New Microbes and New Infections 55 (2023) 101172

Contents lists available at ScienceDirect

New Microbes and New Infections

journal homepage: www.journals.elsevier.com/new-microbes-and-new-infections

Original Article

Efficacy and safety of in-hospital treatment of Covid-19 infection with low-dose hydroxychloroquine and azithromycin in hospitalized patients: A retrospective controlled cohort study

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ARTICLE INFO

Handling Editor: Patricia Schlagenhauf

Keywords:
COVID-19
SARS-CoV-2
Treatment
Hydroxychloroquine
Azithromycin

ABSTRACT

Objectives: In this study we evaluate the efficacy and safety of a treatment protocol with standard dose of hydroxychloroquine plus azithromycin in patients hospitalized with COVID-19 infection.
Methods: We conducted a retrospective analysis to compare the 28-day mortality rate in 352 patients treated with hydroxychloroquine with or without azithromycin (HCQ-group) in our hospital with a contemporary control group of 3533 patients receiving standard of care from the Belgian Collaborative Group on COVID-19 Hospital Surveillance.
Results: All patients who received at least one dose of treatment were included in the analysis. A statistically significant reduction in crude mortality rate at 28 days was observed in the HCQ-group compared to standard of care (16.8% vs 25.9%,p = 0.001).
Patients in the treatment group were on average younger (69,7 vs73,1 years, p = 0,0002), were less likely to smoke or to have malignancy and more likely to be male. Patients in the treatment group were more likely to be obese, immunocompromised or to have arterial hypertension, liver disease and lung disease.
After adjustment for these variables the OR for mortality was 0.635 (95%CI 0.464–0.875). Patients who did not receive HCQ had a 57% higher risk of mortality. A survival benefit in the treatment group was consistent across all age groups. 13 patients discontinued treatment due to side effects (4 with QTc-prolongation>60msec (1.1%) and 9 because of gastro-intestinal symptoms (2.55%)). No episodes of ventricular arrhythmia or torsade de pointes were recorded during treatment.
Conclusion: Treatment of COVID-19 using a combination of hydroxychloroquine plus azithromycin was safe and was associated with a statistically significant mortality benefit in the treatment of COVID-19 infection in hospitalized patients. Our findings do not support the current negative recommendations regarding this treatment.

1. Introduction

In March 2020, the pandemic outbreak with SARS-CoV-2 started an unprecedented global health crisis. Following encouraging in vitro data [1–4] and preliminary clinical results, treatment with hydroxychloroquine was recommended in China [5]. Gautret reported a synergistic effect on viral clearance when azithromycin was added to hydroxychloroquine [6–8].

Pending results of clinical trials, off-label administration of low-dose HCQ was accepted as a treatment option for hospitalized COVID-19

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https://doi.org/10.1016/j.nmni.2023.101172
Received 30 January 2022; Received in revised form 19 June 2023; Accepted 4 September 2023
Available online 30 September 2023

patients in Belgium [9]. However, following safety concerns [10] and a lack of benefit in the preliminary results of the RECOVERY trial [11], the authorisation for use of hydroxychloroquine or azithromycin was rescinded from June 10, 2020 onwards [9].

Intriguingly, a national retrospective cohort study of 8075 hospitalized patients later found a significant 32% mortality reduction in patients receiving monotherapy with low-dose hydroxychloroquine versus standard of care [12].

Our hospital adopted a strategy of combination treatment with hydroxychloroquine plus azithromycin for all patients. These patients were not included in the aforementioned analysis. Our patient cohort therefore provides an opportunity to verify these results in a different set of patients. s.

In this article we compare the safety and efficacy outcomes of a single centre cohort of 352 consecutive patients with COVID-19 treated with this combination with the contemporary control group of 3533 patients from the national cohort study receiving standard of care.

2. Materials and methods

2.1. Patients and study design

The study was conducted in AZ Groeninge Hospital in Kortrijk, Belgium. Treatment was proposed for all individuals >18 years who were admitted with positive real-time PCR for SARS-CoV-2 RNA or CT-findings with high probability for COVID-19-infection [13–15]. Data were prospectively collected from March 16 until May 20, 2020 and were analyzed retrospectively.

