

Early hydroxychloroquine is associated with an increase of survival in COVID-19 patients: an observational study.

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Summary: Hydroxychloroquine has in vitro activity against SARS-CoV-2. We present an observational study. We analysed 164 patients admitted to our hospital with COVID-19 diagnosis. Hydroxychloroquine treatment was associated with an increase in the mean cumulative survival.

ABSTRACT

Background: there is no treatment proven effective against COVID-19. Several drugs with in vitro potential against SARS-CoV-2 virus have been proposed. Hydroxychloroquine has in vitro anti-viral and immunomodulatory activity, but there is no current clinical evidence of its effectiveness changing the outcome of the disease.

Methods: We enrolled all 18-85 years old inpatients from Central Defense Hospital “Gómez Ulla”, Madrid, Spain, who were hospitalised for COVID-19 and had a definitive outcome (dead or discharged). We used a statistical survival analysis to detect treatment differences associated with in-hospital death.

Results: We analysed first 220 medical records. 166 patients met the inclusion criteria. 48,8 % of patients not treated with HCQ died, 22% of those treated with hydroxychloroquine ($p=0,002$). According to clinical picture at admission, hydroxychloroquine increased the mean cumulative survival in all groups from 1,4 to 1,8 times. This difference was statistically significant in the mild group.

Conclusions: in a cohort of 166 patients from 18 to 85 years hospitalised with COVID-19, hydroxychloroquine treatment with 800mg added loading dose increased survival when patients were admitted in early stages of the disease. There was a non-statistically significant trend towards survival in all groups, which will have to be clarified in subsequent studies.

Type of article: Major article

Keywords: COVID-19, treatment, drug, survival, antiviral, hydroxychloroquine.

Word count: abstract: 200 words. Manuscript: 2797 words.

FOOTNOTE PAGE

The corresponding author certifies that:

-No funding sources were used in this study

-All the authors declare not having any conflict of interests

-This study has not been presented previously

Yours sincerely,

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INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by SARS-CoV-2, a newly discovered coronavirus in China. Until April 29th, 2020, the disease has spread over 213 countries, with almost 3 million infected people and more than 200.000 deaths (1). Globally considered a mild infection in 80% of cases, moderate and severe cases can lead to death. At present, clinical management includes only supportive care, with supplementary oxygen and mechanical ventilatory support when indicated. Many old and novel therapeutic approaches are being evaluated, since there is no specific treatment proven effective (2). Spain is being strongly hit by COVID-19, with more than 200.000 people infected and more than 24.000 deaths.

At the beginning of the pandemic, clinical guideline in Spain was performed by Ministry of Health supported by several study groups and scientific societies. Several drugs were recommended for treatment (3): lopinavir/ritonavir (4,5,6), remdesivir (4,7) (only for severe cases), interferon alfa (8,9) and beta (10) and tocilizumab (11,12). However, the expansion of epidemic, with increasing number of severe cases and deaths, along with stock problems and lack of definitive clinical evidence resulted in different local hospital guidelines. Each guideline was adapted resting on personal experience and limited reports of cases, while others were based on not proven pathophysiological theories. Glucocorticoids (13), azithromycin (14), and other immunomodulators have been used among some others.

Our institution added to clinical protocol the use of hydroxychloroquine (HCQ) after reviewing recommendations of guidelines by the National Health Commission of the People's Republic of China for treatment of COVID-19(15). Chloroquine (CQ), an aminoquinoline that has been used for malaria prevention and treatment, has shown efficacy in vitro against SARS-CoV(16,17) and its use for COVID-19 has been hypothesized. CQ can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes

endosomes for entry. Furthermore, HCQ has been found to be more potent than CQ to inhibit SARS-CoV-2 in vitro (18). However, there is no current clinical evidence of use of CQ/HCQ for treatment of COVID-19 from the published literature till date.

We conducted a systematic search of the literature using MEDLINE (covering January 1st, 2000 to April 3rd, 2020) using the following terms: (COVID-19 OR coronavirus OR sars-cov2) AND (hydroxychloroquine OR chloroquine). We excluded duplicated studies, those articles related to coronavirus animal infections, and related to other diseases. The records have been classified by two independent reviewers ($\kappa=1$). We selected 11 original studies (including 2 clinical trials), 11 reviews (1 systematic, 10 non-systematic) and 21 other publications (letters, case reports, news, consensus documents). There were only 2 original articles including patients with COVID-19 infection: 1 randomized clinical trial (19) including 10 patients (3 severe and 7 moderate cases) treated with CQ 500mg orally twice-daily for 10 days, and 12 patients (5 severe and 7 moderate cases) treated with Lopinavir/Ritonavir 400/100mg orally twice-daily for 10 days. The other article is a non-randomized clinical trial (14) including 26 patients receiving HCQ 200 mg, three times per day during ten days (6 of them with azithromycin) and 16 controls.

