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Features of COVID-19 adult patients and the treatment in Indonesia: a retrospective cohort study

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ABSTRACT

Background: Coronavirus disease of 2019 (COVID-19) is a new disease that causes clinical symptoms that vary from mild to severe. As a new disease, there is no standard treatment for the disease. Several drugs are used to treat COVID-19, most of which were previously used for other diseases, and the efficacy in COVID-19 is not yet known. This study aimed to evaluate COVID-19 therapy in the early phase of the pandemic.

Methods: In this study, we evaluate data on the characteristics of hospitalized COVID-19 patients in several hospitals in Indonesia from March until December 2020. We also evaluate the therapy given and the results of the therapy.

Results: Most hospitalized patients in this study were mild to moderate COVID-19 patients. The most common combination therapy was chloroquine/ hydroxychloroquine + Azithromycin (79.4%). A small number of patients received chloroquine/ hydroxychloroquine without Azithromycin (9.3%), and only a few did not get chloroquine/ hydroxychloroquine therapy (10.8%). The clinical outcome appeared to be better in the chloroquine/ hydroxychloroquine + azithromycin group than in the other groups. The mortality rate was lower in the chloroquine/ hydroxychloroquine + azithromycin group (2.6%) compared to those in the chloroquine/ hydroxychloroquine group (52%) and the group without chloroquine/ hydroxychloroquine (38%). However, the chloroquine/ hydroxychloroquine + azithromycin group had better baseline characteristics and received more additional medications, such as oseltamivir, corticosteroid, and levofloxacin, rather than levofloxacin, the other groups.

Conclusion: Hospitalized COVID-19 patients in Indonesia from March until December 2020 mostly had mild to moderate COVID-19. Most of them received treatment combinations consisting of chloroquine/ hydroxychloroquine and Azithromycin. The most common combination therapy for hospitalized COVID-19 patients was chloroquine/ hydroxychloroquine + Azithromycin. The clinical symptom improvement was seen mainly in this group.

Keywords: COVID-19, Hospitalized patient, Indonesia, Chloroquine/ Hydroxychloroquine, Azithromycin.
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INTRODUCTION

The disease caused by SARS-CoV-2, known as Coronavirus Disease of 2019 (COVID-19), was initially discovered in Hubei Province, the Republic of China, around December 2019. Since then, the disease has spread rapidly worldwide.[1] Infection of SARS-CoV-2 can cause a broad spectrum of disease severity, ranging from asymptomatic infection, mild upper respiratory tract infection, severe viral pneumonia, respiratory failure, organ failure, and death.[2] Several studies have demonstrated the clinical features of some patients with SARS-CoV-2.[3] Of the 44,672 patients confirmed as COVID-19 patients in China, nearly 5% had severe disease conditions, and nearly 50% of patients had severe conditions finally died. The case fatality rate of COVID-19 is greater than the case fatality rate of the common cold.[4] Even after one year of the pandemic, the virus still has a devastating effect. Therefore, effective and safe therapy is urgently needed to overcome this disease.

Most drugs used to treat COVID-19 are drugs developed for other diseases. During this emergency, they are approved to be used to treat COVID-19. Since the outbreak's start, several medications have been used to treat patients with COVID-19, namely Chloroquine (CQ)/ Hydroxychloroquine (HCQ), Azithromycin Oseltamivir, Levofloxacin, and Corticosteroids.[5,6] The therapy regimen for COVID-19 varied among countries in the early phase of the COVID-19 pandemic. Guideline in China recommended

using Alpha-interferon, Lopinavir/Ritonavir, Ribavirin, Chloroquine phosphate, and Abidol as antiviral for COVID-19.[7] In Belgium, the therapy regimen for COVID-19 on March 19, 2020, included Remdesivir, Lopinavir/Ritonavir, and Chloroquine/Hydroxychloroquine.[8] The therapy regimen for COVID-19 in Italia in March 2020 also included some antivirals such as Lopinavir/Ritonavir, Darunavir/Ritonavir, Remdesivir, and antimalarial, turning into an antiviral, Chloroquine.[9] Treatment guidelines for COVID-19 during the early COVID-19 pandemic in Indonesia also included some repurposed drugs for COVID-19 treatment such as Remdesivir, Favpiviravir, and Chloroquine/Hydroxychloroquine, Azithromycin, Lopinavir/Ritonavir, and Oseltamivir.[10]

However, despite their intensive use, a lack of evaluation has been done regarding using those medications for COVID-19. This study will describe the features of hospitalized COVID-19 patients and the treatment at several hospitals in Indonesia.

METHODS

This study was a retrospective cohort study. We collected random medical records of COVID-19 patients admitted to hospitals in Yogyakarta, Banjarmasin, and Solo from March until December 2020. The inclusion criteria were hospitalized COVID-19 patients aged 18 years old. They were excluded if no Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) result was available, death or discharge from hospital before treatment, and the medical record was not complete. The medical records were checked for their completeness and then further evaluated. Demographic data (age and gender), clinical characteristics (vital signs, comorbidities), swab PCR results, laboratory findings, chest X-rays, supplemental oxygen requirement, length of stay in the hospital, and treatment regimens were retrieved from medical records in each hospital.

The data were analyzed using SPSS version 26. Descriptive analysis was used to describe the characteristics of hospitalized COVID-19 patients and is displayed in a table of subject characteristics. The table presents data in the form of means with standard deviation (including age and vital signs data), and categorical data are presented in proportions. The difference in outcome between therapy groups was evaluated using Pearson's chi-square method when data were categorical. If the data is in the form of a mean, it is analyzed first to determine whether the data is normally distributed (homogeneous) or not. If the data is normally distributed, parametric analysis with One-Way ANOVA is used, but non-parametric analysis using the Kruskal-Wallis test is used if the data is not normally distributed. Statistical significance was determined with a p-value <0.05. The Tukey posthoc analysis was carried out to determine which variables had significant differences.

