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COVID-19: Effects of Azithromycin/Hydroxychloroquine/Ivermectin in ambulatory and hospitalized patients

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Abstract

Introduction: At the end of 2019, the outbreak of a new coronavirus emerged triggering the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Hubei Province, Wuhan City, People's Republic of China, causing a global pandemic and a threat to public health. **Objective**: This systematic review aims to determine the effects of azithromycin, hydroxychloroquine and ivermectin in ambulatory and hospitalized patients with covid-19. **Methods**: This systemic review included: observational and experimental studies, such as randomized controlled trials (RCTs) and clinical trials; studies in ambulatory and hospitalized patients infected by SARS-CoV-2. The quality of evidence for each outcome was determined according to the Grading of Recommendations Assessmet, Developmet and Evaluation (GRADE) methodology. **Results**: In the initial search, 832 studies were recorded, of which 17 publications were included. In addition, we included a secondary article from the additional search of the 17 articles. Azithromycin and/or hydroxychloroquine increase mortality and cause adverse events compared to usual care groups (27% vs 25%, OR = 0.98, 95% CI = 0.58-1.74, p = 1.00) and ivermectin with respect to the group control in the resolution of symptoms (82% vs 79%) and adverse events (52% vs 56%), from various studies. **Conclusions**: The quality of evidence on the effectiveness and benefits of azithromycin, hydroxychloroquine, and ivermectin in the treatment of COVID-19 in outpatients and inpatients was limited with no benefit.

Key word: COVID-19, SARS-CoV-2, azithromycin, hydroxychloroquine, ivermectin (Source: MeSH-NCBI)

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Introduction

In the last two decades, outbreaks of coronavirus have been evident, such as severe acute respiratory syndrome (SARS-CoV-1) and Middle Eastern respiratory syndrome (MERS-CoV) in 2002 and 2012, respectively. At the end of 2019, the outbreak of a new coronavirus emerged, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 19 (COVID-19). It generated a global pandemic with high rates of morbidity and mortality (1, 2).

To date, there is no effective treatment for SARS-CoV-2, but some antivirals, antibiotics, immunosuppressors and antiparasitic drugs have been proposed and authorized, with known doses and pharmacokinetics, for the management and treatment of the COVID- 19 disease. Clinical trials are carried out that seek to reduce and inhibit the effect of the virus to minimize hospital stays, the requirement for mechanical ventilation, and the mortality associated with COVID-19 (3, 4).

The use of immunosuppressive / immunomodulatory and anti-inflammatory drugs, such as hydroxychloroquine and corticosteroids, respectively, was proposed with the purpose of suppressing the release of pro-inflammatory cytokines produced by pro-inflammatory cells, caused by SARS-CoV-2. In vitro studies of the drugs hydroxychloroquine, azithromycin, and ivermectin have shown efficacy against some viruses and are excellent anti-inflammatories (5, 7); however, large-scale human trial studies are still being conducted to evaluate efficacy of the different drugs against COVID-19. Also, emergency treatments were used during the pandemic, in the absence of essential clinical data, such as the antivirals remdesivir and favipiravir (8,9).

Due to the need for evidence and to be able to evaluate it, the present systematic review was developed with the objective of determining the effects of azithromycin, hydroxychloro-quine and ivermectin in outpatients and hospitalized patients due to COVID-19.

Methods

This systemic review report was realized in accordance with the reference items for publishing systematic review and meta-analysis protocols (PRISMA) (10).

Eligibility criteria

This systemic review included a) observational and experimental studies, such as randomized controlled trials (RCTs) and clinical trials; b) studies in ambulatory and hospitalized patients infected by SARS-CoV-2 and c) studies in the English language were included. We excluded a) Studies in populations with infections of other types of coronavirus, such as SARS-CoV-1 and MERS-CoV; b) narrative reviews, preclinical trials, letters to the editor, and clinical guidelines; c) intervention studies corresponding to supportive treatment in critical or severe patients; d) Languages other than Spanish and English.

Bibliographic search strategy

A literature search of the literature was performed in Pub Med, MEDLINE and JAMA until June 4, 2021. The authors developed the search strategies (LRC and HMZ), according to the recommendations of the Cochrane Manual of Systemic Reviews. Controlled vocabulary search terms for MEDLINE (MeSH) were used, linked in text term for each of the selected concepts using boolean operators. No date filters or format restriction of the search document were used. Search strategies were performed, with the advanced search tool in the database, before approving a final consensus of the search strategies. The complete search strategy can be found in the supplementary material to this review report. We used the Mendeley Desktop program for manage the bibliographic references and eliminate duplicate articles.

Study selection and data extraction

The complete texts of the articles were retrieved to verify eligibility and to verify the inclusion and exclusion list. Disagreements were discussed until a consensus was reached. The Microsoft Excel program was used for data extraction, storage and analysis. The following data was extracted: author, year of publication, population characteristics, description of the intervention, outcomes evaluated and results.

