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

Benjamin Davido[1,§], Thibaud Lansaman[2], Simon Bessis[1], Christine Lawrence[3], Jean-Claude Alvarez[4], Hélène Mascitti[1], Frédérique Bouchand[5], Pierre Moine[6], Véronique Perronne[1], Aurélie Le Gal[1], Djillali Annane[6], Christian Perronne[1], Pierre De Truchis[1,§], on behalf of the COVID-19 RPC Team*

[1] Maladies Infectieuses, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

[2] Rééducation fonctionnelle, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

[3] EOH, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

[4] Pharmaco-toxicologie, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

[5] Pharmacie Hospitalière, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

[6] Réanimation médicale, Université Paris-Saclay, AP-HP Hôpital Raymond Poincaré, Garches, France

§: Both authors contributed equally to this work.

Keywords: hydroxychloroquine, azithromycin, Covid-19, pneumonia

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of interest statement: The authors have no specific conflict of interest.

Corresponding author:

Benjamin Davido, Service de Maladies Infectieuses et Tropicales

Hôpital Raymond-Poincaré, Garches 92380, France.

Tel: +33-1-47107758, e-mail: benjamin.davido@aphp.fr

Abstract word count: 220/250

Body of text word count: 2100 words

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 ≥ 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 ≥ 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.

Introduction:

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

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

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

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

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

Methods:

Setting

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

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

Data collection

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

- Patient characteristics: age, sex, diabetes, cardiovascular risk factor, smoking habits, obesity, chronic pulmonary disease, Charlson comorbidity score,

- Infection characteristics: delay between onset of symptoms and admission, presence of super-infection, C-reactive protein (CRP) and white blood cell count (WBC) at admission, percentage of lung injuries on CT-scan if applicable, positive PCR amplifying the betacoronavirus E gene and the SARS-CoV-2 RdRp gene on nasopharyngeal swab or sputum,

- Treatment characteristics: requiring ICU support with invasive ventilation, associated therapeutic strategies (especially HCQ and azithomycin),

- Unfavorable outcome was evaluated after admission, by the need for ICU support and/or death,

- The patients were followed-up until hospital discharge.

Treatment strategies

All patients under oxygen received systematically a beta-lactam for at least 5 days, using preferentially ceftriaxone to treat a potential super-infection.

Patients were eligible to a targeted therapy against COVID-19 considering the following indications: i) patient presenting a clinical pneumonia confirmed by SARS-CoV-2 PCR requiring oxygen therapy (independently of the CT scan findings); ii) high suspicion of COVID-19 pneumonia considering the clinical presentation and

confirmed by a pulmonary CT-scan showing ground-glass opacity affecting ≥ 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 ≥ 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/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 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.

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

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

279

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).

Acknowledgments:

First author (BD) would like to thank Azzam Saleh-Mghir for his unfailing support.

Contributors' Statement:

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.

List of Collaborators

**COVID-19 RPC Team*

Department of Intensive Care

Djillali Annane, MD, PhD (1,2,5)
Xavier Ambrosi, MD (4)
Suzanne Amthor, MD (1)
Rania Bounab, MD (1,2)
Ryme Chentouh, MD (1)
Bernard Clair, MD (1)
Abdallah Fayssoil, MD (1,2,5)
Diane Friedman, MD (1)
Nicholas Heming, MD, PhD (1,2,5)
Virginie Maxime, MD, (1)
Pierre Moine, MD, PhD (1,2,5)
Myriam Niel Duriez, MD (1)
David Orlikowski, MD, PhD (1,2,5,8)
Francesca Santi, MD (1,2)

Pharmacy

Frédérique Bouchand, PharmD (1)
Muriel Farcy-Afif, PharmD (1)
Hugues Michelon, PharmD, MSc (1)
Maryvonne Villart, PharmD (1)

Research Staff

Isabelle Bossard (8)
Tiphaine Barbarin Nicolier (1)
Stanislas Grassin Delyle, MCUPH (2,3,5)
Elodie Lamy (2,5)
Camille Roquencourt, MD (5)
Gabriel Saffroy (2)
Etienne Thevenot (5)

Department of Intensive Care Interns

Baptiste Abbar (1)
Steven Bennington (1)
Juliah Dray (1)
Pierre Gay (1)
Elias Kochbati (1)
Majistor Luxman (1)
Myriam Moucachen (1)
Alice Pascault (1)
Juan Tamayo (1)
Justine Zini (1)

