

## Review Article

# Observational Study of the Effect of the Hydroxychloroquine/Azithromycin Combination in Patients Hospitalized for a Severe Form of COVID-19

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## Abstract

Following the demonstration in vitro of the efficiency of a synergistic effect of hydroxychloroquine (HCQ) associated with azithromycin (AZI) against the SARS-CoV-2, some studies have aimed to evaluate its efficiency in a clinical setting. We present the results of a non-randomized observational study of patients admitted for a severe form of COVID-19 disease who have been treated by HCQ/AZI after collegial physicians' decision. Of the 306 patients included (average age: 72.8 years), 53 received the HCQ/AZI association. Univariate analysis shows in non-survivors a higher average age, more severe clinical signs on admission (lung invasion rate > 50%, Dyspnea and creatinine > 133 μmol/L) and more comorbidities (cerebrovascular accident, chronic kidney disease, immunodeficiency). We evaluated the efficiency of the HCQ/AZI treatment on a population (n=96) with comparable characteristics (age, risk factor, gravity...). If mortality of the patients treated with HCQ/AZI seems different in this sub-study population (HCQ/AZI: 0% vs. Other: 8%), the methods of the study and its size do not allow the identification of a statistically significant difference (p=0.122).

At this time of the epidemic, the HCQ/AZI must be evaluated in a randomized trial at the right and safe dosage.

## What is Already Known about This Subject?

The discussion on the efficiency of the hydroxychloroquine/azithromycin combination remains open. To date, no randomized trial has demonstrated the efficiency of this combination in patients with a severe form of COVID-19.

## What This Study Adds?

We report the results of a non-randomized observational study compared hydroxychloroquine/azithromycin combination to any antiviral treatment for patients with a severe form of COVID-19. We warn of the difficulty of interpreting these results in the absence of randomization.

## Introduction

At the end of 2019, a new coronavirus, designated SARS-CoV-2, was causing an epidemic of respiratory diseases in China. The city of Wuhan (China) went into full confinement on January 23, 2020<sup>1</sup>. On March 12, 2020, the World Health Organization (WHO) declared the COVID-19 pandemic. The importance of the number of symptomatic patients and the particular gravity of some of them lead the Hospitals to reorganize in emergencies on an almost daily basis both at the structural, organizational and medical level. Among the antiviral treatments likely to be effective on the symptoms of SARS-CoV-2, three molecules or associations stood out: remdesivir, the fixed combination ritonavir/lopinavir and (hydroxy) chloroquine associated or not with azithromycin [1].

In mid-March, remdesivir and the ritonavir/lopinavir combination were announced as a complete disruption by the laboratories producing them. The French Ministry of Health then supervised the off-label use of hydroxychloroquine, conditioning it to severity criteria and subject to a collegial decision by the medical profession. We present the results of a monocentric, observational, retrospective study aimed at evaluating the efficiency of the hydroxychloroquine/azithromycin combination on the COVID-19 disease.

## Methods

All patients hospitalized at our center for a severe form of COVID-19 disease were included in the study. The diagnosis of COVID-19 disease combined the recording of symptoms (fever, cough, fatigue, myalgia, headache, dyspnea, diarrhea, nausea, vomiting, anorexia, anosmia, aguesia, dizziness, fall, hypoxemia) with a SARS-CoV-2 reverse-transcriptase-polymerase-chain-reaction (RT-PCR) and/or standard low dose CT imaging. The following characteristics were sought in the study population: age, body mass index (BMI), active or history of smoking, chronic kidney/heart/respiratory disease, hypertension, diabetes mellitus, dyslipidemia, cerebrovascular accident and immunodeficiency (including cancer under treatment). The home drugs treatment of interest were sought: angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) calcium-channel inhibitor, diuretics, betablockers, corticosteroids and aspirin. We have listed antivirals under evaluation: remdesivir, hydroxychloroquine (HCQ), azithromycin (AZI), ritonavir/lopinavir. The severity of the COVID-19 stage of the patients included was assessed on the basis of at least one of the following criteria: dyspnea, O<sub>2</sub> saturation  $\leq 93\%$ , radiological pulmonary infiltrates  $>50\%$  at 24-48 hours of admission [2].

