The Efficacy of Hydroxychloroquine and Azithromycin Combination Therapy on Hospital Mortality in COVID 19 Pneumonia Patients

Abstract

Background/aim: Effective therapeutic approaches for SARS-CoV-2 pandemic are urgently needed. Hydroxychloroquine (HCQ) alone or in combination with azithromycin has been used in several countries, without any clear evidence. This study aimed to determine the effectiveness and safety of hydroxychloroquine as compared to hydroxychloroquine and azithromycin combination in patients with COVID-19 pneumonia.

Materials and methods: This retrospective study evaluated all patients admitted to two university hospitals between 18 March and 20 May 2020 with the diagnosis of COVID-19 pneumonia. Out of 496 patients, 370 met the eligibility criteria and were included in the final analysis. The primary outcome was in-hospital mortality. Secondary outcomes were time to recovery, presence of severe acute respiratory infection (SARI), the requirement for oxygen therapy, and/or mechanical ventilation, length of hospital stay, and adverse events.

Results: A total of 222 patients received hydroxychloroquine and 148 were treated with HCQ and azithromycin combination. The in-hospital mortality rates were similar in the two groups (10.8% vs. 6.8%, respectively, p=0.186). Additionally, the needs for oxygen therapy, invasive mechanic ventilation (IMV) and intensive care unit (ICU) admission

were not different. The rate of the requirement of non-invasive mechanic ventilation (NIV) was higher in patients receiving HCQ plus azithromycin (10.1% vs. 4.5%, p=0.035). Time to recovery was 3.5 days in HCQ and 5.0 days in HCQ plus azithromycin group (p<0.001). The median length of hospital stay was longer in patients with the combination therapy (7.0 vs. 5.5 days, p<0.001). Amongst all patients, only 3 patients developed electrocardiographic changes needing discontinuation of therapy.
Limitations: Observational design of the study is the main limitation.

Conclusions: The present findings suggest that adding azithromycin to HCQ is not associated with any improvement in clinical outcome and mortality in patients with COVID-19 pneumonia and supports the current knowledge not to include azithromycin in the initial treatment of COVID-19.

Keywords: SARS-CoV-2, COVID-19, hydroxychloroquine, azithromycin, mortality, COVID-19 pneumonia

1. Introduction

As of August 30th, more than 24 million people have been infected and more than 838.924 people have lost their lives around the world[1]. In an effort to reduce the severe toll on human lives, several studies have investigated the safety and effectiveness of various drugs used in the treatment. However, as yet, there are few options with good evidence justifying their use.

Hydroxychloroquine (HCQ), the hydroxy- form of antimalarial drug chloroquine, is an FDA-approved immunomodulator used for systemic lupus erythematosus and rheumatoid arthritis [1]. HCQ has been suggested as a potential therapeutic option for SARS-CoV-2 infection, based on former studies showing the antiviral effect of chloroquine against enveloped viruses and SARS-CoV infection [2,3,4]. In-vitro studies also showed that HCQ reduced viral activity by inhibiting virus entry and it affected intracellular mechanisms by increasing endosomal pH and blocking endosome maturation [5,6]. Based on these data and the urgency of the situation, HCQ initially became a reasonable treatment option for SARS-CoV-2 infection. Clinicians were also encouraged by a study which showed that HCQ treatment was associated with a faster virologic conversion [7] This finding, however, could not be replicated in another clinical study [8]. Several other studies reporting on the clinical outcomes of HCQ treatment have appeared within a relatively short period of time, most showing no effect on mortality or recovery rate [8,9,10].

[1] WHO (2020). Coronavirus Disease Dashboard [online]. Website https://covid19.who.int [accessed 30.08.2020]

Azithromycin has frequently been used in combination with HCQ as an in-vitro study demonstrated that, when combined with HCQ, it improved viral clearance [7,11]. On the other hand, both HCQ and azithromycin are known to cause QTc prolongation, which raises safety concerns [12].

