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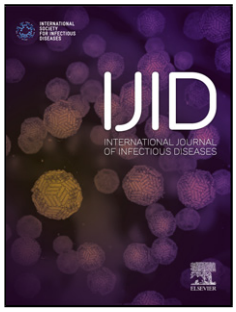

Early Hydroxychloroquine but not Chloroquine use reduces ICU admission in COVID-19 patients

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TITLE PAGE

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Highlights

- After the global push for the use of Hydroxychloroquine and Chloroquine there is ongoing discussion about the effectivity of these drugs.
- Findings of this observational study provide crucial data on a potential protective effect of Hydroxychloroquine in non-ICU, hospitalized COVID-19 patients.
- Early treatment with HCQ on the first day of admission is associated with a reduced risk of 53% in transfer to the ICU for mechanical ventilation
- This protective effect was not observed for Chloroquine, therefore these drugs cannot be regarded as interchangeable.

Abstract

Background

The global push for the use of hydroxychloroquine (HCQ) and chloroquine (CQ) against COVID-19 resulted in an ongoing discussion about the effectivity and toxicity of these drugs. Recent studies report no effect of (H)CQ on 28 day-mortality. We investigated the effect of HCQ and CQ in hospitalized patients on the non-ICU COVID-ward.

Methods

A nationwide, observational cohort study was performed in The Netherlands. Hospitals were given the opportunity to decide independently on the use of three different COVID-19 treatment strategies: HCQ or CQ, or no treatment. We compared the outcome between these groups. The primary outcomes were 1) death on the COVID-19 ward, and 2) transfer to the Intensive Care Unit (ICU).

Results

The analysis contained 1064 patients from 14 hospitals: 566 patients received treatment with either HCQ (n=189) or CQ (n=377), and 498 patients received no treatment. In a multivariate propensity matched weighted competing regression analysis, there was no significant effect of (H)CQ on mortality on the COVID-ward. HCQ however was associated with a significant decreased risk of transfer to the ICU (Hazard ratio (HR) = 0.47, 95%CI = 0.27 - 0.82, p = 0.008), when compared to controls. This effect was not found in the CQ group (HR = 0.80; 95%CI = 0.55 - 1.15, p = 0.207), and remained significant after competing risk analysis.

Conclusion

The results of this observational study demonstrate a lack of effect of (H)CQ on non-ICU mortality. However, we show that the use of HCQ - but not CQ - is associated with 53% decreased risk of transfer of COVID-19 patients from the regular ward to the ICU. Recent prospective studies have reported on 28 days all-cause mortality only, therefore additional prospective data on the early effect of HCQ in preventing transfer to the ICU is still needed.

Abbreviations: HCQ = hydroxychloroquine, CQ = chloroquine, AZM= azithromycin

ICU = intensive care unit, ED = emergency department.

Key words: COVID-19, hydroxychloroquine, chloroquine, azithromycin, clinical course

Introduction

After the emergence of SARS-CoV-2 in December 2019, the new coronavirus spread around the world, resulting in a pandemic. Unfortunately, there is still no proven effective drug or vaccine available against COVID-19, and hospitalized patients with COVID-19 are at high risk for admission to the ICU (10-20%), 3-10% of patients require intubation, and 2-5 % of patients die [1].

Among the drugs candidates to treat COVID-19 are hydroxychloroquine (HCQ) and chloroquine (CQ) [2]. Insights into the underlying mechanism of action of HCQ and CQ are still emerging. Both drugs have a large volume of distribution [3,4]. Their molecular structures are comparable, except that HCQ has an extra hydroxyl-group. Both interfere with lysosomal activity and decrease membrane stability, reduce Toll-like-receptors 7 and 9 signaling pathways and impact on transcriptional activity inhibiting cytokine production [4].

There are only few differences between the drugs, of which the most important is drug clearance [4].

Some observational studies on the efficacy of (H)CQ report clinical benefit and antiviral effects [5–8] , but others do not [9,10]. A few small controlled trials were inconclusive [11,12] . The Recovery study included 176 UK hospitals, comprising 1395 patients receiving high dosed HCQ (9200 mg cumulative dose) reports no beneficial effect on all-cause mortality at 28 days (26.8% of treated patients versus 25% of controls) [13]. The risk of admission to the ICU could not be calculated, since 17-60% of patients was already on (non-invasive) ventilation at randomization. A recent systematic review and meta-analysis including 11.932 patients on HCQ found that its use was not associated with reduced mortality (pooled relative risk of RCTs of HCQ use of 1.09) [14].

Results of other prospective trials are not expected, since the European Discovery trial and the WHO Solidarity trial have discontinued the HCQ treatment arms because of lack of

effect on mortality. Meanwhile, the US FDA and the Infectious Diseases Society of America (IDSA) advise against the use of (H)CQ outside the context of a clinical trial [15,16].

Based on the available evidence present at the start of the outbreak, a Dutch treatment guideline was developed [17]. Off-label use of both HCQ and CQ was given as a treatment option; however, the guidelines did not endorse either treatment in particular. Consequently, hospitals decided independently on a treatment protocol with either HCQ or CQ, or to give no treatment. This policy created a unique situation for comparing the efficacy of HCQ and CQ with no treatment in hospitalized non-ICU patients with a reduction of potential bias by indication.

