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Assessment of Recovery Time, Worsening, and Death among Inpatients and Outpatients with COVID-19, Treated with Hydroxychloroquine or Chloroquine plus Azithromycin Combination in Burkina Faso

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ABSTRACT

Objectives: Our study aimed to assess the statistical relationship between the use of chloroquine phosphate or hydroxychloroquine plus azithromycin (CQ/HCQ + AZ) and virological recovery, disease worsening, and death among out- and inpatients with COVID-19 in Burkina Faso.

Methods and Designs: This was a retrospective observational study that compared outcomes in terms of time to recovery, worsening, and death in patients who received CQ/HCQ + AZ and those who did not using a multivariable Cox or Poisson model before and after propensity matching.

Results: Of the 863 patients included in the study, about 50% (432/863) were home-based follow-up patients and 50% were inpatients. Of these, 83.3% (746/863) received at least 1 dose of CQ/HCQ + AZ and 13.7% (118/863) did not. There were no significant differences in associated time to recovery for patients receiving any CQ/HCQ + AZ (adjusted HR 1.44; 95% CI 0.76–2.71). Similarly, there was no significant association between CQ/HCQ + AZ use and worsening (adjusted IRR 0.80; 95% CI 0.50–1.50). However, compared with the untreated group, the treated group had a lower risk of death (adjusted HR 0.20; 95% CI 0.10–0.44).

Conclusions: The study provided valuable additional information on the use of CQ/HCQ in patients with COVID-19 and did not show any harmful outcomes of CQ/HCQ + AZ treatment.

Background

The COVID-19 is a worldwide, ongoing pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case was identified in the Chinese city of Wuhan in December 2019 (Zhu et al., 2020). On March 11, 2020, the COVID-19 outbreak was declared as pandemic by the WHO (World Health Organization, 2020). In Burkina Faso, the first suspected case of COVID-19 was reported on February 5, 2020 (Tarnagda et al., 2021), while the first confirmed case was notified on March 9, 2020 (WHO, 2020; Worldometer, 2020). In the research of medicines that could potentially reduce the risk for disease worsening or death, the aminoquinolines chloroquine (CQ) and hydroxychloroquine (HCQ), which are commonly used for the treatment of malaria and rheumatic diseases, were suggested as effective treatments for COVID-19

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based on a combination of anti-inflammatory and antiviral effects (Devaux et al., 2020; Fox, 1993).

HCQ was used for the first time in China during an early stage of the pandemic in a small randomized controlled trial of 62 patients to improve pneumonia regression and reduce the recovery time (Zhaowei et al., 2020). However, the first peer-review published study (open-label, single-arm, nonrandomized study enrolling 26 subjects) reporting the effectiveness of hydroxychloroquine in reducing the viral burden in patients with COVID-19 was conducted in France (Gautret et al., 2020a). Although this empirical scientific evidence has motivated several countries to use this old drug in association with or without azithromycin (AZ) for COVID-19 case management (Dagens et al., 2020; Rouamba et al., 2021; Wilson et al., 2020), it should be highlighted that the efficacy and safety of HCQ in the treatment of patients with SARS-CoV-2 was subject to polemics in the scientific community because of conflicting results. Indeed, while most observational studies reported an improvement of the clinical outcomes with the use of HCQ (Arshad et al., 2020; Ayerbe et al., 2020; Bernaola et al., 2020; Catteau et al., 2020; Gautret et al., 2020b; Lagier et al., 2020; Lammers et al., 2020; Million et al., 2020; MILLION et al., 2021; Yu et al., 2020a), randomized controlled studies (Pan et al., 2020; The RECOVERY Collaborative Group, 2020) were suspended because of apparent ineffectiveness coupled with a tendency for increasing overall mortality.

As of April 6, 2020, based on limited scientific circumstantial evidence and the observations and experiences of clinicians throughout the world, Burkina Faso has adopted the CQ/HCQ + AZ combination for the systematic treatment of detected COVID-19 cases in the country (Ministère de la Santé du Burkina Faso, 2020). In such a context, it was important to carry out an observational study to support the implementation of this new treatment policy to assess its effectiveness and safety. Thus, the CHLORAZ research group proposed to conduct an observational study to evaluate the therapeutic protocol proposed by Burkina Faso Ministry of Health (MoH) for the treatment of COVID-19.