Given these equivocal results and concerns about the effects of HCQ and azithromycin on clinical outcomes, the use of these two drugs in SARS-CoV-2 infection remains controversial. Considering the COVID-19 pandemic caused a large impact on healthcare systems, leading to high rates of mortality around the world, appropriate treatment of SARS-CoV-2 infection has utmost clinical importance. In the present study, we evaluated the effectiveness of HCQ and azithromycin combination therapy compared to HCQ alone on hospital mortality and other clinical outcomes in patients with COVID-19 pneumonia.

2. Methods

2.1. Study Population

The participants of this retrospective cohort study were drawn from the charts of two tertiary-care university hospitals. The medical records of all patients admitted with a diagnosis of definite or probable SARS-Cov-2 infection between March 18 and May 2020 were examined using a standard case report form. The study was approved by the local ethics committee of Ege University (approval number: 20-5T/48) and the Turkish Ministry of Health.

2.2. Case Definition

Patients who met definite or probable case definition criteria for COVID-19 pneumonia were included in the study. Patients with positive PCR tests were defined as definite cases. As per the guideline of the Turkish Ministry of Health[2], probable case definition involved the presence of fever, cough and dyspnea, together with radiographic findings compatible with SARS-CoV-2 infection with or without a history of contact with a confirmed case. We had evaluated all study participants one by one with a multidisciplinary team to reach COVID pneumonia. If a subject was not thought to have COVID-19 pneumonia in terms of clinical and radiological findings, this case was excluded from the study. Our COVID multidisciplinary team used a CT-classification system (with 99.0% sensitivity and 87.1% specificity) which has been recently published [13]. Subjects who did not have radiographically confirmed pneumonia were excluded from the analysis.

2.3. Characteristics of the study population, evaluation of disease severity and of clinical outcomes

The following parameters were retrieved from the medical records: demographic characteristics, comorbidities, laboratory and radiographic findings, time to recovery, the length of hospital stay, need for ICU admission, NIV or IMV and mortality status. The severity of disease was classified according to CALL and GRAM scores [14-15]. Subjects were categorized into three risk groups according to CALL scores (4-6 points=Class A

[2] Turkish Ministry of Health, Department of Public Health (2020). COVID-19 Treatment Guideline (in Turkish) [online]. Website https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html [accessed 14.04.2020]

[low progression risk], 7-9 points =Class B [intermediate progression risk], 10-13 points=Class C [high progression risk]). GRAM score, that consists of ten laboratory and clinical variables, also predicts the likelihood of the progression in hospitalized patients with COVID-19 [15]. The presence of SARI was also recorded. SARI was defined as the necessity of hospital admission related to fever, cough and dyspnea, tachypnea, hypoxemia, hypotension, extensive radiologic findings in chest radiology and the changes in consciousness level of a subject with acute respiratory tract infection within last fourteen days[3].

2.4. COVID-19 Treatment Regimen

Patients were treated with regimens recommended by the Turkish Ministry of Health national SARS-CoV-2 infection guideline[3]. All patients were evaluated by a multidisciplinary COVID-19 pandemic team (consisting of members from the departments of pulmonology, infectious diseases, internal medicine, medical microbiology, radiology and cardiology) during the whole diagnostic and treatment process.

Since SARS-CoV-2 infection was an emerging disease and clinical experience accumulated globally at a rapid rate, the national guideline was updated several times

[3]Turkish Ministry of Health, Department of Public Health (2020). COVID-19 Treatment Guideline (in Turkish) [online]. Website https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html [accessed 14.04.2020].

based on the changing evidence. Briefly, HCQ was recommended for patients with a probable and definite SARS-CoV-2 infection. Additional azithromycin treatment was also given at the discretion of the attending physician, weighing on the benefit/risk ratio. Neither medication was given to patients who had a contraindication to or who did not give consent for the treatment. According to guideline recommendation, all patients were monitored by electrocardiogram at baseline and after 2-3 hours of initial dose, HCQ was given 800 mg/day on the first day of treatment, followed by 400 mg/day for four days (a total dose of 2400 mg)[4]. Similarly, azithromycin treatment was initiated with 500 mg/day, followed by a daily dose of 250 mg (up to 5 days). The upper limit of normal was 500 msn for QTc prolongation.

2.5. Primary and secondary outcomes

The primary outcome of the study was in-hospital mortality. The secondary outcomes were time to recovery, the presence of SARI, the requirement for oxygen therapy, and/or mechanical ventilation including both NIV and IMV, length of hospital stay, and adverse events of therapy. Time to recovery was defined as symptom control and resolution of fever (<37.5° C for at least 48 hours).

