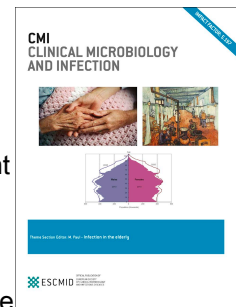# Journal Pre-proof

Outcomes of persons with COVID-19 in hospitals with and without standard treatment with (Hydroxy)chloroquine

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1 Original Article

2 Outcomes of Persons With COVID-19 in Hospitals With and
3 Without Standard Treatment With (Hydroxy)chloroquine
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100 Abstract

101

102 **Objective**

103 To compare survival of subjects with COVID-19 treated in hospitals that either did or did not

104 routinely treat patients with hydroxychloroquine or chloroquine.

105 **Methods**

106 We analysed data of COVID-19 patients treated in 9 hospitals in the Netherlands. Inclusion dates

107 ranged from February 27th 2020, to May 15th, when the Dutch national guidelines no longer

108 supported the use of (hydroxy)chloroquine. Seven hospitals routinely treated subjects with

109 (hydroxy)chloroquine, two hospitals did not. Primary outcome was 21-day all-cause mortality. We

110 performed a survival analysis using log-rank test and Cox-regression with adjustment for age, sex and

111 covariates based on premorbid health, disease severity, and the use of steroids for adult respiratory

112 distress syndrome, including dexamethasone.

113 **Results**

114 Among 1949 included subjects, 21-day mortality was 21.5% in 1596 subjects treated in hospitals that

115 routinely prescribed (hydroxy)chloroquine, and 15.0% in 353 subjects that were treated in hospitals

116 that did not. In the adjusted Cox-regression models this difference disappeared, with an adjusted

117 hazard ratio of 1.09 (95%CI 0.81-1.47). When stratified by actually received treatment in individual

118 subjects, the use of (hydroxy)chloroquine was associated with an increased 21-day mortality (HR

119 1.58; 95%CI 1.24-2.02) in the full model.

120 **Conclusions**

121 After adjustment for confounders, mortality was not significantly different in hospitals that routinely

122 treated patients with (hydroxy)chloroquine, compared with hospitals that did not. We compared

123 outcomes of hospital strategies rather than outcomes of individual patients to reduce the chance of

124 indication bias. This study adds evidence against the use of (hydroxy)chloroquine in hospitalised

125 patients with COVID-19.

126   Introduction

127

128   The spread of SARS-CoV-2, leading to the current pandemic of COVID-19, has a profound global

129   impact on daily life, morbidity and mortality. Several preliminary studies have reported that the

130   antimalarial agents hydroxychloroquine and chloroquine, or (H)CQ, alone or in combination with the

131   antibiotic azithromycin, can have a suppressive effect on the viral replication, and might decrease the

132   mortality of COVID-19[1-5]. So far, clinical studies have been hampered by confounding by

133   indication[1,2,4,5], monocentre setup[2,3], and small numbers of included subjects[3]. A recently published

134   systematic review[6], a published randomized controlled trial[7] and an RCT only available in pre-print[8],

135   suggested that hydroxychloroquine is not effective in patients admitted to hospital. Side effects of

136   (H)CQ are well-known, and include fever and cardiac arrhythmias. While we are awaiting definite

137   results from more RCTs, cohort studies can provide quick closure of existing knowledge gaps. When

138   treatment assignment in cohort studies is based on prescriber discretion, the risk of indication bias

139   (even after covariate adjustment) remains high. However, our database of Dutch hospitals contains

140   data of subjects from hospitals that either routinely prescribed (H)CQ or did not prescribe it at all,

141   offering a unique opportunity to compare both strategies. The comparison of different treatment

142   strategies among hospitals leads to a significant reduction of (indication) bias. The objective of this

143   study was to compare the effect of hospital-wide COVID-19 treatment strategies with or without

144   routine (H)CQ use on all-cause 21-day mortality.

