

**Hydroxychloroquine plus azithromycin: a potential interest in reducing in-hospital morbidity due to COVID-19 pneumonia (HI-ZY-COVID)?**

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**Abstract:**

Introduction: Hydroxychloroquine (HCQ) with or without azithromycin is currently still debated as a potential treatment for the COVID-19 epidemic. Some studies showed discrepant results. However, timing for the treatment initiation and its setting (in-hospital or out-patient) are not consistent across studies.

Methods: Monocentric retrospective study conducted from 2th March to 17th April 2020, in adults hospitalized in a tertiary hospital for COVID-19. Patients characteristics were compared between groups depending on the therapy received (HCQ/azithromycin taken  $\geq 48$  hours or other treatment). Outcomes were evaluated from admission, by the need for intensive care unit (ICU) support and/or death. Univariate analyses were performed using non-parametric tests and confirmed by a multiple logistic regression using Pearson correlation test.

Results: Among 132 patients admitted for COVID-19 in the medicine ward, 45 received HCQ/azithromycin  $\geq 48$  hours, with a favorable outcome in 91.1% of cases (OR=6.2,  $p=0.002$ ) versus others regimen ( $n=87$ ). Groups were comparable at the baseline in terms of age, sex, comorbidities, extend in thoracic imaging, and severity.

Among patients that required to be transferred to ICU ( $n=27$ ) (for mechanical ventilation), median delay for transfer was 2 days (IQR 1-3). We report only 1 patient that presented an adverse event (a prolonged QT interval on EKG) that required to discontinue HCQ.

Conclusion: The present study suggests a potential interest of the combination therapy using HCQ/azithromycin for the treatment of COVID-19 in in-hospital patients.

72 **Introduction:**

73 Hydroxychloroquine (HCQ) is currently still debated as a potential treatment for the  
74 COVID-19 epidemic. In France, Gautret *et al.* [1,2] and Million *et al.* [3] showed in  
75 Marseille that a combination therapy using HCQ and azithromycin could potentially  
76 reduce viral shedding and locally flatten the epidemic curve by reducing the number  
77 of pneumonias associated with COVID-19. Although these studies are of interest  
78 considering the sample size ( $n > 1000$ ) they are partly conducted on outpatients and  
79 do lack a control group without HCQ and azithromycin.

80 Concomitantly, a study conducted by Mahevas *et al.* [4] decided to evaluate HCQ  
81 alone (600 mg per day) prescribed in an in-hospital setting within 48 hours after  
82 admission ( $n=84$ ) in comparison to standard of care, and showed no difference  
83 between groups assessed by a transfer in intensive care unit (ICU) and/or death.  
84 Those findings are concordant with a recent publication issued in United States by  
85 Magagnoli *et al.* [5] despite some bias at baseline.

86 More, recently Esper *et al.* [6] in Brazil reported a potential interest of HCQ (using a  
87 loading dose of 800 mg followed by 600 mg during 6 days) plus azithromycin in the  
88 prevention of hospital admission in patients presenting compatible symptoms of  
89 COVID-19 (a 2.8-fold decrease if HCQ was administered within the first 7 days of  
90 symptoms).

91 To our knowledge, at the time being, there is no study evaluating the interest of an  
92 administration of HCQ plus azithromycin during at least 48 hours in an in-hospital  
93 setting and its impact on the admission in intensive care unit (ICU). Since the 25<sup>th</sup> of  
94 March 2020 in France, in the context of the state of health emergency, the ministerial

95 decree #2020-314 authorized the in-hospital prescription of HCQ for COVID-19  
96 patients. Therefore, we decided to report our own experience of this regimen in order  
97 to draw conclusions whether we pursue such combination therapy for hospitalized  
98 patients.