Methods

Study design

The study was designed as an observational, multicenter, cohort study of hospitalized COVID-19 patients. Before the first patients were admitted, Dutch hospitals individually implemented a treatment protocol with or without (H)CQ. As a consequence, Dutch patients were geographically allocated to their local hospital with or without the intention to treat with (H)CQ. Eligible patients were included retrospectively over the period of February 28th, 2020 to April 1, 2020. Patients were followed up until they reached one of the clinical endpoints: (1) discharge for cured infection to home or rehabilitation center, (2) transfer from the COVID-ward to the intensive care unit (ICU), or (3) death; either during hospital stay at the ward (non-ICU) or transfer to hospice facility. Secondary outcomes were the effect of the use of azithromycin (AZM) and angiotensin-receptor blockers (ARB) on outcome.

Participating hospitals

All hospitals in The Netherlands were considered eligible to participate in the study, academic hospitals as well as (non)-teaching hospitals. Dutch hospitals were asked to participate early in the outbreak. All participating hospitals shared their data with the coordinating hospital Isala, Zwolle, where the statistical analysis was performed. Data-Sharing Agreements were signed, and the Medical Ethics Review Committee (METC) of Isala approved a waiver for informed consent.

Patients

In- and exclusion criteria were designed to select a study sample of hospitalized patients with moderate to severe COVID-19. New COVID-19 confirmed cases were included if they were age >18 years and if they were admitted to the emergency department (ED) and subsequently hospitalized at the non-ICU hospital COVID-19 ward. Exclusion criteria were age < 18 years, admission to the ICU or death within 24 hours after presentation at the ED. Patients transferred between Dutch hospitals, for example due to capacity issues, were also excluded. Confirmed COVID-19 infection was defined as either positive SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (PCR on swab material, sputum or bronchoalveolar lavage samples) [18], or typical findings on chest computed tomography (CT). Typical CT-findings were defined as CO-RAD 4-5, using the CO-RAD classification system (COVID-19 Reporting and Data System, developed by the Dutch Radiology Society describing the level of suspicion for COVID-19 infection) [19]. Routine blood test were done for hematological and biochemical analysis, according to standard hospital laboratory techniques. Since the use of (H)CQ for COVID-19 was off-label, patients were started on (H)CQ only after giving informed consent.

Data collection

Data were extracted from Electronic Health Records (EHR) in all participating hospitals by medical students and/or infectious disease (ID) physicians. Data were collected on site using a standardized data-collection form on a secured website of the coordinating hospital. Patient data were immediately anonymized and encoded upon entry into the online research manager program. Collected data included patient characteristics including comorbidity, registered ICU-restrictive policy by treating physician, routine laboratory results, SARS-Cov2-PCR and chest CT-scan, medical treatment before admission and antibiotic treatment during hospitalization.

Statistical Analysis

Differences between HCQ and CQ users (cases) and non-users (controls) were compared using $\chi 2$ statistics or the Fisher exact test for categorical variables and the independent T or Mann Whitney U tests for continuous variables. The data were analyzed within a Cox proportional hazard regression framework. Follow-up commenced at the date of hospital admission and ended at the dates of death or ICU admission, whilst patients were censored at the time they were discharged from the hospital. Hazard ratios were calculated for (H)CQ use in relation to the primary endpoints death and ICU admission or a combination of these endpoints, denoted as a composite adverse endpoint. Death and ICU admission are competing risk events, therefore competing risk regression analysis was conducted for these two endpoints according to the method of Fine and Gray (1999) [38]. Instead of KM survival curves, survival data were summarized using the cumulative incidence function (CIF) or cumulative risks of an event, which indicates the probability of the event at a given time. The proportional hazards assumption was confirmed by the Schoenfeld's global test and

inspection of log (−log [survival]) curves. Propensity score (PS) matching was used for making causal inferences of the treatment on the clinical outcome. A set of pre-test covariates that were associated with the treatment was selected and PS were estimated using logistic regression with treatment as the outcome measure. Separate PS-matched Cox regression models with and without adjustment for potential confounders were used (see Appendix), but only the results of the overall and inverse-probability-of-treatment-weighted (IPTW) Cox regression analysis are shown. Analyses were adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity Asthma/COPD, use of broad spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day at ED, ICU restriction. The combined endpoint risk regression analyses were stratified by ICU restriction, because of the distinctive patient characteristics in this group. For PS estimation and matching the PS matching R package in SPSS and the PSMATCH2 package in Stata were used. All tests were two-sided and $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 24.0 and the STATA version 14 statistical package (Stata Corporation, College Station TX).

Results

Inclusion and baseline characteristics

Between February 28 and April 1, 2020, 1130 patients admitted to the 14 participating hospitals in The Netherlands met the inclusion criteria; 1106 patients were eligible for inclusion. After propensity score matching the analytic cohort consisted of 1064 patients, comprising 566 (53.2%) treated patients, both with HCQ (N=189 (17.8%)) and CQ (N=377 (35.4%)) and 498 (46.8%) untreated controls (see Figure 1).

Table 1 shows the characteristics of the study population. Distribution of patients over the three hospital groups was as follows: 270 patients (25.4%) were admitted in a HCQ hospital, 532 (50%) in a CQ hospital and 262 (24.6%) in a hospital with a protocol with no additional treatment. In both HCQ and CQ hospitals at least 70% of patients received treatment. Median time from admission to receipt of treatment was short: 1 day in both groups (HCQ 1.00, SD 1.5 days; CQ 1.00, SD 1.19 days). Most patients were male (60%) and body mass index (BMI) was 28 in all three groups. Comorbidities were comparable, except for cardiac disease, which saw a higher incidence in the non-treated group. Some patients had an ICU-restrictive policy, for instance due to comorbidity or high age: in the HCQ group 36% of patients had an ICU restriction (68/ 189), in the CQ group 30.5% (115/377), and 48.5% of patients without treatment (242/498) was not considered eligible for admission to the ICU. During follow-up, 191 (18%) patients deceased, 147 (13.8%) were admitted to the ICU and 726 (68.2%) patients were discharged from the hospital upon recovery.

