs. Initially, tests were completed by the New York City Department of Health and Mental Hygiene for NYU Langone Health Tisch Hospital/Kimmel Pavilion, NYU Brooklyn Hospital, and NYU Winthrop Hospital, and a third party commercial laboratory was utilized for Bellevue Hospital samples. After March 16, 2020, the NYU Langone Health clinical laboratory conducted tests for Tisch Hospital/Kimmel Pavilion, NYU Brooklyn Hospital and NYU Winthrop Hospital using the Roche SARS-CoV-2 assay in the Cobas 6800 instruments, and only nasopharyngeal samples were tested. After April 2, 2020, NYU Winthrop Hospital's clinical laboratory conducted tests for NYU Winthrop Hospital using the Cepheid Xpert instrument, and only nasopharyngeal samples were tested. Symptoms consistent of COVID-19 included, but were not limited to, any of the following: fever, cough, dyspnea, diarrhea, nausea, and diffuse myalgia. The World Health Organization (WHO) classification was used to determine severity of infection, with 3 to 4 considered mild disease, and 5 to 7 considered severe disease.[10]

## NYU Langone Health Interim Guidance for COVID-19

Interim Guidance for the use of potential therapeutic treatments for COVID-19 was developed by the Departments of Medicine and Infectious Diseases at NYU Langone Health, with pharmacotherapy department review and updated regularly as additional data became available.[11,12] Early in the development, the guidance had included use of L/R monotherapy, and HCQ was added in mid-March after data from another institution that suggested benefit was publically available. Both L/R and HCQ were unrestricted and prescribed based on the physicians' discretion, taking into consideration severe drug-drug interactions (ie, L/R with apixaban, rivaroxaban, ticagrelor, clopidogrel, tacrolimus, antiepileptics, and other medications). All patients who received L/R were tested and confirmed negative for human immunodeficiency virus (HIV) infection before starting treatment. The recommended HCQ dosing regimen was 400 mg twice daily for 2 doses followed by 200 mg twice daily for 8 doses. Lopinavir/ritonavir was dosed as 400 mg/100 mg twice daily for 7 days. Order panels with defaulted dosing regimens and duration of therapy were developed within the computerized physician order entry system. Adjunctive off-label medications utilized during this period included azithromycin (500 mg once followed by 250 mg once daily for 4 days), tocilizumab (400 mg once), zinc (220 mg twice daily for 5 days in conjunction with HCQ), nitazoxanide (500 mg twice daily for 5 days), and corticosteroids at the discretion of the primary team with support from the Infectious Disease and Critical Care Medicine consultation services.

## Outcomes

Our primary endpoint was 28-day mortality from the date of admission and time to death. Our secondary endpoints included progression to severe disease, treatment response, and treatment-related ADE. Progression to severe disease was assessed by the need for ICU admission, development of hypotension requiring vasopressor support, or need for escalation of oxygen supplementation to endotracheal tube or extracorporeal membrane oxygenation. Treatment response was assessed by time to defervescence, time of supplemental oxygen requirement, and length of stay in the ICU and/or hospital. We report the outcomes for the full study cohort, patients receiving HCQ or L/R or both (treatment group), and patients who received supportive care only (supportive care group). We also compared patients who died with survivors to identify potential risk factors for mortality.

## Statistical Analysis

All analyses were performed using SPSS Statistics Software (IBM Corp., Armonk, NY; version 25.0). Categorical variables were described as frequencies and proportions and compared using $\chi^2$ test or Fisher exact test. Continuous variables were described as medians with interquartile ranges (IQR) and analyzed using Mann-Whitney U test. *P* values of 0.05 or less denote statistical significance. We also conducted a univariate analysis to compare patients who died with survivors. Variables with *P* values of 0.2 or less on univariate analysis were included in the multivariate logistic regression model to control for differences between groups and identify independent risk factors associated with death. The Hosmer-Lemeshow goodness-of-fit test was used to test the power of the model. A Kaplan-Meier survival curve was performed to illustrate the probability of survival from hospital admission to day 28 in the supportive care and treatment groups.

## Study Approval

The study was approved by the NYU Grossman School of Medicine Institutional Review Board. A waiver of informed consent was granted.

# RESULTS

Of 935 patients with COVID-19 who were admitted to the hospital during March 2020, a total of 296 were excluded (Fig. 1). Requirement of ICU level of care on admission or at the start of treatment with L/R or HCQ or both was the most common reason for exclusion (153/296; 51.7%). A total of 639 consecutive patients with a confirmed COVID-19 test who were initially admitted to acute care services in March 2020, and either died or were discharged before the cut off day of May 8, 2020, were included in the analysis.

