OBJN
ONLINE BRAZILIAN JOURNAL OF NURSING
ISSN: 1676-4285

ORIGINAL

COVID kit adverse effects and mortality in critically ill patients: cross-sectional study

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Submission: 22-Jun-2024
Approved: 03-Nov-2024

ABSTRACT

Objective: To compare the outcomes of the COVID-19 patients who used the COVID Kit in their treatment with those who did not. **Methods:** This was a single-center, analytical, cross-sectional, and observational study. **Results:** The study included 49 COVID-19-positive patients; from those, 65.4% were over 50 years old, 50.0% were male, 36.5% were brown, 44.2% obese, and 73.1% had morbidity. Patients who used the COVID Kit had a higher prevalence of altered platelets, creatine phosphokinase, liver function, and cardiac arrhythmias, with significant changes in intestinal function and potassium level. However, mortality proportions were equal between groups. **Conclusion:** Patients who used the COVID Kit had a higher prevalence of adverse effects, including changes in clinical and laboratory tests. In addition, the COVID-19 Kit did not decrease mortality in these patients.

Descriptors: COVID-19; Drug Therapy; Hydroxychloroquine; Azithromycin; Mortality.

INTRODUCTION

In December 2019, in Wuhan, Hubei Province, China, there was an outbreak of pneumonia of unknown origin. A novel SARS-CoV-related coronavirus, also called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found. On March 12, 2020, due to the intense global spread and high morbidity and mortality due to the virus, the World Health Organization (WHO) declared the health situation as a COVID-19 pandemic[1].

Patients infected with SARS-CoV-2 have mild to severe symptoms, with fever, cough, and shortness of breath being most reported. Although the main target of this virus is the lung, there is an extensive distribution of angiotensin-converting enzyme II (ACE-II) receptors in several other organs, which can cause harm to the central nervous system, liver, kidneys, eyes, as well as gastrointestinal (vomiting, diarrhea, and abdominal pain) and cardiovascular (myocardial lesion, myocarditis, acute myocardial infarction, heart failure, arrhythmias, and venous thromboembolic events) deterioration[1].

Thus, as it is a new coronavirus, there are several studies in progress evaluating the effectiveness of several drugs, both in clinical analysis, which includes new drugs, and with drugs that have already been used to treat other diseases, such as antimalarials, antiretrovirals, anti-inflammatories, as well as the use of adjuvant therapies, such as immunomodulators, for the treatment of patients with COVID-19[1-3].

In this context, the "COVID Kit", which includes hydroxychloroquine, azithromycin, and ivermectin, was constantly used for the treatment of patients with COVID-19, in critically ill patients in the Intensive Care Unit (ICU). However, its effectiveness in reducing patient mortality is not known.

Furthermore, most of these drugs can cause adverse effects such as neurotoxicity[3], retinal toxicity, diplopia, decreased visual acuity, bi-

How to cite: Avilar CTA, Amaral TLM, Nascimento CS, Andrade IMA, Souza GB, Kocaçal E, et al. COVID kit adverse effects and mortality in critically ill patients: cross-sectional study. Online Braz J Nurs. 2024;23:e20246773. https://doi.org/10.17665/1676-4285.20246773

lateral vision loss, hallucinations, paranoia, suicidal thoughts[4], fever, headache, nausea, dizziness, itching, diarrhea, loss of appetite[5], gastritis, gastrointestinal disorders, nausea[6], risks of hemolysis or bone marrow suppression, increased liver enzymes[7], cardiomyopathy manifesting as conduction disorders, causing atrioventricular block[8] which can lead to severe arrhythmias and heart failure, QT interval prolongation[5], potassium channels blocking (causing TdP)[9] and long QT syndrome[10], of which effects are harmful to patients.

In the literature, there is not any study demonstrating the medical status according to the usage of the COVID Kit. In this sense, this study aimed to compare the outcomes of the COVID-19 patients who used the COVID Kit in their treatment with those who did not. The research question was: Is there any difference between the clinical and laboratory tests and mortality among patients who used and did not use the COVID-19 Kit?

METHOD

Study design

This was a single-center, analytical, cross-sectional, and observational study. The Equator network guideline used was the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Setting

Data were collected at the Medical and Statistical Archive Service (SAME) of the Emergency Room in Rio Branco–Acre, where the medical records for the given research were made available between January and August 2021.