2.6. Statistical analysis

[4] Turkish Ministry of Health, Department of Public Health (2020). COVID-19 Treatment Guideline (in Turkish) [online]. Website https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html [accessed 30.08.2020]

SPSS (Statistical Package for the Social Sciences Version 24; IBM Corporation, Armonk, NY, USA) program was used for data analysis. Categorical variables were compared by using the chi-square or Fisher's exact test when cell size less than or equal to five. The Mann–Whitney U-test and student's t-test were implemented to compare continuous variables. The independent effect of the treatment on in-hospital mortality was evaluated in multivariate logistic regression models. A purposeful selection method was used to include a subset of variables which were considered to be clinically relevant in order to adjust for confounders in the regression model. Adjusted odds ratio (OR) were reported for each independent factor. P-value was set at 0.05 two-tailed for statistical significance.

3. Results

3.1. Patients

A total of 496 subjects were admitted to the inpatient unit with a diagnosis of probable or definite COVID-19 pneumonia. Thus, a total of 222 subjects treated with HCQ alone and 148 subjects who received HCQ and azithromycin combination were included in the analysis (Figure 1). The mean age (± SD) was 61.2 ± 18.1 years and 49.7% of patients were female. HCQ and combination therapy groups significantly differed in terms of age (64.5 ± 18.9 vs. 56.3 ± 15.8 years, respectively, $p< 0.001$) and sex (54.5% female vs. 42.6% female, respectively, $p=0.024$). Of 370, 69.5% of the subjects had a positive PCR test result for COVID-19. The median duration of symptoms was 4.0 days (Q1-Q3, 2.0-7.0 days) in the study population and there was not any significant difference between treatment arms ($p=0.327$).

3.2. Comorbidities and medications

The smoking status and frequencies of comorbidities were similar in the two groups, except that hypertension was more prevalent in HCQ group than combination therapy group (48.6% vs. 37.8%, p=0.040) (Table 1). Similarly, there was no difference in the use of an angiotensin-converting enzyme (ACE) inhibitors, angiotensin 2 receptor blockers (ARB), antidiabetic medications and inhaled corticosteroids (Table 1).

With regards to the presenting symptoms, fever and dry cough were more frequent among patients receiving HCQ plus azithromycin than patients treated with HCQ alone (For fever, 45.5% vs 68.9%, respectively, p<0.001; for dry cough, 37.8 % vs 50.7%, respectively, p=0.015).

3.3. Clinical and laboratory findings at the time of admission

The clinical signs were similar between the two groups at the time of admission (Table 2). There was also no significant difference in laboratory findings, except that the neutrophil counts and the neutrophil-to-lymphocyte ratio were significantly higher and alanine transaminase (ALT) levels were lower in the HCQ group (Table 2).

3.4. Other supportive therapies

Of 370, 23.8% of the subjects were treated with beta-lactam antibiotics, 26.2% of the individuals received quinolone antibiotics, and 47.3% of the subjects were given oseltamivir. Beta-lactam antibiotic use did not differ between treatment groups while quinolones were more frequently used in the HCQ group (For beta-lactam antibiotics, HCQ= 24.3% vs. HCQ+azithromycin= 23.0%, p=0.765; for quinolones, HCQ= 35.1% vs. HCQ+azithromycin=12.8%, p<0.001, respectively). Additionally, oseltamivir was more commonly given to the combination therapy group (p<0.001). 9.2% of the subjects also received systemic corticosteroids and 63.5% of all invidivuals were given low-molecular-weight heparin. Systemic corticosteroid usage was similar between treatment arms, while low-molecular-weight heparin was more commonly used in the HCQ group (For, systemic corticosteroids, HCQ= 9.5% vs. HCQ+azithromycin= 8.8%, p=0.826; for low-molecular-weight heparin, HCQ=74.8% vs. HCQ+azithromycin= 46.6% p<0.001, respectively).