The study aimed to assess the statistical relationship between the use of CQ/HCQ + AZ and virological recovery, disease worsening, and death among patients with COVID-19 in Burkina Faso. The research hypothesis of the study was to test whether the use of CQ/HCQ + AZ would have a beneficial effect on reducing the time to viral negativation, worsening/transfer to an intensive care unit (ICU), or death.

Methods

Study design, sites, and participants

This was a retrospective observational cohort study conducted at the two main cities of Burkina Faso, Ouagadougou and Bobo-Dioulasso, which are the two epicenters of the COVID-19 epidemic in the country, while the other cities of the country reported almost no cases or few cases of COVID-19. The study enrolled patients who had a positive test result for the SARS-CoV-2 regardless of sex and age, admitted to a hospital (university hospitals of Tengandogo and Souro Sanou, Princesse Sara polyclinic, and Pissy medical center), or followed-up at home.

Data sources and variables assessed

Patients were included in the study on the basis of the availability of their medical records. These records were reviewed by the study clinicians prior to the data capturing. The data collected included symptoms, medical history, and history of medication use (including HCQ or CQ). At admission, date of diagnosis confirmation by real-time reverse transcriptase polymerase chain reaction (rRT-PCR), CQ/HCQ treatments for the management of the current episode of SARS-CoV-2 infection were collected. Moreover, the duration of the hospital stay (or disease course in terms of worsening or referral to the ICU), date of SARS-CoV-2 negativation confirmed by rRT-PCR, and disease outcomes (in terms of death or recovery) were collected. This study did not consider the viral load because these data were not available for the majority of participants Table 1. summarizes the variables assessed during the study.

Table 1
Summary of parameters used for patient management.

Parameters	Units of measurement/main modalities
Type of follow-up	Hospitalized or followed at home
Patient demographics	Age (Year), sex (Male, Female)
Date of hospitalization	Day/Month/Year
Date of PCR confirmation of diagnosis	Day/Month/Year
Date of SARS-CoV-2 PCR negativity	Day/Month/Year
Medication history on admission	HCQ/CQ, Antibiotics, Antivirals
Comorbidities and risk factors	Types/names of comorbidity/risk factors
Vital signs and general condition and state of consciousness on admission	SaO2, Temperature, Heart rate
Signs and symptoms on admission	General condition: good, fair, poor; Consciousness: good or impaired; Types/names of signs and symptoms
HCQ/CQ treatments	HCQ/CQ prescribed yes or no; Dosage, duration of treatment
Disease progression	Aggravation, referral to intensive care unit; Date of worsening or referral to intensive care unit
Disease outcomes	Recovered or Died; Date of recovery or death

Hydroxychloroquine or chloroquine or exposure and study end points

According to the national protocol, hydroxychloroquine was administered at a dose of 200 mg three times a day for 10 days, whereas chloroquine phosphate was administered at 250 mg twice a day for 10 days. Azithromycin was administered at 500 mg on Day 0 and at 250 mg per day from Day 1 to Day 4, for a total of 5 days of treatment. The definition of patients who received CQ/HCQ in our study consisted of patients who received CQ/HCQ at baseline (once the PCR result was positive) or during the follow-up period before the study outcome occurred without counting the duration of the actual treatment of the patients. The study considered three primary outcomes: recovery time, worsening/transfer to the ICU, and death.

Data management and statistical analysis

Data were collected by the study physicians on an individual paper case report form from the source documents (patient medical records) before being double-entered into an electronic database developed on OpenClinica database management system. The final database was generated after the resolution of all queries by the field coordinators of the study.

Categorical variables were presented as frequencies and percentages, and continuous variables were presented as means with standard deviations or median with interquartile ranges (IQRs) and minimum and maximum values, when appropriate. When required, a comparison of continuous data between groups was performed using the unpaired Student's t-test and categorical data was compared using the chi-square test or Fisher exact test. The

median time to recovery and the 95% confidence intervals (95% CIs) were calculated using the Kaplan-Meier method. The log-rank statistical test was performed to test the null hypothesis of equal survival curves between the CQ/HCQ group and the non-CQ/HCQ group.