Among 639 included patients, 247 received supportive management (supportive care group) whereas 392 patients received off-label COVID-19 antivirals (L/R, n = 36; HCQ, n = 329; or both, n = 27, treatment group). Patients in the treatment group who received both HCQ and L/R received them sequentially (ie, not started on the same day), however may have had some days of concomitant use. There were significant differences between the 2 groups in baseline demographic characteristics, selected vital

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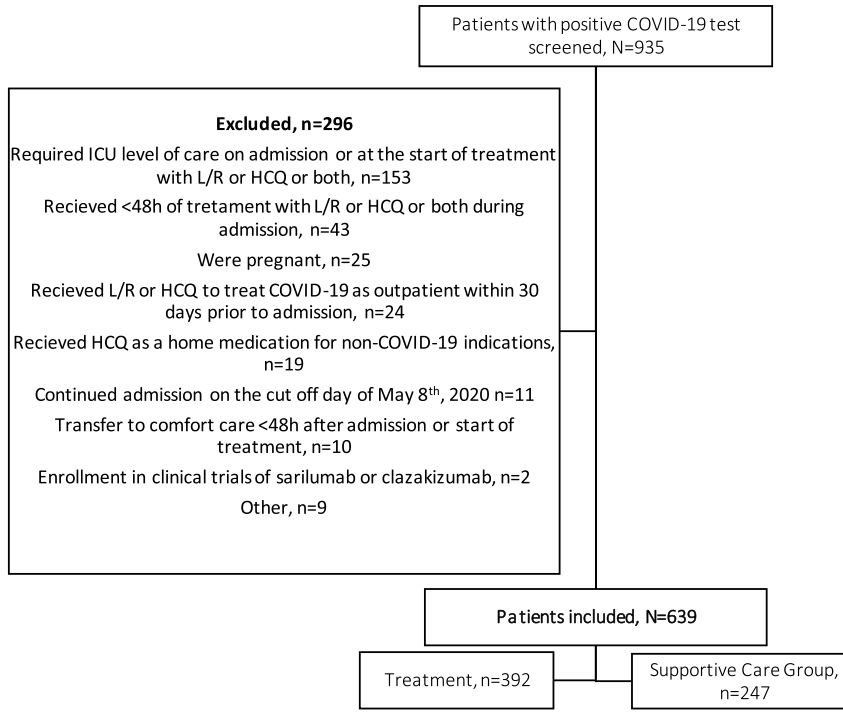


**FIGURE 1.** Study inclusion diagram.

signs, laboratory values and comorbidities (Table 1). Of note, patients at higher risk of progressing to severe disease were more likely to be treated with off-label medications at the discretion of the primary team and are therefore more frequently in the treatment group. The median time to first dose of HCQ from the time of admission was 1 day (IQR, 1–2 days), with a median total inpatient duration of therapy of 5 days (IQR, 4–6 days). The median time to first dose of L/R from the time of admission was 2 days (IQR, 1–5 days), with a median total inpatient duration of therapy of 4 days (IQR, 3–6 days). More patients in the treatment group received concomitant azithromycin (332 [84.7%] vs 112 [45.3%], $P < 0.001$) as well as other concomitant antibiotics (323 [82.4%] vs 158 [64%], $P < 0.001$). Nitazoxanide and tocilizumab were added to the initial treatment regimen in 25 (6.4%) and 37 (9.4%) patients in the treatment group, respectively.

Overall, the 28-day mortality rate was 12.2% (78/639). The mortality was 8.7% higher in the treatment group (15.6% [61/392] versus 6.9% [17/247] of patients in the supportive care group, $P < 0.001$) (Table 2). In patients who received HCQ only, L/R only, and both agents, the 28-day mortality rate was 16.4% (54/329), 8.3% (3/36), and 14.8% (4/27), respectively. Hospital length of stay was 7 days (IQR, 4–11 days) among all the patients admitted to acute care services and was significantly longer for patients in the treatment group (4 days [IQR, 3–7 days] vs 8 days [IQR, 6–13 days] in the supportive care group, $P < 0.001$). Treatment was not protective against progression to severe disease (18.4% vs 3.6% with supportive care, $P < 0.001$). Delayed time to defervescence, prolonged duration of oxygen requirements, and prolonged hospital and ICU lengths of stay were also more frequent in the treatment group (Table 2). Time to death from the date of hospital admission in the overall cohort, supportive care group, and treatment group was 10 days (IQR, 6–13 days), 4 days (IQR, 3–11 day), and 10 days (IQR, 7–14 days), respectively ($P < 0.001$). A Kaplan-Meier analysis (Fig. 2) demonstrated lower cumulative survival in the treatment group compared with supportive care group, but the difference was not statistically significant ($P = 0.915$).

