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1 Effects of Hydroxychloroquine on Covid-19 in Intensive Care Unit Patients:

2 Preliminary Results

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Abstract

During the Covid-19 pandemic, many intensive care unit (ICU) patients received hydroxychloroquine. The primary objective of this study was to assess the effects of hydroxychloroquine according to its plasma concentration in ICU patients. A single-center retrospective study was performed from March to April 2020 in an ICU of a university hospital. All patients admitted to the ICU with confirmed Covid-19 pneumonia and treated with hydroxychloroquine were included. The study compared 17 patients in whom the hydroxychloroquine plasma concentration was in the therapeutic target (on-target) and 12 patients in whom the plasma concentration was below the target (off-target). The follow-up of patients was 15 days. No association was found between hydroxychloroquine plasma concentration and viral load evolution ($P = 0.77$). There was no significant difference between the two groups for duration of mechanical ventilation, length of ICU stay, in-hospital mortality, and 15-days mortality. These findings indicate that hydroxychloroquine administration for Covid-19 patients hospitalized in ICU is not associated with improved outcomes. Larger multicenter studies are needed to confirm these results.

Words count in Abstract: 175

Keywords: Hydroxychloroquine, Intensive care unit, Covid-19 pneumonia

56 **Introduction**

57 In March 2020, the World Health Organization announced the severe acute respiratory syndrome coronavirus 2
58 (SARS-CoV-2) outbreak [1]. Many patients were admitted to intensive care units (ICUs) for acute respiratory failure in
59 the context of Covid-19 [2]. The usefulness of antivirals and other drugs used in these patients is not based on strong
60 evidence.

61 Hydroxychloroquine, a drug mainly used to prevent and treat malaria [3], stops viruses entering the cells by
62 inhibiting glycosylation of host receptors, proteolytic processes and endosomal acidification, and it has
63 immunomodulatory effects by decreasing the cytokine storm [4]. Hydroxychloroquine has an antiviral activity for
64 SARS-CoV-2 in vitro [5]. Gautret et al. reported that hydroxychloroquine and azithromycin were associated with viral
65 load reduction in nasopharyngeal samples in patients after six days of treatment [6]; however, ICU patients were not
66 included in this study. The Surviving Sepsis Campaign guidelines on the management of Covid-19 patients concluded
67 there was insufficient evidence to recommend the use of antiviral drugs and hydroxychloroquine in ICU patients [7].
68 In addition, the use of two different dosing regimens of this drug did not affect the outcomes of critically ill patients
69 [8]. The aim of the current study was to determine the effects of hydroxychloroquine in ICU patients by measuring
70 plasma concentrations of hydroxychloroquine and comparing patients whose concentrations were within the
71 therapeutic target (on-target) to patients whose concentrations were below the therapeutic target (off-target).

72 **Methods**

73 *Design*

74 This single-center, retrospective, observational study was performed in ICU at North Hospital of Marseille from 16th
75 March 2020 to 19th April 2020.

76 *Ethical considerations*

77 The study was approved by the Committee for Research Ethics of French Society of Anesthesia & Intensive Care
78 Medicine (CERAR no. IRB 00010254 - 2020 - 059). Patients were informed regarding the use of their data. Strategies
79 were considered standard care; consent was not required.

80 *Population*

81 Confirmed Covid-19 patients with acute respiratory failure were included in the study if they met the following
82 criteria: i) aged at least 18 and; ii) polymerase chain reaction (PCR)-documented SARS-CoV-2 in nasopharyngeal
83 samples upon ICU admission. Exclusion criteria were known allergy to hydroxychloroquine; a contraindication to

84 treatment like retinopathy, glucose-6-phosphate dehydrogenase deficiency or QT prolongation; preexisting
85 treatment that might interact with hydroxychloroquine, and treatment with another drug. Two groups were
86 identified: i) patients with hydroxychloroquine plasma concentration above the target concentration of 0.1 µg/mL
87 and a full treatment (“on-target group”) between [5]; ii) patients with hydroxychloroquine plasma concentration
88 below the target or treatment discontinuation (“off-target group”).

