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

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Keywords: azithromycin, hydroxychloroquine, Covid-19, pneumonia

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Abstract:

Introduction: Interest of anti-infective agents in COVD-19 showed discrepant results. However, there is no evaluation about the impact in changes of practices on the prognosis over time.

Methods: Single center, retrospective study, conducted from March 5th to April 25th 2020, in adults hospitalized in a medicine ward for a COVID-19. Patient characteristics were compared between 2 periods (before/after March 19th) considering French guidelines issued by learned societies. Aim of the study was to

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

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

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

Introduction:

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

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

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

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

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

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

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

Methods:

Setting

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

We included all the adults admitted in medicine for a COVID-19 infection confirmed by SARS-CoV-2 RT-PCR and/or a compatible pulmonary CT-scan. Exclusion criteria were: i) patients directly admitted in ICU; ii) patients discharged from ICU to a medicine ward; iii) 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 factors, smoking habits, obesity, chronic pulmonary disease, Charlson comorbidity index (CCI) [11],

- 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 and associated therapeutic strategies (e.g. oxygen, anti-infective agents),

- Endpoint was defined as unfavorable outcome assessed by the requirement of a transfer in ICU for invasive ventilation and/or death within 30 days,

- Patients were followed-up until hospital discharge. After discharged, patients were monitored during 30 days by the telemedicine through the French covidom platform [12],

- Derived variables: moderate lymphocytopenia was based on a lymphocyte count with a threshold at 1000/mm^3 and high systemic inflammation was defined as a CRP threshold ≥ 100 mg/L.

Treatment strategies

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

Patients were eligible to a supposed effective anti-infective agent against COVID-19 (HCQ, AZI, lopinavir-ritonavir), independently of biological abnormalities and 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/or pulmonary CT-scan showing ground-glass opacity affecting ≥ 10% of the whole parenchyma.

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

Before HCQ or AZI initiation, patients had systematically an electrocardiogram (ECG) to evaluate the corrected QT interval using the Framingham formula, and monitored 2 times per week during the whole treatment, as well as serum potassium levels. 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 and lopinavir-ritonavir were currently off-label for the treatment of COVID-19 pneumonia until the 25th of March 2020 in France, where the ministerial decree #2020-314 authorized the in-hospital prescription of HCQ in this particular indication. In case they refused the prescription of HCQ or the latter was contraindicated (by ECG or drug interactions), it was noted into their medical chart and patients did not receive HCQ.

Objective

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

Statistical analysis

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

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

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

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

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

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

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

Compliance with Ethical Standards

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

Results:

Description of the population

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

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

Treatment strategies

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

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

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

Unfavorable outcome (ICU admission or death)

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

Potential factors associated with unfavorable outcome:

Overall, the risk of death or admission to ICU was significantly related to the oxygen flow (p<0.001) and to lymphocyte count in a first model (i.e. lymphocyte count<1000/mm3) (HR=4.90, 95% CI [1.95 – 12.3], p=0.0007) or to high systemic inflammation in a second model (i.e. CRP ≥ 100 mg/L) (HR=2.78, 95% CI [1.00 – 5.23], p=0.05). In addition, we observed a relationship between favorable outcome and use of AZI whether or not combined with HCQ, in comparison to patients without any treatment (p=0.04) **(Table 2)**.

Unfavorable outcome according to biological parameters (Kaplan Meier curves)

There was a significant interaction between treatment and CRP level (p=0.02) and at the limit of statistical significance for the lymphocyte count (p=0.06) supporting a subgroup analysis. In univariate analysis, patients who benefited from AZI whether or not combined with HCQ with a lymphocyte count ≥ 1000/mm3, were less likely to have an unfavorable outcome compared to patients without any treatment (p=0.04) (**Fig 2.a**). Concomitantly, patients who benefited from AZI whether or not combined with HCQ with a CRP ≥ 100 mg/L, were less likely to have an unfavorable outcome compared to patients without any treatment (p=0.009) (**Fig 2.b**). However, these results are not reproducible in patients with a lymphocyte count < 1000/mm3 (p=0.80) and similarly in patients with a CRP level < 100 mg/L (p=0.50) **(Figure S3.a, S3.b in Supplementary Data)**.

