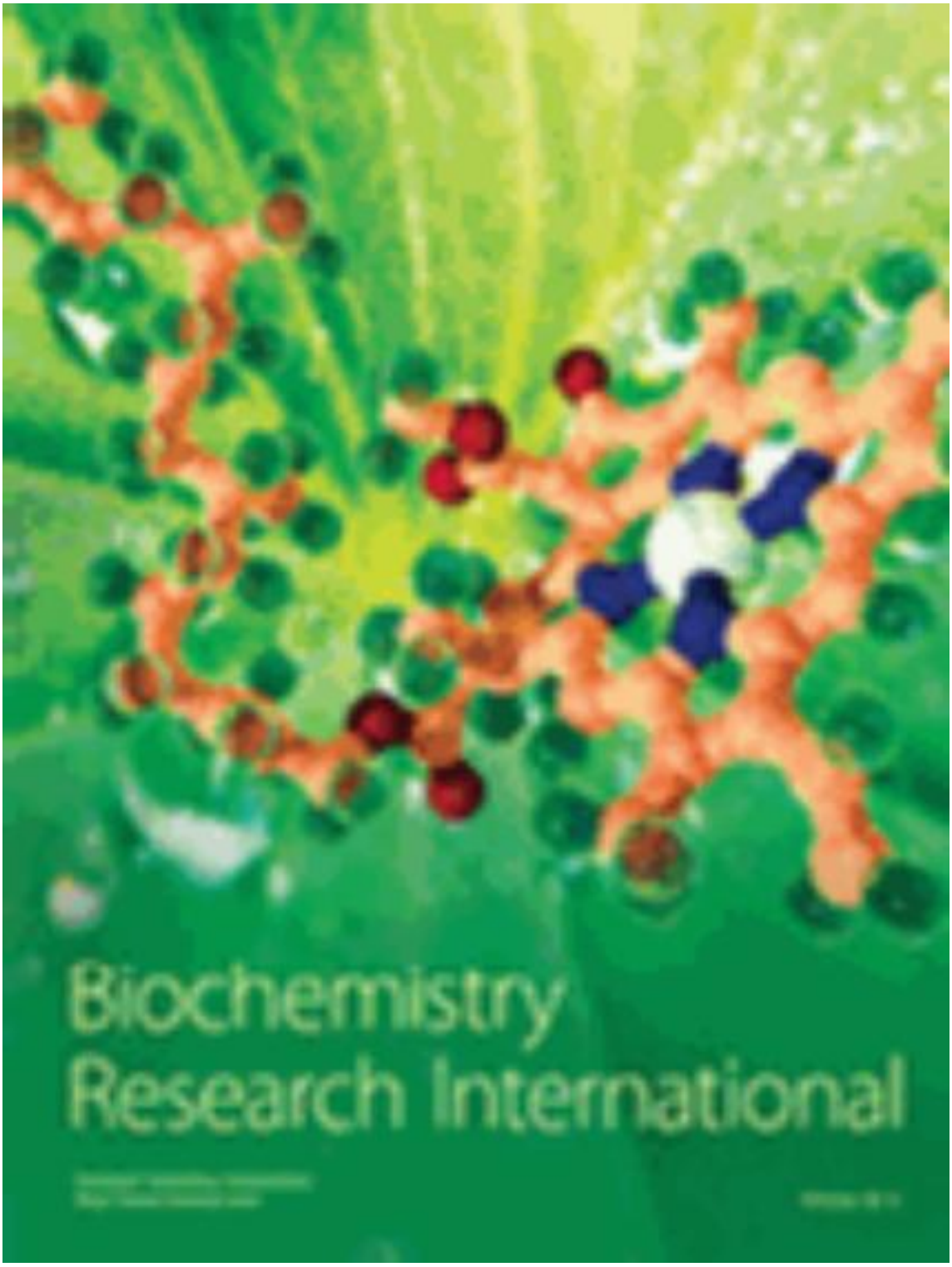
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Received 4 November 2020; Revised 14 December 2020; Accepted 15 January 2021; Published 9 February 2021

Academic Editor: Zubeyir Huyut

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Background. At the present time, COVID-19 vaccines are at the testing stage, and an effective treatment for COVID-19 incorporating appropriate safety measures remains the most significant obstacle to be overcome. A strategic countermeasure is, therefore, urgently required. *Aim*. This study aims to evaluate the efficacy and safety of a combination of lopinavir/ritonavir-azithromycin, lopinavir/ritonavir-doxycycline, and azithromycin-hydroxychloroquine used to treat patients with mild to moderate COVID-19 infections. *Setting and Design*. This study was conducted at four different clinical study sites in Indonesia. The subjects gave informed consent for their participation and were confirmed as being COVID-19-positive by means of an RT-PCR test. The present study constituted a randomized, double-blind, and multicenter clinical study of patients diagnosed with mild to moderate COVID-19 infection. *Materials and Methods*. Six treatment groups participated in this study: a Control group administered with a 500 mg dose of azithromycin; Group A which received a 200/50 mg dose of lopinavir/ritonavir and 500 mg of azithromycin; Group B treated with a 200/50 mg dose of lopinavir/ritonavir and 200 mg of doxycycline; Group C administered with 200 mg of hydroxychloroquine and 500 mg of azithromycin; Group D which received a 400/100 mg dose of lopinavir/

ritonavir and 500 mg of azithromycin; and Group E treated with a 400/100 mg dose of lopinavir/ritonavir and 200 mg of doxycycline. *Results*. 754 subjects participated in this study: 694 patients (92.4%) who presented mild symptoms and 57 patients (7.6%) classified as suffering from a moderate case of COVID-19. On the third day after treatment, 91.7%–99.2% of the subjects in Groups A–E were confirmed negative by a PCR swab test compared to 26.9% in the Control group. Observation of all groups which experienced a significant decrease in virus load between day 1 and day 7 was undertaken. Other markers, such as CRP and IL-6, were significantly lower in all treatment groups ($p < 0.05$ and $p < 0.0001$) than in the Control group. Furthermore, IL-10 and TNF-α levels were significantly elevated in all treatment groups ($p < 0.0001$). The administration of azithromycin to the Control group increased CRP and IL-6 levels, while reduced IL-10 and TNF-α on day 7 ($p < 0.0001$) compared with day 1. Decreases in ALT and AST levels were observed in all groups ($p < 0.0001$). There was an increase in creatinine in the serum level of the Control, C, D, and E groups ($p < 0.05$), whereas the BUN level was elevated in all groups ($p < 0.0001$). *Conclusions*. The study findings suggest that the administration of lopinavir/ritonavir-doxycycline, lopinavir/ritonavir-azithromycin, and azithromycin-hydroxychloroquine as a dual drug combination produced a significantly rapid PCR conversion rate to negative in three-day treatment of mild to moderate COVID-19 cases. Further studies should involve observation of older patients with severe clinical symptoms in order to collate significant amounts of demographic data.

1. Introduction

Since late 2019, a global campaign has been waged against the Coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome (SARS-CoV-2) virus which has infected 70.4 million people and caused 1,599,704 deaths worldwide [1]. Various initiatives have been undertaken in an attempt to eradicate the pandemic. However, to date, all efforts to halt the transmission and spread of COVID-19 have proved unsuccessful.

Several studies have reported that the majority of individuals (80%) infected with COVID-19 have presented mild to moderate symptoms [2–4]. Indonesia is densely populated with 270 million inhabitants, the fourth-largest national population in the world. Consequently, the ongoing pandemic has significantly impacted the country in various sectors, including economy, education, and health (source: http://www.covid19.gov.id). The majority of COVID-19 patients in Indonesia fall within productive age ranges, with an average isolation period between 10 and 14 days, factors which have had a significant negative effect on the economic sector. On the other hand, approximately 35% of individuals falling within the country's productive age range live with their parents who are, consequently, identified as a high-risk group in relation to COVID-19 (source: Statistics Indonesia. http://www.bps.go.id). Therefore, proactive initiatives are required to facilitate the prompt social reintegration of those COVID-19 patients presenting mild and moderate symptoms.

Experts around the world have been working unstintingly to find an effective cure for COVID-19. Various drugs such as azithromycin [5], hydroxychloroquine [5, 6], lopinavir/ritonavir [7], remdesivir [7], homoharringtonine [7], and emetine [7] have been reported as demonstrating antiviral potential during preclinical trials. Most represent newly determined indicative uses of previous drug regimens. In Indonesia, researchers have identified several drugs such as lopinavir/ritonavir, azithromycin, doxycycline, and hydroxychloroquine as potentially having curative effects against COVID-19 infection. In a previous study undertaken by the authors of this article, the CC50 values observed for an *in vitro* cytotoxicity assay on mesenchymal cells indicated that a combination of these drugs had a lower degree of toxicity than that of a single drug (unpublished data). The drug combination employed during the in vitro study proved effective in lowering the viral copy numbers in the Vero cells infected with SARS-CoV-2 which had been isolated from hospitalized patients at 72, 48, and, even, 24 hours after drug incubation (unpublished data). Moreover, the research in question also highlighted certain new combination drugs such as lopinavir/ritonavir and azithromycin, lopinavir/ritonavir and doxycycline. Hydroxychloroquine and azithromycin produced higher efficacy in inhibiting and eradicating the SARS-CoV-2 virus than their single form (unpublished data).

Several other recent studies have reported the efficacy and safety of some single drug [5, 6, 7, 8] or other drug combinations [8, 9]. However, many variations permeate their results. The present study evaluated the efficacy and safety of combinations of lopinavir/ritonavir and azithromycin; lopinavir/ritonavir and doxycycline; and azithromycin and hydroxychloroquine for patients suffering from mild to moderate COVID-19 who are undergoing treatment not involving the use of a ventilator.