## HCQ/AZI

The dosage of HCQ/AZI was: HCQ (D1-D10; 600mg per day in 3 doses) combined with azithromycin (D1: 500mg in 1 dose; D2-D5: 250mg per day). Only patients not on dialysis, with no contraindication to HCQ/AZI treatment (e.g. severe kidney failure, widening of the QTc wave) received treatment with HCQ/AZI after collegial physician decision. All patients on HCQ/AZI underwent an electrocardiogram before initiating treatment. Once treatment was started, an electrocardiogram was performed daily during hospitalization, as

well as a determination of serum potassium, magnesemia and blood sugar. In order to reduce the biases linked to the care of patients, to the comorbidities, to the typology of the medical service (e.g. palliative care, geriatrics) and to the contraindication of HCQ/AZI treatment (dialysis), we have made a sub-study. In this sub-study only patients treated in internal medicine were included and we have excluded dialysis patients.

## Clinical Outcomes

Critical disease defined by death or transfer to intensive care unit (ICU) and death alone were the two main outcomes.

## Statistical Analysis

Continuous data are summarized as mean (standard deviation) and categorical data as frequency (percentage). For univariate comparisons T-test and Chi-2 tests were used as appropriate to compare differences between non-critical and critical disease or survivor and non-survivor. The multivariate analysis used logistic regression adjusted on age, sex, body mass index (BMI), chronic heart disease, hypertension, diabetes mellitus, chronic kidney disease, hemodialysis, chronic lung disease (asthma or chronic obstructive lung disease), personal history of stroke, current or former tobacco use, treatment with immunosuppressive drugs (including anticancer drugs), creatine and C-reactive protein (CRP) levels, percentage of lung affected on CT-scan, low oxygen saturation, dyspnea, oxygen flow. A two-sided p value  $< 0.05$  was considered statistically significant. Statistical analyses were performed with SPSS 26.0 package. Neither patients nor the public were involved in the conception or conduct of the study.

## Results

Between March 15 and April 15, 2020, 314 patients were admitted into the different wards. Eight patients were transferred to another hospital and were considered loss of follow-up: 6 were transferred to another region to vacant intensive care beds and 2 were taken care of for extracorporeal membrane oxygenation. The median age was  $75.6 \pm 14.5$  years. The number of days between the onset of symptoms and hospitalization was  $6.6 \pm 7.8$  days. Men were a little more represented (54%).

## Comorbidities

Table 1 shows major comorbidities recorded on admission. The most common were chronic heart disease (71%), hypertension (58%), dyslipidemia (36%), chronic kidney disease (27%), diabetes mellitus (26%), immunodeficiency (21%) and chronic respiratory disease (19%). Eighty nine percent of the patients have comorbidity with an average number of comorbidities of  $4.1 \pm 2.3$ . Three per cent (8/306) of patients were current smokers and 10% were former smokers. It can be noted that 26% of patients have a BMI  $> 30\text{kg/m}^2$ .

## Home Drug Treatments

Home drug treatments included beta-blockers (31%), aspirin (30%), diuretics (27%), calcium channel blockers (23%), ARBs (22%), ACE inhibitors (20%) and corticosteroids (5%). No patient was treated by non-steroidal anti-inflammatory drugs (Table 1).