2.1.1. Hydroxychloroquine treatment group

Diagnosis was based on a positive nasopharyngeal PCR or abnormalities with high probability of COVID-19-infection (Table 1).

Overall, 409 patients were hospitalized because of COVID-19-infection. A total of 370 patients tested PCR-positive, while 39 were PCR-negative, but showed abnormalities with high probability for COVID-19 on CT-scan. 57 patients were excluded from the analysis because they were transferred from another hospital and had first treatment there, or because they didn't receive treatment according to protocol. Eventually 352 patients were included in the analysis (Fig. 1).

2.2. Control group receiving standard of care without hydroxychloroquine

The control group is based on data collection by the Belgian Collaborative Group on COVID-19 Hospital Surveillance (Sciensano) of hospitalized patients with PCR-confirmed COVID-19, initiated on March 14, 2020 and reported up to May 24, 2020, who received standard of care without hydroxychloroquine. The control group consisted of 3533 patients and was described extensively elsewhere [12].

2.3. Clinical, biological and radiological data and follow-up

Demographics (age, sex), chronic conditions (diabetes mellitus, chronic heart disease, hypertension, chronic respiratory disease, (hematological) malignancy, immunocompromised state, cognitive deficit, neurological disease, liver disease, kidney failure, obesity and active smoker) and concomitant use of ACE-inhibitors and Angiotensin II-receptor blockers were documented.

Patients aged >65 years or with at least one of the conditions described above were defined as patient with risk factors.

CRP, Ferritin, D-dimers, LDH, PaO_2, oxygen saturation (<93%) were documented at admission. A low-dose chest CT exam was performed upon admission in 94.65% (n = 336) of patients.

Table 1
Treatment protocol depending on PCR test and CT examination.

	PCR Test		
	PENDING	POSITIVE	NEGATIVE
CT			
- High probability	HCQ + AZ	HCQ + AZ	HCQ + AZ
- Intermediate probability	Wait	HCQ	No treatment
- Low probability	Wait	HCQ	No treatment
- Not compatible	Wait	HCQ	No treatment

2.4. Management

Treatment initially consisted of hydroxychloroquine (2 × 400 mg day 1, 2 × 200mg day 2–5) as a single agent, but was later modified to include azithromycin (500 mg 5 days: <75 years, >75 years: 500 mg on day 1 followed by 250 mg daily for four days) (Table 2).

All patients without contraindications received treatment. All patients underwent an electrocardiogram (ECG) with QT measurement (Bazett's formula) before treatment and after 24 h. ECG's with abnormalities were referred to a cardiologist for further assessment. If QTc (BAZ) was >480 m s, patients were monitored during treatment. If a QTc (BAZ) > 500 m s was present, no HCQ/AZ was started without approval by a cardiologist.

Amoxicillin-clavulanic acid or ceftriaxone were administered when bacterial pneumonia was suspected. The indication for antibiotic treatment was reassessed after 72 h, based on the result of sputum cultures.

Oxygen supplementation was administered as required. Antithrombotic prophylaxis with low molecular weight heparin was administered to patients not on chronic anticoagulation. Patients on chronic anticoagulation were switched to therapeutic dose of low molecular weight heparin. Use of steroids, immunomodulatory treatment or antiviral medication was reserved for critically ill patients in the intensive care unit.

The primary outcome was mortality at 28 days after diagnosis of COVID-19.

2.5. Statistical methods

Demographic characteristics, pre-existing (baseline) conditions at hospital admission, laboratory parameters and outcome were described by treatment group (HCQ versus no-HCQ). Continuous variables are presented with mean and standard deviation or with median and interquartile range (IQR), depending on normality of the data. Categorical variables are presented as percentages. Comparisons between groups are done with the Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. We performed a stratified Cochran-Mantel-Haenszel (CMH) chi-square test for the possible association between treatment and mortality, controlling for age-subgroups [16]. A multiple imputation (PROC MI) was used to handle missing data (Multivariate Normal (MVN) for continuous variables and Fully Conditional Specification 5 F CS) for categorical variables (for details, see supplement 2) [17].