89 *Study protocol*

90 Upon ICU admission, patient demographic, clinical and biological data for each patient were collected, and the
91 Simplified Acute Physiology Score II (SAPS II) and the Sepsis-related Organ Failure Assessment (SOFA) score were
92 calculated. Covid-19 features, onset of disease, and respiratory and systemic symptoms were reported. Use of
93 catecholamines and duration of mechanical ventilation were also recorded. All patients underwent an
94 electrocardiogram for the detection of QT prolongation. Virus load was determined from nasopharyngeal swab
95 samples collected every 72 h. Recovery was defined as two consecutive negative nasopharyngeal swab samples [9].
96 Follow-up for each patient was 15 days.

97 Treatment consisted of an 800-mg loading dose of hydroxychloroquine and maintenance dose of 400 mg for 9 days.
98 Plasma concentration of hydroxychloroquine was measured every 72 h to adjust dose in the Laboratory of
99 Pharmacokinetics and Toxicology (Timone Hospital – Marseille). The analytical method was previously validated
100 according to European Medicine Agency guidelines and was linear in the 0.015–2.00 µg/mL range [10]. An additional
101 treatment consisted of a 500-mg loading dose of azithromycin and 250-mg maintenance dose and cefotaxime (6 g
102 continuous infusion) for 5 days. Early treatment discontinuation and side effects were recorded.

103 *Outcomes*

104 The primary endpoint was the reduction/disappearance of SARS-CoV-2 in patient samples at Day 15. The secondary
105 endpoints were the number of days before obtaining a negative PCR, length of ICU and hospital stays, length of
106 mechanical ventilation, use of vasopressor and 15-days mortality.

107 *Statistical analysis*

108 No statistical samples were performed a priori, and sample size was equal to the number of treated patients during
109 the period. The X^2 , Fisher’s exact test, t test and Mann Whitney test were used to compare variables between
110 on-target and off-target groups, as appropriate. For viral load, the data were analysed to confirm whether the first

111 endpoint was reached at Day 15. Statistical significance was defined as $P < 0.05$. Analyses were performed using
112 Prism 7 (GraphPad Software, San Diego, CA, USA).

113 **Results**

114 From 16th March to 19th April 2020, 35 Covid-19 confirmed cases were referred to the ICU, 6 of whom were excluded
115 (5 patients received other antiviral drugs and 1 patient had missing data). Finally, 29 patients (17 in the on-target
116 group and 12 in the off-target group) received hydroxychloroquine and azithromycin according to the protocol
117 (Figure 1A). Upon ICU admission, no significant differences in demographic characteristics, severity scores and
118 clinical symptoms were observed between the two groups (Table 1).

119 Plasma concentrations of hydroxychloroquine in the two groups are shown in Figure 1B. Hydroxychloroquine was
120 discontinued in 75% of patients in the off-target group and 6% of patients in the on-target group ($P < 0.001$). Side
121 effects, notably cardiac conduction disorders, were reported in 1 (6%) patient in the on-target group and 6 (50%)
122 patients in the off-target group ($P = 0.01$).

123 *Primary outcome*

124 On Day 15 after ICU admission, nasopharyngeal swab PCR results were negative in 8 (67%) patients in the off-target
125 group and 11 (65%) patients in the on-target group ($P = 0.77$). At Day 1, the viral load was 25 ± 12 Ct in the on-target
126 group and 30 ± 4 Ct in the off-target group ($P = 0.43$). At Day 15, no statistical difference was found between the two
127 groups (Figure 2).