Participants and consent

All COVID-19 patients were diagnosed using real-time polymerase chain reaction (RT-PCR) following admission to the COVID-19 ICU and subsequently included in the study through a non-probability consecutive sampling method. We recruited patients diagnosed with COVID-19 and who used at least one of the drugs in the COVID kit or none of the drugs between March and December 2020, the first wave of the pandemic; thus, none of the patients had a history of vaccination for COVID-19 before SARS-CoV-2 infection. The study was conducted in the laboratory-confirmed with COVID-19 through the RT-PCR test patients and admitted in a COVID ICU of a tertiary care hospital, in the northern region of Brazil.

The sample size calculation was based on an estimated proportion of individuals using the COVID kit of 60%, an alpha error of 5%, and a beta error of 20%, with a minimum sample size of 42 individuals required to detect a difference between categorical groups. An additional 20% was added for possible losses.

Data collection was carried out through clinical records of patients over 18 years of age admitted to a COVID-19 ICU, during the peak of the second wave of the COVID-19 pandemic (from March to December 2020), and who used or did not use the COVID kit (hydroxychloroquine, azithromycin, and ivermectin).

The research exclusion criteria are hospitalization for less than 24 hours, absence of a COVID-19 diagnosis, and pregnancy in women''.

To obtain access to the data in the clinical records of the patients in this research, we were given an informed consent form by SESACRE, as well as compliance with the appropriate ethical roles established in this term.

Variables

Mortality (yes/no) was the primary outcome of interest. The secondary outcomes included adverse effects, such as changes in laboratory tests CPK, urea, liver function, and potassium, increased liver enzymes TGO and TGP, direct bilirubin, and glucose levels, clinical changes such as constipation, emesis, output through SNG, and abdominal distension, as well as electrocardiographic changes such as sinus and junctional tachycardia, long QT interval, intraventricular conduction delay, and altered T wave.

The researchers collected the variables from patients diagnosed with COVID-19, confirmed through RT-PCR examinations, using questionnaires they designed on the Research Electronic Data Capture (REDCap) platform. This data was obtained from physical medical records during the period from January to August 2021.

The dependent variables were the use of the COVID kit (hydroxychloroquine, azithromycin, and ivermectin) and the outcome variable was death.

The independent variables included sociodemographic and clinical data. The sociodemographic variables were: age, sex, skin color, body mass index (BMI), and comorbidities. The clinical variables were: vital signs, laboratory tests (from the hospital's laboratory), hemodialysis, computed tomography, electrocardiogram, lower blood glucose, higher blood glucose, evacua-

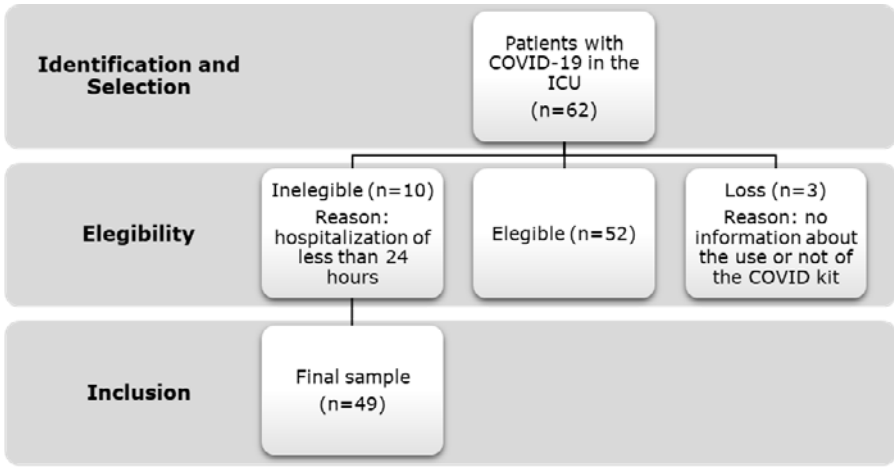
tion, nutrition, and the main complications with the diet.

Data collection
The principal investigator collected data using semi-structured questionnaires from physical patients' records. The questionnaire consisted of demographic and clinical data of the patients. The researchers received expert opinions on the content validity of the questionnaire.

Data analysis
Data were analyzed using descriptive statistics in the SPSS software, version 22.0, using absolute and relative frequency and measures of central tendency, presented in tables. To test the association between the variable of interest (Kit COVID and mortality) and clinical and laboratory characteristics, Student's t-test was used to compare means and Pearson's chi-square test to compare proportions.
The variables associated with the event, in the bivariate analysis, were subjected to the multivariate model (binary logistic regression) to determine independent predictors of death. Those variables that, in the final multivariate model, presented p-values <0.05 were considered significant and independently associated with the event.

