

Compassionate Use of Hydroxychloroquine in Clinical Practice for Patients With Mild to Severe COVID-19 in a French University Hospital

Olivier Paccoud,¹ Florence Tubach,² Amandine Baptiste,² Alexandre Bleibtreu,¹ David Hajage,² Gentiane Monseil,¹ Gianpiero Tebano,¹ David Boutolleau,^{3,4} Elise Klement,¹ Nagisa Godefroy,¹ Romain Palich,¹ Oula Itani,¹ Antoine Faïçal,¹ Marc-Antoine Valantin,¹ Roland Tubiana,¹ Sonia Burrel,^{3,4} Vincent Calvez,^{3,4} Eric Caumes,^{1,4} Anne-Geneviève Marcelin,^{3,4} and Valérie Pourcher^{1,4}

¹Assistance Publique—Hôpitaux de Paris, Hôpitaux Universitaires Pitié-Salpêtrière Charles Foix, Service de Maladies infectieuses et Tropicales, 75013, Paris, France, ²Sorbonne Université, INSERM UMR 1136, Département de Santé Publique, Unité de Recherche Clinique Pitié-Salpêtrière—Charles Foix, Centre de Pharmacopépidémiologie de l'AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière Charles Foix, 75013, Paris, France, ³Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière—Charles Foix, laboratoire de virologie, F75013, Paris, France, and ⁴Sorbonne Université, INSERM 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, F75013, Paris, France

Background. Data from nonrandomized studies have suggested that hydroxychloroquine could be an effective therapeutic agent against coronavirus disease 2019 (COVID-19).

Methods. We conducted an observational, retrospective cohort study involving hospitalized adult patients with confirmed, mild to severe COVID-19 in a French university hospital. Patients who received hydroxychloroquine (200 mg 3 times daily dosage for 10 days) on a compassionate basis in addition to standard of care (SOC) were compared with patients without contraindications to hydroxychloroquine who received SOC alone. A propensity score-weighted analysis was performed to control for confounders: age, sex, time between symptom onset and admission ≤ 7 days, Charlson comorbidity index, medical history of arterial hypertension, obesity, National Early Warning Score 2 (NEWS2) score at admission, and pneumonia severity. The primary endpoint was time to unfavorable outcome, defined as: death, admission to an intensive care unit, or decision to withdraw or withhold life-sustaining treatments, whichever came first.

Results. Data from 89 patients with laboratory-confirmed COVID-19 were analyzed, 84 of whom were considered in the primary analysis; 38 patients treated with hydroxychloroquine and 46 patients treated with SOC alone. At admission, the mean age of patients was 66 years, the median Charlson comorbidity index was 3, and the median NEWS2 severity score was 3. After propensity score weighting, treatment with hydroxychloroquine was not associated with a significantly reduced risk of unfavorable outcome (hazard ratio, 0.90 [95% confidence interval, .38–2.1], $P = .81$). Overall survival was not significantly different between the 2 groups (hazard ratio, 0.89 [0.23; 3.47], $P = 1$).

Conclusion. In hospitalized adults with COVID-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to SOC. Unmeasured confounders may have persisted however, despite careful propensity-weighted analysis and the study might be underpowered. Ongoing controlled trials in patients with varying degrees of initial severity on a larger scale will help determine whether there is a place for hydroxychloroquine in the treatment of COVID-19. In hospitalized adults with COVID-19, no significant reduction of the risk of unfavorable outcomes was observed with hydroxychloroquine in comparison to SOC.

Keywords. COVID-19; SARS-CoV-2; hydroxychloroquine.

Since December 2019, a novel coronavirus, designated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused a worldwide outbreak of respiratory illness known as coronavirus 2019 disease (COVID-19). The spectrum of COVID-19 ranges from mild illness to severe progressive pneumonia, multiorgan failure, and death [1–4]. In

this setting, the repurposing of drugs for use as experimental antiviral agents is of critical importance. To date, there are no specific therapeutic agents approved in the treatment of COVID-19, but the Food and Drug Administration has issued an Emergency Use Authorization on March 28, 2020, for emergency use of hydroxychloroquine (HCQ) in this setting [5]. Following recent publications showing in vitro activity of HCQ against SARS-CoV-2 [6, 7], there are few data on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia with differing levels of severity, but many trials are ongoing [8, 9]. Preliminary results pooled from ongoing randomized, open, controlled studies in China reportedly showed superiority of HCQ compared with a control group (chloroquine or standard of care [SOC]) in terms of reduction of exacerbation of pneumonia, duration

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Correspondence: V. Pourcher, Assistance Publique—Hôpitaux de Paris, Hôpitaux Universitaires Pitié-Salpêtrière Charles Foix, Service de Maladies infectieuses et Tropicales, Sorbonne Université, INSERM 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique 75013, Paris, France (valerie.martinez@aphp.fr).