128 *Secondary outcomes*

129 PCR results were negative on Day 7 in the on-target group and on Day 6 in the off-target group ($P = 0.71$). From Day
130 1 to Day 15, viral load reduction was similar in the on-target group (-15.2 ± 16.2 Ct) and the off-target group ($-19.9 \pm$
131 18.0 Ct) ($P = 0.45$). The numbers of patients still in ICU and in hospital at Day 15 were similar in the two groups
132 ($P > 0.05$; Table 1). Duration of mechanical ventilation and use of vasopressors were also similar ($P = 0.92$ and $P =$
133 0.95 , respectively). No statistical difference was found in 15-day mortality rate (0 [0%] patient in the on-target group
134 and 2 [17%] patients in the off-target group, $P = 0.16$) (Table 1).

135 **Discussion**

136 The current study compared patients in whom the hydroxychloroquine plasma concentration reached the
137 therapeutic target to those in whom it did not. Viral load at Day 15, viral clearance and clinical endpoints did not
138 differ significantly between the two groups.

139 The benefits of hydroxychloroquine for Covid-19 patients are still debated. Due to potential side effects, its
140 indication should be carefully balanced. In ICU patients, the use of antiviral drugs is also discussed. Oseltamivir,
141 which is used to treat or prevent influenza, appears to have no benefits for critically ill patients [11]. In the current
142 study, the mean duration between symptom onset and treatment initiation was seven days, which probably made
143 this treatment ineffective [12]. Antiviral drugs seem to be effective at the onset of infection, and their beneficial
144 effects diminish as the disease progresses [11].

145 In the current study, patients in whom hydroxychloroquine did not reach the therapeutic concentration were used
146 as controls. The pharmacokinetics of hydroxychloroquine have been described [5]. The clinical and viral courses of
147 the disease were similar regardless of the plasma concentration of hydroxychloroquine, indicating a low probability
148 of efficacy in these patients [13]. Moreover, an 800-mg bolus dose followed by daily 400-mg doses did not reach a
149 plasma therapeutic concentration in 14 (82 %) patients between Days 4 and 6. Furthermore, there were a significant
150 number of side effects. These side effects may have been related to the medical histories and comorbidities of the
151 patients and to interactions with other drugs [14]. They resulted in treatment discontinuation in seven patients and
152 were not associated with plasma concentrations.

153 The current study has several limitations. It is a retrospective series with a small patient sample and no placebo
154 group. The effects of azithromycin, which also prolongs QT interval, were not clearly considered as an accompanying
155 factor. Moreover, although the two groups were similar in most demographic and clinical variables, undetermined
156 variables may have resulted in differences between them. The negative results of PCR were meaningful, but the
157 comparison of viral load is controversial because of the limitation of the technical problem to collect samples.
158 Finally, the plasma concentration was arbitrarily determined to reach the therapeutic value between Days 4 and 6,
159 which seems reasonable if an effect is to be expected by Day 15. The choice was based on in vitro data and is
160 debatable [5].

161 In conclusion, the current study results show there was no association between hydroxychloroquine plasma
162 concentration and viral and clinical evolution in Covid-19 patients admitted to the ICU. This finding indicates that the

163 use of hydroxychloroquine at this stage of disease would be not useful. Randomized controlled trials are required to
164 show whether this drug could be useful in ICU patients admitted for Covid-19 [15].

165

166

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170

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173 **Competing Interests:** ML served as lecturer for MSD, Octapharma and 3M and consultant for Gilead, Aguetant and
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175 **Ethical Approval:** The study was approved by the Committee for Research Ethics of French Society of Anesthesia &
176 Intensive Care Medicine (CERAR no. IRB 00010254 - 2020 – 059).

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242 **Table 1. Demographic and Clinical Findings**

243 **Figure 1:**

244 **(A) Flow chart**

245 **(B) Plasma concentration of hydroxychloroquine in the two groups**

246 The median and [IQR] plasma concentrations of hydroxychloroquine (HCQ) were 0.18 [0.14-0.25] vs 0.06
247 [0.04-0.8] ($P < .001$) $\mu\text{g/mL}$ for the on-target and off-target group, respectively (Unpaired t test with Welch's
248 correction).