Department of Anesthesia, Perioperative Care, and Pain

Marie Boutros, MD (1)
Anne Lyse Bron, MD (11)
Denys Coester, MD (12)
Etiennette Defouchecour, MD (11)
Brigitte Dosne Blachier, MD (11)
Léa Guichard, MD (1)
Damien Hamon Pietrin, MD, PhD (1)
Hakim Khiter, MD (1)
Valéria Martinez, MD, PhD (1,2,6)
Simone Meuleye, MD (1)
Suzanne Reysz, MD (1)
Sebastien Schitter, MD (1)
Chawki Trabelsi, MD (1)

Pediatric Critical Care Unit

Helge Amthor, MD, PhD (1,2,7)
Jean Bergounioux MD (1,2,5)
Maud Guillon, MD (1)
Amal Omar, MD (1)

Laboratory of Physiology

Frédéric Lofaso, MD, PhD (1,2,7,10)
Helene Prigent, MD, PhD (1,2,7,10)

Department of Rehabilitation and Physical Medicine

Djamel Bensmail, MD, PhD (1,2,7,10)
Pierre Denys, MD, PhD (1,2,7,10)
Charles Joussain, MD, PhD (1)
Lauren Kagane, MD (1)
Thibaut Lansaman, MD (1)
Hélène Le Liepvre, MD (1)
Antoine Leotard, MD, MS (1)
Jonathan Levy, MD, MS (1,2,7,10)
Claire Malot, MD (1)

Julie Paquereau, MD (1)
Celia Rech, MD (1)

Department of Rehabilitation Interns

Florence Angioni (1)
Elsa Chkron (1)
Céline Karabulut (1)
Jérôme Lemoine (1)
Noémie Trystram (1)
Julien Vibert (1)

Department of Infectious Diseases

Simon Bessis, MD (1,2)
Pascal Crenn, MD, PhD (1,2,7)
Benjamin Davido, MD, MS (1)
Aurélien Dinh, MD, MS (1,2)
Stéphanie Landowski, MD (1)
Hélène Mascitti, MD, MS (1)
Morgan Matt, MD (1,2)
Christian Perronne, MD, PhD (1,2)
Véronique Perronne, MD (1)
Soline Simeon, MD, MS (1)
Pierre de Truchis, MD, MS (1)

Department of Infectious Diseases Interns

Marc Hobeika (1)
Louis Jacob (1)
Nicolas Kiavue (1)
Aymeric Lanore (1)
Aurélie Le Gal (1)
Julia Nguyen Van Thang (1)

Department of Microbiology and Innovative Biomarkers Platform

Coralie Favier (1)
Jean Louis Gaillard, MD, PhD (1,2,5)
Elyanne Gault, MD, PhD (1,2,5)
Jean-Louis Herrmann, PharmD, PhD (1,2,5)
Christine Lawrence, PharmD (1)
Virginie Lebidois, PharmD (1)
Latifa Noussair, MD (1)
Martin Rottman, MD, PhD (1,2,5)
Anne-Laure Roux, PharmD, PhD (1,2,5)
Sophie Tocqueville (1)
Marie-Anne Welti, MD, PhD (1,2,5)
And the nonmedical staff of the Department

Department of Laboratory Medicine and Pharmacology

Jean Claude Alvarez, MD, PhD (1,2,5)
Mehdi Djebrani, PharmD (1)
Pierre-Alexandre Emmanuelli (1)
Firas Jabbour, PharmD (1)
Lotfi Lahjomri, MD (1)
Mathilde Parent, MD (1)
And the nonmedical staff of the Department

Department of Radiology

Amine Ammar, MD (1)
Najete Berradja, MD (1)
Robert-Yves Carlier, MD, MS (1,2,7,14)
Annaelle Chetrit, MD (1,2)
Caroline Diffre, MD (1,2)
Myriam Edjlali, MD, PhD (1,15)
Zaki El Baz, MD (1,14)
Adrien Felter, MD (1)
Catherine Girardot, MD (1,13)
Ahmed Mekki, MD, MS (1,2)
Dominique Mompoint, MD (1)
Dominique Safa, MD (1)
Tristan Thiry, MD (1)

Department of Radiology Interns

Margot Armani (1)
Olivier de Barry (1)
Antoine Kirchner (1)
Jeffery Zhou (1)

Department of Forensic Medicine

Geoffroy Lorin de La Grandmaison MD, PhD (1)

Department of Forensic Medicine Intern

Kevin Mahe (1)