During the first days of the pandemic, HCQ was not considered in the local protocol. Afterwards, there were shortages in HCQ distribution. Because of that, we had two populations of patients treated and not treated with HCQ although they had similar characteristics. That gave us the opportunity to investigate the differences observed between the two groups. On the other hand, some patients didn't receive HCQ because of potential side effects (arrhythmias, drug interactions) or because of patient's denial to give the consent to the out of label use of the drug.

While awaiting the results from larger clinical trials, confirming with endpoints related to the definitive outcomes of patients, retrospective analysis from regular clinical practice may be useful. The main purpose of this study was to assess the survival in two different therapeutic regimens: with or without HCQ.

METHODS

-Study design and participants: observational cohort study. We enrolled all adult inpatients from Central Defense Hospital “Gómez Ulla”, Madrid, Spain, who were hospitalised for COVID-19 infection and had a definitive outcome (dead or discharged). COVID-19 diagnosis was defined according to Spanish Ministry of Health definitions on 31st March, 2020, including confirmed cases (PCR positive for any SARS-CoV-2 gene in respiratory samples -oropharyngeal swabs or sputum) and probable cases (bilateral interstitial pneumonia with clinical picture compatible with a COVID-19 diagnosis with no laboratory tests or non-concluding SARS-CoV-2 test). We considered discharge, but analysed separately, the discharge to origin residence or to a “hotel-hospital” (temporary low-care medical installations in Madrid hotels adapted for patients in recovery phase, with no oxygen or intravenous requirements, who could be discharged from acute hospital but who had no possibility to correctly complete the quarantine period at home).

The research protocol was approved by the Ethics Committee on Clinical Investigation of the Ministry of Defense of Spain. The requirement for informed consent was waived by the Ethics Committee. After a preliminary exploratory analysis of the outcomes of the first 220 patients, study was stopped, and the investigators considered mandatory a deep analysis and early publishing of the results due to the relevant differences on survival according to the treatment used.

-Data collection: demographic, clinical, laboratory, treatment and outcome characteristics of the patients were extracted from the electronic medical records by two physicians. In case of differences of interpretation, a third investigator checked the medical records and adjudicated any difference. After collecting the data, database was anonymized removing any reference to the patient’s ID before the statistical analysis. Primary investigator and statistic analyser had no access to the medical records or patients ID.

-Laboratory procedures: Methods for laboratory confirmation of SARS-CoV-2 infection have been described elsewhere (20). SARS-CoV-2 PCR test were performed in Clinical Microbiology Laboratory, Central Defense Hospital, Madrid.

Routine blood examinations included whole blood count, coagulation profile, serum biochemical tests (including renal and liver function, lactate dehydrogenase, and electrolytes). Interleukin-6 (IL-6), serum ferritin, myocardial enzymes and procalcitonin were recovered for several but not all patients. Chest radiographs were also done for all inpatients. Frequency of examinations was determined by the treating physician.

-Definitions: severity of clinical picture at admission was defined according to Ministry of Health of Spain medical treatment protocol, March 19th, 2020: mild (no hypoxemia, no respiratory insufficiency), moderate (hypoxemia and / or moderate respiratory insufficiency), severe (severe hypoxemia, severe respiratory distress, poor overall status). Hypertension was defined as previous arterial hypertension requiring any pharmacological treatment. Diabetes Mellitus was defined as previous hyperglycaemia requiring any pharmacological hypoglycaemic treatment. Dyslipidaemia was defined as previous alteration in lipid profile requiring pharmacological treatment. Cardiomyopathy was defined as any previous diagnosis of cardiac chronic disease or acute cardiac event. Respiratory disease was defined as any previous lower respiratory tract chronic disease requiring chronic pharmacological treatment. Cancer was defined as any previously diagnosed malignancy. Dementia was defined as any mental chronic disease altering cognitive capabilities. Lymphopenia was defined as less than 1000 lymphocytes/ml. High LDH values were defined as those higher than 400 U/l. High CRP values were defined as those greater than 14 mg/dL. High D-dimer values were defined as those greater than 1000 ng/ml.