3.5. The severity of the disease

CALL and GRAM scores were calculated to assess the severity of the disease (Table 2). The mean CALL score was higher in the HCQ group than in the combination therapy group (8.5 ± 2.6 vs.7.8 ± 2.5, respectively, p=0.012) (Table 2). The GRAM score was also higher in the HCQ group (116.1± 37.4 vs. 105.8 ± 33.4, respectively, p=0.022).

3.6. In-hospital mortality

The in-hospital mortality rate of the whole study population was 9.2%. There was no difference in terms of all-cause in-hospital mortality rates between the two study groups (HCQ 10.8% vs. combination therapy 6.8% p=0.186; Table 3) The mortality rate increased in relation to CALL score severity classes (0% in Class A, 6.1% in Class B and 21.3% in Class C) (Table 4).

In multivariate logistic regression analysis, the presence of SARI was found associated with increased mortality risk (OR=53.97, 95 % CI:7.06-412.50) (Table 5).

3.7. Secondary outcomes

The two groups had similar rates of need for IMV and ICU admission. However, NIV support was more frequently needed in patients receiving HCQ plus azithromycin (4.5% vs. 10.1 %, p=0.035). The median time to recovery and the length of hospital stay was significantly longer in the combination therapy group than HCQ group (Table 3).

QTc prolongation was observed in 11 patients (4 patients in the HCQ group vs. 7 patients in the combination therapy group). Three patients receiving combination therapy developed electrocardiographic changes necessitating discontinuation of therapy. 2.97%,

4. Discussion

This study showed that adding azithromycin to hydroxychloroquine is not associated with any improvement in mortality in patients with COVID-19 pneumonia. On the contrary, patients treated with the combination therapy had longer times to recovery and lengths of hospital stay, possibly because patients who were older and who had comorbidities were

less likely to receive the combination therapy due to concerns of increased risk of arrhythmias. Because there was no control group, these data cannot be used to comment on the effectiveness of HCQ therapy; however, the findings clearly show that combining HCQ with azithromycin provides no additional clinical benefit.

There are relatively few data on the effectiveness and safety of the HCQ-azithromycin combination. In a retrospective analysis, Magagnoli and colleagues (2020) investigated the effect of three treatment regimens (HCQ alone, HCQ + azithromycin regimen, azithromycin alone vs. no treatment) on mortality [16]. They found that, compared with patients who did not receive any treatment, the risk of all-cause mortality was higher in patients receiving HCQ (HR:1.83, 1.26-2.89), but similar in patients receiving the combination treatment (HR: 1.31, 0.80-2.15). In another retrospective, observational study, Rosenberg et al (2020) compared the mortality rates in four treatment regimens (HCQ alone, HCQ and azithromycin, azithromycin alone and control groups) [17]. The overall mortality rates were similar in all groups; however, the study did not exclude patients with normal chest imaging findings and patients receiving HCQ with or without azithromycin had more severe disease and more frequently had diabetes mellitus, making it difficult to draw any conclusions on the effectiveness of the treatments.

It is frequently argued that starting hydroxychloroquine treatment with or without azithromycin early in the disease course may be more effective in controlling the course of the infection. However, the randomized controlled study by Cavalcanti et al. investigated the effectiveness of hydroxychloroquine alone or in combination with azithromycin in mild-to-moderate COVID-19 and found no benefit of either treatment on the clinical status of the patients at 15 days [18].

The in-hospital mortality rate of the whole study group was 9.2%. In the existing literature, there have been varying numbers of mortality rates across different studies. Li and colleagues (2020) found the overall fatality rate as 5% in the meta-analysis of 10 studies [19]. A recently published meta-analysis of 45 studies, including patients from ward and ICU, reported in-hospital mortality as 12.0% but heterogeneity was high among the studies depending on the severity of disease across study populations [20].

It was observed that CALL and GRAM scores were higher in the HCQ group than in the HCQ plus azithromycin receiving patients. Although CALL and GRAM scores were lower in the combination therapy group, we think that this was primarily due to the age difference between groups. In fact, the patients in the combination therapy group had clinically more severe pneumonia with a higher (but statistically non-significant) rate of SARI. Moreover, these patients needed NIV more and sooner than HCQ group. The rationale for the decision of combination therapy in this patient population was under the discretion of the clinician and was possibly based on younger age, with low risk of side effects, and on disease severity. As a result, one may argue sufficiency of CALL and GRAM scores for predicting severe disease which, we believe, merits future research.