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of symptoms, and delay to viral clearance [8]. These results have led to great enthusiasm worldwide and calls for its widespread use in the treatment of SARS-CoV-2-related pneumonia. However, some of the aforementioned studies have since been cancelled or are not currently recruiting, and a recent study by Chen et al showed no impact of HCQ on viral clearance, symptoms, or radiological progression [10]. Overall, data to support the widespread use of HCQ in the treatment of COVID-19 therefore remain inconclusive [11]. On March 11, 2020, Gautret et al reported 20 cases of COVID-19 patients treated with HCQ in a French hospital, showing a significant reduction of SARS-CoV-2 viral loads at day 6 after inclusion compared with controls, and much lower average duration of viral carriage than reported for untreated patients in the literature [12]. At that time, faced with an increasing influx of COVID-19 patients in our infectious diseases ward and before enrollment in randomized clinical trials was made available, we decided to use HCQ on a compassionate basis in our department. Until results of these randomized controlled trials are made available, new data are therefore dramatically needed about the effectiveness of HCQ. In this retrospective cohort study, we evaluated the efficacy and safety of compassionate use of HCQ in hospitalized patients with mild to severe COVID-19 infection compared with SOC patients.

METHODS

Study Design

This is an observational retrospective exposed-nonexposed cohort study aiming at evaluating the efficacy of HCQ treatment compared with SOC in patients hospitalized with a diagnosis of COVID-19. This article complies with the Strengthening the Reporting of Observational Studies in Epidemiology criteria.

Patients

Eligible patients for the study were all patients hospitalized in the infectious diseases ward of the Pitié-Salpêtrière University hospital from January 2020 with a diagnosis of COVID-19. Patients who were admitted in the infectious diseases ward after a stay in an intensive care unit (ICU) were excluded from analysis, as were patients unable to provide an informed consent, those treated with another experimental treatment, and those who presented a contraindication to receiving HCQ. These included: patients with a corrected QT interval longer than 440 ms on the electrocardiogram performed at admission; those with known hypersensitivity to chloroquine or HCQ; those with a history of elongated QT interval or severe cardiopathy, G6PD deficiency, or retinopathy; and, finally, patients receiving comedications known to elongate the QT interval or potentially responsible for drug–drug interactions that would require close monitoring. All patient comedications were cross-referenced with the list of

medications potentially responsible for drug–drug interactions provided by the Liverpool Drug Interactions Group [13].

HCQ Patients

On March 11, 2020, physicians from the infectious diseases ward of the Pitié-Salpêtrière University hospital collectively decided to systematically propose administering HCQ (200 mg 3 times daily for 10 days) on a compassionate basis to adult patients with a diagnosis of laboratory-confirmed COVID-19 infection, based on the promising results of Chinese and French studies [8, 12]. The decision to administer HCQ was ultimately left to the attending physician, and the patient was informed about the rationale to propose the treatment, that efficacy was not proven, and about potential side effects. Only patients who agreed to receive the treatment were treated. In addition to HCQ treatment, SOC was provided (see the following section). Concomitant antibiotherapy could be used, which was left to the discretion of the attending physician. Because of concerns regarding the risk of cardiologic complications, azithromycin was not added to the HCQ treatment regimen with the exception of 1 patient.

SOC-Only Patients

This group consisted of patients hospitalized before the collective decision of treating with HCQ in the ward, patients who had refused, and patients for whom the treatment was not administered (for any reason but contraindication to HCQ). SOC consisted of supplemental oxygen therapy to maintain an oxygen saturation > 96%, intravenous or oral acetaminophen, and antibiotics if deemed necessary. No patient received azithromycin.

Diagnosis and Documentation of COVID-19 Infection

Diagnosis of COVID-19 was confirmed for all patients on the basis of a positive reverse transcriptase-polymerase chain reaction (PCR) assay from a nasopharyngeal swab or induced sputum sample [14]. Systematic follow-up reverse transcriptase-PCR was not performed for already diagnosed COVID-19 patients because tests were prioritized for the diagnosis of new infections.

Clinical, Radiological, and Laboratory Data

Clinical and biological variables were retrospectively collected from the medical files of all patients with laboratory-confirmed COVID-19. Baseline comorbidities and initial severity were retrospectively assessed using the Charlson comorbidity index [15] and the National Early Warning Score 2 (NEWS2) [16], respectively. Grade 2 (moderate) and grade 3 (severe) COVID-19 pneumonia were defined as radiological evidence of COVID-19 pneumonia in association with below or above a cutoff requirement of at least 3 L/min supplemental oxygen to maintain a saturation of > 96%, respectively. Patients with no radiological

evidence of pneumonia at admission, or for whom radiological explorations were not performed, were defined as grade 1.

Outcomes

The primary outcome of this study was time to unfavorable outcome, defined as: death, admission to an ICU, or decision of nonadmission to an ICU because of active care limitations, whichever came first.