Assessment of study quality

The quality of evidence for each outcome was determined according to the Grading of Recommendations Assessmet, Developmet and Evaluation (GRADE) methodology (11), which takes the following criteria: study design, risk of bias, inconsistency in the results, absence of direct evidence, imprecision, publication bias and, in the case of observational studies, the effect size, the dose-response gradient and the residual dose effect are considered. According to this methodology, there are 4 levels for the qualification of the evaluation of the quality of evidence and the references of this review study (Table 1) and (Table 2).

Tabla 1. Grading of Recommendations Assessment, Development, and Evaluation (GRADE): Interpretation of levels of evidence

GRADE Level of Evidence	Characteristics
High	It is very unlikely that new studies will change the confidence / certainty in the estimated result.
Moderate	New studies are likely to have an important impact on the confidence in the estimated result and that they may modify the result
Low	It is very likely that new studies will have an important impact on the confidence in the estimated result and that they may modify the result
Very low	Any estimated result is highly uncertain

Table 2. Evidence Profile for Azithromycin / Hydroxychloroquine / Ivermectin in patients with covid-19 (most important)

Certainty assessment						Number of patients		Effect	
# Study reference	Design of study	Risk of bias	Inconsistency	Evidence hint	Vagueness	HCQ/ AZT o IVM	Control	Relative (95)IC	Certainty
(12)	Test random	Low	moderate	very serious	moderate	217/667 (32,5%)	221/667 (33,1%)	OR 1,21 (0,69-2,11)	high
(13)	Test random	Low	moderate	serious	moderate	214/397 (32%)	183/397 (46%)	OR 1,36 (0,94-1,97)	Moderate
(14)	Test random	moderate	Low	less serious	Low	26/42 (61%)	16/42 (38%)	OR 0,08 (0,01-0,04)	Low
(15)	Test random	Low	moderate	serious	moderate	441/821 (53,7%)	407/821 (49,6%)	OR -2,4 (-7,0-2,2)	Moderate
(16)	Test random	Low	moderate	serious	moderate	1561/7513 (20,7%)	3155/7513 (41,9%)	OR. 1,9 (0,97-1,23)	Moderate
(25)	Test random	moderate	moderate	serious	moderate	238/476 (50%)	238/476	OR 1,07 (0,87-1,32)	Moderate

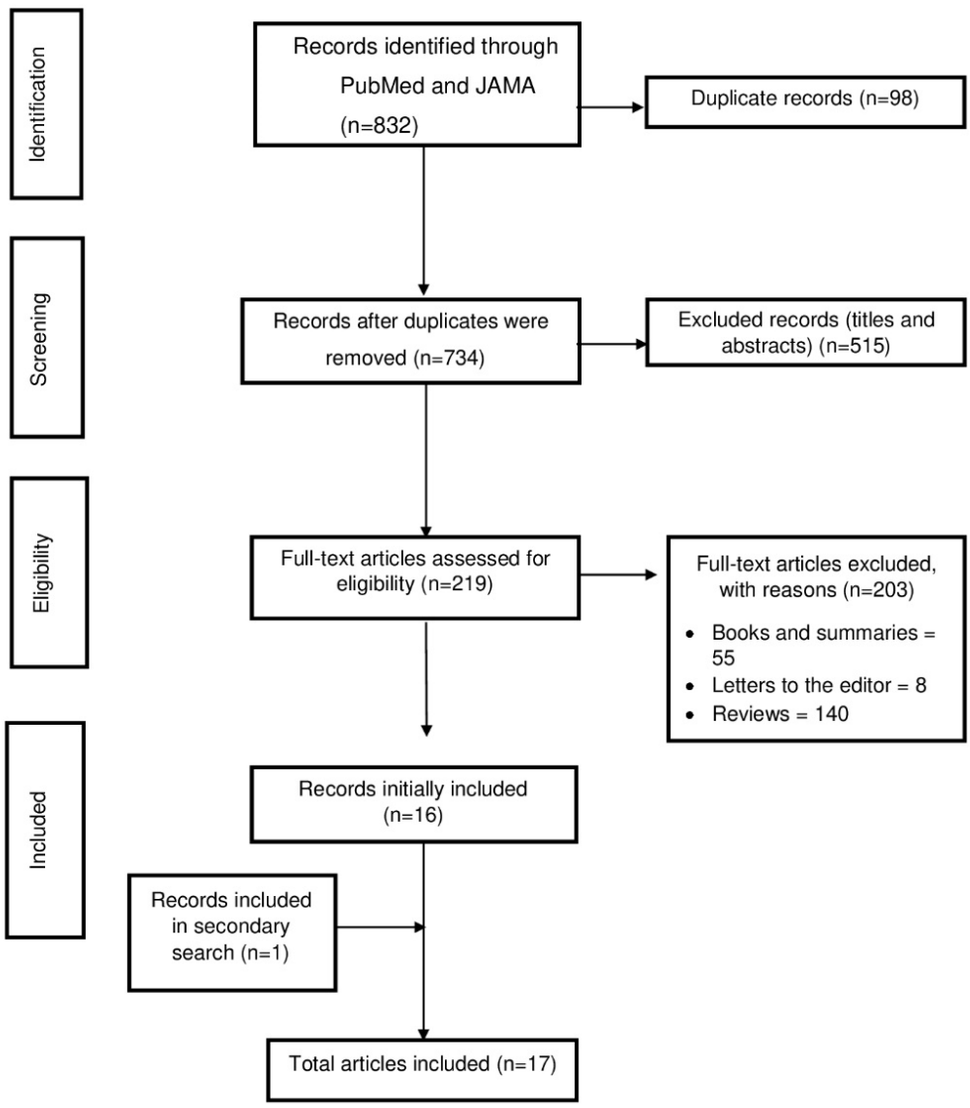
IVM:ivermectin, HCQ: hydroxychloroquine, AZT: azithromycin, OR: odds Rattio, IC 95%: 95% confidence interval.