Primary outcomes

Table 2 shows the results of the unadjusted and adjusted overall and weighted competing risk analyses for the different endpoints by type of medication. Figure 2A and 2B show the corresponding cumulative incidence functions (CIF). Multivariate analysis proves that both CQ and HCQ use were not statistically associated with a risk of death on the non-ICU COVID-ward (Hazard ratio (HR) = 0.99; 95%CI= 0.70 - 1.43 in CQ; and 0.96, 95%CI = 0.63 - 1.45 in HCQ). However, HCQ use was associated with a statistically significantly decreased risk of

transfer to the ICU (HR = 0.47, 95%CI = 0.27-0.82, p = 0.008), when compared to controls. This effect was not found in the CQ group (HR = 0.80; 95%CI = 0.55 – 1.15, p =0.207). In addition, for the composite adverse endpoint, a significantly decreased risk was observed for HCQ (HR = 0.68, 95%CI = 0.49 - 0.95, p = 0.024), but not for CQ use (HR = 0.85, 95%CI = 0.66 - 1.10, p= 0.224).

Secondary outcomes

Since the use of azithromycin (AZM) and angiotensin-receptor blockers (ARB) has been postulated to have an effect on COVID-19, we additionally analyzed the effect of this treatment on outcome; 210 patients were started on AZM therapy on admission, 854 patients did not receive AZM. In the KM analysis there was no significant difference between these two groups in reaching the composite adverse endpoint ($P_{logrank} = 0.071$) and no significant interaction effect was found for H(CQ) combined with AZM use (p = 0.2195). In total, 180 patients were using angiotensin-II receptor antagonists (ARB, n = 70) or angiotensin converting enzyme inhibitors (ACEi, n = 110), and continued treatment during admission. There was no difference in outcome on the composite adverse endpoint for continued ACEi use (HR = 1.21; 95%CI = 0.78 – 1.90, p = 0.397) nor for continued ARB use (HR = 1.21; 95%CI = 0.70 – 2.10, p = 0.498), as compared to no therapy.

Discussion

This study demonstrates a new and clinically important finding: the use of HCQ on the COVID-19 ward is associated with a decreased risk of transfer to the ICU. After competing risk analysis, the risk of admission to the ICU is reduced by 53%. This finding suggests that starting early treatment with HCQ (within 1 day of admission) on the regular COVID-ward

might prevent progression to critical respiratory illness. This is consistent with the suggestion that HCQ treatment reduces the risk of disease progression more effectively earlier in the course of the disease [20,21]. This holds true for many other viral infections such as influenza and herpes simplex, where treatment must be initiated soon after onset of symptoms in order to confer benefit. However, treatment with HCQ before onset of symptoms did not prevent COVID-19, as was demonstrated in a randomized controlled trial investigating post-exposure use of HCQ [22].

Second, we cannot demonstrate a significant effect of treatment with HCQ or CQ on the on-ward-mortality. One of the strengths of our study is that we have selected a clearly defined cohort of patients on the regular non-ICU COVID-ward, thus our results reflect mortality before transfer to the ICU only. In recent literature, evidence is accumulating that there is no beneficial effect of HCQ on mortality. Mortality numbers in systematic reviews and in prospective HCQ-studies such as the Recovery trial, are frequently reported as 28-day all-cause mortality and do not differentiate between on-ward mortality and mortality after transfer to the ICU [13,14]

In our study, there was no significant difference in outcome between patients treated with AZM, nor in patients on ACEi or ARB therapy. ARB-therapy was suggested to increase the susceptibility to COVID-19, but other studies report conflicting results [23,24]. Our data confirm the lack of effect on outcome, both of pre-hospital use, as well as in-hospital continuation of ACEi or ARB therapy.

Surprisingly, we found a differential effect of HCQ and CQ in COVID-19, while in literature these drugs are frequently reported as a composite outcome. There are several possible

explanations for this differential effect. The first explanation is a possible difference in pharmacokinetics of both drugs. There is a substantial difference in renal drug-clearance, 51% in CQ and 21% in HCQ [4]. Furthermore, the distribution volumes of HCQ and CQ are different; HCQ has a volume of distribution of 5522 liter (whole blood), as compared to 14000-56000 liters in CQ [25–27]. It is still a matter of debate whether the 4-aminoquonolone drugs have anti-viral activity or immuno-modulating properties[6,28]. The immuno-modulating effect of HCQ in has been reported in rheumatology literature[4]. In clinical practice, patients with rheumatoid disease are treated with HCQ but not CQ as anti-inflammatory therapy, according to clinical guidelines[29] . It is conceivable that the beneficial effect of early HCQ in COVID-19 lies in the reduction of localized inflammation in the lung. This is supported by the results of a recent observational study that indicate that the use of moderate-dose systemic corticosteroids on the general ward lowered the hazard of ICU transfer[30].

Another important strength of our study is the random distribution of patients between hospitals with different treatment protocols. Unintentionally, three groups of patients were created, almost as in prospective research. We were able to investigate the difference between patients on or off treatment with a reduced risk on bias by indication.

