PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Hydroxychloroquine in Hospitalized Patients with COVID-19: Real-World Experience Assessing Mortality

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INTRODUCTION Hydroxychloroquine (HCQ) for coronavirus disease 2019 (COVID-19) is presently being used off-label or within a clinical trial.

OBJECTIVES We investigated a multinational database of patients with COVID-19 with real-world data containing outcomes and their relationship to HCQ use. The primary outcome was all-cause mortality within 30 days of follow-up.

METHODS This was a retrospective cohort study of patients receiving HCQ within 48 hours of hospital admission. Medications, preexisting conditions, clinical measures on admission, and outcomes were recorded.

RESULTS Among patients with a diagnosis of COVID-19 in our propensity-matched cohort, the mean ages ± SD were 62.3 ± 15.9 years (53.7% male) and 61.9 ± 16.0 years (53.0% male) in the HCQ and no-HCQ groups, respectively. There was no difference in overall 30-day mortality between the HCQ and no-HCQ groups (HCQ 13.1%, n=367; no HCQ 13.6%, n=367; odds ratio 0.95, 95% confidence interval 0.62–1.46) after propensity matching. Although statistically insignificant, the HCQ-azithromycin (AZ) group had an overall mortality rate of 14.6% (n=199) compared with propensity-matched no-HCQ–AZ cohort's rate of 12.1% (n=199, OR 1.24, 95% CI 0.70–2.22). Importantly, however, there was no trend in this cohort's overall mortality/arrhythmogenesis outcome (HCQ-AZ 17.1%, no HCQ–no AZ 17.1%; OR 1.0, 95% CI 0.6–1.7).

CONCLUSIONS We report from a large retrospective multinational database analysis of COVID-19 outcomes with HCQ and overall mortality in hospitalized patients. There was no statistically significant increase in mortality and mortality-arrhythmia with HCQ or HCQ-AZ.

KEY WORDS Antimalarial, azithromycin, coronavirus, hydroxychloroquine, macrolide, severe acute respiratory syndrome coronavirus 2.

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The search for safe and effective coronavirus disease 2019 (COVID-19) therapies has accelerated at a frenzied pace. Having advocated for clinicaltrials.gov use in the search for alternative approaches to the patient with COVID-19,[1] searching within the database revealed 3185 COVID-19 clinical trials as of August 31, 2020. Of these registered COVID-19 clinical trials, 1792 appeared to be treatment trials. Repurposed hydroxychloroquine (HCQ) in prospective randomized clinical trials accounted for 251 of these registered trials with completion dates ranging from February 2020 to December 2029. Presently, HCQ for COVID-19 is being used off-label or within one of these clinical trials.

Although understanding HCQ's efficacy profile in COVID-19 is an immediate concern, its safety profile has dominated recent public conversation. Indeed, the United States Food and Drug Administration issued additional safety guidance for use of HCQ after the original, now

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withdrawn, emergency use authorization,[2] which was largely stimulated by Adverse Event Reporting System case reports[3] and a retrospective analysis evaluating outcomes of HCQ use in hospitalized U.S. veterans with COVID-19.[4] Within this investigation, reported mortality rates were doubled in patients taking HCQ compared with those not receiving HCQ; findings that had an immediate impact on care of patients with COVID-19. Importantly, HCQ's most concerning adverse feature, especially in patients at risk, is its likelihood to prolong the QT interval, increasing the risk for polymorphic ventricular tachycardia.

The current evidence base for HCQ's safety in COVID-19 largely consists of inferential studies[5]; case reports[3]; public anecdotes[6]; uncontrolled, severely limited, and conflicting studies[4, 7, 8]; and a singular randomized but open-label investigation[9] with pitfalls.[10] Through an evaluation of a multinational electronic database of administrative and medical records containing real-world patients with COVID-19 and their respective treatments, we sought to provide further clarity on the safety of HCQ in the treatment of COVID-19.

Methods

The study used a new-user design in which the drug exposure started within 48 hours after the hospitalization with a confirmed diagnosis of COVID-19. The design allowed the elimination of patients beginning HCQ when decompensation occurred, a prominent concern observed in earlier analyses.[11] Additional sensitivity analyses using a negative control outcome (bleeding time) with no known causal relationship with the target medications were used to assess the influence of unmeasured confounding variables.[12] No active comparator treatments were included because to date there are no treatments with known efficacy for COVID-19. Propensity matching was used to control for any measured confounding variables previous to the drug exposure. The cohorts exposed to the target treatments (HCQ alone and HCQ plus azithromycin [AZ]) were compared in pairs with cohorts exposed to no HCQ and no HCQ plus AZ treatments.