Affiliations

1. Hôpital Raymond Poincaré, GHU APHP, Université Paris Saclay, Garches, France
2. Faculté Simone Veil Santé, Université Versailles Saint Quentin en Yvelines, Université Paris Saclay, Montigny-le-Bretonneux, France
3. Hôpital Foch, Suresnes, France
4. Centre Hospitalier Universitaire de Nantes, Nantes, France
5. Université de Versailles Saint-Quentin-en-Yvelines/INSERM, Laboratory of Infection & Inflammation–U-1173, Montigny-le-Bretonneux, France
6. Université de Versailles Saint-Quentin-en-Yvelines/INSERM, Centre d'Evaluation et de Traitement de la Douleur–U-987, Boulogne-Billancourt, France

7. Université de Versailles Saint-Quentin-en-Yvelines/INSERM, Handicap Neuromusculaire–U-1179, Montigny-le-Bretonneux, France
8. Centre d'Investigation Clinique, Garches, France
9. Commissariat à l'Energie Atomique, CEA Paris Saclay, Gif-sur-Yvette, France
10. Fondation Garches, Garches, France
11. Clinique Jouvenet, Ramsay Santé, Paris, France
12. Clinique de la Muette, Ramsay Santé, Paris, France
13. Polyclinique Mantaise, Mantes-La-Jolie, France
14. Centre Hospitalier Intercommunal Poissy/Saint-Germain, GHT Yvelines Nord, Poissy, France
15. IMA-BRAIN/INSERM–UMR-1266, DHU-Neurovasc, Centre Hospitalier Sainte-Anne, Paris, France

References:

[1] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. Travel Med Infect Dis 2020:101663. doi:10.1016/j.tmaid.2020.101663.

[2] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949. doi:10.1016/j.ijantimicag.2020.105949.

[3] Million M, Lagier J-C, Gautret P, Colson P, Fournier P-E, Amrane S, et al. Early treatment of 1061 COVID-19 patients with hydroxychloroquine and azithromycin, Marseille, France. n.d.

[4] Mahevas M, Tran V-T, Roumier M, Chabrol A, Paule R, Guillaud C, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely

collected data to emulate a target trial. MedRxiv 2020:2020.04.10.20060699. doi:10.1101/2020.04.10.20060699.

[5] Magagnoli J, Narendran S, Pereira F, Cummings T, Hardin JW, Sutton SS, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. MedRxiv 2020:2020.04.16.20065920. doi:10.1101/2020.04.16.20065920.

[6] Barbosa Esper R, Souza da Silva R, Teiichi Costa Oikawa F, Machado Castro M, Razuk-Filho A, Benedito Batista Junior P, et al. Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine. n.d.

[7] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England) 2020;395:1054–62. doi:10.1016/S0140-6736(20)30566-3.

[8] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020;395:497–506. doi:10.1016/S0140-6736(20)30183-5.

[9] Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents 2020:105982. doi:10.1016/j.ijantimicag.2020.105982.

[10] E T, I N-S, I E, E K, TN S, M P, et al. Hematological Findings and Complications of COVID-19. Am J Hematol 2020. doi:10.1002/AJH.25829.

[11] Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia

predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020;5:33. doi:10.1038/s41392-020-0148-4.

[12] Touret F, Gilles M, Barral K, Nougairède A, Decroly E, Lamballerie X de, et al. In vitro screening of a FDA approved chemical library reveals potential inhibitors of SARS-CoV-2 replication. BioRxiv 2020:2020.04.03.023846. doi:10.1101/2020.04.03.023846.

[13] DH T, R S, T H, S S, Y N, A S, et al. Azithromycin, a 15-membered Macrolide Antibiotic, Inhibits Influenza A(H1N1)pdm09 Virus Infection by Interfering With Virus Internalization Process. J Antibiot (Tokyo) 2019;72. doi:10.1038/S41429-019-0204-X.

[14] LB B, TW G, DT M, S B, A B, AM F, et al. Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. JAMA 2015;314. doi:10.1001/JAMA.2015.13896.

[15] Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection. JAMA Netw Open 2020;3:e208857. doi:10.1001/jamanetworkopen.2020.8857.

[16] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708–20. doi:10.1056/NEJMoa2002032.

