

1 **Preliminary evidence from a multicenter prospective observational**  
2 **study of the safety and efficacy of chloroquine for the treatment of**  
3 **COVID-19**

4 Mingxing Huang<sup>1\*</sup>, Man Li<sup>2\*</sup>, Fei Xiao<sup>1,2\*</sup>, Jiabi Liang<sup>3\*</sup>, Pengfei Pang<sup>2,4\*</sup>,  
5 Tiantian Tang<sup>5\*</sup>, Shaoxuan Liu<sup>6</sup>, Binghui Chen<sup>7</sup>, Jingxian Shu<sup>3</sup>, Yingying You<sup>8</sup>,  
6 Yang Li<sup>2</sup>, Meiwen Tang<sup>9</sup>, Jianhui Zhou<sup>10</sup>, Guanmin Jiang<sup>10</sup>, Jingfen Xiang<sup>11</sup>,  
7 Wenxin Hong<sup>12</sup>, Songmei He<sup>13</sup>, Zhaoqin Wang<sup>14</sup>, Jianhua Feng<sup>15</sup>, Changqing  
8 Lin<sup>16</sup>, Yinong Ye<sup>17</sup>, Zhilong Wu<sup>18</sup>, Yaocai Li<sup>19</sup>, Bei Zhong<sup>20</sup>, Ruilin Sun<sup>21</sup>,  
9 Zhongsi Hong<sup>1</sup>, Jing Liu<sup>22</sup>, Huili Chen<sup>1</sup>, Xiaohua Wang<sup>23</sup>, Zhonghe Li<sup>24</sup>,  
10 Duanqing Pei<sup>25,26†</sup>, Lin Tian<sup>3†</sup>, Jinyu Xia<sup>1†</sup>, Shanping Jiang<sup>5†</sup>, Nanshan  
11 Zhong<sup>27†</sup>, Hong Shan<sup>1,2†</sup>

12

- 13 1. Department of Infectious Diseases, The Fifth Affiliated Hospital, Sun  
14 Yat-sen University, Zhuhai, Guangdong Province, China  
15 2. Guangdong Provincial Key Laboratory of Biomedical Imaging and  
16 Guangdong Provincial Engineering Research Center of Molecular  
17 Imaging, The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai,  
18 Guangdong Province, China  
19 3. Department of Pharmacy, The Fifth Affiliated Hospital, Sun Yat-sen  
20 University, Zhuhai, Guangdong Province, China  
21 4. Interventional Medical Center, Guangdong Provincial Key  
22 Laboratory of Biomedical Imaging, Zhuhai, Guangdong Province,  
23 China  
24 5. Department of Respiratory and Critical Care Medicine, Sun Yat-sen  
25 Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong  
26 Province, China  
27 6. Clinical Research Center Office, The Fifth Affiliated Hospital, Sun  
28 Yat-sen University, Zhuhai, Guangdong Province, China  
29 7. Department of Radiology, The Fifth Affiliated Hospital, Sun Yat-sen  
30 University, Zhuhai, Guangdong Province, China

- 31 8. Department of Oral and Maxillofacial Surgery, The Fifth Affiliated  
32 Hospital, Sun Yat-sen University, Zhuhai, Guangdong Province,  
33 China
- 34 9. Department of Hematology, The Fifth Affiliated Hospital, Sun Yat-  
35 sen University, Zhuhai, Guangdong Province, China
- 36 10. Department of Clinical Laboratory, The Fifth Affiliated Hospital, Sun  
37 Yat-sen University, Zhuhai, Guangdong Province, China
- 38 11. Department of Emergency, Wuhan East West Lake Mobile Cabin  
39 Hospitals, Wuhan, Hubei Province, China
- 40 12. Department of Infectious Diseases, Guangzhou Eighth People's  
41 Hospital, Guangzhou Province, Guangdong Province, China
- 42 13. Department of Infectious Diseases, Dongguan Ninth People's  
43 Hospital, Dongguan, Guangdong Province, China
- 44 14. Department of Infectious Diseases, Shenzhen Third People's  
45 Hospital, Shenzhen, Guangdong Province, China
- 46 15. Department of Infectious Diseases, Zhongshan Second People's  
47 Hospital, Zhongshan, Guangdong Province, China
- 48 16. Department of Respiratory and Critical Care Medicine, Huizhou  
49 Central People's Hospital, Huizhou, Guangdong Province, China
- 50 17. Department of Infectious Diseases, Foshan First people's Hospital,  
51 Foshan, Guangdong Province, China
- 52 18. Department of Respiratory and Critical Care Medicine, Foshan  
53 Fourth People's Hospital, Foshan, Guangdong Province, China
- 54 19. Department of Infectious Diseases, Maoming People's Hospital,  
55 Maoming, Guangdong Province, China
- 56 20. Department of Infectious Diseases, Qingyuan People's Hospital,  
57 Qingyuan, Guangdong Province, China
- 58 21. Department of Respiratory and Critical Care Medicine, Guangdong  
59 Second People's Hospital, Guangzhou, Guangdong Province, China
- 60 22. Department of Respiratory and Critical Care Medicine, The Fifth  
61 Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong  
62 Province, China
- 63 23. Intensive Care Unit, The Fifth Affiliated Hospital, Sun Yat-sen  
64 University, Zhuhai, Guangdong Province, China

65 24. Department of Nephropathy, The Fifth Affiliated Hospital, Sun Yat-  
66 sen University, Zhuhai, Guangdong Province, China

67 25. Guangzhou Regenerative Medicine and Health Guangdong  
68 Laboratory, Guangzhou, Guangdong Province, China

69 26. Guangzhou Institutes of Biomedicine and Health, Chinese Academy  
70 of Sciences, Guangzhou, Guangdong Province, China

71 27. State Key Laboratory of Respiratory Diseases, The First Affiliated  
72 Hospital of Guangzhou Medical University, Guangzhou, Guangdong  
73 Province, China.