Data Source

TriNetX, Inc. (Cambridge, MA) is a global federated health research network combining real-time access to longitudinal electronic medical records and administrative claims. Participating health care organizations span a wide range of geographies, age groups, and income levels. Details and use of the network by our team have been described elsewhere.[13, 14] The TriNetX platform is Health Insurance Portability and Accountability Act and General Data Protection Regulation compliant.

Study Sample

All consecutive patients from the known TriNetX universe were included if they had a COVID-19 diagnosis (based on *International Classification of Diseases, Tenth Revision* codes) and results for any of the laboratory tests used to identify the severe acute respiratory syndrome coronavirus 2 (see used codes in Table S1). Included patients were taken between January 20, 2020, and May 14, 2020. We excluded patients who were not hospitalized and individuals younger than 18 or older than 90 years of age. Also excluded were patients receiving HCQ more than 48 hours after admission.

Exposure

The target treatments considered were HCQ and HCQ plus AZ. The exposure started within 48 hours after hospitalization.

Outcomes

The primary outcome was all-cause mortality within 30 days of follow-up. An additional outcome combining mortality and an arrhythmogenic diagnosis (see Table S1 for used coding) was considered based on the well-known arrhythmogenic effects of both HCQ and AZ.

Index Dates and the Follow-up Duration

The index dates were between January 20, 2020 and May 14, 2020 when the patients met the inclusion-exclusion criteria. Follow-up started one day after the index date and ended when either the outcomes of interest (death or arrhythmogenic diagnoses) or 30 days after the index date (whichever came first) occurred.

Sample Size

A sample size was calculated based on 25% mortality in patients with HCQ and 10% mortality for patients with no HCQ as reported in the

Veterans Administration (VA) study.[4] Based on a 2-sided test with 80% power, an α level of 0.05, and the aforementioned mortality rates, it was determined that a minimum of 220 patients (110 in each arm) would be required to detect a difference between the two groups.

Statistical Analysis

Descriptive statistics were presented as frequencies with percentages for categorical variables as mean ± SD for continuous measures. Baseline characteristics were compared using a Pearson χ^2 test for categorical variables and an independent-samples *t* test for continuous variables. To account for differences in baseline characteristics between the groups, a propensity-score matching (PSM) model was developed using logistic regression to derive well-matched groups for comparative outcomes analysis.

Briefly, the TriNetX platform uses a logistic regression to obtain the listed propensity scores within each covariate selected with the use of the Python libraries (NumPy and sklearn). The platform also runs the PSM in R code to compare and verify the outputs. The final step in verification uses a nearest-neighbor matching algorithm with the tolerance level of 0.01 and a difference between propensity scores no > 0.1. Mortality was displayed in the PSM cohorts using the Kaplan-Meier method, and the statistical significance of the differences between groups was assessed with the log-rank test. To protect patient health information, patient counts were rounded up to the nearest 10. We made every effort to mitigate these results by using a large sample size.

We received an exemption from the Charleston Area Medical Center institutional review board because only aggregated counts, statistical summaries of de-identified information, and no protected health information were received.

Results

A total of 25,958 patients with a diagnosis of COVID-19 between January 20, 2020, and May 14, 2020, were identified using the TriNetX COVID-19 Research Network. The majority of patients were U.S.-based with a distribution as follows: Northeast (25%), Midwest (16%), South (14%), and West (11%); 34% of the cohort was from outside the U.S. Of those hospitalized (n=3012), 367 (12.2%) were on HCQ (HCQ group) and 2645 (87.8%) were not on HCQ (no-HCQ group). Of those hospitalized in the combined analysis (n=2308), 8.8% were on HCQ plus AZ and 91.2% were on neither medication. Patients in the HCQ or in the HCQ plus AZ groups had a higher prevalence of key comorbidities including hypertension, diabetes mellitus, obesity, coronary artery disease, chronic obstructive pulmonary disease, nicotine dependence, and history of stroke and were treated more often with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (Tables 1 and 2).

Comparisons between the Cohorts Treated with and without HCQ

Before PSM, death occurred in 13.1% in the HCQ group and in 12.8% in the no-HCQ group (Table 3). PSM yielded two well-matched cohorts of 367 patients each who were or were not treated with HCQ (Table 1). In these PSM cohorts, all-cause mortality occurred in 13.1% in the HCQ group and in 13.6% in the no-HCQ group (Table 3). In these propensity-matched cohorts, the composite outcome of mortality and arrhythmogenic diagnoses occurred in 17.4% in the HCQ group and in 17.7% in the no-HCQ group.