2. Methods

2.1. Study Conduct. This study constituted a multicenter, double-blind, and randomized controlled clinical trial (RCT) conducted between July and August 2020 at four research sites in Indonesia. The Ethics Committee granted ethical approval for all centers conducting clinical trial protocols (Persetujuan Pelaksanaan Uji Klinik, PPUK) (No. PP.01.01.1.3.07.20.06) issued by the Indonesian Food and Drugs Administration (Badan Pengawas Obat dan Makanan Republik Indonesia) with an additional letter of approval from the National Institute of Health Research and Development, Indonesian Ministry of Health (Balitbangkes Kementerian Kesehatan RI), and ethical approval no. 159/KEP/2020 issued by the Ethics Committee of Universitas Airlangga Hospital (RS UNAIR).

2.2. Research Population. For the purposes of this study, 1,045 subjects from four study sites, namely, Universitas Airlangga Hospital (RSUA), Surabaya; Dustira Hospital,

Bandung; COVID-19 Isolation Center, Lamongan; and POLRI Hospital, Jakarta, were initially assessed for eligibility before being screened and enrolled in accordance with the inclusion criteria of being male or female adults over the age of 18. The screening process produced 754 eligible subjects who were further randomized into six groups for the purposes of the intervention study as shown in Figure 1. The subjects registering a positive result on the COVID-19 PCR swab test presented mild, moderate, or severe symptoms. Those individuals willing to give informed consent prior to the study were then admitted as patients in one of the closest available hospitals or isolation centers. The exclusion criteria applied to the research subjects comprised the following: pregnant or breastfeeding mothers, individuals with severe liver disorders (indicated by increases in transaminases levels three times or more in excess of the normal range), impaired renal functions (indicated by decreases in creatinine clearance of less than 60 mL/minute), arrhythmia, and/or a compromised potassium/magnesium balance. Moreover, individuals receiving conventional plasma therapy and/or anti-IL-6 therapy who experienced QT prolongation when QTc >60 ms, QTc >500 ms with a narrow QRS, or QTc ^{3}550 ms with wide QRS occurring during treatment or who demonstrated proven resistance to one of the combinations of antibiotics studied, drug allergy events, and adverse events due to the administration of other drugs were excluded from the study (as did those who discontinued their participation).

2.3. Randomization and Intervention. The subjects signed an informed consent form confirming their willingness to participate in the study, after which they received the same treatment based on their clinical conditions. Randomized subjects were assigned to one of six treatment groups. The Control group was treated in accordance with the standard of care (SoC), including the administration of 500 mg azithromycin once a day, supplements, and other drugs intended to address clinical symptoms. Group A consisted of subjects treated with a combination of 200/50 mg lopinavir/ritonavir twice a day and 500 mg azithromycin once a day. Group B included subjects treated with a combination of 200/50 mg lopinavir/ritonavir and 100 mg doxycycline twice a day. Group C contained subjects who received 200 mg hydroxychloroquine twice a day and 500 mg azithromycin once a day. Groups D and E were similar to Groups A and B, except that their subjects received a higher dose of 400/100 mg lopinavir/ritonavir twice a day. All groups also received supportive symptom-based treatments.

2.4. Study Evaluation: Schedule of Treatments and Evaluation of Study Endpoints. The subjects were administered drugs, received supportive treatment, and underwent physical health monitoring for 7–14 days to evaluate the study. Moreover, the assessed clinical signs were used to assess drug efficacy. An evaluation drawing on a combination of physical examination, clinical radiology, laboratory parameters, and RT-PCR for viral load was also conducted. Any adverse events, serious or otherwise, occurring during the study period were recorded.

The primary objectives of this study were to measure the efficacy of the drug combinations lopinavir/ritonavir and azithromycin; lopinavir/ritonavir and doxycycline; and hydroxychloroquine and azithromycin in improving the clinical outcomes of those COVID-19 patients hospitalized with mild and moderate symptoms. The clinical outcome parameters consisted of improvements in such physical functions as maintaining optimum body temperature (<37.5oC); respiratory rate (≤20 times per minute without the use of auxiliary respiratory muscles); oxygen saturation/SpO_2 (>95% without provision of supplemental oxygen); and hemodynamic stability (mean arterial pressure/MAP >65 mmHg). Moreover, the decrease in mortality rate was noted to establish the efficacy of drug combination therapy.

The secondary efficacy endpoint was to determine the safety of those drug combinations administered during the study which enhanced the clinical outcomes of COVID-19 patients with mild to moderate symptoms. It also evaluated patient complaints or discomfort, including fever, coughing, breathlessness, sniffles, a sore throat, and other symptoms. Observations were also made using lung X-rays, clinical hematology test results, and cytokine levels, the latter of which were analyzed for IL-2, IL-6, IL-10, and TNF- α by means of a Sandwich ELISA method including the use of BT-Labs reagent kits Cat. No. E0094Hu, Cat. No. E0090Hu, Cat. No. E0102Hu, and Cat. No. E0082Hu purchased from the Bioassay Technology Laboratory, China. The viral load was analyzed through quantitative real-time polymerase chain reaction (qRT-PCR), all assays of which were performed using an Applied Biosystems (AP) 7500 Fast Real-Time PCR system (Enigma, Applied Biosystems, Foster city, CA, USA), with Allplex 2019-nCoV Assay PCR reagent (Cat. No. RP10250X, Seegene, South Korea) and a Tiangen extraction kit (Cat. No. DP315-T8, Beijing, China). Viral load analysis was undertaken by first measuring the positive control virus concentration and cycle threshold (Ct) values, with a Qubit fluorometer (Thermo Fisher Scientific, USA). The positive control was an Allplex 2019-nCoV assay kit. The Ct value was converted into copy viral DNA/μl by plotting it as a linearity curve prepared at 8 concentrations.

2.5. Statistical Analysis. The 754 subjects were randomized into seven groups constituting six treatment groups and one Control group whose members received SoC. The primary efficacy data were analyzed through head-to-head SoC comparison of treatment groups by means of statistical analysis. Despite there being more than 30 patients in each group, the numerical data (ratio or interval) were further analyzed for normal distribution through the use of a Kolmogorov–Smirnov test. If the data distribution was normal (p value ≥0.05), it was further subjected to an analysis of variance (ANOVA) and a least square difference multiple comparison test. However, the data distribution in this study was not normal, leading to further analysis by the administration of Kruskal–Wallis and Mann–Whitney multiple comparison tests. The resulting categorical data

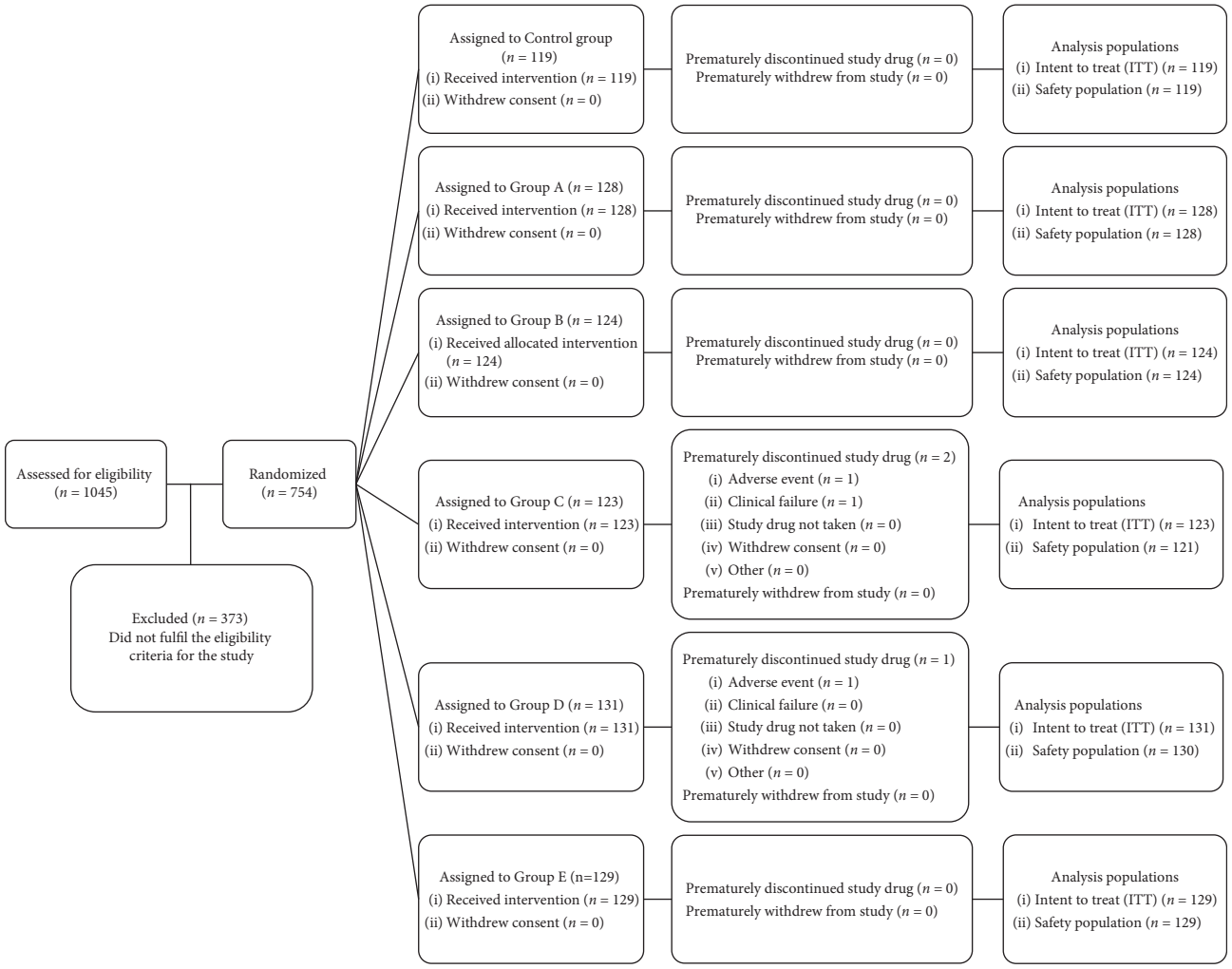

Figure 1: Patients' clinical study disposition algorithm for comparing the efficacy of lopinavir/ritonavir and azithromycin, lopinavir/ritonavir and doxycycline, and hydroxychloroquine and azithromycin drug combinations in improving clinical outcomes of COVID-19 patients hospitalized with mild and moderate symptoms. Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day.

were evaluated using a Chi-square test. Moreover, the study of secondary efficacy data used for prestudy and poststudy evaluation of clinical outcome indicators included lung X-rays, laboratory results, and viral load tests.