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75 \* These authors contributed equally.

76 † These are the co-corresponding authors.

77 **Abstract**

78 **Background** Effective therapies are urgently needed for the SARS-CoV-2  
79 pandemic. Chloroquine has been proved to have antiviral effect against  
80 coronavirus in vitro. In this study, we aimed to assess the efficacy and safety  
81 of chloroquine with different doses in COVID-19.

82 **Method** In this multicenter prospective observational study, we enrolled  
83 patients older than 18 years old with confirmed SARS-CoV-2 infection  
84 excluding critical cases from 12 hospitals in Guangdong and Hubei Provinces.  
85 Eligible patients received chloroquine phosphate 500mg, orally, once (half  
86 dose) or twice (full dose) daily. Patients treated with non-chloroquine therapy  
87 were included as historical controls. The primary endpoint is the time to  
88 undetectable viral RNA. Secondary outcomes include the proportion of  
89 patients with undetectable viral RNA by day 10 and 14, hospitalization time,  
90 duration of fever, and adverse events.

91 **Results** A total of 197 patients completed chloroquine treatment, and 176  
92 patients were included as historical controls. The median time to achieve an  
93 undetectable viral RNA was shorter in chloroquine than in non-chloroquine  
94 (absolute difference in medians -6.0 days; 95% CI -6.0 to -4.0). The duration  
95 of fever is shorter in chloroquine (geometric mean ratio 0.6; 95% CI 0.5 to 0.8).  
96 No serious adverse events were observed in the chloroquine group. Patients  
97 treated with half dose experienced lower rate of adverse events than with full  
98 dose.

99 **Conclusions** Although randomised trials are needed for further evaluation, this  
100 study provides evidence for safety and efficacy of chloroquine in COVID-19  
101 and suggests that chloroquine can be a cost-effective therapy for combating

102 the COVID-19 pandemic.

## 103 **Introduction**

104           The coronavirus disease 2019 (COVID-19) emerged in late 2019,  
105 originating from Wuhan China<sup>1,2</sup>. The responsible virus, severe acute  
106 respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to a distinct clade  
107 from the human severe acute respiratory syndrome CoV (SARS-CoV) and  
108 Middle East respiratory syndrome CoV (MERS-CoV)<sup>3</sup>. It has become a global  
109 pandemic, affecting over 100 countries with more than 240,000 confirmed  
110 cases and over 10,000 deaths globally as of March 20, 2020, calling for an  
111 urgent demand of effective treatment.

112           Chloroquine has been proved effective in vitro to inhibit the replication  
113 of SARS-CoV<sup>4</sup>, HCoV-229E<sup>5</sup>, and the newly discovered SARS-CoV-2<sup>6,7</sup>. To  
114 evaluate the efficacy and safety of chloroquine for COVID-19, we previously  
115 conducted a single-arm pilot clinical study with 10 patients (Huang et al.  
116 *Journal of Molecular Cell Biology*, in press). Encouragingly, all patients  
117 achieved undetectable level of viral RNA within 14 days without serious  
118 adverse events. These results led us to conduct a multicenter prospective  
119 observational study in adult patients with COVID-19 to assess the efficacy  
120 and safety of chloroquine for COVID-19.

121

## 122 **Result**

### 123 **Patients**

124           Of the 233 enrolled patients for chloroquine, 197 (84.5%) completed  
125 treatment and were included in the final analysis (**Figure 1, study flowchart;**  
126 **Supplementary Table 1**). Of the 182 patients collected as historical controls,  
127 176 (96.7%) were included in the final analysis. Their baseline demographic  
128 and clinical features are listed in **Table 1**. The median age of patients were 43

129 years (inter-quartile range [IQR], 33 to 55 years) in the chloroquine group and  
130 47.5 years (IQR, 35.8 to 56 years) in the non-chloroquine group. Across the  
131 two treatment groups, the majority patients were classified as moderate cases  
132 (93.4% in chloroquine; 89.2% in non-chloroquine)<sup>8</sup>. Chloroquine was added  
133 into China's Diagnosis and Treatment Guidelines of COVID-19 later than the  
134 other therapies used in the non-chloroquine group. Therefore, we observed  
135 longer interval time between symptom onset and treatment initiation in  
136 chloroquine versus non-chloroquine (absolute difference 4 days; 95% CI 2 to  
137 6 days;  $P < 0.0001$ ). In addition, due to the rapid rise of patients in Wuhan  
138 and established mobile hospital in early February, the interval time between  
139 symptom onset and treatment initiation in Wuhan (median 17 days, IQR 10.5  
140 to 21 days) is longer than that in Guangdong Province (median 5 days, IQR 3  
141 to 10 days; **Table 1**). In the subgroup of patients from the Fifth Affiliated  
142 Hospital of Sun Yat-sen University (SYSU5), we obtained and evaluated the  
143 viral load at baseline between chloroquine (N=21) and non-chloroquine (N=8)  
144 group and did not observe statistically significant difference (absolute  
145 difference in medians = 2.93, 95% CI -0.8 to 6.6,  $p = 0.09$ ).

## 146 **Outcomes**

147 In the analysis of the full study population, patients in the chloroquine  
148 group have an accelerated time to undetectable viral RNA from that of  
149 patients in the non-chloroquine group (absolute difference in medians -5.4  
150 days; 95% CI -6 to -4;  $P < 0.0001$ ; **Figure 2**). Secondly, by day 10 and day 14  
151 since treatment initiation, higher proportion of patients had undetectable viral  
152 RNA in the chloroquine group (91.4% and 95.9% respectively; **Table 2**)  
153 comparing to the non-chloroquine group (57.4% and 79.6% respectively;

154 **Table 2**). In the aspect of clinical manifestations, we found that the duration of  
155 fevers is shorter in chloroquine versus non-chloroquine among patients  
156 experienced fever symptom (geometric mean ratio 0.6; 95% CI 0.5 to 0.8;  $P =$   
157 0.0029; **Supplementary Figure S1**). To note, the antipyretic effects of  
158 chloroquine may have also contributed to this result. We observed no  
159 difference in the length of hospital stay (**Supplementary Figure S2**). No  
160 patient died or admitted to ICU either in the chloroquine group or in the non-  
161 chloroquine group. There are 1 patient in the chloroquine group experienced  
162 aggravated symptoms from moderate to severe, while 9 patients in the non-  
163 chloroquine group have the same aggravated experience. All of the 10  
164 patients eventually were tested negative for the viral RNA within the study  
165 period.