Secondary outcomes were time to death, time to hospital discharge for a return home or in an aftercare and rehabilitation unit, fever and cough at day 5, and adverse events recorded in the patients receiving HCQ treatment.

Ethical Considerations

All patients provided oral informed consent to receive the drug and they did not object to the analysis of their data for research issues (nonopposition regime). The research protocol was reviewed and approved by the Ethics Committee of the French Infectious Diseases Society (Comité d’Ethique de Recherche en Maladies Infectieuses et Tropicales) under institutional review board no. IRB00011642. According to French law (no. 78-17 of 6 January 1978 on computers, files, and liberties), this study has been registered with the CNIL (French National Agency regulating Data Protection) and was conducted in compliance with the reference methodology 004.

Statistical Analyses

Characteristics at admission of patients and biological parameters were described globally and according to the treatment group (HCQ vs SOC only). The results are expressed as mean (standard deviation) or median [quartile 1-quartile 3] for quantitative variables and number (%) for qualitative variables. All statistical tests are bilateral and used a significance level of 5%. Crude comparisons of qualitative variables were conducted using χ^2 tests or exact Fisher tests, as appropriate, and comparisons of quantitative variables were conducted using Student tests or nonparametric Wilcoxon tests, as appropriate. The clinically relevant outcomes (time to unfavorable event, time to death, or time to hospital discharge for a return home or in an aftercare and rehabilitation unit) were compared using propensity score weighted analysis to balance the main baseline confounding factors between groups. The propensity score here corresponds to the probability that a patient receives HCQ treatment based on initial characteristics. It was estimated using a multivariate logistic model, including most relevant and a priori selected confounders: time between symptom onset and admission ≤ 7 , Charlson comorbidity index, NEWS2 score at admission, pneumonia severity, and medical history of arterial hypertension or obesity. Stabilized Average Treatment Effect (ATE) weights were used [17]. Balance between groups for these factors was assessed by calculating the standardized difference after weighting. An absolute standardized difference < 0.1 was

considered as an evidence of balance. For time-to-event outcomes, Kaplan-Meier curves according to treatment groups were plotted before and after weighting. Standard and weighted Cox proportional hazards regression models were fitted to estimate both crude and propensity score adjusted hazard ratio (HR). For binary outcomes, differences in risk between treatment groups (HCQ – SOC only) were computed before and after propensity score weighting. For all outcomes, 95% confidence intervals were estimated and *P* value corresponding to a robust Wald test were reported. Primary analysis involved HCQ patients who initiated HCQ treatment the day of admission or the day after to avoid immortal time bias in favor of HCQ. In addition, we performed a sensitivity analysis on a wider population, also including the patients who initiated HCQ 2 days or more after admission. Finally, time to event was primarily defined as time from initiation of treatment for HCQ patients and time from admission for the others; in subsequent sensitivity analyses, results were investigated considering a start time from admission for all patients.

Statistical analysis was carried out using R 3.6.3 software [<https://cran.r-project.org/>].

RESULTS

Patients

From January 28, 2020, to March 19, 2020, 117 patients with laboratory-confirmed COVID-19 infection were admitted. Among these, 18 were excluded from analysis because of having a contraindication to receiving HCQ (severe cardiopathy, $n = 4$; drug–drug interactions, $n = 11$; and pretreatment elongated QT interval, $n = 3$) (Figure 1). Overall, 42 patients were treated with HCQ 200 mg 3 times daily and 1 patient was already receiving long-term HCQ at a 200 mg twice-daily dosage and the treatment was maintained. One patient treated by HCQ also received azithromycin (500 mg/d) for 3 days because of concomitant *Salmonella* spp infection. Patients received HCQ for a median (interquartile range) treatment duration of 10 days (8–10). Five of these patients initiated HCQ treatment more than 2 days after hospital admission and were therefore not included in the primary analysis but were kept in a sensitivity analysis.

The clinical and biological characteristics at admission of the 85 patients considered in the primary analysis are summarized in Table 1. In brief, 62% of patients were male, with a mean age of 66 (16) years. Patients had a median of 1 comorbidity, with a median (interquartile range) Charlson comorbidity index of 3 (2–5). Seventy percent were hospitalized within 7 days of symptom onset, had a median NEWS2 score of 3 (1–6) at admission, and 73% presented with grade 2 or 3 pneumonia. Seventy-nine percent received concomitant antibiotics, and no patient received glucocorticosteroid therapy. Characteristics of patients included in the primary analysis according to treatment groups are summarized in Table 1. Overall, significantly