This study has some limitations. First, all observational cohort studies are prone to bias by confounding. We used weighted propensity scores to adjust optimally for differences between treated patients and controls. However, randomized studies are needed to confirm our data. Another limitation of this study is a lack of data on adverse effects of (H)CQ. There is ongoing global discussion about possible drug toxicity in COVID-19 patients and increased mortality associated with HCQ treatment [31,32]. Since HCQ and CQ are FDA and EMA approved drugs, the adverse effects are well documented [24]. Yet, these adverse effects are

similar to the commonly reported COVID-19 symptoms (fever, fatigue, dry cough, dyspnea, myalgia) and also nausea and diarrhea are frequently observed [33,34]. Older patients are more likely to have abdominals complaints as presenting symptoms of COVID-19 [35]. We therefore decided to refrain from collecting patient-reported symptoms retrospectively, because of the difficulty distinguishing symptoms of COVID-19 from adverse effects of (H)CQ treatment.

It is postulated that the pathophysiology of COVID-19 is characterized by three stages of illness [36]. In the initial viral phase (phases 1-2) patients are moderately affected, viral replication and localized inflammation in the lung cause hypoxemia and lymphopenia, and patients are admitted to the hospital cohort-ward. This phase is followed by systemic hyperinflammation (phase 3) and severe disease, where patients are potentially admitted to the ICU for invasive mechanical ventilation. In this phase, the use of stronger immuno-modulating agents such as hydrocortisone, dexamethasone, anakira and tocilizumab can be considered [13,37].

In conclusion, our observational study demonstrates that the early clinical use of HCQ - but not CQ - in hospitalized non-ICU COVID-19 patients is associated with a decreased risk of transfer to the ICU. Once patients are critically ill, the process of hyper-inflammation and – coagulation is probably not influenced by HCQ, and treatment with strong immune-suppressants and anti-coagulant therapy are more important for the survival of patients with severe COVID-19.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We state on behalf of all the authors that there are no known competing financial interests, or personal relationships that could have appeared to influence the work reported in this paper.

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The Medical Ethics Review Committee waived ethical Approval for this study.

Appendix.

This Appendix contains a complete description of the statistical analysis that was performed.

Statistical analysis

Differences between HCQ and CQ and controls were compared using $\chi 2$ statistics or the Fisher exact test for categorical variables and the independent t-test or Mann-Whitney U-test for continuous

variables. HCQ and CQ use was related to the primary endpoints 'death' and 'ICU admission' using univariate and multivariable analyses within a Cox proportional hazard regression framework. Follow-up commenced at the date of hospital admission and ended at the date of death, date of ICU admission or date of discharge; whichever came first. The proportional hazards assumption was confirmed by the Schoenfeld's global test and inspection of log (−log [survival]) curves. Kaplan-Meier estimates were used to construct survival curves and the log-rank $\chi 2$ was used to compare the curves. For correction for the nonrandomized observational design of the study, propensity score (PS) matching was used for making causal inferences of the treatment on the clinical outcome. A set of pre-test covariates that were associated with the treatment was selected, based on results of univariate and stepwise regression analysis together with the clinical relevance. PS were estimated for each patient using logistic regression with the treatment assignment HCQ or CQ as the outcome measure. The balance on the covariates throughout the matching procedure was checked by comparing the treatment and control group before and after matching, using the standardized mean difference of covariates. The treatment effects were estimated by calculating the hazard ratio for HCQ and CQ use in relation the primary endpoints 'death', 'ICU admission' or the combination of these endpoints, denoted as a 'composite adverse endpoint'. Separate Cox regression models with and without adjustment for potential confounders were used to evaluate the effect of treatment on the different endpoints (See Appendix Table). The first model is an overall Cox model without propensity score matching. Three PS matched methods were used: (1) PS pair matching, e.g. k-Nearest neighbors matching: for each treated patient select k controls with closest propensity scores. The Cox model was run on only those patients and their matched controls. (2) PS stratification: group individuals in 5 groups (quintiles) with similar PS values. (3) Inverse probability of treatment weighting (IPTW) by computing the inverse PS followed by weighing the patients accordingly whilst heavy weights were excluded by skimming. As a result, an artificial sample is created in which the distribution of covariates is equal between treatment groups. In addition to the PS matched models, regression adjustment using PS as a covariate was performed. All analyses were

stratified by ICU restriction, because of the distinct patient characteristics of this group. Appropriate sensitivity analyses were performed to determine the validity of the regression analyses. For PS estimation and matching the PS-matching R package in SPSS and the PSMATCH2 package in Stata were used. All tests were two-sided and $p<0.05$ was considered statistically significant. All statistical analyses were performed using the STATA version 14 statistical package (Stata Corporation, College Station TX).

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Figure 1. Number of included COVID-19 patients.

HCQ = hydroxychloroquine, CQ = chloroquine.