166 Due to the significant difference observed in clinical classification between  
167 chloroquine and non-chloroquine group at baseline, we further analyzed the  
168 primary and secondary outcomes in patients with moderate symptoms only.  
169 The number of patients in mild or severe subgroup were too few to compare.  
170 The benefit of chloroquine in viral suppression is consistent with the full  
171 analysis, except for non-significant difference observed for the proportion of  
172 patients with undetectable viral RNA by day 14 (**Supplemental Table 2**).

173 In post hoc analysis, we examined the effect of chloroquine on the time to  
174 undetectable viral RNA stratified by different doses, types of clinical  
175 manifestation, the interaction between province and time from symptom onset  
176 to treatment initiation, and a representative center (**Figure 3**). Chloroquine  
177 showed beneficial effect in all stratum. However, the beneficial effect is not  
178 statistically significant in patients with severe COVID-19 symptoms, patients



179 from Guangdong Province treated later than 14 days after symptom onset, or  
180 patients from SYSU5.

181 In order to assess the effect of chloroquine in more detailed clinical  
182 improvement outcomes in post hoc analysis, we collected detailed clinical  
183 data in patients from SYSU5, including the improvement of chest CT, the  
184 monitoring of serum chloroquine concentration, and the reappearance of  
185 positive viral RNA detection after hospital discharge. In this subgroup of  
186 patients, the interval time between symptom onset and treatment initiation  
187 were comparable. The medians are 7 days in chloroquine group (N=50) and 6  
188 days in non-chloroquine group (N=21) (absolute difference in medians 1 day;  
189 95% CI -3 to 4 days;  $P = 0.99$ ; **Supplemental Table 3**). We did not find  
190 statistically significant difference in the time to undetectable viral RNA  
191 between the two groups (absolute difference in medians -3.5 days; 95% CI -6  
192 to 1 days). The chloroquine group have higher percentage of patients with  
193 improved chest CT by day 10 (absolute difference in proportions 9.7; 95% CI -  
194 16.0 to 35.6) and day 14 (absolute difference in proportions 6.3; 95% CI -22.2  
195 to 32.0) than the non-chloroquine group but the difference is not statistically  
196 significant (**Supplemental Table 3**). This could be due to the small sample  
197 size or the delayed chest CT absorption<sup>9</sup>. We did not observe beneficial effect  
198 of chloroquine in the length of hospital stay and the duration of oxygen  
199 support (**Supplemental Table 3**). Unprecedentedly, we observed 3 cases of so  
200 called “re-positive” patients in the chloroquine group. They were identified with  
201 negative viral RNA test from respiratory tract samples but positive viral RNA  
202 test from fecal samples within 7 days following hospital discharge. No such

203 observation in the non-chloroquine group. Investigation is underway to  
204 examine whether it is due to re-infection or other factors.

205 Among the 12 hospitals, one hospital explored different dosage of  
206 chloroquine, as 500 mg once daily, which is half of the protocol dosage. We  
207 compared the primary and secondary outcomes in patients from this subgroup  
208 (N=29) with the non-chloroquine group in Guangdong Province. The results  
209 mainly showed that chloroquine has benefit effect on the time to undetectable  
210 viral RNA (absolute difference in medians -5 days; 95% CI -6.0 to -4.0 days)  
211 and the proportion of patients with undetectable viral RNA by day 10 is higher  
212 in chloroquine group (absolute difference in proportions 32.7; 95% CI 23.9 to  
213 42.1). The duration of fever was also shorter than those in the non-  
214 chloroquine group (geometric mean ratio 0.8; 95% CI 0.5 to 0.9)  
215 **(Supplemental Table 4).**

216

## 217 **Safety**

218 A total of 53 patients (26.9%) in the chloroquine group and 57 (32.4%) in  
219 the non-chloroquine group reported adverse events during study period  
220 **(Table 3)**. Gastrointestinal events including vomiting, abdominal distension,  
221 nausea, decreased appetite, thirst were more common in chloroquine than in  
222 the non-chloroquine group. The percentage of patients with neurological  
223 adverse events, including dizziness and sleep order, were higher in the  
224 chloroquine than in the non-chloroquine group. In addition, anxiety was  
225 observed more frequently in chloroquine than in the non-chloroquine group.  
226 We observed fewer adverse events in patients with half dose of chloroquine  
227 than full dose (absolute difference in proportions -40; 95% CI -60 to -29).

228 Chloroquine phosphate has a long half-life (20-60 days)<sup>10-12</sup> and its  
229 mean residence time is approximately 20 days<sup>10</sup>. It may have cumulative  
230 effect<sup>13</sup>. In order to determine whether chloroquine has a cumulative effect in  
231 the short-term treatment with COVID-19, we measured the serum  
232 concentration of chloroquine in patients from SYSU5 during and off the  
233 treatment. The results showed that the mean of serum concentration of  
234 chloroquine gradually rising, with the highest reaching 1.80(±0.49) µmol/L  
235 during medication and reduced to 0.13(±0.08) µmol/L within 28±1 days off  
236 chloroquine (**Supplemental Figure 3**).