Unadjusted and adjusted Cox proportional hazards regression models (including demographic variables, Charlson comorbidity index (Charlson et al., 1994), the severity of illness at admission, previous use of other drugs, and period of chloroquine adoption by the MoH) were used to estimate the association between CQ/HCQ + AZ use and cure rate as well as the mortality rate. The association between CQ/HCQ + AZ use and the rate of worsening and/or transfer to the ICU was estimated using Poisson regression. These unadjusted and adjusted models were then stratified according to the type of follow-up (inpatients and outpatients). In addition, to account for the nonrandomized administration of the CQ/HCQ + AZ, propensity score matching method was used to reduce confounding effects. In the propensity score matching analysis, the "nearest neighbor" matching method was applied to create a matched control sample. Individual propensities to receive chloroquine treatment were estimated using a multivariate logistic regression model. The propensity score was based on the following variables: age, sex, SaO2, Charlson comorbidity index, and history of chloroquine or antibiotic use. From the matched sample, we performed a secondary analysis (multivariate Cox proportional hazards regression analysis) using the propensity-matched sample. For the models, complete case analysis was performed.

The statistical analyses were performed with the R software, version 4.1.1 (R Project for Statistical Computing).

Ethical aspects

The Burkina Faso Health Research Ethics Committee approved the research protocol on June 10, 2020, under deliberation no. 2020-000101/MS/MESRSI/CERS.

Results

Characteristics of the Cohort

A total of 863 patients attending the COVID-19 case management centers in Ouagadougou and Bobo-Dioulasso between March 9, 2020, and October 31, 2020, were included in the study. Of them, about 50% (432/863) were followed at home and the other half were inpatients admitted at the hospital. Of the patients included, 83.3% (746/863) received CQ/HCQ + AZ treatment and 13.7% (118/863) did not. Among the inpatients, 80.3% were treated with CQ/HCQ + AZ, whereas 92.4% of the patients followed at home received CQ/HCQ + AZ treatment. About 35.1% of study participants were women ($p = 0.016$). The mean age of patients was estimated at 42.2 years (SD = 15.7). Patients who received CQ/HCQ + AZ had a higher mean age than the untreated group (46 vs 39 years, $p < 0.001$).

About 84.0% of the patients had a good general condition at admission, whereas 8.6% (37/432) had a poor general condition. The mean oxygen saturation (SaO2) was estimated at 97.0% (SD = 7.2). The main clinical signs presented by the patients at admission were cough (29.7%), general malaise (18.3%), headache (13.1%), shortness of breath (12.9%), myalgias (9.5%), arthralgias (9.5%), and rhinorrhea (7.8%). The other signs or symptoms are listed in the Table 2 below.

At admission, the documented medical history was balanced between the two groups of patients (treated with CQ/HCQ vs untreated). There were no significant differences between the groups regarding comorbidities. For the Charlson comorbidity index, 14.4% and 0.5% of patients had an index of 1–2 and 3, respectively. Among the 5 most commonly used therapeutic classes, antibiotics were on top level (16%), followed by antipyretics/NSAIDs (10.9%), chloroquine-based drugs (8.2%), antihypertensive drugs (7.2%), and other antimalarials (5.6%).

Study endpoints

The primary endpoint of rRT-PCR results was available for 701 patients (81.2%). Among the included patients, 10.9% (94/863) worsened or have been admitted to an ICU and 48 died.

The median time to recovery was estimated at 14 days (95% CI 12–15) and 11 days (95% CI 10 to 12), respectively, for the untreated and treated groups. In the crude unadjusted analysis, patients who had received CQ/HCQ + AZ were more likely to have a short rRT-PCR negativation time than patients who did not (hazard ratio 1.30; 95% CI 1.02–1.65). However, in the Cox multivariable analysis, there was no significant association between CQ/HCQ + AZ use and time to recovery (hazard ratio 1.15; 95% CI 0.89–1.49). There was no statistical association between time to recovery and the use of CQ/HCQ + AZ irrespective of the type of follow-up (outpatient or inpatient) (Figure S1). After using the propensity score-matched samples, the Cox multivariable analysis confirmed the absence of statistical association between the use of CQ/HCQ + AZ and recovery time.

