Title: Adjusting series of patients for trial comparisons for COVID-19 treatments

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Key words: COVID-19; Treatment comparison; Hydroxychloroquine; Azithromycin; Remdesivir; Lopinavir-Ritonavir

Abstract :

Background: SARS-COV-2 has emerged and spread around the world since December 2019. Studies initiated in Marseille by our hospital centre have suggested significant clinical effectiveness of treatment by combining hydroxychloroquine and azithromycin (HCQ+AZ). However, due to the urgency of responding to the pandemic, they were not obtained through randomized controlled trials. Alternative assessment methods are therefore needed.

Methods: We compared our data in silico with those published by two studies comparing other antiviral drugs. For this purpose, random sampling was performed in our cohort to obtain similar groups for disease severity, gender, age and comorbidities associated with chronic diseases with patients included in the remdesivir and lopinavir-ritonavir trials.

Findings: Dual HCQ+AZ therapy was associated with 3 times fewer deaths than similar groups treated either with lopinavir-ritonavir (9% vs 20%, p-value = 0·03) or standard care (8% vs 25·2%, p-value = 0·001). Compared with patients included in the remdesivir study by Wang et al., we also showed a significant difference in the clinical outcome (proportion of cured patients with negative viral load) in favour of HCQ+AZ (77.8% versus 58·2% p = 0·0001).

Interpretation: Although comparison of HCQ+AZ with other antiviral drugs has limitations due to aggregated data, this study provides additional evidence showing that HCQ+AZ should be the systematic treatment of choice after diagnosis of COVID-19-positive cases.

Funding: This work was supported by the French Government under the "Investments for the Future" programme managed by the National Agency for Research (ANR), Méditerranée-

Infection 10-IAHU-03, and was also supported by Région Provence Alpes Côte d'Azur and European funding FEDER PRIMMI (Fonds Européen de Développement Régional - Plateformes de Recherche et d'Innovation Mutualisées Méditerranée Infection).

Research in context

Evidence before this study

Several clinical trials have attempted to demonstrate the efficacy of treatment against COVID-19. The ineffectiveness of lopinavir-ritonavir has been demonstrated in two studies: one against standard care and the second against chloroquine, which is preferable for better recovery and faster recovery of respiratory function. Remdesivir has also been studied. A first study used this treatment in a compassionate context, but no control group was used, which did not allow us to conclude on the true effectiveness of this treatment. A new study found that there were no differences between the remdesivir and placebo groups used. Our institution studied the combination of hydroxychloroquine and azithromycin on COVID-19. However, we were criticized for not comparing to a placebo group or to a group receiving standard care.

Added value of this study

In the current COVID-19 pandemic context, finding treatment is a priority. To demonstrate the effectiveness of a treatment, randomized controlled clinical trials are the gold standard but are long and difficult to set up. This pandemic requires us to be quick in finding a treatment but also to question from an ethical point of view the use of a placebo group in the middle of a terrifying outbreak. The subsequent comparison of several arms treated in different ways but with the same scientific rigor by adjusting for the risk factors involved in the evolution of the disease allows us to discuss the effectiveness of one treatment compared to another.

Implications of all the available evidence

The comparison between our cohort treated with hydroxychloroquine and azithromycin dual therapy versus the other arms in the articles provides additional evidence in favour of using HDQ+AZ as the systematic treatment of choice immediately after diagnosis of a confirmed positive COVID-19 case.

Introduction

In December 2019, a new coronavirus subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in the Wuhan region of China and rapidly spread throughout the world, reaching pandemic status in early March 2020. The question of a treatment for this agent has rapidly become the subject of a multitude of research projects around the world, both in vitro and in clinical trials. A first paper reported the susceptibility to chloroquine and remdesivir on COVID-19 [1]. Then, recommendations issued by Chinese officials reported on the efficiency of chloroquine in 100 patients [2]. As we have considerable experience in the use of hydroxychloroquine (HCQ), derived from chloroquine, in the treatment of Q fever and Whipple's disease [3,4], a first study was conducted in our institute based in Marseille (southeastern France) [5]. It was found that a comparison group of patients hospitalized in another southern French city (Nice) remained carriers of the virus longer than those taking HCQ and that the addition of azithromycin (AZ) had an even more significant effect. Such a combination was also found to be effective in vitro on COVID19 [6]. The results were so significant in a very short period of time and with a small number of patients (26) that under these conditions, in accordance with the usual ethical rules, the trial was stopped because the end point, i.e., viral clearance, had been reached. In the context of a health care crisis, we considered that it was unethical not to prescribe the best treatment