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148   Methods

149

150   We used data from the ongoing CovidPredict Clinical Course Cohort containing over 2,000 persons

151   with COVID-19[9], from 9 hospitals in the Netherlands, including two university hospitals. Included in

152   the database were all subjects admitted to hospital with positive SARS-CoV-2 PCR of nasopharynx,

153   throat, sputum or bronchoalveolar lavage samples, or CT-scan abnormalities that were typical for

154   COVID-19 (CO-RADS 4 and 5)[10], without another explanation for the abnormalities than COVID-19.

155   Inclusion dates ranged from the first admitted case in the Netherlands on February 27th 2020, to May

156   15th, when the Dutch national guidelines no longer advised the use of (H)CQ. We excluded patients <

157   18 years and patients who were transferred to or from another hospital. Dosage of chloroquine base

158   was: loading dose of 600 mg, followed by 300 mg twice a day for a total of 5 days. Dosage of

159   hydroxychloroquine sulphate was 400 mg twice daily on the first day, followed by 200 mg twice daily

160   on days 2 to 5. Among the seven (H)CQ-hospitals, the timing of start of (H)CQ treatment differed;

161   three hospitals started at the moment of COVID-19 diagnosis, four started after diagnosis but only

162   when patients clinically deteriorated e.g., when there was an increase in respiratory rate or increase

163   in use of supplemental oxygen. The two hospitals that did not routinely treat subjects with (H)CQ

164   (i.e., the non-(H)CQ-hospitals), offered best supportive care, including oxygen therapy and

165   potentially antibiotic therapy, according to local guidelines and prescriber discretion. Participating

166   hospitals did not routinely prescribe other experimental medication (e.g., lopinavir/ritonavir,

167   remdesivir or steroids, see Table 1). Subjects who were incidentally treated with these drugs were

168   included in the study. Primary outcome was 21-day all-cause mortality, defined as hospital mortality,

169   or discharge to a hospice care facility. A waiver for the use of hospital record data was obtained

170   through the Institutional Review Board of Amsterdam UMC; however, patients were given the

171   opportunity to opt out. We collected data according to the collection protocol of the World Health

172   Organization. Missing covariates were imputed using multiple imputation with the MICE package

173   (version 3.8.0) and the outcomes were determined by pooling the results of 25 imputed datasets [11].

174   We performed a regression analyses and determined the pooled effect. Missing data range for all

175   covariates was less than 2.8%, except for obesity (missing data 6.2%) and use of corticosteroids

176   (22.3%). In the primary analysis, we compared effectiveness of (H)CQ versus non-(H)CQ hospital

177   strategies, irrespective of actual individual (H)CQ treatment. We performed a survival analysis using

178   log-rank test and Cox-regression with adjustment for age, sex, time in the pandemic (i.e., the number

179   of elapsed days after March 1st 2020 at hospital admission),and covariates based on premorbid

180   health (i.e., history of lung, kidney and cardiovascular disease, diabetes mellitus, obesity, and

181   neoplasms or hematologic disease), disease severity during presentation (respiratory rate, oxygen

182   saturation) and the use of steroids, including dexamethasone, for adult respiratory distress

183   syndrome (ARDS)[12,13]. We repeated the analyses comparing actually received treatment, with (H)CQ.

184   In a secondary analysis, we used a composite endpoint (either mechanical ventilation or all-cause

185   mortality) at 21 days. As a sensitivity analysis, we performed a complete case analysis using inverse

186   probability weighting of propensity scores (determined using the same covariates). We performed a

187   subgroup analysis in (H)CQ hospitals that started (H)CQ directly from the moment of diagnosis versus

188   outcomes in non-(H)CQ hospitals. All statistical analyses were performed using R versions 3.6.3 (R

189   Foundation, Vienna, Austria).

190

Results

192

193   We analysed results of 1949 of 2152 subjects admitted before May 15th 2020. 203 were excluded

194   because they were transferred from another hospital. No subject opted out. Demographic data are

195   shown in Table 1. Follow-up data were missing for 20 (1.0%) subjects. The patients with missing

196   outcome data were included Table 1 and in the survival analysis, and were censored at the last day at

197   which clinical information was available in the database. In total, 1596 subjects were treated in

198   hospitals where (H)CQ was a standard part of treatment strategy ((H)CQ hospitals) and 353 in