Throughout the follow-up, 10.1% (75/745) and 16.1% (19/118) experienced a worsening of their clinical conditions in the CQ/HCQ group and in the non-CQ/HCQ group, respectively. Crude and adjusted analysis (and stratified by type of follow-up) to assess association between patients who received CQ/HCQ and the rate of disease worsening or ICU transfer seemed to show a decrease in the rate of ICU transfer (especially in the outpatient group), but this was not statistically significant (Table S1). After controlling for the period of chloroquine uptake (before vs after) in the adjusted Poisson regression, treatment with CQ/HCQ did not show a statistically significant association (odds ratio 0.76; 95% CI 0.43–1.30).

Table 3.

Of the 44 deaths, 68.2% (30/44) were in bad general conditions at admission. Of them, 45.4% (20/44) were recorded in the CQ + AZ treatment group. Compared with the untreated group, the treated group had lower probability (log-rank test, $p < 0.001$) of death (Figure 1). Similarly, after controlling for the period of adoption of chloroquine-based treatment (before vs after the introduction of CQ/HCQ in the treatment policy), as well as age, history of drug use (chloroquine, antibiotic, and antimalarial), Charlson comorbidity index, and general conditions at inclusion, the association between mortality and CQ/HCQ treatment was consistent with the crude results (adjusted hazard ratio 0.20; 95% CI 0.10– 0.44).

Discussion

Relationship between the use of CQ/HCQ + AZ and virological recovery, disease worsening, and deaths among patients with COVID-19

Our study showed that the time to viral clearance and risk of worsening or transfer to an ICU were not significantly higher or lower in patients who received CQ/HCQ + AZ than in those who did not. Similar results have also been reported in other studies carried out in several countries worldwide (Chen et al., 2021; Chivese et al., 2021; Elavarasi et al., 2020; Eze et al., 2021; Fiolet et al., 2021; Maraolo and Grossi, 2021; Mittal et al., 2021). Consistent with other studies, the overall mortality over our study period was significantly lower in the CQ/HCQ + AZ group (Arshad et al., 2020; Ayerbe et al., 2020; Bernaola et al., 2020; Catteau et al., 2020; Lagier et al., 2020; MILLION et al., 2021; Yu et al., 2020b); although the sample selection in our study did

Table 2
Measured vital signs and reported clinical signs at admission.

Vital signs/clinical signs	Overall	HCQ/CQ Treatment		
		Untreated	Treated	
General condition, n/N (%)				<0.001
Good	704/836 (84.2)	75/112 (67.0)	629/724 (86.9)	
Fair	96/836 (11.5)	18/112 (16.1)	78/724 (10.8)	
Bad	36/836 (4.3)	19/112 (17.0)	17/724 (2.3)	
SaO2, Mean (SD)	95.7 (7.2)	90.6 (15.0)	96.5 (4.6)	<0.001
Temperature (°C), Mean (SD)	37.0 (0.6)	37.2 (0.9)	36.9 (0.6)	0.004
History of fever, n/N (%)	239/863 (27.7)	49/118 (41.5)	190/745 (25.5)	<0.001
Cough, n/N (%)	254/856 (29.7)	46/114 (40.4)	208/742 (28.0)	0.031
Malaise, n/N (%)	157/856 (18.3)	27/114 (23.7)	130/742 (17.5)	0.17
Headache, n/N (%)	110/840 (13.1)	17/114 (14.9)	93/726 (13.3)	0.54
Shortness of breath, n/N (%)	110/856 (12.9)	26/114 (22.8)	84/742 (11.3)	0.001
Myalgia, n/N (%)	81/856 (9.5)	14/114 (12.3)	67/742 (9.0)	0.40
Arthralgia, n/N (%)	81/856 (9.5)	20/114 (17.5)	61/742 (8.2)	<0.001
Rhinorrhea, (runny nose), n/N (%)	67/856 (7.8)	12/144 (10.5)	55/742 (7.4)	0.36
Throat pain, n/N (%)	61/856 (7.1)	11/114 (9.6)	50/742 (6.7)	0.34
Chest pain, n/N (%)	53/856 (6.2)	11/114 (9.6)	42/742 (5.7)	0.22
Anosmia, n/N (%)	33/856 (3.9)	2/114 (1.8)	31/742 (4.2)	0.30
Agueusia, n/N (%)	24/856 (2.8)	2/114 (1.8)	22/742 (3.0)	0.76
Wheezing, n/N (%)	4/856 (0.5)	2/114 (1.8)	2/742 (0.3)	0.09
Charlson comorbidity index, n/N (%)				0.043
0	728/856 (85.0)	91/114 (79.8)	637/742 (85.8)	
1 – 2	123/856 (14.4)	23/114 (20.2)	100/742 (13.5)	
3 – 4	4/856 (0.5)	0/114 (0.0)	4/742 (0.5)	