Kaplan-Meier survival analysis confirmed the lack of statistically significant association between HCQ and all-cause mortality as well as the combined all-cause mortality plus arrhythmogenic diagnoses outcome (Figure 1).

Comparisons between the Cohorts Treated with and without HCQ Plus AZ

In the nonmatched cohorts, there was an all-cause mortality of 14.4% in the HCQ plus AZ group and 13.3% in the no-HCQ–no-AZ group (Table 3). Based on PSM, two well-matched cohorts of 199 patients each who were or were not treated with HCQ and AZ were identified (Table 2). In the PSM cohorts treated with and without HCQ plus AZ, there was no significant difference in all-cause mortality between groups (14.6% in the HCQ plus AZ group and 12.1% in the no-HCQ–no-AZ group). In the propensity-matched cohorts treated with and without HCQ plus AZ, there were identical percentages (17.1% in both groups) of mortality and arrhythmogenic diagnoses (Table 3).

Table 1. Baseline Characteristics of the HCQ Study Cohort

Baseline Characteristic	Unmatched Cohorts, Mean ± SD or %			Standardized Mean Difference	Propensity-Matched Cohorts, Mean ± SD or %			Standardized Mean Difference
	HCQ (N=367)	No HCQ (N=2645)	p-Value		HCQ (N=367)	No HCQ (N=367)	p-Value	
Age, yrs	62.3 ± 16	60.8 ± 17	0.11	0.09	62.3 ± 16	61.9 ± 16	0.80	0.02
Male	53.7	52.0	0.50	0.04	53.7	53.0	0.90	0.01
Female	46.3	48.0	0.50	0.04	46.3	47.0	0.90	0.01
Hypertension	77.7	65.0	< 0.01	0.28	77.7	77.1	0.90	0.01
Diabetes mellitus	48.0	40.2	0.05	0.16	48.0	48.0	0.90	0.01
Smoking history	38.1	18.0	< 0.01	0.46	38.1	39.0	0.90	0.01
Chronic kidney injury	30.0	26.7	0.19	0.10	30.0	29.7	0.90	0.01
CAD	23.4	18.3	0.02	0.13	23.4	23.0	0.90	0.01
Heart failure	25.0	22.2	0.32	0.05	25.0	25.0	1.00	< 0.01
COPD	18.0	14.4	0.01	0.10	18.0	18.0	1.00	< 0.01
Personal history of stroke	11.2	8.2	0.01	0.10	11.2	11.4	0.90	0.01
Obesity[a]	63.5	22.7	< 0.01	1.0	63.5	63.5	1.00	< 0.01
ACE inhibitor	36.0	25.4	< 0.01	0.22	36.0	36.2	0.90	0.01
ARB	24.0	20.0	0.01	0.10	24.0	24.0	1.00	< 0.01

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HCQ = hydroxychloroquine.
[a]Obesity was defined as a body mass index ≥ 30 kg/m^2.

Table 2. Baseline Characteristics of the HCQ Plus AZ Study Cohort

Baseline Characteristic	Unmatched Cohorts, Mean ± SD or %			Standardized Mean Difference	Propensity-Matched Cohorts, Mean ± SD or %			Standardized Mean Difference
	HCQ + AZ (N=202)	No HCQ + No AZ (N=2106)	p-Value		HCQ + AZ (N=199)	No HCQ + No AZ (N=199)	p-Value	
Age, yrs	60.6 ± 16	61.0 ± 17	0.80	0.03	61.0 ± 16	60.1 ± 16	0.80	0.03
Male	56.4	51.6	0.20	0.10	55.8	54.8	0.84	0.02
Female	43.6	48.4	0.20	0.10	44.2	45.2	0.84	0.02
Hypertension	75.2	63.2	0.01	0.30	74.9	71.4	0.43	0.01
Diabetes mellitus	49.0	38.3	0.03	0.22	48.7	47.7	0.84	0.02
Smoking history	41.6	12.4	< 0.01	0.70	40.7	42.7	0.70	0.04
Chronic kidney injury	28.2	26.5	0.60	0.04	28.6	31.7	0.51	0.07
CAD	24.3	16.9	0.01	0.20	24.6	24.1	0.91	0.01
Heart failure	23.3	20.9	0.44	0.10	23.6	23.6	1.00	< 0.01
COPD	19.8	11.9	0.01	0.22	19.6	24.6	0.23	0.12
Personal history of stroke	9.41	7.2	0.30	0.10	9.6	9.6	1.00	< 0.01
Obesity[a]	73.7	13.6	< 0.01	1.53	73.3	73.3	1.00	< 0.01
ACE inhibitor	35.2	23.0	0.01	0.27	34.7	36.2	0.80	0.03
ARB	20.3	18.7	0.60	0.04	20.6	19.6	0.80	0.03

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; AZ = azithromycin; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HCQ = hydroxychloroquine.
[a]Obesity was defined as a body mass index ≥ 30 kg/m^2.

