Original Article

Day-90 survival in critically-ill patients with COVID-19 and hydroxychloroquine: a propensity analysis

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Background: There are limited data on the effect of hydroxychloroquine on medium term outcomes in patients with coronavirus disease 2019 (COVID-19) requiring intensive care. We aimed to evaluate the effects of hydroxychloroquine on day 90 mortality in this specific population.

Methods: This retrospective, multicenter, propensity matched cohort analysis, used data of adult patients with laboratory confirmed COVID-19 admitted to 3 university affiliated intensive care units between March 7, 2020, to April 7, 2020 in Lyon, France. Patients received either hydroxychloroquine (loading dose of 400 mg twice daily at day 1 followed by 200 mg twice daily from day 2 to day 10) or standard of care without hydroxychloroquine. We compared all-cause mortality at day-90 after ICU admission between propensity score matched groups receiving hydroxychloroquine or standard of care.

Results: A total of 157 patients were included with a day-28 and day-90 mortality rate of 23.6% and 32.5%, respectively. The median (interquartile) age was 67 years (56–76 years), 105 (66.9%) were men, 65 (41.4%) fulfilled criteria for acute respiratory distress syndrome, and 64 (41%) received hydroxychloroquine (HCQ) for 10 days (4–10 days). In the propensity score matched cohort (59 patients in each group), day-90 mortality was 35.6% for patients who received HCQ and 23.7% for patients who did not (P=0.23). Kaplan Meier survival analysis showed no statistically significant association between HCQ therapy and mortality (P=0.20 by log-rank test).

Conclusions: In this study, off-label use of HCQ in critically ill patients with COVID-19 was not associated with any significant change in medium-term prognosis, confirming results of studies in less severe patients.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); hydroxychloroquine (HCQ); acute respiratory distress syndrome; propensity score

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health crisis responsible for more than one million deaths (1). Very quickly after the first cases were observed, off-label use of hydroxychloroquine (HCQ) has been proposed for its potential antiviral/immunomodulatory properties to treat patients with COVID-19 infection (2). Preliminary reports had suggested clinical benefits for patients with mild COVID-19 symptoms, without major safety concerns (3,4). This led many physicians to also consider HCQ for patients requiring intensive care for acute respiratory failure, i.e., those who might most benefit from effective drugs with both antiviral and anti inflammatory therapy (5). As of May 2020, based on the neutral results of both observational studies and trials assessing whether HCQ would improve short-term outcomes (i.e., <30 days) in patients with mild-to-moderate COVID-19 (6-10), many national public health agencies have recommended not to use HCQ to treat the disease. In November 2020, a large trial reported no short-term benefits of this treatment, including in the subgroup of patients receiving invasive mechanical ventilation (11). However, there is still a lack of data supporting or disproving off-label use of HCQ in the specific population of critically ill patients, while safety concerns have been reported (5,12). Moreover, to our knowledge, no study has evaluated the potential benefits/harms of HCQ on medium-term outcomes. This is all the more important as a high proportion of critically ill COVID-19 patients remain hospitalized in ICU or even mechanically one month after admission with still a risk of poor outcome.

Therefore, we conducted a propensity-matched cohort analysis to determine the effect of HCQ on day-90 mortality of patients with COVID-19 admitted to ICU as compared to standard of care.

We present the following article in accordance with the STROBE reporting checklist (13) (available at http://dx.doi.org/10.21037/atm-20-7811).

Methods

This study was approved by our institutional ethics committee (Comité d'Ethique du CHU de Lyon), approval protocol number n°20-42, with a waiver for written inform consent because of the retrospective nature of the study. All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the 1964 Declaration of Helsinki and its later amendments. The methodology of this study was consistent with the STROBE statement for observational studies (13).

Study population

We retrospectively reviewed all adult patients with laboratory-confirmed COVID-19, admitted from 7 March 2020 to 7 April 2020, to 3 university-affiliated ICUs in Lyon, France. Those who stayed at least 24 hours in ICU and who received HCQ or no antiviral against SARS CoV-2 were included in this study. Follow-up continued until 5 July 2020. HCQ (loading dose of 400 mg twice daily at day 1 followed by 200 mg twice daily from day 2 to day 10) was prescribed at the discretion of the physician in charge, in accordance to national interim guidance on the management of critically ill patients with COVID-19 (14).