available in standard care. A second observational study with a larger number of COVID-19 patients reinforced these initial results [7]. A third study conducted by our team also reported that HCQ+AZ was associated with low mortality compared to published series [8].

However, an obvious limitation of our results comes from the absence of a controlled comparison of those treated with dual therapy to a placebo group or to patients receiving standard care. To evaluate our treatment from our current cohort, we performed a review of published studies and decided to perform a case-control type comparison with data published in the literature and include either competing treatments for HCQ+AZ or a placebo. The aim of this study is therefore to construct and compare a group treated with HCQ+AZ dual therapy randomly selected from the Marseille cohort of nearly 3,000 patients to date and groups of patients included in two studies comparing remdesivir and lopinavir - ritonavir to placebo controls [9,10]. The individual patient data of Cao's study were requested in order to perform individual-by-individual matching, but we were not able to obtain these data. For that reason, we then selected groups of patients from our cohort to make them similar to those included in these two trials using the aggregated information about patients included in these two trials that we had at our disposal, i.e., disease severity at initiation of treatment, gender, age and comorbidities.

Materials and methods

The process flow of this study is described in Figure 1.

Publications reviewed

The purpose of this study is to compare our cohort treated with hydroxychloroquine + azithromycin (HCQ+AZ) dual therapy to groups of patients included in trials discussing the efficacy of alternative antiviral treatments for COVID-19. The selection of these publications

was based on the existence of a group of a minimum 70-positive COVID-19 patients treated with one of the following two treatments: remdesivir and lopinavir-ritonavir or controlled by standard care or placebo. Two publications were selected: the study by Cao et al., where the efficacy of lopinavir-ritonavir was evaluated, and the article by Wang et al., which compared one remdesivir arm to a placebo arm [9,10]. The quality of these two studies was also analysed.

Extraction of information from articles

To build a comparable sample from our cohort treated with HCQ+AZ dual therapy, different parameters were searched in the selected publications.

First, to obtain comparable populations at initiation of treatment, patient demographic and clinical characteristics were identified: the number of patients in each group included in the trial (both cases and controls), the median age and its interquartile range, the sex ratio (male/female), the number of patients with chronic diseases (diabetes, hypertension, brain diseases, cancer or other) and the severity of COVID-19 at inclusion. In the 2 analysed publications, disease severity was defined according to oxygen supplementation and the type of ventilation used: ambient air, low or high flow oxygen, high flow nasal canula for oxygen therapy (HFNC), non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

In a second step, to evaluate the effectiveness of HCQ+AZ dual therapy compared to the other two treatments, the number of deaths, the median length of hospitalization (1st quartile - 3rd quartile) and the median duration of oxygenation were used for each publication. The median time from treatment to death and the number of patients discharged from the hospital were also reported by Wang et al. and the number of patients who died before 10 days in the Wang et al. study and before 12 days in the Cao et al. study.

Construction of our groups treated by HCQ+AZ from the 3,000-patient cohort

Our observational cohort treated at HCQ+AZ has included nearly 3,000 patients since March 3, 2020 at IHU Méditerranée Infection. The majority of these patients were followed on an outpatient basis; however, 1/3 of this cohort was hospitalized. In view of the large number of patients followed and having heterogeneous clinical and demographic profiles, we could not directly compare our cohort to the groups presented in the articles. A sampling step based on precise criteria was therefore necessary. To evaluate the efficacy of HCQ+AZ treatment and have it be comparable, only 472 hospitalized patients were sampled for this analysis. For these patients, HCQ and AZ were given within 48 hours of each other. The first sampling criterion is based on the disease severity, defined according to the type of ventilation used: not supplemental oxygen, supplemental oxygen, HFNC, non-invasive mechanical ventilation, invasive mechanical ventilation or ECMO. The second sampling criterion is based on the sex ratio. Finally, a group comparability test was performed by comparing the median age and the number of patients with chronic diseases, including hypertension, diabetes, brain disease or cancer.