Results

Characteristics of the included studies

The initial search identified 832 results. 734 duplicate results were removed. After filtering by titles and abstracts, we evaluated 219 full-text articles. Sixteen articles were initially registered that provide specific information related to the objectives of this study. In addition, a secondary search of the 16 initially included studies was performed, of which one additional study was included. Finally, 17 articles were included, where 13 randomized open trials (ROTs) and 4 observational studies were included (Figure 1).

Figure 1. Data selection flowchart



Most of the articles was authors from China (3/17), USA (2/17), Canada (4/17), Brazil (2/17), Spain (1/17), France (1/17), Colombia (1/17), Egypt (1/17), Iran (1/17), and United Kingdom (1/17). There were 16,970 patients with covid-19 who participated in the effect of azithromycin and hydroxychloroquine, the mean age of the men was 57.5 years and the majority of the participants were men 52% (Table 3) (Table 4)

Characteristics of the effects of azithromycin and / or hydroxychloroquine

Cavalcanti A et al (12) realized a multicenter, randomized, open and controlled study of three groups, which involved a total of 667 patients; 504 had confirmed COVID-19, that they were not receiving supplemental oxygen. Patients were randomized 1: 1: 1 to standard care, standard care plus hydroxychloroquine at a dose of 400 mg twice daily or standard care plus hydroxychloroquine at a dose of 400 mg twice daily plus azithromycin in a dose of 500 mg once a day for 7 days, where they used a 7-level ordinal scale (levels between one to seven and higher scores indicating worse condition) at 15 days. Compared with standard care, the proportional odds of having a poor high score on the 7-point ordinal scale were unaffected by hydroxychloroquine alone versus control (odds ratio, 1.21; confidence intervals [CI] 95%, 0.69 to 2.11; P = 1.00) and hydroxychloroquine plus azithromycin vs control (Odds Ratio [OR]: 0.99; 95% CI, 0.57 to 1.73; P = 1 .00) or hydroxychloroquine plus azithromycin versus hydroxychloroquine alone (OR: 0.82, 95% CI 0.47 to 1.43, P = 1.00).

A total of 43 patients received ventilation (11% received hydroxychloroquine plus azithromycin; 7.5% received

Table 3. Characteristics of the clinical trials identified in the review of the effects of Azithromycin and / or hydroxychloroquine in outpatients and hospitalized patients