There were a total of 41 (10.5%) ADEs in the treatment group, with the majority being QT prolongation (63%) and gastrointestinal effects (20%) (Table 2). Premature discontinuation of HCQ before completion of the recommended regimen occurred in 67 (17%) patients, primarily due to physician preference and patient improvement or discharge (52%). The median baseline QTc in the treatment group was 439 ms (IQR, 424–457 ms). In the treatment group, 41 (10%) patients were receiving other QT prolonging medications, of which 12 of these patients had their QT prolonging agent held for HCQ administration. The QTc in the treatment group increased during admission by 30 ms or greater in 120 (34.9%) patients, by 60 ms or greater in 52 (15.1%) patients and from less than 500 to 500 ms or greater in 52 (15.1%) patients. Hydroxychloroquine was discontinued before completion of the recommended treatment regimen due to QT prolongation in 4 (1%) patients, none of which were on concomitant QT prolonging medications.

In univariate analysis, patients who received treatment with HCQ, L/R, or both agents; received nitazoxanide; presented with severe disease on admission; required ICU admission; had cardiovascular disease including heart failure, coronary artery disease, hypertension, or hyperlipidemia; or had chronic kidney disease were more likely to die (Table 3). In multivariate analysis, after controlling for differences between groups, 60 years or older (odds ratio [OR], 5.2; 95% confidence interval [CI], 2.54–10.7, $P < 0.001$), presence of severe disease on admission (OR, 4.5; 95% CI, 1.3–15.7, $P = 0.017$), and need for ICU admission during the hospital stay (OR, 11.8; 95% CI, 5.9–23.5, $P < 0.001$) were identified as independent predictors of 28-day mortality.

## DISCUSSION

In this retrospective cohort study of consecutive patients at 4 large academic centers in the New York metropolitan area early


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**TABLE 1.** Baseline Demographics and Treatment Characteristics of Patients Receiving or Not Receiving Non–FDA-approved Medication(s) for COVID-19 With the Intent to Treat SARS-CoV-2

| | All Patients, N = 639 | Supportive Care Group, n = 247 | Treatment Group, n = 392 | *P** |
|---|---|---|---|---|
| Age: median (IQR), y | 61 (48–75) | 56 (42–72) | 62 (51–75) | 0.002 |
| Age group, y | | | | 0.001 |
| <40 | 99 (15.6) | 55 (22.3) | 44 (11.3) | |
| 40–59 | 219 (34.3) | 84 (34) | 135 (34.4) | |
| 60–79 | 223 (34.9) | 71 (28.7) | 152 (38.8) | |
| ≥80 | 98 (15.3) | 37 (15.0) | 61 (15.6) | |
| Age ≥60 y | 321 (50.2) | 108 (43.7) | 213 (54.3) | 0.009 |
| Male sex | 411 (64.3) | 165 (66.8) | 246 (62.8) | 0.298 |
| Race | | | | <0.001 |
| White | 259 (40.5) | 72 (29.1) | 187 (47.7) | |
| Asian | 21 (3.3) | 8 (3.2) | 13 (3.3) | |
| African American | 102 (16) | 46 (18.6) | 56 (14.3) | |
| Hispanic | 35 (5.5) | 9 (3.6) | 26 (6.6) | |
| Other | 132 (20.7) | 63 (25.5) | 69 (17.6) | |
| Unknown | 90 (14.1) | 49 (19.8) | 41 (10.5) | |
| BMI, kg/m$^2$, median (IQR), n = 604 | 28.1 (24.8–32.3) | 27.0 (23.2–31.9), n = 224 | 28.4 (25.6–32.5), n = 380 | 0.002 |
| BMI ≥ 30 kg/m$^2$ | 213 (35.3) | 73 (32.6) | 140 (36.8) | 0.291 |
| Former smoker, n = 612 | 129 (21.1) | 43 (18.4) | 86 (21.1) | 0.197 |
| Current smoker, n = 613 | 34 (5.5) | 24 (10.3) | 10 (2.6) | <0.001 |
| Comorbidities | | | | |
| HTN | 325 (50.9) | 108 (43.7) | 217 (55.4) | 0.004 |
| HLD | 226 (35.4) | 70 (28.3) | 156 (39.8) | 0.03 |
| DM | 188 (29.4) | 57 (23.1) | 131 (33.4) | 0.005 |
| Cardiac disease (HF, CAD) | 120 (18.8) | 46 (18.6) | 74 (18.9) | 0.936 |
| Chronic lung disease† | 93 (14.6) | 32 (13) | 61 (15.6) | 0.363 |
| CKD | 65 (10.2) | 20 (8.1) | 45 (11.5) | 0.168 |
| Immunosuppression‡ | 59 (9.2) | 23 (9.3) | 36 (9.2) | 0.957 |
| AF | 55 (8.6) | 16 (6.5) | 39 (9.9) | 0.128 |
| Liver disease | 9 (1.4) | 2 (0.8) | 7 (1.8) | 0.308 |
| No. comorbidities per patient, median (IQR) | 2 (1–4) | 2 (1–3) | 3 (1–4) | <0.001 |
| >1 comorbidities | 427 (66.8) | 139 (56.3) | 288 (73.5) | <0.001 |
| COVID-19 patient–reported symptoms | | | | |
| Days of symptoms before admission, median (IQR), n = 632 | 5 (2–7) | 3 (2–7) | 5 (3–7) | 0.001 |
| Subjective fever | 489 (76.5) | 178 (72.1) | 311 (79.3) | 0.035 |
| Cough | 460 (72.0) | 162 (65.6) | 298 (76.0) | 0.004 |
| SOB/dyspnea | 361 (56.5) | 108 (47.3) | 253 (64.5) | <0.001 |
| Fatigue | 176 (27.5) | 55 (22.3) | 121 (30.9) | 0.018 |
| Body aches | 144 (22.5) | 47 (19.0) | 97 (24.7) | 0.092 |
| Diarrhea | 117 (18.3) | 41 (16.6) | 76 (19.4) | 0.434 |
| Chills | 114 (17.8) | 40 (16.2) | 74 (8.9) | 0.449 |
| Nausea | 90 (14.1) | 33 (13.4) | 57 (14.5) | 0.763 |
| Headache | 62 (9.7) | 27 (10.9) | 35 (8.9) | 0.405 |
| Sore throat | 40 (6.3) | 16 (6.5) | 24 (6.1) | 0.857 |
| Nasal congestion | 21 (3.3) | 10 (4.0) | 11 (2.8) | 0.391 |
| Syncope | 7 (1.1) | 3 (1.2) | 4 (1.0) | 1.000 |
| Vital signs | | | | |
| Documented fever during admission | 476 (74.5) | 162 (65.6) | 314 (80.1) | 0.0005 |
| $O_2$ saturation at admission, %, median (IQR) | 95 (93–97) | 96 (94–97) | 95 (93–97) | 0.087 |
| WHO classification on day of hospital admission[10] | | | | <0.001 |
| 3—Hospitalized mild disease/no oxygen therapy | 386 (60.4) | 203 (82.2) | 183 (46.7) | |