199 hospitals where (H)CQ was not a standard part of treatment (non-(H)CQ hospitals). The two non-

200 (H)CQ hospitals were both university hospitals. In (H)CQ-hospitals, 54.7% of the subjects received

201 (H)CQ, compared with 2.0 of the subjects in the non-(H)CQ-hospitals. In (H)CQ hospitals that

202 routinely starting (H)CQ at the moment of COVID-19 diagnosis, 48.3% of subjects received (H)CQ, in

203 hospitals that started (H)CQ at clinical deterioration, 61.9% received (H)CQ. Among the seven (H)CQ-

204 hospitals, two used hydroxychloroquine during the first half and chloroquine during the second half

205 of the epidemic, whereas five hospitals used chloroquine only. Subjects in (H)CQ-hospitals were

206 older (68 (SD: 14) vs 62 (SD: 15) years) and had a higher prevalence of chronic pulmonary disease

207 (27.7 vs 22.1) than subjects in the non-(H)CQ-hospitals. Respiratory rate and peripheral oxygen

208 saturation during admission were similar in both hospital groups (see Table 1). In (H)CQ-hospitals,

209 9.6% of subjects received corticosteroids for ARDS and 4.0 were in a study protocol of an

210 experimental SARS-CoV-2 directed antiviral (e.g., lopinavir/ritonavir) or immunomodulatory drug trial

211 (e.g., imatinib, anti-complement C5), versus 2.3% and 11.3% in non-(H)CQ-hospitals, respectively.

212 Figure 1 shows the survival of subjects in (H)CQ- versus non-(H)CQ-hospitals. Unadjusted mortality at

213 day 21 was significantly higher in the (H)CQ hospitals (343/1596, 21.5%) compared with the non

214 (H)CQ-hospitals (53/353, 15.0%, p=0.008). However, in the Cox-regression models, this difference

215 disappeared, with an adjusted hazard ratio of 1.09 (95%CI 0.81-1.47, Figure 1, Table 2). When

216 stratified by actually received treatment, the use of (H)CQ was associated with an increased 21-day

217 mortality (HR 1.58; 95%CI 1.24-2.02, Table 3) in the full model. In the secondary analysis with either

218 mechanical ventilation or all-cause mortality at 21 days, there were no statistically significant

219 differences between the (H)CQ and non-(H)CQ hospitals (crude p=0.055, adjusted HR 0.87 (95%CI

220 0.68-1.10), Online Supplement 1). The complete analysis using propensity scores for treatment

221 strategy and actual treatment showed similar results (see Table 4). An overview of the distribution of

222 the propensity scores is given in Online Supplement 2[14]. The sensitivity analysis of hospitals routinely

223 starting (H)CQ treatment from the moment of COVID-19 diagnosis (i.e., (H)CQ hospitals without the

224 hospitals that initiated (H)CQ treatment upon clinical deterioration) compared with non-(H)CQ-

225 hospitals, showed similar results with a significantly higher unadjusted 21-day mortality in (H)CQ-

226 hospitals (154/670, 23.0%), compared with non-(H)CQ hospitals (53/353, 15.0%, p=0.002). This was

227 attenuated towards a HR of 0.98 (95%CI 0.70-1.37) after adjustment for age, sex, comorbidities, and

