

Early Treatment with Hydroxychloroquine and Azithromycin in 10,429 COVID-19

Outpatients: A Monocentric Retrospective Cohort Study

SUPPLEMENTARY DATA

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SUPPLEMENTARY METHODS

Study design, setting and participants

Approximately 800 patients have already been reported in our previous work (1). Here, we analyzed the IFR, ICU admission rate and HC rate of patients with a PCR-proven diagnosis of COVID-19 seen in a day hospital. Patients with HC on the same day for a severe disease or any other reason were excluded and will be analyzed separately. Other exclusion criteria were refusal to allow use of data, minor patients (<18 years), participants considered cured, absence of a positive PCR result and missing data for treatment (whether or not HCQ+AZ was used). Age, sex, date of day hospital attendance, and treatment were collected. Based on the date of day hospital attendance, three periods were defined and corresponded to three bell-shaped incidence curves associated with different variants (2,3).

We assessed the time between the onset of symptoms and day hospital attendance and the time between the positive PCR sample and day hospital attendance for a subgroup of patients who arrived in December 2020. For patients who died, we evaluated comorbidities with the Charlson Comorbidity Index (CCI) to assess what would have been the probability of death within 1 year of these patients in the absence of COVID-19, and we examined initial severity with the NEWS-2 score, as in our previous report (1).

Charlson Comorbidity Index

This index is designed to predict 1-year mortality on the basis of a weighted composite score for the following categories: cardiovascular, endocrine (only diabetes), pulmonary, neurologic, renal, hepatic, gastrointestinal, and neoplastic diseases. It takes into account 19 comorbidities. Comorbidities are weighted from 1 to 6 for mortality risk and disease severity. The final score is obtained by summation of the weighted comorbidity scores adjusted for the

patient's age (1 point for each decade from the age of 41 years). The higher the score is, the higher the likelihood of mortality will be within a one-year period according to the following algorithm: Score = 0 → Estimated 1-year mortality = 12%; Score = 1-2 → Estimated 1-year mortality = 26%; Score = 3-4 → Estimated 1-year mortality = 52%; Score \geq 5 → Estimated 1-year mortality = 85% or more (4,5).

Pandemic periods

The period of Act I (March - June 15, 2020) corresponds to the first circulation of SARS-CoV-2 in our region with a peak around April 1 and a strain identical to the strain described in Wuhan, called Marseille-0 in our center (2). Act II (16 June 2020 - 31 August 2020) corresponds to the reintroduction of a different variant from North Africa called Marseille-1 (2). From September onwards, the variants Marseille-0 and Marseille-1 were no longer detected, but new variants were identified, the majority of which were Marseille-4 associated with Mink and Denmark (3). The UK variants were detected only at the end of December 2020, and their circulation therefore had no impact on the patients described here.

Statistical methods

The IFR and ICU and HC rates are presented according to 10-year age intervals (0-9 to 90-99 years). Comparisons to the Diamond Princess cruise data (6), for which results for the same age class were available, was made by comparing the 95% confidence intervals for each age class using the exact Clopper-Pearson method. Differences between epidemic periods were also analyzed. Categorical variables are presented as n (%). We used Student's t-test, the χ^2 test, or Fisher's exact test to compare differences between groups of patients where appropriate. For each outcome, only age classes including the youngest patient with the

outcome and older groups were included in the analysis. A two-way interaction between age and treatment was tested.

Ethics statement

Data presented herein were collected retrospectively from the routine care setting using the electronic health recording system of the hospital. The retrospective nature of the study was approved by our institutional review board committee (Mediterranée Infection N°: 2021–007). As previously reported (1), for all patients, the prescription of HCQ+AZ was made during day hospital attendance by one of the physicians, after a collegial decision based on the most recent scientific data available and after assessment of the benefit/harm ratio of the treatment. According to European General Data Protection Regulation No 2016/679, patients were informed of the potential use of their medical data and that they could refuse the use of their data. Data processing was carried out in accordance with the reference methodology MR-004 registered on N° MR 2020-151 in the AP-HM register and public register (<https://www.health-data-hub.fr/projets>).