Discussion:

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

Because of lockdown, it looks like patients were admitted later in the second period than during the first period of the epidemic and it might explain why they required more oxygen therapy at baseline. We suggest that in case of a second wave, it could be relevant to introduce telemedicine monitoring of vital signs including pulse 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 ≥ 1000/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 ≥ 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

with a mild lymphocytopenia (≥ 1000/mm^3). At last Mahevas *et al.* [4] observed 15/15 favorable outcome in a subgroup of patients receiving HCQ with AZI.

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

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

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

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

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

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

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

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

Numerous factors might be involved in the improvement of care, including the implementation of routine pulmonary CT-scan, better management of oxygen therapy in medicine ward and possibly anti-infective agents. Indeed, our study suggests that AZI±HCQ might have impacted COVID-19 outcome in a subpopulation of patients (lymphocyte count ≥ 1000/mm3 or CRP ≥ 100 mg/L), raising the question of optimal timing of treatment interventions. A larger and randomized controlled study is necessary to explore the profiles of patients responding to this therapeutic and confirm the potential interest of biological parameters for treatment initiation.

Contributors' Statement:

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

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

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

Acknowledgments:

Authors would like to thank Pr Xavier Paoletti for his proofreading of the manuscript and his particular attention to the statistical analyses.

Declarations

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

Competing Interests: BD has received consulting fees or travel grants from ViiV Healthcare and Gilead Sc. PdT has received consulting fees or travel grants from ViiV Healthcare, M.S.D and Gilead Sc. The remaining authors have no specific conflict of interest.