RESULT

After receiving ethical approval, the data were collected from 4 hospitals in 3 different cities in Indonesia, namely Yogyakarta, Banjarmasin, and Solo. Two hundred and fourteen medical records of hospitalized COVID-19 patients during March 2020-December 2020 were collected and analyzed for this study. Fourteen of them were excluded due to the unavailability of the swab real-time PCR test result during hospitalization, and 6 of them were dead before even getting the treatment. Figure 1 presents the patient disposition.

The average patient age was 40.36 ± 12.97 years old. More male patients than female patients (55.2% vs. 44.8%) were admitted to the hospital with COVID-19. The three most common comorbidities in those patients are hypertension (15.9%), Diabetes Mellitus (14.43%), and obesity (3.61%). The mean blood pressure, heart rate, respiratory rate, and temperature are still within the normal range. Most of them did not need supplemental oxygen (52.4%). The leucocyte counts were normal. However, the percentage of the neutrophil count was high (69.58%). The radiographic findings show abnormality in more than half of the patients (69.6%).

Five primary medications were used to treat hospitalized COVID-19 patients: Azithromycin, CQ/HCQ, oseltamivir, lopinavir/ritonavir, and levofloxacin. Here, we report CQ/ HCQ and Azithromycin-based treatment which consists of CQ/ HCQ + Azithromycin (79.4 %), CQ/ HCQ only (9.3%), and No CQ/ HCQ/ azithromycin (10.8%). Table 1 shows the baseline characteristics of the hospitalized COVID-19 patients included in this study.

Most of the medications are given in combination. Figure 2 shows the combination of the drug given.

Only 21 hospitalized COVID-19 patients in our study did not receive CQ/ HCQ. Those who received CQ/ HCQ have mostly received it with other medications. Our study's most common medication combination given to the hospitalized COVID-19 patient was CQ/ HCQ + Azithromycin (79.4%). Among all who received CQ/ HCQ + Azithromycin, 131 (67.52%) also received oseltamivir, 48 (24.74%) also received levofloxacin, and 11 (5.67%) received lopinavir/ritonavir. Only 14 patients did not receive CQ/HCQ in their treatment combination, and seven patients did not receive any medication.

There were no significant differences in terms of the mean of age, percent of gender, and comorbidities between CQ/ HCQ + Azithromycin, CQ/ HCQ, and no CQ/ HCQ/azithromycin group. However, the heart rate is significantly higher in the no CQ/ HCQ/ azithromycin group than in others. The respiratory rate was the highest in CQ/ HCQ group. The erythrocytes count and hemoglobin level are the highest in CQ/ HCQ+ azithromycin group. The

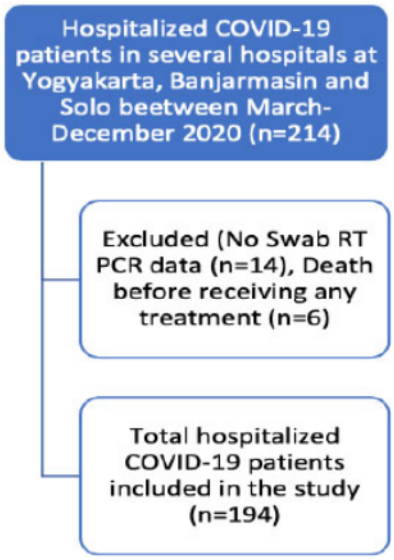

Figure 1. Patient disposition.

Table 1. Subject Characteristics.

Characteristics	Numbers (n=194)
Age, year (Mean ± Std. Deviation)	40.63 ± 12.97
Gender, n (%)	
Male	107 (55.2)
Female	87 (44.8)
Comorbidities, n (%)	71 (36.6)
Hypertension	31 (15.98)
Diabetes Mellitus	28 (14.43)
Obesity	7 (3.61)
Heart Failure	5 (2.58)
The vital sign (Mean ± Std. Deviation)	
Systolic Blood Pressure (mmHg)	129.78 ± 19.32
Diastolic Blood Pressure (mmHg)	80.41 ± 11.67
Heart rate (bpm)	90.11 ± 16.01
Respiratory rate (bpm)	21.48 ± 3.12
Temperature (°C)	36.67 ± 0.60
Supplemental oxygen requirement, n(%)	
No need	100 (51.54)
Need supplemental oxygen	
Nasal cannula	83 (42.78)
Non-invasive	1 (0.52)
Invasive	6 (3.1)
No data	4 (2.06)
Laboratory findings (Mean ± Std. Deviation)	
Erythrocytes (10^{12}/L)	4.78 ± 0.63
Haemoglobin (g/dL)	13.41 ± 2.15
Haematocrit (%)	39.45 ± 5.21
MCV (fl)	82.65 ± 5.90
MCH (pg)	28.41 ± 2.63
MCHC (g/dL)	34.21 ± 1.40
Leucocytes (10^9/L) (Mean ± Std. Deviation)	9.17 ± 4.99
Eosinophil (%)	1.21 ± 1.60
Basophil (%)	0.47 ± 1.12
Neutrophil (%)	69.58 ± 16.36
Lymphocytes (%)	22.22 ± 11.62
Monocytes (%)	6.63 ± 2.84
Thrombocytes (10^9/L)	292.46 ± 98.01
AST (mg/dl)	67.36 ± 161.93
ALT (mg/dl)	57.40 ± 119.19
Blood Urea Nitrogen (mg/dl)	32.96 ± 39.13
Blood Creatinine (mg/dl)	1.04 ± 1.04
Radiological findings, n (%)	
Abnormal	135 (69.6)
Normal	59 (30.4)
Treatment, n (%)	
Azithromycin	160 (82.47)
Hydroxychloroquine/chloroquine	173 (89.17)
Oseltamivir	131 (67.52)
Lopinavir/Ritonavir	11 (5.67)
Levofloxacin	48 (24.74)
Hydroxychloroquine/chloroquine-based Combination treatment, n (%)	
Hydroxychloroquine/chloroquine + Azithromycin	154 (79.4)
Hydroxychloroquine/chloroquine	19 (9.3)
No Hydroxychloroquine/chloroquine/Azithromycin	21 (10.8)

leucocyte count was significantly higher in the no CQ/ HCQ/azithromycin group than in others. However, the highest neutrophil count was in the CQ/ HCQ group. The AST and ALT levels were the lowest in the CQ/ HCQ + azithromycin group. Serum urea and serum creatinine levels are also the lowest in the CQ/ HCQ + azithromycin group. The percentage of patients who needed supplemental oxygen during admittance to the hospital was the highest in the no CQ/ HCQ group. Oseltamivir was more often given to the patient in CQ/ HCQ group compared to those in other groups. Lopinavir/ Ritonavir was most often given to no CQ/ HCQ group. Table 2 presents the baseline characteristic of the hospitalized COVID-19 patients based on the treatment given.