The safety of HCQ, particularly when combined with azithromycin, has been a major source of concern. Of the patients with COVID-19 treated with HCQ, 12% were reported to reach critical QTc prolongation. Changes in QTc were highest in patients who received combination treatment with azithromycin [21, 22]. However, this study, reflecting the real-life experience in two tertiary care centers, did not reveal any significant cardiac hazard. Thus, as was done at these centers, it would be prudent to screen the patients for risk of arrhythmia with a detailed clinical history (including prior history or use of anti-arrhythmic agents, presence of other risk factors causing QTc prolongation) and a

baseline ECG and limit the use of HCQ with or without azithromycin to patients without any significant risk.

The study has several limitations. First, as previously acknowledged, there was no control group which received usual care. This stems from the fact that the national guideline-recommended that all inpatients be given hydroxychloroquine. Thus, it is not possible to evaluate the effectiveness of the individual drugs. Second, the study was not prospective and randomized, which resulted in differences in demographic and clinical characteristics of the two treatment groups. However, the patients who received HCQ alone appeared to be older and to have more severe disease, as reflected from the CALL and GRAM scores, possibly due to consideration of the increased risk of cardiac adverse events with combination therapy in such patients. Yet, the clinical outcomes were worse in patients receiving the combination therapy. Strengths of the study also have to be discussed when to interpret the results. All patients were evaluated by multidisciplinary teams in two university hospitals. Moreover, side effects were monitored meticulously, therefore, the present study results reflect the safety of medications in patients with COVID 19 pneumonia.

In conclusion, the current study did not demonstrate any significant benefit from combining azithromycin with hydroxychloroquine and support the current recommendation in the updated national guideline not to include azithromycin in the initial treatment of COVID-19[5]. The findings of this study do not provide any evidence on the effectiveness of HCQ treatment. As HCQ is still recommended as a first-line agent in the updated national guideline, controlled studies need to be performed to evaluate the

[5] (Turkish Ministry of Health, Department of Public Health (2020). COVID-19 Treatment Guideline (In Turkish) [online]. Website https://covid19bilgi.saglik.gov.tr/tr/covid-19-rehberi.html [accessed:31.07.2020]).

validity of this recommendation, considering HCQ has not been shown to provide any clinical benefit in several studies.

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448 Table 1: Characteristics of the patients with COVID-19 pneumonia

	Total, n=370	HCQ group, n=222	HCQ+azithromycin group, n=148	t / χ^2	P
Age, years, mean ± SD	61.2 ± 18.1	64.5 ± 18.9	56.3 ± 15.8	4.5	**<0.001**
Sex, female, n (%)	184 (49.7)	121 (54.5)	63 (42.6)	5.1	**0.024**
Smoking status, n (%) [a]				0.1	0.946
Non-smoker	84 (56.0)	49 (55.1)	35 (57.4)		
Former smoker	54 (36.0)	33 (37.1)	21 (34.4)		
Current smoker	12 (8.0)	7 (7.9)	5 (8.2)		
Comorbidities, n (%)					
Hypertension	164 (44.3)	108 (48.6)	56 (37.8)	4.2	**0.040**
Coronary artery disease	40 (10.8)	26 (11.7)	14 (9.5)	0.5	0.494
Congestive heart failure	21 (5.7)	14 (6.3)	7 (4.7)	0.4	0.521
Diabetes	73 (19.7)	42 (18.9)	31 (20.9)	0.2	0.631
COPD	22 (5.9)	14 (6.3)	8 (5.4)	0.1	0.720
Asthma	21 (5.7)	12 (5.4)	9 (6.1)	0.1	0.783
Malignant disease					
Remission	13 (3.5)	10 (4.5)	3 (2.0)	1.6	0.205
Active cancer	18 (4.9)	15 (6.8)	3 (2.0)	4.3	**0.038**
Treatments, n (%)					
ACE inhibitors	43 (11.6)	27 (12.2)	16 (10.8)	0.2	0.691
ARBs	38 (10.3)	25 (11.3)	13 (8.8)	0.6	0.442
Insulin	19 (5.1)	10 (4.5)	9 (6.1)	0.5	0.501
Oral antidiabetics	45 (12.2)	28 (12.6)	17 (11.5)	0.1	0.745
Inhaled corticosteroids	16 (4.3)	10 (4.5)	6 (4.1)	0.0	0.835
Sign and symptoms, n (%)					
Fever (BT ≥ 37.5°C)	203 (54.9)	101 (45.5)	102 (68.9)	19.7	**<0.001**
Dry cough	159 (43.0)	84 (37.8)	75 (50.7)	6.0	**0.015**
Dyspnea	111 (30.0)	65 (29.3)	46 (31.1)	0.1	0.711