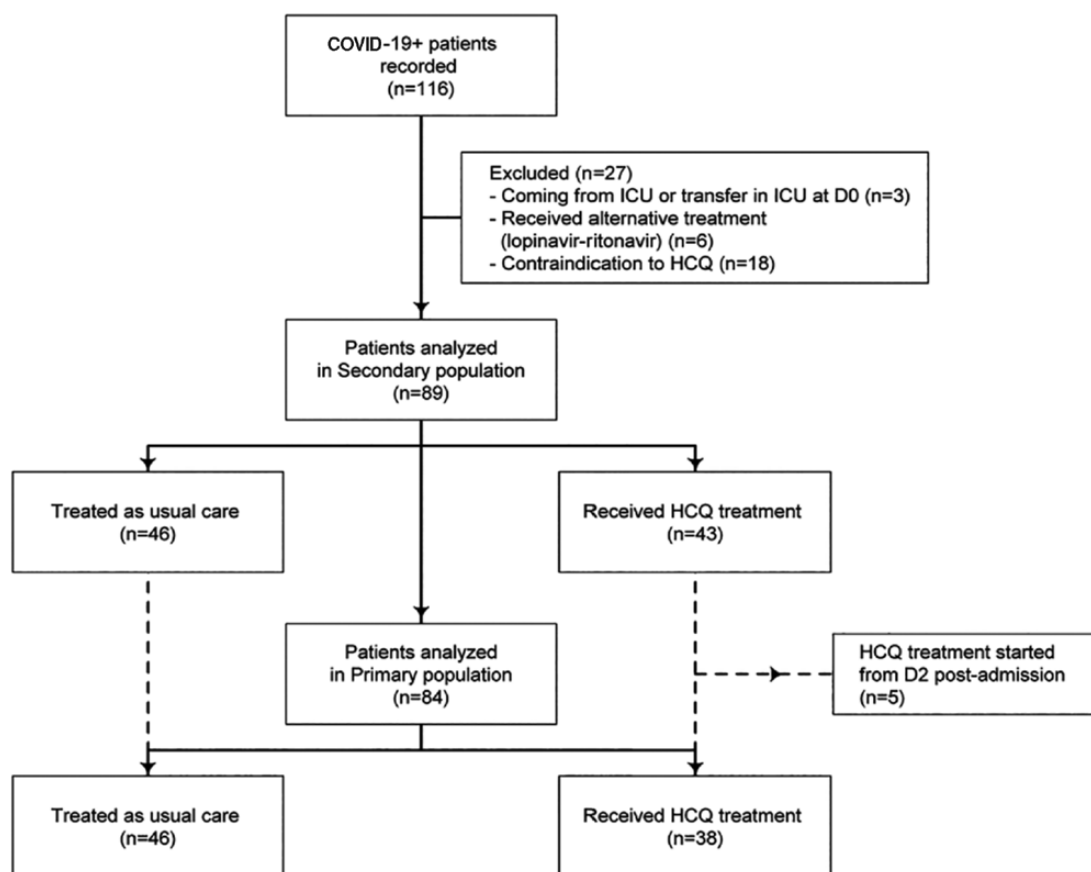


Figure 1. Flow chart. Abbreviations: COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; ICU, intensive care unit.

more patients in the HCQ group presented with coughing than in the control group, and they had a significantly higher median heart rate and respiratory frequency.

Balance After Propensity Score Weighting

Table 1 reports the standardized differences after propensity score weighting. All variables included in the propensity score model were well balanced. Despite the propensity weighting, differences persisted between groups for some baseline characteristics that could not be handled in the propensity score, namely a higher number of patients with altered mental status (given HCQ was first offered to patients able to give informed consent) and a lower baseline cycle threshold on PCR at admission in the control group, but lower lymphocyte counts at admission in the HCQ group (there was a large amount of missing data on these last 2 factors: respectively, 39% and 23%).

Primary Outcome

Median follow-up of patients was 10 days (95% confidence interval, 10–10). A total of 29 unfavorable events were considered in the time-to-event analysis. There were 18 transfers to the ICU (8 among patients treated with HCQ and 10 in others) and 11

decisions of nonadmission to an ICU because of active care limitations (5 in patients treated with HCQ and 6 in SOC group). Overall, 3 patients treated with HCQ and 6 patients with SOC died; for all of them, a previous transfer to ICU or decision of active care limitation was recorded before. Results of primary and secondary outcomes in primary analysis are shown in **Table 2**. After propensity score weighting to balance confounding factors, treatment with HCQ was not associated with a significant reduction of the risk of unfavorable outcome compared to the SOC group (HR, 0.90 [0.38; 2.1], $P = .81$). (**Figure 2**)

Sensitivity analyses including patients who received HCQ after day 2 of admission ($n = 5$) yielded similar results (HR, 0.81 [0.36; 1.83], $P = .62$). Considering time to event starting from admission did not change the conclusions (**Supplementary data**).