- HCQ/CQ selection and dose: Hospital treatment protocol selected hydroxychloroquine over chloroquine considering the best *in vitro* activity profile (EC₅₀=0.72 µM vs. EC₅₀=5.47 µM)

(18). Despite Yao et al. suggest in their manuscript a loading dose of 400 mg twice daily of hydroxychloroquine (18), we have finally considered a loading dose of 800 mg + 400 mg, followed by a maintenance dose of 400 mg a day based on: 1) the hypothetical benefit of reaching the steady state and the EC90 as soon as possible in the case of this acute viral infection, 2) this is the schedule accepted by the regulatory agency in the attacks of acute malaria treatment, and therefore a safe and well-known doses by the physicians. Nevertheless, a few elder patients didn't receive the extra loading dose of 800mg to avoid said effects and drug interactions.

-Other treatments: patients in both groups were treated with other specific drugs with potential activity against SARS-CoV-2 and/or COVID-19 immune disorders leading to ARDS. These drugs could include antivirals (lopinavir/ritonavir), immunomodulators (interferon beta), and/or anti-inflammatory drugs (steroids and/or tocilizumab)

-Statistical analysis: The quantitative variables were described with the arithmetic mean with its standard deviation and the median with its interquartile range. We used the absolute and relative frequency (%) for qualitative variables. The hypothesis tests used were the Chi2 Pearson or Fisher's exact test, the Student's t test or the Mann Whitney test, the one-way ANOVA, with the Bonferroni test for multiple comparisons, and Kruskal Wallis test. The survival study was performed with the Kaplan Meier test and the comparison of factors with the Mantel Cox Log Rank test. A $p < 0.05$ was considered statistically significant. Logistic regression for multivariate analysis was performed with $p < 0,250$ level as a screening criterion for selection of candidate variables. Statistical analysis were done using the software package SPSS Windows (version 25)

FINDINGS

We studied the first 220 discharge or death medical reports on COVID-19 wards, Central Defense Hospital “Gómez Ulla”. We excluded 22 patients who were admitted to a COVID-19 ward but finally didn’t have a confirmed clinical or microbiological diagnosis of COVID-19, and 32 patients older than 85 years (in whom the Hospital's COVID-19 treatment protocol decided not to use off-label treatments in the first weeks of the epidemic after evaluating the risk-benefit balance) and 1 patient younger than 18 years (not attended by COVID-19 team). We finally included 166 patients in the study (figure 1). 83 patients had mild clinical picture at admission, 48 moderate and 35 severe. 118 Patients survived (90 were discharged and 29 to “hotel-hospital”) and 48 dead.

123 patients were treated with HCQ and 43 patients didn’t receive HCQ. 48,8 % of patients not treated with HCQ died and 22% of those treated with HCQ ($p=0,002$). Age distribution according to the severity at admission was homogeneous between HCQ and non-HCQ treatment groups when the clinical picture was mild (57,6 years HCQ – 58,4 years non-HCQ, $p=0,865$) or moderate (63,8 years HCQ – 70 years non-HCQ, $p=0,269$). Patients with severe clinical picture at admission treated with HCQ were younger than those who were not treated (70,4 years HCQ -78,3 years non-HCQ, $p=0,036$) (table 1).

Comorbidities (table 2) were similar in both groups, except for cardiopathy ($p=0,05$) and dementia ($p=0,022$). Differences in treatment according with cardiopathy were expected because of the side effects of CQ/HCQ (prolongation of QT interval). Analytical data at admission had similar values on both groups (table 2).

Mean hospital stay was 6 (5) days in the HCQ group and 5(7) days in the non-HCQ group (no significant difference, $p=0,25$).

Median (IQR) from symptoms begin to the start of treatment with HCQ: 7(6) days. Mode was 7 days after symptoms onset. The median Md (IQR) of time elapsed from onset of symptoms

to start of treatment were for the mild group of 7 (7.25) days, for the moderate group of 7 (6.8) days and for the severe of 5 (4) these differences being statistically significant ($p = 0.01$). Nevertheless, median (IQR) from hospital admission to the start of treatment with HCQ was 1(1) days, with no differences according to clinical picture at admission ($p=0,223$).

