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## **Impact of medical care, including use of anti-infective agents, on prognosis of COVID-19 hospitalized patients over time**

Benjamin Davido, Ghilas Boussaid, Isabelle Vaugier, Thibaud Lansaman, Frédérique Bouchand, Christine Lawrence, Jean-Claude Alvarez, Pierre Moine, Véronique Perronne, Frédéric Barbot, et al.

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1 **Impact of medical care including anti-infective agents use on the prognosis of**  
2 **COVID-19 hospitalized patients over time**

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21

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40 **Abstract:**

41 Introduction: Interest of anti-infective agents in COVID-19 showed discrepant results.

42 However, there is no evaluation about the impact in changes of practices on the  
43 prognosis over time.

44 Methods: Single center, retrospective study, conducted from March 5<sup>th</sup> to April 25<sup>th</sup>

45 2020, in adults hospitalized in a medicine ward for a COVID-19. Patient

46 characteristics were compared between 2 periods (before/after March 19<sup>th</sup>)

47 considering French guidelines issued by learned societies. Aim of the study was to

48 evaluate how medical care impacted unfavorable outcome, namely admission in  
49 intensive care unit (ICU) and/or death.

50 **Results:** One hundred thirty-two patients were admitted, mean age was  $59.0 \pm 16.3$   
51 years, mean CRP level was  $84.0 \pm 71.1$  mg/L, 46% had a lymphocyte  
52 count  $< 1000/\text{mm}^3$ . When prescribed, anti-infective agents were lopinavir-ritonavir  
53 (n=12), azithromycin (AZI) (n=28) and AZI combined with hydroxychloroquine (HCQ)  
54 (n=52). Between the 2 periods we noted a significant decrease of ICU admission,  
55 from 43% to 12% ( $p < 0.0001$ ). Delays until transfer in ICU were similar between  
56 periods ( $p = 0.86$ ). Pulmonary CT-scan were significantly more performed (from 50%  
57 to 90%,  $p < 0.0001$ ), as oxygen-dependency (53% vs 80%,  $p = 0.001$ ) and prescription  
58 of AZI $\pm$ HCQ (from 25% to 76%,  $p < 0.0001$ ) were greater over time. Multivariate  
59 analyses showed a reduction of unfavorable outcome in patients receiving AZI $\pm$ HCQ  
60 (HR=0.45, 95%IC [0.21-0.97],  $p = 0.04$ ), especially among an identified category of  
61 individuals (lymphocyte  $\geq 1000/\text{mm}^3$  or CRP  $\geq 100$  mg/L).

62 **Conclusion:** The present study revealed a significant decrease of admission in ICU  
63 over time probably related to multiple factors, including a better indication of  
64 pulmonary CT-scan, of oxygen therapy, and a suitable prescription of anti-infective  
65 agents.

66

67 **Introduction:**

68 Management and medical care of COVID-19 pneumonia in hospitalized patients is  
69 currently still debated, especially because data regarding an emerging pathogen are

70 constantly evolving over time and across countries. Numerous therapies including  
71 oxygen, anti-infective agents and corticosteroids have been proposed.

72 Historically, Gautret *et al.* [1,2] and Million *et al.* [3] observed in Marseille (France)  
73 that a combination therapy using hydroxychloroquine (HCQ) and azithromycin (AZI)  
74 could potentially reduce viral shedding and the incidence of COVID-19 pneumonia.  
75 Concomitantly, an observational study conducted by Mahevas *et al.* [4] evaluating  
76 HCQ alone prescribed in an in-hospital setting, showed no impact of HCQ on the  
77 transfer rate in intensive care unit (ICU) and/or death. This study is concordant with a  
78 publication issued in the United States by Geleris *et al.* [5] who concluded that HCQ  
79 administration was not associated with a greatly lowered risk of intubation or death.

80 Interestingly, although corticosteroids were considered potentially harmful in the early  
81 care of COVID-19 infected patients [6], the RECOVERY trial (NCT04381936) stated  
82 that dexamethasone could reduce mortality rate up to 30% in severely-ill patients  
83 admitted for a COVID-19 pneumonia and revealed no interest of HCQ (data not  
84 published), meanwhile the azithromycin arm is still being investigated. Very recently a  
85 multicenter study in the United States reopened the debate concerning the efficacy of  
86 HCQ with or without AZI [7]. Furthermore antiviral therapies, notably lopinavir–  
87 ritonavir, revealed no benefit in comparison to standard of care in a large  
88 randomized trial [8], whereas remdesivir showed a reduction in time to clinical  
89 improvement in 2 trials but no significant impact on mortality [9,10].

90 Overall those reports have raised concerns about the true interest of anti-infective  
91 agents in COVID-19 pneumonia in a context where medical practices between these  
92 different studies are heterogeneous and have evolved over time. Indeed, in the

93 absence of a clear recommendation for treatment initiation, it is difficult to assume or  
94 to invalidate the effect of anti-infective agents on the prognosis of COVID-19 patients.