The treatment outcomes were examined on the 7th and 14th days of the treatment. The average of changes in each outcome parameter of each treatment group is presented in Table 3. The mean change of the respiratory rate was significantly different among treatment groups. The CQ/ HCQ group showed the highest respiratory rate decrease on day 7. Meanwhile, patients in the No CQ/HCQ group showed an increase in respiratory rate on day 7 of treatment. The temperature in CQ/ HCQ group increased on day 7 of treatment. Only those in the CQ/ HCQ + azithromycin group showed decreased temperature and respiratory rate on day 7. The percentage of neutrophil count on day 7 was significantly different among the treatment group. The percentage decrease in the number of neutrophils only occurred in CQ/ HCQ + azithromycin group. The percentage of participants with swab RT-PCR negative conversion was significantly different on day 14 but not on day 7 of the treatment. The negative conversion of swab RT-PCR result is more often found in CQ/ HCQ + azithromycin group.

The comparison of the clinical outcomes in the CQ/ HCQ group between day 0, day 7, and day 14 is presented in Table 4. There was a significant difference in the mean respiratory rate of patients on day 0 vs. day 7 of hospitalization. Initially, the average respiratory rate was high, but the average respiratory rate had decreased significantly (Table 4).

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Characteristics	Numbers (n=194)
Other treatment (miscellaneous), n (%)	
Acetaminophen	60 (30.9)
Corticosteroid	21 (10.8)
Vitamin C	161 (83.0)
Vitamin D	2 (1.0)
Zinc	41 (21.1)

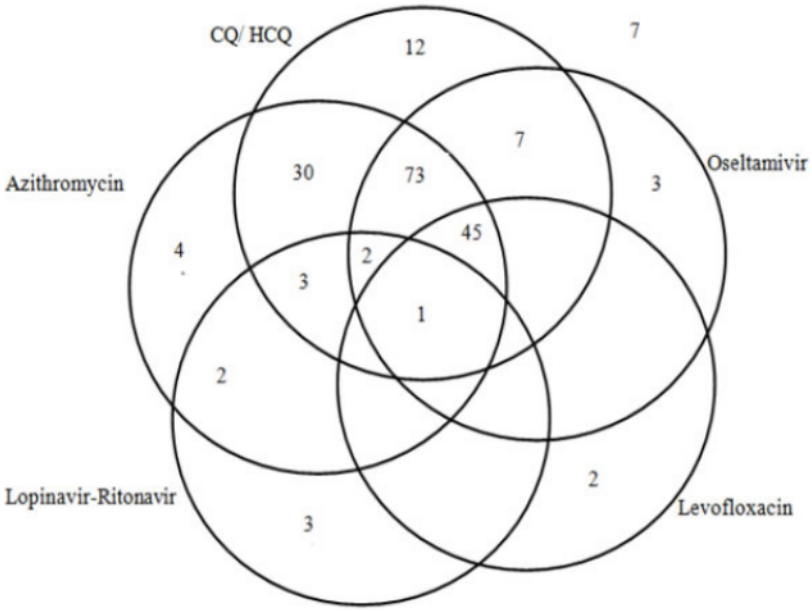

Figure 2. Treatment pattern of hospitalized COVID-19 patient.

The comparison of the clinical outcomes in the No CQ/ HCQ/ azithromycin group between day 0, day 7, and day 14 is presented in Table 5. There was no significant difference between days 0, 7, and 14 in the entire outcome parameters measured.

In the group receiving CQ / HCQ + azithromycin, there were several outcome parameters between day 0, day seven, and day 14 that were different significantly. In this group, there was a decrease in the average systolic blood pressure from day 0 to day 7. However, there was an increase in the average systolic blood pressure from day 7 to day 14. These two differences are significant. There was also a decrease in diastolic blood pressure, heart rate, and temperature level between day 0 to day 7, but only the differences in the heart rate were significant. There was also a reduction in respiratory rate from day 0 to day seven, but the difference was insignificant. The mean respiratory rate declined on the 14th day, and this reduction is statistically significant. Blood creatinine also increases significantly on day seven from day 0.

Regarding the hematological examination result, there was a reduction in the average total erythrocyte count, hemoglobin, hematocrit, and MCHC levels between the first day of admission, day 7, and day 14. Meanwhile, the blood urea level increases significantly from day 0 to day 14 and eosinophil, thrombocytes, and monocytes. No blood creatinine level data was available on day 14 (Table 6).

The comparison of the hospitalization duration (days) and percentage of patients who die during treatment is presented in Table 7.

The longest mean of hospitalization duration was in the No CQ/ HCQ group, and the shortest hospitalization duration was in CQ/ HCQ+ azithromycin group. However, the difference was not statistically significant. The percentage of participants who died during treatment was significantly lower in the CQ/HCQ + azithromycin group than in the other groups.