Ethical considerations
This study was approved by the Research Ethics Committee, and the ethical principles were observed according to the National Health Council (CNS) Resolution CONEP No. 466/2012.
When patients had physiological capacity, they were informed about the objective of the research and signed and received a copy of the Free and Informed Consent Form. Otherwise, family members signed and received a copy of the Free and Informed Assent Form. The study was conducted through the Helsinki Declaration.

RESULTS
Of the 62 patients with COVID-19 in the ICU, 10 were excluded because they did not meet the research criteria, with 52 remaining patients being included in the sample; however, we had three losses during the study, due to the lack of information about the presence or absence of the COVID Kit medications, with 49 clinical records of patients hospitalized in the COVID-ICU (Figure 1) being considered.



Source: Adapted from Malta *et al*., 2010[11].
Figure 1 - Flowchart for capturing participants. Rio Branco, AC, Brazil, 2021

Among 49 patients, 67.3% were 50 years of age or older, 51% were male, 34.7% were brown, 40.8% were obese, according to the BMI, 71.4% had some type of comorbidity, and the mean hospital stay was approximately 13 days (Table 1).
Most patients (65.3%) did not require hemodialysis. Regarding gastrointestinal complications, 8.2% had emesis, 36.7% had output through the nasogastric tube (NGT), and 26.5% had abdominal distension. In addition, most patients (63.3%) had their diet suspended and died (71.4%) (Table 1).
The elimination variable showed a statistically significant difference in individuals who took any of the medications in the COVID Kit when compared to those who did not take any of these medications (Table 1).

Table 1 - Clinical characteristics of patients with COVID-19 in an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49) (cont.)

Variables	Total N (%)	No COVID KIT N (%)	With COVID KIT N (%)	p-value¥
Age (Mean ± SD)	55.57 ± 14.8	54.14 ± 15.6	57.48 ± 13.8	0.442†
Age group (years)				0.598
≤49	16 (32.7)	10 (35.7)	6 (28.6)	
≥50	33 (67.3)	18 (64.3)	15 (71.4)	
Gender				0.187
Male	25 (51.0)	12 (42.9)	13 (61.9)	
Female	24 (49.0)	16 (57.1)	8 (38.1)	
BMI*∩				0.656
Eutrophic	9 (18.4)	4 (15.4)	5 (26.3)	
Overweight	16 (32.7)	10 (38.5)	6 (31.6)	
Obese	20 (40.8)	12 (46.2)	8 (42.1)	
Skin color*				0.055
White	6 (12.2)	3 (11.1)	3 (23.1)	
Brown	17 (34.7)	9 (33.3)	8 (61.5)	
Yellow	17 (34.7)	15 (55.6)	2 (15.4)	
Comorbidities*				0.204ᶠ
Yes	35 (71.4)	20 (100.0)	15 (88.2)	
No	2 (4.1)	0 (0.0)	2 (11.8)	
Length of hospitalization (day) (Mean ± SD)	12.67 ± 9.2	11.96 ± 9.4	13.62 ± 9.1	0.539†
Hemodialysis*				0.665
No	32 (65.3)	19 (67.9)	13 (61.9)	
Yes	17 (34.7)	9 (32.1)	8 (38.1)	
Elimination				0.034
Diarrhea	5 (10.2)	2 (7.1)	3 (14.3)	
Constipation	27 (55.1)	12 (42.9)	15 (71.4)	
Normal	17 (34.7)	14 (50.0)	3 (14.3)	
Complications				
Emesis				0.625ᶠ
No	45 (91.8)	25 (89.3)	20 (95.2)	
Yes	4 (8.2)	3 (10.7)	1 (4.8)	
Debt by NGT«				0.864
No	31 (63.3)	18 (64.3)	13 (61.9)	
Yes	18 (36.7)	10 (35.7)	8 (38.1)	
Abdominal distension				0.348ᶠ
No	36 (73.5)	19 (67.9)	17 (81.0)	
Yes	13 (26.5)	9 (32.1)	4 (19.0)	
Diet suspension*				0.959
No	17 (34.7)	10 (35.7)	7 (35.0)	
Yes	31 (63.3)	18 (64.3)	13 (65.0)	

Table 1 - Clinical characteristics of patients with COVID-19 in an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49)

Variables	Total N (%)	No COVID KIT N (%)	With COVID KIT N (%)	p-value¥
Outcome				1.000
High	14 (28.6)	8 (28.6)	6 (28.6)	
Death	35 (71.4)	20 (71.4)	15 (71.4)	
TOTAL	49 (100.0)	28 (100.0)	21 (100.0)	

*Missing; ¥p-value: Chi-square test; †p-value: Independent T test; ┌p-value: Fisher's exact test; «NGT: Nasogastric tube; ∩BMI: Body Mass Index.