Table 3
Statistical associations between chloroquine or hydroxychloroquine use and rRT-PCR negativation, worsening, and death in crude analysis, multivariable analysis, and propensity score analyses.

Analysis items	Recovery	Worsening	Death
No. of events/no. of patients at risk (%)			
Treated with HCQ/CQ	608	75/745 (10.1)	20/336 (5.9)
Not treated with HCQ/CQ	73	19/118 (16.1)	24/73 (32.9)
Measures of association (95% CI)			
Crude analysis	1.30 (1.02–1.65)†	0.62 (0.38–1.03)‡	0.15 (0.08–0.27)†
Multivariate analysis	1.25 (0.97–1.62)†	0.72 (0.43–1.30)‡	0.22 (0.10–0.46)†
Multivariate analysis adjusted by timing of HCQ/CQ adoption	1.15 (0.89–1.49)†	0.80 (0.50–1.50)‡	0.20 (0.10–0.44)†
Propensity-score analysis			
No. of events/no. of patients at risk (%)			
Treated with HCQ/CQ	67	3/67 (6.0)	0/71 (0.0)
Not treated with HCQ/CQ	67	4/67 (4.5)	22/71 (31.0)
Measures of association (95% CI)			
With matching	1.31 (0.72–2.40)†	–	–
Adjusted for propensity score	1.44 (0.76–2.71)†	–	–

Adjusted for age, history of chloroquine, antibiotic, antimalarial drug use, Charlson comorbidity index, general condition at inclusion, and timing of chloroquine adoption.
† Hazard ratio; ‡ Incidence Rate Ratios.

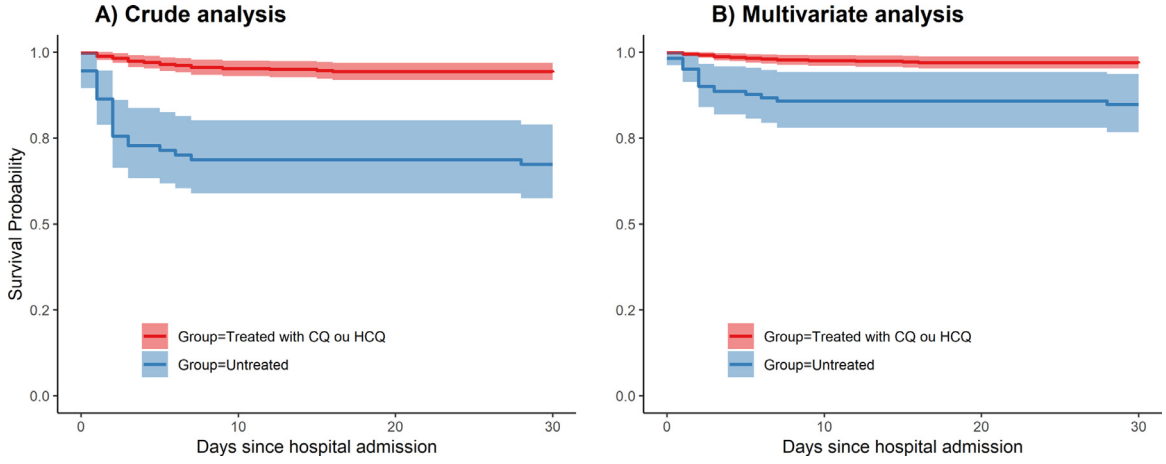

Figure 1. Death at 30 days in treated and untreated group.

not allow for propensity score-adjusted analysis of risk of death, making it difficult to conclude in one direction or the other. However, it is important to stress that the introduction of chloroquine-based treatment for the management of COVID-19 cases in Burkina Faso occurred in a context of improved knowledge of SARS-CoV-2, both internationally and nationally, which may have resulted in a better organization of the response through improved medical practices. Our study (comparison of survival curves between the periods before and after the introduction of CQ/HCQ + AZ in the treatment policy), did not show a statistically significant decrease or increase in mortality attributable to the post-adoption period (April 07, 2020–October 31, 2020) of CQ/HCQ.