THERAPEUTIC PROTOCOL FOR THE AMBULATORY MANAGEMENT OF COVID-19 AT IHU MEDITERRANEE INFECTION (UPDATED JANUARY 29, 2021)

WHO?

- All adults with a positive PCR result (cycle threshold (Ct) < 35) regardless of symptoms.
- For children, pediatric advice is sought.
- For pregnant women, gynecological advice is sought.

WHEN?

As soon as possible.

HOW IS VITAL DISTRESS AND THE INDICATION FOR HOSPITALIZATION ELIMINATED?

- Measurement of vital signs: oxygen saturation, respiratory rate, pulse, blood pressure, and temperature (equipment used at the IHU: Rad-97®, MASIMO® - this device measures the respiratory rate automatically from the oxygen saturation signal).

Evaluation of the NEWS score modified by Liao according to the table below:

PARAMETERS	3	2	1	0	1	2	3
Age				<65			≥65
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Consciousness				Alert			Drowsiness Letargy Coma Confusion
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	

News score ≥ 5 = systematic hospitalization.

- For saturation < 95% or respiratory rate > 25, the patient is immediately placed in a bed; if the arterial gasometry result was 02 2 L/min or saturation is ≥ 95%, the doctor is called by the nurse.
- Patients are systematically hospitalized for any suspicion of superinfection (high fever ≥ 39.5°C, auscultatory focus, high C-reactive protein, high neutrophils, CT scan with condensation). No antibiotics other than azithromycin are used in outpatient care.
- Patients with any suspected thrombosis that cannot be ruled out during outpatient management (phlebitis, pulmonary embolism, etc.) should be hospitalized.
- In patients with a very inflammatory pneumopathy documented on CT scan (CRP > 100 mg/L), a high low viral load (CT qPCR ≥ 30) or on a case-by-case basis, low-dose corticosteroid therapy (dexamethasone 6 mg/d) can be proposed in conventional hospitalization in combination with broad-spectrum antibiotics.
- For patients in respiratory distress despite 15 L/min of oxygen (high-concentration mask) and contraindications to intensive care unit (ICU) transfer, high-flow oxygen

therapy (machine used at the IHU: Optiflow™ Nasal High Flow) can be proposed in the absence of contraindications (hypercapnia) and would save 30% of these patients.

- In the absence of vital distress (ICU advice) and no other indication for hospitalization, the planned management is ambulatory. The patient undergoes a pretherapeutic assessment.

WHAT IS THE PRETHERAPEUTIC ASSESSMENT IN THE ABSENCE OF AN INDICATION FOR HOSPITALIZATION?

- o Rapid point-of-care kalemia (results in 20 min). Equipment used at the IHU (i-STAT®1, Abbott & GEM5000, Instrumentation Laboratory)
- o CBC
- o D-Dimer
- o ECG with QTc measurement
- o Low-dose chest CT scan: Indication according to patient characteristics (age > 60 years, diabetes, hypertension, obesity, cancer, respiratory disease, cardiac disease and others defining a patient "at risk") and/or clinical (dyspnea, auscultatory focus, pulmonary sign).

WHAT TREATMENT?

- A treatment is proposed to the patient who is informed that there is no treatment against the virus with a labeled authorization in France for the ambulatory management of COVID-19 from January 2021. The proposed off-label treatment is based on our analysis of the literature, the results obtained in our laboratory and our experience on more than 13,000 patients. Consent for the prescription of hydroxychloroquine for "off-label" use is requested from each patient.
- Each treatment must be prescribed after eliminating contraindications. Only the most frequent contraindications in our experience ($\geq 10,000$ patients managed as outpatients at IHU since March 2020) are described here.