Admission vital signs show that the Mean Blood Pressure of patients who used the COVID Kit has reduced compared to patients who did not use it but with no statistical significance (Table 2).

Table 2 – Admission vital signs of the patients with and not using the COVID Kit. Rio Branco, AC, Brazil, 2020 (n=49)

Variables	Total	No COVID KIT N (%)	With COVID KIT N (%)	p-value†
MBP‖ (Mean ± SD)	90.51 ± 18.1	91.85 ± 20.5	87.10 ± 14.6	0.257
HR§ (Mean ± SD)	94.04 ± 20.0	94.81 ± 21.9	94.81 ± 17.7	0.819
RR*ϟ (Mean ± SD)	22.04 ± 6.4	22.81 ± 6.9	21.10 ± 5.5	0.363
Taxⁿ (Mean ± SD)	36.43 ± 1.3	36.36 ± 1.2	36.51 ± 1.5	0.715
TOTAL	49 (100.0)	28 (100.0)	21 (100.0)	

**Missing*; †p-value: Independent T test; ‖MBP: Mean Blood Pressure; §HR: Heart Rate; ϟRR: Respiratory rate; ⁿ Tax: Axillary temperature.

Regarding the admission laboratory tests, it is observed that leukometry and C-reactive protein of patients who used the COVID Kit were reduced compared to those who did not. Creatine phosphokinase, blood glucose, urea, lactate, AST, ALT, and direct bilirubin were higher in patients who received the COVID Kit, but with no statistical significance. In addition, potassium levels were higher in patients who used the COVID Kit, with a statistically significant difference (Table 3).

Table 3 – Admission laboratory tests according to the use or not of the COVID Kit in patients of an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49) (conti.)

Variables	Total	No COVID KIT N (%)	With COVID KIT N (%)	p-value†
Hemoglobin* (Mean ± SD)	11.33 ± 2.3	11.16 ± 2.3	11.55 ± 2.3	0.563
Leukocytes (Mean ± SD)	15,007.35 ± 8,264.26	15,748.57 ± 7,464.8	14,019.05 ± 9,321.6	0.474
Lymphocytes (Mean ± SD)	8.94 ± 4.65	9.07 ± 4.4	8.76 ± 5.1	0.820
Platelets (Mean ± SD)	228,377.55 ± 81,845.92	246,892.86 ± 83,142.2	203,690.48 ± 75,000.7	0.067
CPK*Ω (Mean ± SD)	290.52 ± 312.11	225.71 ± 173.1	360.31 ± 410.4	0.271
Blood glucose* (Mean ± SD)	186.51 ± 104.33	172.33 ± 69.1	205.65 ± 138.4	0,284

Table 3 – Admission laboratory tests according to the use or not of the COVID Kit in patients of an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49)

Variables	Total	No COVID KIT N (%)	With COVID KIT N (%)	p-value†
Urea* (Mean ± SD)	67.06 ± 55.98	64.11 ± 54.2	70.86 ± 59.4	0.683
Creatinine (Mean ± SD)	1.8204 ± 2.32	1.80 ± 2.6	1.84 ± 1.8	0.954
Sodium (Mean ± SD)	140.80 ± 5.98	140.79 ± 6.6	140.81 ± 5.2	0.989
Potassium* (Mean ± SD)	3.925 ± 0.77	3.72 ± 0.7	4.21 ± 0.7	0.029
Lactate* (Mean ± SD)	27.630 ± 14.23	27.39 ± 10.9	27.88 ± 17.5	0.914
C-reactive protein* (Mean ± SD)	117.212 ± 89.52	129.40 ± 93.2	87.96 ± 81.7	0.402
AST* ◇ (Mean ± SD)	61.57 ± 80.12	48.24 ± 43.3	77.00 ± 107.7	0,257
ALT* ◇ (Mean ± SD)	68.68 ± 68.28	60.45 ± 48.6	78.72 ± 87.1	0.407
Direct Bilirubin* (Mean ± SD)	0.382 ± 0.38	0.24 ± 0.2	0.51 ± 0.5	0.096
Indirect Bilirubin* (Mean ± SD)	0.302 ± 0.35	0.22 ± 0.2	0.37 ± 0.5	0.304
TOTAL	49 (100.0)	28 (100.0)	21 (100.0)	

**Missing*; †p-value: Independent T test; ΩCPK: Creatine phosphokinase; ◇AST: Aspartate Transaminase; ∞ALT: Alanine Transaminase.