DISCUSSION

In our study, the average of hospitalized COVID-19 patients was 40.63 years old, and most of them were male (55.2%). Compared to the average hospitalized COVID-19 patient's age in other studies, the average hospitalized COVID-19 patient's age in our study is younger. Previous studies from other countries showed a different mean of the hospitalized COVID-19 patient's age. The average hospitalized COVID-19 patient age in Sofia, Bulgaria, was 52.9 years,[11] in Beijing, China, the average was 44 years,[12] and in Hubei, China, was 57 years.[13] We suggest that the average age difference is due to the difference in the age demographic in Indonesia compared to other countries. In Indonesia, 70.72% of the population is between 15-and 64 years old.[14] Moreover, based on a survey related to behavior to prevent COVID-19 in Indonesia, the older the age, the higher the percentage of compliance to COVID-19 prevention protocol, which means that older people are more obedient to the COVID-19 prevention protocol.[15]

As much as 36.5% of the hospitalized COVID-19 patients in our study have comorbidity. The most common comorbidities in those patients are hypertension (15.9%), diabetes mellitus (14.43%), and obesity (3.61%). This result is the same as those from other countries. A study in Italy found that the three most common comorbidities for COVID-19 are Hypertension, DM type 2, and cardiopathy.[16] Meta-analysis study of COVID-19 patient data also showed that hypertension and diabetes mellitus were included in 3 most common COVID-19 comorbidities.[17]

The hospital admission vital sign data showed a high respiratory rate value (21.48 ± 3.12 breaths per minute) despite abnormal radiologic findings (69,6%). Only 52.4% of them need oxygen

supplementation. This result is similar to the previous study from Japan, which showed that despite >90% of COVID-19 patients showing abnormal radiological findings by chest CT, 47% of the patients do not have any respiratory symptoms.[18] It might be because of the slow progress of the COVID-19 clinical course.

Table 2. Baseline characteristics based on the treatment given.

Characteristics	Treatment Group			P-value
	CQ/HCQ +Azithromycin (n=154)	CQ/HCQ (n=19)	Non-CQ/HCQ (n=21)	
Age (year)	40.90 ± 13.12	39.11 ± 11.01	40.00 ± 13.97	0.898
Male (n)	80	13	14	0.212
Comorbidities (n)				
Hypertension	25	4	2	0.601
Diabetes Mellitus	18	4	6	0.083
Obesity	6	0	1	0.662
Heart failure	5	0	0	0.515
Vital sign				
Systolic blood pressure (mmHg)	129.82 ± 17.85	130.21 ± 22.74	129.05 ± 26.43	0.915
Diastolic blood pressure (mmHg)	80.18 ± 11.84	81.53 ± 10.18	81.05 ± 12.06	0.602
Heart rate (bpm)*	87.82 ± 14.89	94.89 ± 16.29	102.57 ± 17.59	<0.001
Respiratory rate (bpm)**	20.73 ± 2.19	25.21 ± 4.97	23.57 ± 3.59	<0.001
Temperature (°C)	36.65 ± 0.55	36.82 ± 0.82	36.69 ± 0.68	0.825
Laboratory findings				
Erythrocytes (10^{12}/L)*	4.83 ± 0,63	4.66 ± 0.43	4.45 ± 0.73	0.033
Haemoglobin (g/dL)***	13.67 ± 1.92	12.09 ± 3.23	12.75 ± 2.11	0.043
Haematocrit (%)	39.87 ± 5.02	37.99 ± 4.79	37.71 ± 6.49	0.163
MCV (fl)	82.54 ± 5.55	81.80 ± 8.83	84.21 ± 5.14	0.340
MCH (pg)	28.46 ± 2.36	27.93 ± 4.59	28.51 ± 2.22	0.995
MCHC (g/dL)***	34.36 ± 1.31	33.38 ± 1.96	33.89 ± 1.22	0.015
Leukocyte (10^9/L)****	8.95 ± 5.16	8.4 ± 3.27	11.59 ± 4.54	0.007
Eosinophil (%)	1.24 ± 1.61	1.39 ± 1.82	0.78 ± 1.22	0.274
Basophil (%)	0.51 ± 1.23	0.34 ± 0.35	0.23 ± 0.19	0.542
Neutrophil (%)****	68.64 ± 14.66	79.69 ± 10.43	70.25 ± 26.39	0.025
Lymphocytes (%)	22.73 ± 11.59	19.91 ± 13.15	18.51 ± 10.48	0.245
Monocytes (%)	6.76 ± 2.79	5.89 ± 4.18	5.75 ± 2.22	0.377
Thrombocytes (10^9/L)	290.99 ± 92.97	288.89 ± 104.82	307.05 ± 129.22	0.911
AST (U/L)**	38.7 ± 40.54	152.12 ± 328.89	164.65 ± 297.78	0.005
ALT (U/L)**	34.48 ± 30.75	99.71 ± 118.66	159.41 ± 295.78	0.005
Urea (mg/dl)***	28.78 ± 35.99	46.34 ± 43.53	48.27 ± 50.23	0.004
Creatinine (mg/dl)****	0.92 ± 0.99	1.60 ± 1.22	1.25 ± 1.03	0.030
Radiological finding				
Abnormal	102	17	16	0.092
Supplemental oxygen requirement				
Yes (n,%)**	63 (40.9%)	14 (73.7%)	14 (66.67%)	0.002
Concomitant medication (n, %)				
Oseltamivir **	121 (78.6%)	8 (42.1%)	3 (14.3%)	<0.001
Lopinavir/Ritonavir**	6 (3.9%)	0 (0%)	5 (23.8%)	0.002
Levofloxacin	46 (29.9%)	3 (15.8%)	2 (9.5%)	0.077
Acetaminophen	50 (32.5%)	6 (31.6%)	4 (19.0%)	0.460
Corticosteroid	20 (13.0%)	1 (5.3%)	0	0.143
Vitamin C	130 (84.4%)	17 (89.5%)	14 (66.7%)	0.094

Note: n= number of patients
* p< 0.05 between CQ/HCQ+Azithromycin vs. non-CQ/HCQ group
** p< 0.05 between CQ/HCQ+Azithromycin vs. CQ/HCQ and non-CQ/HCQ group
*** p< 0.05 between CQ/HCQ+Azithromycin vs. CQ/HCQ group
**** p < 0.05 among treatment group

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Table 3. Changes in the Parameters in Each Treatment Group.