2.6. Ethical considerations

Patients were informed of the off-label character of the prescription of HCQ and AZ prior to receiving treatment. Data were collected retrospectively using the electronic health record. This non-interventional retrospective study was approved by our institutional review board committee (B3962020000025, AZGS2020071). HCQ for COVID-19 treatment was approved off-label for hospital delivery only. Data from the control group receiving standard of care was used thanks to the kind permission of the Belgian Collaborative Group on COVID-19 Hospital Surveillance (Sciensano).

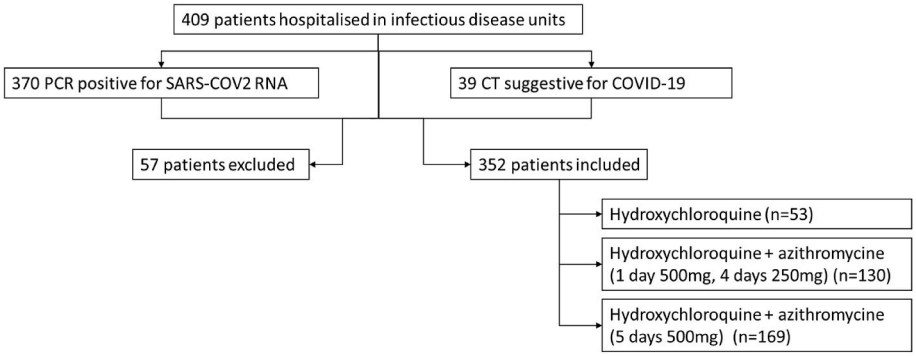

Fig. 1. Inclusion and exclusion flowchart of the treatment group.

Table 2
Baseline characteristics of the patients according to treatment.

	ALL		Therapy 5 days		Therapy <5 days		HCQ		HCQ/AZ (1D 500.4D 250)		HCQ/AZ (5D 500)	
	n = 352		n = 309		n = 43		n = 53		n = 130		n = 169	
	n	%	n	%	n	%	n	%	n	%	n	%
Age												
- Age 0–64 years	138	39.20	129	41.75	9	20.93	14	26.42	12	9.23	112	66.27
- Age 65–74 years	58	16.48	54	17.48	4	9.30	5	9.43	4	3.08	49	28.99
- Age >75 years	156	44.32	126	40.78	30	69.77	34	64.15	114	87.69	8	4.73
Chronic conditions												
- min. 1 chronic condition or >65 y	288	81.82	248	80.26	40	93.02	48	90.57	124	95.38	116	68.64
DNR code												
0 or 1	249	70.74	234	75.73	15	34.88	36	67.92	61	46.92	152	89.94
2 or 3	103	29.26	75	24.27	28	65.12	17	32.08	69	53.08	17	10.06

3. Results

3.1. Patient characteristics

In the treatment group, age was over 65 years in 214 patients (60.79%). At least one chronic condition or age over 65 years was present in 288 patients (81.82%) (Table 2). Patients in the treatment group were younger on average (69.7 vs 73.1 years, $p = 0.0002$) and were less likely to smoke (1.7 vs 10.2%, $p < 0.0001$). Patients in the treatment arm were more likely to be male (53.6 vs 47.9%, $p = 0.0457$) and had more arterial hypertension, liver disease and lung disease (Table 3) (see Table 4).

3.2. Disease severity

Markers for disease severity at baseline were higher in the treatment group, with a higher proportion of patients with PaO_2 <60 mmHg (43.0 vs 28.4%, $p < 0.0001$), lower median PaO_2 (65.6 vs 71.3 mmHg, $p = 0.0002$) and higher average CRP (56.0 vs 50.6 mg/L, $p = 0.0339$) (Table 3).