1. HYDROXYCHLOROQUINE 200 mg times 3 daily for 10 days with a meal.

- No hydroxychloroquine is used if hypokalemia occurs, but azithromycin and zinc are started. Potassium chloride 600 mg 2 cp 3 times per day is given. The ionogram is checked every 48 hours. Hydroxychloroquine was started as soon as potassium is normalized, and potassium chloride 600 mg 1 tablet is continued 3 times a day until the end of the treatment.
- If on ECG, long QTc > 460 ms or there is abnormality, cardiological advice is given to look for a contraindication to hydroxychloroquine.
- Elimination of a contraindication with the patient's usual medications that cannot be prevented is performed using prescription analysis software (software used at the IHU, namely, Theriaque® (<https://www.theriaque.org/apps/contenu/accueil.php>)).
- There is no hydroxychloroquine use if the patient has a QT-prolonging drug that cannot be stopped for 10 days even if there are no contraindications according to the interaction analysis software. The continuously updated list of QT-prolonging drugs used at the IHU is available at <https://www.crediblemeds.org/index.php/login/dlcheck>.

- 2. AZITHROMYCIN 250 mg 2 tablets the first day, then 1 tablet per day for 4 days, for a total of 5 days with a meal**

Most frequent contraindications are allergies to macrolides and comedication with colchicine.

Are there other options in case of contraindication to hydroxychloroquine (HCQ) azithromycin (AZ)?

There is emerging evidence of the value of off-label use of ivermectin for patients with contraindication for HCQ + AZ.

- 3. Elemental zinc 15 mg 3 per day for 10 days on an empty stomach with a large glass of water (10 am, 4 pm and 10 pm).**

Most frequent contraindication: first-trimester pregnancy.

- 4. Enoxaparin 0.4 mL SC per day (0.6 mL SC per day if body mass index (BMI) > 30)**

Systematic at once if and only under the following conditions:

Age >70 years

Obesity (body mass index > 30)

Cancer under treatment or history of cancer

History of thromboembolic disease (phlebitis, pulmonary embolism)

History of major surgery < 3 months

Autoimmune disease: Thyroiditis, Lupus, Rheumatoid arthritis, Spondylarthritis

Severe hemoglobinopathies: Thalassemia, Sickle cell disease

Crohn's disease - Hemorrhagic rectocolitis

Medical indication on a case-by-case basis, decision of the clinician during the consultation:

Prolonged bed rest

Postpartum if there is prolonged bed rest or delivery hemorrhage

Oral contraception: to be discussed on a case-by-case basis (especially if combined with smoking)

Other factors are considered risk factors by the clinician, especially the accumulation of cardiovascular risk factors.

Administration by nurse at home with daily monitoring of saturation.

CBC, platelets and D-dimer monitoring on day 5 and day 10

WHAT TO DO IF D-DIMER IS POSITIVE?

- If D-dimer is > 500 µg/L: Enoxaparin 0.4 mL SC per day (0.6 mL SC per day if body mass index > 30)
- If D-dimer > 2000 µg/L: Thoracic angioscan
- D-dimer is positive during pregnancy. For pregnant women, there is no anticoagulation treatment unless advised by the gynecologist.

WHAT TO DO IF ANEMIA < 12 g/dL IS DETECTED BY CBC IN AN OLDER PATIENT OR PATIENT WITH PNEUMOPATHY AND DYSPNEA?

Discuss blood transfusion

REMARKS

- STOP nonsteroidal anti-inflammatory drugs, quinolones.
- DO NOT STOP long-term oral corticosteroids as adrenal insufficiency may occur.
- CONTINUE inhaled therapy for asthma (including inhaled corticosteroids).
- Initiation of oral steroids is not indicated in ambulatory patients.
- STOP corticosteroid therapy prescribed for COVID.
- STOP hypokalemic drugs (thiazide or loop diuretics) if possible, after cardiological advice if there is any doubt (do not stop if there is a risk of heart failure). Hospitalize if necessary to treat as soon as possible.

Do not hesitate to return the patient on a daily basis if the patient has many risk factors or refuses hospitalization.