There was a clear increase in the accumulated survival rates at the 3 levels of clinical picture at admission favourable to the group treated with HCQ (table 3). In the mild group: their average cumulative survival is increased 1.8 times in those treated. In the moderate group the cumulative median survival was 1.4 times higher in those treated. In the severe group the cumulative median survival was 1.6 times greater in the those treated.

In the mild group, the mean cumulative survival was 14.4 days (95% CI: 13.7-15.2 days) in those treated with HCQ and 8.2 days (95% CI: 6.5-9.9 days) in the untreated, being this difference of 6.2 days statistically significant ($p = 0.032$).

In the moderate group, a trend towards longer survival was observed, but without reaching statistical significance. The accumulated survival average was 10.9 days (95% CI: 9.3-12.5 days) in those treated with HCQ and 7.7 days (95% CI: 4.4-10.9 days). In the untreated, this difference of 3.1 days was not statistically significant ($p = 0.205$).

In the severe group, the mean cumulative survival was 6 days (95% CI: 3.3-8.5 days) in those treated with HCQ and 4 days (95% CI: 1.7-6.1 days) in those not treated. This difference of 2 days was not statistically significant ($p = 0.297$).

A multi-variant analysis of survival was performed, including comorbidities and analytical values at admission (table 4). The analysis excluded confusion bias on the increased survival in HCQ group: HCQ treatment was an independent predictor of lower mortality ($p=0,003$, 95% CI 0,012 – 0,402). Other independent predictors of survival were two comorbidities (cardiopathy, $p=0,010$, 95% CI 0,053-0,672, and dementia, $p=0,013$, 95% CI 0,002

to 0,489), and two analytical conditions at admission: lymphopenia ($p=0,026$, 95% CI for lymphocytes higher than 1.000/ml: 1,212-19,686).

INTERPRETATION

From our known this is the first study showing increase of survival in a significant number of patients with a specific drug treatment for COVID-19. There was a whole increased survival from 1,4 to 1,8 times to survival in those treated with HCQ. The cohort of patients with mild clinic at admission had clearly better outcomes when treated with HCQ.

These results were obtained in patients treated early (first week since symptoms onset, first day after admission). We theorise that the antiviral effect is only effective in early stages of the disease, before the immunomodulated ADRS development (21). This could explain the better outcomes with HCQ in mild patients, treated before the establishment of ADRS. Similarly, the different outcomes with other drugs with potential activity against SARS-CoV-2 as lopinavir/ritonavir which failed to show effect on mortality reduction with a mean of 14 days since symptoms onset (22). Anyway, our findings in an easily available, low-cost drug with few side effects makes HCQ/CQ a good choice to start clinical trials in hospitalised patients, and to consider an out-of-label most extended use in early stages of the disease (taking care of all the legal and ethical considerations about this use).

Subgroups of patients in moderate and severe condition at admission showed a tendency to survival, but with no statistically significant differences in their outcomes. Probably, due to the physiopathology of COVID-19 (21), once the patient starts the “cytokine storm” phase, antiviral effect it’s less or not useful and immunomodulation of HCQ it’s not enough powerful to cut the progression of ADRS. Anyway, this could be cleared with a higher sample size, which we’ll continue studying for further reports.

There were significant differences in age mean in the HCQ / non-HCQ groups with severe disease at admission. This could be explained due to the higher comorbidities of elder patients with severe condition at admission, what may have led clinicians to decide limitation of therapeutic effort in some of them. Anyway, this should be studied deeper in further studies.

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Table 1. General characteristics of the patients in both treatment groups (with and without HCQ)

		HCQ Yes n=123	No n=43	p
Age (years) $\bar{x}(DE)$	Clinical picture at admission	61,5(16,2)	68,7(18,8)	0,012*
	Mild	57,6(15,7)	58,4(17,8)	0,865*
Age (years) $\bar{x}(DE)$	Moderate	63,8(16,5)	70(13,2)	0,269*
	Severe	70,4(13,4)	78,3(7,2)	0,036*
Sex n(%)	Male	76(61,8)	27(62,8)	0,907**
	Female	47(38,2)	16(37,2)	
Final outcome n(%)	Death	27(22)	21(48,8)	0,002**
	"Hospital Hotel"	26(21,1)	3(7)	
	Home	70(56,9)	19(44,2)	

*t Student; ** χ^2 Pearson

Table 2. Clinical Comorbidities and Analytical Parameters of Patients on Admission in Both Treatment Groups.