249 We did not represent patients who were a treatment discontinuation.

250 **Figure 2: Viral load in nasopharyngeal swab at Day 15 in the two groups**

251 The viral load (in cycle threshold [Ct] of PCR assay) between the on-target and off-target groups ($P = 0.98$).

252

Figure 1A: Flow chart

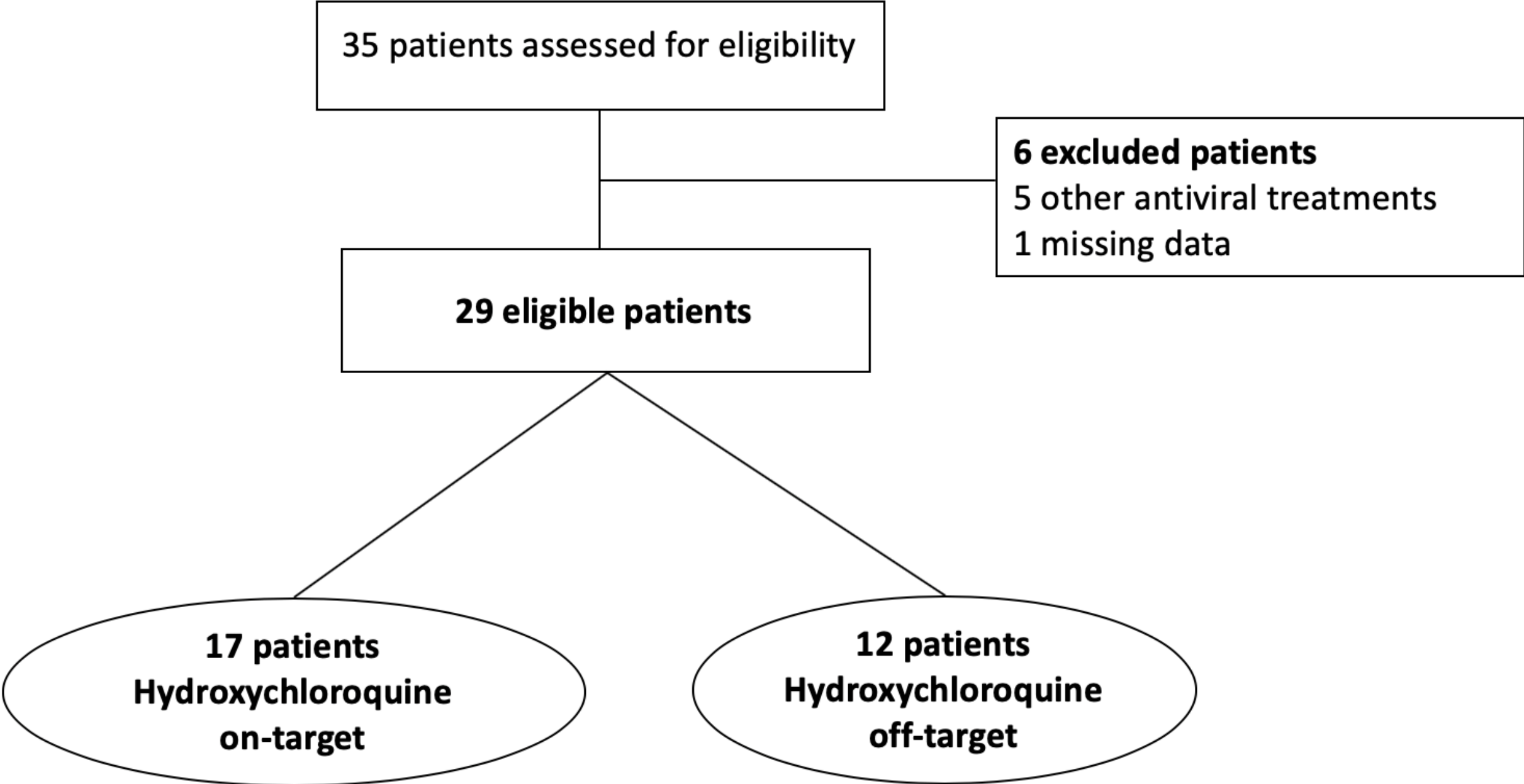


Figure 1B: Plasma concentration of hydroxychloroquine in the two groups

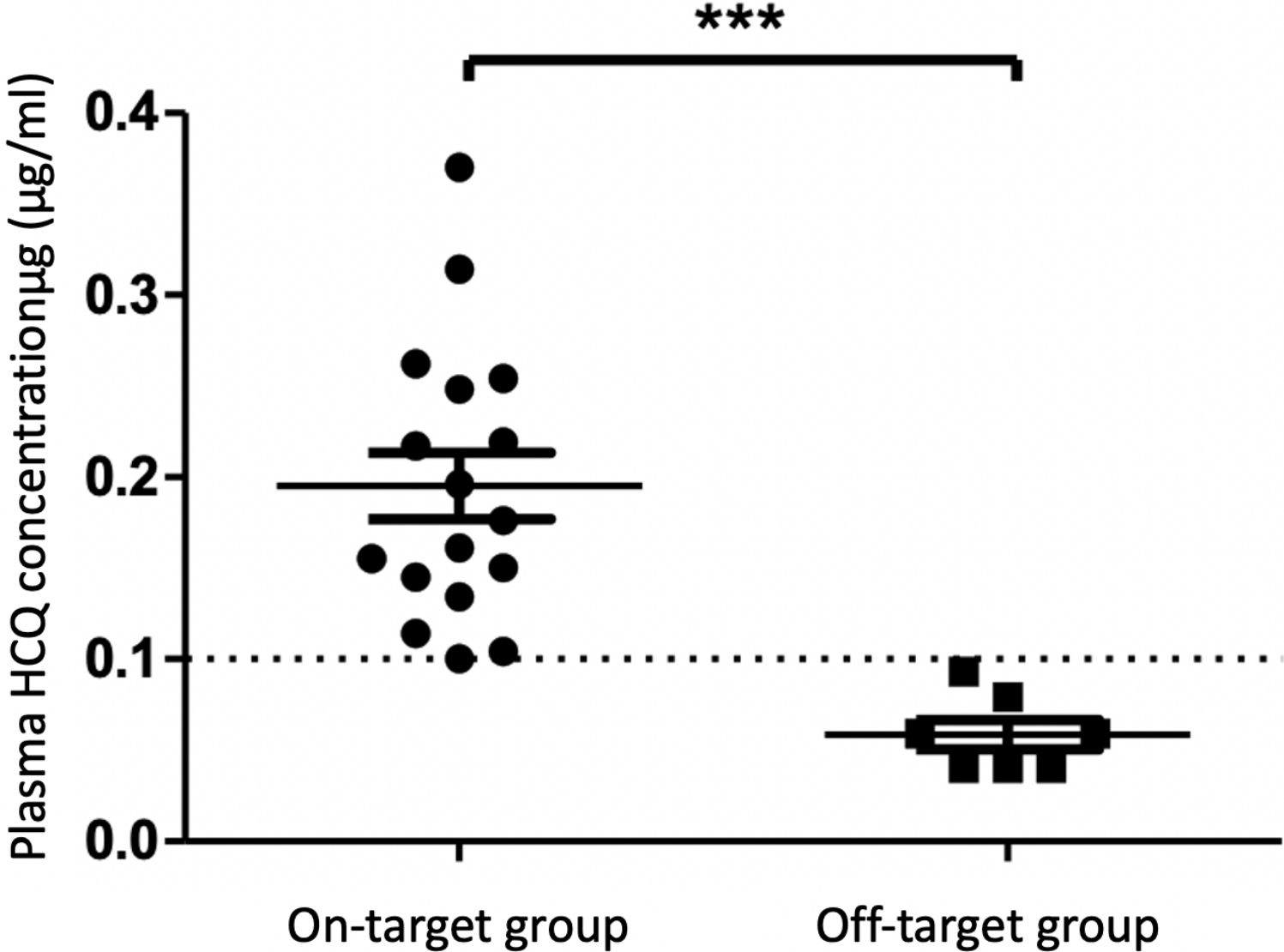


Figure 2: Viral load in nasopharyngeal swab at Day 15 in the two groups

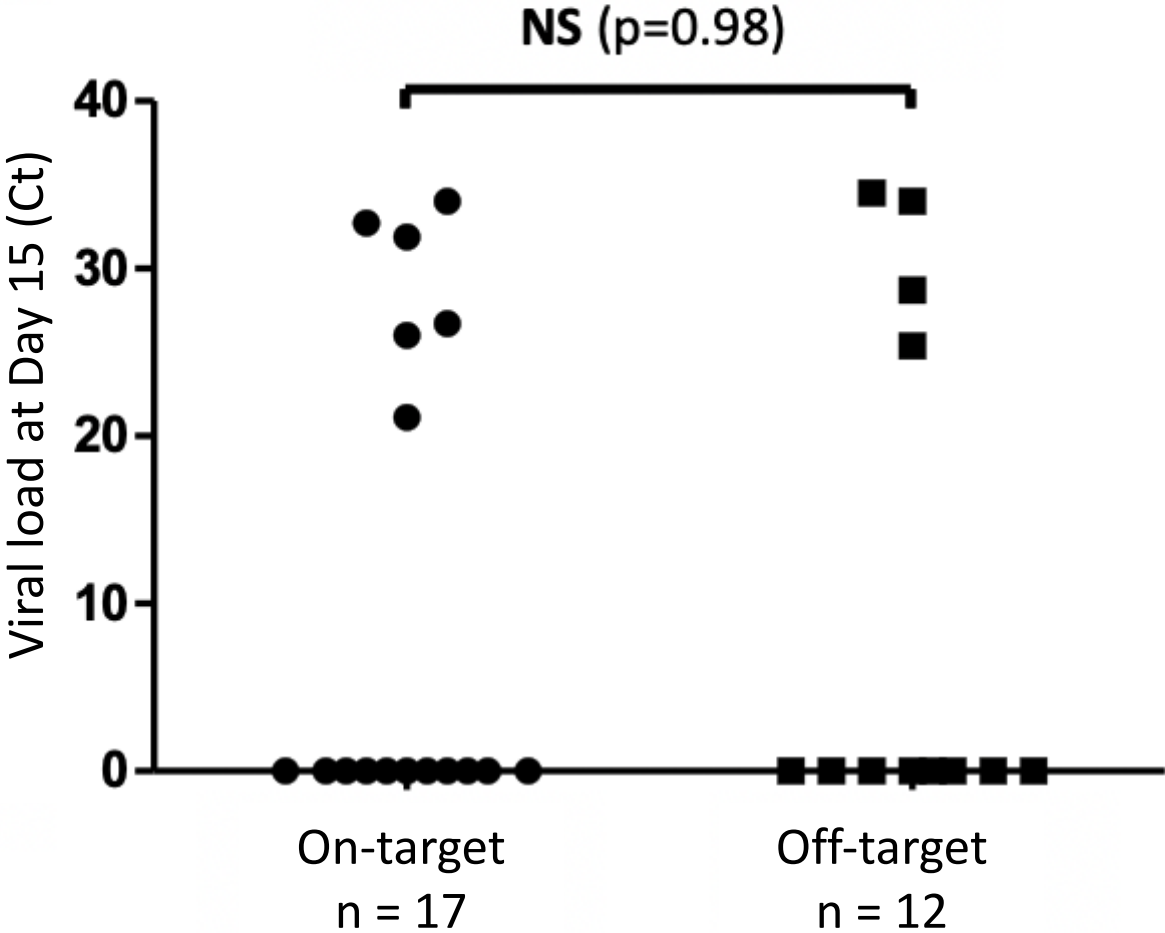


Table 1. Demographic and Clinical Findings

Characteristics		On-target group	Off-target group	P-value
		n = 17	n = 12	
Sex	Men, n (%)	12 (71)	12 (100)	0.06
Age, mean \pm SD, years		56 \pm 15	62 \pm 15	0.30
BMI, mean \pm SD, kg/m ²		31 \pm 5	29 \pm 4	0.51
Co-morbidities, n (%)				