ENOXAPARIN IN A PATIENT ALREADY ON ANTIAGGREGANTS/ANTICOAGULANTS

Long-term antiplatelet agents:

Usual treatment with aspirin: YES, enoxaparin is started

Usual treatment with two antiplatelet agents (clopidogrel + acetylsalicylic acid): YES, enoxaparin is started; hospitalization is discussed on a case-by-case basis.

Long-term anticoagulants

Usual treatment with rivaroxaban, apixaban, anti-vitamin K: maintain anticoagulant treatment. NO, do not start enoxaparin.

WHAT ABOUT FOLLOW-UP?

Prescription for daily oxygen saturation measurement for 10 days for all patients at risk (age > 60 years, obesity, high blood pressure, diabetes, risk factors for thrombosis, other chronic diseases).

Digital saturometer is available over the counter in pharmacies.

Connected smart watch (equipment used at the IHU: SmartWatch android, Withings

ScanWatch - other equipment usable: AppleWatch) with electrocardiogram and measurement of QTc (ECG) and pulsed oxygen saturation (SpO2)

Instructions to return in case of

- Treatment intolerance
- Dyspnea
- Oxygen saturation $\leq 95\%$.
- Abnormal QTc
- Any other problem (with the slightest doubt)

Immediate rehabilitation of anosmia

By following the tutorial made by Pr MICHEL's team, "I lost my taste and smell: concretely what to do" accessible at <https://www.youtube.com/watch?v=mUy27VKvwfw>

Nasal corticosteroids are likely to improve the symptoms at this level.

PCR tests are performed between day 7 and day 10 to evaluate the persistence of the contagion.

If no worsening occurs, follow-up is performed by the treating physician.

If symptoms persist, particularly ENT (anosmia), neurological or respiratory symptoms, reconsultation in a specialized center for long COVID-19 is advised.

IMPORTANT INFORMATION

The university hospital doctors of the IHU Méditerranée Infection do not make recommendations. They describe and share their experiences in caring for informed patients within the framework of a doctor-patient relationship and the results of their research work, their observational studies and their analysis of the literature.

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Bibliographical research

The bibliographic search on the ambulatory management of COVID was performed using the keywords 'outpatient' and 'ambulatory' with 'COVID' or 'SARS-CoV-2' or 'coronavirus' in Google Scholar, Google and PubMed without date restriction.

Supplementary Table 1. Age and sex according to epidemic period (n = 10,429)

	Period 1 (n = 3,279)	Period 2 (n = 1,656)	Period 3 (n = 5,494)	Total (n = 10,429)
Age				
Means (std)	42.3 (14.5)	39.3 (16.1)	48.2 (16.0)	45.0 (16.0)
Q1 MED Q3	30-41-53	25-36-52	36-49-60	32-45-57
Sex				
% Men	43.9	50.9	46.4	46.3
n Men	1440	842	2550	4832
% Women	56.1	49.2	53.6	53.7
n Women	1839	814	2944	5597

Compared those in period 1, patients were significantly younger in period 2 and older in period 3. The sex ratio was significantly different from 50% for periods 1 and 3 but not for period 2.

Supplementary Table 2. Delay from symptom onset and positive PCR test to day hospital attendance (days) by age intervals (n = 1,119)

Age class		Symptoms		Positive PCR		
(yrs)	n	Mean (SD)	Q1-MED-Q3	n	Mean (SD)	Q1-MED-Q3
18-29	124	4.23 (3.14)	2-4-5	130	2.28 (2.44)	1-1-3
30-39	178	4.31 (2.89)	2-4-5	180	2.09 (2.02)	1-1-3
40-49	227	4.46 (2.71)	3-4-6	227	2.26 (2.27)	1-2-3
50-59	254	4.51 (3.10)	3-4-6	269	1.98 (1.90)	1-1-3
60-69	177	4.47 (3.23)	2-4-6	189	2.13 (2.34)	1-1-3
70-79	76	3.79 (2.74)	2-3-5	92	2.13 (3.00)	1-1-3
80-89	27	4.33 (2.87)	2-4-6	30	1.40 (1.33)	0-1-3
>89	2	3.00 (1.41)	2-3-4	2	0.50 (0.71)	0-0.5-1
Total	1066	4.37 (2.30)	2-4-6	1119	2.11 (2.23)	1-1-3

Analysis was performed on patients consulting in December 2020. 53 patients were asymptomatic.