		HCQ		p
		Yes n=123 n(%)	No n=43 n(%)	
Hypertension	Yes	49(69)	22(31)	0,214*
	No	74(77,9)	21(21,1)	
Diabetes	Yes	19(65,5)	10(34,5)	0,246*
	No	104(75,9)	33(24,1)	
Dyslipidaemia	Yes	39(68,4)	18(31,6)	0,190*
	No	84(77,8)	24(22,2)	
Cardiopathy	Yes	23(62,2)	14(37,8)	0,050*
	No	100(78,1)	28(21,9)	
Cancer	Yes	15(65,2)	8(34,8)	0,268*
	No	108(76,1)	34(23,9)	
Dementia	Yes	6(46,2)	7(53,8)	0,022**
	No	117(77)	35(23)	
Pulmonary disease	Yes	15(62,5)	9(37,5)	0,143*
	No	108(76,6)	33(23,4)	
Leukocytes μ l		6320(3395)	8004(4530)	0,696***
Lymphocytes μ l		1160(545)	860(730)	0,997***
LDH U/l		328(141)	296(216)	0,971***
GOT U/l		36(24)	28,5(37)	0,923***
PCR mg/dl		6,2(10,7)	12,1(16,8)	0,845***
PCT ng/ml		0,13(0,29)	0,59(4,38)	0,730***
Ferritin ng/ml		375(827)	321,5(1158)	0,144***
D dimer ng/ml		558(716)	1511(4570,5)	0,168***

*Chi2 Pearson; **Exact Fisher test; ***Mann Whitney test

Table 3. Increase of survival with HCQ according to clinical picture at admission (days)

	Total	HCQ group	Non-HCQ group
Mild	14(IC95%:13-14,8)	14,4(IC95%:13,7-15,2)	8,2(IC95%:6,5-9,9)
Moderate	10,3(IC95%: 8,7-11,9)	10,9(IC95%:9,3-12,5)	7,7(IC95%:4,4-11)
Severe	5,2(IC95%:3,4-7,1)	5,9(IC95%:3,3-8,5)	3,9(IC95%:1,7-6,1)

*Log Rank (mantel Cox)

Table 4. Significant outcomes of the multi-variant analysis of survival

	B	Standard error	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Higher
Cardiopathy	-1,671	,650	6,609	1	,010	,188	,053	,672
Dementia	-3,426	1,384	6,132	1	,013	,033	,002	,489
Lymphopenia	1,586	,711	4,973	1	,026	4,884	1,212	19,686
High RCP values	-1,413	,645	4,803	1	,028	,243	,069	,861
HCQ treatment	-2,654	,889	8,914	1	,003	,070	,012	,402