3. Results

3.1. Patient Demographics. Of the 1,045 study subjects, 754 were enrolled according to the eligibility criteria shown in Figure 1. The 119 Control group members received a single dose of azithromycin. The 128 Group A patients were administered 200/50 mg lopinavir/ritonavir +500 mg azithromycin. The 124 Group B patients received 200/50 mg lopinavir/ritonavir +100 mg doxycycline. The 123 Group C patients were given a combination of 200 mg hydroxychloroquine and 500 mg azithromycin. The 131 Group D patients were treated with a combination of 400/100 mg lopinavir/ritonavir and 500 mg azithromycin. The medication administered to 129 patients of Group E consisted of 400/100 mg lopinavir/ritonavir + 100 mg doxycycline. Two patients of Group C experienced adverse events during the study and deteriorated clinically causing the researchers to exclude them from further participation in the study. Furthermore, a Group D patient suffered from severe nausea and vomiting, resulting in the immediate termination of the treatment and the removal of that individual from the study.

3.2. Evaluation of the Clinical Efficacy of Drug Combination Therapy for COVID-19. Of the 751 study subjects given in Table 1, 694 (92.4%) suffered from mild disease, while 57 (7.6%) presented moderate symptoms. The analysis focused only on the mild symptom group in order to avoid bias. 716 of the research subjects were male (95.3%), while females accounted for only 4.7% (35). Gender was evenly distributed

Table 1: The baseline physical characteristics and clinical laboratory data of enrolled subjects who completed treatment during the study.

	Total ($n = 751$)	Control	A	B	C	D	E	p value
Disease severity*								
Mild, n (%)		115 (96.6)	120 (93.8)	113 (91.1)	113 (93.4)	117 (90.0)	116 (89.9)	0.303
Moderate, n (%)		4 (3.4)	8 (6.3)	11 (8.9)	8 (6.6)	13 (10.0)	13 (10.1)	
Gender**								
Male	716 (95.3)	113 (95.0)	123 (96.1)	119 (96.0)	118 (97.5)	119 (91.5)	124 (96.1)	
Female	35 (4.7)	6 (5.0)	5 (3.9)	5 (4.0)	3 (2.5)	11 (8.5)	5 (3.9)	0.305
Age (in years)								
Median		37#	37	37#	36#	37	37#	0.105
Minimum		23	32	26	32	21	20	
Maximum		55	49	49	51	55	45	
Laboratory examination								
Median AST (U/L, minimum–maximum)		27 (13–69)	25 (12–78)	26 (12–78)	25 (5–68)	26 (13–65)	26 (13–213)	0.159
Median ALT (U/L, minimum–maximum)		34 (12–144)	32 (16–142)	33 (3–106)	31 (14–141)	36 (11–116)	35 (7–337)	0.317
Median creatinine serum (mg/dL. minimum–maximum)		0.96 ± 0.13	0.94 (0.68–1.34)	0.96 ± 0.12	0.95 (0.77–1.51)	0.98 ± 0.50	0.98 ± 0.12	0.712
BUN level (mg/dL)		10.7 ± 2.2	11.3 ± 1.8	11.1 (6.4–15.8)	11.2 (7.2–18.6)	11.1 ± 2.3	11.1 ± 2.1	
C-reactive protein (CRP)		2.0 (0.1–69.1)	1.5 (0.1–35.2)	1.0 (0.1–32.4)	1.5 (0.1–43.7)	1.0 (0.0–77.3)	1.2 (0.1–65.1)	0.026
D-dimer		203 (99–1,085)	166.5 (73–776)	177 (84–981)	176 (63–18,460)	191 (75–4,474)	180 (53–2,393)	0.078

*$\chi^2 = 6.031$; **$\chi^2 = 3.952$; #significant difference from Group D. Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; AST: aspartate aminotransferase serum; ALT: alanine aminotransferase serum; BUN: blood urea nitrogen; D-dimer: fibrin degradation fragment.

across all treatment groups as confirmed by the Chi-square test results which showed no significant difference ($p > 0.05$). The age range of participants enrolled in this study was between 20 and 55, with a median age of 36-37. A Mann–Whitney study indicated a substantial difference between the Control and D groups and the Control and Groups B, C, and E; however, they were in a close range. The laboratory data results showed that the AST, ALT, serum creatinine, BUN, CRP, and D-dimer values were relatively equal in the Control and A–E groups.

Clinical improvement was assessed on the basis of several symptoms such as fever, sore throat, cough, cold/sniffle, inability to breathe, chest pains/breathlessness, and diarrhea. On day 3, a number of participants continued to experience clinical discomfort, namely, 22 patients in the Control group (18.5%) and 5 subjects (3.9%), 9 subjects (7.3%), 11 subjects (9.1%), 12 subjects (9.2%), and 6 subjects (4.7%), respectively, in Groups A, B, C, D, and E. According to these data, all forms of discomfort had been relieved on the fourth day of treatment.

A report was produced regarding the increase in the D-dimer value related to a poor prognosis, resulting in thrombosis, bleeding, and mortality. This research, therefore, contains an analysis of D-dimer. Based on the data contained in Table 2, a deterioration in the D-dimer rate occurred in all posttherapy groups. No significant difference exists between the Control group and the drug treatment groups. This study also evaluated the CRP rate. The data contained in Table 2 indicate that the CRP value of the Control group and treatment groups A–E ranged from 1.0 to 2.0 on D-1 before experiencing a significant decrease ($P < 0.0001$) to a value of <1.0 on D-7 due to the administration of medication.

To analyze the effectiveness, cytokine levels in the blood including IL-6, IL-10, and TNF-α were analyzed on days 1 and 7. On initial examination of the subjects, most of the IL-6 rate values had increased compared to the normal rate in the range of values 7.8–22,022.3 pg/ml with a cutoff point of 9.16 pg/ml in the median value as shown in Table 2. After administering a combination of drug therapies for seven days, an improvement in the Il-6 rate was recorded from a median value of 167.9 ng/ml to one of 186.7 ng/ml ($p < 0.0001$). In Groups A–E, a decrease in the IL-6 rate occurred. In Group A, the median value of 191.0 ng/ml became one of 146.9 ng/ml ($p < 0.0001$); in Group B, the median value of 183.2 ng/ml fell to 145.8 ng/ml ($p < 0.0001$); in Group C, the median value decreased from 180.4 ng/ml to 145.5 ng/ml ($p < 0.0001$); in Group D, the median value fell from 194.2 ng/ml to 170.1 ng/ml ($p < 0.0001$); and in Group E, there was a decrease in the median value from 190.7 ng/ml to 144.2 ng/ml ($p < 0.0001$). These results indicated a significant difference ($p < 0.0001$) between the Control group and the A–E combination drug groups.

Table 2: Analysis of laboratory data profiles of D-dimer, CRP level, interleukins, and TNF-α of subjects in the Control group and Groups A–E on day 1 and day 7 during treatment.

Group	Control	A	B	C	D	E	p value
Median level of D-dimer (ng/mL FEU, minimum–maximum)							
Day 1	203 (99–1,085)	166.5 (73–776)	177 (0–981)	176 (63–18,460)	191 (75–4,474)	180 (53–2,393)	0.078
Day 7	169 (70–1,309)	158 (66–481)	152 (66–1,156)	160 (56–485)	173 (68–1,842)	161 (60–819)	0.549
CRP level (mg/L, minimum–maximum)							
Day 1	2.0 (0.1–69.1)	1.5 (0.1–35.2)	1,0 (0.1–32.4)	1.5 (0.1–43.7)	1.0 (0.0–77.3)	1.2 (0.1–65.1)	0.026
Day 7	0.7 (0.0–14.2)	0.6 (0.1–41.5)	0.6 (0.1–24.2)	0.6 (0.1–44.4)	0.6 (0.1–18.1)	0.8 (0.1–34.5)	0.039
IL-6 level (ng/mL, minimum–maximum)							
Day 1	167.9 (7.8–500.4)	191.0 (10.2–1,348.9)	183.2 (25.8–2,934.9)	180.4 (13.2–22,022.3)	194.2 (15.7–1,452.2)	190.7 (32.5–1,348.9)	<0.0001
Day 7	186.7* (18.3–2,432.9)	146.9* (0.2–407.1)	145.8* (19.8–1,753.9)	145.5* (6.3–2,940.0)	170.1* (0.4–820.2)	144.2* (3.5–476.7)	<0.0001
IL-10 level (ρg/mL, minimum–maximum)							
Day 1	141.7 (53.7–1,702.9)	82.1 (35.5–342.5)	89.3 (35.5–404.1)	86.9 (30.9–388.8)	92.1 (32.7–408.1)	76.0 (39.3–319.9)	<0.0001
Day 7	105.9* (36.8–396.3)	128.6* (45.1–1,190.9)	142.0* (45.9–2,132.9)	144.8* (48.0–2,132.9)	145.7* (51.5–740.0)	147.2* (62.4–586.0)	<0.0001
Plasma level of TNF-α (ρg/mL, minimum–maximum)							
Day 1	149.3 (5.2–821.0)	168.5 (49.9–2,316.7)	176.6 (56.0–872.2)	165.1 (52.9–1,185.5)	171.5 (47.1–1,026.4)	197.7 (59.4–808.6)	<0.0001
Day 7	179.0* (26.0–1,152.2)	137.9* (28.1–622.0)	143.8* (36.3–641.7)	138.6* (31.7–631.8)	142.6* (1.3–593.4)	130.8* (37.4–380.9)	<0.0001

Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; IL-6: interleukin-6; IL-10: interleukin-10; TNF-α: tumor necrosis factor-α; * $p = 0.0001$ compared with day 1.