Author and Year / Country (#Ref)	Design	Number	population characteristics	Intervention	Comparison	Results
Cavalcant i, et al. 2020/ Brasil (12)	Multicenter, randomized, open and controlled trial	667 patients 217 received HCQ + AZT, 221 received HCQ and 229 from the control group	Hospitalized patients with suspected or confirmed Covid-19 by PCR, who are not receiving oxygen. Age 50.3 ± 14.6 Male sex 388 (58%)	HCQ 400 mg plus AZT 500 mg twice daily, orally for 7 days. (N = 217) HCQ 400 mg twice daily, orally for 7 days (N = 221)	Control group or standard care (N = 229)	Compared with the control group and HCQ (OR 1.21; 95% CI 0.69-2.11; p = 1.00), or HCQ + AZT (OR 0.99; 95% CI 0.57- 1.73; p = 1.00), of having a higher probability of seven points, at 15 days.
Furtado, et al. 2020/ Brasil (13)	Randomized, open-label clinical trial	447 patients (397 with covid-19) 214 received AZT and 183 received the control group	Suspicious or Covid-19 hospitalized patients and at least one additional severity criterion. Age: 59.8 years (men)	AZT 500 mg once daily PO, nasogastric, or IV for 10 days (N = 214)	Control group without macrolides (N = 183)	The primary endpoint was not significantly different in the AZT and control groups (OR 1.36 [95% CI 0.94-1.97], p = 0.11).
Gautred, et al. 2020/ Francia (14)	Non-randomized, open-label clinical trial	42 patients 20 received HCQ, 6 HCQ + AZT and 16 from the control group	Hospitalized patients confirmed with Covid-19 (asymptomatic, ITRS, ITRI) Age> 12 years	HCQ sulfate 200 mg orally three times a day for 10 days. (N = 20) AZT 500 mg per day followed by 250 mg per day, for 4 days orally (N = 6)	Control group (N = 16)	Treatment with HCQ plus AZT is associated with a decrease in contagion on day seven (adjusted OR = 0.08, 95% CI 0.01 to 0.40, P = 0.016) and a reduction in hospital stay (OR adjusted = -12.54, 95% CI -18.96 to -6.11, p <0.0001)
Boulware, et al. 2020/ EE.UU y Canadá (15)	Randomized, double-blind, controlled trial	821 participants 414 HCQ group 407 placebo group	Participants exposed without any protection to covid-19 patients Age 33 to 50 years Women: 51.6% Chronic diseases: 27.4%	HCQ sulfate 800 mg daily, then 600 mg three times daily, orally for 5 days (N = 414)	Control group (N = 407)	The incidence of a new disease compatible with Covid-19 did not differ significantly between participants who received HCQ 49 of 414 (11.8%) and those who received placebo 58 of 407 (14.3%); the absolute difference was -2.4 percentage points (95% confidence interval, -7.0 to 2.2; p = 0.35). Side effects were more frequent with HCQ than with placebo (40.1% vs 16.8%)
Mitja´, et al. 2021/ España (16)	Open-label, cluster-randomized trial	2314 patients 1116 HCQ group, 1198 control group	Participants exposed to confirmed COVID-19 patients. Age:> 18 years (48.6 ± 19.0). Chronic disease: 912 (39.4%)	HCQ 800 mg daily followed by 400 mg daily for 6 days, po (N = 1116)	Usual care group (N = 1198)	HCQ was not associated with a lower incidence of SARS-VOC-2 transmission than usual care (18.7% and 17.8%, respectively). The incidence of adverse events was higher in the HCQ group than in the usual care group (56.1% vs 5.9%).
Horby, et al. 2020/ UK (17)	Open, controlled and randomized trial.	11197 patients 7513 eligible 1561 belong to the HCQ group 3,155 belong to the usual care group	Suspected or confirmed hospitalized patients with covid-19. Mean age: 65.4 ± 15.3 years. General chronic disease: 53%	HCQ sulfate 800 mg twice daily PO followed by 400 mg daily for 9 days.	Usual care group	Mortality at 28 days was 27% in the HCQ group and 25% in the usual group (OR 1.9, 95% CI 0.97-1.23, P = 0.15). In relation to the HCQ and usual care groups, at hospital discharge in 28 days (56% vs 62.9%; OR 0.90; 95% CI 0.83-0.98). The HCQ group had a higher frequency of mechanical ventilation compared to the usual care group (30.7% vs 26.9%; OR 1.14; 95% CI 1.03-1.27).