**Table 1:** Demographic findings of patients on admission.

Demographic data	Total (N=306)	Survivor (N=231)	Non-survivor (N=75)	p-value *
Age – yr	75.6 ± 14.5	72.8 ± 14.7	84.0 ± 9.9	<0.0001
Sex (male sex)	54%	55%	49%	0.394
Weight (kg)	74.8 ± 15.8	76.3 ± 15.7	70.2 ± 15.4	0.007
Body mass index (kg/m <sup>2</sup> )	26.8 ± 5.0	27.2 ± 5.0	25.6 ± 4.9	0.03
BMI<25 kg/m <sup>2</sup> (%)	59%	61%	50%	0.11
BMI 25–29.9 kg/m <sup>2</sup> (%)	32%	34%	28%	0.396
BMI≥30 kg/m <sup>2</sup> (%)	26%	27%	22%	0.376
Nursing home resident (%)	13%	10%	23%	0.003
<b>Severity and mortality</b>				
Death (%)	25%	0%	100%	-
ICU transfer (%)	3%	3%	3%	0.871
Critical cases (Death or transfer to ICU) (%)	27%	3%	100%	<0.0001
Time from symptom onset to admission (days)	6.6 ± 7.8	7.2 ± 7.5	4.5 ± 8.5	0.013
Length of stay in hospital (days)	11.3 ± 10.0	12.2 ± 9.4	8.5 ± 11.3	0.005
Time between admission and ICU transfer (days)	1.1 ± 1.7	1.2 ± 1.7	1.0 ± 1.9	0.802
<b>Comorbidities (%)</b>				
Hypertension	58%	55%	67%	0.065
Diabetes mellitus	26%	27%	25%	0.797
Chronic heart disease	71%	67%	84%	0.005
Dyslipemia	36%	33%	44%	0.094
Chronic respiratory disease	19%	20%	15%	0.276
Chronic kidney disease	27%	23%	43%	0.001
Dialysis	4%	3%	7%	0.232
Immunodeficiency	21%	16%	36%	<0.0001
Cerebrovascular accident	20%	16%	32%	0.002
At least one comorbidity	89%	87%	97%	0.009
<b>Smoking status (%)</b>				
Current smoker	3%	3%	1%	0.424
Former smoker	10%	9%	15%	0.134
<b>Home drug treatments (%)</b>				
ACE inhibitors	20%	19%	24%	0.31
ARBs	22%	22%	21%	0.955
Calcium-channel inhibitor	23%	22%	24%	0.729
Diuretics	27%	22%	44%	<0.0001
Betablockers	31%	27%	44%	0.007
Corticosteroids	5%	3%	11%	0.008
Aspirin	30%	25%	45%	0.001

\*p-value univariate statistical test between Survivor VS Non-Survivor. - : statistical test non applicable.

### Severity of the Clinical Case

At the admission, 43% of the patients presented a C-reactive protein >100mg/L, 43% an oxygen saturation ≤93%, 21% a creatinine >133µmol/L and 7% of the patient presented a proportion of lung

**Table 2:** Clinical, laboratory and radiographic findings of patients on admission.

Symptoms at onset of illness (%)	Total (N=306)	Survivor (N=231)	Non-survivor (N=75)	p-value*
Fever	60%	62%	55%	0.266
Cough	51%	52%	51%	0.898
Fatigue	59%	58%	60%	0.812
Myalgia	18%	20%	11%	0.058
Headache	8%	9%	4%	0.184
Dyspnea	67%	64%	77%	0.028
Diarrhea	30%	33%	21%	0.058
Nausea or vomiting	9%	11%	1%	0.008
Anorexia	11%	12%	11%	0.809
Anosmia or ageusia	6%	7%	1%	0.054
Dizziness. fall	17%	16%	19%	0.657
Hypoxemia (oxygen saturation < 93%)	43%	40%	55%	0.024
<b>Inpatient drug treatments (%)</b>				
Hydroxychloroquine with azithromycin	17%	22%	4%	<0.0001
Hydroxychloroquine alone	2%	1%	3%	0.417
Azithromycin alone	4%	5%	1%	0.184
Lopinavir with Ritonavir	4%	4%	5%	0.593
Oxygen therapy	87%	86%	91%	0.269
Invasive ventilation	9%	9%	9%	0.858
<b>Laboratory findings</b>				
PCR confirmed diagnosis (%) n=213	79%	75%	90%	0.023
C-reactive protein (mg/L)	101.2 ± 83.6	95.9 ± 83.5	118.0 ± 82.3	0.05
CRP<5 mg/L (%)	5%	6%	1%	0.108
CRP<100 mg/L (%)	57%	60%	47%	0.051
CRP 100–199 mg/L (%)	28%	25%	36%	0.075
CRP≥200 mg/L (%)	15%	14%	17%	0.64
Creatinine (µmol/L)	115.7 ± 110.4	103.6 ± 93.2	154.6 ± 147.6	0.001
Creatinine ≥ 133µmol/L (%)	21%	17%	33%	0.003
<b>Radiologic findings (n=250)</b>				
Percentage of lung affected on the CT scan (%)	29 ± 18	28 ± 17	31 ± 22	0.253
Proportion of lung affected on the CT scan > 50% (%)	7%	5%	14%	0.028
Typical CT-scan (%)	14%	15%	7%	0.125
Bilateral pulmonary infiltration (%)	46%	48%	36%	0.120
Ground-glass opacities (%)	29%	33%	14%	0.008