Data collection

For each patient, demographics, comorbidities, time from onset of COVID-19 symptoms to ICU admission, initial presentation of the disease (within 24 hours after ICU admission) including presence of acute respiratory distress syndrome (ARDS) in patients receiving invasive mechanical ventilation according to the Berlin criteria (15), Sequential Organ Failure Assessment score (16) (range, 0–24, with higher scores indicating more severe organ failures) calculated using the worst clinical and/or biological values from ICU admission to 24 hours later, organ dysfunctions as defined by a SOFA sub-score ≥1, and Simplified Acute Physiology Score II (17) (SAPS II; range, 0–164, with higher scores indicating greater severity of illness) were documented. Severity of hypoxemia at ICU admission was estimated with the ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen (PaO_2/FiO_2); in case of missing data (i.e., when arterial blood gas was not performed), the PaO_2/FiO_2 ratio was imputed from pulse oximetry and FiO_2, as previously described (18). Organ supports during the first 28 days after ICU admission were also collected.

Outcomes

The primary outcome was all-cause mortality at day-90 after ICU admission.

Statistical analysis

Continuous data are expressed as median (interquartile

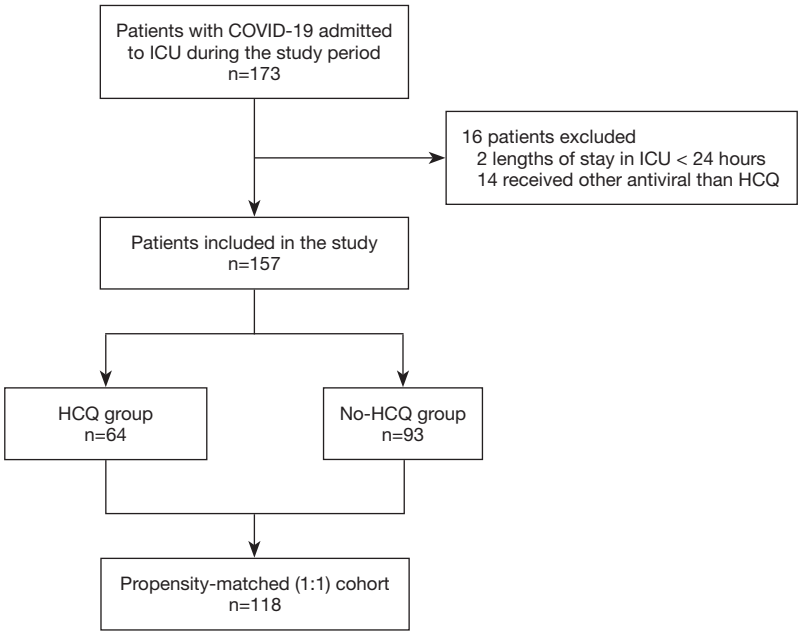

Figure 1 Study cohort. COVID-19, coronavirus disease 2019; ICU, intensive care unit; HCQ, hydroxychloroquine.

range) and qualitative data as number (proportion). Continuous and categorical variables were compared using Student's t test or Wilcoxon-Mann-Whitney test, and Chi^2 or Fisher's exact test, as appropriate. Logistic regression analysis was used to determine baseline factors independently associated with day-90 mortality.

Since patients were not randomly assigned to receive HCQ, propensity score matching (19) was used to compare similar patient population receiving or not HCQ. The sample size was determined by the number of eligible patients admitted to ICU during the study period. We compared groups by intention-to-treat analysis, regardless of the discontinuation of HCQ during follow-up. There was no imputation for missing data. Covariates presumed to be associated with both the decision of HCQ therapy and outcomes or unbalanced between groups were used to build the propensity score (i.e., age, sex, chronic renal and cardiac diseases, ARDS, duration of symptoms before admission and SOFA score). The nearest neighbor method with a caliper of 0.2 was applied to create a matched cohort of HCQ-treated and untreated patients.

Survival curves among propensity-matched patients were constructed using Kaplan Meier estimates with comparison between curves based on the log-rank test.

All statistical analyses were performed using R (version 3.3.3, R Foundation for Statistical Computing) software. Statistical significance was considered at 2-sided $P<0.05$.