The sampling process was created using R software (version 3.1.3) [11]. A bootstrap of 1,000 iterations was performed as soon as a random draw was made to increase robustness.

Statistical analysis

The statistical analyses were performed with the OpenEpi website (https://www.openepi.com/TwobyTwo/TwobyTwo.htm?fbclid=IwAR0NjbfgL6G7d77LiFSYTzdJAbK3YIPaYi2ZDFEeCnhFqbHFuMfibs1jaWI). A chi-square test or Fisher's exact test was used to compare the groups, depending on the data.

Results

Remdesivir

The article by Wang et al. discussed the efficacy of remdesivir (200 mg intravenously on day 1, then 100 mg daily for the next 9 days) on COVID-19. One hundred fifty-eight patients were included in this cohort with a median age of 66 years (1st quartile = 57 and 3rd quartile = 73) (Table 1). Eighty-nine were male (56%). Forty (25%) had diabetes, and 72 (46%) had hypertension (HTA) [10].

A random draw according to ventilation type and gender was conducted on our inpatient cohort (Supplementary data S1). To match the deceased patient in the study at baseline, we selected a deceased man who had ECMO. Twenty-eight patients (9 females and 19 males) who were in the intensive care unit (ICU) but had received a type of ventilation other than ECMO or invasive mechanical ventilation were sampled to match the "HFNC or non-invasive mechanical ventilation" subgroup. Sixty-nine men and 60 women were sampled from the "Supplemental oxygen" subgroup.

No significant differences in demographic and clinical characteristics were found between the remdesivir group and the HCQ+AZ group. The two groups were thus strictly comparable at baseline. There were no significant differences in death between the two treatments. Sixteen patients (10%) died in the HCQ+AZ group versus 22 (14%) in the remdesivir group (p-value = 0·30) (Table 1). However, more patients left the hospital cured following HCQ+AZ treatment (123 (78%) versus 92 (58%), p-value = 0·0001). The median hospital stay length and median oxygenation duration were shorter.

Lopinavir-ritonavir

Lopinavir-ritonavir was randomly assigned to 99 patients in the article by Cao et al [9]. The median age of this group was 58 years (1st quartile = 50 and 3rd quartile = 68), and 61 (62%)

were male (Table 2). Ten (10%) patients had diabetes, 5 (5%) patients had HTA, and 5 (5%) patients had cancer.

To construct a comparable HCQ+AZ group to this baseline population, a first random draw of 11 patients was performed in the "Ambient air" subgroup (corresponding to the "not requiring supplemental oxygen" subgroup in the article) (Supplementary data S2). To respect the sex ratio of 62%, 6 men and 5 women were sampled in this subgroup. Seventy-two (45 males and 27 females) of our inpatients were sampled to form our "Supplemental oxygen" subgroup. To match the “HFNC or non-invasive ventilation” subgroup, a sampling of 15 patients was performed in the “ICU – other types of ventilation” subgroup. One patient (male) was randomly selected from the "Invasive mechanical ventilation" subgroup. With 99 patients sampled from our cohort, the median age was 63 years (1st quartile = 55 and 3rd quartile = 75). The sex ratio was identical to that of the lopinavir group. No significant difference could be noted between the groups for chronic diseases (Table 2).

At the end of the study, only 95 patients received lopinavir treatment. Fewer deaths were counted in the HCQ+AZ group than in the lopinavir group (9% vs 20%, p-value = 0·03) (Table 2). The median length of hospitalization and median duration of oxygenation were shorter in the HCQ+AZ group (10 days vs 14 and 3 vs 12).