The electrocardiogram revealed that patients who used the COVID Kit had a higher frequency of changes in the long QT interval, intraventricular conduction delay, junctional tachycardia, and altered T wave, but with no statistical significance (Table 4).

Table 4 - Electrocardiographic information according to the use or not of the COVID Kit in patients in an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49) (cont.)

Variables	Total	No COVID KIT N (%)	With COVID KIT N (%)	p-value†
Sinus tachycardia*				0.646
No	16 (32.7)	8 (66.7)	8 (80.0)	
Yes	6 (12.2)	4 (33.3)	2 (20.0)	
Long QT interval*				0.078
No	19 (38.8)	12 (100.0)	7 (70.0)	
Yes	3 (6.1)	0 (0.0)	3 (30.0)	
Intraventricular conduction delay*				0.293
No	18 (36.7)	11 (91.7)	7 (70.0)	
Yes	4 (8.2)	1 (8.3)	3 (30.0)	
Junctional Tachycardia*				0.455
No	21 (42.9)	12 (100.0)	9 (90.0)	
Yes	1 (2.0)	0 (0.0)	1 (10.0)	
Altered T wave*				0.172

Table 4 - Electrocardiographic information according to the use or not of the COVID Kit in patients in an Intensive Care Unit. Rio Branco, AC, Brazil, 2020 (n=49)

Variables	Total	No COVID KIT N (%)	With COVID KIT N (%)	p-value†
No	15 (30.6)	10 (83.3)	5 (50.0)	
Yes	7 (14.3)	2 (16.7)	5 (50.0)	
Short PR interval*				0.221
No	19 (38.8)	9 (75.0)	10 (100.0)	
Yes	3 (6.1)	3 (25.0)	0 (0.0)	
Atrial fibrillation*				1.000
No	20 (40.8)	11 (91.7)	9 (100.0)	
Yes	1 (2.0)	1 (8.3)	0 (0.0)	
TOTAL	49 (100.0)	28 (100.0)	21 (100.0)	

*_Missing_; †p-value: Fisher's exact test.

DISCUSSION

Patients who used the COVID Kit had a higher prevalence of altered platelets, CPK, liver function, and cardiac arrhythmias, with significant changes in intestinal function and potassium level. However, mortality was equal between groups, suggesting the low efficacy of this treatment.

Studies have reported[8-7] that hydroxychloroquine presents a series of adverse events due to cumulative doses and its affinity with parenchymal organs such as the liver and kidneys[7]. This drug can cause liver enzyme elevation, therefore monitoring bilirubin and potassium levels is extremely important.

It is crucial to note that hydroxychloroquine can cause hemolysis or bone marrow suppression, requiring proper monitoring and blood cell counts[7]; however, in this study, hemoglobin levels were very similar between groups.

Macrolide medications can cause fluid and electrolyte disturbances such as hypocalcemia, hypomagnesemia, and hypokalemia, resulting in prolonged QT syndrome[10]. In this case, it is recommended that patients who are using HCQ/AZ should maintain strict control of the electrolytes levels: calcium (Ca++), potassium (K+), and magnesium (Mg++) since hospital admission, as these are essential for ventricular repolarization stability, and it is required to maintain K+ > 4.0, Mg++ > 2.0, and to avoid hypocalcemia[9].

Patients who used the COVID Kit presented some clinical changes such as constipation, emesis, NG tube output, and abdominal distension. Chloroquine and hydroxychloroquine lead to gastrointestinal disorders such as vomiting and diarrhea, with these two symptoms being known as the most common adverse effects of both drugs[12-13].