Characteristics	Treatment Group			P-value
	CQ/HCQ +Azithromycin	CQ/HCQ	Non-CQ/HCQ	
Vital signs				
Systolic Blood Pressure (mmHg)				
Day 7	-7.06 (n=151)	-4.86 (n=14)	-12.82 (n=17)	0.448
Day 14	3.27 (n=75)	0.50 (n=4)	6.33 (n=6)	0.898
Diastolic Blood Pressure (mmHg)				
Day 7	-2.39 (n=151)	-5.71 (n=14)	-6.88 (n=17)	0.244
Day 14	-0.47 (n=75)	3.5 (n=4)	1.33 (n=6)	0.657
Heart rate (bpm)				
Day 7	-6.76 (n=151)	-2.00 (n=14)	-10.76 (n=17)	0.340
Day 14	-0.12 (n=75)	6.5 (n=4)	2.5 (n=6)	0.692
Respiratory rate (bpm)				
Day 7	-0.34 (n=151)	-1.86 (n=14)	1.41 (n=17)	0.007
Day 14	-0.32 (n=75)	1.00 (n=3)	-1.5 (n=6)	0.237
Temperature (C)				
Day 7**	-0.10 (n=151)	2.51 (n=13)	0.04 (n=16)	0.004
Day 14	-0.02 (n=75)	-0.13 (n=4)	0.05 (n=6)	0.778
Laboratory findings				
Erythrocytes (10^{12}/L)				
7th day***	-0.28 (n=60)	-0.09 (n=12)	0.23 (n=15)	0.011
14th day	0.06 (n=41)	0.01 (n=3)	0.15 (n=5)	0.915
Haemoglobin (g/dL)				
7th day***	-0.85 (n=59)	0.11 (n=12)	0.41 (n=15)	0.003
14th day	0.17 (n=41)	0.17 (n=3)	0.50 (n=5)	0.867
Haematocrit (%)				
7th day***	-2.21 (n=60)	0.25 (n=12)	1.35 (n=15)	0.005
14th day	0.73 (n=41)	0.57 (n=3)	1.20 (n=5)	0.964
MCV (fl)				
7th day	0.08 (n=59)	1.66 (n=11)	-0.24 (n=14)	0.340
14th day	0.10 (n=40)	1.17 (n=3)	-0.15 (n=4)	0.478
MCH (pg)				
7th day	-0.28 (n=60)	-0.05 (n=11)	-0.34 (n=13)	0.846
14th day	-0.10 (n=41)	0.57 (n=3)	-0.13 (n=4)	0.569
MCHC (g/dL)				
7th day	-0.38 (n=59)	0.43 (n=11)	-0.74 (n=14)	0.135
14th day	-0.09 (n=41)	0.27 (n=3)	0.00 (n4)	0.892
Leukocytes (10^9/L)				
Day 7	-1.55 (n=60)	2.45 (n=11)	1.53 (n=15)	0.101
Day 14	0.34 (n=39)	-2.37 (n=3)	-3.06 (n=5)	0.167
Eosinophil (%)				
7th day	1.39 (n=60)	1.15 (n=8)	1.86 (n=13)	0.504
14th day	0.73 (n=41)	0.41 (n=3)	-0.32 (n=5)	0.415
Basophil (%)				
7th day	0.17 (n=60)	0.22 (n=8)	0.88 (n=13)	0.880
14th day	0.05 (n=41)	-0.54 (n=3)	0.02 (n=5)	0.136
Neutrophil (%)				
Day 7***	-5.01 (n=30)	0.24 (n=5)	16.13 (n=12)	0.023
Day 14	-2.19 (n=24)	-4.33 (n=3)	-2.60 (n=4)	0.939
Lymphocyte (%)				
Day 7	5.08 (n=59)	1.10 (n=9)	0.51 (n=8)	0.476
Day 14	1.36 (n=39)	6.80 (n=2)	-1.18 (n=5)	0.626

Characteristics	Treatment Group			P-value
	CQ/HCQ +Azithromycin	CQ/HCQ	Non-CQ/HCQ	
Monocytes (%)				
7th day	1.37 (n=58)	2.33 (n=5)	1.58 (n=6)	0.801
14th day	-0.35 (n=40)	-2.10 (n=1)	-2.19 (n=5)	
Thrombocytes (%)				
7th day	57.60 (n=58)	94.91 (n=11)	31.46 (n=13)	0.763
14th day	-42.27 (n=41)	-76.00 (n=3)	-66.25 (n=4)	0.898
AST (U/L)				
Day 7	-12.25 (n=4)	-191.29 (n=7)	-50.00 (n=8)	0.578
Day 14				
ALT (U/L)				
Day 7	15.50 (n=4)	-30.71 (n=7)	-121.38 (n=8)	0.446
Day 14				
Blood Urea (mg/dl)				
Day 7	-5.33 (n=3)	6.85 (n=7)	11.89 (n=7)	0.910
Day 14				
Serum creatinine (mg/dl)				
Day 7	-0.29 (n=3)	0.67 (n=5)	-0.13 (n=7)	0.735
Day 14				
Negative conversion (n,%)				
Day 7	66 (56.4%)	8 (44.4%)	9 (45.0%)	0.456
Day 14	36 (50.0%)	1 (10.0%)	1 (9.1%)	0.002
Radiological finding (n.%)				
Day 7	60 (57.1%)	8 (61.5%)	4 (40%)	0.114
Day 14	5 (12.5%)	1 (25%)	0 (0%)	0.630
Oxygen supplementation (n.%)				
Day 7	6 (9.4%)	3 (20%)	2 (13.3%)	0.463
Day 14	11 (20.4%)	0 (0%)	2 (25%)	0.566
Swab examination result (n,%)				
Conversion on 7th day	66 (56.4%)	8 (44.4%)	9 (45.0%)	0.456
Conversion on 14th day	36 (50.0%)	1 (10.0%)	1 (9.1%)	0.002

Note: n= number of patients

*Changes in the mean respiratory rate on day 7: CQ/HCQ+Azithromycinvs No CQ/ HCQ/ Azithromycin (p=0.046), CQ/HCQ vs. No CQ/ HCQ/ Azithromycin (p=0.005) and CQ/HCQ+Azithromycinvs CQ/HCQ (p=0.145)

**Changes in the mean of temperature on day 7: CQ/HCQ+Azithromycinvs CQ/ HCQ (p=0.003), No CQ/HCQ/Azithromycin vs. CQ/ HCQ (p=0.040) and CQ/HCQ+Azithromycin vs. No CQ/HCQ/ Azithromycin (p=0.979).