Standard care group

The lopinavir - ritonavir trial had a control group of 100 patients who received only standard care [9]. The median age in the control group was 58 years (1st quartile = 48 and 3rd quartile = 68), and 59 (59%) were male (Table 3).

To constitute a sampled HCQ+AZ group comparable to this control group and to respect the sex ratio (59% men), 7 women and 10 men were randomly selected in the "Ambient air" subgroup and 27 women and 40 men were selected in the "Supplemental oxygen" subgroup

(Supplementary data S3). Sixteen additional patients were sampled in the "ICU – other types of ventilation" subgroup to correspond to the "HFNC or non-invasive ventilation" subgroup. The median age in the sampled group was 62 years (1st quartile = 54 and 3rd quartile = 74) (Table 3). However, this group had more cancer patients than the control group (11% vs 1%, p-value = 0·005). No other significant differences in demographic characteristics or disease severity were found between the groups.

Of the 100 patients in the control group, 1 patient received lopinavir-ritonavir. As before, fewer deaths occurred in the HCQ+AZ group (8% deaths versus 25%, p-value = 0·001). The median duration of hospitalization was also shorter, as was the median duration under oxygenation (Table 3).

Placebo group

To evaluate the benefits of remdesivir, Wang compared it to a placebo group of 78 inpatients[10]. The median age was 64 years (1^{st} quartile = 53 and 3^{rd} quartile = 70), and 51 (65%) were males (Table 4).

Nine patients were sampled in the "Ambient air" subgroup from our cohort, 65 in "Supplemental oxygen", 9 in "HFNC or non-invasive ventilation" and 1 in "Invasive mechanical ventilation" to constitute the most comparable group at baseline (Supplemental data S4). No significant differences in clinical or demographic characteristics were found (Table 4).

Eight patients from our sampled cohort died against 10 in the placebo group (p-value = 0·62). However, a larger number of patients were discharged cured in our cohort (78% vs 58%, p-value = 0·006). As noted earlier, the median length of hospitalization and the median duration of oxygenation were also shorter in our cohort (Table 4).

Discussion

The purpose of this study was to perform an in silico comparison between a comparable sample treated with HCQ+AZ dual therapy from our observational cohort of 3,000 patients in the remdesivir, lopinavir-ritonavir study or its control groups to evaluate the most effective treatment against COVID-19 [9,10].

Although we were only able to use aggregated data to perform our matching, it was demonstrated that the treatment combining HCQ and AZ was more effective than those used in each of the two arms of the Wuhan study [9], i.e. the untreated arm and the arm with lopinavir-ritonavir. In addition, HCQ+AZ was found to be more effective in curing patients than remdesivir (success rate = 77·8% vs 58·2%), but due to limited sample size, no significant difference in terms of deaths could be demonstrated.

Many confounding factors are present in the studies through the use of other treatments such as lopinavir-ritonavir, interferons or corticosteroids, for example, or a different standard care between countries [10]. In our cohort, there was no use of other antivirals or corticosteroids, whereas this is commonly the case in Chinese studies.

Epidemiological studies recognize obvious limitations when matching aggregated data, and individual-by-individual matching remains the reference methodology. Unfortunately, individual data were not available from the two trials of antiviral drugs for which comparison was worth performing. In the current context, it has become essential to make raw individual data available to the scientific community to respond rapidly to the pandemic and to demonstrate the efficacy or otherwise of a treatment. The speed of finding a treatment for COVID-19 is a real challenge that can be facilitated by sharing information, as is already the case with the genomic sequences of the SARS-CoV-2 strains [13]. Contacts with the authors of these articles have been made, and we hope this analysis will be carried out shortly.