The interleukin-10 (IL-10) rate was also monitored. IL-10 is an anti-inflammatory cytokine found in humans whose IL-10 gene encodes IL-10. In this research, there was a mild to moderate increase in IL-10 levels in subjects with a cutoff point of 25.66 pg/ml at the outset of the examination. IL-10 levels ranged from 30.9 to 1,702.9 pg/ml with median values, as listed in Table 2. After seven days of therapy, the results showed that the SoC group demonstrated a reduced level of Il-10 from a median of 141.7 ng/ml to 105.9 ng/ml ($p < 0.0001$). In comparison, the treatment groups recorded an increase in Il-10 levels. In Group A, there was a significant increase from a median value of 82.1 ng/ml to 128.6 ng/ml ($p < 0.0001$). In Group B, the IL-10 value increased from a median value of 89.3 ng/ml to 142.0 ng/ml ($p < 0.0001$); in Group C, the median value increased from 86.9 ng/ml to 144.8 ng/ml ($p < 0.0001$); in Group D, the median value 92.1 ng/ml became 145.7 ng/ml ($p < 0.0001$); and in Group E, the median value increased from 76.0 ng/ml to 147.2 ng/ml ($p < 0.0001$). Based on these results, it can be concluded that a significant difference ($p < 0.0001$) existed between the Control and the A–E combination drug groups. IL-10 plays a role in preventing the occurrence of tissue injury. Consequently, the treatment groups had significantly increased levels of the anti-inflammatory cytokines compared to those of the SoC group.

An initial examination of the research subjects indicated an improvement in TNF-α levels on the normal level with a minimum value (5.2–2,316.7) pg/ml, a cutoff point of 3.79 pg/ml, and a median value as shown in Table 2. Following the provision of therapy for seven days, the results showed that the Control group had experienced an increase from a median of 149.3 ng/ml to 179.0 ng/ml ($p < 0.0001$). Meanwhile, there was a significant decrease in TNF-α levels ($p < 0.0001$) on the seventh day of therapy. Moreover, significant differences ($p < 0.0001$) were also found between the Control group and the combination drug A–E groups.

The RT-PCR analysis on day 3 showed that 26.9% of subjects in the Control group returned a negative result. In contrast, the negative PCR results were in 91.7–99.2% of all the tested subjects observed in Groups A–E. On day 7, there was 31.1% increase in the Control group and about 93.0–98.3% in Groups A–E. A Chi-square analysis revealed a significant difference ($p < 0.0001$) between all tested and Control groups on day 3 and day 7 of treatment, as presented in Figure 2.

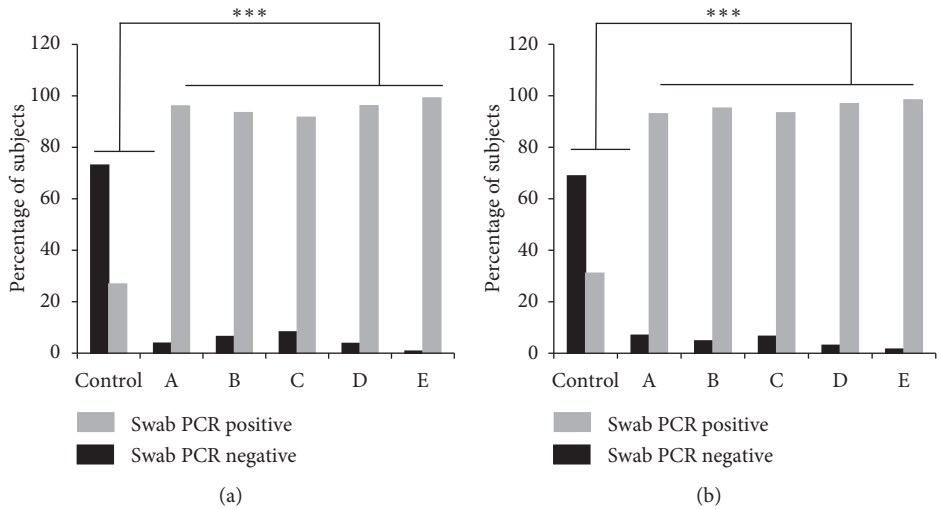

Figure 2: The RT-PCR analysis results of all subjects in the Control and treatment groups of A–E on day 3 (a) and day 7 (b) during the study period (*** $p < 0.0001$ compared with the Control). Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day.

In addition to the qualitative analysis conducted, this research undertook quantitative analysis relating to the number of virus copies. There was a significant decrease in this from D-1, D-3, and D-7 in both the SoC and treatment groups. On the other hand, Group E, which was given the usual lopinavir/ritonavir dose, experienced no significant decrease on D-3 or D-7. The pretreatment virus copy inspection results showed that the descending order of groups was that of D, E, Control, C, B, and A. The Kruskal–Wallis test result value was one of $p < 0.05$, indicating a significant pretreatment difference in virus copies. The results of the statistical analysis of observations indicated a tendency for the number of virus copies to have decreased when observed on days 1, 3, and 7, with the median value of the number of virus copies being as listed in Table 3.

3.3. Evaluation of Clinical Safety and Tolerability of Drug Combination Therapy for COVID-19. As shown in Table 4, all the treatment groups participating in this study had experienced adverse events. Four Group C subjects complained of headaches, a rapid pulse rate (tachycardia), and pruritus (itchiness) lasting for two days during treatment. Similar symptoms were also observed in four Group A members who experienced headaches for a day, a rapid pulse rate lasting 15 minutes, impaired hearing for a day, and abdominal pain for 30 minutes. Only one Group B subject experienced rapid heartbeat for 15 minutes, while two Group C subjects complained of hearing problems for two days and a rapid heart rate for two hours. Moreover, six subjects experienced diarrhea for one day in addition to headache, nausea, vomiting, abdominal pain, and a rapid pulse rate for 15 minutes. In Group E, three subjects reported experiencing discomfort such as a bitter taste in the mouth, nausea, and abdominal pain for one day. Two Group C subjects dropped out of the study due to severe adverse conditions of a prolonged QT interval >60 ms and clinical failure. The individuals concerned should have started using a ventilator on day 4. Moreover, one Group D subject experienced severe nausea caused by double consumption of antituberculosis drugs, which resulted in his/her withdrawal from the project.

According to the data in Table 4, 24 of the subjects had high leukocyte levels above 12,000 per μL, although there was an improvement (a decrease in the number of leukocytes to within normal limits) on the seventh day. There was no significant difference between the Control group and the A–E drug treatment groups ($p = 0.543$). Furthermore, six of the 751 research subjects experienced thrombocytopenia during D-1 therapy. This number was relatively unchanged on D-7, except in Group B which initially contained one person on D-1, subsequently becoming zero on D-7 following treatment. In general, patients did not have lymphocytopenia, with 90–95% of normal patients being on D-1. Only 6–12 of the 751 study subjects experienced lymphocytopenia during D-1 therapy, and this number decreased by half relative to D-7, except in Group B whose members received 200/50 mg of lopinavir/ritonavir and 500 mg of azithromycin combination therapy. Of the 12 individuals on D-1, 11 moved on to D-7 therapy. Overall, there was no significant difference between the Control group and the A–E drug treatment groups.

The research results showed that between 17.7% and 30.5% of research subjects demonstrated high aspartate aminotransferase (AST) levels on D-1. Compared with the Control group, the drug treatment group experienced significantly decreasing numbers between 6.8% and 19.0% as a result of D-7 therapy. Furthermore, as shown in Table 3, SGOT levels decreased significantly between days 1 and 7 in all treatment groups. Furthermore, as many as 164 research

Table 3: The results of the copy number of the virus of Control and treatment groups were analyzed in subjects with mild severity and total subjects evaluated using qRT-PCR on treatment days 1, 3, and 7.