228 disease severity at presentation (Online Supplement 3).
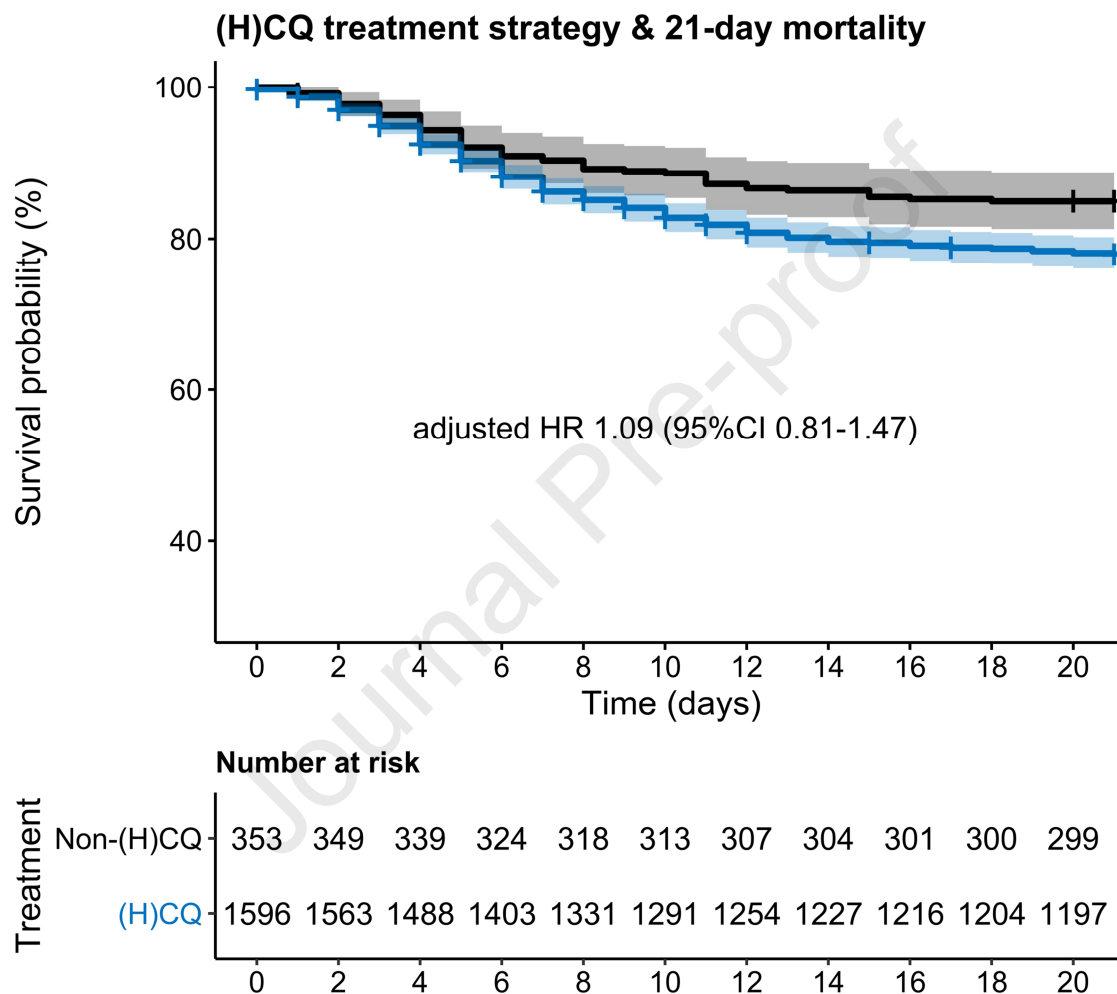
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231 Figure 1: Kaplan-Meier analysis of 21 day mortality of subjects in the (H)CQ-hospitals (blue) versus

232 non-(H)CQ-hospitals (black), showing a significantly higher 21-day mortality in (H)CQ hospitals,

233 p=0.004. This was attenuated towards a HR of 1.09 (95%CI 0.81-1.47) in the full regression model,

234 see Table 2. Shaded areas indicate 95% confidence interval.

235

236

Discussion

238

239 Mortality in subjects treated in hospitals that routinely prescribed (H)CQ was not significantly

240 different from those treated in hospitals that routinely did not prescribe (H)CQ after adjustment for

241 age, sex, medical history, disease severity at presentation and steroid use during treatment.

242 Similarly, we found an increased risk of death among subjects who had actually received treatment

243 with (H)CQ, which has likely been driven by indication bias, as in four of the seven (H)CQ-hospitals,

244 (H)CQ was only prescribed upon clinical deterioration. The unique characteristics of our study cohort

245 enabled a study design that minimized indication bias. Our results add further weight to existing

246 evidence against the use of (H)CQ for the treatment COVID-19.