237

## 238 **DISCUSSION**

239 In this study, we found that patients in the chloroquine group experienced  
240 significantly faster and higher rate of viral suppression comparing to the non-  
241 chloroquine group in both the full analysis and the post hoc stratified analysis.  
242 Even when the dose reduced to half, the benefit of chloroquine still remained  
243 (**Figure 3**). These findings indicate that chloroquine could be effective in  
244 treating patients with COVID-19. To our knowledge, this is the first and largest  
245 clinical study on chloroquine phosphate for treating COVID-19 to date.

246 We recognize that our study has several limitations. This study was  
247 carried out under the COVID-19 public health emergency. Due to the limited  
248 medical capacity and urgent clinical situation, we were unable to conduct a  
249 standard randomised controlled study to formally evaluate efficacy and safety  
250 of chloroquine versus placebo. As an observational study, we have to note  
251 that several factors may influence the interpretation of the result. It is  
252 reasonable to suspect that the dramatic improvement in the primary outcome

253 in chloroquine could be due to the later treatment initiation since symptom  
254 onset. Firstly, gaining experience in treatment management and attenuation of  
255 the virus during the course of the epidemic could contribute to the improved  
256 outcomes. Secondly, we cannot rule out the possibility that among those with  
257 longer interval time between symptom onset and treatment, some may  
258 already have been on the course of recovery. Nevertheless, post hoc analysis  
259 dividing subgroups according to the interval time did not change the  
260 conclusion that the chloroquine group had a better outcome than the non-  
261 chloroquine group. Notably, some of the strata were incomparable due to  
262 small sample size. Thirdly, although it is impossible to dissect the influence  
263 from other antiviral therapies used before chloroquine, it is a plausible  
264 assumption that chloroquine is the first antiviral therapy used in the group of  
265 patients treated within 3 days since symptom onset. In this stratum,  
266 chloroquine still benefits patients with faster viral suppression (**Figure 3**).  
267 Lastly, due to the differences in personnel and technical equipment of among  
268 all hospitals, we could not fully collect clinical and laboratory data of all  
269 patients. However, detailed clinical data were obtained from the chloroquine  
270 patients enrolled from SYSU5, enabling advanced analysis of clinical  
271 outcomes and pharmacokinetics.

272 As of this time, there are more than 20 trials ongoing for evaluating the  
273 efficacy and safety of chloroquine or hydroxychloroquine in treating COVID-19.  
274 Magagnoli et al. recently published a retrospective study indicating that the  
275 use of hydroxychloroquine with or without azithromycin does not reduced the  
276 risk of mechanical ventilation in United States veterans hospitalized with  
277 COVID-19<sup>14</sup>. Comparing with this study, our study population included both

278 genders, was much younger, has fewer patients with severe symptoms that  
279 requires ventilation. Therefore, prospective randomised trials are needed to  
280 see if the results can be replicated.

281 Till now, the mechanism of chloroquine's effect against SARS-CoV-2  
282 remained unelucidated. Clathrin-mediated endocytosis is required for entry  
283 of coronavirus into host cells and meanwhile autophagy involves in viral  
284 replication<sup>15</sup>. Chloroquine inhibits clathrin-mediated endocytosis by  
285 suppressing acidification of endosomes, and autophagy by raising its  
286 lysosomal pH and blocking fusion of autophagosome with lysosome and  
287 lysosomal protein degradation<sup>16</sup>. A recent study has shown that the  
288 development of COVID-19 disturbed metabolic patterns, which aligned with  
289 the progress and severity of COVID-19 (Wu et al. National Science Review  
290 2020, in press). Chloroquine has a favorable effect on glucose and lipid  
291 metabolism<sup>17</sup>. Therefore, chloroquine may exert its antiviral effect against  
292 SARS-CoV-2 by inhibiting endocytosis and autophagy, and stabilizing glucose  
293 and lipid metabolism.

294 The adverse reactions of chloroquine drugs are of great concern to the  
295 community. Although it is an old anti-malarial drug, its safety in treating  
296 COVID-19 patients is still unknown. In the present study, we did not observe  
297 serious adverse events in patients with chloroquine. All adverse events  
298 observed during the study period are known side-effects for chloroquine  
299 (**Table 3**). The main adverse events were symptoms in gastrointestinal and  
300 neuropsychiatric systems. Chloroquine is known for its side effects in  
301 cardiovascular system. In the chloroquine group, we did not find significantly  
302 higher rate of adverse events in patients older than 65 or with pre-existing

303 conditions (**Supplement Table 5**). Adverse event appeared in 1 out of 29  
304 patients (3.5%) with half dose while in 52 out 168 patients (31.0%) with full  
305 dose, indicating that the half dose group has lower adverse event rate  
306 (absolute rate difference -27.5; 95% CI -45.0 to -19.2). Although previous  
307 studies suggested that chloroquine may have cumulative effect<sup>11,18,19</sup>, we did  
308 not observe cumulative effects among 50 patients from SYSU5 by monitoring  
309 the serum concentration of chloroquine for up to 28 days after treatment  
310 completion. Future studies are needed to determine the optimal dosing for  
311 treating COVID-19 and the cumulative effect of chloroquine in tissues and  
312 organs. Severe cases are underrepresented in the present study, and thus  
313 should be focused in the future studies to evaluate the efficacy and safety  
314 profile in this population. In addition, it will be important to study the  
315 prophylaxical use of chloroquine in areas with high rate of COVID-19 or in  
316 health professionals working with COVID-19 patients.

317 In conclusion, our preliminary evidence showed that chloroquine has the  
318 potential to shorten the time to SARS-CoV-2 viral suppression and duration of  
319 fever, even with reduced dose. Further randomised studies are needed to  
320 determine the optimal dose, to assess its benefit for both severe cases and to  
321 assess its benefit in settings other than secondary care. Considering that  
322 there is no better option at present, chloroquine could be a viable option to  
323 combat the coronavirus pandemic under proper management.