Ethical Approval: Not required

Randomized Controlled Trial : NCT04453501

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

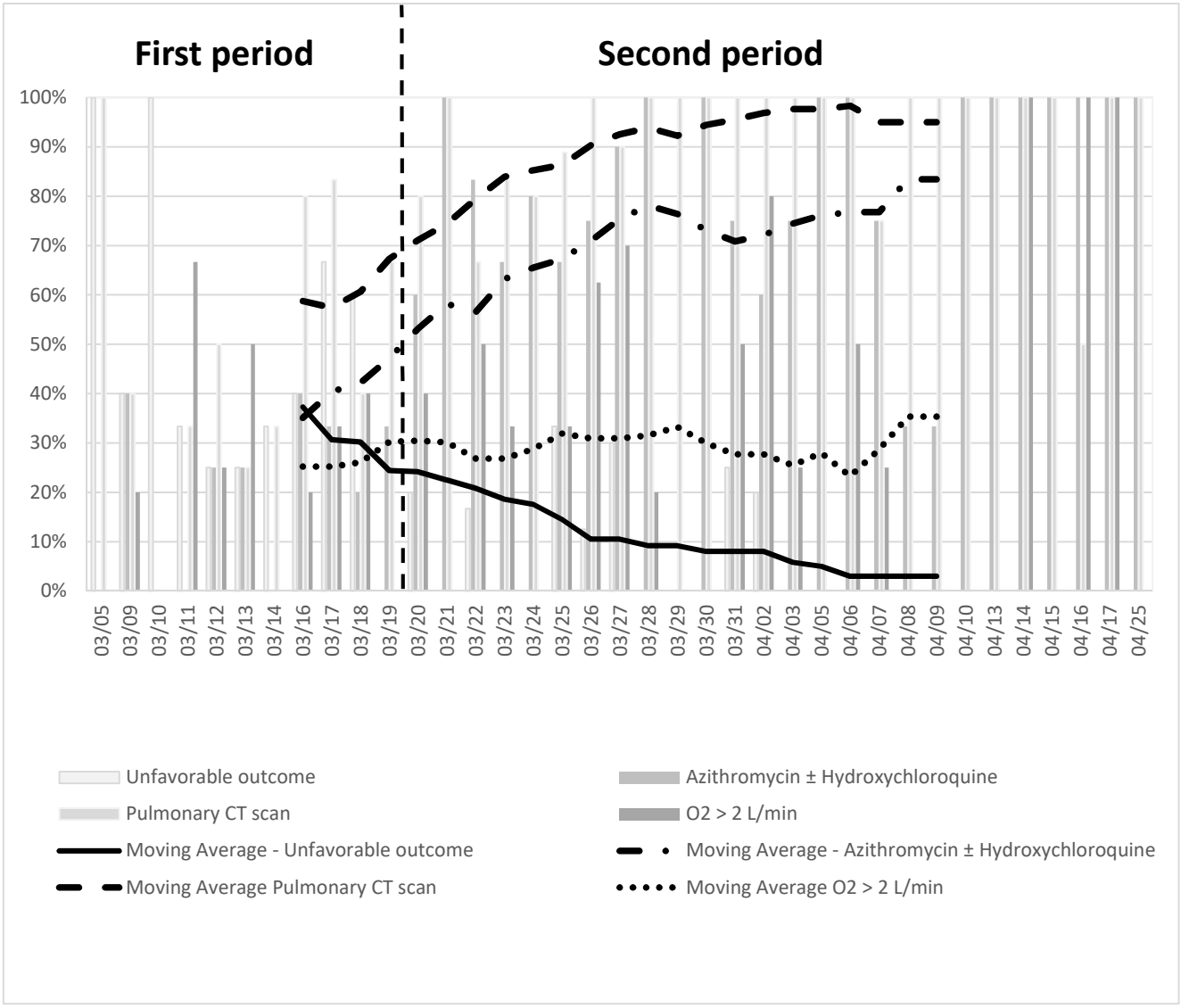

Figure 2.a. Kaplan-Meier survival curve for patients with an unfavorable outcome in function of treatment according to lymphocyte count ≥ 1000/mm3 (Log-Rank, *p* = 0.04).

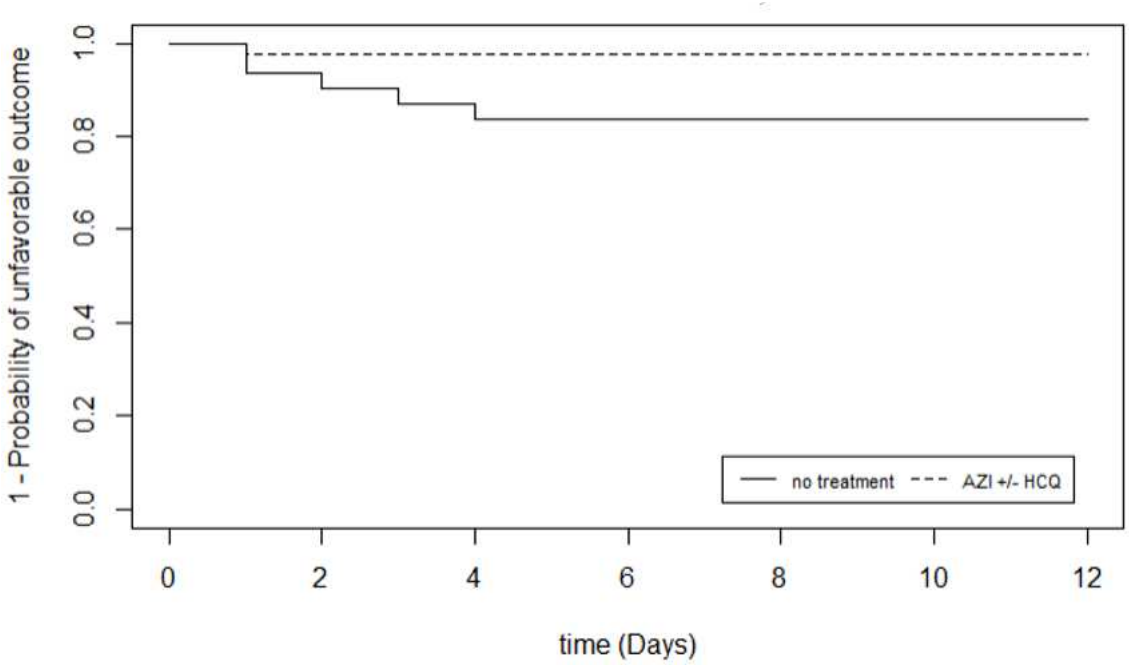

Figure 2.b. Kaplan-Meier survival curve for patients with an unfavorable outcome in function of treatment according to CRP ≥ 100 mg/L (Log-Rank, *p* = 0.009).