We were, however, able to adjust for severity, comorbidities, sex and age, which are the most important factors in the evolution of the disease, and thus to minimize the most important biases [8,12]. Comparison with groups included in the remdesivir and lopinavir-ritonavir trials showed that our cohort (currently being analysed in its entirety) of more than 3,000 people treated with HCQ and AZ has a better prognosis than patients receiving either standard care or no specific treatment, patients receiving remdesivir, or patients receiving lopinavir-ritonavir. This was also confirmed by preliminary studies showing that remdesivir does not improve survival in patients receiving it. Indeed, the primary endpoints of the remdesivir study, currently underway in the United States, are no longer the respective proportions of patients with outcomes graded on an 8-point ordinal scale with death as the worst outcome but time to recovery [10,14]. Our study provides additional evidence in favour of using HDQ+AZ as the systematic treatment of choice immediately after diagnosis of a confirmed positive COVID-19 case.

Contributors

Conceived and designed the study: DR. Designed and/or performed experiments: AGG, JCL, and HC. Analysed and interpreted data: AGG and DR. Wrote the manuscript: AGG, YO and DR. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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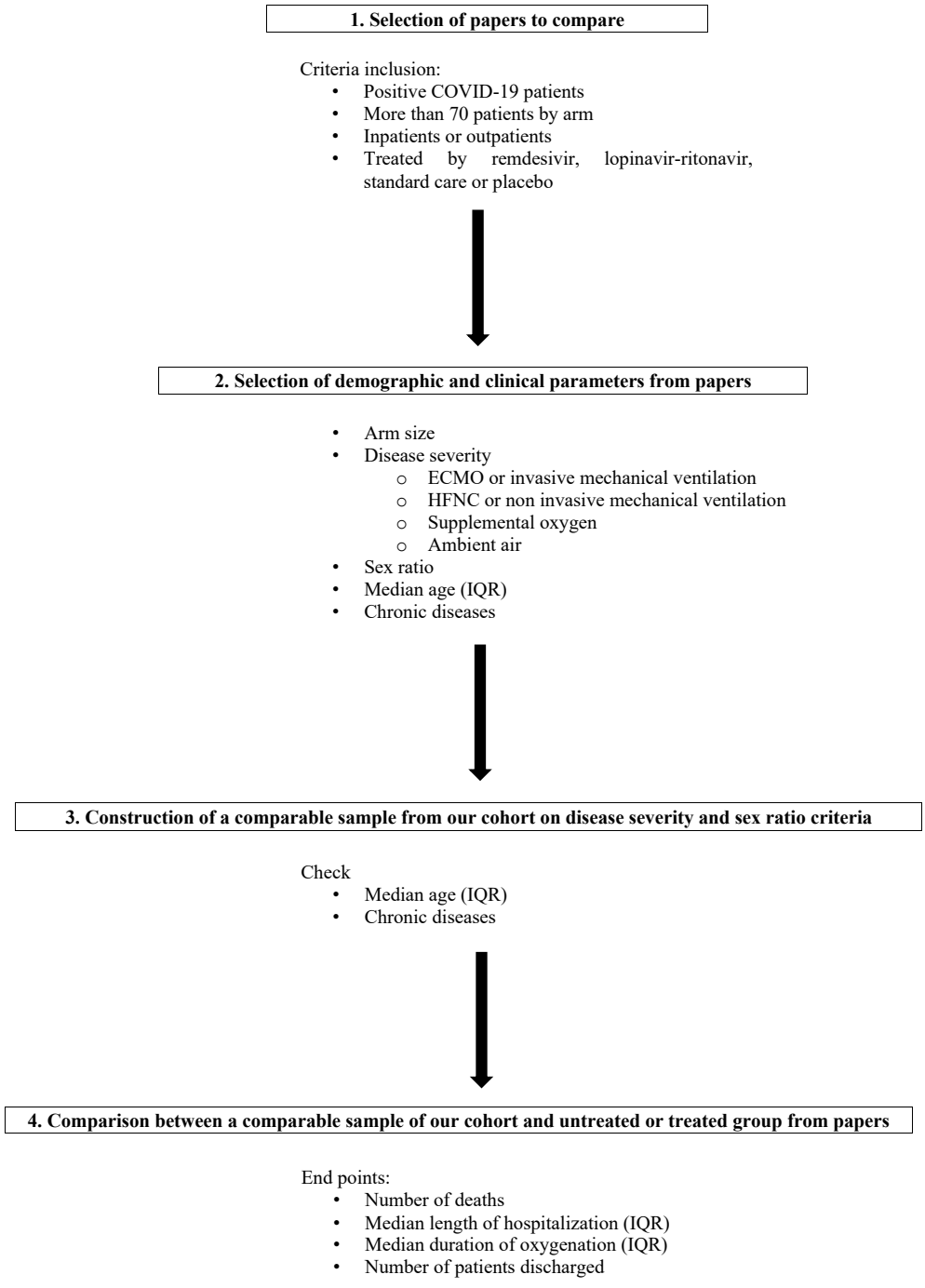