Note ACE=Angiotensin-converting-enzyme, ARB=Angiotensin 2 receptor blocker, BT= Body temperature, COPD=Chronic Obstructive Lung Disease, HCQ=Hydroxychloroquine

[a] This variable was available for 150 cases.

Table 2: Clinical and laboratory findings of the patients with COVID-19 pneumonia

	n	Total sample	n	HCQ group	n	HCQ+azithromycin group	t / Z	p
Clinical signs								
Heart rate, median (IQR), bpm	326	90.0 (81.0-103.3)	184	90.0 (81.0-104.8)	142	90.5 (81.8-102.3)	0.9	0.358
Respiratory rate, median (IQR)	282	20.0(20.0-22.0)	153	20.0 (18.0-22.5)	129	20.0 (20.0-20.5)	0.2	0.870
MAP, median (IQR), mm Hg	330	93.3(86.7-101.4)	191	95.0 (86.7-105.7)	139	92.3 (86.0-99.7)	1.9	0.055
Laboratory values								
Neutrophil, median (IQR), 10^3/Ul	367	4.0 (2.8-6.2)	219	4.2 (2.8-6.5)	148	3.7 (2.7-5.4)	2.2	**0.031**
Lymphocytes, median (IQR), 10^3/Ul	367	1.2 (0.9-1.7)	219	1.2 (0.8-1.7)	148	1.2 (0.9-1.7)	0.8	0.435
Neutrophil-lymphocyte ratio	367	3.2 (2.0-5.6)	219	3.4 (2.1-5.9)	148	2.8 (1.9-5.2)	2.1	0.036
CRP, median (IQR), mg/L	360	33.3 (11.2-82.9)	216	33.3 (11.1-89.7)	144	33.1 (12.3-72.0)	0.6	0.577
Procalcitonin, median (IQR), ng/ml	278	0.06 (0.04-0.12)	186	0.06 (0.03-0.12)	92	0.06 (0.04-0.11)	0.3	0.774
LDH, median (IQR), U/L	288	238 (192-320)	179	232 (183-315)	109	242 (210-337)	1.9	0.054
Ferritin, median (IQR), ng/ml	231	196 (80-387)	170	171 (71-366)	61	250 (141-473)	1.9	0.054
Troponin, median (IQR), ng/L	305	8.8 (5.5-13.9)	201	7.5 (5.5-14.6)	104	13.0 (5.5-13.0)	1.7	0.083
ALT, median (IQR), U/L	355	22.0 (15.0-35.0)	212	21.0 (14.0-35.0)	143	25.0 (16.0-37.0)	2.4	**0.016**
D-dimer, median (IQR), ug/ml,	336	0.7 (0.4-1.3)	205	0.8 (0.4-1.5)	131	0.6 (0.4-1.0)	1.9	0.058
CALL Score, mean± SD [a]	328	8.2 ± 2.6	210	8.5 ± 2.6	118	7.8 ± 2.5	2.5	**0.012**
CALL Class, n (%)	328		210		118		5.0	0.084
Class A		88 (26.8)		51 (24.3)		37 (31.4)		
Class B		132 (40.2)		81 (38.6)		51 (43.2)		
Class C		108 (32.9)		78 (37.1)		30 (25.4)		
GRAM Score, mean ± SD [b]	271	112.1 ± 36.2	165	116.1 ± 37.4	106	105.8 ± 33.4	2.3	**0.022**
Presence of SARI, n (%)	369	135 (36.6)	222	73 (32.9)	147	62 (42.2)	3.3	0.070

Note ALT=alanine aminotransferase, CRP=C-reactive protein, HCQ=Hydroxychloroquine, IQR= interquartile range, LDH= Lactate dehydrogenase, MAP=Mean arterial pressure, SARI= Severe acute respiratory infection

[a] CALL score was calculated based on the findings of the study by Ji et al., 2020. Class A= 4-6 points, Class B=7-9 points, Class C=10-13 points.