3.3. Treatment-related characteristics

Combination treatment with HCQ plus AZ was administered in 299 patients (84.94%), while 53 (15.06%) were treated with HCQ alone (Table 2). The administered (age-dependent) dose was azithromycin 500 mg at day 1 and 4 days azithromycin 250 mg in 130 patients (43.48%) and azithromycin 500 mg a day for five days in 169 patients (56.52%).

309 patients (=87.78%) received five days of treatment, whereas 43 patients (=12.22%) received a shorter course at the discretion of the attending physician. Main reasons for treatment interruption were intolerance, ECG changes and conversion to palliative management. All patients receiving at least one dose of HCQ were included for analysis of the treatment group.

Adverse events were observed in 197 patients. Adverse events were mild and were mostly gastrointestinal in nature. One patient had hallucinations. Two patients developed a skin rash.

Patients were monitored for electrolyte disorders and potential medication interactions.

QTc prolongation (>60 m s) was observed in 15 (4.14%) patients, including 2 patients treated with HCQ alone, and 13 patients treated with HCQ-AZ.

Treatment was discontinued because of side effects in 13 patients: four for QTc prolongation (>60 m s), 9 for gastro-intestinal discomfort. One patient developed nonfatal ventricular tachycardia after treatment was completed. No torsade de pointes or sudden death were observed during treatment (Table 5).

Twenty-six (6.7%) patients had a proven bacterial infection but 260 patients (67.53%) received antibiotics upon admission.

3.4. Primary outcome

The average age of death was 84 years. Twenty-three patients (41.38%) died in the Intensive Care Unit. A 'do not reanimate'-order to withhold mechanical ventilation or to discontinue treatment was in effect in 43 deceased patients (72.88%) (Table 6).

In the treatment group, 59 patients died within 28 days (16.76%). In the control group, 916 of 3533 patients died within 28 days (25.93%). For treated patients, there was a statistically significant crude mortality reduction of 0.6464 (95% CI 0.5089–0.8213).

The adjusted common relative risk for mortality after controlling for age was 0.7597 (95% CI 0.6053–0.9534, $p = 0.0097$). Treatment with hydroxychloroquine plus azithromycin was associated with a reduction in mortality in all age groups. There were no fatalities in patients younger than 45 in the treatment group. (Fig. 2).

After multivariable adjustment for comorbid conditions and for CRP and LDH as markers for severity of disease, mortality reduction

Table 3
Overview of baseline patient characteristics (a) and comorbidities (b) for control group and treatment group.

	Control group	Treatment group	*P*-value
	no-HCQ	HCQ	
	(n = 3533)	(n = 352)	
(a) Demographics			
Age			
o Mean. Y±SD	73.1 y ± 16.3	69.7 y ± 15.2	0.0002**
o Median. Y (IQR)	77 y (63–85)	72 y (59–82)	<0.0001**
o Age categories.	n (%)	n (%)	
- 16 y-30 y	72 (2.0)	3 (0.9)	
- 31 y-44 y	175 (5.0)	15 (4.3)	
- 45 y-64 y	695 (19.7)	120 (34.1)	
- 65 y-79 y	1015 (28.8)	96 (27.3)	
- ≥ 80 y	1573 (44.6)	118 (33.5)	
Gender			
o Male	47.9%	53.6%	0.0457
(b) Comorbidities			
Cardiovascular condition	40.9%	43.8%	0.3068
Hypertension	42.8%	56.3%	<0.0001**
Diabetes	22.5%	26.7%	0.0836
GFR<45 ml/min/1.73m^2	16.6%	17.1%	0.8217
Liver disease	2.8%	5.7%	0.0054**
Lung disease	14.6%	20.2%	0.0078**
Neurological disease	12.7%	14.5%	0.3588
Cognitive deficit	17.8%	17.7%	1
Immunocompromised state	2.2%	11.1%	<0.0001**
Malignancy	9.8%	5.4%	0.0054**
Hematological malignancy	2.0%	3.7%	0.0496*
BMI>30 kg/m^2	8.1%	24.5%	<0.0001**
Active smoker	10.2%	1.7%	<0.0001**
Use of ACE-inhibitor	17.5%	17.7%	0.941
Use of angiotensin II-receptor blocker	9.8%	11.2%	0.395
pO_2			
o pO2 <60 mmHg at admission (%)	28.4	43.0	<0.0001**
o mean pO2 at admission (mmHg)	71.3 ± 26.9	65.6 ± 23.4	0.0002*
o median pO2 (mmHg)	68.0 (IQR: 58.0–80.0)	63.2 (IQR: 55.0–71.6)	<0.0001**
LDH (unit/l)	314 (239–442)	314 (257–404)	0.9031
CRP (mg/l)	50.6 (16.0–105.2)	56.0 (27.5–107)	0.0339*

