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CLINICAL OUTCOMES AND ADVERSE DRUG REACTIONS IN COVID-19 PATIENTS TREATED WITH HYDROXYCHLOROQUINE AND AZITHROMYCIN ALONE OR COMBINED

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Background. *Use of Hydroxychloroquine with or without Azithromycin is repurposed in SARS-CoV-2 in the absence of definitive treatment.*

Objective. *To evaluate the association between the use of Hydroxychloroquine and Azithromycin when given alone or in combination on clinical outcomes and adverse drug reactions among lab confirmed SARS CoV-2 positive patients admitted in a COVID tertiary care hospital of a University Medical college.*

Methods. *a retrospective observational comparative study was conducted. COVID-19 positive patients admitted in study hospital for management of COVID-19 were enrolled into the study. The patients were categorized into 4 treatment groups based on having received the following treatment during hospitalization: (A) Hydroxychloroquine with Azithromycin, (B) Hydroxychloroquine without Azithromycin (Hydroxychloroquine alone), (C) Azithromycin alone, and (D) Neither drug, defined as no receipt of either Hydroxychloroquine or Azithromycin in the record; other medications may have been dispensed.*

Results. *800 patients were enrolled. Mean±Standard deviation of duration of hospital stay (in days) for study Group A was 11.37±7.11, for Group B was 8.37±4.77, for Group C was 18.22 ± 5.69 and for Group D was 6.12±2.97. Mortality in Group A was 29.74%, Group B – 33.16%, Group C – 0% and in Group D – 1.32%.*

Conclusion. *Among hospitalized patients with COVID-19 treatment, Group C was associated with good clinical outcome. However, the interpretation of these findings may be limited by the observational design.*

KEYWORDS: COVID-19; hydroxychloroquine; azithromycin; SARS CoV-2

Introduction

In December 2019, several cases of pneumonia like disease were reported in the Wuhan city of China [1, 2]. The World Health Organisation (WHO) named this disease COVID-19. The causative agent for COVID-19 is the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2).

SARS-CoV-2 is the newest of the family and is currently the cause of COVID-19 across the world [3]. Within months after its onset in China, this virus had spread involving most of the countries of the world. In March 2020, WHO declared it as a pandemic [4]. According to the recent available data by the end of December 2020, approximately 95 million populations worldwide and 10 million individuals in India have been diagnosed as COVID-19 positive. Until December 2020, the recovery rate in Indian population was 95.77% while the mortality rate was 1.45 %.

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The sources of infection of SARS-CoV-2 are reported to be infected animal hosts and infected humans. Bats [7] are considered to be initial hosts of this virus strain [5]. Main modes of transmission for interhuman spread of SARS CoV-2 are respiratory droplets and contact transmission. Patients of COVID-19 commonly present with symptoms like fatigue, cough, fever, myalgia, and diarrhoea.

Most of the people infected with the virus experience mild-to-moderate respiratory illness and recover without requiring any special treatment. However, elderly and those with underlying medical problems or diseases are more likely to develop serious illness. Research published till date has shown evidence that COVID-19 cause cytokine storm [6]. Some reports also revealed that patients of COVID-19 are associated with hyper inflammation and increased production of cytokines such as interleukin (IL)-1, 2, 6, 8, 10, and 17 [4, 7]. This may be the reason of tissue damage in the lungs of moderate to severely infected patients. Reports have also suggested that cytokine storm may

cause cellular demise and tissue injury in cardiac system which may lead to cardiovascular arrest [5]. Conditions like ARDS and cardiac arrest require an emergent medical attention in an intensive care unit.

Since no drug therapy has been specifically and conclusively established for the prevention, control, and cure at the time of its onset. So, several drugs have been repurposed to manage the rapidly deteriorating public health situation.

Many initial researches published during the early months of 2020 had suggested that Hydroxychloroquine is highly effective in both prophylaxis and treatment of COVID-19 positive patients. In vitro studies have demonstrated that Chloroquine and Hydroxychloroquine can inhibit viral replication at multiple points in the initial phase of viral infection [8]. It is postulated to exert a direct antiviral activity by increasing intracellular pH resulting in decreased phagolysosome fusion, impairing viral receptor glycosylation [9].