## 100 **Methods:**

### 101 *Setting*

102 We conducted a monocentric and retrospective study, from 2th March 2020 to 17th  
103 April 2020, regarding adults admitted in our medicine wards in a tertiary university  
104 hospital namely Hôpital Raymond Poincaré (AP-HP), Garches, France. For decades,  
105 this hospital, and particularly the ICU, is specialized in the management of  
106 neurological impairment and infectious diseases. Since the beginning of the COVID-  
107 19 outbreak, an entire building, namely Widal (in honor of Doctor Fernand Widal),  
108 was entirely dedicated to admit only COVID-19 positive patients. During the peak of  
109 the epidemic, we had a maximum capacity of 85 beds for medicine and 32 beds for  
110 ICU.

111 We included all the adults admitted in medicine for a COVID-19 infection confirmed  
112 by SARS-CoV-2 PCR and/or a compatible pulmonary CT-scan. Exclusion criteria  
113 were i) patients discharged from ICU to a medicine ward; ii) opposition to collect data  
114 expressed by the patient.

### 116 *Data collection*

117 The following data were collected from patient's medical charts:

- 118 - Patient characteristics: age, sex, diabetes, cardiovascular risk factor, smoking
- 119 habits, obesity, chronic pulmonary disease, Charlson comorbidity score,
- 120 - Infection characteristics: delay between onset of symptoms and admission,
- 121 presence of super-infection, C-reactive protein (CRP) and white blood cell count
- 122 (WBC) at admission, percentage of lung injuries on CT-scan if applicable, positive
- 123 PCR amplifying the betacoronavirus E gene and the SARS-CoV-2 RdRp gene on
- 124 nasopharyngeal swab or sputum,
- 125 - Treatment characteristics: requiring ICU support with invasive ventilation,
- 126 associated therapeutic strategies (especially HCQ and azithomycin),
- 127 - Unfavorable outcome was evaluated after admission, by the need for ICU support
- 128 and/or death,
- 129 - The patients were followed-up until hospital discharge.

130

### 131 *Treatment strategies*

132 All patients under oxygen received systematically a beta-lactam for at least 5 days,

133 using preferentially ceftriaxone to treat a potential super-infection.

134 Patients were eligible to a targeted therapy against COVID-19 considering the

135 following indications: i) patient presenting a clinical pneumonia confirmed by SARS-

136 CoV-2 PCR requiring oxygen therapy (independently of the CT scan findings); ii) high

137 suspicion of COVID-19 pneumonia considering the clinical presentation and

confirmed by a pulmonary CT-scan showing ground-glass opacity affecting  $\geq 10\%$  of the whole parenchyma

Before HCQ initiation, patients had systematically an EKG to evaluate the corrected QT interval using the Framingham formula, and monitored 2 times per week during 10 days. A loading dose at day 1 with 800 mg/day was administered followed by a maintenance dose of 400 mg/day up to 600 mg/day in case of obesity (body mass index (BMI)  $> 30$ ) for a total 10 days. In addition, 500 mg of azithromycin was prescribed the first day, followed by 250 mg for 4 days. Patients were informed that HCQ is currently off-label for the treatment of COVID-19. In case they refused the prescription of HCQ or the latter was contraindicated, it was noted into their medical chart and patients were eligible for other therapeutic strategies.

Primary objective was to evaluate whether HCQ plus azithromycin (HI-ZY-COVID) initiated after their admission was associated with a favorable outcome. For analysis purposes, we stated that patients should receive at least 48 hours of the above combination therapy to be considered effective. Therefore, patients were divided into 2 groups: the ones who received specifically HCQ/azithromycin for 48 hours or more and the remaining.

### *Statistical analysis*

Quantitative variables were expressed using mean and standard deviation or median and interquartile range (IQR) when appropriate. Qualitative variables were described by percentage. Comparisons were performed using non-parametric tests with a Yates' continuity corrected chi-square test for qualitative variables and a Mann-Whitney test for quantitative variables. Multiple logistic regression test was performed

using Pearson correlation test. Analyses were performed using GraphPad Prism v.8.3.1 (GraphPad Software Inc., La Jolla, CA). Statistical significance was defined for  $p \leq 0.05$ .

#### *Compliance with Ethical Standards*

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This cohort is registered on ClinicalTrials.gov (NCT04364698). The study was approved by the local Ethics Committee. As data used in the study were anonymous and retrospective, the requirement for informed consent was waived by the Ethics Committee.