Secondary Outcomes

After adjusting for confounding factors, overall survival was not significantly different between the 2 groups (HR, 0.89 [0.23; 3.47], $P = .86$) (**Figure 3**). Similarly, time to hospital discharge was not significantly different between the 2 groups (HR, 1.18 [0.63; 2.22], $P = .61$, cause-specific approach). At day 5 after admission, in the

Table 1. Clinical and Biological Characteristics at Admission of the 85 Patients Considered in the Primary Analysis

Variable	Before Weighting				After Weighting			
	Global	SOC Only (N = 46)		HCO (N = 38)	PValue ^a	SOC Only (N = 46)	HCO (N = 38)	Standardized Mean Difference (%)
		nb	NA					
Sex, M ^b	52 (62%)	...	31 (67%)25	59%	59%	0.01
Age, Y ^b	65.5 ± 16	...	64.3 ± 17.945	66.2 ± 17.1	67.1 ± 13.4	0.06
Charlson score ^b	3 [2–5] 3.5 ± 2.2	...	3.6 ± 2.455	3.6 ± 2.2	3.7 ± 2	0.02
Hospitalization < D7 symptoms, yes ^b	59 (70%)	...	33 (72%)74	72%	76%	0.08
NEWS2 score ^b	3 [1–6] 3.6 ± 2.8	...	3.2 ± 3.1079	3.5 ± 2.8	3.3 ± 2.5	0.09
HTA, yes ^b	29 (35%)	...	14 (30%)39	34%	35%	0.01
Obesity (BMI > 30), yes ^b	7 (8%)	...	3 (7%)7	6%	7%	0.02
Pneumonia severity, 1 ^b	23 (27%)	...	14 (30%)68	27%	28%	0.01
Pneumonia severity, 2 ^b	42 (50%)	...	23 (50%)	49%	51%	0.04
Pneumonia severity, 3 ^b	19 (23%)	...	9 (20%)	23%	21%	0.06
Diabetes, yes	17 (20%)	...	9 (20%)87	15%	18%	0.09
Asthma/COPD, yes	11 (13%)	...	6 (13%)	...	1	18%	20%	0.04
Number of comorbidities	1 [0–2] 1.4 ± 1.2	...	1.4 ± 1.263	1.4 ± 1.1	1.2 ± 1.1	0.16
Symptoms								
Fever, yes	43 (51%)	...	26 (57%)28	61%	31%	0.62
Cough, yes	57 (68%)	...	25 (54%)004	59%	84%	0.55
Headaches, yes	15 (18%)	...	5 (11%)07	13%	21%	0.21
Diarrhea, yes	8 (9%)	...	3 (7%)46	5%	29%	0.65
Mental confusion, yes	12 (14%)	...	10 (22%)032	23%	5%	0.53
Anosmia, yes	1 (1%)	...	1 (2%)	...	1	3%	0%	0.23
Dyspnea, yes	43 (51%)	...	18 (39%)015	48%	64%	0.32
Oxygen								
O ₂ , mL/min	0 [0–2] 1.3 ± 1.6	...	1.2 ± 1.815	1.2 ± 1.7	1.2 ± 1.3	0.03
Vital and biological parameters								
O ₂ saturation	96 [95–97] 96 ± 2.2	...	96.7 ± 1.9001	96.5 ± 2	95.3 ± 2	0.61
Respiratory rate	20 [14–24] 19.3 ± 5.3	2	17.9 ± 5.4007	18.3 ± 5	20.4 ± 5.1	0.42
Heart rate	82 [72–92] 82.6 ± 13.4	...	80.1 ± 12.904	79.8 ± 13.1	84.4 ± 15	0.33
CRP	57 [21–113] 74.7 ± 66.4	21	68.7 ± 66.4	6	.61	66.8 ± 64.7	82.7 ± 69.7	0.24
Lymphocytes	1.1 [0.8–1.3] 1.2 ± 0.6	16	1.3 ± 0.7	3	.032	1.3 ± 0.6	1 ± 0.5	0.53
Virology								
CT measured at diagnosis PCR	20.6 [18.7–26.8] 22.1 ± 4.7	20	20.7 ± 4.2	13	.018	20.4 ± 4.1	23 ± 5.3	0.56

^aχ² (or exact Fisher test) was used for qualitative variables and Student test (or nonparametric Wilcoxon test) for quantitative variables.^bOnly these variables were included in the model to estimate the propensity score.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, cycle threshold; HTA, arterial hypertension; HCO, hydroxychloroquine; NEWS2, National Early Warning Score 2; PCR, polymerase chain reaction; SOC, standard of care.