Various other studies showed the potential role of Azithromycin in treatment of COVID-19 patients. Azithromycin is a potent immunomodulator with significant antiviral properties. Azithromycin, a macrolide antibiotic, has in-vitro antiviral properties such as decreased viral replication, blocking entrance into host cells, and a potential immunomodulating effect [10].

According to other researches, combination of both the drugs may be more effective in curing the disease but some have also contradicted this line of treatment and several studies have even supported the statement that combination of both is harmful to the patient because the combination may add or increase the severity of their adverse effects.

All the above reasons led us to carry out this pilot study including drugs Hydroxychloroquine and Azithromycin. The aim of this study was to evaluate clinical outcome and adverse drug reactions among hospitalised laboratory confirmed COVID-19 positive patients treated with Hydroxychloroquine and Azithromycin either given alone or in combination.

Methods

This study received ethical approval from institutional ethics committee.

Study design: A retrospective, observational, comparative study.

Study population: All laboratory confirmed COVID-19 positive patients admitted in study hospital from March 2020 to July 2020.

Sample size: COVID-19 positive patients have been admitted in study hospital for management of COVID-19. Out of these, all those patients, who matched the inclusion and exclusion criteria, were enrolled in the study.

Inclusion and Exclusion criteria

Inclusion criteria:

1. All laboratory confirmed COVID-19 positive patients admitted in RUHS-HMS between March-July 2020.

2. Patients of both genders and above the age of 12 years old.

Exclusion criteria:

1. Patients whose hospital stay was less than 5 days (due to any reason).

2. Incomplete case files.

Study Groups:

Patients were categorized into 4 treatment Groups based on having received the following treatment during hospitalization:

(A) Hydroxychloroquine with Azithromycin,

(B) Hydroxychloroquine without Azithromycin (Hydroxychloroquine alone),

(C) Azithromycin alone, and

(D) Neither drug, defined as no receipt of either Hydroxychloroquine or Azithromycin in the record; other medications may have been dispensed.

Results

A total of 800 case records of lab confirmed COVID-19 positive patients admitted to RUHS Hospital of Medical Sciences from March to July were reviewed and enrolled in the study.

All the study Groups were compared via ANOVA test. This comparison included the parameters such as age, systolic blood pressure, diastolic blood pressure, SPO_2, and duration of hospital stay. Mean±standard deviation of each parameter of all groups were calculated. The obtained results of ANOVA test for all the study groups has p value less than 0.05, which represents a higher significance for the study. Observations and results of this test is shown in Table 1.

1. Gender distribution of patients as per groups

Results and observations obtained are presented in Fig. 1.

2. SPO_2 distribution as per group

Mean±Standard deviation of SPO_2 for study Group A was 89.6±7.1, for Group B was 90.24±7.44, for Group C was 91.63±5.34 and for Group D was 96.12±3.62. Results and observations obtained are presented in Fig. 2.

Table 1. ANOVA of the groups (N=800)

Parameters	ANOVA	Significance
Age	12.46	0.000001
Systolic BP	3.07	0.0271
Diastolic BP	3.01	0.02971
SPO_2 (in %)	19.01	0.000001
Hospital Stay	103.03	0.000001