Kaplan-Meier survival analysis indicated no statistically significant association between HCQ plus AZ use and all-cause mortality in either the unmatched or PSM-matched cohorts (Figure 2). Similarly, there was no statistically significant association between HCQ plus AZ and the combined all-cause mortality plus arrhythmogenic diagnoses in the PSM-matched cohorts (Figure 2).

Sensitivity analysis indicated no significant difference in the falsification end point (bleeding) between the cohorts treated with and without HCQ, suggesting the absence of a significant unmeasured confounding that would explain the results of the primary outcome (all-cause mortality; Figures 1d and 2d). In addition, two independent analyses were conducted to validate the primary analysis. We explored these end points using the diamond and research networks within the TriNetX platform. The diamond network is made of health care

Table 3. Summary of Outcomes

Outcome	Type	HCQ n	No HCQ n	HCQ Events n	HCQ Events %	No HCQ Events n	No HCQ Events %	Odds Ratio	Lower 95% CI	Upper 95% CI	p-Value
M	NOPSM	367	2645	48	13.1	338	12.8	1.03	0.74	1.42	0.872
M	PSM	367	367	48	13.1	50	13.6	0.95	0.62	1.46	0.828
M + A	PSM	367	367	64	17.4	65	17.7	0.98	0.67	1.44	0.923

Outcome	Type	HCQ + AZ n	No HCQ + AZ n	HCQ + AZ Events n	HCQ + AZ Events %	No HCQ + AZ Events n	No HCQ + AZ Events %	Odds Ratio	Lower 95% CI	Upper 95% CI	p-Value
M	NOPSM	202	2106	29	14.4	280	13.3	1.09	0.72	1.65	0.672
M	PSM	199	199	29	14.6	24	12.1	1.24	0.70	2.22	0.461
M + A	PSM	199	199	34	17.1	34	17.1	1.00	0.59	1.69	1.000

95% CI = 95% confidence interval; AZ = azithromycin; HCQ = hydroxychloroquine; M + A=overall mortality-arrhythmia; M = overall mortality; NOPSM = unmatched and not adjusted; PSM = propensity-score matched comparison.

organizations (HCOs) that include ambulatory care and medical and pharmacy claims data from 92 HCOs. The research network is made of 40 HCOs. These differing research networks are defined by varying agreements between HCOs and TriNetX. Ensuing results from the diamond and research network data can be found in Appendix S1. Substantively, results of these analyses were consistent with primary findings.

Discussion

Based on promising cell culture data from chloroquine's impact on the 2002 severe acute respiratory syndrome coronavirus,[15] HCQ, largely because of its known less-toxic profile, was considered to be an ideal COVID-19 treatment candidate. Briefly, HCQ may reduce both the viral entry of COVID-19 into hosts and decrease the inflammatory response. This alkaline drug can inhibit the pH-dependent portions of viral replication.[16] Entry by endocytosis is disrupted by HCQ as a result of the need for a low pH to release viral nucleic acids.[16] HCQ also decreases production of tumor necrosis factor-α and interleukin 6, which have been found to be upregulated in COVID-19 infection and can create an overabundance of inflammation.[17] HCQ also decreases the expression of tumor necrosis factor-α receptors, reducing signaling.[16] Uncertainty does exist, though, whereas HCQ may actually increase viral load initially through its antiinflammatory properties.[18]

Converse to its antiviral properties, HCQ possesses actions that may be detrimental, especially in the patient with significant cardiovascular (CV) morbidity. Most notable is its potential to provoke polymorphic ventricular tachycardia (including torsades de pointes [TdP]) via prolongation of the QT interval through various mechanisms including a block of the voltage-gated ion channel that controls the rapid component of the delayed rectifier potassium current.[19] Moreover, AZ, possessing a similar independent QT-prolonging effect, likely increases this risk when used concomitantly with HCQ. Fortunately, TdP is often self-terminating; but if sustained, it can degenerate into ventricular fibrillation in approximately 10% of cases and cause sudden cardiac death.[20] Importantly, in a document specifically examining the cardiotoxicity of antimalarial agents, the World Health Organization Evidence Review Group states that QT-prolonging antimalarials, including HCQ, have been associated with a very low risk of cardiotoxicity.[21] Although somewhat limited by lack of a priori systematic investigation into cardiac effects, this examination was comprehensive, including various analyses of published studies, reviews, pharmacovigilance registries, and manufacturer data repositories.