***band neutrophil on day 7: CQ/HCQ+Azithromycinvs noCQ/HCQ/ Azithromycin (p=0.017), CQ/HCQ vs. No CQ/HCQ/ Azithromycin (p=0.359), and CQ/HCQ+Azithromycinvs CQ/HCQ (p=0.870).

The complete blood count showed a high value of neutrophils despite the standard value of leukocyte count (69.58%). Neutrophils are involved in innate immunity since they are the first to respond during infection.[19] They have various roles, including phagocytosis to clear pathogens like cell-infected viruses.[20] In COVID-19 cases, neutrophil-to-lymphocyte ratio (NLR) is an essential marker of infection and inflammation, which show inflammatory response in COVID-19 patients.[21]

The three most common medications given to the hospitalized COVID-19 patient in this study were Azithromycin, CQ/ HCQ, and oseltamivir. The most common combination of those medications was CQ/ HCQ + Azithromycin (79.4%). Most of the patients (83%) received vitamin C, 30.9% received acetaminophen, and 10.8% received corticosteroids. In this study, we also compare the baseline characteristic of the patient given different kinds of combination treatment, namely CQ/HCQ + azithromycin, CQ/ HCQ, and No-CQ/ HCQ. Overall, the patients who received CQ/ HCQ + Azithromycin were better than those in the other group in terms of heart rate, respiratory rate, erythrocyte count, hemoglobin, AST, ALT, and serum urea and serum creatinine level.

The poor parameter outcome on day 7 of treatment often happened in the No-CQ/ HCQ group, such as temperature, respiratory rate, and neutrophil percentage. The patient in the No CQ/ HCQ group did not significantly improve all outcome parameters in the before-after analysis. Meanwhile, the patients receiving CQ/ HCQ showed symptom improvement on day 7 of treatment regarding respiratory rate and hemoglobin. The patients in CQ/HCQ + Azithromycin showed symptom improvement after seven days of

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Table 4. The characteristics of subjects in the CQ/HCQ group.

Characteristics	CQ/HCQ group			P-value
	1st day (n=19)	7th day (n=15)	14th day (n=6)	
Vital signs				
Systolic blood pressure (mmHg)	130.21 ± 22.74	130.07 ± 21.59	122.50 ± 23.57	0.758
Diastolic blood pressure (mmHg)	81.53 ± 10.18	78.00 ± 13.54	83.00 ± 16.47	0.586
Heart rate (/minutes)	94.89 ± 16.29	91.07 ± 28.33	86.25 ± 18.71	0.382
Respiratory rate (/minutes)*	25.21 ± 4.97	21.36 ± 3.49	21.00 ± 1.00	0.019
Temperature (°C)	36.82 ± 0.82	36.32 ± 0.33	36.23 ± 0.59	0.147
Laboratory findings				
Erythrocytes (10^{12}/L)	4.66 ± 0.43	4.59 ± 0.56	4.79 ± 0.38	0.790
Haemoglobin (g/dL)	12.09 ± 3.23	12.41 ± 2.02	12.50 ± 2.05	0.985
Haematocrit (%)	37.99 ± 4.79	37.28 ± 5.09	38.17 ± 5.06	0.652
MCV (fl)	81.80 ± 8.83	83.25 ± 7.24	79.53 ± 9.52	0.641
MCH (pg)	27.93 ± 4.59	27.98 ± 3.49	26.17 ± 4.30	0.527
MCHC (g/dL)	33.38 ± 1.96	33.51 ± 1.82	32.77 ± 1.72	0.657
Leukocytes (10^9/L)	8.4 ± 3.27	10.39 ± 7.42	5.47 ± 1.82	0.219
Eosinophil (%)	1.39 ± 1.82	3.07 ± 2.85	4.27 ± 3.42	0.088
Basophil (%)	0.34 ± 0.35	0.55 ± 0.52	0.43 ± 0.40	0.600
Band neutrophils (%)	79.69 ± 10.43	74.15 ± 14.92	60.17 ± 5.81	0.069
Lymphocytes (%)	19.91 ± 13.15	20.72 ± 14.13	25.75 ± 3.18	0.448
Monocytes (%)	5.89 ± 4.18	8.54 ± 1.24	8.00	0.369
Thrombocytes (10^9/L)	288.89 ± 104.82	381.09 ± 180.15	273.67 ± 131.77	0.350
AST (U/L)	152.12 ± 328.89	76.14 ± 73.64	25.50 ± 9.19	0.256
ALT (U/L)	99.71 ± 118.66	89.57 ± 84.98	54.50 ± 57.28	0.842
Urea (mg/dl)	46.34 ± 43.53	67.11 ± 96.39	20.50 ± 2.12	0.499
Creatinine (mg/dl)	1.60 ± 1.22	4.77 ± 4.94	0.84 ± 0.02	0.277

Note: * p< 0.05 between 1st day vs 7th day

Table 5. The characteristics of subjects in the non-CQ/HCQ group.