#### **Results:**

Overall 132 were eligible for the analysis (see flowchart in Figure 1). Forty-five patients received HCQ plus azithromycin for more than 48 hours after admission. The remaining patients (n=87) were in the others regimen group. Of note, in patients who did not receive HCQ, 5 had cardiac contraindication and 2 refused to be treated with this molecule.

Patient characteristics between HCQ/azithromycin  $\geq 48$  hours and the no-HCQ/azithromycin (control group) were comparable and are detailed in Table 1. It should be noted that patients receiving HCQ/azithromycin had higher need for oxygen and higher CRP level at admission than the control group.



For analysis purposes the cohort was divided according to the outcome into 2 groups: “favorable outcome” and “unfavorable outcome” (ICU and/or death). Main findings are summarized in Table 2. Well-known comorbidities in COVID-19 (cardiovascular, respiratory, diabetes, immune deficiency, obesity) that were similar at baseline were not associated with the outcome ( $p>0.2$ ). During the course of HCQ/azithromycin, we report only 1 patient that presented an adverse event (a prolonged QT interval on EKG) without clinical event that required to discontinue HCQ before 48h, and was therefore placed in the azithromycin group.

Among patients that required to be transferred to ICU ( $n=27$ ) (for mechanical ventilation), median delay for transfer was 2 (1-3) days. Up to this day, 10 (37%) patients died in ICU and 2 in medical ward.

For clarification, outcomes according to therapeutic strategy are illustrated in Figure 2.

Multiple logistic regression confirmed that a favorable outcome was associated with receiving HCQ plus azithromycin ( $p=0.009$ ), oxygen flow ( $p<0.0001$ ), lymphocyte count ( $p=0.002$ ) and CRP ( $p=0.002$ ) detailed in Figure 3.

## **Discussion:**

Our study supports that in-hospital patients treated with HCQ plus azithromycin for more than 48 hours, have a reduced risk to be transferred to ICU and/or to decease (OR=6.2).

Our findings are concordant with Gautret *et al.* [1,2] who revealed good clinical and virologic outcomes using this combination therapy, in the limit of the absence of a

control group in his study conducted especially among ambulatory care patients. Furthermore, Esper *et al.* [6] reported efficacy of the combination therapy of HCQ/azithromycin in outpatients exclusively. The main limit of this study is the lack of PCR testing, despite the fact the majority of patients included in the HCQ/azithromycin arm had a high rate of CT-scan lung injuries compatible with COVID-19.

To support our results, we ensured that the difference accounting for the HCQ/azithromycin arm was not associated with an earlier initiation of treatment (see Table 1). Interestingly, despite the fact HCQ was initiated after a median delay of 9 days from onset of symptoms, period approaching the so-called “cytokine storm” [7,8], we can hypothesize that HCQ might have played a role in the second stage of the disease as an immune-modulator as previously described [9].

Mahevas *et al.* [4] studied patients hospitalized for COVID-19 as we did and showed no evidence of clinical efficacy of HCQ alone (n=84) in a retrospective and comparative study. However, we have no information if patients categorized as control group received azithromycin or a symptomatic treatment. These results’ discrepancies in comparison to our findings should be discussed. First, we used a combination therapy with HCQ plus azithromycin and second our patients were considered to be treated efficiently only if they received a course of at least 48 hours of this combination therapy. However, Magagnoli *et al.* [5] reported, in 368 hospitalized veterans with COVID-19, a higher death rate with HCQ treatment with or without azithromycin. This study has numerous bias, including a higher lymphocytopenia ( $<500/\text{mm}^3$ ) and more comorbidities at baseline in the patients who received HCQ, a population exclusively composed of male, including 66% of black

Americans. Also, the posology of HCQ is lacking and 31% had azithromycin in the control group.

Our findings are all the more remarkable, considering that patients in the HCQ/azithromycin group required significantly more oxygen ( $p=0.005$ ) and had higher CRP ( $p=0.008$ ) at baseline, which is deemed to be a predictive factor of severity in COVID-19 pneumonia [10]. Of note, in multivariate analysis our patients in ICU had lower lymphocyte count and higher CRP level ( $p=0.002$ ) as commonly described [11].