invasion rate>50% (average percentage of invasion: 29% ± 18) (Table 2). Among the 306 patients eligible for analysis, 250 had a lung CT scan and 213 a RT-PCR.

### Symptoms

The most common symptoms were dyspnea (67%), fever (60%), fatigue (59%), cough (51%), diarrhea (30%), myalgia (18%) and dizziness/fall (17%). Only 6% of patients reported ageusia/anosmia on admission (Table 2).

### Analysis of Non-survivors as Compared with Survivors

Tables 1 and 2 show the distribution of demographic characteristics and coexisting conditions among survivors and non-survivors. Non-survivors were older ( $p < 0.0001$ ) and had a greater prevalence of chronic heart disease ( $p = 0.005$ ), cerebrovascular accident ( $p = 0.002$ ), chronic kidney disease ( $p = 0.001$ ), and immunodeficiency ( $p < 0.0001$ ). Among medication, aspirin ( $p = 0.001$ ), corticosteroids ( $p = 0.008$ ), betablockers ( $p = 0.007$ ) and diuretics ( $p < 0.0001$ ) were more commonly used by non-survivor patients. The non-survivors were faster hospitalized after the first symptoms ( $4.5 \pm 8.5$  days vs.  $7.2 \pm 7.5$  days). Among non-survivors mortality rate was of 25% and transfer to ICU was of 3%. Laboratory and radiologic findings for non-survivors reveal fewer signs at admission of renal dysfunction (creatinine  $\geq 133 \mu\text{mol/L}$ ;  $p < 0.003$ ) and lung invasion rate ( $> 50\%$ ;  $p < 0.028$ ). The multivariate analysis of factors associated with non-survival reveals that increasing age was a strong predictor of in hospital mortality after adjusting for major comorbidity (per additional year, OR 1.083;  $p = 0.003$ ) (Figure 1). Stroke history (OR: 2.983;  $p = 0.027$ ), immunodeficiency (OR: 4.665;  $p = 0.002$ ) and percentage of the lung affected on the CT scan were also statistically associated with increased hospital mortality (OR: 1.032 per additional percent of lung affected;  $p = 0.009$ ). The other factors don't show a significant implication on the patient outcomes.

### Antiviral Treatment

Fifty-three patients received the HCQ/AZI association, 13 the lopinavir/ritonavir association, 12 azithromycin alone and 5 HCQ alone. The HCQ/AZI have been administered an average of  $7.9 \pm 3.1$  days of treatment. Among 16 patients who did not receive the 10 days of treatment, the causes were: transfer to ICU ( $N = 6$ ), widening of the QTc wave ( $N = 6$ ; occurring between 1 and 8 days after initiation of treatment), renal failure ( $N = 1$ ), death ( $N = 2$ ; after 1 and 3 days of treatment), pseudo-cerebellar syndrome attributed to viral damage combined with HCQ ( $N = 1$ ). The patients treated by HCQ/AZI had

severe form of COVID-19 (9% of lung affected on CT-scan), were younger patient (13 years) and tend to have more comorbidities except diabetes and immunodeficiency. Percentage of lung affected on CT-scan was the only variable statistically associated with death or ICU transfer (OR: 1.033 [1.002-1.064],  $p = 0.039$ ) among patients admitted into the two internal medicine ward where HCQ-AZI were used. The sub-study ( $N = 96$ ) which evaluate the efficacy of treatment with HCQ/AZI for the patients admitted into the two internal medicine units included 96 patients. There was no significant difference in demographic, comorbidities, smoking status, home drug treatment and laboratory/radiologic findings between the treated and untreated population. If the mortality of patients treated with HCQ/AZI seems different, this result is not statistically significant (0% vs. 8%;  $p = 0.122$ ).