324

## 325 **METHODS**

### 326 **Study Design and participants**

327 This study was a multicenter prospective observational study  
328 conducted from February 7 through March 8, 2020 at 11 hospitals in

329 Guangdong Province and 1 mobile cabin hospital in Wuhan, Hubei Province,  
330 China. The study protocol was approved by the ethics committee of Fifth  
331 Affiliated Hospital of Sun Yat-sen University (SYSU5), located in Zhuhai,  
332 Guangdong Province, and registered at Chinese Clinical Trial Registry  
333 (ChiCTR2000029609). We did this study in accordance with the principles of  
334 the Declaration of Helsinki and Good Clinical Practice. Written informed  
335 consent was obtained from all patients or their legal guardians. During the  
336 study period, each hospital had various choices of antiviral regimen, and the  
337 sample size of Lopinavir/Ritonavir (the historical control group in the original  
338 protocol) for single-use were underpowered. Thus, we updated the inclusion  
339 criteria of the historical control group as patients receiving non-chloroquine  
340 treatment.

341 Eligible patients were aged 18 years or older with confirmed SARS-  
342 CoV-2 infection, tested by the local Center for Disease Control (CDC) or by a  
343 designated diagnostic laboratory, using reverse-transcriptase-polymerase-  
344 chain-reaction (RT-PCR) assay (Shanghai ZJ Bio-Tech Co Ltd) for SARS-  
345 CoV-2 in a respiratory tract sample. Patients were ineligible if he/she met any  
346 of the following criteria: pregnant women, with known allergies to 4-  
347 aminoquinoline compounds, blood system diseases, chronic liver or kidney  
348 diseases in end-stage, arrhythmia or second/third degree heart block, with  
349 known to have retinopathy, hypoacusis or hearing loss, mental disease,  
350 glucose-6-phosphate dehydrogenase (G6PD) deficiency, had received  
351 digitalis drugs within the 7 days preceding enrollment, or is classified as  
352 critical case according to China's Novel Coronavirus Pneumonia Diagnosis  
353 and Treatment Plan (4<sup>th</sup> Edition). Enrolled patients received 500mg

354 chloroquine Phosphate (equivalent of 300 mg chloroquine base, Shanghai  
355 Xinyi Pharmaceutical Co., Ltd) orally, once/twice-daily with no other antiviral  
356 therapies. The criteria of stopping chloroquine was defined as undetectable  
357 viral RNA for two consecutive respiratory tract samples. The duration of  
358 medication in chloroquine group is no more than 10 days. Patients in the  
359 historical control group were treated according to China's Novel Coronavirus  
360 Pneumonia Diagnosis and Treatment Plan (details described in  
361 **Supplemental Table 6**).

362

### 363 **Outcome and measurements**

364 The primary outcome is the time from treatment initiation to  
365 undetectable viral RNA for two consecutive respiratory tract samples. The  
366 secondary outcomes include the proportion of patients with undetectable viral  
367 RNA by day 10 and 14, duration of fevers, time in hospital, and adverse  
368 events. The detailed definition of outcomes is described in **Supplementary**  
369 **Methods**. Respiratory tract sample was collected from patients daily  
370 to conduct RT-PCR assay for SARS-CoV-2 infection. The epidemiological  
371 characteristics, clinical symptoms and signs, adverse reactions/events were  
372 collected with data collection forms. The outcomes, clinical characteristics,  
373 laboratory findings, chest computed tomographic (CT) scans were recorded  
374 on case record forms and then double-entered into an electronic database  
375 and validated by trial staff. After hospital discharge, patients were followed up  
376 once weekly. Patients with "re-positive" viral RNA detection within one week  
377 after hospital discharge are defined as having either 2 consecutive RT-PCR  
378 positive result from either respiratory tract sample or fecal specimen. In the



379 subgroup of patients in SYSU5, all CT images were reviewed by two  
380 fellowship-trained cardio-thoracic radiologists by using a viewing console.  
381 Images were reviewed independently, and final decisions were reached by  
382 consensus <sup>9</sup>.

383 To fully assess the safety of chloroquine, we monitor the serum  
384 concentration of chloroquine at the day 1, 3, 5, 7, 10 during drug  
385 administration and day 1 to 7, and day 14, day 21 after treatment completion  
386 in a subgroup of samples enrolled from SYSU5 (N=50). Details about the  
387 measurement of serum concentration of chloroquine are described in

### 388 **Supplemental Methods.**

### 389 **Statistical Analysis**

390 The original plan was to compare the efficacy between three groups,  
391 chloroquine only, Lopinavir/Ritonavir only, and chloroquine plus  
392 Lopinavir/Ritonavir. At the beginning of the outbreak, different therapies were  
393 proposed and tested for the treatment of COVID-19. Therefore, it is  
394 challenging to find sufficient patients with unified treatment across all centers.  
395 The epidemic in Guangdong had been brought under control rapidly during  
396 the study making it difficult to recruit patients as planned. The history of  
397 changes to the protocol is listed in **Supplemental Table 7**. Thus, a decision  
398 was made to focus on recruiting chloroquine only and compare the efficacy  
399 with historical controls. The current sample size was based on feasibility  
400 within the fixed trial recruitment window and was felt would provide sufficient  
401 precision for the estimation of plausible effects. With right-censoring in time-  
402 to-event variables, generalized Wilcoxon test was used to compare the  
403 difference in medians and the 95% confidence intervals were calculated by

404 bootstrapping<sup>20</sup>. For binary outcomes, Wilson test was implemented to  
405 calculate the difference in proportions and 95% confidence intervals. As this  
406 was an observational study, imbalance in the baseline characteristics of the  
407 two groups was expected. To adjust for this imbalance, we performed post  
408 hoc analyses within various subgroups by two dosage options, by clinical  
409 manifestation, by the interaction of province and the interval time between  
410 symptom onset and treatment initiation ( $\leq 3$  days; 3~7 days; 7~14 days; > 14  
411 days), and by center. For all comparative analyses,  $P < 0.05$  was considered  
412 statistically significant. No allowance for multiplicity. All P values are two tailed.  
413 All statistical analyses were performed in R, version 3.6.1 (R Foundation for  
414 Statistical Computing)<sup>21</sup>.