Interestingly, patients who received azithromycin alone had a trend to a better outcome than standard of care (multivariate analysis,  $p=0.05$ ), in the limit of the sample size ( $n<30$ ). Azithromycin's potential antiviral activity is concordant with previous *in vitro* studies regarding SARS-CoV-2 [12] or H1N1-pdm09 [13] and one clinical randomized trial in the prevention of children respiratory infections [14]. As azithromycin is commonly prescribed and authorized in ambulatory care, a study conducted among general practitioners could be relevant to evaluate this single therapy for the control of COVID-19 in outpatients.

In addition, our experience confirms the safety of HCQ, without any serious side effect, as long as we take the necessary caution at the initiation of therapy and during follow-up EKG. This low risk of toxicity using a conventional dose of HCQ associated with azithromycin is concordant with Borba *et al.* [15].

Finally, we believe the combination using HCQ plus azithromycin is relatively cost-effectiveness and makes it particularly attractive to better control the hospital overflow during the pandemic.

However, our study has several limitations. First, it is a retrospective study with a limited sample size (n=132), with a pre-established statement that considered HCQ plus azithromycin had to be received for at least 48 hours to interpret its impact. Second, groups were not balanced in terms of individuals notably because prior to the 25<sup>th</sup> of march, HCQ was not authorized by the French Minister for Solidarity and Health and drug was therefore out of stock. Third, we performed less frequently lung CT-scans in the no-HCQ/azithromycin group, partly because CT-scans were not recommended for COVID-19 at the beginning of the outbreak in our hospital (in early March). Also, in our ICU critical care physicians do not systematically perform CT-scans in intubated patients considering the higher risk of contamination from those patients. Fourth, as we are facing a recent outbreak of COVID-19 in France where knowledge and criteria of ICU transfer might have changed over time and considering prolonged length of stay in ICU [16], the overall mortality might have been underestimated, as (n=6/29) are still under mechanical ventilation assistance. Finally, we can discuss our decision not to exclude patients receiving lopinavir from the control group (n=14), however there is currently no solid data supporting its efficacy against SARS-CoV-2 [17].

In conclusion, our study confirms already known risk factors for unfavorable outcomes in COVID-19 hospitalized patients. Moreover, the present work highlights the potential interest of the combination therapy of HCQ/azithromycin (≥48 hours' intake) by limiting the rate of ICU transfer. A larger and randomized controlled study is necessary to confirm those preliminary findings. Our data constitute a hope to flatten the epidemic curve and prevent ICU overflow in case of a possible second wave.

**Figure 1:** Flowchart of the studied population.

**Figure 2:** Outcome pictured depending on the received therapeutic strategy. HCQ = hydroxychloroquine; AZI = azithromycin; SOC = standard of care which includes no targeted therapy, or lopinavir/r or treatment received <48h until unfavorable outcome (transfer to ICU or death).

**Figure 3:** Factors influencing the outcome in a multiple logistic regression using a Pearson correlation test. Coefficient values can range from +1 to -1, where +1 indicates a perfect positive relationship, -1 indicates a perfect negative relationship, and a 0 indicates no relationship exists. HCQ = hydroxychloroquine; AZI = azithromycin; SOC = standard of care which includes no targeted therapy, or lopinavir/r or treatment received <48h until unfavorable outcome (transfer to ICU or death).

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BD and PDT conceptualized and designed the study, carried out the initial analyses, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript.