95 To our knowledge, there is no evaluation over time about changes of practices,  
96 including anti-infective agents, and their impact on the prognosis of patients admitted  
97 in a medical ward for a COVID-19 pneumonia. Considering controversies, we  
98 retrospectively evaluated the potential factors associated with an unfavorable  
99 outcome, namely admission in ICU and/or death, during this first wave of the  
100 epidemic.

101

## 102 **Methods:**

### 103 *Setting*

104 We conducted a single center and retrospective study, from March 5<sup>th</sup> to April 25<sup>th</sup>  
105 2020, regarding adults admitted in our medicine wards in a tertiary university hospital  
106 namely Hôpital Raymond Poincaré (AP-HP), Garches, France.

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

111

### 112 *Data collection*

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

- 114 - Patient characteristics: age, sex, diabetes, cardiovascular risk factors, smoking  
115 habits, obesity, chronic pulmonary disease, Charlson comorbidity index (CCI) [11],
- 116 - Infection characteristics: delay between onset of symptoms and admission,  
117 presence of super-infection, C-reactive protein (CRP) and white blood cell count  
118 (WBC) at admission, percentage of lung injuries on CT-scan if applicable, positive  
119 PCR amplifying the betacoronavirus E gene and the SARS-CoV-2 RdRp gene on  
120 nasopharyngeal swab or sputum,
- 121 - Treatment characteristics: requiring ICU support with invasive ventilation and  
122 associated therapeutic strategies (e.g. oxygen, anti-infective agents),
- 123 - Endpoint was defined as unfavorable outcome assessed by the requirement of a  
124 transfer in ICU for invasive ventilation and/or death within 30 days,
- 125 - Patients were followed-up until hospital discharge. After discharged, patients were  
126 monitored during 30 days by the telemedicine through the French covidom platform  
127 [12],
- 128 - Derived variables: moderate lymphocytopenia was based on a lymphocyte count  
129 with a threshold at  $1000/\text{mm}^3$  and high systemic inflammation was defined as a CRP  
130 threshold  $\geq 100$  mg/L.

131

### 132 *Treatment strategies*

133 All patients who required oxygen received systematically a beta-lactam for at least 5  
134 days, using preferentially ceftriaxone or cefotaxime to treat a potential super-  
135 infection.

136 Patients were eligible to a supposed effective anti-infective agent against COVID-19  
137 (HCQ, AZI, lopinavir-ritonavir), independently of biological abnormalities and  
138 considering the following indications: i) patient presenting a clinical pneumonia  
139 confirmed by SARS-CoV-2 PCR, requiring oxygen therapy (independently of the CT  
140 scan findings); ii) high suspicion of COVID-19 pneumonia considering the clinical  
141 presentation and/or pulmonary CT-scan showing ground-glass opacity affecting  $\geq$   
142 10% of the whole parenchyma.

143 Patients were categorized as receiving an anti-infective agent once they received at  
144 least one dose. Patients who received lopinavir-ritonavir were categorized in no  
145 treatment group, considering this antiviral drug did not show any benefit for the  
146 treatment of COVID-19 [7].

147 Before HCQ or AZI initiation, patients had systematically an electrocardiogram (ECG)  
148 to evaluate the corrected QT interval using the Framingham formula, and monitored 2  
149 times per week during the whole treatment, as well as serum potassium levels. A  
150 loading dose at day 1 with 800 mg/day was administered followed by a maintenance  
151 dose of 400 mg/day up to 600 mg/day in case of obesity (body mass index (BMI) >  
152 30) for a total 10 days. In addition, 500 mg of azithromycin was prescribed the first  
153 day, followed by 250 mg for 4 days. Patients were informed that HCQ and lopinavir-  
154 ritonavir were currently off-label for the treatment of COVID-19 pneumonia until the  
155 25<sup>th</sup> of March 2020 in France, where the ministerial decree #2020-314 authorized the  
156 in-hospital prescription of HCQ in this particular indication. In case they refused the  
157 prescription of HCQ or the latter was contraindicated (by ECG or drug interactions), it  
158 was noted into their medical chart and patients did not receive HCQ.

159



160 *Objective*

161 Aim of the study was to describe the medical care over time (oxygen therapy, anti-  
162 infective agents, pulmonary CT-scan) and to determine whether potential factors  
163 were related to an unfavorable outcome (transfer in ICU and/or death).

164

165 *Statistical analysis*

166 Descriptive statistics are presented as counts and percentages, or means and  
167 standard deviations, with skewed continuous data summarized as medians and  
168 interquartile ranges.

169 Two periods have been defined, the first two weeks (March 5<sup>th</sup> to March 19<sup>th</sup>) and  
170 thereafter where practices have become more standardized (March 20<sup>th</sup> to April 25<sup>th</sup>)  
171 considering the French COVID-19's guidelines issued by learned societies  
172 concerning the management of patients in ICU [13]. Patients were grouped according  
173 to these two periods, and compared. A Student test (equal variance) or Welch  
174 Satterthwaite t-test (unequal variance) was used to analyze quantitative variables, a  
175 Mantel-Haenszel Chi-Square test was used to analyze qualitative variables and  
176 Fisher's exact test was used when the sample sizes were small ( $n < 5$ ).