Table 2. Primary and Secondary Outcomes in the Primary Analysis Population

Outcomes	SOC Only		HCQ		Crude Analysis Without IPTW Weighting		IPTW-weighted Analysis	
	N patients	n events	N patients	n events	HR (95% CI)	P	HR (95% CI)	P ^a
Time to events outcomes								
Unfavorable outcome (ICU, limitation, or death)	46	16	38	13	1.04 (.5–2.17)	.91	0.90 (.38–2.1)	.81
Death	46	6	38	3	0.66 (.16–2.64)	.55	0.89 (.23–3.47)	.86
Hospital discharge for home or aftercare and rehabilitation center	46	26	38	21	0.87 (.49–1.56)	.64	1.18 (.63–2.22)	.61
Symptoms at clinical evaluation of day 5	N patients	n (%)	N patients	n (%)	Risk Difference HCQ – SOC (95% CI)	P	Risk Difference HCQ – SOC (95% CI)	P ^a
Cough	24	13 (54%)	20	13 (65%)	10.8% (–18.1 to 39.7)	.46	4.3% (–20.3 to 28.8)	.77
Fever	24	5 (21%)	20	4 (20%)	–0.8% (–24.7 to 23.1)	.95	–9.6% (–23.9 to 4.7)	.27

^aWald test performed using a robust estimator of variance.

Abbreviations: CI, confidence interval; HCQ, hydroxychloroquine; HR, hazard ratio; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; SOC, standard of care.

44 patients that could be evaluated, there were no significant differences between the 2 groups with regard to cough (% after propensity score weighting: SOC alone, 56.3% vs HCQ, 60.6%, risk difference (RD) = 4.26% [–20.3; 28.8], $P = .77$) and fever (SOC alone: 23% vs HCQ: 13.4%, RD = –9.6% [–23.9; 4.7], $P = .27$).

The conclusions regarding secondary outcomes were unchanged when investigated in sensitivity analyses (Supplementary data).

Thirteen patients treated with HCQ (34%) underwent an acute respiratory distress syndrome test (16 [35%] patients who received SOC). At the end of follow-up, among patients alive, 38 returned home (HCQ: $n = 16$; SOC: $n = 22$), 9 were in a rehabilitation and care center (HCQ: $n = 5$; SOC: $n = 4$),

15 were in the ICU (HCQ: $n = 7$; SOC: $n = 8$), and 13 were still hospitalized in the ward (HCQ: $n = 7$; SOC: $n = 6$). Among patients treated with HCQ, 6 (14%) reported side effects of HCQ, of which 4 (7%) resulted in premature discontinuation of treatment (corrected QT interval elongation, $n = 2$; cytopenia, $n = 1$; and paresthesia, $n = 1$). The 2 other side effects reported were headaches ($n = 1$) and diarrhea ($n = 1$).

DISCUSSION

In this observational retrospective study, no significant reduction in the risk of unfavorable outcome was observed in patients hospitalized with COVID-19 treated with HCQ as compared with SOC alone.