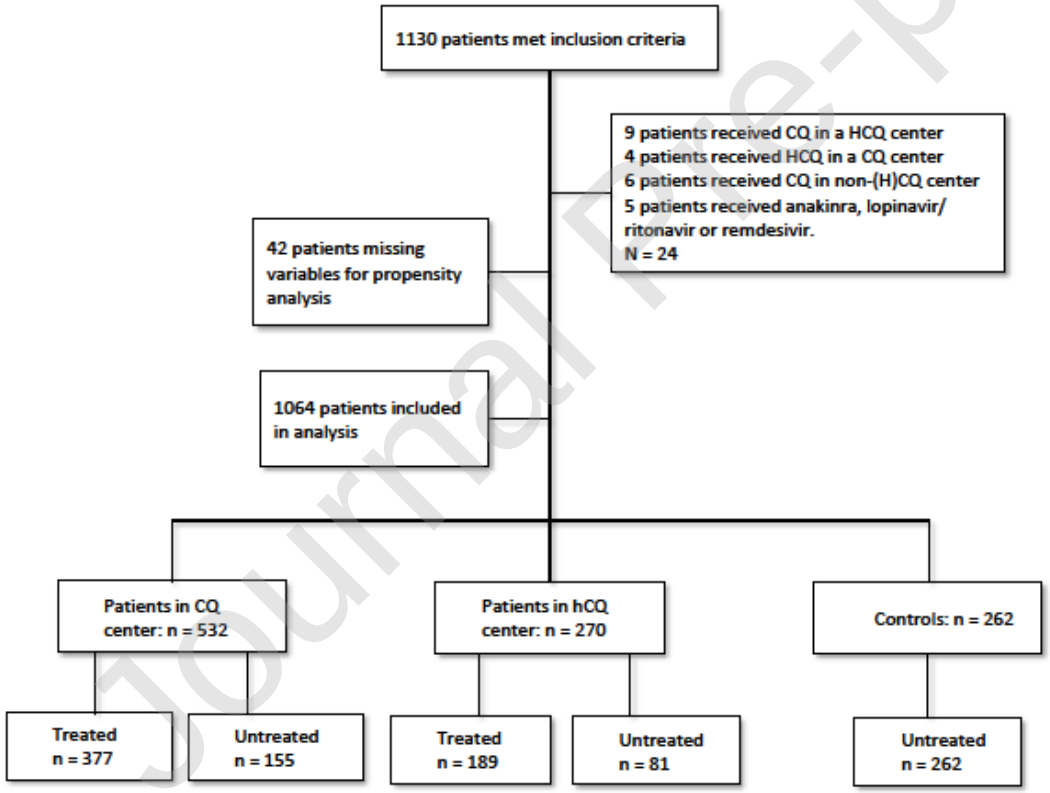

Table 1. Characteristics of the study population.

Total N=1064	Chloroquine centers (N=532)						Hydroxychloroquine centers (N=270)						No therapy centers (N=262)		
Variable	**Treated**		**No treatment**		**Missing**	***P***	**Treated**		**No treatment**		**Missing**	***P***	**All**		**Missing**
Total - N. %	377	35.4	155	14.6			189	17.8	81	7.6			262	24.6	
Gender. Male – N, %	244	64.7	78	50.3	0	0.002*	123	65.1	43	53.1	0	0.063*	156	59.5	0
Age - M. SD	66.4	13.5	71.8	15.3	0	0.000‡	64.7	14.5	63.9	17.2	0	0.944‡	68.8	14.8	0
BMI - M. SD	28.2	4.9	28.1	5.3	98	0.996‡	27.5	4.1	28.5	6.2	147	0.537‡	27.7	5.4	69
ICU-Restriction – N, %	115	30.8	86	55.5	0	0.000*	68	36	29	36	0	0.978*	127	48.5	0
Comorbidities – N, %															
Hypertension	133	35.3	65	41.9	0	0.149*	62	32.8	25	30.9	0	0.755*	103	39.3	0
Heart failure	15	4	24	15.5	0	0.000*	12	6.3	11	13.6	0	0.051*	36	13.7	0
Myocardial infarction	29	7.7	16	10.3	0	0.322*	6	3.2	7	8.6	0	0.054*	27	10.3	0
Atrial fibrillation	43	11.4	41	26.5	0	0.000*	22	11.6	13	16	0	0.323*	34	13	0
CVA	31	8.2	22	14.2	0	0.037*	10	5.3	3	3.7	0	0.577*	20	7.6	0
Diabetes type 1 / 2	69	18.3	46	29.7	0	0.004*	47	24.9	17	21	0	0.492*	49	18.7	0
Asthma or COPD	80	21.2	35	22.6	0	0.729*	21	11.1	17	21	0	0.032*	54	20.6	0
OSAS	24	6.4	6	3.9	0	0.261*	9	4.8	2	2.5	0	0.382*	18	6.9	0
Chronic kidney dis. (creat. >150 umol/L)	14	3.7	7	4.5	1	0.670*	12	6.3	5	6.2	0	0.956*	20	7.6	1
Active malignancy	29	7.7	12	7.7	0	0.984	14	7.4	6	7.4	0	1*	17	6.5	0