BD, SB, TL, CP designed the data collection instruments, collected data and PDT and AD reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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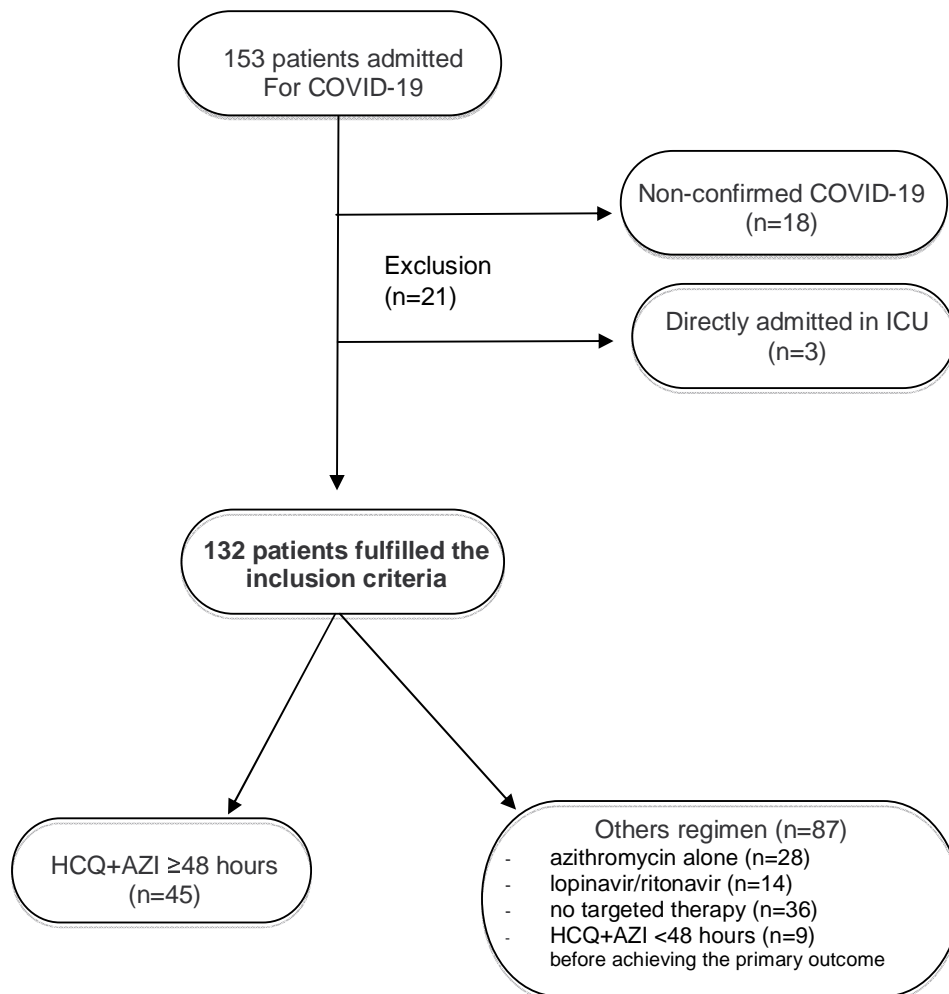
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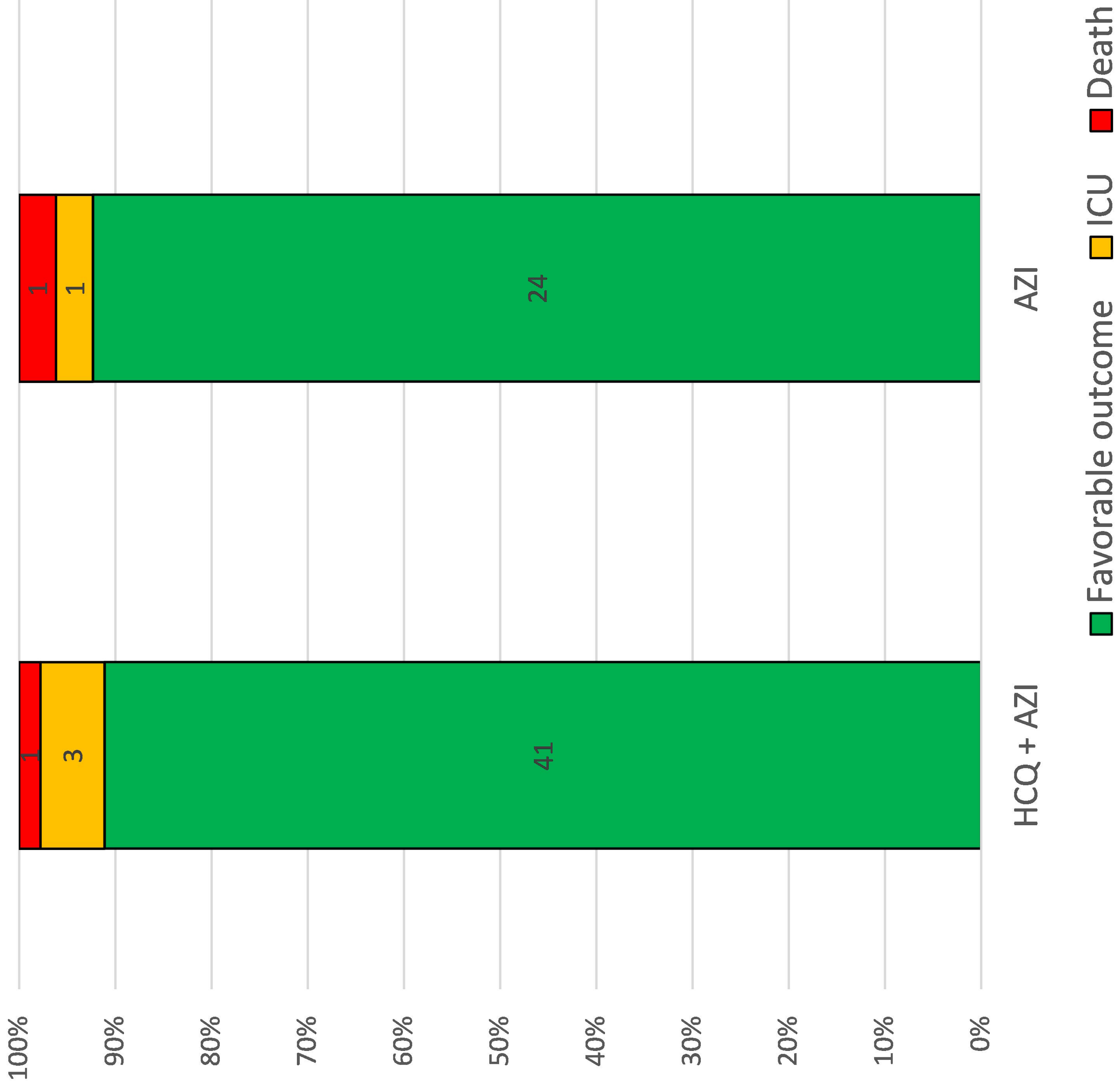
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**Table 1:** Demographic and clinical characteristics at baseline