177 Moving averages over 15 days have been plotted to describe the evolution of care  
178 management over time using the following formula:

179 
$$\bar{x}_n = \frac{1}{15} \sum_{k=-7}^{k=+7} x_{n-k}$$

180 Time to endpoint was calculated from the date of hospitalization to the date of  
181 unfavorable outcome or hospital discharge. Two Cox proportional-hazards models

182 were used to estimate hazard ratios (HR) for unfavorable outcome associated with  
183 medical care, after adjustment on risk factors and one biological parameter (one  
184 included the lymphocyte count and the other one included the CRP level). Potential  
185 factors included were CCI (including age), obesity, oxygen flow and treatment.  
186 Interactions between treatment and lymphocyte count or CRP level were tested and  
187 Kaplan-Meier curves were plotted to assess unfavorable outcome from admission  
188 depending on these biological parameters.

189 Statistical significance was set at 0.05 (two-tailed test). All statistical calculations  
190 were performed using R software version 4.2.0.

191

#### 192 *Compliance with Ethical Standards*

193 All procedures performed in studies involving human participants were in accordance  
194 with the ethical standards and with the 1964 Helsinki Declaration and its later  
195 amendments or comparable ethical standards. This study has passed the  
196 CESREES/Health Data Hub regarding ethics committee approval (MR1811190620)  
197 and is registered on ClinicalTrials.gov (NCT04453501). As part of an anonymous and  
198 retrospective study, a non-opposition and information letter was sent to participants  
199 afterwards.

200

#### 201 **Results:**

##### 202 **Description of the population**

203 Between March 5<sup>th</sup> and April 25<sup>th</sup> 2020, 132 patients with Covid-19 were hospitalized.  
204 At baseline, mean age was 59.0 ± 16.3 years with 64% male. Among them, 11%

205 were obese (BMI>30), 22% were smokers, 23% had a CCI > 5 and 46% had a  
206 lymphocyte count <1000/mm<sup>3</sup>. Mean CRP level was 84.0 ± 71.1 mg/L with 46%  
207 greater than 100 mg/L. Seventy-two percent of patients were oxygen-dependent at  
208 admission, with 8% of patients with an oxygen flow therapy greater than 5 L/min.  
209 Among the patients who underwent a pulmonary CT scan, 83% had lung injuries  
210 compatible with COVID-19 greater than 10% of the whole parenchyma. SARS-CoV-2  
211 RT-PCR was positive in 95.5% (n=126) of cases.

212

### 213 **Treatment strategies**

214 Overall, 92 (70%) patients received one anti-infective agent. Among them, 12 (13%)  
215 received lopinavir-ritonavir, 28 (29%) azithromycin (AZI) and 52 (55%) AZI combined  
216 with HCQ (**Table S1 in Supplementary Data**). Mean delay from admission to  
217 treatment initiation was 0.7 +/- 1.5 days. Moreover, delay before treatment initiation  
218 was similar between first and second period (1.3 +/- 1.9 days vs 0.8 +/- 1.1 days,  
219 p=0.46). Of note, only one patient in the no treatment group received after 14 days of  
220 hospitalization a short course of oral corticosteroids.

221 During the first period, 40 (30%) patients were hospitalized whereas 92 (70%) were  
222 admitted thereafter. There were significantly more oxygen-dependent patients  
223 hospitalized during the second period than the first one (80% vs 53%, p=0.001). Also,  
224 a significant higher number of pulmonary CT scan performed was observed over time  
225 between periods of hospitalization from 50% to 90% (p<0.0001), independently of  
226 CT-scan severity (**Table 1**). Concomitantly, prescription of AZI whether or not  
227 combined with HCQ increased over time, from 25% to 76% between the 2 periods  
228 (p<0.0001) (**Figure 1**).

229 Of note, among patients who did not receive HCQ, 5 had cardiac contraindication  
230 and 2 refused to be treated with this molecule. During the course of treatment using  
231 AZI in combination with HCQ, we report only 1 patient that presented an adverse  
232 event (a prolonged QT interval on ECG without clinical event) that led to  
233 discontinuation of HCQ within 48h, and was switched to azithromycin alone.

234

### 235 **Unfavorable outcome (ICU admission or death)**

236 A total of 28 (21%) patients had an unfavorable outcome, among them 26 (93%)  
237 were transferred to ICU and 2 (7%) died without being transferred in ICU. Mean delay  
238 between hospitalization and admission in ICU was  $2.45 \pm 1.45$  days ( $2.4 \pm 1.5$  days  
239 during the first period vs  $2.4 \pm 1.6$  days during the second one,  $p=0.86$ ). A trend  
240 towards a lower frequency of admission to ICU was observed, from 43% in the first  
241 period to 12% in the second period ( $p<0.0001$ ) (**Figure 1**).