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**TABLE 1.** *(Continued)*

| | All Patients, N = 639 | Supportive Care Group, n = 247 | Treatment Group, n = 392 | P* |
|---|---|---|---|---|
| 4—Hospitalized mild disease/oxygen by mask or nasal prongs | 234 (36.6) | 41 (16.6) | 193 (49.2) | |
| 5—Hospitalized severe disease/noninvasive ventilation or high flow oxygen | 19 (3.0) | 3 (1.2) | 16 (4.1) | |
| Laboratory values[§], median (IQR) | | | | |
| D-dimer, ng/mL, n = 297 | 304 (196–519) | 256 (177–524), n = 97 | 313 (202–514), n = 200 | 0.215 |
| CRP, mg/L, n = 491 | 73 (26.7–125.3) | 44.3 (12.8–99), n = 166 | 84 (40.2–132.9), n = 325 | <0.001 |
| LDH, units/L, n = 444 | 306 (238–412) | 269 (212–352), n = 155 | 324 (251–444), n = 289 | <0.001 |
| AST, units/L, n = 572 | 39 (28–57) | 34 (26–53), n = 215 | 41 (30–59), n = 357 | 0.001 |
| ALT, units/L, n = 574 | 31 (22–47) | 28 (20–42), n = 217 | 33 (24–51), n = 357 | 0.004 |
| Ferritin, ng/mL, n = 427 | 558 (243–1111) | 431 (188.4–1008.0), n = 137 | 624 (281.6–1234.2), n = 290 | 0.004 |
| Procalcitonin, ng/mL, n = 493 (3–3) | 0.1 (0.05–0.23) | 0.08 (0.05–0.23), n = 173 | 0.11 (0.06–0.25), n = 320 | 0.033 |
| WBC, cells × $10^3$/mcL, n = 635 | 6.0 (4.6–8.0) | 5.8 (4.4–8.2), n = 243 | 8.2 (4.7–7.8), n = 392 | 0.272 |
| ALC, cells × $10^3$/mcL, n = 575 | 1.0 (0.61–1.3) | 0.9 (0.6–1.2), n = 205 | 0.9 (0.6–1.2), n = 370 | 0.133 |
| Significant chest imaging findings[‖], n = 632 | 502 (79.4) | 138 (57.5), n = 240 | 364 (92.9), n = 392 | <0.001 |
| Initial QTc, ms, median (IQR) n = 577 | 438 (422–457) | 436 (418–457), n = 191 | 439 (424–457), n = 386 | 0.324 |
| Treatment characteristics | | | | |
| HCQ only | — | — | 329 (83.9) | — |
| L/R only | — | — | 36 (9.1) | — |
| Both HCQ and L/R | — | — | 27 (6.9) | — |
| Time to HCQ start from admission date, d, n = 356 | — | — | 1 (1–2) | — |
| HCQ DOT, d, n = 356 | — | — | 5 (4–6) | — |
| Time to L/R start from admission date, d, n = 63 | — | — | 2 (1–5) | — |
| L/R DOT, d, n = 63 | — | — | 4 (3–6) | — |
| Anti-infectives[¶] | 481 (75.3) | 158 (64.0) | 323 (82.4) | <0.001 |
| Anti-infectives DOT, d, median (IQR) | 3 (2–7) | 2 (1–4) | 4 (2–8) | <0.001 |
| Azithromycin | 444 (69.5) | 112 (45.3) | 332 (84.7) | <0.001 |
| Z-pak dosing[#] | 82 (21.4) | 19 (23.5) | 63 (20.9) | 0.613 |
| Azithromycin DOT, d, median (IQR) | 3 (1–5) | 1 (1–2) | 4 (2–5) | <0.001 |
| Steroids | 58 (9.1) | 24 (9.7) | 34 (8.7) | 0.655 |
| Zinc | 70 (11.0) | 68 (27.5) | 2 (0.5) | <0.001 |
| Nitazoxinide DOT, d, median (IQR), n = 25 | — | — | 5 (4–7) | — |
| Tocilizumab** | — | — | 37 (9.4) | — |