*p < 0.05. **p < 0.001.

Table 4
Time of onset symptoms before admission and CT findings upon admission.

	ALL	
	(n = 352)	
	n	%
Symptoms		
>5 days	183	51.99
≤ 5 days	139	39.49
unknown	30	8.52
CT thorax		
No CT	19	5.40
No abnormalities	11	3.13
Atypical	27	7.67
Indeterminate	47	13.35
Typical	248	70.45

remained significant, with an adjusted OR of 0.619 (95% CI 0.424–0.904).

In both the complete case analysis and the MI model, the beneficial effect of treatment was statistically significant (p = 0.0055 in the MI model, p = 0.0046 in the complete case analysis). The odds ratio for treatment in the MI model is 0.635, (95% CI 0.464–0.875). Patients who did not receive HCQ had a 57% higher risk of death at 28 days (Fig. 3).

To account for other treatment or hospital-related factors (staffing, ICU availability), we compared our treatment group with the contemporary HCQ-treatment group in Catteau [12]. Mortality between treatment groups was not significantly different for HCQ alone (16.76 vs 17.7%, p = 0.6557) or in combination with azithromycin (16.76 vs 18.9% (p = 0.3853).

Table 5
Special considerations during treatment.

	n	%
Potential risk for drug interaction with combined therapy	149	42.33
Hallucination	2	0.57
Skin rash	17	4.83
Gastro-intestal problems	99	28.13
Electrolyte disturbance (dyskalaemia. hyponatraemia)	46	279.17
QTc prolongation (>60 m s)	15	4.26
Ventricular tachycardia or arrhythmia	2	0.57
Cessation of treatment	41	11.65

Table 6
Stratification of clinical outcome in treatment group.

	All	HCQ	HCQ/AZ (a)	HCQ/AZ (b)
	(n = 352)	(n = 53)	(n = 130)	(n = 169)
Clinical outcome				
- Death	59 (16.76%)	10 (18.87%)	38 (29.23%)	11 (6.51%)
- Mean hospitalisation stay (days)	13.00 d	17.66 d	14.81 d	12.77 d
- Hospitalisation >13 d	106 (30.11%)	20 (37.74%)	43 (33.08%)	43 (25.44%)
- Death and DNR 2.3	43 (72.88%)	–	–	–

(a)1D 500.4D 250. (b) 5D 500.

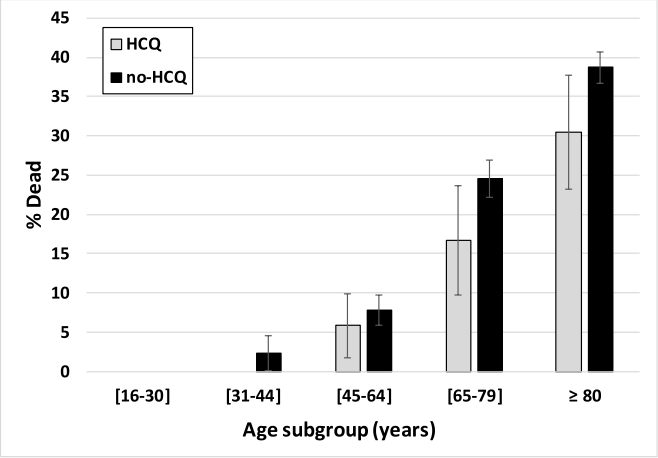

Fig. 2. Association between group (HCQ vs no-HCQ) and mortality (status at 28 days), controlling for age. Treatment with hydroxychloroquine (HCQ) plus azithromycin was associated with a reduction in mortality in all age groups. The adjusted common relative risk for mortality after controlling for age was 0.7597 (95% CI 0.6053–0.9534. p = 0.0097).