In a recent retrospective analysis of 90 patients with COVID-19 administered HCQ, of whom 53 received concomitant AZ, QT interval prolongation was noted.[22] Of patients receiving HCQ alone and HCQ concomitant with AZ, 19% and 21%, respectively, experienced a rate-corrected QT interval (QTc) of 500 msec or greater. In a retrospective study of 40 patients treated in the intensive care with COVID-19, prolonged QTc (QTc 500 msec or greater) occurred in 5% of patients receiving HCQ alone and 33% of patients receiving both HCQ and AZ.[23] Relatively small sample sizes, retrospective analyses,

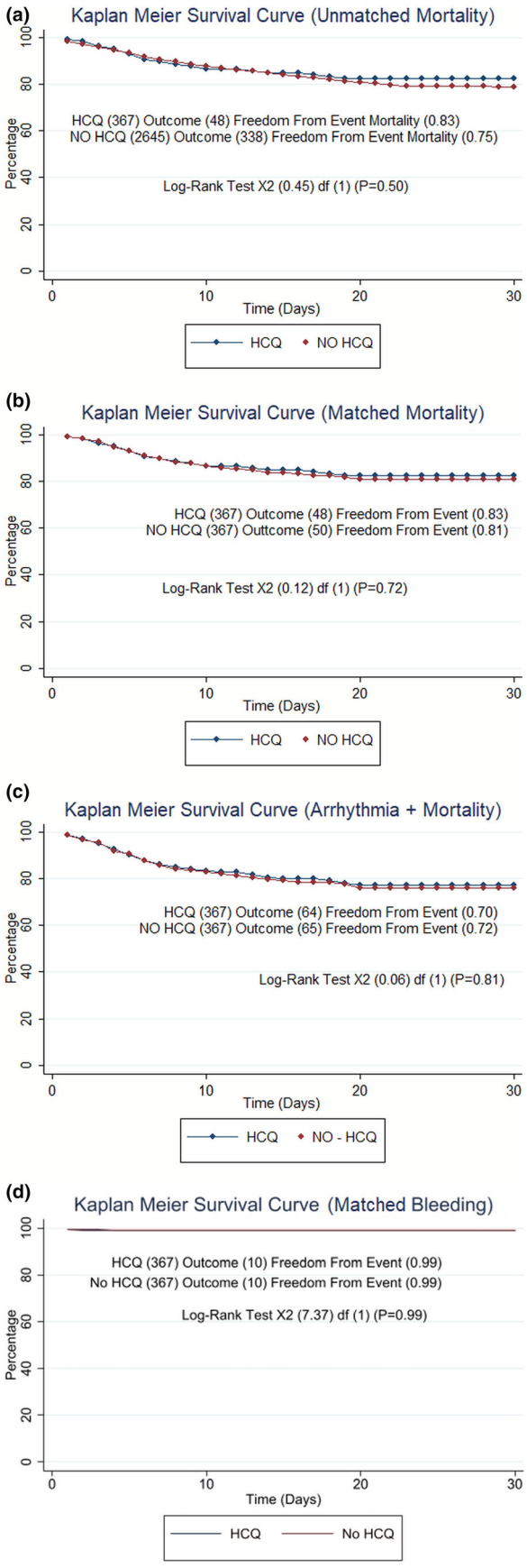

Figure 1. (a) Kaplan-Meier survival analysis of the study groups before propensity-score matching: HCQ and no HCQ (unmatched mortality). (b) Kaplan-Meier survival analysis of the study groups after propensity-score matching. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ and no HCQ [matched mortality]). (c) Kaplan-Meier survival in propensity-matched patients with mortality-arrhythmia outcome. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ and no HCQ [matched mortality-arrhythmia]). (d) Kaplan-Meier survival in propensity-matched patients with bleeding outcome. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ and no HCQ [matched bleeding]). HCQ = hydroxychloroquine. [Color figure can be viewed at wileyonlinelibrary.com]

confounding medications, limited populations studied, and lack of morbidity/mortality outcomes are associated limitations of these investigations. Yet, they do bring to our attention the likelihood of meaningful QT prolongation with use of HCQ alone or in combination with AZ in patients with COVID-19.

Despite safety concerns, widespread interest in the use of HCQ for COVID-19 increased with the U.S. President's emphatic support.[6] This likely was driven from very few treatment options for COVID-19 and further encouraged by an uncontrolled, but promising, report from a highly publicized French study.[7] So it appeared to be with good intent that an emergency use authorization for HCQ was issued (then retracted on June 15, 2020), permitting the emergency use from the Strategic National Stockpile to treat patients hospitalized with COVID-19 for whom a clinical trial was not available or participation was not feasible. However, an evaluation of supporting prospective evidence is warranted.