Muscle disease	5	1.3	1	0.6	0	0.499*	1	0.5	1	1.2	0	0.536*	6	2.3	1
History of DVT / LE	23	6.1	8	5.2	0	0.686*	11	5.8	5	6.2	0	0.91*	23	8.8	0
Immune suppressive	23	6.1	8	5.2	0	0.674*	8	4.2	1	1.2	0	0.208*	32	12.2	0
Diagnosis based on – N, %															
PCR	359	95.2	145	93.5	0	0.431*	180	95.2	79	96.3	0	0.699*	252	96.2	0
CT	16	4.2	8	5.2	0	0.643*	9	4.8	2	2.5	0	0.382*	9	3.4	0
Clinical Judgement	2	0.5	2	1.3	0	0.357*	0	0	0	0	0	N/A	1	0.4	0
Vitals and laboratory results at presentation - m (N), sd															
Temperature	38.1	1.0	37.9	1.0	1	0.009§	38.1	1.0	38.0	1.0	1	0.476‡	38.0	1.05	1
Oxygen needed.- N.%	326	86.5	93	60	0	0.000*	167	88.4	56	69.1	0	0.000*	163	62.2	0
CRP	97	72.9	83.1	75.8	2	0.003‡	105.3	76.9	64.1	48.5	28	0.0000‡	88.3	74.9	3
Leucocytes	7.0 .	3.1	6.9	3.4	6	0.313‡	7.0	5.1	7.3	4.0	29	0.524‡	7.0	3.0	3
Lymfocytes	1.0	1.4	1.0	1.0	20	0.901‡	1.3	4.4	1.3	1.1	63	0.006‡	1.1	1.0	37
Platelets	207.9	83.5	204.9	81.2	11	0.443‡	205.6	95.68	177.6	107.4	67	0.357‡	203.3	86.2	6
Creatinine	93.1	44.7	106	68.1	3	0.090‡	92.8	73.5	103.0	112.6	29	0.096‡	107.9	107.6	4
LDH at presentation	356.2	142.3	312.2	118.5	40	0.000‡	346.7	148.1	340.1	140.1	54	0.692‡	347.2	143.6	22
Pre-hospital medication - N. %															
ACE inhibitors	55	14.6	34	22.1	2	0.037*	30	16.0	15	18.8	0	0.588*	52	20.1	3
Angiotensine-2 receptor antagonists	48	12.8	24	15.6	2	0.390*	25	13.4	9	11.3	4	0.624*	27	10.5	4
Therapeutic. anticoag.	50	13.3	37	24	2	0.002*	29	15.8	17	21.5	7	0.26*	51	19.9	6
In-hospital medication															

Broad-spectr.antibiotics, N. %	327	86.7	99	63.9	0	0.000*	185	97.9	71	87.7	0	0.0010*	196	74.8	0
Azithromycin - N. %	31	8.2	33	21.3	0	0.000*	48	25.4	45	55.6	0	0.0000*	53	20.2	0
Cumulative dosage AZM - m (N). sd	833.3	461.1	1241.9	560.8	3	0.001‡	2020.8	1115.5	1661.1	834.5	0	0.137‡	2264.4	925.4	1
Cumulative dosage CQ / HCQ - m (N). sd	2179.5	897.6	N/A	N/A	1	N/A	1823.5	636.1	N/A	N/A	19	N/A	N/A	N/A	N/A
Therapeutic. anticoag.- N, %	66	17.5	51	32.9	0	0.000*	38	20.1	19	23.5	0	0.536*	56	21.4	0
Prophilactic anticoag. – N, %	318	84.4	99	63.9	0	0.000*	161	85.2	57	70.4	0	0.005*	148	56.5	0
Deep venous thrombosis – N, %	1	0.3	0	0	3	0.519*	0	0	0	0	1	N/A	2	0.8	3
Pulmonary embolism - N. %	6	2.1	1	0.8	115	0.355*	3	1.6	0	0	4	0.253*	4	1.5	3
Endpoints															
Discharged for cured infection - N. %	245	65.0	107	69.0	0	0.370*	139	73.5	58	71.6	0	0.742*	177	67.6	0
ICU-admission - N. %	72	19.1	10	6.5	0	0.000*	20	10.6	3	3.7	0	0.064*	42	16.4	0
Death or hospice - N. %	60	15.9	38	24.5	0	0.020*	30	15.9	20	24.7	0	0.087*	43	16.0	0

M = mean. SD = standard deviation. *=χ2 test. †=Fisher- exact test. §=Independent t-test. ‡=Non-parametric Mann-Whitney test.

HCQ= hydroxychloroquine. CQ = chloroquine. AZM = azithromycin. BMI = body mass index. ICU = intensive care unit. CVA = cerebrovascular accident. OSAS = obstructive sleep apnea syndrome. DVT = deep venous thrombosis. PE = pulmonary embolism.

Table 2: Clinical outcome Hazard Ratio (HR) estimates for HCQ and CQ use among COVID19 patients under separate risk models.

N=1012*		Endpoint: death						Endpoint: ICU admission						Combined endpoint					
		unadjusted			Adjusted [3]			unadjusted			Adjusted [4]			unadjusted			Adjusted [5*]		
model	**drug use**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**
overall[1]	None (ref)	1.0			1.0			1.0			1.0			1.0			1.0		
	CQ	0.64	0.47-0.88	0.007	1.01	0.71-1.44	0.937	1.50	1.05-2.13	0.024	0.91	0.63-1.31	0.619	0.94	0.74-1.18	0.590	0.97	0.75-1.24	0.795
	HCQ	0.62	0.41-0.93	0.020	0.92	0.58-1.46	0.736	0.82	0.49-1.37	0.453	0.56	0.33-0.95	0.031	0.69	0.50-0.95	0.023	0.73	0.51-1.02	0.068
Weighted Competing Risk[2]	None (ref)	1.0												1.0			1.0		
	CQ	0.86	0.61-1.21	0.392	0.99	0.70-1.43	0.991	0.93	0.64-1.35	0.708	0.80	0.55-1.15	0.207	0.85	0.67-1.10	0.205	0.85	0.66-1.10	0.224
	HCQ	0.87	0.58-1.32	0.518	0.96	0.63-1.45	0.681	0.52	0.30-0.89	0.017	0.47	0.27-0.82	0.008	0.66	0.48-0.91	0.011	0.68	0.49-0.95	0.024

[1] Cox regression model without propensity score (PS) adjustment and competing regression analysis; [2] Competing Risk regression with weighted PS adjustment (see statistical method section for explanation of the different models), HR= Hazard Ratio, CI=confidence Interval, CQ = Chloroquine, HCQ=hydroxychloroquine, * total number patients in the analysis

[3, 4, 5] Adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity Asthma/COPD, use of broad spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day at ED, ICU restriction.