All results reported as n (%) unless otherwise stated.

*$P$ value provided based on comparison of supportive care and treatment groups.

[†]Chronic lung disease includes asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, emphysema, and other interstitial lung diseases.

[‡]Immunosuppression includes history of transplantation, HIV, active malignancy, and immunosuppressive mediation use.

[§]Laboratory values within 24 hours of hospital admission.

[‖]Significant chest imaging findings include ground glass opacities, patchy consolidation or interpretation "consistent with atypical/viral infection."

[¶]Anti-infectives: any antimicrobial agent excluding azithromycin, hydroxychloroquine, nitazoxanide, remdesivir, and antiretroviral medications.

[#]Z-pak dosing: 500 mg once then 250 mg daily for 4 days.

**35/37 received one dose of tocilizumab 400 mg IV, 2/37 received 2 doses of tocilizumab 400 mg IV.

AF indicates atrial fibrillation; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney diseases 3–5; CRP, C-reactive protein; DM, diabetes mellitus; DOT, days of therapy (inpatient only); HF, heart failure; HLD, hyperlipidemia; HTN, hypertension; LDH, lactate dehydrogenase; SOB, shortness of breath; WBC, white blood cell.

in the COVID-19 pandemic, we described real world experience focusing on prescribing patterns and outcomes of a cohort of COVID-19 hospitalized patients admitted to acute care units before initiation of randomized clinical trials. We excluded patients who required ICU level of care on admission or at the start of COVID-19 treatment, making our cohort unique compared with other recently published retrospective studies from the early pandemic in New York Hospitals.[13,14] Geleris et al[13] (n = 1376) and Rosenberg et al[14] (n = 1438) described larger New York populations of diverse groups of hospitalized COVID-19 patients, including critically ill patients initially admitted to an ICU level of care.[13,14] Because of the prescribing patterns early in the pandemic, similarly to our population, patients treated with HCQ in both of these studies were more severely ill at baseline compared with those who were not treated, and the mortality rate in the treatment group was higher before controlling for differences in patients' characteristics or propensity matching. An early smaller retrospective analysis of patients hospitalized with COVID-19 in