4. Discussion

This study has two important findings. First, combination treatment with hydroxychloroquine and azithromycin was safe and generally well-tolerated. In view of safety concerns about cardiac toxicity [18,19], our

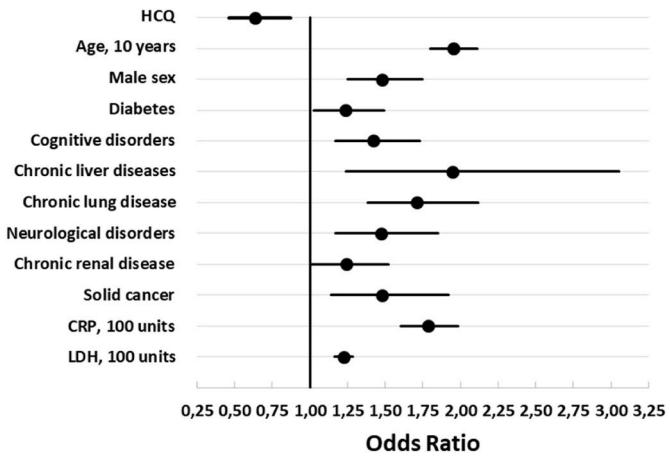

Fig. 3. Risk factors associated with mortality. Figure based on the Multiple imputation model. HCQ = Treatment with hydroxychloroquine.

data are reassuring. Cessation of treatment due to QTc-prolongation was necessary in only 1,1% of patients. No episodes of torsade de pointes or sudden cardiac death occurred during treatment. These findings are in accordance with other studies that found no increase in severe cardiac arrhythmias, even when higher doses of hydroxychloroquine were used [20,21].

Previously hydroxychloroquine was shown to confer cardiovascular protection in long-term users [22].

Second, treatment was found to be associated with a statistically significant 36,5% reduction of mortality. This survival benefit was present across all age groups and remained significant after adjustment for comorbid conditions and disease severity upon admission. This result is remarkable because treatment with hydroxychloroquine was abandoned following the results of the SOLIDARITY and RECOVERY trial, which did not find a clinical benefit [20,21].

Our results are in accordance with several observational trials and large case series reporting survival benefit in patients treated with hydroxychloroquine [12], [23–29]. Other studies found no benefit, but often reserved treatment for severely ill patients [18,19,30].

A potential explanation for the discrepancy between the results in the observational trials and the large randomized trials may be the use of a different dose of hydroxychloroquine.

We and others used a dose of HCQ of 2 × 400mg on day one, followed by 200 mg bid for five days, according to national guidelines. This regimen was shown to achieve therapeutic drug concentrations in lung tissue for up to ten days after treatment interruption [3,31]. Both SOLIDARITY and RECOVERY [20,21] used a fourfold higher total dose, including a loading dose that exceeded the maximum labelled dose of 5 mg/kg by a factor of seven. It can not be excluded that this high dose affected the results, given the concerns of cardiac toxicity [20,21] and the premature interruption of a Brazilian study with a similar high-dose regimen because of excess cardiac toxicity [32].

Other randomized controlled trials with low-dose HCQ were not adequately powered to demonstrate a survival benefit of the magnitude that was seen in our study [33–35]. For example, Dubée [35] found a 44% reduction in 28-day mortality, which did not reach statistical significance.

Our retrospective study has limitations. Retrospective studies are more prone to confounding than randomized controlled trials [13,36] and our study is no exception. There were significant differences between the treatment and the control group, which may influence outcomes. We sought to determine to what extent these differences may have influenced our results.