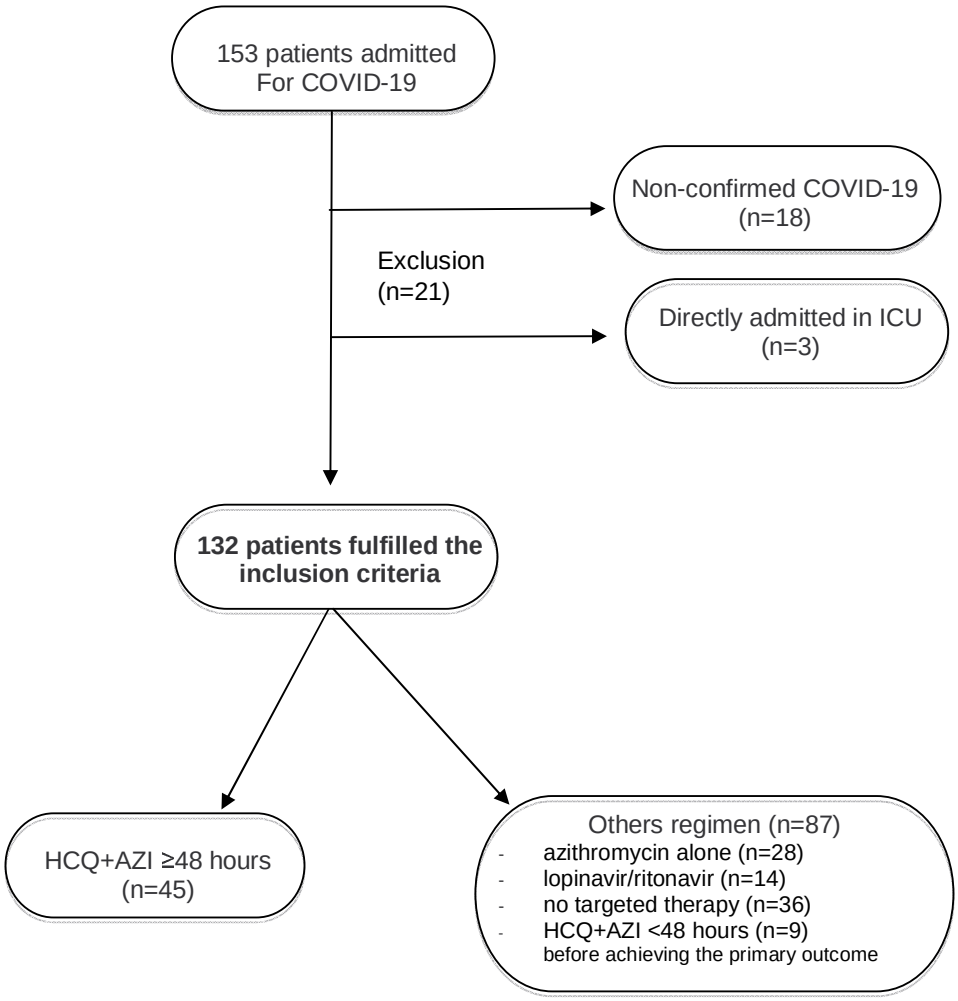
[17] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–

554 Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med

555 2020:NEJMoa2001282. doi:10.1056/NEJMoa2001282.