Variables	HCQ+AZI ≥ 48h (n=45)	Others regimen* (n=87)	p-value (α=0.05)
<b>Demographic data</b>			
Age, mean ± SD	58 ± 17	59 ± 16	0.74
Male sex – no (%)	31 (68.9)	55 (63.2)	0.65
Patients with a Charlson Comorbidity Index (CCI) ≥ 5**, no (%)	7 (15.5)	23 (25.9)	0.23
Comorbidities - no (%)			
- Cardiovascular disease (incl. HBP)	17 (37.8)	40 (46.0)	0.47
- Chronic respiratory disease (incl. COPD)	8 (17.8)	14 (16.1)	0.99
- Diabetes	7 (15.5)	18 (20.7)	0.63
- Chronic kidney failure	1 (2.2)	3 (3.4)	0.88
- Chronic liver disease (≥ Child-Pugh B)	0	1 (1.2)	0.73
- Immunodepression	4 (8.9)	7 (8.0)	0.86
- Obesity (BMI> 30 kg/m <sup>2</sup> )	8 (17.8)	6 (6.9)	0.1
<b>COVID-19 data</b>			
Median delay from onset of symptoms until admission, (IQR) in days	8 (6-11)	7 (4-8)	0.005
Median delay between initiation of therapeutic strategy and onset of symptoms, (IQR) in days	9 (6-12)	7 (6-9)	0.04
PCR COVID-19 positive – no (%)	43 (95.5)	83 (95.5)	0.99
Oxygen flow at admission, median (IQR) – L/min	2 (2-4)	2 (0-3)	0.001
<b>Thoracic imaging</b>			
Patients with a lung CT scan – no (%)	44 (97.8)	59 (67.8)	0.0002
Normal CT scan – no (%)	1 (2.3)	3 (5.1)	0.83
Limited extend on CT scan <10%	7 (15.9)	9 (15.3)	0.85
Mild extend on CT scan 10-25%	11 (25)	16 (27.1)	0.99
Moderate extend on CT scan 25-50%	19 (43.2)	24 (40.7)	0.96
Severe extend on CT scan 50-75%	6 (13.7)	6 (10.2)	0.81
Critical extend on CT scan >75%	0	1 (1.7)	0.88
<b>Biological tests</b>			
Median lymphocyte count (IQR) - /mm <sup>3</sup>	920 (710-1160)	1065 (745-1530)	0.16
Median C-reactive protein (CRP) (IQR) – mg/L	90.5 (55-152)	62 (14-106)	0.008