[b]COVID-GRAM score was proposed by Liang et al., 2020

Table 3: Treatments and clinical outcomes of the patients with COVID-19 pneumonia

	n	Total sample	n	HCQ alone	n	CT	t / Z / χ^2	p
Length of stay, median (IQR)	365	6.0 (4.0-11.0)	220	5.5 (3.0-10.0)	145	7.0 (5.0-13.0)	4.1	<0.001
Time to recovery, median (IQR)	365	4.0 (2.0-9.0)	220	3.5 (1.0-8.0)	145	5.0 (3.0-11.0)	4.1	<0.001
Favipiravir treatment, n (%)	370	84 (22.7)	222	43 (19.4)	148	41 (27.7)	3.5	0.061
Tocilizumab treatment, n (%)	370	21 (5.7)	222	9 (4.1)	148	12 (8.1)	2.7	0.099
Convalescent plasma, n (%)	370	4 (1.1)	222	2 (0.9)	148	2 (1.4)	FT	1.0
Oxygen therapy, n (%)	369	134 (36.3)	222	72 (32.4)	147	62 (42.2)	3.6	0.057
Noninvasive ventilation n (%)	370	25 (6.8)	222	10 (4.5)	148	15 (10.1)	4.7	0.035
Invasive mechanic ventilation, n (%)	370	37 (10.0)	222	20 (9.0)	148	17 (11.5)	0.6	0.436
Time to progression to O2, median (IQR)	130	0.0 (0.0-2.0)	69	1.0 (0.0-2.0)	61	0.0 (0.0-3.0)	0.4	0.700
Time to progression to NIV, median (IQR)	25	4.0 (2.0-5.5)	10	5.0 (0.8-6.5)	15	3.0 (2.0-5.0)	0.3	0.779
Time to progression to IMV median (IQR)	37	5.0 (3.0-9.0)	20	6.5 (3.5-9.8)	17	4.0 (2.5-5.0)	2.1	0.039
ICU admission, n (%)	369	57 (15.4)	221	29 (13.1)	148	28 (18.9)	2.3	0.131
ICU-free day, median (IQR)	57	3.0 (1.0-5.5)	29	5.0 (1.0-8.5)	28	3.0 (2.0-5.0)	1.0	0.330
Hospital mortality, n (%)	370	34 (9.2)	222	24 (10.8)	148	10 (6.8)	1.7	0.186

Note ICU= Intensive care unit, IQR= Interquartile range, IMV=Invasive mechanic ventilation, HCQ= hydroxychloroquine, NIMV=non-invasive mechanic ventilation

Table 4: Mortality rates between treatment groups according to CALL Risk Groups

	n	Total sample	n	HCQ alone	n	CT	χ^2	*p*
CALL risk groups [a], n (%)								
Class A	88	0 (0.0)	51	0 (0.0)	37	0 (0.0)	-	-
Class B	132	8 (6.1)	81	7 (8.6)	51	1 (2.0)	FT	0.151
Class C	108	23 (21.3)	78	15 (19.2)	30	8 (26.7)	0.7	0.398

[a] CALL score was calculated based on the findings of the study by Ji et al., 2020. Class A= 4-6 points, Class B=7-9 points, Class C=10-13 points.