242

### 243 **Potential factors associated with unfavorable outcome:**

244 Overall, the risk of death or admission to ICU was significantly related to the oxygen  
245 flow ( $p<0.001$ ) and to lymphocyte count in a first model (i.e. lymphocyte  
246 count $<1000/mm^3$ ) (HR=4.90, 95% CI [1.95 – 12.3],  $p=0.0007$ ) or to high systemic  
247 inflammation in a second model (i.e. CRP  $\geq 100$  mg/L) (HR=2.78, 95% CI [1.00 –  
248 5.23],  $p=0.05$ ). In addition, we observed a relationship between favorable outcome  
249 and use of AZI whether or not combined with HCQ, in comparison to patients without  
250 any treatment ( $p=0.04$ ) (**Table 2**).

251

### 252 **Unfavorable outcome according to biological parameters (Kaplan Meier curves)**

253 There was a significant interaction between treatment and CRP level ( $p=0.02$ ) and at  
254 the limit of statistical significance for the lymphocyte count ( $p=0.06$ ) supporting a  
255 subgroup analysis. In univariate analysis, patients who benefited from AZI whether or  
256 not combined with HCQ with a lymphocyte count  $\geq 1000/\text{mm}^3$ , were less likely to  
257 have an unfavorable outcome compared to patients without any treatment ( $p=0.04$ )  
258 (**Fig 2.a**). Concomitantly, patients who benefited from AZI whether or not combined  
259 with HCQ with a CRP  $\geq 100$  mg/L, were less likely to have an unfavorable outcome  
260 compared to patients without any treatment ( $p=0.009$ ) (**Fig 2.b**). However, these  
261 results are not reproducible in patients with a lymphocyte count  $< 1000/\text{mm}^3$  ( $p=0.80$ )  
262 and similarly in patients with a CRP level  $< 100$  mg/L ( $p=0.50$ ) (**Figure S3.a, S3.b in**  
263 **Supplementary Data**).

264

#### 265 **Discussion:**

266 Our study highlights that unfavorable outcome (transfer to ICU and/or death)  
267 decreased over time during the management of the first wave of the epidemic and  
268 was associated with an increased realization of pulmonary CT-scan and prescription  
269 of anti-infective agents despite an increased need of oxygen therapy at admission.  
270 This suggests that medical care of COVID-19 patients improved over time in our  
271 hospital.

272 Because of lockdown, it looks like patients were admitted later in the second period  
273 than during the first period of the epidemic and it might explain why they required  
274 more oxygen therapy at baseline. We suggest that in case of a second wave, it could  
275 be relevant to introduce telemedicine monitoring of vital signs including pulse  
276 oximetry at home. Indeed, oxygen therapy at home, as proposed by the French

277 covidom platform in patients discharged from the hospital during the first wave of the  
278 epidemic was of interest [12].

279 In multivariate analyses, our models adjusted on the lymphocyte count or CRP,  
280 showed that patients who benefited from AZI whether or not combined with HCQ  
281 were 2.2 and 2.4 times less likely to have an unfavorable outcome than patients  
282 without treatment ( $p=0.04$ ), respectively. This finding suggests that the lymphocyte  
283 count which is already known to be closely related to COVID-19 disease severity  
284 [14,15] could be also a predictive factor of anti-infective therapy response. Indeed,  
285 patients with lymphocyte count  $\geq 1000/\text{mm}^3$  might be patients at an early stage of  
286 COVID-19, arguing for the earliest initiation of anti-infective agents, as previously  
287 demonstrated with oseltamivir treatment in severely-ill patients with 2009 pandemic  
288 influenza A (H1N1) [16]. However, we did not study whether there was a relationship  
289 between the lymphocyte count and the delay from first onset of symptoms to the  
290 admission, because this variable is declarative and thus not reliable. Likewise, AZI  
291 whether or not combined with HCQ showed interest in hospitalized patients with a  
292 high systemic inflammation (CRP level  $\geq 100$  mg/L), known as the so called “cytokine  
293 storm”. This is one argument pleading for a possible immune-modulator effect of the  
294 treatment as previously described by Zhao *et al.* [17].

295 Our findings are concordant with a recent study conducted in the United States by  
296 Arshad *et al.* [7] who concluded in multicenter retrospective observational study that  
297 treatment with HCQ alone and in combination with AZI was associated with reduction  
298 in COVID-19 associated mortality in hospitalized patients. Another study design  
299 issued by Lagier *et al.* [18], partly composed of ambulatory care patients, revealed a  
300 favorable outcome and a decreased virological shedding using the combination  
301 therapy of HCQ with AZI in a large sample size ( $n>3000$ ), in a majority of patients

302 with a mild lymphocytopenia ( $\geq 1000/\text{mm}^3$ ). At last Mahevas *et al.* [4] observed 15/15  
303 favorable outcome in a subgroup of patients receiving HCQ with AZI.