The most critical difference between treatment groups was age, as the treatment group was 3.4 years younger on average. Yet, the mortality benefit was consistent across all age categories, including octogenarians, making age as a confounding factor unlikely. A mortality benefit was also reported in elderly nursing home residents in France [37].

Patients in the treatment group were less likely to smoke or to have malignancy and more likely to be male, and were more likely to be obese, immunocompromised, to have arterial hypertension, liver disease or lung disease.

Of these factors, four (male sex, hypertension, liver disease and lung disease) were found to be associated with negative outcomes in a multiple imputaton model, thus favouring the control arm. Conversely, solid malignancy was more prevalent in the control group and was also associated with worse outcomes in this model (Fig. 3).

After multivariable adjustment for these and other comorbidities the survival benefit remained statistically significant.

Patients in the treatment group were more likely to present with hypoxemia and had a higher average CRP level than controls. Therefore, lower disease severity is unlikely to account for the observed survival benefit.

All patients that received at least one treatment dose were included in the analysis. While it is unlikely that receiving one dose of treatment has an effect on clinical outcomes, this approach ensures that the outcomes of severely ill patients with incomplete treatment due to rapid deterioration were included in the study results, as well as the outcomes of patients who discontinued treatment with HCQ-AZ due to side effects or ECG abnormalities.

Hospital-related factors like ICU overflow can affect the outcomes of a single centre study. The fact that mortality in our treatment group is not significantly different from the treatment group reported by Catteau [12] (which shares the control group with our study) implies that this is probably not a major factor. Moreover, treatment with hydroxychloroquine remained associated with improved survival in Belgium after taking ICU overflow into account [38]. An indirect effect cannot be excluded, as HCQ was reported to prevent ICU overflow [22].

Another consequence of the consistent results of the treatment groups is that it is unlikely that any non-HCQ treatment is responsible for the observed survival benefit, because this would result in an increased survival difference between HCQ-treated groups in both studies.

While residual confounding can never be fully excluded, we were to the best of our ability unable to identify a confounder that was likely to explain the difference between groups. Therefore, it is very plausible that the observed survival benefit reflects a true treatment effect.

Apart from the synergistic effect on viral clearance from the combination of azithromycin and hydroxychloroquine several other factors may contribute to the observed benefit. Both drugs act as immunomodulators which may prevent the cytokine storm of COVID-19. The antithrombotic effects of HCQ may also be useful in the context of Covid-associated coagulopathy and azithromycin can help prevent bacterial surinfection [39].

Finally, our study reports on outcomes from the first half of 2020, before vaccination became available and before the emergence of new COVID-19 variants. Since that time several drugs, like remdesivir, molnupiravir and nirmatrelvir/ritonavir were approved for the treatment of Covid-19.

It is unclear to what extent our data still apply in the current phase of the pandemic. On the other hand, the efficacy of vaccination and treatment is compromised by the emergence of new variants and the use of novel treatments like nirmatrelvir/ritonavir is expensive. Moreover, their use is limited because of severe medication interactions. Therefore there is a continued need for widely available, effective and affordable treatment. Our study suggests that, despite the controversy surrounding its use, treatment with hydroxychloroquine and azithromycin remains a viable option. The favorable results and reassuring safety data support the need for adequately powered confirmatory randomized controlled trials using low dose hydroxychloroquine plus azithromycin. Given the pandemic emergency it is reasonable to give this treatment the benefit of

the doubt pending the results of these trials or the advent of better treatment options.

Declaration of competing interest

The authors declare they have no conflicting interest to declare.

Acknowledgements

The authors would like to thank Dominique van Beckhoven and Sciensano for their generous cooperation and kind permission to use the Database from the Belgian Collaborative Group on COVID-19 Hospital Surveillance. The use of this dataset made an enormous contribution to the strength of our findings. We also wish to thank all the medical staff, pharmacists, nurses and coworkers of the AZ Groeninge hospital for their hard work and unyielding commitment to our patients in the very difficult conditions that we were confronted with during the first phase of the pandemic. Without their dedication and meticulous work it would have been impossible to perform our data analysis.

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