	Coronary disease	5 (29)	4 (33)	0.86
	Hypertension	10 (59)	9 (75)	0.61
	Chronic obstructive pulmonary disease	2 (12)	1 (8)	1
	Habitual smoker	4 (24)	3 (25)	1
	Active cancer	2 (12)	1 (8)	1
	Immunodepression	0	1 (8)	0.41
	Chronic kidney disease	1 (6)	0	1
	Diabetes	6 (35)	6 (50)	0.68
Pregnant women, n (%)		3 (18)	0	0.25
In ICU Admission				
SAPS II, mean \pm SD		29 \pm 11	38 \pm 16	0.10
SOFA Score, mean \pm SD ^b		4 \pm 2	5 \pm 4	0.46
PaO ₂ /FiO ₂ ratio, mean \pm SD		167 \pm 74	127 \pm 52	0.12
Mechanical ventilation, n (%)		10 (59)	8 (67)	0.97
Covid-19 Infection history and treatment				
Respiratory symptoms at hospital admission, n (%)				
	Cough	13 (76)	8 (67)	0.87

	Dyspnea	17 (100)	11 (92)	0.41
Systemic symptoms at admission, n (%)				
	Fever	15 (88)	11 (92)	1
	Diarrhea	3 (18)	4 (33)	0.40
	Myalgia	11 (65)	7 (58)	0.97
	Anosmia, dysgeusia	5 (29)	6 (50)	0.46