304 Interestingly, our study does focus on the potential interest of treatment with  
305 azithromycin whether or not combined depending on certain biological parameters.  
306 Indeed, azithromycin's potential antiviral activity is concordant with previous in vitro  
307 studies regarding SARS-CoV-2 [19] or H1N1-pdm09 [20] and one clinical randomized  
308 trial in the prevention of children respiratory infections [21]. In addition a recent  
309 publication emphasized the role of azithromycin against COVID-19 through the  
310 CD147 receptor of stem cell [22]. Moreover, one study published in the JAMA by  
311 Rosenberg *et al.* [23] highlighted a potential trend to a decreased mortality in patients  
312 receiving azithromycin versus HCQ or standard of care despite being non-statistically  
313 significant ( $p=0.14$ ). Moreover, authors discussed that the rapidity with which patients  
314 entered the ICU (within 48 hours) might have underestimated the treatment efficacy.  
315 Also, as azithromycin is commonly prescribed for bronchitis and authorized in  
316 ambulatory care, a study conducted among general practitioners could be relevant to  
317 evaluate early indication of this single therapy for the treatment of COVID-19 in  
318 fragile outpatients.

319 In addition, our experience does not report any serious side effect of this combination  
320 therapy as long as we take the necessary caution and perform follow-up ECG using a  
321 conventional dose of HCQ as proposed by Borba *et al.* [24].

322 Our study has several limitations. The first limitation is the single center nature of the  
323 study, describing the experience of a unique center whose results might not be  
324 generalizable. However, it was carried out in a hospital specialized for decades in the  
325 treatment of infectious diseases, ICU and rehabilitation. Since the beginning of the  
326 COVID-19 epidemic, an entire building has been entirely dedicated to admitting only

327 COVID-19 positive patients. During the peak of the epidemic, we had a maximum  
328 capacity of 85 beds in medicine ward and 32 beds in ICU.

329 Furthermore, we observed a better favorable outcome over time related to an  
330 increased number of pulmonary CT-scan performed (not recommended at the  
331 beginning of the epidemic in our hospital) and therefore a more relevant prescription  
332 of anti-infective agents. Nevertheless, we cannot exclude that other confounding  
333 factors might have played a role, as we were facing an unpredictable epidemic, which  
334 urged to update constantly guidelines about ICU admission, notably recommending  
335 to keep patients longer in medicine wards with high oxygen flow (>6L/min) during the  
336 second period of the epidemic. Nevertheless, delay between admission and transfer  
337 in ICU were similar between the 2 periods of time which minimizes this confounding  
338 factor.

339 Moreover, considering inherent limitation of a descriptive study with a limited sample  
340 size (n=132), we could not infer causality in the association between the use of  
341 AZI±HCQ and the ameliorated prognosis in COVID-19 patients. Besides, we also  
342 noted that some unforeseen confounders (e.g., pre-hospital medication and delay to  
343 admission) may still potentially alter the magnitude of azithromycin effects on the  
344 outcome of COVID-19 pneumonia. Also, choices in anti-infective agents have differed  
345 between the first and second period, notably because prior to March 25<sup>th</sup>, HCQ was  
346 not authorized by the French minister of Health and explained partly the common use  
347 of lopinavir-ritonavir at this period.

348 Finally, we decided to choose a multivariate model rather than a propensity score  
349 because the aim of this study was not to evaluate the effect of AZI±HCQ on the  
350 prognosis but to evaluate all factors which could have impacted on medical care.



351 In conclusion, findings from this study showed that rate of admission in ICU  
352 decreased from 43% during the first period (from March 5<sup>th</sup> to March 19<sup>th</sup>) to 12%  
353 during the second period (from March 20<sup>th</sup> to April 25<sup>th</sup>).

354 Numerous factors might be involved in the improvement of care, including the  
355 implementation of routine pulmonary CT-scan, better management of oxygen therapy  
356 in medicine ward and possibly anti-infective agents. Indeed, our study suggests that  
357 AZI±HCQ might have impacted COVID-19 outcome in a subpopulation of patients  
358 (lymphocyte count  $\geq 1000/\text{mm}^3$  or CRP  $\geq 100 \text{ mg/L}$ ), raising the question of optimal  
359 timing of treatment interventions. A larger and randomized controlled study is  
360 necessary to explore the profiles of patients responding to this therapeutic and  
361 confirm the potential interest of biological parameters for treatment initiation.

362

### 363 **Contributors' Statement:**

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

367 BD, FB, PDT, TL designed the data collection instruments, collected data and  
368 reviewed and revised the manuscript. VP, DA, PM, AL participated to patients  
369 enrollment.

370 GB and IV were in charge of the statistical analyses and contributed to the final  
371 version of the manuscript.

372 All authors approved the final manuscript as submitted and agree to be accountable  
373 for all aspects of the work in ensuring that questions related to the accuracy or  
374 integrity of any part of the work are appropriately investigated and resolved.

375

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385 ViiV Healthcare, M.S.D and Gilead Sc. The remaining authors have no specific  
386 conflict of interest.