Results

Of 173 patients with COVID-19 who were admitted to ICUs during the study period, 16 (9.2%) were excluded because ICU length of stay was less than 24 hours or because they received antivirals other than HCQ or HCQ before ICU admission (*Figure 1*). Thus, 157 patients [median age 67 years (interquartile range, 56–76 years); 105 men (66.8%)] were included in the analysis with no loss in follow-up. At admission, all patients presented with COVID-19-induced acute respiratory symptoms, including measured or imputed PaO_2/FiO_2 ratios <400 mmHg, and required oxygen supplementation. A large majority of them (125/157, 80%) were severely hypoxemic with PaO_2/FiO_2 ratio <200 mmHg. Among the 157 patients, 64 (40.8%) received HCQ for 10 days (4–10 days). HCQ treatment was prematurely stopped after 4 days (3–6 days) for 28 (43.8%) patients due to acute renal failure in 13 (20.3%) cases, QT interval prolongation in 10 (15.6%) cases or for preventing drug drug interaction in 5 (7.8%) cases. No long QT induced arrhythmia was recorded in HCQ treated patients.

Before matching, patients receiving HCQ were significantly younger, had less chronic heart disease, and lower SAPS II than patients not treated with HCQ (*Table 1*). Mortality at day 90

Table 1 Patients' characteristics and outcomes before and after matching on the propensity score for hydroxychloroquine therapy

Variables	Before matching			After matching		
	HCQ (n=64)	No-HCQ (n=93)	P	HCQ (n=59)	No-HCQ (n=59)	P
Demographics						
Age (years)	64 [53–70]	72 [61–79]	0.001	65 [53–72]	65 [56–73]	0.457
Male sex, n (%)	47 (73.4)	58 (62.4)	0.202	43 (72.9)	42 (71.2)	0.999
Body mass index ($kg.m^{-2}$)	27 [25–31]	27 [24–30]	0.319	28 [24–31]	28 [24–30]	0.500
Comorbidities, n (%)						
Hypertension	29 (45.3)	51 (54.8)	0.312	28 (47.5)	29 (49.2)	0.999
Diabetes	16 (25.0)	28 (30.1)	0.603	14 (23.7)	18 (30.5)	0.534
Chronic renal diseases	7 (10.9)	14 (15.1)	0.613	7 (11.9)	6 (10.2)	0.999
Chronic cardiac disease	3 (4.7)	20 (21.5)	0.007	3 (5.1)	2 (3.4)	0.999
Symptom duration before ICU admission (days)	7 [5–10]	8 [5–11]	0.423	7 [5–10]	8 [5–11]	0.443
Simplified Acute Physiology Score II (points)	33 [25–37]	35 [29–47]	0.044	35 [26–38]	32 [25–44]	0.974
Initial presentation						
ARDS, n (%)	28 (43.8)	37 (39.8)	0.741	26 (44.1)	26 (44.1)	0.999
Severity of ARDS, n (%)			0.116			0.071
Mild	0 (0.0)	3 (8.1)		0 (0.0)	3 (11.5)	
Moderate	15 (53.6)	24 (64.9)		14 (53.8)	17 (65.4)	
Severe	13 (46.4)	10 (27.0)		12 (46.2)	6 (23.1)	
Lowest PaO_2/FiO_2 (mmHg)[†]	142 [82–215]	141 [98–186]	0.661	142 [82–228]	143 [98–180]	0.580
Organ dysfunction[‡]						
Type, n (%)						
Respiratory	59 (92.2)	86 (92.2)	0.999	55 (93.2)	53 (89.8)	0.741
Cardiovascular	36 (56.2)	65 (69.9)	0.113	33 (55.9)	40 (67.8)	0.255
Neurological	12 (18.8)	21 (22.6)	0.704	11 (18.6)	12 (20.3)	0.999
Hematological	13 (20.3)	13 (14.0)	0.406	12 (20.3)	9 (15.3)	0.630
Renal	13 (20.3)	28 (30.1)	0.235	12 (22.0)	11 (18.6)	0.819
Hepatic	5 (7.8)	6 (6.5)	0.992	4 (6.8)	4 (6.8)	0.999
Number	2 [1–3]	2 [2–3]	0.229	2 [1–3]	2 [1.5–3]	0.805
SOFA score (points)	3 [2–7]	3 [3–7]	0.279	3 [2–7]	3 [2–6]	0.883
Organ support, n (%)						
Invasive mechanical ventilation	37 (57.8)	46 (49.5)	0.386	35 (59.3)	32 (54.2)	0.710
Vasoactive drugs	35 (54.7)	45 (48.4)	0.540	33 (55.9)	31 (52.5)	0.853
Renal replacement therapy	16 (25.0)	17 (18.3)	0.414	15 (25.4)	12 (20.3)	0.661