Supplementary Table 3. Reasons for nontreatment (n = 816)

	N	%
No details	375	46.0
Contraindications	182	22.3
Refusal	159	19.5
Because asymptomatic^a	80	9.8
Pregnancy^b	11	1.3
Breastfeeding^c	5	0.6
Language barrier	3	0.4
Noncompliance^d	1	0.1

These reasons correspond to the reasons mentioned in the medical file and do not represent our therapeutic protocol. ^aThe protocol has always been provided to propose the treatment to all patients with a positive PCR test, whether or not they were symptomatic. ^bPregnancy was not a contraindication for HCQ and AZ. Zinc was contraindicated during pregnancy. ^cBreastfeeding was not a contraindication. ^dThis patient had no contraindication and was prescribed HCQ-AZ but decided not to take it. He started AZ when his cough worsened. Unfortunately, his disease progressed to respiratory failure, and he was hospitalized. Then, HCQ-AZ was administered, but this late treatment did not prevent death. Strikingly, his brother, of similar age and health status, was also infected, strictly followed the protocol, and was rapidly cured.

Supplementary Table 4. ICU transfer according to age, HCQ-AZ and other treatments

	<i>All patients</i>		<i>HCQ-AZ</i>		<i>Other treatments</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
<i>n</i>	24/10,429	0.2	17/8,315	0.2	7/2,114	0.3
<i>Age interval (years)</i>						
18-29	0/2,157	0.00	0/1,752	0.00	0/405	0.00
30-39	0/2,004	0.00	0/1,650	0.00	0/354	0.00
40-49	2/2,074	0.10	2/1,692	0.12	0/382	0.00
50-59	5/2,179	0.23	3/1,726	0.17	2/453	0.44
60-69	11/1,286	0.85	7/1,003	0.70	4/283	1.41
70-79	5/555	0.90	4/395	1.01	1/160	0.62
80-89	1/158	0.63	1/93	1.07	0/65	0.00
>89	0/16	0.00	0/4	0.00	0/12	0.00

Supplementary Table 5. Effect of HCQ-AZ on ICU transfer - Multivariable logistic regression (n=6,268)

		OR	95% CI	p
Age (ref. 60-69)	40-49	0.13	0.03 - 0.48	0.0023
	50-59	0.27	0.10 - 0.72	0.0091
	70-79	1.16	0.43 - 3.16	0.7696
	>79	0.96	0.18 - 5.11	0.9588
Sex (ref. female)	Male	4.09	1.68 - 9.96	0.0019
Epidemic period (ref. period 1)	Period 2	0.75	0.23 - 2.44	0.6262
	Period 3	0.44	0.19 - 1.02	0.0556
Treatment (ref. no dual therapy)	HCQ+AZ	0.56	0.24 - 1.30	0.1756

OR: odds ratio, CI: confidence interval, ref: reference, HCQ: hydroxychloroquine, AZ: azithromycin. The two-way interaction between treatment and age was not statistically significant.