Figure 1. Patient inclusion flow chart

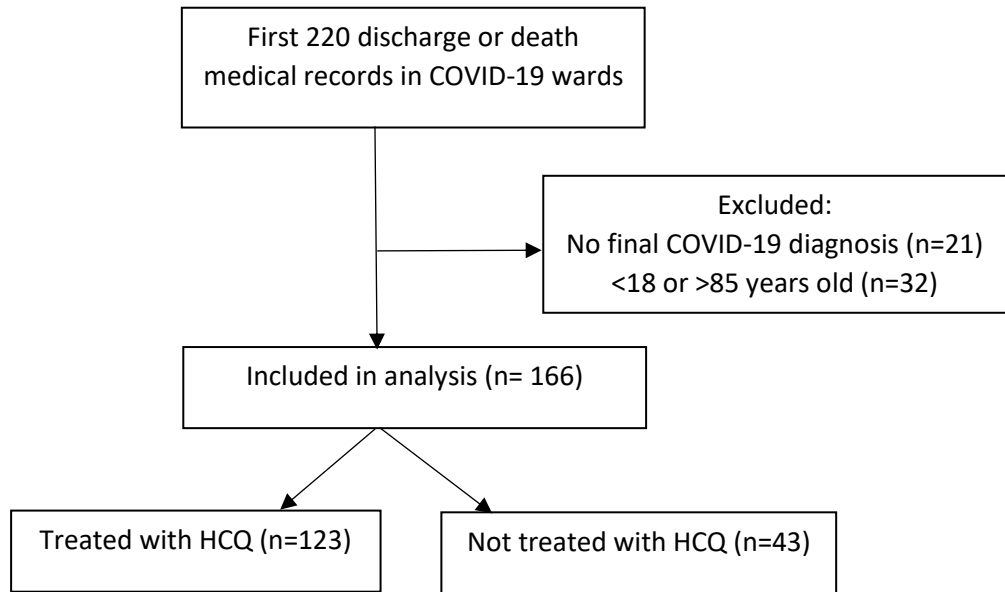


Figure 2. Age distribution, according to severity at admission

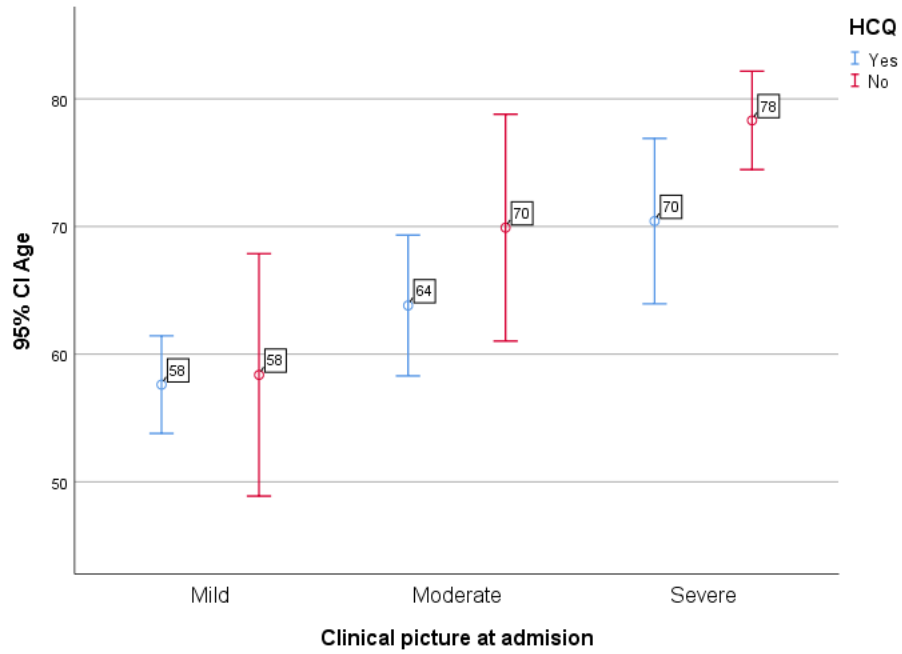
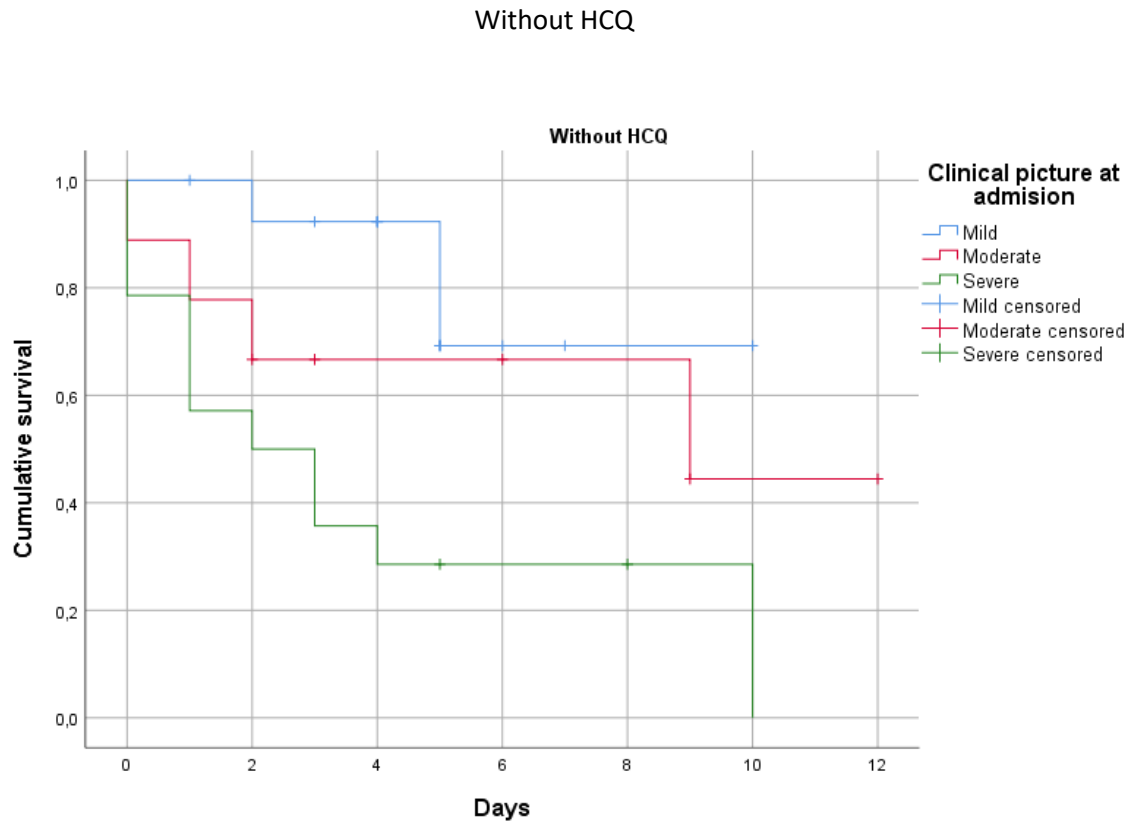