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Before matching			After matching		
	HCQ (n=64)	No-HCQ (n=93)	P	HCQ (n=59)	No-HCQ (n=59)	P
Outcomes						
Day-28 mortality, n (%)	15 (23.4)	22 (23.7)	0.999	13 (22.0)	10 (16.9)	0.642
Day-28 ventilation free days	6.5 [2–28]	16 [3–28]	0.396	5 [2–28]	13 [3–28]	0.357
Day-90 mortality, n (%)	23 (35.9)	28 (30.1)	0.553	21 (35.6)	14 (23.7)	0.227

Continuous values are expressed median (interquartile range). †, 5 values were missing (2 in the HCQ group and 3 in the No-HCQ group) within the first 48 hours; ‡, Organ dysfunction was defined as a SOFA sub-score ≥1. HCQ, hydroxychloroquine; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; PaO_2/FiO_2, ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen; SOFA, sequential organ failure assessment.

did not significantly differ between the 2 unmatched groups (35.9% in the HCQ group versus 30.1% in the No-HCQ group; P=0.553). Age, duration of symptoms before admission, SAPS II, ARDS, lowest PaO_2/FiO_2 ratio and renal failure within the first 24 hours after ICU admission, SOFA score at 24 hours after ICU admission and organ supports during ICU stay were significantly associated with day 90 mortality (*Table 2*). In multivariate analysis, age and SOFA score at day 1 were independently (P<0.01) associated with day-90 mortality (*Table 2*).

Propensity score matching patients treated with HCQ or not yielded 59 matched pairs with well-balanced baseline characteristics (*Table 1* and *Figure 2*). In this matched cohort, day-28 mortality and day-90 mortality were 22.0% and 35.6%, respectively, for patients who received HCQ versus 16.9% and 23.7% for patients who did not (*Table 1*). As reported in *Figure 3*, Kaplan-Meier survival analysis before and after matching showed no statistically significant association between HCQ therapy and mortality.

Discussion

This report presents new data regarding day-90 mortality of critically ill patients with COVID-19 and on the efficacy of HCQ for treating this specific population. In this study involving patients with COVID-19 requiring intensive care, off-label use of HCQ was not associated with any significant change in day-90 mortality as compared to standard of care, even after matching patients with similar characteristics.

To our knowledge, no previous study had specifically examined the effects of HCQ on clinically relevant medium-term outcomes in patients with the most severe presentations of COVID-19. The absence of benefits of HCQ reported herein is in line with previous well designed observational studies and randomized trials showing no improvement in survival in non critically ill patients receiving HCQ (6-10). The efficacy and safety of HCQ in the most severe patients who often require mechanical ventilation and receive multiple co medications but also benefit from close monitoring could not be extrapolated from these studies. Our study population comprising critically ill patients with a median age over 60 years with major comorbidities requiring organ support in more than half of cases, was quite similar to other unselected ICU cohorts in western countries (20-23). Propensity matching was unable to detect any benefit of HCQ on the day-90 mortality rate. It is difficult to compare the mortality observed in this work to other studies because data on medium-term survival in patients with COVID 19 are scarce. In most observational studies or randomized trials, the follow up did not exceed 28 days (6-11,20-23). At this timepoint, mortality in both groups was more than 10% lower than the one reported in the RECOVERY trial (11). Interestingly, we found that mortality increased by about 30% between day 28 and day 90. We should therefore be cautious when interpreting the short-term results of studies investigating drugs or intervention with the potential of modifying mortality in this specific population.