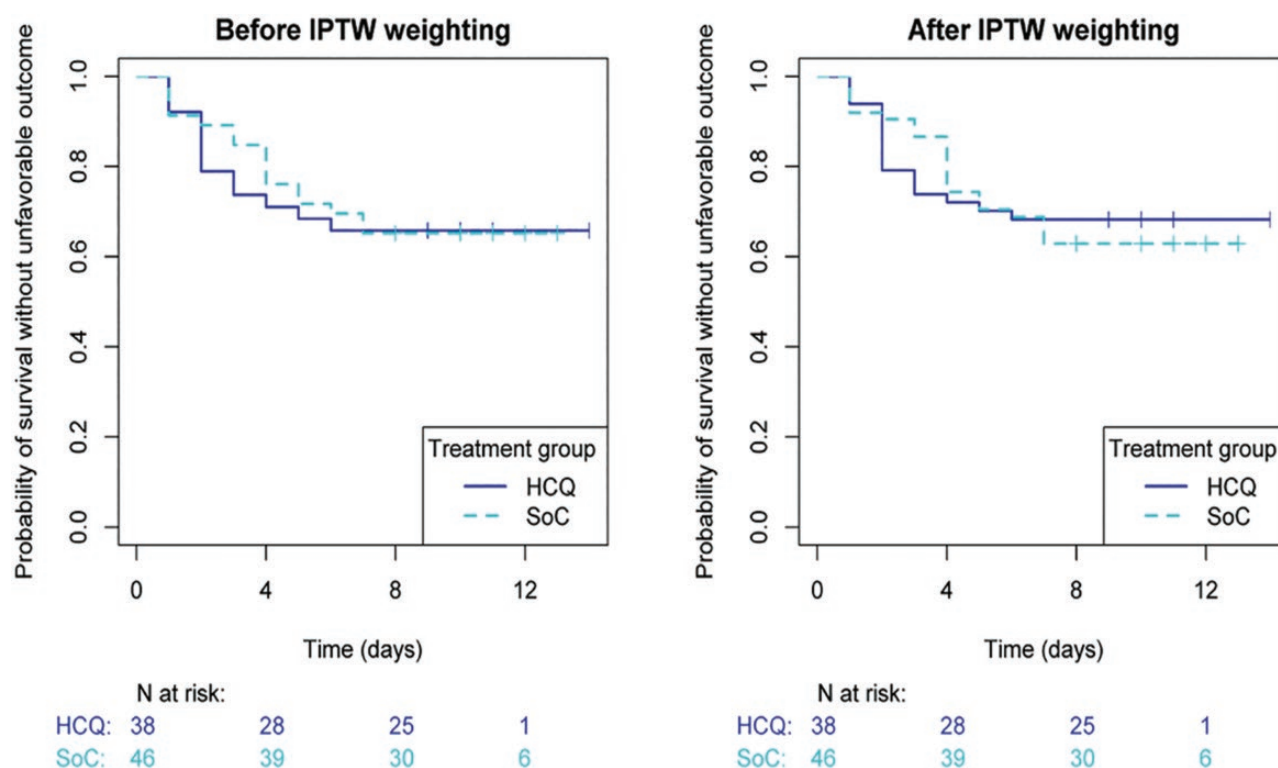


Figure 2. Probability of survival without unfavorable outcomes. Abbreviations: HCQ, hydroxychloroquine; IPTW, inverse probability of treatment weighting; SoC, standard of care.

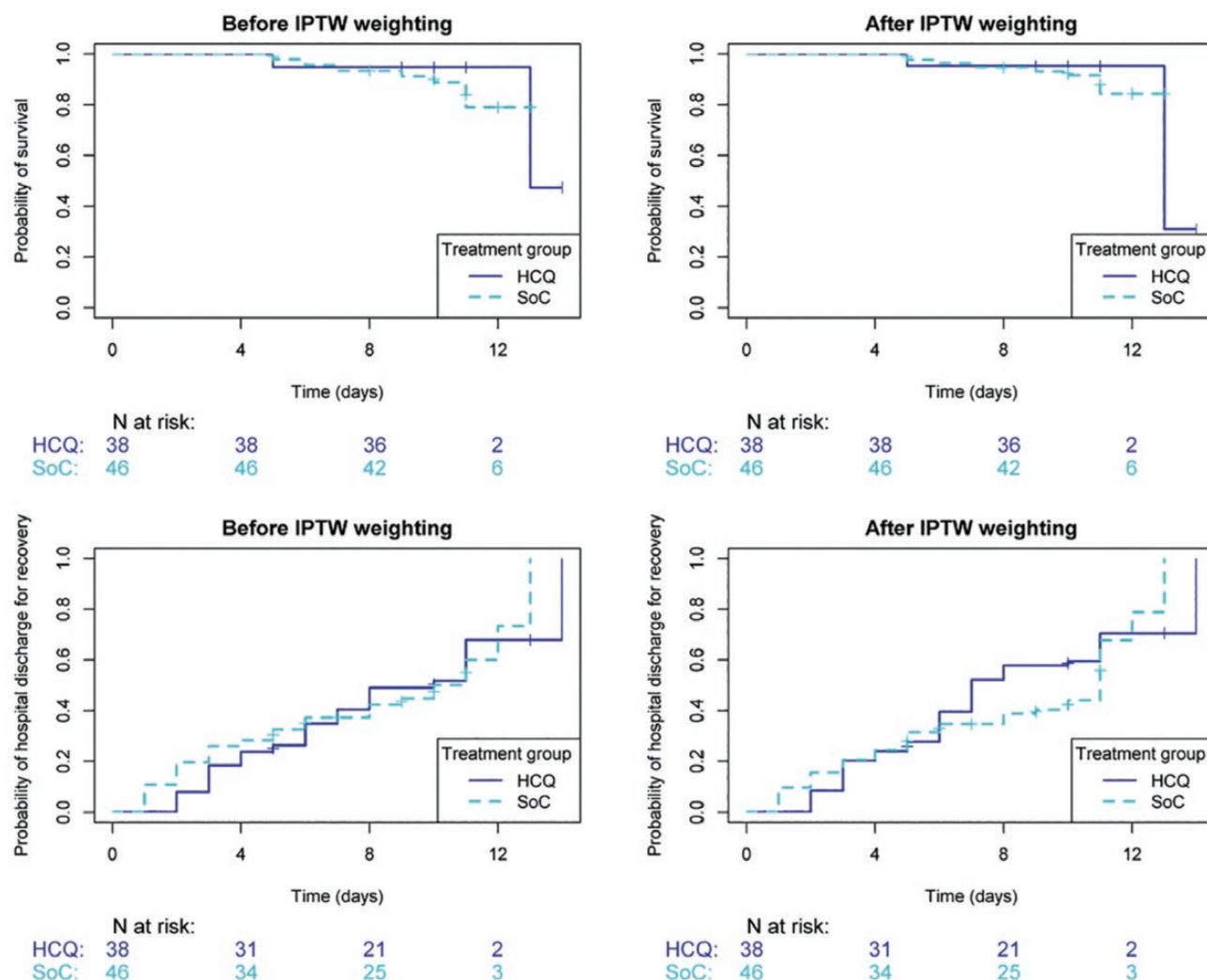


Figure 3. Probability of survival. Abbreviations: HCQ, hydroxychloroquine; IPTW, inverse probability of treatment weighting; SoC, standard of care.