All analyses except the compering risks regression were stratified by ICU restriction to reflect underlying potential differences in adverse incidences and risk factor prevalences.

Figure 2. Cumulative incidence functions (CIF) by type of medication.

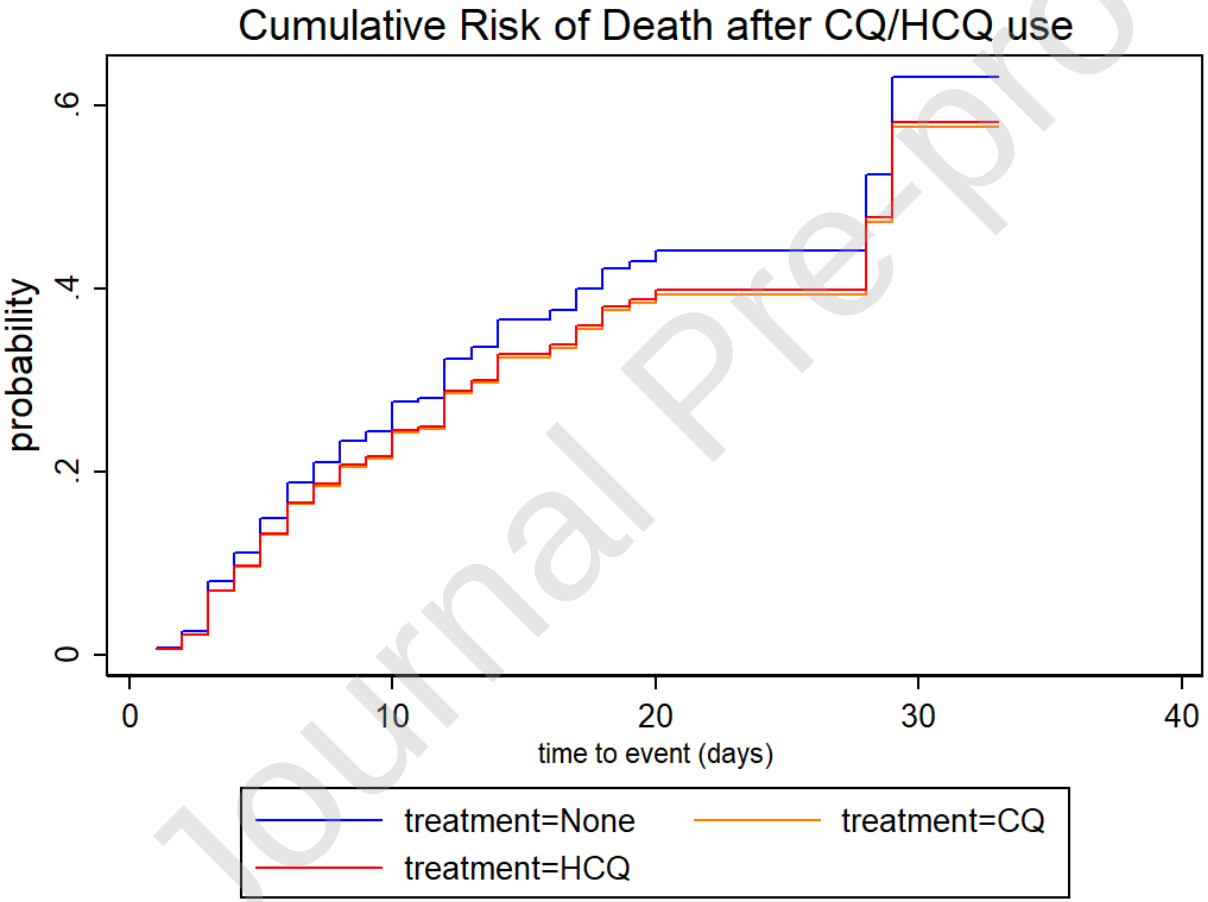

Figure 2A. Cumulative risk of death.