Self, et al. 2020/ EE.UU (18)	Randomized, multicenter, blinded and controlled trial	479 patients 242 belong to the HCQ group and 237 belong to the placebo group	Hospitalized patients with symptoms of ARDS with confirmed covid-19 for less than 10 days. Age 18 (M.E 57 years); 43% women; 46.8% in ICU; 11.5% high flow nasal oxygen.	HCQ sulfate 400 mg twice daily for two doses, then 200 mg twice daily for 8 doses	Placebo group	The clinical status on the ordinal outcome scale at 14 days did not differ significantly between the HCQ and placebo groups ([IQR], 6 [4-7] vs 6 [4-7]; ORa, 1.02 [95 CI % 0.73-1.42]). At 28 days after randomization, 25 of 241 patients (10.4%) in the HCQ group and 25 of 236 (10.6%) in the placebo group had died (absolute difference, -0.2% [CI 95% -5.7% -5.3%]; ORa 1.07 [95% CI, 0.54-2.09])
Abella, et al. 2020/ EE.UU (19)	Randomized, double-blind, controlled trial	125 participants 64 participants in the HCQ group and 61 participants in the placebo group.	Health workers who worked 20 hours a week in the hospital, have no symptoms and a history of sars-cov-2 in the last 15 days. Average age 33 years (20-66 years) and 91% of women.	HCQ Sulfate 600 mg PO for 8 weeks	Full-size placebo	There was no significant difference between the two groups (4 of 64 [6.3%] vs 4 of 61 [6.6%]; p> 0.99). Mild adverse events were greater in the HCQ group versus placebo (45% vs 26%; p = 0.04). The change in QTc (4 weeks) did not differ in both arms (HCQ: 4 ms; 95% CI; -9 to 17; vs placebo: 3 ms; 95% CI -5-11; p = 0.98)
Tang, et al. 2020/ China (20)	Open-label, multicenter, randomized controlled trial	150 hospitalized patients 75 belong to the HCQ and standard care group and 75 belong to the standard care group	Hospitalized patients confirmed with covid-19 by PCR. Age: 18 years (MS 46 years) Males: 82 (55%)	HCQ dose of 1200 mg on 3 days followed by a maintenance dose of 800 mg daily, orally, for 2 or 3 weeks.	Standard care	The probability of negative conversion at 28 days in the HCQ group plus standard care 85% (95% CI 0.74-0.94) versus standard care 81.3% (95% CI 0.71-0.9) . The difference between the groups was 4.1% (95% CI 0.10-0.18). HCQ adverse events versus standard care 30% vs. 9%, respectively.
Abd-Elsalam, et al. 2020/ Egipto (21)	Controlled, randomized and multicenter study	194 patients 97 belong to the HCQ group and 97 belong to the standard care group	Hospitalized patients with covid-19 confirmed by PCR for less than 15 days. Age: 40.72 ± 19.32 Women: 114 (58.8%), Men: 80 (41.2%) Comorbidities: 27 (14.3%)	HCQ doses of 400 mg twice daily, followed by 200 mg tablets twice daily added to standard treatment for 15 days.	Standard care for 15 days	There was no significant difference between the groups, with respect to any baseline or laboratory characteristics. 4.1% of HCQ and 5 (5.2%) of the control group, need mechanical ventilation (p = 0.75). Mortality did not differ between the groups, 6 (6.2%) from the HCQ and 5 (5.2%) from the control group (p = 0.77).
Skipper, et al. 2020/ EE.UU y Canadá (22)	Randomized, double-blind, controlled trial	423 patients 157 received HCQ and 166 received placebo	Symptomatic, non-hospitalized adult patients with confirmed or probable covid-19 and high-risk exposed patients in the 4 days after the symptoms in the 14 days Average age: 40 years and 56% women. Chronic diseases: 68%	HCQ orally 800 mg once a day, followed by 600 mg in 6 to 8 hours, then 600 mg a day for 4 more days	Masked placebo	At 14 days, 24% (49 of 201) of the HCQ group had continuous symptoms compared to 30 (59 of 194) who received placebo (p = 0.21). Medication adverse effects occurred in 43% (92 of 212) of participants who received HCQ versus 22% (46 of 211) who received placebo (p <0.001). With placebo, there were 10 hospitalizations (2 not related to COVID-19), including hospitalized death. With HCQ, there were 4 hospitalizations plus 1 non-hospitalized death.
Sekhavati, et al. 2020/ Irán (23)	Open-label randomized controlled trial	111 patients 56 of the case group 55 from the control group	Symptomatic patients with covid-19 confirmed by PCR. Age> 18 years	AZT of 500 mg daily orally, 400/100 mg of LPV / r orally twice a day and 400 mg of HCQ orally. For 5 days.	400/100 mg of LPV / r orally twice a day and 400 mg of HCQ orally. For 5 days.	Symptoms in both groups were not significant (p> 0.05), control patients initially reported myalgia, headache and vomiting (p = 0.000, 0.005 and 0.031 respectively). The mean SpO2 levels at admission and on the third day were not significant between the groups (p = 0.920 and 0.610). Admission to the ICU was greater in