Supplementary Table 6. Hospitalization according to age, HCQ-AZ and other treatments

	<i>All patients</i>		<i>HCQ-AZ</i>		<i>Other treatments</i>	
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>
<i>n</i>	278/10,429	2.7	214/8,315	2.6	64/2,114	3.0
<i>Age interval (years)</i>						
18-29	7/2,157	0.3	7/1,752	0.4	0/405	0.0
30-39	26/2,004	1.3	22/1,650	1.3	4/354	1.1
40-49	33/2,074	1.6	27/1,692	1.6	6/382	1.6
50-59	68/2,179	3.1	52/1,726	3.0	16/453	3.5
60-69	64/1,286	5.0	46/1,003	4.6	18/283	6.4
70-79	55/555	9.9	44/395	11.1	11/160	6.9
80-89	22/158	13.9	15/93	16.1	7/65	10.8
>89	3/16	18.8	1/4	25	2/12	16.7

Supplementary Table 7. Effect of HCQ-AZ on hospitalization - Multivariable logistic regression (n=10,150)

		OR	95% CI	p
Age (ref. 60-69)	20-29	0.07	0.04 - 0.16	<0.0001
	30-39	0.24	0.15 - 0.38	<0.0001
	40-49	0.30	0.20 - 0.46	<0.0001
	50-59	0.60	0.43 - 0.85	0.0043
	70-79	2.17	1.49 - 3.17	<0.0001
	>79	3.41	2.08 - 5.60	<0.0001
Sex (ref. female)	Male	1.52	1.19 - 1.94	0.0007
Epidemic period (ref. period 1)	Period 2	0.64	0.42 - 0.98	0.0420
	Period 3	0.68	0.52 - 0.90	0.0059
Treatment (ref. no dual therapy)	HCQ+AZ	0.96	0.71 - 1.29	0.7653

OR: odds ratio, CI: confidence interval, ref: reference, HCQ: hydroxychloroquine, AZ: azithromycin. The two-way interaction between treatment and age was not statistically significant.

Supplementary Table 8. Clinical studies on ambulatory treatment of COVID-19^a

Study	Country	Treatment	Total sample size	Treated	Not treated	Overall mortality / 1000	Odds ratio 95% CI	p-value
Studies controlling for age								
Mokhtari, 2021 (7)	Iran	HCQ	22,784 ^b	5,964 ^b	16,820 ^b	7.0	aOR 0.33 (0.21 – 0.55)	0.0000082 ^c
Present Study	France	HCQ+AZ	2,015 ^d	1,495 ^d	520 ^d	1.5	aOR 0.17 (0.06 – 0.48)	0.0007
Sulaiman, 2020 (8)	Saudi Arabia	HCQ	5,541	1,817	3,724	11.0	aOR 0.36 (0.16 – 0.80)	0.012
Ip, 2021 (9)	USA	HCQ	1,274	97	970	40.0	aOR 0.44 (0.11 – 1.86)	0.38
Studies not controlling for age								
Szente Fonseca, 2020 (10)	Brazil	HCQ	717	334	383	15.3	unadj. OR 0.25 (0.05 – 1.17) ^e	0.10 ^f
Guerin, 2020 (11)	France	HCQ+AZ	80	20	34	11.4	Only 1 death in untreated	0.99 ^e
Seftel, 2021 (12)	USA	Fluvoxamine	113	65	48	8.8	Only 1 death in untreated	0.85 ^e