We did not record any excess of life threatening arrhythmia in HCQ-treated patients. This might partly be due to the close monitoring of drug-related cardiac adverse events in ICU and to the fact that HCQ was stopped preemptively for 43.8% of patients, mostly because of prolonged QT interval and renal failure. Nevertheless, high proportion of patients who could not receive the complete

Table 2 Patient characteristics according to day-90 mortality

Variable	Survivors (n=106)	Non-survivors (n=51)	Univariate analysis P	Multivariate analysis†, OR (95% CI)
Demographics				
Age (years)	64 [54–72]	76 [66–82]	<0.001	1.07 (1.03–1.12)
Male sex, n (%)	65 (61.3)	40 (78.4)	0.051	2.43 (1.02–6.14)
BMI ($kg.m^{-2}$)	27 [25–30]	27 [24–30]	0.271	
Comorbidities, n (%)				
Hypertension	52 (49.1)	28 (54.9)	0.606	
Diabetes	27 (25.5)	17 (33.3)	0.402	
Chronic renal diseases	9 (8.5)	12 (23.5)	0.019	1.45 (0.48–4.37)
Chronic cardiac disease	15 (14.2)	8 (15.7)	0.989	
Symptoms duration (days)	9 [6–12]	6 [4–8]	0.001	0.93 (0.84–1.03)
SAPS II	32 [24–38]	39 [34–50]	<0.001	
Initial presentation				
ARDS	35 (33.0)	30 (58.8)	0.004	
Severity of ARDS, n (%)			0.032	
Mild	3 (8.6)	0 (0.0)		
Moderate	24 (68.6)	15 (50.0)		
Severe	8 (22.9)	15 (50.0)		
Lowest PaO_2/FiO_2 (mmHg)	170 [119–205]	95 [66–129]	<0.001	
Organ dysfunction‡				
Type, n (%)				
Respiratory	94 (88.7)	51 (100.0)	0.029	
Cardiovascular	64 (60.4)	37 (72.5)	0.189	
Neurological	15 (14.2)	18 (35.3)	0.005	
Hematological	12 (11.3)	14 (27.5)	0.021	
Renal	18 (17.0)	23 (45.1)	<0.001	
Hepatic	5 (4.7)	6 (11.8)	0.198	
Number	2 [1–2]	3 [2–4]	<0.001	
SOFA score (points)	3 [2–6]	5 [3–8]	<0.001	1.21 (1.05–1.39)
Organ support, n (%)				
Invasive mechanical ventilation	46 (43.4)	37 (72.5)	0.001	
Vasoactive drugs	42 (39.6)	38 (74.5)	<0.001	
Renal replacement therapy	16 (15.1)	17 (33.3)	0.016	

†, SAPSII, ARDS, lowest PaO_2/FiO_2 and organ dysfunctions were not entered into the model because of collinearity with the SOFA score. ‡, Organ dysfunction was defined as a SOFA sub-score ≥1. Continuous values are expressed median (interquartile range). OR, odds ratio; CI, confidence intervals; BMI, body mass index; ICU, intensive care unit; SAPS II, simplified acute physiology score II; ARDS, acute respiratory distress syndrome; PaO_2/FiO_2, ratio of the arterial partial pressure of oxygen to the fractional inspired oxygen; SOFA, sequential organ failure assessment.