Characteristics	No -CQ/HCQ Group			P-value
	1st day (n=21)	7th day (n=21)	14th day (n=9)	
Vital sign				
Systolic blood pressure (mmHg)	129.05 ± 26.43	114.82 ± 20.64	130.50 ± 9.97	0.088
Diastolic blood pressure (mmHg)	81.05 ± 12.06	74.00 ± 9.94	77.83 ± 8.35	0.131
Heart rate (/minutes)	102.57 ± 17.59	92.18 ± 23.85	86.67 ± 12.64	0.062
Respiratory rate (/minutes)	23.57 ± 3.59	24.06 ± 5.39	21.33 ± 2.07	0.408
Temperature (°C)	36.69 ± 0.68	36.63 ± 0.62	36.55 ± 0.35	0.991
Laboratory findings				
Erythrocytes (10^{12}/L)	4.45 ± 0.73	4.58 ± 0.93	4.46 ± 0.61	0.997
Haemoglobin (g/dL)	12.75 ± 2.11	12.92 ± 2.28	12.80 ± 1.39	0.981
Haematocrit (%)	37.71 ± 6.49	38.33 ± 7.07	38.00 ± 3.81	0.993
MCV (fl)	84.21 ± 5.14	84.30 ± 7.27	85.60 ± 6.46	0.541
MCH (pg)	28.51 ± 2.22	28.25 ± 2.76	28.84 ± 2.17	0.804
MCHC (g/dL)	33.89 ± 1.22	33.14 ± 1.68	33.74 ± 1.01	0.380
Leukocytes (10^9/L)	11.59 ± 4.54	13.66 ± 5.38	9.54 ± 3.93	0.197
Eosinophil (%)	0.78 ± 1.22	2.27 ± 4.33	1.48 ± 1.03	0.182
Basophil (%)	0.23 ± 0.19	1.02 ± 2.77	0.38 ± 0.15	0.420
Band neutrophils (%)	70.25 ± 26.39	79.44 ± 16.98	75.18 ± 17.33	0.318
Lymphocytes (%)	18.51 ± 10.48	14.99 ± 11.94	17.98 ± 12.98	0.650
Monocytes (%)	5.75 ± 2.22	6.35 ± 2.24	3.90 ± 1.64	0.226
Thrombocytes (10^9/L)	307.05 ± 129.22	354.79 ± 147.14	383.80 ± 122.63	0.315
AST (U/L)	164.65 ± 297.78	132.56 ± 168.86	-	0.169
ALT (U/L)	159.41 ± 295.78	119 ± 128.05	-	0.124
Urea (mg/dl)	48.27 ± 50.23	64.89 ± 49.32	-	0.256
Creatinine (mg/dl)	1.25 ± 1.03	1.49 ± 1.02	-	0.427

treatment in respiratory rate, temperature, and neutrophil percentage. However, the patient numbers with the negative conversion of the swab RT-PCR were the same between treatment groups on day 7. Interestingly, on day 14, the percentage of the patient with the negative conversion of swab RT-PCR was higher in CQ/ HCQ + azithromycin group.

The data was collected from the hospitalized COVID-19 patient from March to December 2020. At that time, CQ or HCQ and lopinavir-ritonavir were still recommended to be given to COVID-19 patients. The treatment guideline in Indonesia was revised in December 2020, in which the use of CQ or HCQ and lopinavir-ritonavir were no longer included in the guideline.[22] Based on treatment guidelines for COVID-19 in Indonesia, Azithromycin and oseltamivir were also recommended either for mild, moderate, or severe COVID-19 patients. Therefore, most of the patients involved in this study also received Azithromycin and oseltamivir. Some of the patients also receive levofloxacin which was given as an alternative to Azithromycin.[22] In addition to CQ, HCQ, and Azithromycin, more patients in the CQ/ HCQ + Azithromycin group also received oseltamivir than those in the other group. Although the differences were not statistically significant, treatment combinations with corticosteroid and levofloxacin were also more frequent in the CQ/ HCQ + Azithromycin group than

Table 6. The characteristics of subjects in the CQ/HCQ+Azithromycin group.

Characteristics	CQ/HCQ+Azithromycin group			P-value
	1st day (n=154)	7th day (n=152)	14th day (n=79)	
Vital signs				
Systolic blood pressure (mmHg)****	129,82 ± 17,85	122,63 ± 16,49	129,30 ± 18,83	0,002
Diastolic blood pressure (mmHg)	80,18 ± 11,84	77,79 ± 10,54	78,95 ± 9,58	0,266
Heart rate (/minutes)*	87,82 ± 14,89	80,79 ± 11,58	82,82 ± 12,81	<0,001
Respiratory rate (/minutes)**	20,73 ± 2,19	20,31 ± 2,01	20,07 ± 0,99	0,005
Temperature (°C)	36,65 ± 0,55	36,54 ± 0,38	36,64 ± 0,29	0,115
Laboratory findings				
Erythrocytes (10^{12}/L)***	4.83 ± 0.63	4.52 ± 0.71	4.44 ± 0.56	<0.001
Haemoglobin (g/dL)***	13.67 ± 1.92	12.48 ± 2.05	12.38 ± 2.03	<0.001
Haematocrit (%)***	39.87 ± 5.02	37.26 ± 5.47	37.39 ± 5.29	0.003
MCV (fl)	82.54 ± 5.55	83.28 ± 5.95	84.31 ± 6.54	0.076
MCH (pg)	28.46 ± 2.36	27.96 ± 2.50	27.93 ± 2.85	0.332
MCHC (g/dL)***	34.36 ± 1.31	33.49 ± 1.63	33.07 ± 1.52	<0.001
Leukocytes (10^9/L)	8,95 ± 5,16	7,72 ± 3,66	9,06 ± 5,56	0,072
Eosinophil (%)***	1.24 ± 1.61	2.03 ± 2.04	2.63 ± 1.99	<0.001
Basophil (%)	0.51 ± 1.23	0.51 ± 0.35	0.62 ± 0.42	0.797
Neutrophils (%)	68,64 ± 14,66	67,84 ± 14,54	65,84 ± 15,91	0,595
Lymphocytes (%)	22,73 ± 11,59	24,84 ± 11,25	22,27 ± 10,31	0,650
Monocytes (%)*	6.76 ± 2.77	7.98 ± 2.95	7.16 ± 2.38	0.020
Thrombocytes (10^9/L)****	290.99 ± 92.97	334.20 ± 102.71	287.91 ± 85.31	0.014
AST (U/L)	38,7 ± 40,54	56 ± 32,81	40,5 ± 12,02	0,114
ALT (U/L)**	34,48 ± 30,75	59,25 ± 55,90	96,5 ± 20,51	0,046
Urea (mg/dl)	28,78 ± 35,99	58,6 ± 43,83	28,0 ± 2,83	0,105
Creatinine (mg/dl)	0,92 ± 0,99	1,57 ± 0,93	-	0,031

Note: n= number of patients
* p< 0.05 between 1st day vs. 7th day
** p< 0.05 between 1st day vs. 14th day
*** p< 0.05 between 1st day vs. 7th day and 1st day vs. 14th day
**** p< 0.05 between 1st day vs. 7th day and 7th day vs. 14th day

Table 7. Duration of hospitalization and number of death during the hospital stay.