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**TABLE 2.** Outcomes

| | All Patients, N = 639 | Supportive Care Group, n = 247 | Treatment Group, n = 392 | *P** |
|---|---|---|---|---|
| Primary | | | | |
| 28-d mortality | 78 (12.2) | 17 (6.9) | 61 (15.6) | 0.001 |
| Time to death, d, median (IQR) | 10 (6–13) | 4 (3–11) | 10 (7–14) | 0.001 |
| Secondary | | | | |
| Progression to severe disease | 81 (87.3) | 9 (3.6) | 72 (18.4) | <0.001 |
| Need for ICU admission | 77 (12.1) | 9 (3.6) | 68 (17.3) | <0.001 |
| Time to ICU admission, d, median (IQR) | 4 (3–6) | 2 (2–3) | 5 (3–6) | <0.001 |
| ICU LOS, d, median (IQR) | 10 (3–19) | 3 (2–5) | 10 (4–21) | 0.002 |
| Highest oxygen requirement during hospital stay | | | | <0.001 |
| ETT | 62 (9.7) | 5 (2) | 57 (14.5) | |
| HFNC | 22 (3.4) | 4 (1.6) | 18 (4.6) | |
| BIPAP | 2 (0.3) | 1 (0.4) | 1 (0.3) | |
| NRB | 87 (13.6) | 9 (3.6) | 78 (19.9) | |
| Mask | 4 (0.6) | 0 | 4 (1.0) | |
| NC | 238 (37.2) | 57 (23.1) | 181 (46.1) | |
| RA | 224 (35.1) | 171 (69.2) | 53 (13.5) | |
| Time to oxygen requirements, d, median (IQR) | 2 (1–2) | 1 (1–2) | 1 (1–2) | 0.469 |
| Duration of oxygen requirement, d, median (IQR) | 8 (3–11) | 2 (1–3) | 7 (4–12) | <0.001 |
| Time to MV, d, median (IQR) | 5 (3–6) | 2 (2–3) | 5 (36) | 0.001 |
| Hypotension requiring vasopressor support | 56 (8.8) | 1 (0.4) | 55 (14) | <0.001 |
| Time to vasopressor use, d, median (IQR) | 6 (4–7) | 2 | 5 (4–7) | 0.09 |
| Vasopressor DOT, d, median (IQR) | 10 (4–11) | 3 | 8 (4–11) | 0.182 |
| Time to defervescence, d, median (IQR) | 2 (1–5) | 2 (1–3) | 3 (2–6) | <0.001 |
| Hospital LOS, d, median (IQR) | 7 (4–11) | 4 (3–7) | 8 (6–13) | <0.001 |
| QTc increased by 30 ms | 127 (25.8) | 7 (4.7) | 120 (34.9) | <0.001 |
| QTC increased by 60 ms | 54 (11.0) | 2 (1.3) | 52 (15.1) | <0.001 |
| QTC increased from <500 ms to >500 ms | 78 (15.8) | 26 (17.4) | 52 (15.1) | 0.554 |
| ADEs | 41 (6.4) | 0 | 41 (10.5) | <0.001 |
| QTc prolongation | — | — | 26 (63) | — |
| Gastrointestinal† | — | — | 8 (20) | — |
| Rash | — | — | 2 (5) | — |
| LFTs increase | — | — | 2 (5) | — |
| Hemolytic anemia | — | — | 1 (2) | — |
| Hallucinations | — | — | 1 (2) | — |
| Unknown | — | — | 1 (2) | — |
| Premature discontinuation of HCQ‡ | — | — | 67 (17) | — |
| Discharge/patient Improvement | — | — | 35 (52) | — |
| Comfort care/hospice | — | — | 9 (13) | — |
| Death | — | — | 7 (10) | — |
| ADE | — | — | 5 (7) | — |
| Patient refusal or inability to take orally | — | — | 4 (6) | — |
| QT prolongation | — | — | 4 (6) | — |
| Unknown | — | — | 3 (4) | — |

All results reported as n (%) unless otherwise stated.

**P* value provided based on comparison of supportive care and treatment groups.

†Gastrointestinal ADEs included nausea, vomiting, diarrhea, and gastroesophageal reflux (GERD).

‡Premature discontinuation defined as HCQ stopped before completion of 400 mg twice daily for 2 doses then 200 mg twice daily for 8 doses.

ETT indicates endotracheal tube; HFNC, high flow nasal cannula; LOS, length of stay; MV, mechanical ventilation; NC, nasal cannula; NRB, nonrebreather; RA, room air.

all the Veterans Health Administration medical centers across the United States by Magagnoli et al[15] (n = 368) also evaluated a diverse group of COVID-19 hospitalized patients that included critically ill patients on admission.

Cavalcanti et al[16] published a multicenter, randomized, open-label, controlled trial from Brazil involving hospitalized patients with mild-to-moderate COVID-19 who were receiving either no supplemental oxygen or a maximum of 4 L per minute supplemental

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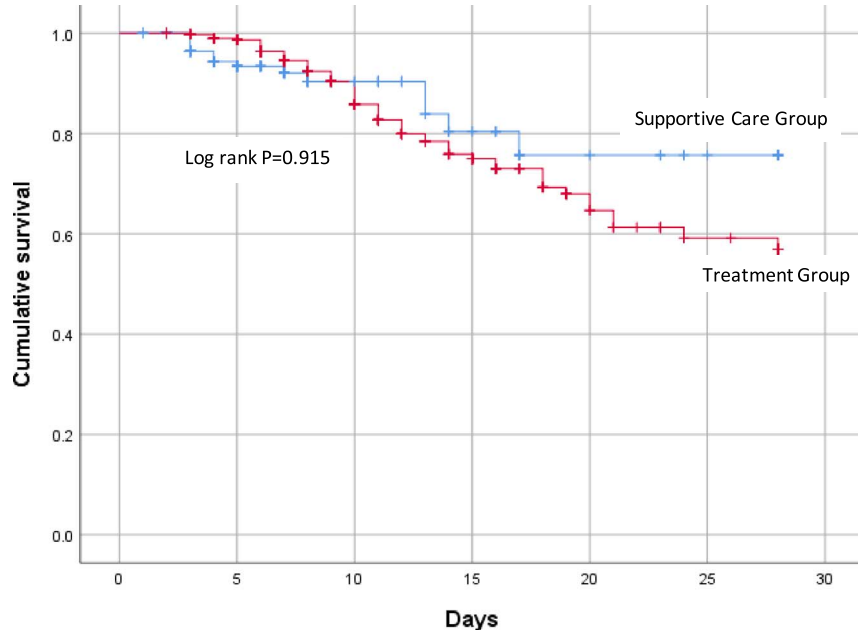