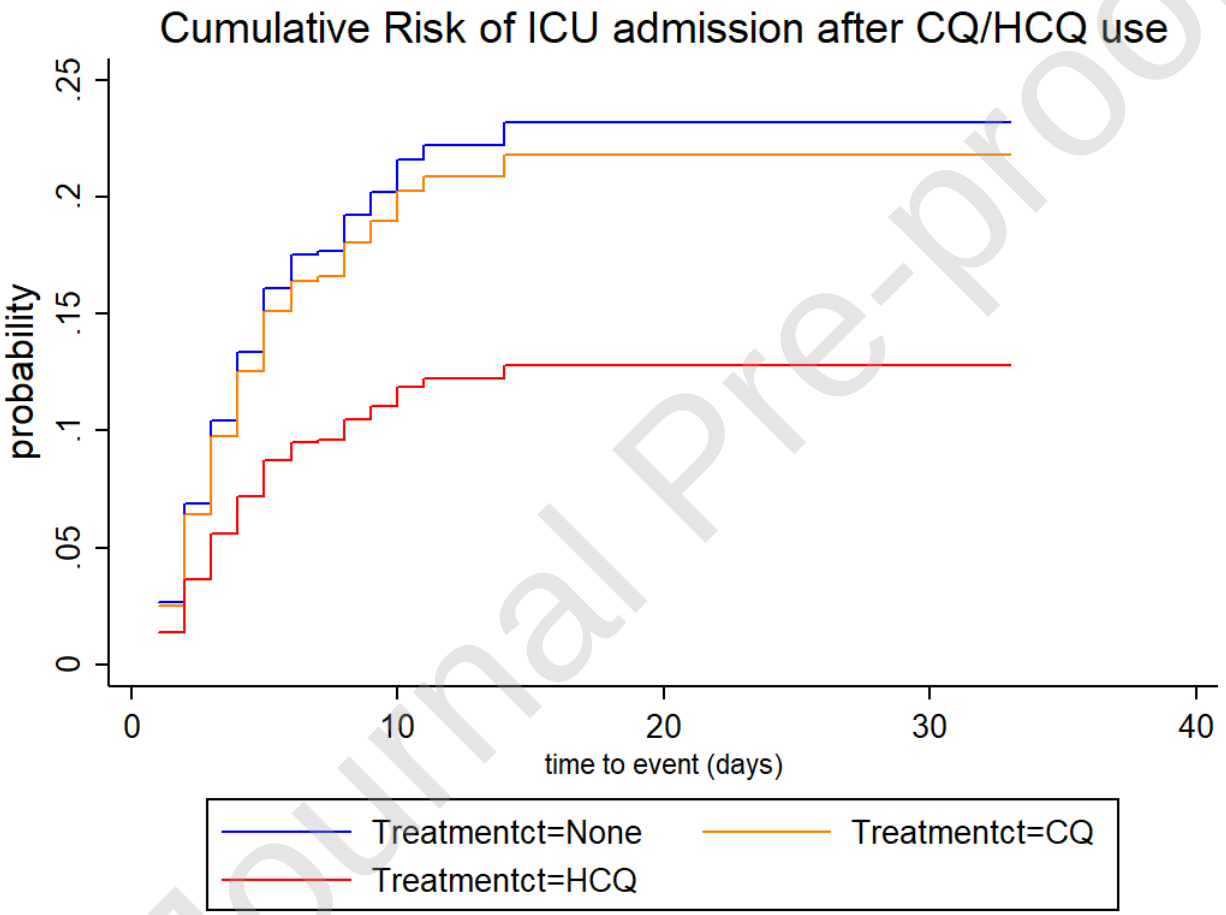

Figure 2B. Cumulative risk of transfer to ICU.

Appendix table: Clinical outcome Hazard Ratio estimates for HCQ and CQ use, among COVID19 patients under separate propensity risk models.

N=1012*		Endpoint: death						Endpoint: ICU admission						Combined endpoint					
		unadjusted			adjusted[3]			unadjusted			adjusted[3]			unadjusted			adjusted[4]		
model	**drug use**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**	**HR**	**95%CI**	**Pvalue**
overall[1]	None (ref)	1.0			1.0			1.0			1.0			1.0			1.0		
	CQ	0.64	0.47-0.88	0.007	1.01	0.71-1.44	0.937	1.50	1.05-2.13	0.024	0.91	0.63-1.31	0.619	0.94	0.74-1.18	0.590	0.96	0.75-1.24	0.772
	HCQ	0.62	0.41-0.93	0.020	0.92	0.58-1.46	0.736	0.82	0.49-1.37	0.453	0.56	0.33-0.95	0.031	0.69	0.50-0.95	0.023	0.71	0.51-1.01	0.054
Matched paired[2]	None (ref)	1.0			1.0			1.0			1.0			1.0			1.0		
	CQ	0.66	0.38-1.13	0.130	0.59	0.23-1.52	0.272	0.85	0.53-1.38	0.523	0.82	0.41-1.64	0.567	0.77	0.53-1.10	0.144	0.85	0.50-1.43	0.535
	HCQ	0.66	0.34-1.26	0.207	0.35	0.12-1.03	0.057	0.41	0.22-0.78	0.007	0.48	0.21-1.08	0.075	0.51	0.32-0.81	0.004	0.50	0.28-0.91	0.023
Stratified quintiles[2]	None (ref)	1.0			1.0			1.0			1.0			1.0			1.0		
	CQ	0.77	0.54-1.08	0.124	0.98	0.68-1.41	0.919	0.97	0.67-1.40	0.863	0.79	0.54-1.14	0.204	0.86	0.67-1.11	0.242	0.89	0.69-1.15	0.373
	HCQ	0.84	0.55-1.30	0.431	0.86	0.54-1.39	0.547	0.48	0.29-0.82	0.007	0.50	0.29-0.84	0.010	0.65	0.46-0.91	0.011	0.66	0.46-0.94	0.020
Weighted[2]	None (ref)	1.0			1.0			1.0			1.0			1.0			1.0		
	CQ	0.81	0.58-1.15	0.243	0.94	0.65-1.35	0.732	0.91	0.63-1.32	0.615	0.79	0.55-1.15	0.217	0.85	0.67-1.10	0.205	0.85	0.66-1.10	0.228
	HCQ	0.78	0.52-1.18	0.244	0.93	0.61-1.41	0.734	0.50	0.29-0.85	0.011	0.47	0.27-0.82	0.008	0.66	0.48-0.91	0.011	0.68	0.49-0.95	0.022

[1] Cox regression model without propensity score (PS) adjustment; [2] PS adjustment see statistical method section for explanation of the different models, HR= Hazard Ratio, CI=confidence Interval, CQ = Chloroquine, HCQ=hydroxychloroquine

[3] Adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity Asthma/COPD, use of of broad spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day at ED.

[4] Adjusted for gender, age, comorbidity Asthma/COPD, use of broad spectrum antibiotics, prophylactic anticoagulation, first day at ED.

* All analyses were stratified by ICU restriction to reflect underlying potential differences in adverse incidences and risk factor prevalences.