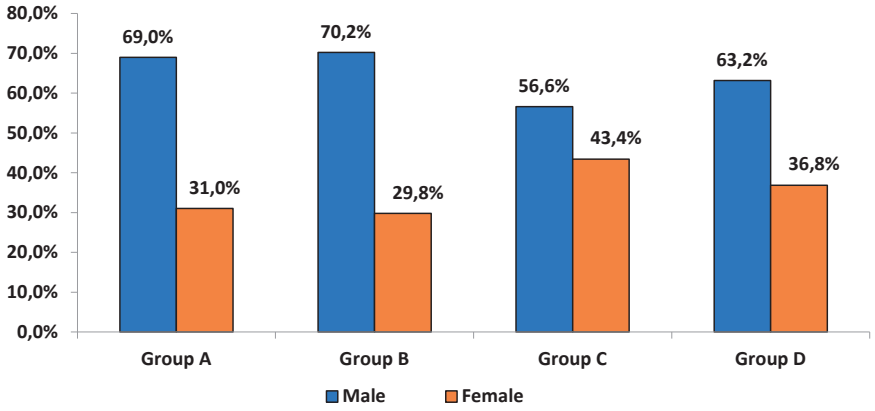

Fig. 1. *Gender distribution of patients as per groups (N=800).*

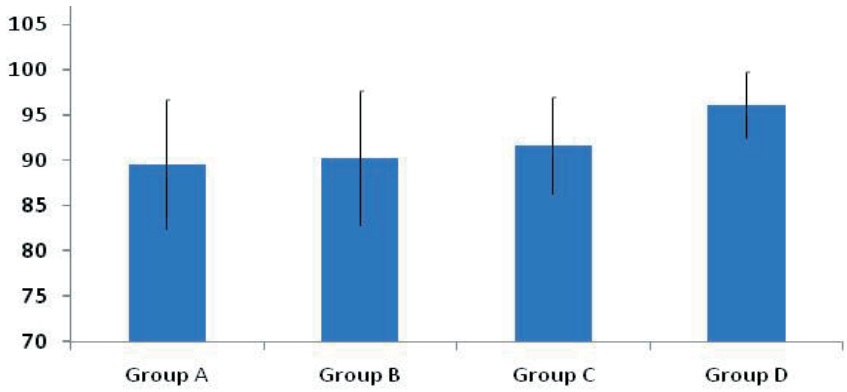

Fig. 2. *Mean and SD of SPO_2 (in %).*

3. Duration of Hospital stay distribution as per group

Mean±Standard deviation of duration of hospital stay (in days) for the study Group A was 11.37±7.11, for Group B – 8.37±4.77, for Group C – 18.22±5.69 and for Group D – 6.12±2.97. Results and observations obtained are presented in Fig. 3.

4. Severity of illness in study population

Severity of illness in study population in the study is classified as:

Asymptomatic – flu-like symptoms, patients are not hospitalized, and recover at home.

Mild symptoms – runny nose, sore throat, congestion, and dry cough.

Moderate symptoms – high fever, tiredness and fatigue, and chest pain.

Patients with severe symptoms – respiratory distress syndrome (shortness of breath, increased blood pressure, and decreased oxygen saturation).

Patients in the critical stage – Severe Acute Respiratory Syndrome (SARS) (high fever, chest pain, and breathlessness).

Patients with mild-moderate symptoms were categorized in one group and patients with severe symptoms and patients with critical stage were categorized in another group.

Chi-square test was applied for evaluation which was 72.73, and p value for this was

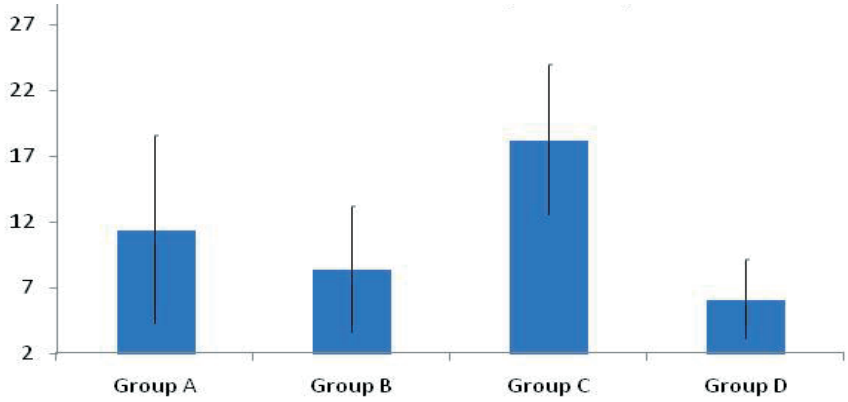

Fig. 3. *Mean and SD of hospital stay (in days).*

0.0000001, which was highly significant for our study. Severity of illness was highly significant with p-value 0.000001 (chi-square=72.73). Results and observations obtained are presented in Fig. 4.

5. Comparison of the clinical outcome of all the groups on the basis of illness severity and presence or absences of co-morbidity (Table 2).

6. Adverse events observed during study

Total numbers of adverse events observed in this study were 3. Two patients experienced itching over the body and they were associated to Group A and 1 patient of Group B experienced diarrhoea. Observations and results are shown in Table 3.