**FIGURE 2.** Kaplan-Meier survival. Gray line—supportive care group, black line—treatment group, log rank test ($P = 0.915$).

**TABLE 3.** Risk Factors for 28-Day Mortality

| | Died, n = 78 | Did Not Die, n = 561 | Univariate Analysis, OR (95% CI) | *P* | Multivariate Analysis, OR (95% CI) | *P* |
|---|---|---|---|---|---|---|
| Received HCQ or L/R or both, n = 392 | 61 (78.2) | 331 (59) | 2.5 (1.420–4.379) | 0.002 | 1.8 (0.482–6.566) | 0.387 |
| Received HCQ only, n = 329 | 54 (69.2) | 275 (49) | 2.3 (1.407–3.891) | 0.001 | 1.8 (0.533–5.524) | 0.365 |
| Received HCQ + azithro, n = 306 | 55 (70.5) | 251 (44.7) | 3.0 (1.766–4.940) | <0.001 | 1.6 (0.558–4.637) | 0.379 |
| Received HCQ + azithro + Zn, n = 63 | 10 (12.8) | 53 (9.4) | 1.4 (0.685–2.900) | 0.463 | | |
| Received L/R only, n = 36 | 3 (3.8) | 33 (5.9) | 0.6 (0.192–2.139) | 0.639 | | |
| Received L/R + HCQ, n = 27 | 4 (5.1) | 23 (4.1) | 1.3 (0.425–3.758) | 0.902 | | |
| Nitazoxanide, n = 25 | 9 (11.5) | 16 (2.9) | 4.4 (1.891–10.439) | 0.001 | 2.1 (0.703–6.423) | 0.181 |
| Tocilizumab, n = 37 | 4 (5.1) | 33 (5.9) | 0.9 (0.298–2.511) | 0.993 | | |
| Steroids | 12 (15.4) | 46 (8.2) | 2.0 (1.026–4.038) | 0.063 | 0.7 (0.281–1.714) | 0.428 |
| Age ≥60 y | 65 (83.3) | 256 (45.6) | 6.0 (3.210–11.054) | <0.001 | 5.2 (2.539–10.7) | <0.001 |
| BMI, n = 604 | 27.5 (24.4–31.6) | 28.1 (24.9–32.3) | | 0.779 | | |
| BMI ≥ 30 | 26 (36.6) | 187 (35.5) | 1.1 (0.639–1.788) | 0.903 | | |
| Severe disease on admission | 8 (10.3) | 11 (2) | 5.7 (2.223–14.688) | <0.001 | 4.5 (1.309–15.660) | 0.017 |
| African American | 10 (12.8) | 92 (16.4) | 0.8 (0.372–1.510) | 0.419 | | |
| ICU admission | 37 (47.4) | 40 (7.1) | 11.8 (6.791–20.344) | <0.001 | 11.8 (5.909–23.495) | <0.001 |
| Cardiac disease (HF, CAD) | 25 (32.1) | 95 (6.9 | 2.3 (1.370–3.908) | 0.002 | 1.5 (0.718–3.035) | 0.219 |
| AF | 10 (12.8) | 45 (8.0) | 1.7 (0.812–0.950) | 0.230 | 1.2 (0.513–2.738) | 0.774 |
| HTN | 54 (69.2) | 271 (48.3) | 2.4 (1.448–1.004) | 0.001 | 1.3 (0.619–2.549) | 0.527 |
| HLD | 41 (52.6) | 185 (33.0) | 2.3 (1.396–3.632) | 0.001 | 1.3 (0.652–2.443) | 0.491 |
| DM | 29 (37.2) | 159 (28.3) | 1.5 (0.913–2.454) | 0.141 | 1.0 (0.524–1.889) | 0.987 |
| CLD* | 15 (19.2) | 78 (13.9) | 1.5 (0.800–2.718) | 0.211 | 1.141 (0.534–2.436) | 0.734 |
| Liver disease | 2 (2.6) | 7 (1.2) | 2.1 (0.425–10.210) | 0.302 | | |
| CKD | 14 (17.9) | 51 (9.1) | 2.2 (1.147–4.173) | 0.026 | 1.7 (0.760–3.838) | 0.195 |
| Immunosuppression† | 10 (12.8) | 49 (8.7) | 1.5 (0.744–3.175) | 0.337 | | |

Hosmer-Lemeshow goodness of fit test, $\chi^2 = 4.411$, $P = 0.713$.