### Discussion

The COVID-19 situation worldwide, as of 1 July 2020 based on the data transmitted by the different countries is 10 446 353 cases of COVID-19 including 511 037 deaths [1]. If the number of new cases seems to decrease in Europe, the world wide situation continues to worsen. The average incubation period for COVID-19 is 5 days [3]. The interval from symptom onset the hospital admission is 6, days in our study. The average age of patients in our study (75.6 years) is higher than the studies currently published (47-73 years) with a male preponderance<sup>3</sup>. The clinical manifestation of COVID-19 is various. We found standard symptoms in hospitalized patients included: dyspnea, fever, asthenia, cough, diarrhea, muscle ach and dizziness/fall. Anosmia ageusia may be identified in only 6% of patients. If comorbidities presented by 89% of our patients are among the most common (hypertension, diabetes mellitus), they are present in a remarkably high rate of our patients (chronic heart disease  $> 70\%$ , chronic kidney disease  $> 25\%$ , immunodeficiency  $> 20\%$ ) [4,5]. Obesity seems to play a special role affecting more than 25% of our patients. Obesity or excess ectopic fat deposition are suspected of unifying

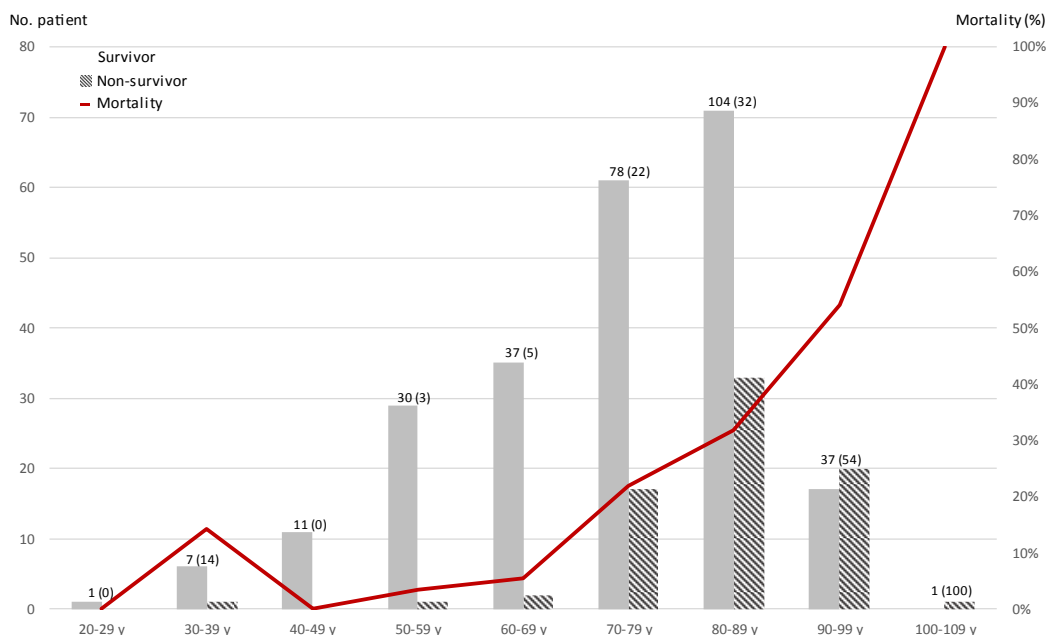


Figure 1: Mortality by age.