HCQ clinical trial results were reported in a news briefing by the Chinese government in February 2020, revealing that the treatment of more than 100 patients with COVID-19 had resulted in significant improvements of pneumonia and lung imaging, with reductions in the duration of illness. No adverse events were reported. It appeared that these findings were a result of combining data from several ongoing trials using a variety of study designs. No empirical data supporting these findings have been published to date. Additional results from randomized controlled trials conducted in China

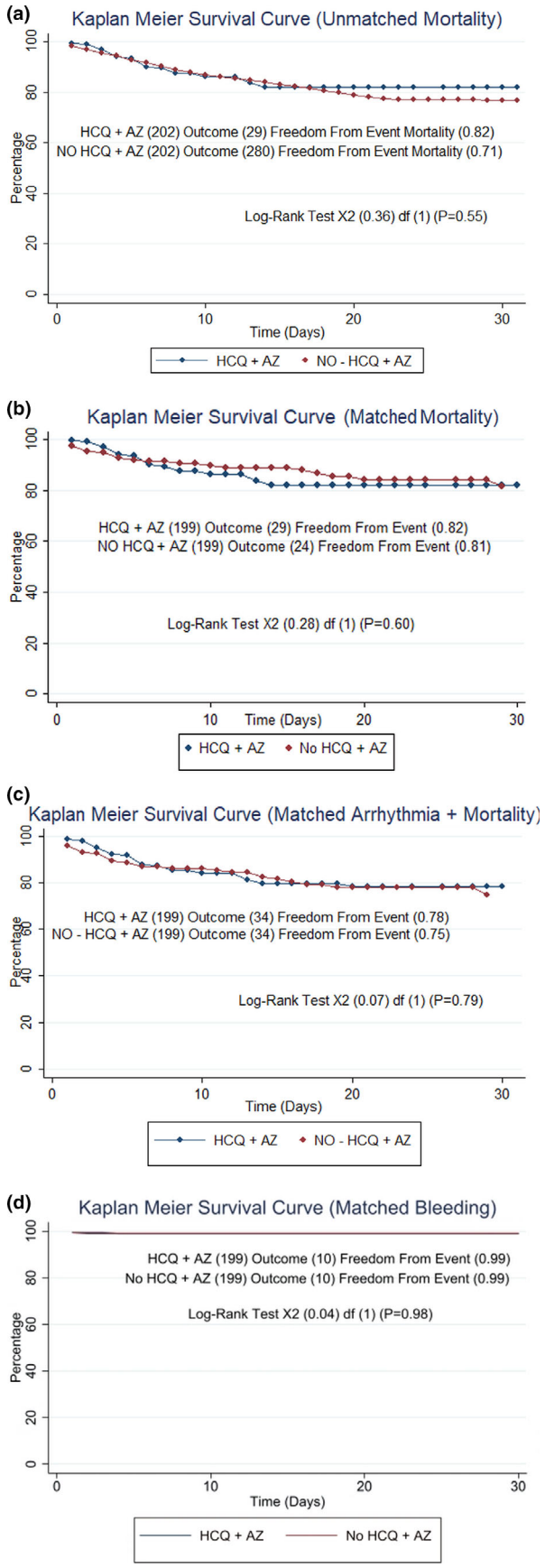

Figure 2. (a) Kaplan-Meier survival analysis of the study groups before propensity-score matching: HCQ + AZ and no HCQ + no AZ (unmatched mortality). (b) Kaplan-Meier survival analysis of the study groups after propensity-score matching. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ + AZ and no HCQ + no AZ [matched mortality]). (c) Kaplan-Meier survival in propensity-matched patients with mortality-arrhythmia outcome. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ + AZ and no HCQ + no AZ [matched mortality-arrhythmia]). (d) Kaplan-Meier survival in propensity-matched patients with bleeding outcome. Variables used for propensity matching included hypertension, diabetes mellitus, chronic obstructive lung disease, heart failure, obesity, nicotine dependence, and history of stroke (HCQ + AZ and no HCQ + no AZ [matched bleeding]). AZ = azithromycin; HCQ = hydroxychloroquine. [Color figure can be viewed at wileyonlinelibrary.com]

have shown reduced severity and course of disease with HCQ compared with placebo without detecting serious adverse effects, although others have suggested no difference in outcome from conventional treatment.[24]

In March 2020, the earlier cited French data were published.[7] This was an open-label, nonrandomized trial of 36 patients diagnosed with COVID-19 (20 HCQ, 16 control). Of the 20 patients in the HCQ group, 6 were also prescribed AZ. The main outcome was viral carriage at day 6. Impressively, patients in the HCQ treatment group were significantly more likely to test negative than patients in the ill-defined control group (70% vs 12.5%, p<0.001, respectively). All 6 patients treated with the combination of HCQ and AZ tested negative on day 6. Substantive limitations exist within this trial, including the open-label, nonrandomized design; number of patients lost to follow-up; control cohort recruited from a different medical center; viral load conversion after testing negative; and lack of intent-to-treat analysis.