The study also demonstrated electrocardiographic changes manifested in patients using the COVID Kit, such as sinus and junctional tachycardia, long QT interval, intraventricular conduction delay, and altered T wave. Other researchers claim that HCQ triggers cardiomyopathy, manifested as conduction abnormalities, causing atrioventricular blocking[8], prolonged QT syndrome, and cardiomyopathies[7]. In addition, AZ also has a great tendency to prolong the QT interval, so the association between CQ/HCQ + AZ potentiated the worsening of cardiotoxicity, increasing the chances of irreversible cardiac arrhythmias, which can lead to death[5], and its use shall be controlled, and changes monitored and corrected.

In the RECOVERY randomized controlled trial, hydroxychloroquine was proposed as a treatment against COVID-19. The results showed that the group of patients who received hydroxychloroquine had a higher risk of death from cardiac causes and other non-SARS-CoV-2 infections. The study determined that hydroxychloroquine is not an effective drug for patients with COVID-19. In addition, the study reveals that hydroxychloroquine is a weak antiviral agent[14].

Thus, during the COVID-19 pandemic, the scientific community sought a way to manage serious cases of COVID-19, bringing several studies with drugs to fight this virus[15-16]. However, there are still no drugs that can specifically treat people infected with COVID-19.

Since the beginning of the pandemic, the fede-

ral government has encouraged early therapy called the COVID Kit. Nevertheless, so far, the Kit has not demonstrated any proven effectiveness[14-16]. Thus, the recommended measures are still hygiene measures and mass vaccination of the population[16].

Faced with the pandemic scenario and the absence of effective treatment, teams of medical professionals prescribed and encouraged the use of these drugs as an early and off-label therapy; however, concerning the responsibility of the prescriber, the Federal Council of Medicine (CFM), which regulates medical practice in Brazil, provided for in Law 12.842/13, in Opinion No. 13/2004, which deals with the experimental use of medications aiming to evaluate their efficacy and safety, clarifies that prescribing drugs for therapeutic purposes other than those they had at the time of approval by the Brazilian Health Surveillance Agency (Anvisa) will be considered as medical research combined with professional care (clinical research), with free and informed consent being required from the patient. However, this is not the Brazilian reality[16]. Thus, drug off-label use is carried out at the discretion of the physician who prescribes it and may become a medical error[16].

Moreover, Recommendation No. 42, of the CNS, of May 22, 2020, proposes to the Ministry of Health (MS) not to allow the use of any medication for the prevention or treatment of COVID-19 because there is no confirmation of safe use to patients. Otherwise, the Federal Prosecution Service will take the necessary measures so that the use of these drugs by patients diagnosed with COVID-19 is suspended[17].

Furthermore, this study corroborates the recommendation of the WHO that contraindicates the use of hydroxychloroquine and chloroquine for the treatment of COVID-19, highlighting that these drugs do not reduce mortality, the need for mechanical ventilation or length of hospital stay, and may also increase the risk of diarrhea, nausea, vomiting, hypovolemia, hypotension, and acute kidney injury[17]. Excessive utilization of Chloroquine or Hydroxychloroquine either alone or in conjunction with Azithromycin led to negative outcomes such as QT prolongation. Finally, there is insufficient evidence to advocate for the use of Hydroxychloroquine, with or without Azithromycin, in treating COVID-19[18].

The limitation of this study is that cross-sectional studies do not allow for the distinction between cause and effect because information on individuals and their exposure are collected simultaneously. However, observational (cross-sectional) studies provide an excellent basis for understanding diseases and other events of interest, such as COVID-19, and are often used to plan and develop case-control and cohort studies and to design randomized clinical trials. Furthermore, in this study, the information was obtained from medical records and should be interpreted with caution due to incomplete information and lack of standardization in the documentation by the medical team. However, the research team collected the data using structured forms, all team members were trained, and only variables with less than 20% missing data were used.

However, as strengths, it revealed the clinical and laboratory differences in critical patients who used and did not use the COVID Kit, a result aimed by science. Furthermore, we suggest that randomized clinical studies be carried out to identify a specific drug for the control of COVID-19, aiming at reducing mortality and patients' clinical and laboratory alterations.

CONCLUSION

Patients who used the COVID Kit showed important clinical and laboratory changes and its use did not bring benefits to reduce mortality. Therefore, its use shall not be indicated to critically ill patients with COVID-19. COVID-19 with ongoing mutations has still a threatening effect on human life. Scientific studies aimed at solving this situation should not be interrupted. Although it may seem effective in the short term, the use of methods whose effects are unknown in the medium-long term should be approached with caution. Conducting in-service training and research are suggested by the researchers.

CONFLICT OF INTERESTS

The authors have declared that there is no conflict of interests.

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