#### 415 **Role of the funding source**

416 The sponsor of the study had no role in study design, data collection, data  
417 analysis, data interpretation, or writing of the report. The corresponding author  
418 had full access to all the data and had final responsibility for the decision to  
419 submit for publication.

420 **Contributors**

421 S.H, N.Z, S.J. J.X. L.T and D.P. had the idea for and designed the study and had full  
422 access to all data in the study and take responsibility for the integrity of the data and  
423 the accuracy of the data analysis. M.L, F.X, Y.L., M.H, J.L, P.P and T.T contributed  
424 to writing of the report. M.L, F.X, M.H, Y.L., J.L and P.P contributed to critical  
425 revision of the report. M.L contributed to the statistical analysis. All authors  
426 contributed to data acquisition, data analysis, or data interpretation, and reviewed  
427 and approved the final version.

428

429 **Declaration of interest**

430 All authors declare no competing interests.

431

432 **Data sharing**

433 The data that support the findings of this study are available from the corresponding  
434 author on reasonable request. Participant data without names and identifiers will be  
435 made available after approval from the corresponding author and Ministry of science  
436 and technology and Health Committee in Guangdong province. After publication of  
437 study findings, the data will be available for others to request. The research team will  
438 provide an email address for communication once the data are approved to be  
439 shared with others. The proposal with detailed description of study objectives and  
440 statistical analysis plan will be needed for evaluation of the reasonability to request  
441 for our data. The corresponding author and Ministry of science and technology and  
442 Health Committee in Guangdong province will make a decision based on these  
443 materials. Additional materials may also be required during the process.

444

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462 **Table 1. Baseline characteristics in chloroquine and non-chloroquine among**  
 463 **people with COVID-19.**  
 464

	<b>chloroquine (N=197)</b>	<b>Non-chloroquine (N=176)</b>
Guangdong, N (%)	118 (60)	96 (54)
Hubei, N (%)	79 (40)	80 (46)
Age, mean (SD)	43.8 (13.1)	45.6 (13.5)
Age ≤ 65	190 (96)	171 (97)
Age > 65	7 (4)	5 (3)
Female sex, N (%)	101 (51)	97 (55)
Clinical manifestation <sup>†</sup> , N (%)		
Mild	9 (5)	5 (3)
Moderate	184 (93)	157 (89)
Severe	4 (2)	14 (8)
Comorbidities, N (%) <sup>*</sup>		
Hypertension	13 (17)	11 (17)
Type 2 diabetes	4 (5)	5 (8)
Interval time from symptom onset to treatment initiation, median (IQR)		
Guangdong	7 (3, 10.8)	4 (2, 7)
Hubei	19 (17, 24.5)	11 (7, 16)
Body temperature, median (IQR), °C	36.7 (36.5, 37.0)	36.6 (36.4, 37.3)
Pneumonia from chest CT, N (%) <sup>§</sup>	173 (89)	137 (93)

465 \* The number of patients with valid record of comorbidities are 78 in chloroquine  
 466 group and 66 in non-chloroquine group

467 § The number of patients with valid record of chest CT image are 194 in chloroquine  
 468 group and 148 in non-chloroquine group.

469 † clinical manifestation type definitions: 1) Mild, mild clinical symptoms with no signs  
 470 of pneumonia on chest radiological imaging; 2) Moderate, fever, respiratory  
 471 symptoms, imaging with pneumonia changes; 3) Severe, meet any of the following  
 472 criteria: shortness of breath, respiratory rate > 30 times per minute, resting stable  
 473 oxygen saturation in fingertip < 93%, oxygenation index < 300, pulmonary imaging  
 474 showed that the lesion progressed significantly more than 50% within 24-48 hours; 4)  
 475 Critical, if any of the following occurs: respiratory failure requiring mechanical  
 476 ventilation; shock, concurrent with other organ failure requires intensive care.

477 **Table 2. Outcomes in the overall population with confirmed SARS-CoV-2**  
 478 **infection<sup>§</sup>.**  
 479

	<b>chloroquine (N=197)</b>	<b>Non- chloroquine (N=176)</b>	<b>Difference (95% CI)<sup>†</sup></b>	<b>P value</b>
Time to undetectable viral RNA, median no. of days (IQR)	3.0 (3.0, 5.0)	9.0 (6.0, 12.0)	-6.0 (-6.0, -4.0)	< 0.0001
Patients with undetectable viral RNA by, N (%)				
Day 10	180.0 (91.0)	101.0 (57.0)	34.0 (25.6, 42.9)	< 0.0001
Day 14	189.0 (96.0)	140.0 (80.0)	16.0 (9.2, 23.3)	< 0.0001
Duration of fever*, no. of days, geometric mean (CV)	1.2 (53.5)	1.9 (110.0)	0.6 (0.5, 0.8)	0.0029
Length of hospital stay, median no. of days (IQR)	19.0 (16.0, 23.0)	20.0 (15.8, 24.0)	-1.0 (-3.0, 0.0)	0.25

480 Abbreviations: CI, confidence interval; IQR, inter-quartile range; CV, coefficient of  
 481 variation.

482 <sup>§</sup> Definitions of outcomes are listed in Supplemental Methods.

483 <sup>†</sup> 95% CI for continuous variables are calculated by bootstrapping. 95% CI for binary  
 484 variables are calculated with Wilson method. The difference for duration of fever is  
 485 geometric mean ratio of chloroquine group to non-chloroquine group. The  
 486 differences for all other variables are the absolute difference between chloroquine  
 487 group and non-chloroquine group.