556

557



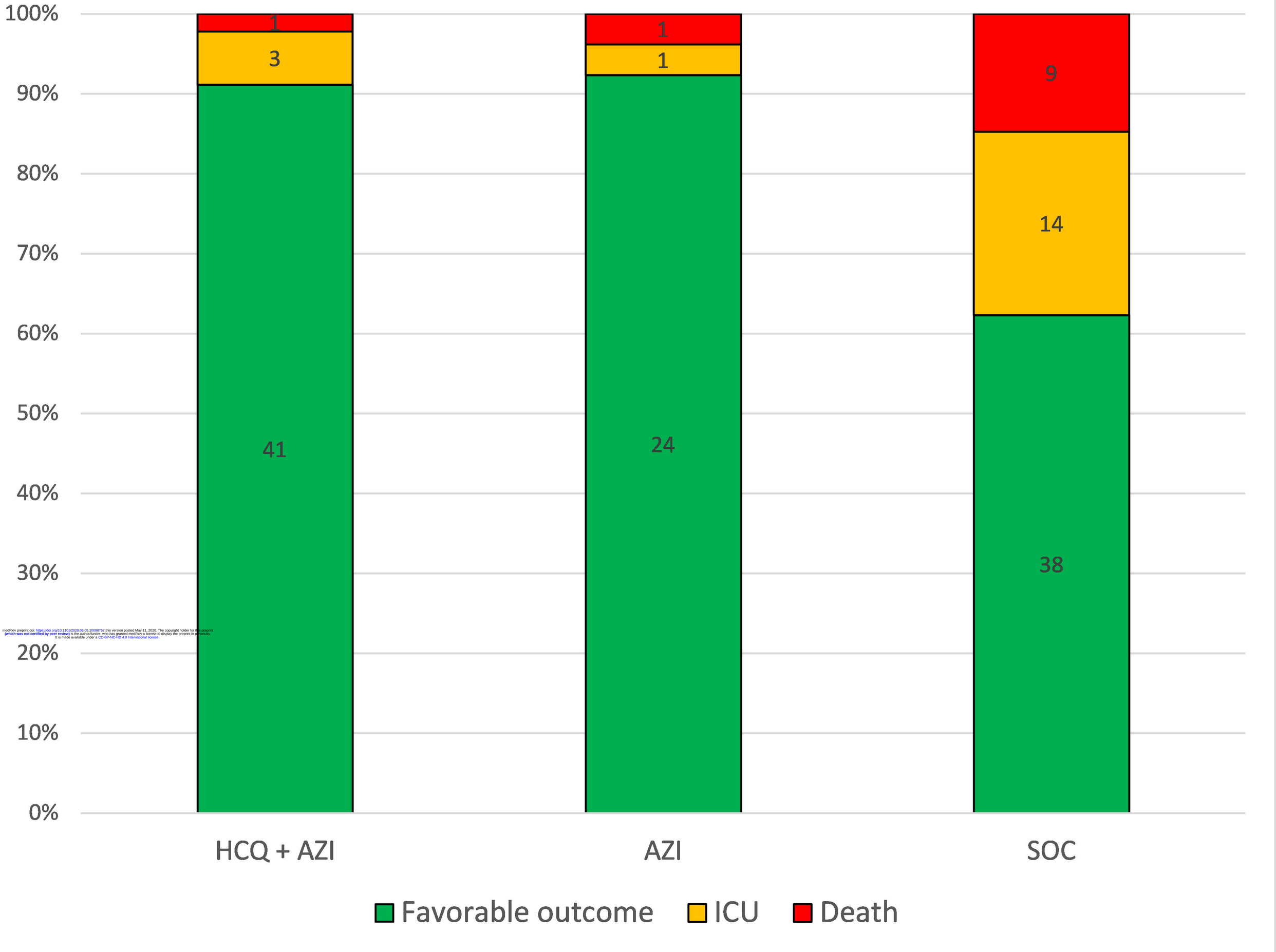


Table 1: Demographic and clinical characteristics at baseline

Variables	HCQ+AZI ≥ 48h (n=45)	Others regimen* (n=87)	p-value (α=0.05)
Demographic data			
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^2)	8 (17.8)	6 (6.9)	0.1
COVID-19 data			
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
Thoracic imaging			
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
Biological tests			
Median lymphocyte count (IQR) - /mm^3	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.

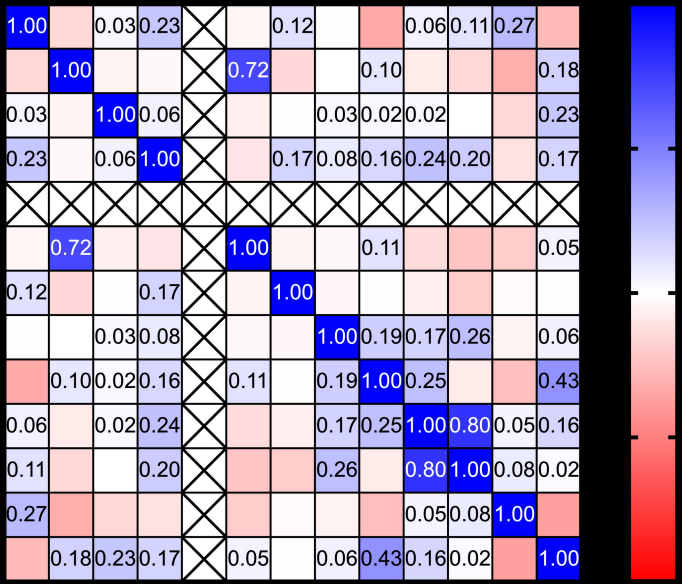
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HBP, high blood pressure

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 r 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^3	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^2)						
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 ≥5 are considered as severe and fragile


1.00 0.03 0.23 0.12 0.06 0.11 0.27
1.00 0.72 0.10 0.18
0.03 1.00 0.06 0.03 0.02 0.02 0.23
0.23 0.06 1.00 0.17 0.08 0.16 0.24 0.20 0.17
0.72 1.00 0.11 0.05
0.12 0.17 1.00
0.03 0.08 1.00 0.19 0.17 0.26 0.06
0.10 0.02 0.16 0.11 0.19 1.00 0.25 0.43
0.06 0.02 0.24 0.17 0.25 1.00 0.80 0.05 0.16
0.11 0.20 0.26 0.80 1.00 0.08 0.02
0.27 0.05 0.08 1.00
0.18 0.23 0.17 0.05 0.06 0.43 0.16 0.02 1.00