HCQ: hydroxychloroquine, AZT: azithromycin, IQR: interquartile range, ORa: adjusted odds ratio, LPV / r: lopinavir / ritonavir, ICU: intensive care unit, ARDS: acute respiratory distress syndrome, SpO2: peripheral capillary oxygen saturation, PCR: polymerase chain reaction, 95% CI: 95% confidence interval, p: significance level VO: oral route, EV: intravenous route.

Table 4. Characteristics of the observational studies and clinical trial in the review on the effect of ivermectin in outpatients and hospitalized patients

Author / Place (#ref)	Study design	Population	Intervention	Control	Results of the intervention group	Control group results	Adverse events
Shouman/ Egipto (24)	Randomized, sequential masking	340 participants 203 belong to the IVM group and 101 belong to the control group	IVM, two doses orally every 72 hours for 14 days	Prophylaxis only	The development of symptoms (fever, cough, sore throat, myalgia, diarrhea and difficulty breathing) in the IVM group 15 (7.4%)	Any result	In adverse events, the IVM group was 5.42%, compared to the control group 0%.
E. Lopez-Medina, et al/ Colombia (25)	Randomized, double-blind clinical trial	476 patients 476 patients 238 received IVM and 238 received placebo	IVM, 300 ug / Kg of weight v.o during 5 days	Placebo only	Symptom resolution in 21 days: 82%	Symptom resolution in 21 days: 79%	The adverse event of headache in the IVM group, 52% and in the
Rajter, et al/ EE.UU (26)	Prospective cohort study	280 patients with covid-19 173 treated with IVM and 107 without IVM	IVM, at least an oral dose of IVM 200 mg / Kg along with usual care	Usual care	Overall mortality: 15% Mortality in patients with severe disease: 38.8%	Overall mortality: 25.2% Mortality in seriously ill patients: 80.7%	None
Rahman, et al/India (27)	Comparative descriptive study	400 patients with mild to moderate COVID-19 200 belong to the IVM plus DXC group and 200 to the control group.	IVM (18 mg a day) and DXC (100 mg twice a day PO for 5 days)	HCQ (800 mg per day and then 400 mg every day for 10 days) and AZT (500 mg per day and then 250 mg every day for 4 days)	66% viral clearance on day 5 and 83.5% on day 6. 16.5% remained positive on PCR after the sixth day of taking IVM	77% viral clearance on day 11 and 81.5% on day 12 of taking HCQ. 18.5% remained PCR positive after day 12	Anorexia, in the intervention and control group (23.5% vs 31%); diarrhea (12% vs 7%) and skin rash (10% vs 1%)
Mahmud/ India (28)	Randomized parallel and double blind.	400 participants 200 belong to the intervention group and 200 to the control group	IVM, 6 mg 2 tab and DXC 100 mg twice daily orally for 5 days	Standard treatment	Patients with clinical improvement: (95% CI 0.53. 0.3-0.96) 111 (60.7%) Patients with late recovery: 42 (23.0%) p <0.004	Patients with clinical improvement: 80 (44.4%) Late recovery patients: 67 (37.2%).	Adverse events in the intervention and placebo groups (1.09% vs 0%)

IVM: ivermectin, DXC: doxycycline, HCQ: hydroxychloroquine, AZT: azithromycin, OV: oral route, 95% CI: 95% confidence interval

hydroxychloroquine alone and 6.9% of the control group). 18 patients died in hospital during the trial (5 patients receiving hydroxychloroquine plus azithromycin; 7 in the hydroxychloroquine alone group and 6 in the control group). Long QT syndrome and elevation of liver enzymes were very common in groups that received hydroxychloroquine alone or with azithromycin, compared to the control group.

Furtado R et al (13), realized a randomized and open clinical trial in 57 health centers in Brazil, where 447 suspected or confirmed patients and seriously ill patients were enrolled; where 397 patients were diagnosed with COVID-19 that constituted the modified intention-to-treat (mITT) population, of which 214 were assigned to the azithromycin group (500 mg orally, nasogastric or intravenous once a day for 10 days) plus standard care and 183 were standard care without macrolides. All patients received hydroxychloroquine (400 mg twice a day for 10 days) because it was part of the standard treatment of the Ministry of the Health in Brazil for severe COVID-19 patients. They evaluated a six-point ordinal scale, with levels from one to six and higher scores indicating a serious condition, for 15 days. In the mITT population, the primary endpoint was not significantly different in the azithromycin and control groups (OR 1.36 [95% CI 0.94-1.97], p = 0.11). Among the 214 patients in the azithromycin group, 90 (42%) had died within 29 days, compared with 73 (40%) of the 183 patients in the control group (HR 1.08 [95% CI 0.79-1.47], p = 0.63).

Gautred P et al (14) conducted a non-randomized open clinical trial; a preliminary study, where 42 patients were approached. Increased length of hospital stay was found to be associated with male sex (adjusted coefficient = 5.76, 95% CI 1.33 to 10.18, P = 0.01) and lower respiratory infections symptoms at admission (adjusted coefficient = 6.48, 95% CI 1.01 to 12.66, p = 0.02). Treatment with hydroxychloroquine plus azithromycin is associated with a decrease in contagion on day seven (adjusted OR = 0.08, 95% CI 0.01 to 0.40, P = 0.016) and a reduction in hospital stay (OR adjusted = -12.54, 95% CI -18.96 to -6.11, p <0.0001).

Boulware D and et al (15) developed a randomized, double-blind, placebo-controlled trial in the United States and part of Canada in which hydroxychloroquine was evaluated as post-exposure prophylaxis. 821 asymptomatic participants were enrolled. Overall, 87.6% of participants (719 out of 821) reported a high-risk exposure (domestic or occupational, to someone with confirmed COVID-19, without a mask and eye

shield, for 10 minutes) with COVID-19. The incidence of a new disease compatible with COVID-19 did not differ significantly among participants who received hydroxychloroquine (800 mg once a day, followed by 600 mg in 6 to 8 hours, then 600 mg a day for an additional 4 days) 49 of 414 (11.8%) and those who received placebo 58 of 407 (14.3%); the absolute difference was -2.4 percentage points (95% confidence interval, -7.0 to 2.2; p = 0.35) (13). Side effects were more frequent with hydroxychloroquine than with placebo (40.1% vs 16.8%), with no adverse reactions reported.