247

248 The strength of this study is that data were collected in nine hospitals, including two university

249 hospitals, in the Netherlands during the COVID-19 epidemic. Data collection was set up prospectively

250 and the database included data on all consecutive subjects admitted to general medicine and

251 pulmonology wards, and to intensive care units. The database was set up according to the WHO

252 standards, which enabled data comparison and uniformity of data among the different participating

253 centres. The comparison of hospital-defined treatment strategies rather than the treatment actually

254 received led to a lower risk of indication bias compared with previous studies[1,2,4,5]. We roughly

255 estimate the extend of the effect of indication bias to be the difference in outcome between the

256 uncorrected and the corrected model. Further strengths include the multicentre setup[2,3], as

257 mentioned above, and the relatively large numbers of included subjects[3].

258

259 There are some limitations we need to address. Although health care in the Netherlands has a

260 homogeneous setup, there was some variability in standard protocols among the hospitals that could

261 have led to residual confounding. The two non-(H)CQ-hospitals were tertiary (university) centres,

262 whereas the (H)CQ-hospitals comprised both secondary and tertiary care hospitals. Before the

263 COVID-19 pandemic, the tertiary care hospitals and their intensive care units function as referral

264 centres for local secondary care hospitals. Since we excluded subjects transferred to and from other

265 hospitals, the referral role of the tertiary care hospitals, including the university hospitals, was

266 minimized. Furthermore, subjects in the (H)CQ hospitals were more likely to receive steroid

267 treatment, while subjects in the non-(H)CQ hospitals were more likely to receive other experimental

268 immunomodulatory drugs. The numbers of the individual types of medication were small, making it

269 impossible to draw conclusions from these differences. The results of the RECOVERY trial, suggested

270 a lower mortality in patients treated with dexamethasone[15]. Treatment with dexamethasone could

271 therefore have resulted in a lower mortality in the group of (H)CQ hospitals. We did not find such an

272 effect, even after correction in the full model. We also used extensive covariate adjustments, using

273 various methods to minimize influence of differences in patient population among hospitals, and the

274 similarity in outcomes between these methods is reassuring in this regard. Finally, because not every

275 subject in the (H)CQ-hospitals actually received (H)CQ, the current efficacy estimate in our study is

276 likely an underestimation of the true (H)CQ effect. Performing an instrumental variable analysis

277 would have provided an approximation of this true effect, but because the current efficacy point

278 estimates point toward harm rather than benefit of (H)CQ, this likely would not have changed our

279 conclusions.[16]

280

281 Despite the positive results of some studies resulting in widespread use of (H)CQ, our study did not

282 show a benefit of (H)CQ treatment. This may be explained by the timing of the administration of the

283 drug and its specific working mechanism. Chloroquine binds *in silico* and *in vitro* with high affinity to

284 sialic acids and gangliosides of SARS-CoV-2. These bindings inhibit the interaction at non-toxic plasma

285 levels with ACE-2 receptors and could hypothetically stop the cascade from formation of pulmonary

286 infiltrations to full blown ARDS and death[17-19]. The antiviral activity might be more effective in the

287   pre-clinical setting as the deterioration in the hospital is more an effect of the cytokine storm

288   provoked by SARS-CoV-2 than an effect of the viral infection itself. This hypothesis might explain why

289   the clinical benefit for admitted subjects was absent in our study, although we did not observe a

290   difference in outcome among subjects treated early (at diagnosis) and among those treated later

291   upon clinical deterioration.

292

293   Our results are in line with recently published studies. A RCT suggest a similar lack of effect of

294   hydroxychloroquine with higher rate of adverse effect than in supportive care[7]. Another RCT,

295   published in preprint only, suggested a higher mortality in patients treated with hydroxychloroquine

296   compared with those treated with supportive care[8]. Given the current evidence, we would argue

297   against the use of (H)CQ in hospitals outside the setting of randomized controlled clinical trials.

298

299

Conflict of Interest Disclosure

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Contribution of authors

312

313   All authors have made substantial contributions to the following: (1) the conception and design of

314   the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or

315   revising it critically for important intellectual content, (3) final approval of the version to be

316   submitted.