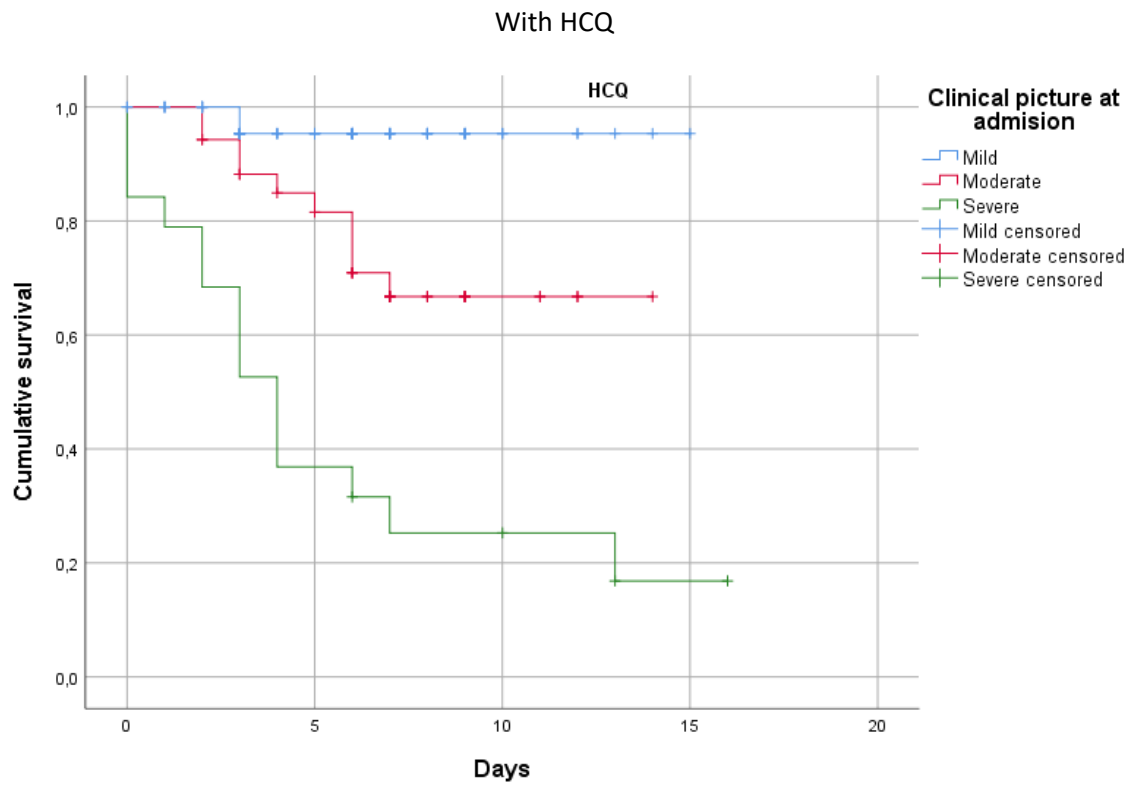


Figure 3. Kaplan-Meier Survival functions with/without HCQ



ANNEX 1. MEMBERS OF THE COVID 19 CENTRAL DEFENSE HOSPITAL "GÓMEZ ULLA" TEAM

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