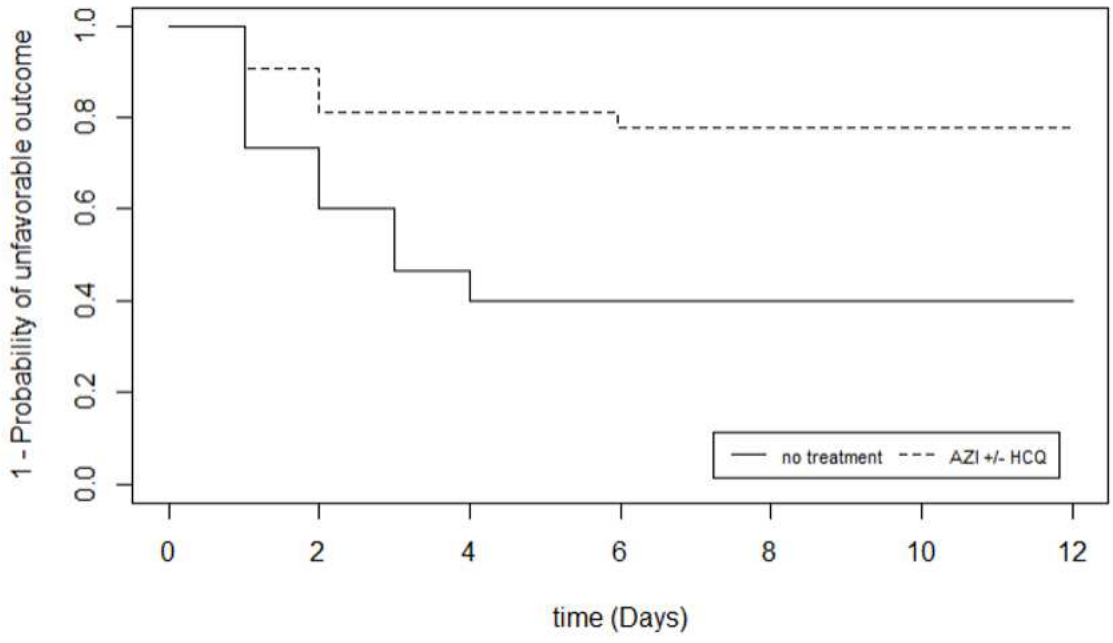

Table 1: Baseline characteristics of patients with COVID-19 according to periods of hospitalization

Characteristics at baseline	In first period † N= 40	In second period ‡ N= 92	*p* value
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)	0.38
1-2	14 (35)	33 (36)	
3-4	11 (28)	20 (22)	
≥5	11 (28)	19 (21)	
Pulmonary CT scan — no. (%)	20 (50)	83 (90)	**<0.0001**
Normal	2 (10)	5 (6)	0.46
Limited	6 (30)	11 (13)	
Mild	0 (0)	24 (29)	
Moderate	9 (45)	32 (39)	
Severe	3 (15)	11 (13)	
Lymphocyte count < 1000/mm3 — no. (%)	17 (42)	54 (59)	0.13
PMN count >8000/mm3	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)	**0.001**
≤2L/min	10 (48)	38 (51)	0.55
2 – 5 L/min	10 (48)	27 (36)	
>5 L/min	1 (5)	9 (12)	
Treatment strategies — no. (%)			
No treatment	30 (75)	22 (24)	**<0.0001**
AZI ± HCQ	10 (25)	70 (76)	

† 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/m²; *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 Welche-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		
Characteristics at baseline											
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	0.39	1.30 [0.37 – 4.54]	0.68	0.97	1.74 [0.52 – 5.81]	0.37	0.73
	≥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]	**0.0007**		-	-	
CRP ≥100 mg/L		85/132	2.86 [1.35 – 6.05]	0.006		-	-		2.78 [1.00 – 5.23]	**0.05**	
Treatment strategies											
Oxygen (L/min)			1.20 [1.10 - 1.31]	**<0.0001**		1.25 [1.13 – 1.38]	**<0.0001**		1.20 [1.08 - 1.32]	**0.0005**	
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]	**0.04**		0.42 [0.18 – 0.95]	**0.04**	

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.