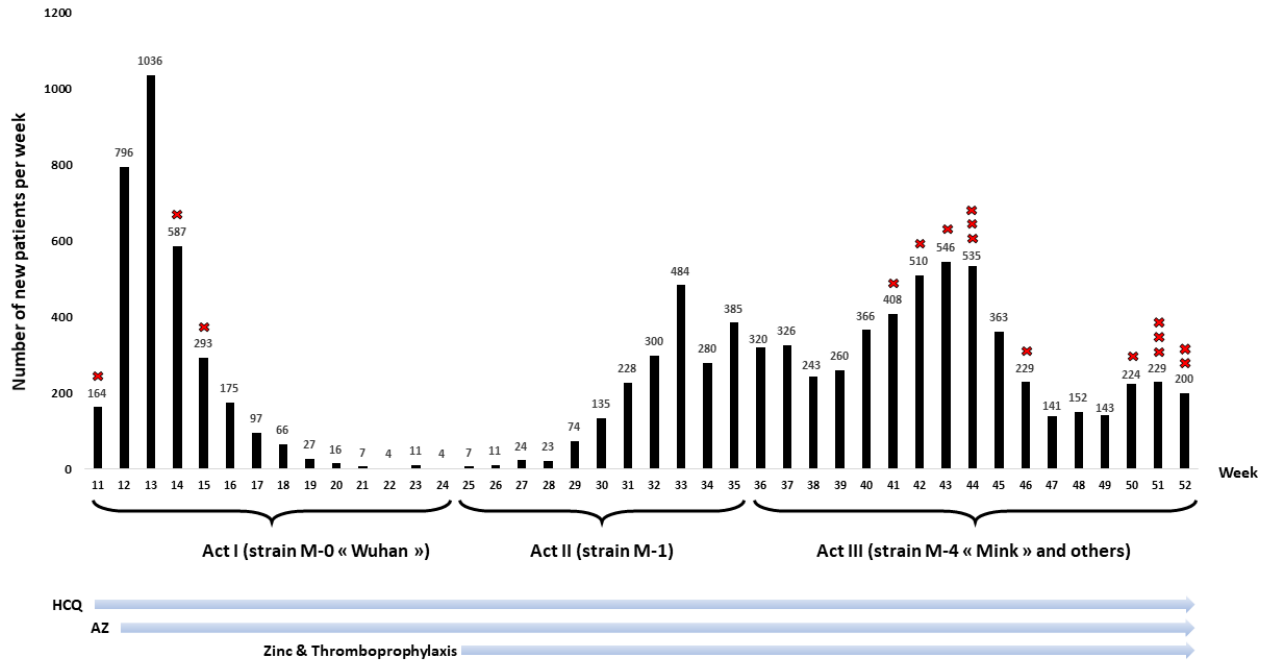
HCQ: hydroxychloroquine, AZ: azithromycin, aOR: adjusted Odds ratio.^aOnly community studies are included with exclusion of study including specific patients with cancer, hemodialysis or institutionalized, ^bAfter exclusion of 5,975 without positive PCR. ^cCalculated from 95% confidence interval using the formula provided in Altman *et al.* (13) ^dOnly patients ≥ 60 yrs are included in the analysis because no death was observed in those younger than 60 yrs, ^eFor the present study, adjusted risk ratio (aRR) was used in place of adjusted OR. Since the study outcome was very rare in all age strata, the aRR can also be interpreted as an aOR, ^fThe inclusion of this study in the meta-analysis did not change the results (summary OR : 0.31 (0.20 – 0.47)). ^gFisher exact test (calculated based on number provided in the article).

Supplementary Table 9. Studies on outpatient treatment of COVID-19 excluded from meta-analysis on death and reason of exclusion.

Study	Country	Population	Treatment	Sample size	Exclusion criteria
Mitja, Clin Infect Dis, 2020 (14)	Spain	Community	HCQ	293	No death
Lenze, JAMA, 2020 (RCT) (15)	USA	Community	Fluvoxamine	152	No death
Chowdhury, researchsquare, 2020 (16)	Bangladesh	Community	HCQ+AZ vs IVM+DOXY	116	No death
Oteo, MedRxiv, 2020 (17)	Spain	Community	HCQ	80	No death
Chen, NEJM, 2020 (18) & Gottlieb, JAMA, 2021 (19) (BLAZE-1 study (RCT))	USA	Community	Ly-CoV555	613	No death
Feld, Lancet Respir Med, 2021 (RCT) (20)	Canada	Community	PegIFN lambda	60	No death
Derwand, IJAA, 2020 (21)	USA	Community	HCQ+AZ	518	Inadequate control (decreased mortality)
Skipper, Ann Intern Med, 2020 (22)	USA	Community	HCQ	423	No PCR (1 death in each group)
Barbosa Esper, internet, 2020 (23)	Brazil	Community	HCQ	636	No PCR (decreased mortality)