Clinical Outcome	Group of Treatment			P-value
	CQ/HCQ +Azithromycin (n=154)	CQ/HCQ (n=19)	No CQ/HCQ/ Azithromycin (n=21)	
Hospitalization duration(day)	14.40 ± 7.77	15.44 ± 6.46	16.00 ± 8.60	0.732
Number of patients who died during treatment*	4	10	8	<0.001

* Number of death: CQ/HCQ+Azithromycinvs CQ/HCQ group and CQ/ HCQ+Azithromycin vsNo CQ/HCQ (p<0.001).
Number of death: CQ/HCQ vs. NoCQ/HCQ (p=0.356)

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in other groups. Meanwhile, those without CQ/ HCQ treatment received lopinavir-ritonavir compared to other groups.

CQ/ HCQ for COVID-19 was started based on the in vitro study findings. In vitro study on Chloroquine and its derivate, hydroxychloroquine activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) showed that both can decrease SARS-CoV-2 RNA copy number in veroE6 cell line.[13] The first clinical study of the drug was done by Gautret et al.,[23] in France, which involved 36 COVID-19 patients and showed that the administration of hydroxychloroquine decreased viral content on the sixth day after the treatment given. However, the study only included a small number of participants, and the treatment in the control group was not homogenous. Some more recent studies on CQ/ HCQ effect on COVID-19 showed different results. Another study[23] in France found that 80% of patients receiving HCQ and Azithromycin tested positive by swab RT-PCR test after the treatment course.[24] This might be because the patient enrolled in this study were older than those in a study by Gautret et al.[23] Studies in China conducted on 30 patients showed contradicting results. The first study revealed that the viral clearance and temperature normalization were the same between those on HCQ and the control group.[25] Another study in China involving 62 patients, treatment of 200 mg HCQ for five days resulted in faster time to clinical recovery and some other parameter improvement such as radiological findings compared to those without HCQ.[26] Multi-centre randomized control trial studies in China showed no difference in the rate of viral clearance between those receiving HCQ and those treated by standard treatment. However, this study revealed that those on HCQ treatment showed faster clinical improvement than those on standard treatment only.[27] Studies based in the United States of America showed that mortality was higher in those on HCQ treatment than in those without HCQ treatment. However, the baseline characteristic of the patient involved in the study was different. The condition of the patients receiving HCQ was more severe than those without HCQ treatment.[28] Randomized controlled trials conducted in Brazil that studied the efficacy and safety of low versus high dose CQ in critically ill patients confirmed or suspected COVID-19 revealed that the mortality was no different between the groups.[29] In our study, we did not directly compare the outcome parameters between the groups studied since some of the baseline characteristics differed. However, based on pre-post data analysis, it was revealed that those on CQ/ HCQ + azithromycin treatment showed clinical improvement and a low mortality rate. Meanwhile, those on No-CQ/ HCQ treatment showed no clinical improvement. The mortality rate in CQ/ HCQ and No CQ/ HCQ groups were high, 52 % and 38 %, respectively.

Azithromycin is one of the macrolides antibiotics suggested to have additional pharmacological effects besides an antibiotic. Studies on Azithromycin had shown its potential as immunomodulatory.[30–32] Study of Azithromycin's pharmacological effect on cystic fibrosis revealed the ability of the drug to reduce the replication of rhinovirus.[33] In vitro studies have been done to evaluate Azithromycin antiviral activity towards SAR-CoV-2.[34] Quantitative structure-activity relationship studies have shown that Azithromycin and some other macrolide antibiotics were able to inhibit SARS-CoV-2 spike in the protein. The study also validated this in silico result by conducting an in vitro study that revealed that Azithromycin reduced the accumulation of viral RNA in the cell and prevented virus-induced cell death.[35] An observational study conducted in New York revealed that treatment of hospitalized COVID-19 patients with Azithromycin alone showed a lower hazard ratio for in-hospital mortality than those in HCQ and HCQ + azithromycin groups; the difference was not statistically significant.[36] Studies from Brazil also showed that Azithromycin administration to severe COVID-19 patients did not improve the clinical outcomes.[37] Well-designed and well-conducted randomized controlled trial study is needed to prove the Azithromycin potential for COVID-19 treatment.

Despite most of the patients having mild to moderate COVID-19, most of the patients received medication, and mainly, the medication was given in combination with some medications. During this emergency, where many things were unknown, giving medications without solid evidence of their safety and efficacy seemed inevitable. Continuous evaluation is needed to improve disease management and prevent the development of adverse drug reactions and unnecessary expenditure.

The strength of this study is we used all the COVID-19 data during the study from 3 hospitals in different cities in Indonesia. The ideal study design for evaluating therapy efficacy is Randomized Controlled Trial (RCT). However, this study was an observational study which means the result should be carefully interpreted because some uncontrolled confounders can influence the result.

CONCLUSION

Most of the patients included in this study had mild-moderate COVID-19. The medication is given mainly in combination with CQ/ HCQ, Azithromycin, oseltamivir, and lopinavir/ritonavir. The most common combination is CQ/HCQ + Azithromycin. Treatment with the CQ/ HCQ + azithromycin combination showed better clinical improvement and lower mortality rates than other groups. Still, the patient in this group had better clinical characteristics at baseline and received more treatment.

ETHICAL STATEMENT

This study was conducted based on the protocol, which has been granted ethical approval from the Faculty of Medicine, Public Health, and Nursing Universitas Gadjah Mada Institutional Review Board (EK/FK/0825/EC/2020).

AUTHOR CONTRIBUTION

All of the authors contributed equally to this article.

CONFLICT OF INTEREST

We have no conflicts of interns to disclose.

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