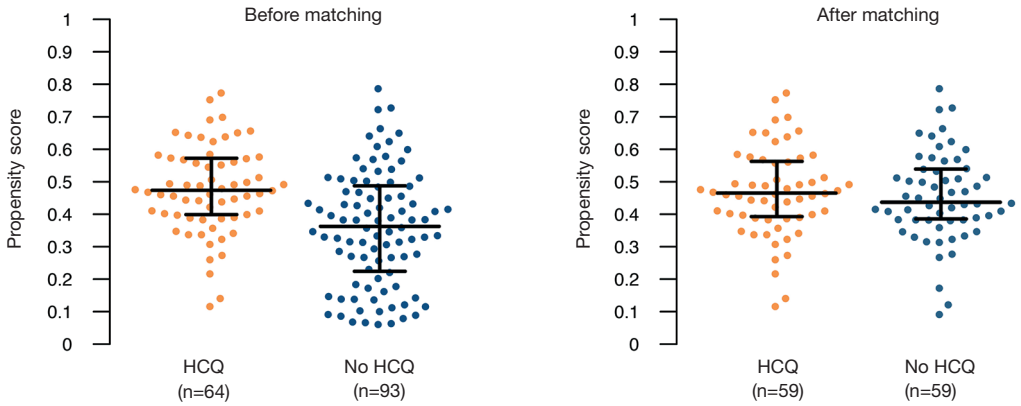

Figure 2 Individual propensity scores before and after matching. Individual propensity score values are shown for patients with COVID-19 treated with HCQ or No-HCQ before (left panel) and after (right panel) matching. Median and interquartile range of propensity scores are also presented. COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine.

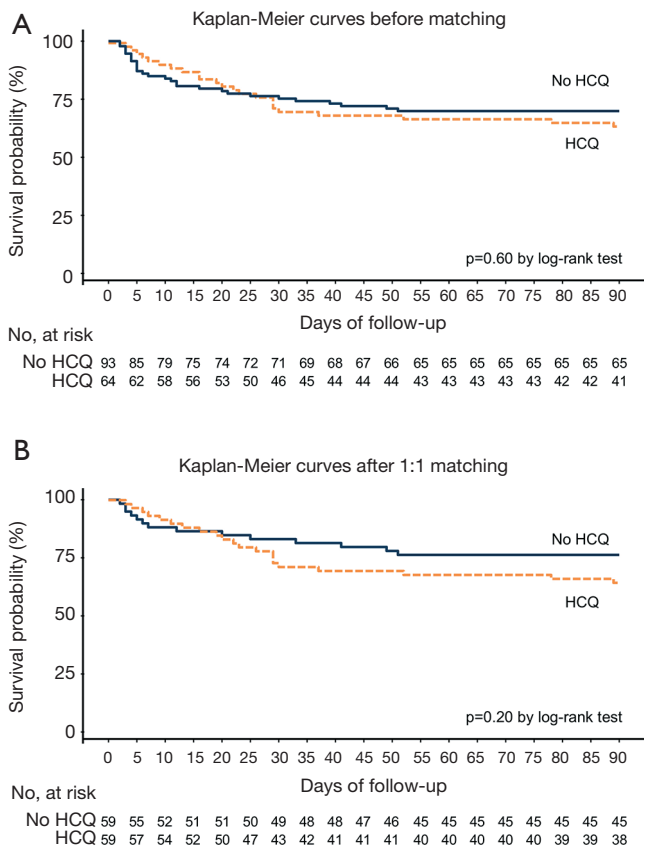

Figure 3 Kaplan-Meier survival curves of propensity score matched patients with COVID 19 treated or not with hydroxychloroquine. Kaplan-Meier curves are presented before (panel A) and after (panel B) matching patients receiving HCQ or standard of care (No HCQ). COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine.

treatment highlights difficulties in managing this therapy in ICU where contraindications and warning of use (e.g., acute renal failure) or the need for other therapy prolonging the QT interval, are frequent.

The study has several limitations. First, although we used propensity score matching to ensure comparability between study groups, potential unmeasured confounders could have biased our conclusion. Second, the small sample size could have led to underpowered analysis and did not allow subgroup analysis. Third, we cannot rule out that other HCQ regimen could have provided different results. Nevertheless, we used dose of HCQ and duration that have been determined as optimal for treating hospitalized patients with COVID-19 (24). Yet, the fact that HCQ had to be stopped prematurely in half of patients might limit the conclusions about its efficacy and/or toxicity in critically-ill patients. Fourth, the study was conducted in 3 French academic ICUs, which may limit its generalizability to other settings or countries, even if characteristics of our cohort were comparable to other cohorts from western countries (20-23).

Conclusions

In summary, among critically ill patients with COVID-19, off-label use of HCQ was not associated with any significant change in day-90 mortality when compared with standard of care, after matching patients to account for baseline differences. Our results suggest that HCQ should not be used to treat the most severe forms of the disease.

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Footnote

Reporting Checklist: Available at http://dx.doi.org/10.21037/atm-20-7811

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-7811

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7811). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved the institutional ethics committee of the CHU de Lyon, approval protocol number n°20-42, with a waiver for written inform consent because of the retrospective nature of the study.

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