387 **Ethical Approval:** Not required

388 **Randomized Controlled Trial :** NCT04453501

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**Figure 1:** Evolution of medical care for COVID-19 patients from March 5th to April 25th

25th

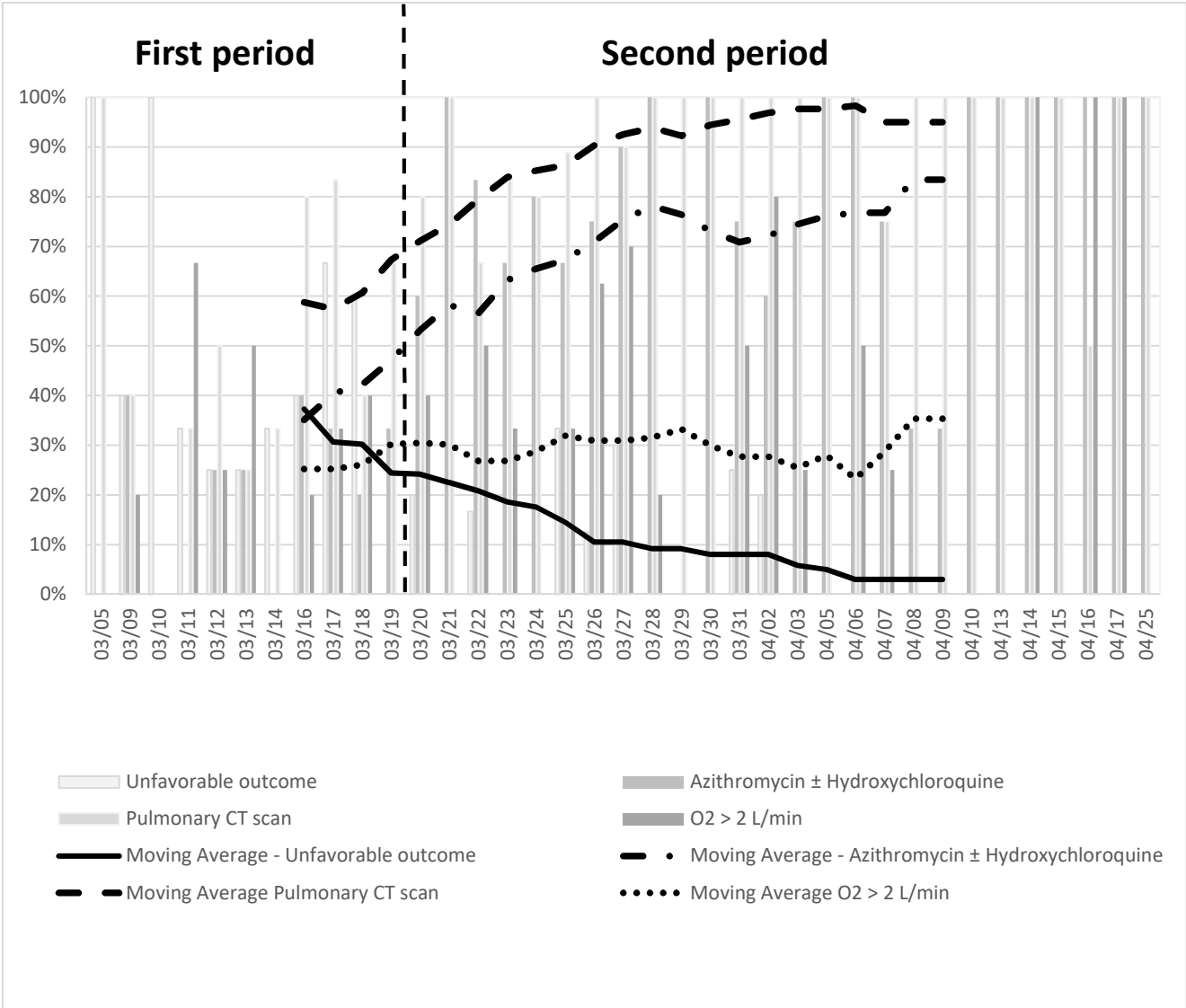


Figure 2.a. Kaplan-Meier survival curve for patients with an unfavorable outcome in function of treatment according to lymphocyte count  $\geq 1000/\text{mm}^3$  (Log-Rank,  $p = 0.04$ ).