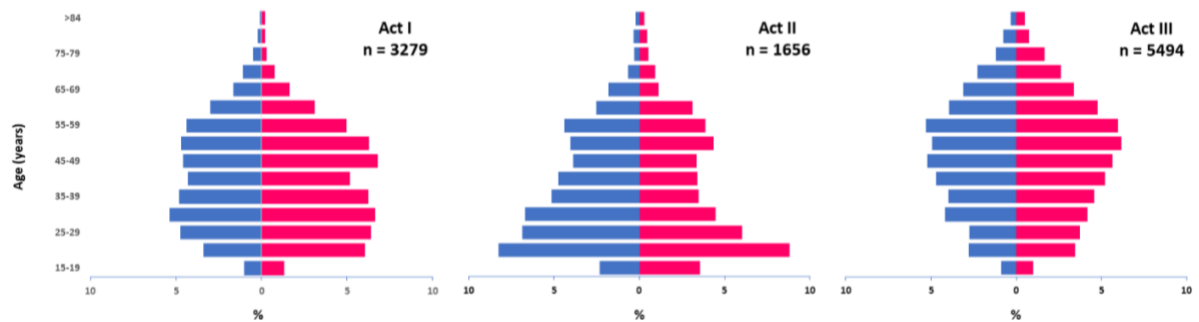
HCQ: hydroxychloroquine, AZ: azithromycin, IVM: ivermectin, DOXY: doxycycline, RCT: randomized controlled trials, IFN: Interferon.

Supplementary Figure 1. Pandemic periods and number of ambulatory patients treated in our daycare hospital (n =10,429)



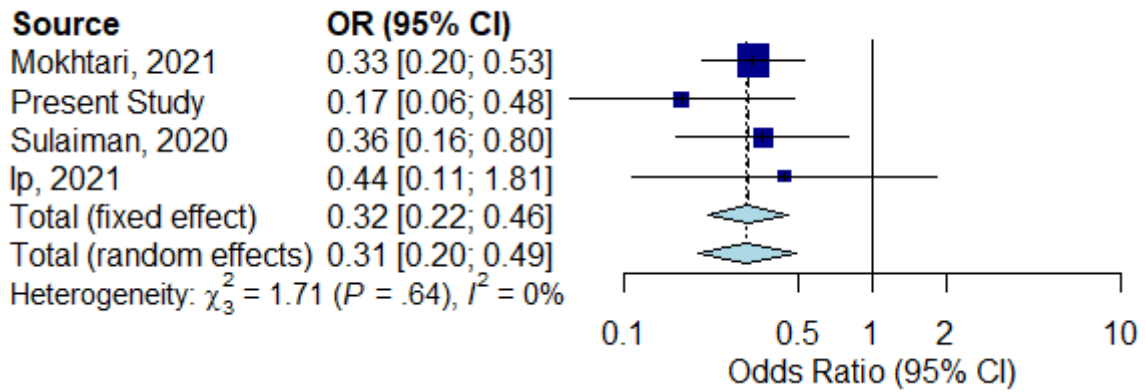
AZ: Azithromycin, HCQ: Hydroxychloroquine. The three pandemic periods corresponded to different SARS-CoV-2 variants (Marseille-0 similar to the Wuhan strain for Act I, Marseille-1 for Act II, Marseille-4 and others for Act III). Red crosses represent deaths.

Supplementary Figure 2. Age distribution according to sex and epidemic period (n = 10,429)



Act I: From March 17 to June 14 (median age 41 years (interquartile range 30 – 53)), Act II: from June 15 to August 31 (36 years (25 – 52)), Act III: From September 1 to December 31 (49 years (36 – 60)). The sex ratio differed, with proportions of males of 43.9%, 50.9% and 46.4% for Act I, II and III, respectively.

Supplementary Figure 3. Meta-analysis of studies reporting HCQ for COVID-19 mortality in outpatients (sensitivity analysis excluding one study not controlling for age, n = 31,407 with 9,373 treated)



See statistical methods and Supplementary Table 8 and 9 for details.

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