The aforementioned trials were devoid of a mortality end point and were not designed as such, instead having surrogate and symptomatology outcomes. Furthermore, the relationship of viral load and morbidity/mortality is largely unknown. However, independent of this fact, if a relationship of viral load and transmission exists, this might be a worthy societal therapeutic pursuit.

As we patiently awaited findings from prospective double-blinded controlled experiments, additional United States Food and Drug Administration guidance ensued reminding

providers that HCQ should not be used (even within the now withdrawn emergency use authorization) outside the hospital setting or within a clinical trial for treatment of COVID-19. This governmental response was stimulated from Adverse Event Reporting System reports[3] and a relatively small retrospective VA trial of all male and predominantly Black patients hospitalized with COVID-19 that showed an association of higher mortality with HCQ use.[4] In this unpublished and non-peer-reviewed trial, treating COVID-19 with HCQ was associated with an increase in mortality. Mortality in this sample of 368 patients was 27.8%, 22.1%, and 11.4% in the HCQ, HCQ-AZ, and no-HCQ groups, respectively. These concerning findings accelerated our current investigation. We believed our propensity-matched cohort study being more gender and ethnicity inclusive and representing a larger sampling would add to the growing evidence.

Our findings do not substantiate the work of the VA study.[4] After propensity matching, there was no difference in overall mortality (HCQ 13.1%, no HCQ 13.6%; OR 0.95, 95% CI 0.62–1.46) or mortality combined with cardiac arrhythmia (HCQ 17.4%, no HCQ 17.7%; OR 0.98, 95% CI 0.67–1.44) between the groups. When HCQ was combined with AZ, these findings remained insignificant. On further review of the previous work,[4] explanation of the reported findings might be attributed to "dynamic" reallocation of patients who died to the HCQ group later in the course of disease. Briefly, patients from the no-HCQ group (n=177 for ventilation outcome) were moved to the HCQ and HCQ-AZ groups for the mortality outcome (n=158). The timing of the shift in group membership is important because it occurred postventilation and suggests these patients were placed on HCQ or HCQ-AZ to improve their trajectory. We attempted to overcome this shortcoming by limiting our cohorts to patients prescribed HCQ and AZ within 2 days of hospitalization.

Our findings do corroborate a previous work that was a worldwide database of 14 sources of claims data comprising nearly 1 million users of HCQ and more than 300,000 users of HCQ plus AZ.[5] Unlike the analysis in the VA study, the investigators found no excess risk in short-term (30-day) CV mortality in HCQ users (calibrated hazard ratio [HR] 1.35, 95% confidence interval [CI] 0.51–3.63). However, the authors did find that when AZ was added to HCQ, there was an increased risk of 30-day CV mortality (calibrated HR 2.19, 95% CI 1.22–3.94). Indeed, although statistically insignificant in our data, when combined with AZ, HCQ had a mortality relative risk of 1.24 (95% CI 0.70–2.2). In Lane et al's data, long-term use of HCQ was associated with an increased CV-related mortality (calibrated HR 1.65, 95% CI 1.12–2.44), whereas long-term use in combination with AZ resulted in a disappearance of CV-related mortality (calibrated HR 1.20, 95% CI 0.96–1.50). Lane et al's cohorts consisted largely of patients with rheumatoid arthritis versus patients with COVID-19. This fact combined with the study's inconsistent 30-day and long-term findings provoked further need for study of HCQ's association with mortality.

A study[25] shared results from a single-center retrospective cohort of 811 patients with COVID-19 receiving HCQ compared with 274 patients (n=565 unadjusted prematch) not receiving HCQ. As with our findings, there was no significant association between HCQ and the combined end point of intubation or death (HR 1.04, 95% CI 0.82–1.32). Experience from a single center may limit its generalizability as does its lack of bifurcating its composite outcome. It is uncertain if their mortality outcome in isolation would emulate our findings.