Table 5: Logistic regression analysis for the mortality including SARI and medications used during clinical follow-up

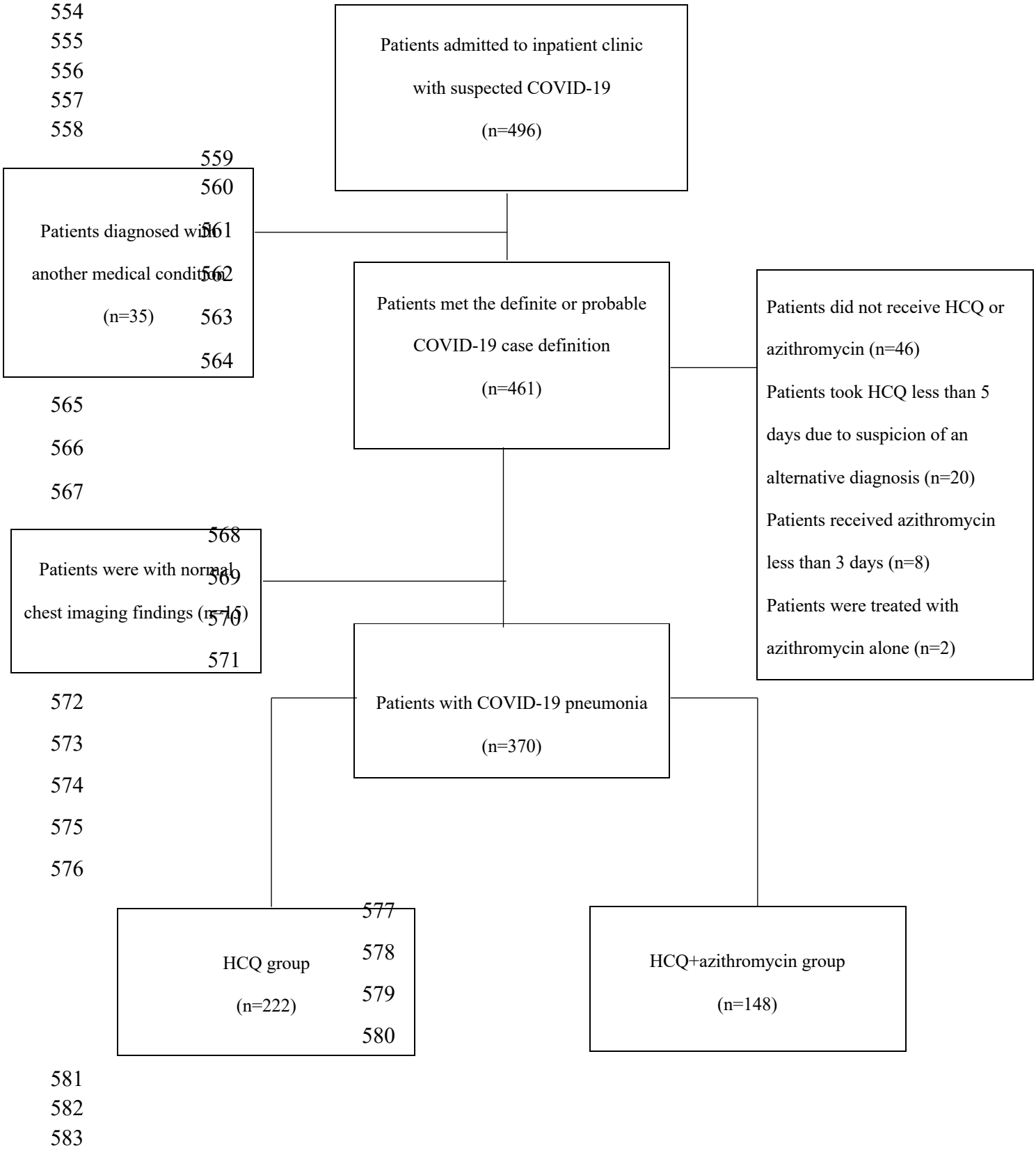
[a] Adjusted odds ratio was calculated for males. Female sex was referent.

	B	SE	p	OR	95 % CI
Age	0.07	0.02	**<0.001**	1.08	1.04-1.12
Sex [a]	0.35	0.45	0.439	1.42	0.58-3.46
Hypertension	-0.04	0.49	0.934	0.96	0.37-2.50
SARI [b]	3.99	1.03	**<0.001**	**53.97**	7.06-412.50
Treatment group [c]	-0.50	0.49	0.312	0.61	0.23-1.59

[b] SARI= Severe acute respiratory infection

[c] Adjusted odds ratio was calculated for the combination therapy. Hydroxychloroquine alone group was referent.

Figure : Flow chart of the study



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