\*Others regimen include azithromycin (n=28), lopinavir/ritonavir (n=14) or no targeted therapy (n=36) and 9 individuals treated with HCQ plus azithromycin for less than 48 hours before transfer to ICU and/or death

\*\*Patients with a CCI scores ≥5 are considered as severe and fragile.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HBP, high blood pressure



**Table 2:** Risk-factors and clinical outcome of COVID-19 hospitalized patients. Variables are compared using Chi-square test with Yates' correction. Odds ratio (OR) were obtained using Baptista-Pikes method. Multiple logistic regression was performed to calculate a correlation factor using Pearson test.

Variables	Favorable outcome n (%)	ICU or death n (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI) for favorable outcome	p-value	r (95% CI) for favorable outcome	p-value
Baseline characteristics						
Age, mean ± SD	57 ± 1.6	64 ± 2.8	-	0.05	-0.32 to 0.011	0.067
Gender (% male)	68 (66)	18 (62)	-	0.82	-	-
Median delay between onset of symptoms and admission, (IQR) in days	7 (4-10)	6 (5-9)	-	0.31	-0.11 to 0.22	0.52
Median delay between initiation of therapeutics and onset of symptoms, (IQR) in days	8.5 (6-10)	7 (6-10)	-	0.29	-0.09 to 0.3	0.27
Median oxygen flow at admission (IQR) - L/min	2 (0-3)	3 (2-4)	-	0.003	-0.48 to -0.17	<0.0001
CT scan lung affected > 50%						
Yes	10 (76.9)	3 (23.1)				
No	76 (84.5)	14 (15.5)	1.62 (0.43 to 6)	0.78	-	-
Median lymphocyte count at admission (IQR) - /mm <sup>3</sup>	1110 (780-1450)	810 (700-955)	-	0.0005	0.1 to 0.42	0.002
Median CRP count at admission (IQR) - mg/L	62 (16-112.5)	112 (82-161.5)	-	0.001	-0.42 to -0.1	0.002
Charlson Comorbidity Index (CCI)**						
CCI <5	81 (79.4)	21 (20.6)				
CCI ≥5	22 (73.3)	8 (26.7)	0.7 (0.27 to 1.82)	0.65	-	-
Obesity (BMI> 30 kg/m <sup>2</sup> )						
Yes	13 (92.8)	1 (7.2)				
No	90 (76.3)	28 (23.7)	0.25 (0.02 to 1.46)	0.28	-0.04 to 0.29	0.15
Therapeutic data						
HCQ + azithromycin ≥ 48 hours	41 (91.1)	4 (8.9)	6.2 (2.1 to 17.6)	0.002	0.06 to 0.38	0.009
Azithromycin ≥ 48 hours	24 (92.3)	2 (7.7)	7.2 (1.76 to 33.0)	0.01	-0.0001 to 0.33	0.05
Standard of care*	38 (62.3)	23 (37.7)	1	-	1	-
Total	103	29	-			

\*standard of care includes no targeted therapy, or lopinavir/r or treatment received <48h until unfavorable outcome (transfer to ICU or death)

\*\* Patients with CCI scores  $\geq$ 5 are considered as severe and fragile