488 \* The number of patients had at least one day of fever is 42 and 51 in the  
 489 chloroquine and non-chloroquine group respectively.

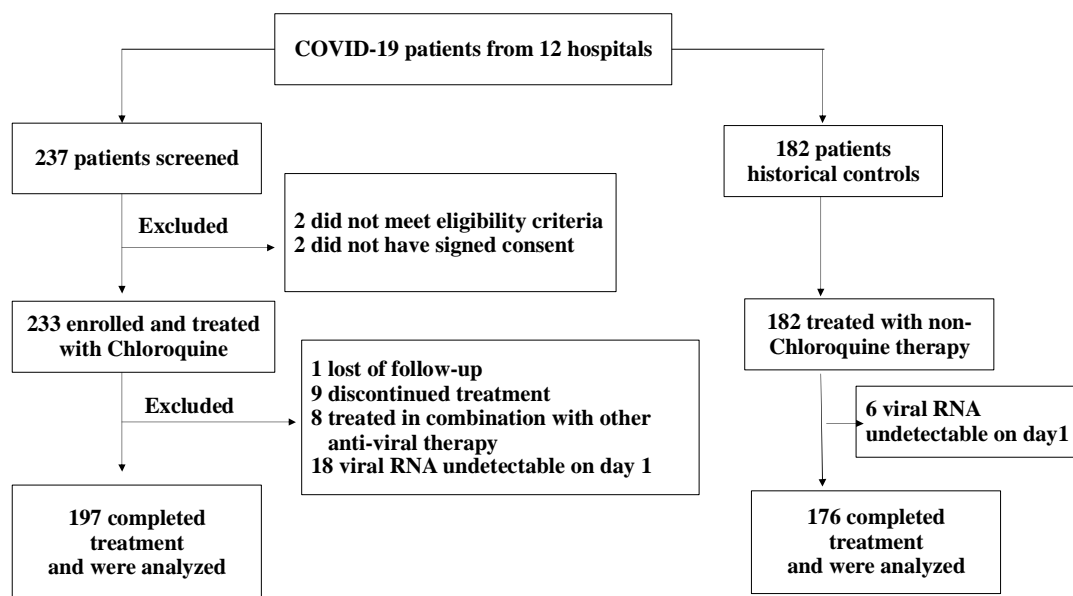
490 **Table 3. Summary of adverse events<sup>§</sup>.**

491

<b>Event, N (%)</b>	<b>chloroquine (N=197)</b>	<b>Non-chloroquine (N=176)</b>
Any adverse event	53 (26.9)	57 (32.4)
Gastrointestinal		
Vomiting	9 (4.6)	2 (1.1)
Abdominal distension	2 (1.0)	1 (0.6)
Abdominal pain	2 (1.0)	2 (1.1)
Nausea	18 (9.1)	7 (4.0)
Diarrhea	6 (3.0)	11 (6.3)
Decreased appetite	7 (3.6)	0 (0)
Thirst	4 (2.0)	0 (0)
Acid reflux	1 (0.5)	0 (0)
Belching	1 (0.5)	0 (0)
Neurological		
Dizziness	20 (10.2)	4 (2.3)
Headache	3 (1.5)	3 (1.7)
Sleep disorder	10 (5.1)	1 (0.6)
Psychological		
Anxiety	6 (3.0)	0 (0)
Depression	1 (0.5)	0 (0)
Delirious	1 (0.5)	1 (0.6)
Dysphoria	1 (0.5)	0 (0)
Emotional Unstable	1 (0.5)	0 (0)
Cardiovascular		
Pain under xiphoid	1 (0.5)	0 (0)
Chest tightness	2 (1.0)	6 (3.4)
Ventricular premature beat	0 (0)	1 (0.6)
Other		
Hand shaking/numbness	2 (1.0)	0 (0)
Muscle soreness	0 (0)	4 (2.3)
Blurred vision	3 (1.5)	0 (0)
Rash	1 (0.5)	0 (0)
Weight loss	1 (0.5)	0 (0)
Fatigue / Weakness	2 (1.0)	1 (0.6)
Shortness of breath	1 (0.5)	3 (1.7)
Unsteady gait	1 (0.5)	0 (0)

492 <sup>§</sup> Adverse events that occurred in more than 1 patient after treatment initiation during  
 493 study period are shown. Some patients had more than one adverse event.