Period of treatment	Control	A	B	C	D	E	p value
Copy number of virus in subjects with mild severity							
Day 1	193.2 (14.1–48,113.7)	67.0 (11.9–4,531.4)	73.2 (11.9–2,945.8)	173.3 (12.4–5,116.0)	828.8 (11.8–370,523.6)	588.4 (11.0–11,877.6)	
Day 3	49.9.0 (0.0–15,085.1)	0.0 (0.0–120.6)	0.0 (0.0–172.8)	0.0 (0.0–617.9)	0.0 (0.0–1,341.9)	0.0 (0.0–1,547.8)	
Day 7	19.8 (0.0–1,445.6)	0.0 (0.0–3,191.4)	0.0 (0.0–66.7)	0.0 (0.0–100.7)	0.0 (0.0–114.8)	0.0 (0.0–148.3)	
Copy number of virus in total subjects							
Day 1	193.2 (14.1–48,113.7)	67.0 (11.9–4,531.4)	73.2 (11.9–2,945.8)	183.6 (12.4–5,116.0)	854.8 (11.8–370,523.6)	670.0 (11.0–11,877.6)	0.001
Day 3	45.4 (0.0–15,085.1)	0.0 (0.0–120.6)	0.0 (0.0–172.8)	0.0 (0.0–617.9)	0.0 (0.0–2,900.6)	0.0 (0.0–1,547.8)	0.012
Day 7	19.8 (0.0–1,445.6)	0.0 (0.0–3,191.4)	0.0 (0.0–66.7)	0.0 (0.0–100.7)	0.0 (0.0–278.0)	0.0 (0.0–148.3)	0.039

Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day.

sample subjects (21.9%) had pretreatment alanine aminotransferase (ALT) levels above 50 U/L, with this number decreasing to 108 (15.5%) on D-7. Based on the Chi-square test results, no significant difference existed between treatment groups in terms of the number of subjects with ALT levels above 50 U/L either before treatment or on the seventh day after treatment. However, there was an improvement in the liver condition, which was indicated by a significant reduction in ALT levels on day 7 of therapy ($p < 0.0001$) for both treatment and Control groups. Based on these data, nearly a quarter of the total research samples had decreased liver function based on AST and ALT checkup before drug administration. After the 7th day, there was an improvement in liver function. Accordingly, there was no significant difference between AST and ALT in the treatment groups, both before treatment and on the 7th day after treatment.

Furthermore, 29 patients in the study had pretreatment serum creatinine levels above 1.2 mg/dL, a total which increased to 62 on D-7. The Chi-square test results indicated no significant difference after treatment in serum creatinine above 1.2 mg/dL between treatment groups on both D-1 and D-7. Although a statistical increase in the median serum creatinine level occurred, it remained biologically safe. All study samples had BUN levels ≤43 mg/dL, which were still within normal limits on both D-1 and D-7. Paired t-test results showed an increase in BUN levels in all treatment groups. However, again, the levels continued to fall within normal limits.

4. Discussion

In the present study, the efficacy and safety of drug combination therapies consisting of lopinavir/ritonavir, azithromycin, doxycycline, and hydroxychloroquine were investigated in a randomized, double-blind clinical study design. Several parameters have been determined, including clinical signs and hematological laboratory data comprising blood count, D-dimer, CRP, cytokines profiling, and qualitative and quantitative PCR assays for the virus load to evaluate the efficacy of the drug combinations used in COVID-19 therapy. The safety aspect of the drugs was assessed by observation of clinical discomfort and liver-kidney function test results. The subjects in this study were reasonably distributed in age, ranging between 21 and 55 years, with the majority diagnosed with a mild case of COVID-19. However, the disease progression of COVID-19 increased the mortality rate. Moreover, the disease proved to be both highly contagious and promoting high-risk comorbidity. Therefore, curative action on mild COVID-19 cases constitutes an essential step in preventing the infection from spreading and worsening clinical conditions. Such action also has benefits in terms of reducing the period of self-isolation required for daily work stimulating economic growth.

Treatment groups A–E participating in this study showed improved PCR conversion results on day 3 when 92.9%–98.3% of subjects were confirmed as PCR negative. This figure differed significantly from that of the Control group which had been given azithromycin ($p < 0.05$). This result supports previously reported nonrandomized clinical trials that suggested a combination of several drugs was more effective than individual drugs [10]. However, only a particular type of medications was used to treat severe cases of COVID-19. However, the result of this study did not match that of the clinical trial conducted in China [11]. Moreover, the Chinese patients received lopinavir/ritonavir via a nasogastric tube due to their inability to swallow. Other studies reported that, for such cases, lopinavir/ritonavir would worsen the patient's condition [12].

Table 4: The adverse events observed in the research subjects during the study period.

Adverse events		Number of subjects (n)						p value
		Control	A	B	C	D	E	
Nausea						1	1	
Vomiting						1		
Dizziness		2	1			1		
Pruritus		1						
Tachycardia		1	1	1	1	1		
Hearing loss			1					
Abdominal pain			1			1	1	
Otalgia					1			
Diarrhea						1		
Taste loss							1	
Number of patients with leukocytosis (platelet count >12,000 per μL), n (%)								
Day 1		4 (3.4)	4 (3.1)	4 (3.2)	4 (3.3)	3 (2.3)	5 (3.9)	0.543
Day 7		1 (1.0)	0 (0.0)	2 (1.7)	1 (0.9)	1 (0.9)	2 (1.7)	0.891
Number of patients with thrombocytopenia (platelet count <150,000 per μL), n (%)								
Day 1		2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	3 (2.3)	0.331
Day 7		1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.6)	0.147
Number of patients with lymphocytopenia (lymphocyte count <1,500 per μL), n (%)								
Day 1		6 (5.1)	6 (4.7)	12 (9.7)	10 (8.3)	12 (9.2)	10 (7.8)	0.559
Day 7		2 (1.9)	3 (2.4)	11 (9.3)	7 (6.1)	5 (4.4)	7 (6.0)	0.102
Number of patients with an increase of AST level, n (%)								
Day 1	>33 U/L	36 (30.5)	31 (24.4)	22 (17.7)	23 (19.0)	31 (23.8)	35 (27.1)	0.168
Day 7	>33 U/L	19 (18.1)	13 (10.2)	8 (6.8)	20 (17.4)	13 (11.4)	22 (19.0)	0.029
Number of patients with an increase of ALT level, n (%)								
Day 1	>50 U/L	27 (22.8)	27 (21.3)	22 (15.7)	19 (15.7)	34 (26.2)	35 (27.1)	0.185
Day 7	>50 U/L	21 (20.0)	19 (14.8)	12 (10.2)	21 (18.3)	14 (12.3)	21 (18.1)	0.270
Number of patients categorized according to serum creatinine level, n (%)								
Day 1	>1.2 mg/dL	4 (3.4)	6 (4.8)	4 (3.2)	3 (2.5)	7 (5.4)	5 (3.9)	0.860
Day 7	>1.2 mg/dL	9 (8.6)	8 (6.3)	8 (6.8)	11 (9.6)	11 (9.6)	15 (12.9)	0.515
Median level of AST (U/L, min–max)								
Day 1		27 (13–69)	25 (12–78)	26 (12–78)	25 (5–68)	26 (13–65)	26 (13–213)	
Day 7		27 (17–49)*	22 (14–55)***	24 (14–58)**	25 (6–92)*	25 (14–53)*	25 (16–73)*	<0.05*
Median level of ALT (U/L, min–max)								
Day 1		34 (12–144)	32 (16–142)	32 (3–106)	31 (14–141)	36 (11–116)	35 (7–337)	
Day 7		33 (16–106)***	26 (12–140)***	28 (2–137)***	35 (14–205)***	32 (2–91)***	28 (8–128)***	<0.05*

Table 4: Continued.

Adverse events	Number of subjects (n)						p value
	Control	A	B	C	D	E	
Median level of creatinine serum (mg/dL, min–max)							
Day 1	0.95 ± 0.12	0.93 (0.68–1.34)	0.96 ± 0.12	0.95 (0.77–1.34)	0.97 ± 0.14	0.97 ± 0.13	
Day 7	0.99 ± 0.16**	0.94 (0.67–1.37)	0.95 ± 0.13	0.96 (0.71–1.31)*	1.02 ± 0.16***	0.99 ± 0.15**	<0.05*
BUN level (mg/dL)							
Day 1	10.7 ± 2.2	11.3 ± 1.8	11.1 (6.4–15.8)	11.2 (7.2–18.6)	11.1 ± 2.3	11.3 ± 2.1	
Day 7	11.6 ± 2.5***	11.9 ± 2.2***	11.7 (7.0–21.3)***	12.0 (8.3–20.1)***	12.4 ± 2.5***	13.0 ± 2.6***	<0.05*

Control group: 1 × 500 mg azithromycin per day; Group A: 2 × 200/50 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group B: 2 × 200/50 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; Group C: 2 × 100 mg hydroxychloroquine + 1 × 500 mg azithromycin per day; Group D: 2 × 400/100 mg lopinavir/ritonavir + 1 × 500 mg azithromycin per day; Group E: 2 × 400/100 mg lopinavir/ritonavir + 2 × 100 mg doxycycline per day; AST: aspartate aminotransferase serum; ALT: alanine aminotransferase serum. Normally distributed data presented in mean ± SD was analyzed by means of a paired t-test, whereas the other data was analyzed using a Wilcoxon signed-rank test. * $p < 0.05$ compared to day 1, ** $p < 0.001$ compared to day 1, and *** $p < 0.0001$ compared to day 1.

During the viral copy number or viral load measurement, subgroups other than mild COVID-19 were included since the high rate of recovery in this group enabled rapid positive PCR conversion. The comprehensive analysis showed a significant decrease in subjects with positive PCR for COVID-19 in Groups A to E, which differed significantly from the Control group ($p < 0.0001$). This remarkable discovery revealed that treated groups whose drug combinations contain azithromycin experienced rapid declining rates compared to nonazithromycin groups (day 3 as against day 7). Azithromycin plays a role in rapidly decelerating the process of viral penetration of a cell and as an immunemodulator agent in increasing the production of interferon types I and III [13]. Moreover, azithromycin could activate MDA-5, while RIG-1 genes regulated the viral presentation in cells [14]. The unforeseen result of Group B was a consequence of administering a half dose of lopinavir/ritonavir compared to Group E which experienced a significant decline in viral load. The subanalysis was applied to the group receiving azithromycin combined with hydroxychloroquine (Group C) and resulted in higher viral load declining rates than in the group treated with lopinavir/ritonavir (Group A), 87% and 74.8%, respectively. This result was noteworthy since a previous study had reported that, in mild and moderate COVID-19, a single dose of these drugs produced the opposite effect [15]. Despite using the drug combination therapy, the present investigation involved a larger sample size and several study centers-conducted evaluations.