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344 Figure 1 – Process flow of the study (HFNC: high flow nasal canula for oxygen therapy, ECMO:
345 extraeorporeal membrane oxygenation, IQR: interquartile range, HCQ+AZ:
346 hydroxychloroquine+azithromycin)

Table 1 - Comparison between the group treated with remdesivir[10] (Wang et al. 2020) (N = 158) and the group treated with HCQ+AZ from the 472 inpatients in the 3,000-patient cohort at IHU Méditerranée Infection, Marseille, France.

	Remdesivir	**HCQ + AZ at intention-to-treat**	**p-value**
N	158	158	
Median age	66	63	
- IQR	(57 - 73)	(56 - 76)	
Gender			
- Male – no. (%)	89 (56·3)	89 (56·3)	>0·99
- Sex ratio (M:F)	1·29	1·29	
Disease severity			
- ECMO or invasive mechanical ventilation – no. (%)	1 (0·6)	1 (0·6)	>0·99
- HFNC or noninvasive mechanical ventilation – no. (%)	28 (17·7)	28 (17·7)	>0·99
- Supplemental oxygen – no. (%)	129 (81·6)	129 (81·6)	>0·99
- Ambient air – no. (%)	0	0	>0·99
Chronic diseases			
- Diabetes – no. (%)	40 (25·3)	34 (21·5)	0·43
- HTA – no. (%)	72 (45·6)	68 (43·0)	0·65
Outcomes			
- Day 28 mortality – no. (%)	22 (13·9)	16 (10·1)	0·30
- Earlier (≤ 10 days after onset of symptoms) – no. (%)	8 (5·1)	12 (7·6)	0·36
- Later (> 10 days after onset of symptoms) – no. (%)	12 (7·6)	4 (2·5)	0·07
- Hospital stay – median no. of days	25	11	
- IQR	(16 - 38)	(6 - 15)	
- Oxygen support – median no. of days	19	3	
- IQR	(11 - 30)	(2 - 6)	
- Discharge	92	123	0·0001

Table 2 - Comparison between the group treated with lopinavir-ritonavir[9] (Cao et al. 2020) (N = 99) and the group treated with HCQ+AZ from the 472 inpatients in the 3,000-patient cohort at IHU Méditerranée Infection, Marseille, France.

	Lopinavir-Ritonavir	**HCQ + AZ at intention-to-treat**	**p-value**
N	99	99	
Median age	58·0	63·0	
- IQR	(50·0 - 68·0)	(55·0 - 75·0)	
Gender			
- Male – no. (%)	61(61·6)	61(61·6)	
- Sex ratio (M:F)	1·61	1·61	
Disease severity			
- ECMO or invasive mechanical ventilation – no. (%)	1 (1)	1 (1)	>0·99
- HFNC or noninvasive mechanical ventilation – no. (%)	15 (15·2)	15 (15·2)	>0·99
- Supplemental oxygen – no. (%)	72 (72·7)	72 (72·7)	>0·99
- Ambient air – no. (%)	11(11·1)	11 (11·1)	>0·99
Chronic diseases			
- Diabetes – no. (%)	10 (10·1)	20 (20·2)	0·05
- Cerebrovascular disease – no. (%)	5 (5·1)	12 (12·1)	0·08
- Cancer – no. (%)	5 (5·1)	11 (11·1)	0·12
Outcomes			
- Day 28 mortality – no. (%)	19 (20)	9 (9·1)	0·03
- Earlier (≤ 12 days after onset of symptoms) – no. (%)	8 (8·4)	7 (7·1)	0·72
- Later (> 12 days after onset of symptoms) – no. (%)	11 (11·6)	2 (2)	0·01
- Hospital stay – median no. of days	14	10 (10·1)	
- IQR	(12 - 17)	(5 - 14)	
- Oxygen support – median no. of days	12	3	
- IQR	(9 - 16)	(2 - 6)	