In our analysis, HCQ was devoid of an overall mortality difference (HCQ 13.1%, no HCQ 13.6%). When combined with AZ, although statistically insignificant, the HCQ cohort had an overall mortality rate of 14.6% compared with the propensity-matched no HCQ–no AZ cohort's rate of 12.1%. Importantly, however, there was no trend in this cohort's overall mortality-arrhythmogenesis outcome (HCQ-AZ 17.1%, no HCQ–no AZ 17.1%; OR 1.0, 95% CI 0.6–1.7), and the combination group could quite possibly represent a sicker group despite the careful matching (i.e., unmeasured covariates).

The findings in a multicenter retrospective cohort study of 1438 patients with COVID-19 in the New York metropolitan region did not find an effect of HCQ (HR 1.08, 95% CI 0.63–1.85) or HCQ-AZ (HR 1.35, 95% CI 0.76–2.40) on mortality relative to no HCQ or AZ. After adjustment, there were no significantly different abnormal electrocardiogram findings in the HCQ or HCQ-AZ groups.[26]

A series of recent COVID-19 investigations now add weight to the premise of HCQ safety in a hospitalized population. Indeed, three of these investigations[27–29] produced HRs ranging from 0.487 to 0.684, all statistically significant and demonstrating mortality benefit with HCQ. However, two other studies with arguably

superior designs[9, 30] did not reveal a mortality benefit with HCQ with a relative ratio of 1.09[9] and OR of 1.21.[30]

The safety profile of HCQ-treated patients with COVID-19 in the ambulatory setting has recently been demonstrated by other studies.[31 32] Unlike the touted Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial,[9] these randomized investigations were both blinded and placebo controlled. In patients at high risk for developing COVID-19, there was a nonstatistically significant 17% relative risk reduction of developing COVID-19 when taking prophylactic HCQ (n=821).[31] A study demonstrated a nonsignificant 6% absolute risk reduction in COVID-19 symptomatology in 423 ambulatory nonhospitalized patients with COVID-19.[32] Both investigations lacked sufficient sample sizes to demonstrate statistically meaningful findings. Most important, and common to these hospital and ambulatory-based trials, is the fact of a favorable cardiotoxicity profile of HCQ in patients with COVID-19.

It appears that the story of HCQ's use in hospitalized patients with COVID-19 is coming to an end, largely because of its lack of efficacy in the RECOVERY trial.[9] Despite the trial's shortcomings,[10] the findings have had an indelible impact on several other awaited trials, among which are an international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care[33] and Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease.[34] On probing of several investigators of ongoing trials, it is likely that the medical community will not have additional robust data of HCQ use in hospitalized patients with COVID-19. If able to withstand existing pressures to terminate, we can be hopeful that additional data will be forthcoming regarding the utility of HCQ prophylaxis against COVID-19 in ambulatory settings.[35]

Present recommendations from the National Institutes of Health's Treatment Guidelines Panel recommends against the use of HCQ for treatment of COVID-19 in hospitalized patients.[36] When adding AZ to HCQ, they recommend against except in a clinical trial. In nonhospitalized patients, the guidelines recommend against the use of HCQ except in a clinical trial.

In early April 2020, the American College of Cardiology, American Heart Association, and Heart Rhythm Society warned providers to use caution when considering HCQ and AZ to treat COVID-19 especially if the patient has CV disease.[37] Our data add support to this advice. Furthermore, a study[38] provides not only the review of modifiable and nonmodifiable risk factors for drug-induced TdP but also risk-mitigating approaches to HCQ use in COVID-19.

Our results demonstrated that short-term use of HCQ with or without AZ is not associated with a higher overall mortality. QT lengthening is a known effect associated with both HCQ and AZ. Additive or synergistic effects could lead to TdP. Although there was no benefit of HCQ in hospitalized patients with COVID-19, the current trial builds confidence around the safety profile for short-term use of HCQ in COVID-19. Furthermore, these results provide support for continued investigation in the ambulatory setting.[35, 39]

Limitations of this analysis are the following: (i) the observational retrospective nature of the study and associated inherent limitations, such as selection bias; (ii) residual confounders, although we took into consideration known COVID-19 comorbidities; (iii) granular data regarding medication dosages were not available; (iv) other QT-prolonging medications were not considered; and (v) QT intervals were unavailable within the data set.

Conclusions

We report from a large, retrospective, multinational database analysis of COVID-19 outcomes with HCQ and overall mortality in hospitalized patients. This propensity-matched study showed no association of an increase in overall mortality or other safety signal with HCQ or HCQ-AZ in hospitalized patients with COVID-19.

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Supporting Information

The following supporting information is available in the online version of this paper:

Table S1. Coding used in analyses.

Appendix S1. Supporting Information.