Hyperinflammatory responses in COVID-19 cases indicated a major decline in the patient's clinical condition. Moreover, the worsening condition was due to the elevation of proinflammatory cytokines levels, i.e., IL-6. Serologically, the IL-6 level increased in COVID-19 patients as their clinical symptoms worsened [16, 17], together with the initial indicator of their cytokine-level fluctuations [18–20]. Other symptoms included an impaired coagulation predictor [21] and severe lung damage [22] necessitating emergency mechanical ventilation [23] and increasing COVID-19 patient mortality [24]. The present study revealed a significant decrease in IL-6 ($p < 0.0001$) on day 7 across all treatment groups (Groups A–E and the Control group). This inconsistency might be due to the role of SARS-CoV-2 in modulating the immune system. As previously reported, the level of IL-6 expression could be activated with other cytokines like TNF-α and IL-1β [25], as shown in the murine protein model of SARS-CoV-1. This protein has a high structural similarity to SARS-CoV-2 that N (nucleocapsid) protein directly influenced the secretion of IL-6 through NF-$\kappa\beta$ [26]. The previous discovery was strongly supported by the relation between IL-6 serological level and viral load counts [27]. However, significant variation of IL-10 level was only observed in Groups A and B. Despite its full mechanism remaining unknown, a contradictive result of IL-10 measurement indicated more severity and a higher mortality rate in MERS [28]. The complete opposite is shown in SARS-CoV-1 [29]. The dynamic of IL-10 alteration rates indicates that, as an anti-inflammatory marker, the cytokines level fluctuates in response to a high level of proinflammatory cytokine. Based on this theory, the cytokine level measurement in this study could not depict the dynamic changes during the COVID-19 infection since it had been taken twice during the treatments administered.

Another inflammation indicator used to predict worsening clinical condition in COVID-19 patients is the C-reactive protein (CRP) level [30, 31]. CRP levels decreased significantly on day 7 in all treated groups (Group A–E and the Control group) with a median level of 0.6-0.7 mg/dL which was lower than the cutoff value for high-risk patients (2.69 mg/dL). In this study, the decrease of CRP and D-dimer levels was measured on days 3 and 7. However, there were no significant differences with the Control group ($p > 0.05$) which was probably due to the anti-inflammation effect of azithromycin and doxycycline [32].

Due to the patient's pre-COVID-19 infection medical history, he/she often suffered liver damage as a direct result of the severity of treatment [33, 34]. The condition was worsened by the continued use of hepatotoxic medications such as lopinavir/ritonavir [5, 35]. In this study, a significant rise in the ALT level was observed only in Group C ($p < 0.05$), although no significant clinical effect ensued from the difference (31 mg/dL on day 1 to 35 mg/dL on day 7). Moreover, the prolonged QT interval represented a severe adverse event for hydroxychloroquine-based therapy such as was the case for one subject in Group C. The previous prediction had been based on a toxicity test of mesenchymal cells which reported that the CC_{50} level used in drug combination therapies was lower than that of a single administration of each drug (unpublished data). A kidney function test revealed that the BUN level increased significantly ($p < 0.05$) in all treated groups (Groups A–E and the Control group), although it had no effect on the patient's clinical condition. However, there were no significant differences in any treatment groups other than the Control group, which suggests that every subject experienced different effects during treatments.

During the evaluation, the imbalanced proportional subject distribution and the inadequate analytical laboratory equipment employed at different research sites emerged as the significant drawbacks of this study. Nevertheless, this did not reflect the current condition of hospitals in Indonesia. The broad range of patient symptoms and degree of severity of the disease should be further investigated to enhance current understanding of the benefits of drug combination therapies in relation to the contrasting severity of the disease in COVID-19 patients. The last drawback was due to the upper age limit of subjects being set at 55. This study did not demonstrate the nature of the efficacy of drug combination therapies and drug safety with regard to the geriatric age group.

5. Conclusion

The present study confirmed that the proposed combined therapies successfully accelerated the process of PCR negative conversion compared to the Control group which had been administered with azithromycin. Moreover, the inflammation rate decreased on day 7 of the study. Clinical test and liver-kidney function examination results confirmed that the proposed combination of drugs is safe for clinical use. Further studies must be conducted in the near future with older subjects presenting severe symptoms in order to obtain advanced demographic data.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

The researchers conducted the clinical trials across multicenter sites through collaboration between Universitas Airlangga, the Indonesian Intelligence Agency (BIN), and the Indonesian National Army (TNI-AD). This study was conducted in strict accordance with the approved clinical trial protocols (PPUK) provided by BPOM (No. PP.01.01.1.3.07.20.06) with an additional letter of approval from the National Institute of Health Research and Development, Indonesian Ministry of Health (Balitbangkes Kementerian Kesehatan RI), and ethical approval no. 159/KEP/2020 issued by the Ethics Committee of Universitas Airlangga Hospital (RS UNAIR) on June 23, 2020. The documents submitted to secure PPUK clearance can be found at the following URL: https://www.ina-registry.org/?act=registry_trial_detail&code_trial=11202034090121TX6YYSS.

Conflicts of Interest

The authors declare no conflicts of interest regarding this work.

Acknowledgments

The authors express their gratitude to the Indonesian Intelligence Agency (BIN) as the primary sponsor of this research and collaboration with the Indonesian National Army (TNI-AD). They also thank Universitas Airlangga for its invaluable support of the publication of the research and all the clinicians and medical and laboratory staff for their indispensable assistance with this study.

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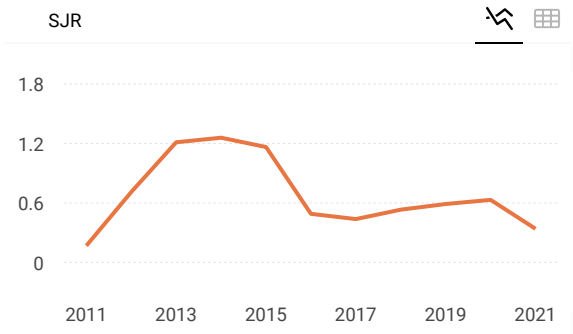

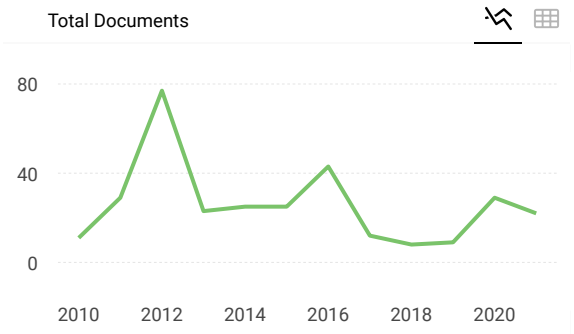

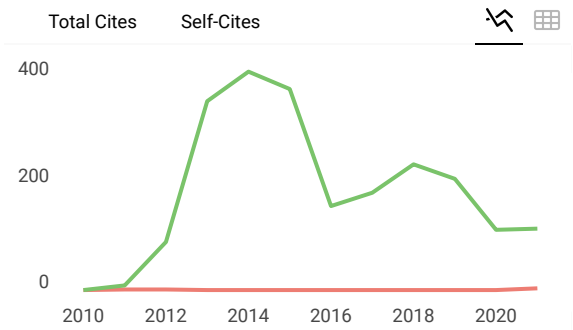

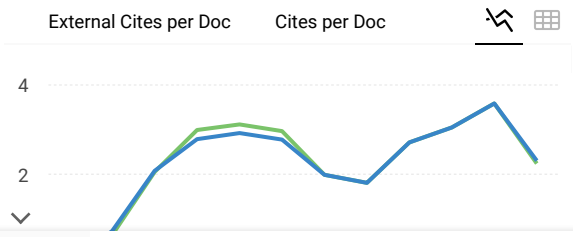

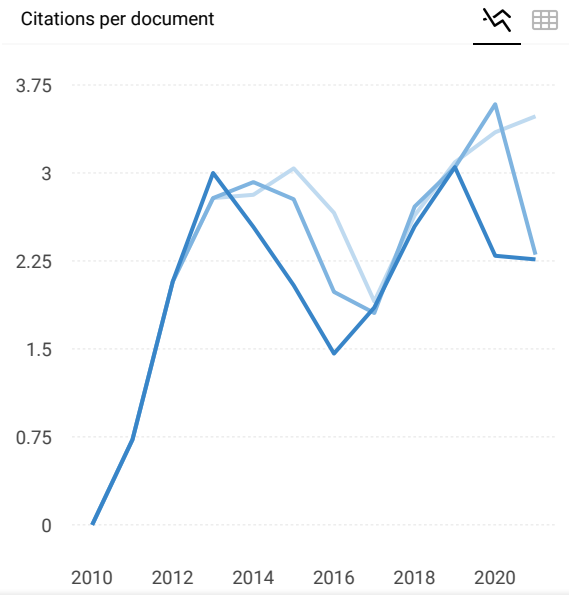

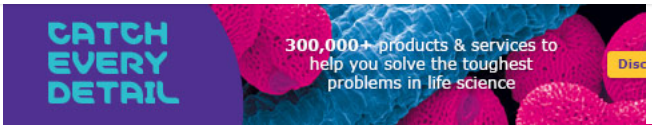

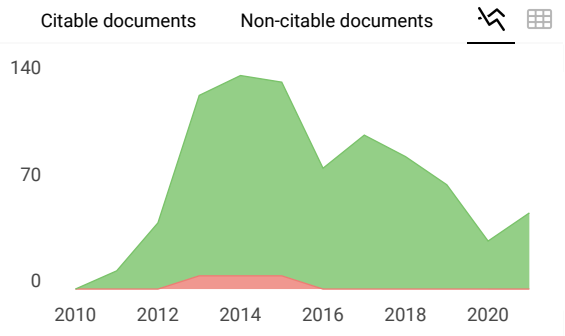

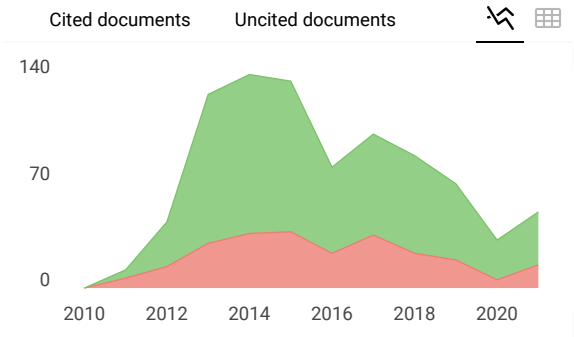

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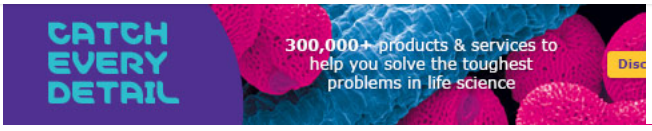