317   Table 1: Baseline characteristics

318

	Overall	Non-(H)CQ hospital	(H)CQ hospitals
N	1949	353	1596
Age (mean (SD))	66.71 (14.60)	62.02 (15.14)	67.75 (14.28)
Women (%)	771 (39.6)	155 (43.9)	616 (38.6)
Chronic cardiac disease (%)	587 (30.7)	75 (21.3)	512 (32.8)
Hypertension (%)	915 (47.6)	162 (46.2)	753 (47.9)
Asthma or chronic pulmonary disease (%)	510 (26.7)	78 (22.1)	432 (27.7)
Chronic kidney disease (%)	221 (11.6)	38 (10.8)	183 (11.8)
Diabetes (%)	501 (26.4)	96 (27.2)	405 (26.2)
Malignancy or chronic hematologic disorder (%)	194 (10.2)	44 (12.5)	150 (9.6)
Smoking (%)	92 (6.2)	18 (6.3)	74 (6.2)
Obesity (%)	556 (30.4)	107 (35.3)	449 (29.4)
Use of (H)CQ	648 (42.6)	7 (2.0)	641 (54.7)
Use of steroids for ARDS (%)	120 (7.9)	8 (2.3)	112 (9.6)
Participation in drug trial (%)	85 (5.7)	39 (11.3)	46 (4.0)
Respiratory rate (mean (SD))	23.20 (6.94)	24.29 (7.32)	22.95 (6.83)
Temperature, ℃, (median [IQR])	37.80 [37.00, 38.60]	37.30 [36.50, 38.20]	38.00 [37.10, 38.70]
Peripheral oxygen saturation, %, (median [IQR])	94.00 [91.00, 96.00]	95.00 [91.00, 97.00]	94.00 [91.00, 96.00]
CRP, mg/L, (median [IQR])	792 (40.8)	157 (44.9)	635 (40.0)
WBC, 10^9 /L, (median [IQR])	79.00 [40.38, 135.00]	82.60 [40.72, 134.62]	78.00 [40.25, 135.00]

PCR positive (%)	1844 (95.7)	314 (89.2)	1530 (97.1)
Time between onset of symptoms and hospital admission, days, (median [IQR])	7.00 [5.00, 12.00]	8.00 [5.00, 13.00]	7.00 [5.00, 12.00]
ICU-admission (%)	348 (17.9)	70 (19.8)	278 (17.4)
In patients admitted to the ICU; days between admission and start of mechanical ventilation *	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]	1.00 [0.00, 3.00]

319

320 (H)CQ denotes (hydroxy)chloroquine; CRP C-reactive protein; WBC white blood cell count; PCR-

321 positive a positive test for COVID-19 based on polymerase chain reaction; ICU intensive care unit. *

322 Data of one centre were missing.

323

324

325   Table 2: Results of Cox-regression models for treatment strategy

326

Cox-regression for treatment strategy

	HR	95%CI		p-value
(H)CQ treatment strategy	**1.09**	**0.81**	**1.47**	**0.568**
Women	1.04	0.84	1.29	0.715
Age	1.07	1.06	1.08	<0.001
Chronic cardiac disease	1.23	0.98	1.53	0.068
Asthma or chronic pulmonary disease	1.14	0.91	1.42	0.250
Chronic kidney disease (%)	0.99	0.74	1.31	0.919
Malignant neoplasm or chronic hematologic disorder (%)	1.34	1.00	1.79	0.051
Diabetes	1.34	1.07	1.68	0.010
Hypertension	1.06	0.85	1.33	0.577
Obesity	1.23	0.97	1.57	0.087
Peripheral oxygen saturation	0.95	0.94	0.97	<0.001
Respiratory rate	1.04	1.03	1.06	<0.001
Use of steroids for ARDS	1.78	1.26	2.52	0.001
Time in pandemic	0.98	0.97	0.99	<0.001

327   **(**H)CQ denotes (hydroxy)chloroquine, ARDS acute respiratory distress syndrome. HR indicate

328   multivariable hazard ratios, 95%CI the lowest and highest values of confidence interval.