Mitja´ O et al (16) conducted an open, cluster-randomized trial that included asymptomatic contacts with confirmed COVID-19. The analysis included 2,314 healthy contacts from 672 confirmed COVID-19 patients. A total of 1,116 contacts were randomized to receive hydroxychloroquine (800 mg once daily, followed by 400 mg daily for 6 days) and 11,989 to receive usual care. Results were similar in the hydroxychloroquine and usual care groups with respect to the incidence of CRP-confirmed symptomatic 8 (5.7% and 6.2%, respectively; hazard ratio 0.86, 95% CI 0.52-1.42). Furthermore, hydroxychloroquine was not associated with a lower incidence of SARS-CoV-2 transmission than usual care (18.7% and 17.8%, respectively). The incidence of adverse events was higher in the hydroxychloroquine group than in the usual care group (56.1% vs. 5.9%), with no reported treatment-related adverse events.

Horby P et al (17) conducted a double-blind, randomized trial. Where they observed that death in 28 days occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual care group (OR = 1.09; 95% CI, 0.97 to 1.23; p = 0.15). Consistent results were seen in all subgroups of prespecified patients. The results suggest that patients in the hydroxychloroquine group were less likely to be discharged alive from the hospital within 28 days than those in the usual care group (59.6% vs 62.9%; OR = 0.90; 95% CI = 0.83 to 0.98). Between the patients who did not undergo mechanical ventilation at baseline, those in the hydroxychloroquine group had a higher frequency of invasive mechanical ventilation or death (30.7% vs. 26.9%; IR = 1.14; CI of the 95% = 1.03 to 1.27). There was a small numerical excess of cardiac deaths (0.4 percentage points) but there was no difference in the incidence of new major cardiac arrhythmias among the patients receiving hydroxychloroquine.

Self W et al (18), conducted a randomized and double-blind trial, where they observed that among the 479 patients (mean age = 57 years; 44.3% women; 37.2% Hispanic / Latin; 23.4% black; 20.1% in the intensive care unit; 46.8% received supplemental oxygen without positive pressure; 11.5% received non-invasive ventilation or high-flow nasal oxygen and 6.7% received invasive mechanical ventilation or membrane oxygenation extracorporeal), 433 (90.4%) completed the primary outcome assessment at 14 days and the rest had imputed clinical status. The median duration of symptoms before randomization was 5 days (interquartile range [IQR], 3 to 7 days). The clinical status on the ordinal outcome scale at 14 days did not differ significantly between the hydroxychloroquine and placebo groups (mean score [IQR], 6 [4-7] vs 6 [4-7]; OR = 1.02 [95% CI = 0.73 to 1.42]). None of the 12 secondary outcomes were significantly different between the groups. By 28 days after randomization, 25 of 241 patients (10.4%) in the hydroxychloroquine group and 25 of 236 (10.6%) in the placebo group had died (absolute difference, 0.2% [95% CI, 5.7% to 5.3%]; OR =. 1.07 [95% CI = 0.54 to 2.09]).

Abella B et al (19) conducted a randomized, double-blind trial, which included 132 randomized participants (median age, 33 years; 91 women [69%]), 125 (94.7%) were evaluable for the primary outcome. There was no significant difference in infection rates in participants randomized to receive hydroxychloroquine compared with placebo (4 of 64 [6.3%] versus 4 of 61 [6.6%]; P> 0.99). Mild adverse events were more common in participants taking hydroxychloroquine compared with placebo (45% vs 26%; P = 0.04); treatment discontinuation rates were similar in both arms (19% vs 16%; P = 0.81). Median QTc change (baseline at 4 weeks) did not differ between arms (hydroxychloroquine: 4 milliseconds, 95% CI -9 to 17; vs placebo: 3 milliseconds, 95% CI -5 to 11; P = .98). Of the 8 participants with positive results for SARS-CoV-2 (6.4%), 6 developed viral symptoms; none required hospitalization and all recovered clinically.

Tang W et al (20) conducted a randomized, double-blind trial, observed that of 150 patients, 148 had mild to moderate disease and two had severe disease. The mean duration from symptom onset to randomisation was 16.6 days. A total of 109 (73%) patients (56 standard of care; 53 standard of care plus hydroxychloroquine) had negative conversion long before 28 days, and the remaining 41 (27%) patients (19 standard of care; 22 standard of attention plus hydroxychloroquine) were censored as they did not achieve a negative virus conversion. The probability of negative conversion at 28 days in the standard care plus hydroxychloroquine group was 85.4% (95% CI = 73.8% to 93.8%), similar to that in the standard care group (81.3%; 71.2% to 89.6%). The difference between the groups was 4.1% (95% CI –10.3% to 18.5%). In the safety population, adverse events were recorded in 7/80 (9%) of those who did not receive hydroxychloroquine and in 21/70 (30%) of those who did not receive hydroxychloroquine. The most common adverse event in hydroxychloroquine recipients was diarrhea, reported in 7/70 (10%) patients. Two hydroxychloroquine recipients reported serious adverse events.