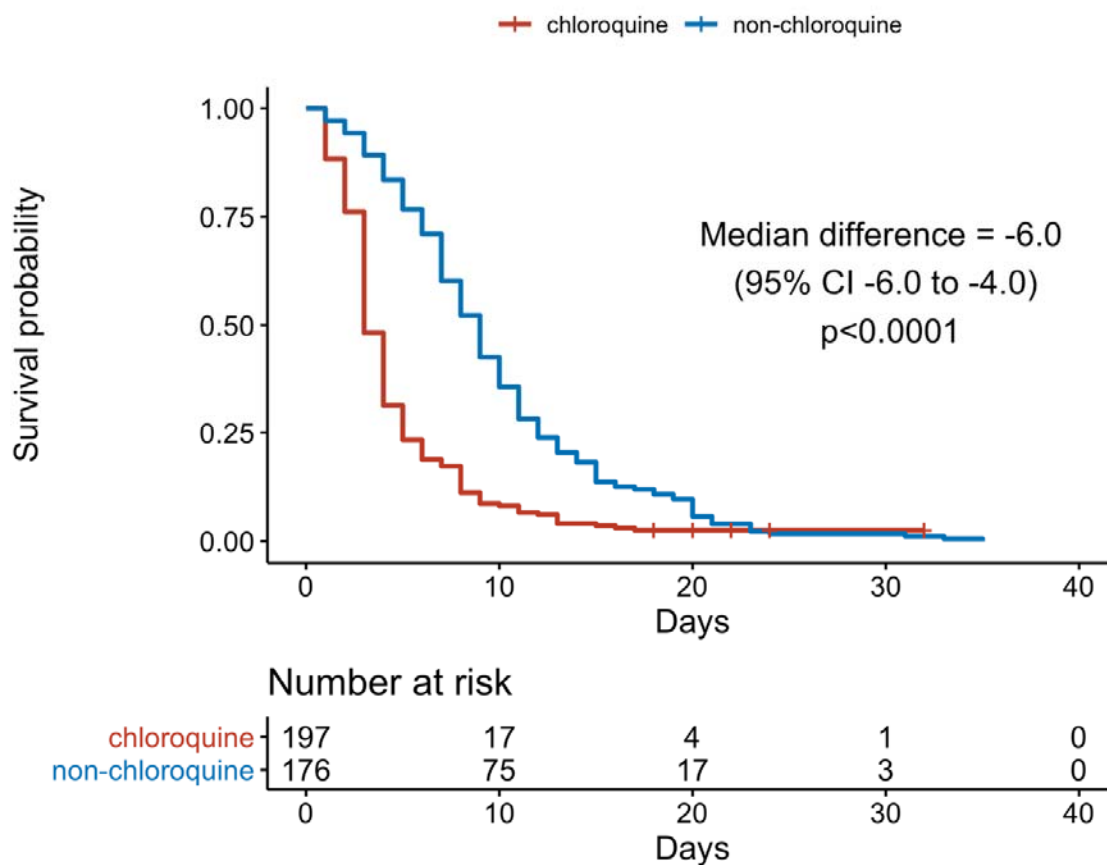
494 **Figure 1. Study flowchart.**



495



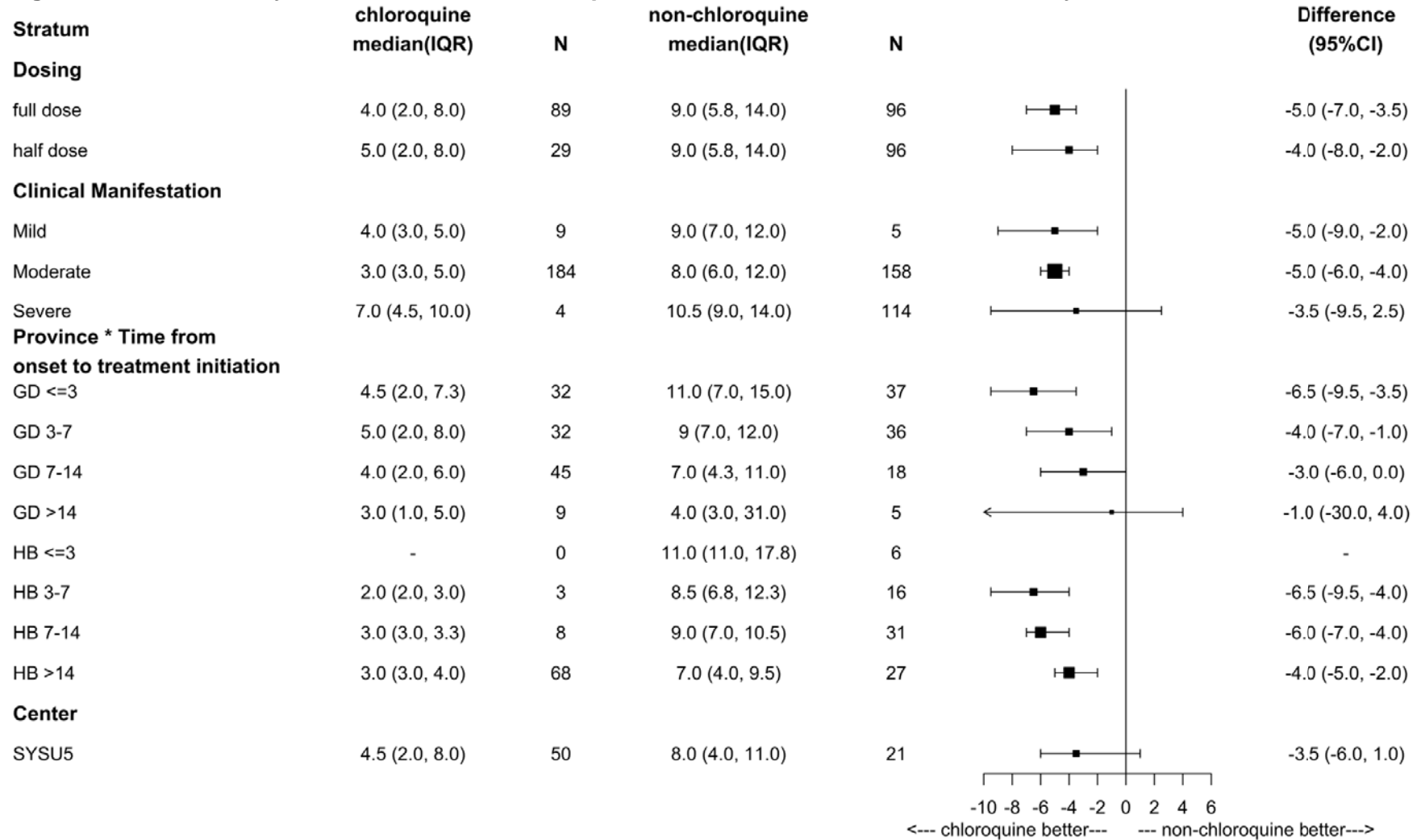
496 **Figure 2. Kaplan-Meier curve for time to undetectable viral RNA comparing**  
497 **treatment groups.**  
498



499

500

**Figure 3. Post hoc analysis on the effect of chloroquine on time to undetectable viral RNA by stratification.**



501  
502

Abbreviations: GD, Guangdong; HB, Hubei.

503 95% CI are calculated by bootstrapping. The differences for all other variables are the absolute difference between chloroquine  
504 group and non-chloroquine group.

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