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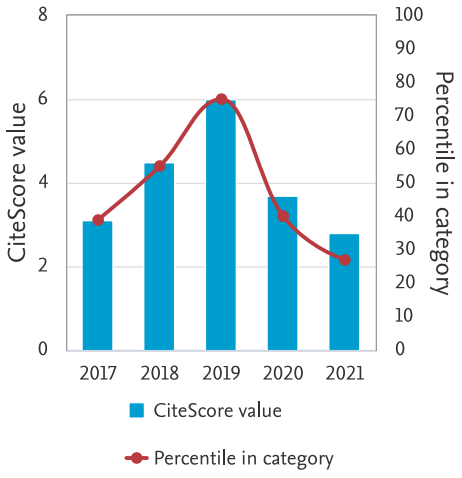

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☆	#190	Advances in Heterocyclic Chemistry	5.5	55th percentile
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☆	#192	Journal of Biomolecular NMR	5.4	54th percentile
☆	#193	Microvascular Research	5.4	54th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#194	Cell Biochemistry and Function	5.4	54th percentile
☆	#195	European Food Research and Technology	5.4	54th percentile
☆	#196	Chinese Journal of Chemical Engineering	5.3	54th percentile
☆	#197	Bioactive Carbohydrates and Dietary Fibre	5.3	53rd percentile
☆	#198	Pharmacology Biochemistry and Behavior	5.2	53rd percentile
☆	#199	Biomimetics	5.2	53rd percentile
☆	#200	BioTech	5.2	53rd percentile
☆	#201	Journal of Cluster Science	5.2	52nd percentile
☆	#202	ChemBioEng Reviews	5.2	52nd percentile
☆	#203	Current Plant Biology	5.2	52nd percentile
☆	#204	Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology	5.2	52nd percentile
☆	#205	Chemical Biology and Drug Design	5.2	51st percentile
☆	#206	Computational Biology and Chemistry	5.1	51st percentile
☆	#207	Bioinspiration and Biomimetics	5.1	51st percentile
☆	#208	Applied Biochemistry and Biotechnology	5.1	51st percentile
☆	#209	Journal of Biochemical and Molecular Toxicology	5.0	50th percentile
☆	#210	Hormone and Metabolic Research	5.0	50th percentile
☆	#211	Cytokine: X	5.0	50th percentile
☆	#212	Bioorganic and Medicinal Chemistry Letters	5.0	50th percentile
☆	#213	Integrative Biology (United Kingdom)	4.9	50th percentile
☆	#214	Steroids	4.9	49th percentile
☆	#215	Molecular Biotechnology	4.9	49th percentile
☆	#216	Water (Switzerland)	4.8	49th percentile
☆	#217	Journal of Chemical Ecology	4.7	49th percentile
☆	#218	Molecular Omics	4.7	48th percentile
☆	#219	Metabolites	4.7	48th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#220	Journal of Thermal Biology	4.6	48th percentile
☆	#221	International Journal of Genomics	4.6	48th percentile
☆	#222	Current Bioinformatics	4.6	47th percentile
☆	#223	Journal of Magnetic Resonance	4.6	47th percentile
☆	#224	Chemical and Biological Technologies in Agriculture	4.6	47th percentile
☆	#225	Journal of Biochemistry	4.5	47th percentile
☆	#226	Crystallography Reviews	4.5	46th percentile
☆	#227	Tetrahedron	4.5	46th percentile
☆	#228	Current protocols in mouse biology	4.5	46th percentile
☆	#229	Plasmonics	4.5	46th percentile
☆	#230	Food Bioscience	4.5	46th percentile
☆	#231	Biophysical Chemistry	4.5	45th percentile
☆	#232	Peptide Science	4.4	45th percentile
☆	#233	Biocatalysis and Biotransformation	4.4	45th percentile
☆	#234	Journal of Organometallic Chemistry	4.4	45th percentile
☆	#235	Fish Physiology and Biochemistry	4.3	44th percentile
☆	#236	Biopolymers	4.3	44th percentile
☆	#237	Journal of Muscle Research and Cell Motility	4.3	44th percentile
☆	#238	Brazilian Journal of Medical and Biological Research	4.3	44th percentile
☆	#239	Tetrahedron Letters	4.3	43rd percentile
☆	#240	Biomarkers	4.2	43rd percentile
☆	#241	Comparative Biochemistry and Physiology - B Biochemistry and Molecular Biology	4.2	43rd percentile
☆	#242	Biochemistry (Moscow)	4.2	43rd percentile
☆	#243	Comparative biochemistry and physiology. Part A, Molecular & integrative physiology	4.2	42nd percentile
☆	#244	Iranian Journal of Basic Medical Sciences	4.1	42nd percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#245	Alcohol	4.1	42nd percentile
☆	#246	BioData Mining	4.1	42nd percentile
☆	#247	Journal of Labelled Compounds and Radiopharmaceuticals	4.0	42nd percentile
☆	#248	Glycoconjugate Journal	4.0	41st percentile
☆	#249	Comparative Biochemistry and Physiology - Part D: Genomics and Proteomics	4.0	41st percentile
☆	#249	Current protocols in plant biology	4.0	41st percentile
☆	#251	Protein Journal	4.0	41st percentile
☆	#252	Cold Spring Harbor Symposia on Quantitative Biology	4.0	40th percentile
☆	#253	Bioinformatics and Biology Insights	4.0	40th percentile
☆	#254	Natural Product Research	4.0	40th percentile
☆	#255	Antibiotics	3.9	40th percentile
☆	#256	Journal of Fluorine Chemistry	3.9	39th percentile
☆	#257	Channels	3.9	39th percentile
☆	#258	Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology	3.9	39th percentile
☆	#259	Advances in neurobiology	3.8	39th percentile
☆	#260	Carbohydrate Research	3.8	38th percentile
☆	#261	Matrix Biology Plus	3.8	38th percentile
☆	#262	Physiological and Biochemical Zoology	3.8	38th percentile
☆	#263	Prion	3.8	38th percentile
☆	#264	Current Medical Science	3.8	38th percentile
☆	#265	Current Molecular Medicine	3.7	37th percentile
☆	#266	Chemistry and Biodiversity	3.7	37th percentile
☆	#267	Analytical Letters	3.7	37th percentile
☆	#268	Proteome Science	3.7	37th percentile
☆	#269	Acta Crystallographica Section A: Foundations and Advances	3.7	36th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#270	Chromatographia	3.6	36th percentile
☆	#271	Frontiers in Molecular Biosciences	3.5	36th percentile
☆	#272	Journal of Peptide Science	3.5	36th percentile
☆	#273	Epigenetics Insights	3.4	35th percentile
☆	#273	Journal of Receptor and Signal Transduction Research	3.4	35th percentile
☆	#275	Preparative Biochemistry and Biotechnology	3.4	35th percentile
☆	#276	Journal of Fluorescence	3.4	35th percentile
☆	#277	Current Organic Synthesis	3.4	34th percentile
☆	#278	Helvetica Chimica Acta	3.4	34th percentile
☆	#279	ChemTexts	3.4	34th percentile
☆	#280	OCL - Oilseeds and fats, Crops and Lipids	3.4	34th percentile
☆	#281	Xenobiotica	3.3	34th percentile
☆	#282	Lipids	3.3	33rd percentile
☆	#283	Bioscience, Biotechnology and Biochemistry	3.3	33rd percentile
☆	#284	Journal of Berry Research	3.3	33rd percentile
☆	#285	Cell Biochemistry and Biophysics	3.3	33rd percentile
☆	#286	Biomedical Chromatography	3.3	32nd percentile
☆	#287	Archives of Insect Biochemistry and Physiology	3.2	32nd percentile
☆	#288	Analytical and Bioanalytical Chemistry Research	3.2	32nd percentile
☆	#289	Chemical and Biochemical Engineering Quarterly	3.2	32nd percentile
☆	#290	Protein Engineering, Design and Selection	3.2	31st percentile
☆	#291	Plant Gene	3.2	31st percentile
☆	#292	Biochemistry and Biophysics Reports	3.1	31st percentile
☆	#293	Open Biotechnology Journal	3.1	31st percentile
☆	#294	Enzymes	3.1	30th percentile
☆	#295	Genes and Genomics	3.1	30th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#296	Chemical Papers	3.1	30th percentile
☆	#297	Computational and Theoretical Chemistry	3.1	30th percentile
☆	#298	Protein and Peptide Letters	3.1	30th percentile
☆	#299	Phytochemistry Letters	3.1	29th percentile
☆	#300	Journal of Essential Oil-Bearing Plants	3.0	29th percentile
☆	#301	Acta Naturae	3.0	29th percentile
☆	#302	Archives of Microbiology	3.0	29th percentile
☆	#303	Biochemical Genetics	2.9	28th percentile
☆	#304	Current protocols in chemical biology	2.9	28th percentile
☆	#305	Epigenomes	2.9	28th percentile
☆	#306	International Journal of Peptide Research and Therapeutics	2.9	28th percentile
☆	#307	Human Genome Variation	2.8	27th percentile
☆	#308	Biochemistry Research International	2.8	27th percentile
☆	#309	International Journal of Molecular and Cellular Medicine	2.8	27th percentile
☆	#310	Molecular Cytogenetics	2.8	27th percentile
☆	#311	Fisheries and Aquatic Sciences	2.7	26th percentile
☆	#312	Methods in Enzymology	2.7	26th percentile
☆	#313	Acta Histochemica et Cytochemica	2.7	26th percentile
☆	#314	Chemoecology	2.7	26th percentile
☆	#315	Journal of Solution Chemistry	2.6	26th percentile
☆	#316	Molecular Biology Research Communications	2.6	25th percentile
☆	#317	Cellular and Molecular Biology	2.6	25th percentile
☆	#318	International Journal of Chemical Kinetics	2.6	25th percentile
☆	#319	Annual Reports in Medicinal Chemistry	2.4	25th percentile
☆	#320	eMagRes	2.4	24th percentile
☆	#321	Indian Journal of Biochemistry and Biophysics	2.4	24th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#322	Journal of Bioinformatics and Computational Biology	2.4	24th percentile
☆	#323	Biointerface Research in Applied Chemistry	2.4	24th percentile
☆	#324	Journal of Liquid Chromatography and Related Technologies	2.3	23rd percentile
☆	#325	Advances and Applications in Bioinformatics and Chemistry	2.3	23rd percentile
☆	#326	Journal of Stem Cells and Regenerative Medicine	2.2	23rd percentile
☆	#327	Nanomedicine Research Journal	2.2	23rd percentile
☆	#328	Microbial Physiology	2.2	22nd percentile
☆	#329	Open Stem Cell Journal	2.2	22nd percentile
☆	#330	Journal of Carbohydrate Chemistry	2.2	22nd percentile
☆	#331	Advances in Biomembranes and Lipid Self-Assembly	2.2	22nd percentile
☆	#332	Biochemical Systematics and Ecology	2.1	22nd percentile
☆	#333	Biochemistry and Molecular Biology Education	2.1	21st percentile
☆	#334	Phosphorus, Sulfur and Silicon and the Related Elements	2.1	21st percentile
☆	#335	Biologia (Poland)	2.1	21st percentile
☆	#336	Iranian Journal of Biotechnology	2.0	21st percentile
☆	#337	Reports of Biochemistry and Molecular Biology	2.0	20th percentile
☆	#338	Rasayan Journal of Chemistry	2.0	20th percentile
☆	#339	Carbohydrate Chemistry	2.0	20th percentile
☆	#340	Fluoride - Quarterly Reports	2.0	20th percentile
☆	#341	Acta Crystallographica Section F:Structural Biology Communications	2.0	19th percentile
☆	#342	Nutrire	2.0	19th percentile
☆	#343	Journal of International Medical Research	2.0	19th percentile
☆	#344	Nucleosides, Nucleotides and Nucleic Acids	1.9	19th percentile
☆	#345	Magnesium Research	1.9	18th percentile
☆	#346	Reference Series in Phytochemistry	1.8	18th percentile