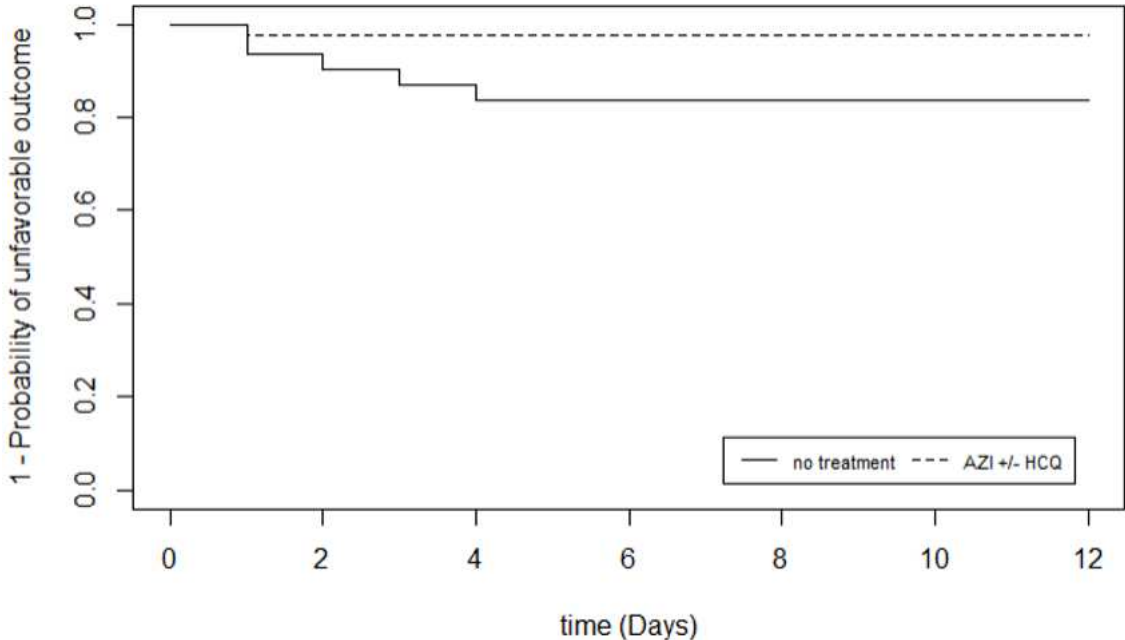
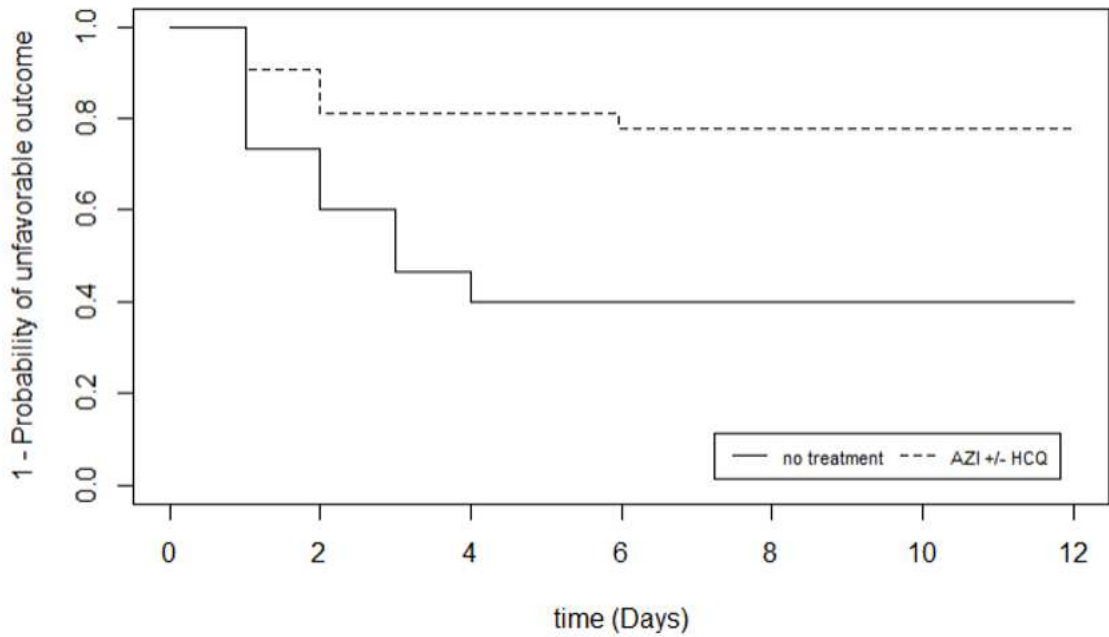


Figure 2.b. Kaplan-Meier survival curve for patients with an unfavorable outcome in function of treatment according to CRP  $\geq 100 \text{ mg/L}$  (Log-Rank,  $p = 0.009$ ).