Discussion

For the evaluation of the treatment efficacy in our study two variables were examined. The first was the duration of hospital stay and the second was outcome (discharged or death). In the present study, duration of hospital stay for Group A was 8 days (IQR: 5-16), Group B – 7 days (IQR: 5-9), Group C – 18 days (IQR: 15-20), and Group D – 5 days (IQR: 5-6). The Mean±SD for Group A, B, C, D was 11.37±7.11, 8.37±4.77, 18.22±5.69, and 6.12±2.97 respectively. p value was 0.000001 and was highly significant. Group D had the shortest duration of hospital stay. Possible reasons for this could be that in Group D, 98.68% were mild-moderately ill. Also, SPO_2 which was an important clinical feature in COVID-19 was maximum for Group D (median 97.5, IQR: 95-99, and mean±SD 96.12±3.62) with a p value of 0.000001. Therefore, we can infer that milder disease severity and least deranged clinical features in Group D may have resulted in faster recovery and a shorter duration of hospital stay. Another reason can be that in Group D only 14.47% patients were having underlying comorbidities. This could also be important factor since presence of co-morbidities is now known to adversely affect the course of illness.

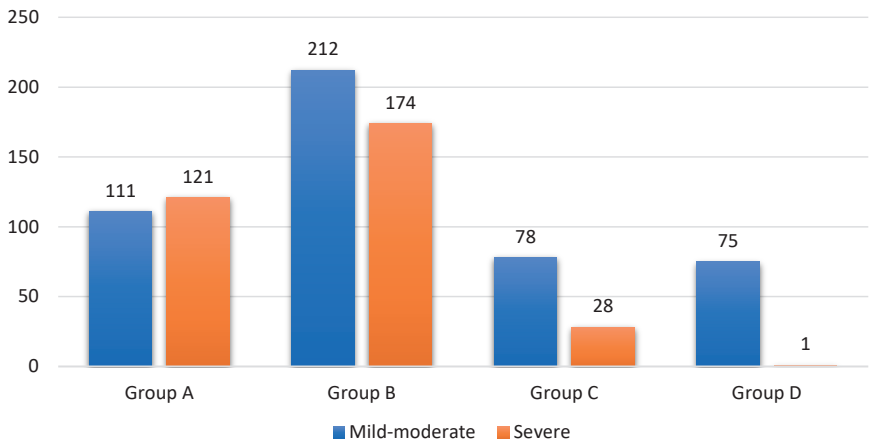

Fig. 4. *Distribution of illness severity (N=800).*

Table 2. Comparison of clinical outcome among all groups

	A			B			C			D		
	Hospital stay	Recovery	Death	Hospital stay	Recovery	Death	Hospital stay	Recovery	Death	Hospital stay	Recovery	Death
Mild-moderate comorbid patients	16.1	27.03% (N=30)	0% (N=0)	8.3	13.67% (N=29)	0% (N=0)	18.94	88.46% (N=69)	0% (N=0)	6.9	13.33% (N=10)	0% (N=0)
Mild-moderate patients without comorbidity	10.6	72.97% (N= 81)	0% (N=0)	8.4	86.32% (N=183)	0% (N=0)	8.25	11.53% (N=9)	0% (N=0)	6.3	86.66% (N=65)	0% (N=0)
Severe comorbid patients	11.97	33.88% (N=41)	42.14% (N=51)	7.7	16.66% (N=29)	56.32% (N=98)	21.04	100% (N=28)	0% (N=0)	14	0% (N=0)	100% (N=1)
Severe patients without comorbidity	7.9	9.09% (N=11)	14.8% (N=18)	8.2	9.77% (N=17)	17.24% (N=80)	0	0% (N=0)	0% (N=0)	0	0% (N=0)	0% (N=0)

Table 3. Adverse events observed during study

ADR	Group A	Group B	Group C	Group D
Diarrhoea	0	1	0	0
Itching	2	0	0	0
NIL	230	385	106	76
Total	232	386	106	76

The longest duration of hospital stay was in Group C which was having Median 18, IQR: 15-20 and mean±SD for 18.22±5.69. Despite of having borderline SPO_2 (Median 92, IQR:88-96 and mean±SD 91.63 ±5.34) with 73.58% patients of this Group being mild-moderately ill, still this Group had the longest duration of hospital stay. Possible reasons could be that 92.45% patients of this group were having underlying comorbidities.

Second variable which was observed in our study was clinical outcome. Two possible clinical outcomes were considered; recovered and discharged – meaning a good clinical outcome, and death -denoting a poor clinical outcome.