With an observational design and a relatively large confidence intervals, this study could not be considered to exclude the benefits or harms of CQ/HCQ + AZ treatment. Indeed, referring to published research on the same topic, several observational cohort studies have shown conflicting results. Some have shown a decrease in mortality that could be attributed to the use of HCQ (Arshad et al., 2020; Ayerbe et al., 2020; Bernaola et al., 2020; Di Castelnuovo et al., 2020; Catteau et al., 2020; Lagier et al., 2020), while others have shown no difference (Baguiya et al., 2021; Geleris et al., 2020; Ip et al., 2020; Lammers et al., 2020; Rosenberg et al., 2020; Sbidian et al., 2020; Singh et al., 2020). Randomized clinical trials that minimize unmeasured confounding and bias are the best approaches for determining whether a benefit can be attributed to a given therapeutic intervention. Thus, the RECOVERY randomized clinical trial that investigated the efficacy of HCQ on mortality concluded that there was no significant difference between standard treatments (25% mortality) and HCQ treatment (26.8% mortality) (The RECOVERY Collaborative Group, 2020).

Weighting to be done in this study

Although this study has provided additional insight into the use of CQ/HCQ + AZ as a treatment for COVID-19 in sub-Saharan Africa, it had several weaknesses that were primarily inherent to its design. Indeed, the lack of a priori designing of methodological criteria such as patient follow-up criteria and the lack of standardization of practices (in the different COVID-19 case management centers, including home follow-up) suggested numerous biases and confounding factors. First of all, as most infected patients in the African context are asymptomatic, it is possible that many infected patients did not visit the health centers at the infection onset, which may lead to over- or underestimation of the statistical relationships that the study postulates. Second, similar to the hypothesized relationship between the implementation of the treatment regimen and the reduction of severe cases or mortality, patient-related factors and/or factors related to the characteristics of the medical management, the quality and reliability of the diagnostic, and therapeutic approach including the follow-up could influence the occurrence of symptoms attributed to COVID-19 and/or their worsening and/or viral clearance. Third, information bias could arise from the definition of virological recovery, worsening, or death attributable to COVID-19. Furthermore, although the time (in days) from the diagnosis to the confirmation of virological recovery by rRT-PCR was similar in both groups, it should be noted that the date of the rRT-PCR result release varied between 48 and 72 hours. Only the date of the result (without the date of sampling) was recorded in the patient's records. This could extend the time of the patient's recovery. A fourth limitation of this study could also come from the adherence of the CQ/HCQ treatment, particularly for patients followed at home.

Nevertheless, the results of this study and the recommendations that follow are to be considered within the framework of scientific presumption and not that of firmly scientific evidence.

Conclusion

This observational study provided valuable additional information on the use of CQ/HCQ in patients with COVID-19 in Burkina Faso and did not show any harmful outcomes of CQ/HCQ + AZ treatment. In accordance with data from several published retrospective studies and in contrast with data from other observational studies and randomized clinical trials on the effectiveness of this combination treatment, our study showed that the use of CQ/HCQ appeared to be associated with a reduced risk of mortality after adjusting for measured potential confounders (propensity score matching not done). However, the observational methodological approach of the study requires that these results be interpreted with caution despite the 95% confidence level of the statistical tests. In the absence of an approach that generates a level A scientific evidence, these results could guide health care decisions that should be made based on bundles of evidence including those from this study.

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Competing interests

The authors declare that they have no competing interests.

Data sharing

Anonymized participant data could be made available upon requests directed to the corresponding author. If agreed, data can be shared through a secure online platform after signing a data transfer agreement.

Contributions

All authors conceived the study, carried out the analysis, wrote the draft, discussed the results, revised the manuscript critically, and approved it for publishing.

Ethics approval

This study was approved by the National Ethics Committee (Deliberation number: 2020-000101/MS/MESRSI/CERS) and was registered on ClinicalTrials.gov (NCT04445441).

Consent for publication

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.02.034.

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