In a recent nonrandomized study, Gautret et al reported that treatment with HCQ at a 200 mg 3 times daily dosage was associated with higher rates of SARS-CoV-2 viral clearance after 6 days of treatment, particularly when associated with azithromycin, compared with an untreated control group consisting of patients from different medical centers [12]. However, some methodological flaws were noted that may affect the validity of the findings, notably a small sample size, the use of a control group that included patients with a contraindication to HCQ, and the exclusion before analysis of patients transferred to an ICU or deceased [18, 19]. In a study with similar methodological limitations, Molina et al report their experience with compassionate use of HCQ, also at a 200 mg 3 times daily dosage in association with azithromycin, in 11 patients with moderate to severe COVID-19 (10 of 11 required supplemental oxygen therapy). The authors found no evidence of rapid viral clearance, with 8/10 surviving patients still having positive PCR results at days 5–6 after treatment initiation [20].

Compared with most previous studies, we chose a clinical outcome, namely time to unfavorable outcome, as the primary clinical endpoint rather than surrogate markers of cure such as SARS-CoV-2 viral clearance or time to clinical improvement, which we felt was a more pertinent marker of efficacy in this setting.

Our study has nonetheless several obvious limitations. The first major limitation is that the study was not randomized and thus is open to potential biases. To address this weakness, we performed a rigorous statistical analysis using propensity score weighting to control for main known confounders. Despite this propensity weighting, differences persisted between groups for some baseline characteristics, most notably regarding altered mental status, baseline lymphocyte counts, and baseline cycle threshold values for PCR. Finally, the small sample size also limits the power of our analyses. This sample size also limits the number of variables that could be included in the propensity score model, so we carefully prespecified a

list of the most important prognostic factors [21]. Our study population nevertheless reflects clinical practice in terms of the demographics of patients hospitalized at the beginning of the outbreak in France (ie, primarily older patients with significant comorbidities).

Chloroquine and HCQ have previously shown promising results in the in vitro inhibition of a variety of viral pathogens in cell culture [22], including SARS-CoV-2 [23], but there have been no successful translations to clinical efficacy in preventive or therapeutic clinical trials using HCQ as an antiviral agent [24, 25]. Various dosing regimens for HCQ have been proposed in the treatment of COVID-19, and it is possible that using different doses may yield different results, in particular with the use of a loading dose on day 1 as is currently being evaluated in ongoing clinical trials [26]. Side effects of HCQ were seldom reported in our study, although the retrospective nature of the study may lead to significant underreporting. There have however been valid concerns regarding the risk of cardiologic complications, namely ventricular arrhythmias and QT prolongation, related to the use of HCQ in the treatment of COVID-19, particularly in treating a condition already at risk of cardiovascular complications [27]. Although the urgency of the current situation and lack of proven efficacy of any antiviral therapy against COVID-19 may justify the off-label use of treatments such as HCQ in selected cases, the authors recommend exercising caution when extrapolating results of in vitro studies and preliminary clinical studies regarding the efficacy of HCQ against COVID-19, in light of the limited overall evidence to support its use and its potential cardiovascular side effects.

In conclusion, in hospitalized adults with COVID-19, no significant reduction of the risk of unfavorable outcomes was observed with HCQ in comparison to standard of care. Unmeasured confounders may however have persisted despite careful propensity weighted analysis and the study might be underpowered. Ongoing controlled trials in patients with varying degrees of initial severity on a larger scale will help determine whether there is a place for HCQ in the treatment of COVID-19.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Substantial contributions to the conception or design of the work: O. P., F. T., A. Baptiste, V. P. Acquisition, analysis, or interpretation of data for the work: O. P., F. T., A. B., A. B., D. H., G. M., G. T., D. B., E. K., N. G., R. P., O. I., A. F., M.-A. V., R. T., S. B., V. C., E. C., A.-G. M., V. P. Drafting the work or revising it critically for important intellectual content: O. P., F. T., A. Baptiste, A. Bleibtreu, D. H., G. M., G. T., D. B., E. K., N. G., R. P., O. I., A. F., M.-A. V., R. T., S. B., V. C., E. C., A.-G. M., V. P. Final approval of the version to be published: O. P., F. T., A. Baptiste, A. Bleibtreu, D. H., G. M., G. T., D. B., E. K., N. G., R. P., O. I., A. F., M.-A. V., R. T., S. B.,

V. C., E. C., A.-G. M., V. P. Agreement to be accountable for all aspects of the work: O. P., F. T., A. Baptiste, A. Bleibtreu, D. H., G. M., G. T., D. B., E. K., N. G., R. P., O. I., A. F., M.-A. V., R. T., S. B., V. C., E. C., A.-G. M., V. P.

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