**Table 1: Baseline characteristics of patients with COVID-19 according to periods of hospitalization**

Characteristics at baseline	In first period †	In second period ‡	p value
	N= 40	N= 92	
Age (year) — mean ± SD	62.17 ± 15.24	57.59 ± 16.64	0.13
Sex (M) — no. (%)	26 (58)	59 (64)	0.99
Obesity — no. (%)	2 (4)	13 (14)	0.22
Smoking (yes) — no. (%)	13 (29)	16 (17)	0.09
CCI* — no. (%)			
0	4 (10)	20 (22)	
1-2	14 (35)	33 (36)	
3-4	11 (28)	20 (22)	0.38
≥5	11 (28)	19 (21)	
Pulmonary CT scan — no. (%)	20 (50)	83 (90)	<b>&lt;0.0001</b>
Normal	2 (10)	5 (6)	
Limited	6 (30)	11 (13)	
Mild	0 (0)	24 (29)	0.46
Moderate	9 (45)	32 (39)	
Severe	3 (15)	11 (13)	
Lymphocyte count < 1000/mm <sup>3</sup> — no. (%)	17 (42)	54 (59)	0.13
PMN count >8000/mm <sup>3</sup>	5 (13)	9 (10)	0.64
CRP mg/L — mean ± SD	84.59 ± 70.31	83.70 ± 71.86	0.95
Oxygen (yes) — no. (%)	21 (53)	74 (80)	<b>0.001</b>
≤2L/min	10 (48)	38 (51)	
2 – 5 L/min	10 (48)	27 (36)	0.55
>5 L/min	1 (5)	9 (12)	
Treatment strategies — no. (%)			
No treatment	30 (75)	22 (24)	
AZI ± HCQ	10 (25)	70 (76)	<b>&lt;0.0001</b>

† In first period is define between 03/05 to 03/19; ‡ In second period is define between 03/20 to 04/25; AZI, Azithromycin; HCQ, Hydroxychloroquine; N, number; %, percent; SD, standard deviation; M, men; Obesity with body mass index ≥ 30 kg/m<sup>2</sup>; \*CCI, Charlson Comorbidity Index; PMN, polymorphonuclear leukocyte; CRP, c-reactive protein; CT : computerized tomography; pulmonary CT scan category normal [0%], limited <10%, mild 10% – 25%, Moderate 25% – 50%, Severe >50%; A Student test (equal variance) or a Welch-Satterthwaite t test (unqual variance) was used to analyze the quantitative variables, a Mantel-Haenszel Chi-Square test was used to analyze the qualitative variables and the exact test of Fisher was used when the sample sizes were small (<5). Test significant (p<0.05)

**Table 2: Potential factors associated to unfavorable outcome: Cox model regression**

Variables	n/N	Univariate model		Multivariate model 1		Multivariate model 2	
		HR [IC95%]	p value	HR [IC95%]	p value	HR [IC95%]	p value
				Adjusted on ICC, obesity, O2, lymphocyte count and treatments		Adjusted on ICC, obesity, O2 CRP and treatments	
<b>Characteristics at baseline</b>							
Age (years)	132/132	1.02 [1.00 – 1.05]	0.07	-	-	-	-
Sex (M)	85/132	0.86 [0.40 – 1.85]	0.71	-	-	-	-
Obesity (yes)	15/132	0.27 [0.04 – 1.98]	0.20	0.47 [0.06- 3.63]	0.47	0.44 [0.06 – 3.45]	0.43
Smoking (yes)	29/132	1.00 [0.41 - 2.48]	0.99	-	-	-	-
CCI*							
	0 24/132	1*	-	1*	-	1	-
	1-2 47/132	0.88 [0.26 - 3.00]	0.83	1.05 [0.29 – 3.87]	0.47	1.10 [0.31 – 3.92]	0.89
	3-4 31/132	1.88 [0.58 – 6.12]	0.29	1.30 [0.37 – 4.54]	0.68	1.74 [0.52 – 5.81]	0.37
	≥5 30/132	1.63 [0.49 – 5.43]	0.42	1.10 [0.32 – 3.75]	0.87	1.08 [0.32 – 3.71]	0.90
PMN count≥8000/mm3	14/132	1.42 [0.49 – 4.10]	0.52	-	-	-	-
Lymphocyte count < 1000/mm3	71/132	4.91 [1.99 – 12.1]	0.0006	4.90 [1.95 – 12.3]	<b>0.0007</b>	-	-
CRP ≥100 mg/L	85/132	2.86 [1.35 – 6.05]	0.006	-	-	2.78 [1.00 – 5.23]	<b>0.05</b>
<b>Treatment strategies</b>							
Oxygen (L/min)		1.20 [1.10 - 1.31]	<b>&lt;0.0001</b>	1.25 [1.13 – 1.38]	<b>&lt;0.0001</b>	1.20 [1.08 - 1.32]	<b>0.0005</b>
No treatment and	52/132	1*	-	1*	-	1*	-
AZI ± HCQ	80/132	0.63 [0.30 – 1.23]	0.23	0.45 [0.21 – 0.97]	<b>0.04</b>	0.42 [0.18 – 0.95]	<b>0.04</b>

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n/N number/total; 1\* indicates the reference category; HR, Hazard ratio; CI, confidence interval; NS, not significant ( $p > 0.05$ ); PMN, polymorphonuclear; \*CCI, The Charlson Comorbidity Index; CRP, C Reactive protein; AZI, Azithromycin; HCQ, Hydroxychloroquine; No treatment defined as patients who have had no treatment or lopinavir-ritonavir; Multivariate Cox model regression was used to identify the potential factors associated with unfavorable outcome (ICU admission or death after ICU), adjusted on CCI (including age), obesity, oxygen and treatment strategies groups according to CRP.