Rank	Source title	CiteScore 2021	Percentile
#347	Applied Biochemistry and Microbiology	1.7	18th percentile
#348	RSC Chemical Biology	1.7	18th percentile
#349	Planta Daninha	1.7	18th percentile
#350	Current Protocols in Nucleic Acid Chemistry	1.6	17th percentile
#351	AIMS Biophysics	1.5	17th percentile
#352	Amino Acids, Peptides and Proteins	1.5	17th percentile
#353	Turkish Computational and Theoretical Chemistry	1.5	17th percentile
#354	Folia Biologica	1.5	16th percentile
#355	Journal of Planar Chromatography - Modern TLC	1.4	16th percentile
#356	EuPA Open Proteomics	1.4	16th percentile
#357	Letters in Organic Chemistry	1.4	16th percentile
#358	Doklady Biochemistry and Biophysics	1.4	15th percentile
#358	Russian Journal of Bioorganic Chemistry	1.4	15th percentile
#360	RSC Green Chemistry	1.4	15th percentile
#361	Functional Foods in Health and Disease	1.4	15th percentile
#362	Biomolecular NMR Assignments	1.4	14th percentile
#363	Current Proteomics	1.3	14th percentile
#364	Phyton	1.3	14th percentile
#365	Comparative Exercise Physiology	1.3	14th percentile
#366	Biochemistry (Moscow) Supplement Series A: Membrane and Cell Biology	1.2	14th percentile
#367	Current Pharmaceutical Analysis	1.2	13th percentile
#368	Chinese Journal of Chromatography (Se Pu)	1.2	13th percentile
#369	Scientia Sinica Chimica	1.1	13th percentile
#370	Pteridines	1.1	13th percentile
#371	Current Chemical Biology	1.1	12th percentile
#372	Ukrainian Biochemical Journal	1.0	12th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#373	Mongolian Journal of Chemistry	1.0	12th percentile
☆	#374	International Journal Bioautomation	1.0	12th percentile
☆	#375	Progress on Chemistry and Application of Chitin and its Derivatives	1.0	11th percentile
☆	#376	Current Enzyme Inhibition	1.0	11th percentile
☆	#377	Ecological Genetics	1.0	11th percentile
☆	#378	Vestnik Tomskogo Gosudarstvennogo Universiteta, Biologiya	0.9	11th percentile
☆	#379	Current Issues in Pharmacy and Medical Sciences	0.9	10th percentile
☆	#380	Molekul	0.9	10th percentile
☆	#381	International Journal of Environmental Health Engineering	0.8	10th percentile
☆	#382	Journal of Hard Tissue Biology	0.8	10th percentile
☆	#383	Journal of Cellular Neuroscience and Oxidative Stress	0.8	10th percentile
☆	#384	Food Science and Technology (United States)	0.8	9th percentile
☆	#385	MolBank	0.8	9th percentile
☆	#386	Turkish Journal of Biochemistry	0.8	9th percentile
☆	#387	Biochemistry (Moscow) Supplement Series B: Biomedical Chemistry	0.7	9th percentile
☆	#388	Comprehensive Series in Photochemical and Photobiological Sciences	0.7	8th percentile
☆	#389	BBA Advances	0.7	8th percentile
☆	#390	Progress in Biochemistry and Biophysics	0.7	8th percentile
☆	#391	RSC Soft Matter	0.7	8th percentile
☆	#392	Cell Reports Methods	0.6	7th percentile
☆	#393	Malaysian Journal of Biochemistry and Molecular Biology	0.6	7th percentile
☆	#394	Organophosphorus Chemistry	0.6	7th percentile
☆	#395	Journal of Integrated OMICS	0.6	7th percentile
☆	#396	RNA Technologies	0.6	6th percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#397	Trends in Phytochemical Research	0.5	6th percentile
☆	#398	Chem-Bio Informatics Journal	0.5	6th percentile
☆	#399	Trends in Glycoscience and Glycotechnology	0.5	6th percentile
☆	#400	Chemical Physics Impact	0.5	6th percentile
☆	#401	Terra Latinoamericana	0.5	5th percentile
☆	#402	Current Bladder Dysfunction Reports	0.5	5th percentile
☆	#403	American Journal of Biochemistry and Biotechnology	0.5	5th percentile
☆	#404	Indian Journal of Heterocyclic Chemistry	0.4	5th percentile
☆	#405	Research Journal of Chemistry and Environment	0.4	4th percentile
☆	#406	Basrah Journal of Agricultural Sciences	0.4	4th percentile
☆	#407	Proceedings on Applied Botany, Genetics and Breeding	0.4	4th percentile
☆	#408	Tropical Journal of Natural Product Research	0.4	4th percentile
☆	#409	Nuclear Magnetic Resonance	0.4	3rd percentile
☆	#410	Indian Journal of Agricultural Biochemistry	0.4	3rd percentile
☆	#411	Current Topics in Peptide and Protein Research	0.4	3rd percentile
☆	#412	Progress in Plant Protection	0.3	3rd percentile
☆	#413	Research in Plant Disease	0.3	2nd percentile
☆	#414	Chinese Journal of Applied Chemistry	0.2	2nd percentile
☆	#415	Journal of Caffeine and Adenosine Research	0.2	2nd percentile
☆	#415	Synthesis Lectures on Biomedical Engineering	0.2	2nd percentile
☆	#417	International Journal of Membrane Science and Technology	0.2	2nd percentile
☆	#418	Pesticide Research Journal	0.2	1st percentile
☆	#419	Chinese Journal of Biologicals	0.2	1st percentile
☆	#420	Ratarstvo i Povrtarstvo	0.1	1st percentile
☆	#421	Advances in Weed Science	0.1	1st percentile

☆	Rank	Source title	CiteScore 2021	Percentile
☆	#422	Borneo Journal of Resource Science and Technology	0.1	0th percentile
☆	#423	International Journal of Secondary Metabolite	0.1	0th percentile
☆	#424	Seikagaku. The Journal of Japanese Biochemical Society	0.0	0th percentile
☆	#425	International Journal of Chemical and Biochemical Sciences	0.0	0th percentile

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