Samia Arshad et. al [9] found in a retrospective observational study that overall mortality was 18.1%, 20.1% by treatment with the combination of Hydroxychloroquine with Azithromycin, 13.5% with Hydroxychloroquine alone, 22.4% with Azithromycin alone and 26.4% with neither drug. According to their results Hydroxychloroquine provided 66% hazard ratio reduction and Hydroxychloroquine with Azithromycin 71% compared to neither treatment ($p<0.001$).

In the present study good clinical outcome was observed in Group C. In Group C 100% of the patients were discharged whether in Group A only 66.37% were discharged. Various factors could cause this. Chi square test was applied to measure the significance of illness severity in the population. Results of this test showed p=0.000001, it means severity of illness was highly significant. In Group C 98.68% patients were mild moderately ill and only 1.34% were severely ill. Another reason could be that SPO_2 as SPO_2 was 91.63±5.34 (p value 0.000001), which showed high significance. It may have led to decreased mortality in this Group.

To validate this overall result sub-Group analysis was performed. Thus it was established that in the patients, who were mild to moderately ill with comorbidities, maximum recovery or good clinical outcome were observed in Group C (88.46%). Similarly, when severely ill comorbid patients were evaluated again maximum recovery or good clinical outcome were observed in Group C (100%). It was also observed that in both groups of comorbidities (mild-moderate and severe) the longest duration of hospital stay was in Group C. In Group C the mean of

hospital stay for mild-moderate comorbid patients was 18.24 and for severely ill co-morbid patients it was 21.04. It proved that in our study effective treatment in the co-morbid patients was observed in Group C among all patients but it took more time to recover comparatively to other groups.

However, in patients without co-morbidities maximum recovery was evidenced in Group B. For Group B patients, who were mild-moderately ill with no co-morbidities, recovery was 86.32% and for severely ill without co-morbidity, recovery was 9.77%. In Group D recovery in mild-moderate non-co-morbid patients was 86.6%, which was slightly higher than in Group B, but for severely ill non-comorbid patients, recovery rate was higher in Group B. So, the overall recovery for non-comorbid patients was higher in Group B. The duration of hospital stay for mild-moderately ill Group B patients with comorbidities was 8.3 and for patients without comorbidities it was 8.4. For severely ill Group B patients with comorbidities it was 7.7 and for patients without comorbidities – 8.2. This data also revealed that patients of Group B without comorbidities had longer duration of hospital stay than the non-co-morbid patients.

Poor clinical outcome was measured by number of deaths. The highest mortality was observed in Group B with 33.16% death. Factors which influenced this result could be that 70.2% of patients of this Group were males. Males were more prone to lung infection due to their habits like smoking. Smoking habit is associated with males in Indians comparative to females. Therefore, this could be a reason for a greater number of deaths. In this Group 45.07% patient were severely ill. So, risk was higher for them compare to mild-to-moderate ill patients. 40.9% patients with underlying comorbidities were present in this Group which can have led to poor clinical outcome.

Sub-Group analysis revealed that there were no deaths in mild-moderately ill patients in both co-morbid and non-co-morbid groups. All the deaths were associated with severely ill patients. The highest mortality among all severely co-morbid patients was associated with Group D, which was 100%. There were no patients in Group D with non-co-morbidity. After that, the maximum deaths of non-co-comorbid patients were seen in Group B (17.24%).

Results of our study revealed that Group C treatment in comorbid patients were more effective and similar treatment in Group D was not safe. Recovery ratein mild-moderately ill comorbid patients was higher (27.03%) in the Group A compare to Group B (13.67%). However, in mild-moderately ill non-co-morbid patients, higher recovery was observed in Group B (86.32%) compared to Group A (72.97%). In severely ill co-morbid patients decreased mortality (42.14%) and increased recovery (33.88%) was seen in Group A compare to Group B, where mortality was 56.32% and recovery was 16.66%. In non-co-morbid severely ill patients, recovery in both groups (A – 9.09% and B – 9.77%) was almost the same but mortality was lesser in Group A (14.80%) compare to Group B (17.24%). These findings revealed that on the whole Group C treatment was the best among all and among groups A and B, Group A was better than B.