329

330   Table 3: Results of Cox-regression models for actual treatment

331

Cox-regression for actual treatment

	HR	95%CI		p-value
(H)CQ treatment				
	1.58	1.24	2.02	<0.001
Women	1.06	0.86	1.31	0.587
Age	1.07	1.06	1.08	0.000
Chronic cardiac disease	1.26	1.01	1.57	0.041
Asthma or chronic pulmonary disease	1.10	0.89	1.37	0.377
Chronic kidney disease (%)	1.00	0.75	1.32	0.977
Malignancy or chronic hematologic disorder (%)	1.36	1.02	1.82	0.037
Diabetes	1.33	1.06	1.66	0.014
Hypertension	1.06	0.85	1.32	0.610
Obesity	1.25	0.98	1.59	0.074
Peripheral oxygen saturation	0.95	0.94	0.97	0.000
Respiratory rate	1.04	1.02	1.06	0.000
Use of steroids for ARDS	1.62	1.14	2.28	0.007
Time in pandemic	0.99	0.98	0.99	0.001

332   (H)CQ denotes (hydroxy)chloroquine, ARDS acute respiratory distress syndrome. HR indicate

333   multivariable hazard ratios, 95%CI the lowest and highest values of confidence interval.

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335

336   Table 4: Complete cases analysis using inverse probability weighting

Complete case analysis using inverse probability weighting

For **treatment strategy**

	HR	95%CI		p-value
(H)CQ treatment strategy	1.17	0.99	1.40	0.072

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338   (H)CQ denotes (hydroxy)chloroquine.

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340   **Complete case analysis using inverse probability weighting**

341   For **actually received treatment**

	HR	95%CI		p-value
(H)CQ received treatment	1.41	1.19	1.66	<0.001

342   (H)CQ denotes (hydroxy)chloroquine.

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345   References

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347   1.   Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or
348   Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA 2020.
349   2.   Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized
350   Patients with Covid-19. N Engl J Med 2020.
351   3.   Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of
352   COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents
353   2020:105949.
354   4.   Covid R, Treatments Collaboration m. Use of hydroxychloroquine in hospitalised COVID-19
355   patients is associated with reduced mortality: Findings from the observational multicentre Italian
356   CORIST study. Eur J Intern Med 2020.
357   5.   Catteau L, Dauby N, Montourcy M, et al. Low-dose Hydroxychloroquine Therapy and
358   Mortality in Hospitalized Patients with COVID-19: A Nationwide Observational Study of 8075
359   Participants. Int J Antimicrob Agents 2020:106144.
360   6.   Fiolet T, Guihur A, Rebeaud M, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of
361   hydroxychloroquine with or without azithromycin on the mortality of COVID-19 patients: a
362   systematic review and meta-analysis. Clin Microbiol Infect 2020.
363   7.   Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate
364   coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849.
365   8.   Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients
366   with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. medRxiv
367   2020:2020.07.15.20151852.
368   9.   https://covidpredict.nl/en. 2020. (Accessed 9 June, 2020,
369   10.   Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS - A categorical CT
370   assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology
371   2020:201473.
372   11.   Wulff J, Ejlskov L. Multiple Imputation by Chained Equations in Praxis: Guidelines and Review.
373   Electronic Journal of Business Research Methods 2017;15:41-56.
374   12.   Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2
375   pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir
376   Med 2020;8:475-81.
377   13.   Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical
378   illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study.
379   BMJ 2020;369:m1966.
380   14.   Lee J, Little TD. A practical guide to propensity score analysis for applied clinical research.
381   Behav Res Ther 2017;98:76-90.
382   15.   Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized
383   Patients with Covid-19 - Preliminary Report. N Engl J Med 2020.
384   16.   Instrumental variable analysis. 2020, at
385   https://journals.lww.com/epidem/Fulltext/2006/05000/Evaluating_Short_Term_Drug_Effects_Using
386   _a.11.aspx.)
387   17.   Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a
388   new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J
389   Antimicrob Agents 2020;55:105960.
390   18.   Fan J, Zhang X, Liu J, et al. Connecting hydroxychloroquine in vitro antiviral activity to in vivo
391   concentration for prediction of antiviral effect: a critical step in treating COVID-19 patients. Clin
392   Infect Dis 2020.

393   19.   Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing
394   Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus
395   2 (SARS-CoV-2). Clin Infect Dis 2020.

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