*Chronic lung disease includes asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, emphysema, and other interstitial lung diseases.

†Immunosuppression includes history of transplantation, HIV, active malignancy, and immunosuppressive mediation use.

azithro indicates azithromycin; CLD, chronic lung disease.


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oxygen, during the later phase of the pandemic from March 29, 2020, to May 17, 2020. They reported an overall in-hospital mortality rate of 2.7% (18/665) (2.7% [12/438] in treatment vs 2.6% [6/227] in control group).[16] This mortality rate is much lower compared with the 28-day mortality rate of 12.2% found in our study (8.6% in treatment vs 6.9% in supportive care group), likely explained by different definitions of mild-to-moderate disease, based on supplemental oxygen requirements vs WHO classification on admission used in our study.[10] Despite the ideal randomized design by Cavalcanti et al,[16] limitations include the long time to treatment from symptom onset (up to 14 days) and inclusion of patients who began treatment before randomization in the study. Comparatively, time to initiation of COVID-19 off-label antivirals from symptom onset was shorter in our study, reflecting real word practice before randomized trials, where the need to consent, randomize, and wait for other study logistics before initiation of therapy was not a factor in patient care.

We found a 10.5% (41/392) incidence of ADE with the use of HCQ and/or L/R in our population based on documentation in the EHR, with the majority being QTc prolongation and gastrointestinal effects including nausea, diarrhea, and gastroesophageal reflux. In a retrospective analysis of 1061 cases, an overall rate of ADE with HCQ and azithromycin was reportedly lower at 2.4% (25/1061), consisting mainly of gastrointestinal symptoms (18/25, 72%), with only 3 patients requiring discontinuation of treatment because of ADE.[17] In a randomized, double-blind, placebo-controlled trial of 423 patients with COVID-19, medication ADE occurred in 43% (92/212) of participants receiving HCQ versus 22% (46/211) receiving placebo ($P < 0.001$).[18] Of the HCQ-related ADE, gastrointestinal symptoms were the most commonly reported, with 31% (66/212) reporting upset stomach or nausea, 24% (50/212) reporting abdominal pain, diarrhea, or vomiting, and no patients experiencing cardiotoxicity.[18]

There were several limitations of this review. Because of the retrospective, observational study design, there were significant baseline differences between the supportive care and treatment groups, which may reflect a willingness to give patients at higher risk for progression of disease during the early pandemic an unproven treatment in the absence of proven options. Despite use of a binary logistic regression model to adjust for these differences, we cannot exclude the possibility of unmeasured confounders. Collection of ADE and QT prolongation relied on documentation in the EHR and may, therefore, underestimate the true incidence. Our description of QTc changes relied on uploaded electrocardiograms into the EHR and did not include data being monitored via telemetry without EHR documentation. In addition, evaluation of 28-day mortality has some limitations because of the retrospective design, including the inability to capture mortality in the outpatient setting if not updated in the EHR. The primary outcome of in-hospital mortality was expanded to 28-day mortality because of the knowledge of COVID-19–related readmissions leading to an outcome of death within 14 days of the index admission. We also were unable to assess virologic effects because of the absence of standardized retesting of patients and exclusion of collection of follow-up RT-PCR data. Finally, although patients from 4 large academic medical centers were included, outcomes of our patient cohort early in the pandemic still might not be generalizable to other populations.

Throughout the pandemic, health care providers may have become more knowledgeable and skilled in performing standard supportive management and care of COVID-19 patients, leading to improved outcomes as the pandemic went on. Of importance, the growing body of evidence led to the FDA Emergency Use Authorization for remdesivir and convalescent plasma for the treatment of hospitalized patients with COVID-19. Results of the RECOVERY trial provided support for dexamethasone use for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated, and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated.[19] Based on published data, Infectious Diseases Society of America and National Institute of Health (NIH) COVID-19 guidelines recommend against the use of HCQ for the treatment of COVID-19 in hospitalized patients.[11,12] Among patients who have been admitted to the hospital with COVID-19, the Infectious Diseases Society of America guideline panel recommends the combination of L/R only in the context of a clinical trial.[12] Our local COVID-19 Guidance has been updated on a regular basis throughout the pandemic to account for these recommendations. Overall, this retrospective observational study adds to the collective knowledge of real-world practice during the early COVID-19 pandemic by describing prescribing patterns and evaluating the mortality and safety outcomes in hospitalized patients initially admitted to acute care services before initiation of randomized controlled trials.

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