risk factor for severe COVID-19 infection, reducing both protective cardiorespiratory reserve as well as potentiating the immune dysregulation that appears, at least in part, to mediate the progression to critical illness and organ failure in a proportion of COVID-19 patients [6]. However, it should be noted that it does not appear as a factor of death. Concerning the long-term treatments taken by the patient, the patients treated with aspirin, diuretics, betablockers or corticoids are significantly higher in the non-survivor group. But, it is difficult to attribute excess mortality to these treatments, since they are generally used to manage the comorbidity previously mentioned. The search for a predictive sign of worsening of a patient's condition at admission is a major issue in medical management. There is an excess mortality in patients more older (Figure 1), patients who on admission have dyspnea, oxygen saturation  $\leq 93\%$ , a lung invasion rate  $> 50\%$  or a creatinine  $> 133 \mu\text{mol/L}$ . These elements are warning signs for the physician supported by other publications on the subject [7]. On the other hand, on the advanced side on antiviral treatment, there has been no notable progress to date. Among the treatments discussed, remdesivir, the ritonavir/lopinavir and HCQ/AZI combination were the first treatments offered in France. For reasons essentially of availability, hydroxychloroquine associated or not with azithromycin has become one of the only therapeutic options in the absence of any evidence of effectiveness. Gautret *et al.* published the first result of the HCQ/AZI efficiency in COVID-19 patients [8]. They demonstrated on a series of 80 patients an undetectability of viral load at the nasopharyngeal level in 83% of patients on day 7, 93% on day 8 [9]. Respiratory samples are negative in 97.5% of patients on day 5. However, patients in this study had a low rate of comorbidity for an average age of 52.5 years. They do not appear to be the most at risk of complications given the current state of knowledge. Thus, only 53.8% (43/80) had a CT-scanner lung disease and 15% (12/80) had oxygen need. This population appears to have a relatively mild impairment compared to our study population. In agreement with the relative viral RNA load reduction, *in vitro* tests show a cytopathic effect of SARS-CoV2 could be observed in only 16% (5/31) wells at 60 h post infection after HCQ/AZI exposition as compared to 100% (13/13) in positive controls [9]. Rosenberg *et al.* publish an observational study to report adverse events and mortality of HCQ and/or azithromycin among patients with COVID-19 (Number of patient: 735 with HCQ/AZI, 271 with HCQ, 211 with azithromycin, 221 any treatment – similar age: 61.4 to 65.5 average) [10]. Cardiac arrest was more frequent in patients who received HCQ with azithromycin, compared with patients who received neither drug, even after adjustment. Moreover, treatment with HCQ, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. Mahevas *et al.* report a study carried out on 181 patients requiring oxygen therapy excluding patients transferred to ICU [11]. In their study, 15 patients were treated with the HCQ/AZI combination, none were transferred to ICU and none died.

The treatment of patients was done according to modalities (collegial doctor's decision) and within deadlines close to ours (7 days after the onset of symptoms). The mortality reported in this study is lower than ours. This can be attributed to the exclusion of patients without ICU need and the average age of the population (60 years vs.