Similar results have been shown in the study by Matthieu Million et. al [11]. They also conducted a retrospective analysis of early treatment of COVID-19 patients with Hydroxychloroquine and Azithromycin. A poor clinical outcome was observed in 4.3%. They concluded that this combination was safe and associated with low fatality rate in patients.

Adverse events distribution in the study

In the present study safety of the treatment was also observed by adverse events. Very few adverse events were reported and they were mild which were associated with Group A and B. Reason for this is because of retrospective study, we are unable to analyse all those events which were not mentioned in case record files.

Conclusion

The present study concluded that no deaths were observed in mild-moderately ill patients with or without comorbidity. Among four groups, treatment in Group C (Azithromycin-500 mg OD for 5 days) had better results. Between groups A (Hydroxychloroquine with Azithromycin) and B (alone Hydroxychloroquine 400 mg BD on day 1 followed by 200 mg BD on day 2 to 5), treatment in Group A had better outcome. The duration of hospital stay was longer for comorbid patients compare to patients with no comorbidity.

Limitations

Though, we did our best to make this study without any blemish but several limitations make the scope for future study. It was a retrospective observational study. Therefore, regarding the data we had to rely on the case records and the mentioned records. There might be a few findings which were not

mentioned in the records but may have been present in the patients. We could not note them. Time constraint was the major limitation. So, we were unable to analyse the data on the basis of each sub-group. The data were incomplete for some patients because services were overwhelmed. CT scans, ECG and potential cofounders such as inflammatory markers associated with severity of the disease were not frequently measured/recorded. Mortality was limited to in-hospital death and patients, who were discharged or referred, were assumed to still be alive during study period. Because of retrospective analysis, we were not able to record all adverse events. Therefore, the evaluation of the safety was not adequate. For this, prospective randomized controlled trials may have been conducted at that time.

Conflict of interest

Authors declare no conflict of interest.

Acknowledgment

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Author's contribution

Heena Rathi, Priyanka Rathi – conceptualization, methodology, formal analysis, writing – original draft; *Heena Rathi, Mohit Biyani* – data curation, investigation; *Heena Rathi, Priyanka Rathi, Mohit Biyani* – writing, reviewing and editing.

НАСЛІДКИ ТА ПОБІЧНІ РЕАКЦІЇ ПРИ ЛІКУВАННІ ПАЦІЄНТІВ З COVID-19 ГІДРОКСИХЛОРОХІНОМ ТА АЗИТРОМІЦИНОМ ОКРЕМО ТА В КОМБІНАЦІЇ

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Вступ. *Застосування гідроксихлорохіну самостійно або у комбінації з азитроміцином – одна з опцій терапії SARS-CoV-2 за відсутності чітко визначеного лікування.*

Мета. *Оцінити вплив застосування гідроксихлорохіну та азитроміцину у якості монотерапії чи у комбінації на клінічні результати та частоту розвитку побічних реакцій серед пацієнтів з лабораторно підтвердженої інфекцією SARS-CoV-2, які були госпіталізовані до спеціалізованої COVID-лікарні при медичному коледжі університету.*

Методи. *Було проведене ретроспективне спостережне порівняльне дослідження. У дослідженні брали участь госпіталізовані пацієнти з лабораторно підтвердженим діагнозом COVID-19. Пацієнти були розділені на 4 групи, базуючись на лікуванні яке вони отримували під час госпіталізації: (A) гідроксихлорохін з азитроміцином, (B) гідроксихлорохін без азитроміцину (лише гідроксихлорохін), (C) лише азитроміцин та (D) жоден з препаратів не призначався; могли застосовуватися інші ліки.*

Результати. *Було залучено 800 пацієнтів. Середнє значення±стандартне відхилення тривалості перебування в лікарні (у днях) для досліджуваної групи A становило 11,37±7,11, для групи B – 8,37±4,77, для групи C – 18,22±5,69 та для групи D – 6,12±2,97. Смертність у групі A становила 29,74%, групі B – 33,16%, групі C – 0%, а групі D – 1,32%.*

Висновок. *Серед госпіталізованих пацієнтів з COVID-19 лікування у групі C (лише азитроміцин) було пов'язане з позитивними клінічними результатами. Однак інтерпретувати висновки остаточно неможливо через обмеження і рамки проведеного дослідження.*

КЛЮЧОВІ СЛОВА: COVID-19; гідроксихлорохін; азитроміцин; SARS-CoV-2.

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