Table 3 - Comparison between the group treated with standard care[9] (Cao et al. 2020) (N = 100) and the group treated with HCQ+AZ from the 472 inpatients in the 3,000-patient cohort at IHU Méditerranée Infection, Marseille, France.

	Standard care	HCQ + AZ at intention-to-treat	p-value
N	100	100	
Median age	58·0	62·0	
- IQR	(48·0 - 68·0)	(54·0 - 74·0)	
Gender			
- Male – no. (%)	59 (59)	59 (59)	>0·99
- Sex ratio (M:F)	1·44	1·44	
Disease severity			
- ECMO or invasive mechanical ventilation – no. (%)	0	0	>0·99
- HFNC or noninvasive mechanical ventilation – no. (%)	16 (16)	16 (16)	>0·99
- Supplemental oxygen – no. (%)	67 (67)	67 (67)	>0·99
- Ambient air – no. (%)	17 (17)	17 (17)	>0·99
Chronic diseases			
- Diabetes – no. (%)	13 (13)	20 (20)	0·18
- Cerebrovascular disease – no. (%)	8 (8)	12 (12)	0·35
- Cancer – no. (%)	1 (1)	11 (11)	0·005
Outcomes			
- Day 28 mortality – no. (%)	25 (25·2)	8 (8)	0·001
- Earlier (≤ 12 days after onset of symptoms) – no. (%)	13 (13·1)	7 (7)	0·15
- Later (> 12 days after onset of symptoms) – no. (%)	12 (12·1)	1 (1)	0·002
- Hospital stay – median no. of days	16	10	
- IQR	(13 - 18)	(5 - 14)	
- Oxygen support – median no. of days	13	3	
- IQR	(6 - 16)	(2 - 6)	

Table 4 - Comparison between the placebo group[10] (Wang et al. 2020) (N = 78) and the group treated with HCQ+AZ from the 472 inpatients in the 3,000-patient cohort at IHU Méditerranée Infection, Marseille, France.

	Placebo group	HCQ + AZ at intention-to-treat	p-value
N	78	78	
Median age	64	64	
- IQR	(53 - 70)	(57 - 76)	
Gender			
- Male – no. (%)	51 (65·3)	51 (65·3)	>0·99
- Sex ratio (M:F)	1·89	1·89	
Disease severity			
- ECMO or invasive mechanical ventilation – no. (%)	1 (1·2)	1 (1·2)	>0·99
- HFNC or noninvasive mechanical ventilation – no. (%)	9 (11·5)	9 (11·5)	>0·99
- Supplemental oxygen – no. (%)	65 (83·3)	65 (83·3)	>0·99
- Ambient air – no. (%)	3 (3·8)	3 (3·8)	>0·99
Chronic diseases			
- Diabetes – no. (%)	16 (20·5)	16 (20·5)	>0·99
- HTA – no. (%)	30 (38·5)	35 (44·9)	0·42
Outcomes			
- Day 28 mortality – no. (%)	10 (12·8)	8 (10·3)	0·62
- Earlier (≤ 10 days after onset of symptoms) – no. (%)	7 (9·0)	6 (7·7)	0·77
- Later (> 10 days after onset of symptoms) – no. (%)	3 (3·8)	2 (2·6)	>0·99
- Hospital stay – median no. of days	24	10	
- IQR	(18 - 36)	(6 - 14)	
- Oxygen support – median no. of days	21	3	
- IQR	(14 - 30·5)	(2 - 6)	
- Discharge	45 (57·7)	61 (78·2)	0·006