Know sick contact. n (%)		8 (47)	3 (25)	0.41
Travel to a country where Covid-19 is endemic previous 3 months. n (%)		0	0	
Mean \pm SD duration of symptoms before hospital admission (days)		5 \pm 2	7 \pm 4	0.15
Mean \pm SD duration between treatment initiation and ICU admission, days		0 \pm 1	0 \pm 1	0.13
Mean \pm SD duration between symptom onset and ICU admission (days)		7 \pm 2	8 \pm 4	0.32
Mean \pm SD viral load at Day 1, Ct		25 \pm 12	30 \pm 4	0.43
15 days follow-up				
4-6 days plasma concentration hydroxychloroquine on-target treatment, n (%)		14 (82)	0	***
Negative PCR, n (%)		11 (65)	8 (67)	0.77
Mean \pm SD viral load change between Day 1 to Day 15, Ct		- 15 \pm 16	- 20 \pm 18	0.45
Mean \pm SD duration to PCR negative under treatment, days		7 \pm 6	6 \pm 5	0.71

Mean \pm SD duration to negative PCR since symptoms onset	13 \pm 6	15 \pm 7	0.43
15 days mortality	0	2 (17)	0.16
Still in ICU at 15 days	9 (53)	9 (75)	0.41
Still in hospital at 15 days	11 (65)	7 (64)	0.95
Length of mechanical ventilation, mean \pm SD, days	7 \pm 7	8 \pm 7	0.92
Length of vasopressor administration, mean \pm SD, days	3 \pm 5	3 \pm 3	0.95

Abbreviations: BMI, Body Mass Index; SAPS II, Simplified Acute Physiology Score II; SOFA, Sepsis-related Organ Failure Assessment; PaO₂/FiO₂ ratio, ratio of partial of arterial oxygen partial to the fraction of inspired oxygen; HC, Hydroxychloroquine; PCR, Polymerase Chain Reaction; ICU, Intensive Care Unit; Ct, Cycle threshold; SD, Standard Derivation.

^a Data are expressed as N (%) of participants unless otherwise indicated.

^b The SAPS II ranges from 0 to 163, with higher scores indicating higher risk of mortality. A patient with a score of 30 has an estimated mortality risk of 10%.

*** $P < 0.001$