75 years), even if the predictors of aggravation are relatively similar (CRP, percentage of pulmonary invasion). Interestingly, the authors put into perspective the importance of treatment with an antiviral during the virus contamination phase. However, HCQ exhibits immunomodulatory properties through its action on interleukin 1, 2 and 6, TNF $\alpha$  and the inhibition of toll-like receptors. This explains its effectiveness in certain autoimmune pathologies which in the case of the inflammatory storm identified in certain forms of COVID-19 could be of theoretical interest. Nevertheless, the latest published clinical data, consistent with our series, point out that during the inflammatory phase (usually on the second week of symptoms) this treatment should have any effectiveness. Side effects, particularly of the heart, in patients with fragility induced by viral infection remain a warning point for physician using the HCQ/AZI combination. In our cohort of treated patients 11.3% (6/53) had heart rhythm problems. As rhythm disturbances were not systematically sought in the untreated group, it is difficult to conclude on an increase in disorders due to COVID-19 disease or to antiviral treatment. A study of 201 patients demonstrated that Baseline QTc intervals did not differ between patients treated with chloroquine/HCQ (monotherapy group) vs. those treated with combination group (chloroquine/HCQ and azithromycin) ( $440.6 \pm 24.9 \text{ ms}$  vs.  $439.9 \pm 24.7 \text{ ms}$ ,  $p = 0.834$ ) [12]. More recently Mehra *et al.* presented a multinational registry analysis carried out on the largest population studied to date (96 032 patients; mean age  $53.6 \pm 17.6$ ; oxygen saturation  $< 94\%$ ; 19.9% of non-survivors patient) [13]. This article which seemed to make everyone agree was retracted a few days after its publication by its authors. However we should note that the authors reported an excess mortality in patients treated with combination of HCQ (main dosage  $587 \text{ mg} \pm 128 \text{ mg}$  during  $4.3 \pm 2.0$  days) with a macrolide (azithromycin or clarithromycin; dosage not communicated) as well as a *de-novo* ventricular arrhythmia in 8.1% of patients treated (versus 0.3% of untreated patients). We find a similar percentage of ventricular rhythm disorders (11.3% vs. 8.1%) in our patients with a more advanced age (75 years vs. 54 years), a comorbidity rate, predictors of severity and duration longer treatment (7.9 vs. 4.3 days). However, we did not find an increase in the mortality of patients treated with the HCQ/AZI combination. In view of these various elements, it remains necessary to remain cautious. The need for QT interval monitoring remains necessary. We draw attention to the difficulty to interpret the results of a non-randomized observational study. Indeed, in the absence of randomization, the mortality comparison data in the group treated by HCQ/AZI and the group not treated are impacted by many biases. Thus, if mortality seems different in the total study population (HCQ/AZI: 6% vs. Other: 28%) and in the sub-study population (HCQ/AZI: 0% vs. Other 8%), it is distorted by populations that are not comparable (age, risk factor) and different treatment methods desired or not by physicians. We no longer observe any significant difference after identifying and taking into account the biases inherent in this type of study. As a conclusion, the question of the efficiency and safety of the HCQ/AZI combination in the treatment of COVID-19 disease remains open pending the results of randomized clinical studies (Figure 1 and Tables 1-3).

**Table 3:** Multivariate analysis of factors associated with death.

Demographic data	Adjusted OR (CI 95%)	p-value**
Age – yr	1.083(1.028-1.142)	<b>0.003</b>
Sex (male sex)	0.52 (0.216-1.25)	0.144
Body mass index (kg/m <sup>2</sup> )	0.971 (0.886-1.063)	0.518
Nursing home resident	1.758 (0.457-6.757)	0.411
<b>Comorbidities</b>		
Hypertension	1.923 (0.758-4.881)	0.169
Diabetes mellitus	0.566(0.201-1.591)	0.281
Chronic heart disease	1.032 (0.34-3.129)	0.955
Chronic respiratory disease	0.759 (0.274-2.103)	0.595
Dialysis	2.045 (0.295-14.149)	0.469
Immunodeficiency	4.665 (1.73-12.58)	<b>0.002</b>
Cerebrovascular accident	2.983 (1.13-7.875)	<b>0.027</b>
<b>Smoking status</b>		
Current smoker	3.564 (0.31-40.92)	0.307
Former smoker	1.448 (0.389-5.393)	0.581
<b>Symptoms at onset of illness</b>		
Dyspnea	1.332 (0.521-3.406)	0.549
Hypoxemia (oxygen saturation < 93%)	0.936 (0.383-2.284)	0.884
<b>Laboratory findings</b>		
Creatinine (μmol/L)	1.002 (0.999-1.006)	0.182
<b>Radiologic findings</b>		
Percentage of lung affected on the CT scan (%)	1.032 (1.008-1.057)	<b>0.009</b>

## Conflict of Interest

The authors declare they have no conflict of interest.

## Ethics Approval

The study has been approved by the ethics committee of the Groupe Hospitalier Saint Vincent (GRE 2020-01). Written informed consent has been waived in light of the urgent need to collect clinical data.

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