Abd-Elsalam S et al (21) conducted a randomized, double-blind trial, where 194 patients with a confirmed diagnosis of COVID-19 were included in the study after signing the informed consent. They were equally randomized into two arms: 97 patients received HCQ plus standard care (HCQ group) and 97 patients received only standard care as control arm (control group). The primary endpoints were 28-day recovery, need for mechanical ventilation, or death. The two groups were matched for age and sex. There was no significant difference between them regarding any of the baseline characteristics or laboratory parameters. Four patients (4.1%) in the HCQ group and 5 (5.2%) patients in the

control group required mechanical ventilation (P = 0.75). Overall mortality did not differ between the two groups, as six patients (6.2%) died in the HCQ group and 5 (5.2%) died in the control group (P = 0.77).

Skipper C et al (22) conducted a double-blind, randomized trial, where 491 patients were randomized, 423 contributed primary endpoint data. Of these, 341 (81%) had laboratory-confirmed SARS-CoV-2 infection or epidemiologically linked exposure to a person with laboratory-confirmed infection. 56% (236 of 423) were enrolled within 1 day of symptom onset. The change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (difference in symptom severity: relative, 12%; absolute, 0.27 points [95% CI, 0, 61 to 0.07 points]; P = 0.117). At 14 days, 24% (49 of 201) of the participants who received hydroxychloroquine had continuous symptoms compared to 30% (59 of 194) who received placebo (P= 0.21). Medication adverse effects occurred in 43% (92 of 212) of the participants who received hydroxychloroquine versus 22% (46 of 211) who received placebo (P <0.001). With placebo, there were 10 hospitalizations (2 not related to COVID-19), including one hospitalized death. With hydroxychloroquine, there were 4 hospitalizations plus 1 non-hospitalized death (P = 0.29).

Sekhavati E et al (23) conducted a double blind trial. The main outcome measures were vital signs, SpO2 levels, duration of hospitalization, need and duration of admission to the intensive care unit, mortality rate, and results of follow-up at 30 days after discharge. Initially, there was no significant difference between the general conditions and vital signs of the two groups. Sp O2 levels at discharge were significantly higher, respiratory rate was lower, and length of stay was shorter in the group of cases. There were no significant differences in the mortality rate between the two groups. Patients who received azithromycin in addition to hydroxychloroquine and lopinavir / ritonavir had a better general condition. The combination of hydroxychloroquine and azithromycin may be beneficial for people who are known to have a very low underlying risk of cardiac arrhythmia.

Characteristics of the effects of Ivermectin

In the different observational studies from different countries, characteristics of the results and adverse events were reported in outpatients and hospitalized patients (Table 4).

Shouman W (24) performed a randomized trial and no blinding. Where it recruited 340 participants confirmed with COVID-19, (203, from the ivermectin group; 101, control group); ivermectin group, two-dose ivermectin tablets 72 hours apart; 40-60 Kg (15 mg / day) 60-80 Kg (18 mg / day)> 80Kg (24 mg / day) and control group (contacts that will be observed without prophylaxis), for 14 days. The primary outcomes described the development of symptoms (fever, cough, sore throat, myalgia, diarrhea, and difficulty breathing) in the ivermectin group 15 (7.4%) and the control group 59 (58.4%). In adverse events, the ivermectin group was 5.42%, compared to the control group 0%.

López-Medina E et al (25) conducted a randomized, double-blind clinical trial, which included 476 patients with COVID-19, confirmed by CRP and antigen tests, 238 received ivermectin (30 ug / Kg of body weight per 5 days) and 238 received placebo, with a follow-up of 21 days. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared to 12 days (IQR, 9-13) in the placebo group (the risk ratio for resolution symptoms, 1.07 [95% CI 0.87-1.32]; P = 0.53). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved the symptoms. The most requested adverse event was headache, reported by 104 patients (52%) who received ivermectin and 111 (56%) who received placebo.

Rajter J and et al (26) conducted a double-blind, randomized trial. Where 280 patients were reviewed, 173 treated with ivermectin and 107 without ivermectin. Most of the patients in both groups also received hydroxychloroquine, azithromycin, or both. Univariate analysis revealed lower mortality in the ivermectin group (15.0% vs 25.2%, OR = 0.52, 95% CI = 0.29-0.96, P = 0.03). Mortality was also lower among ivermectin-treated patients with severe lung involvement (38.8% vs 80.7%, OR = 0.15, 95% CI = 0.05 to 0.47, P = 0.001). No significant differences were found in extubation rates (36.1% vs 15.4%; OR = 3.11; 95% CI = 0.88-11.00; P = 0.07) or length of stay. After multivariate adjustment for confounding factors and mortality risks, the mortality difference remained significant (OR = 0.27, 95% CI = 0.09-0.80, P = 0.03). One hundred and ninety-six patients were included in the propensity-matched cohort.

Rahman MA et al (27) conducted a randomized and double-blind trial, where they observed viral clearance between group A (ivermectin plus doxycycline) and group B (hydroxychloroquine plus azithromycin) is 132 (66%) on day 5 and 167 (83.5%) on day 6, respectively. Between them, 33 (16.5%) remain CRP positive after the sixth day of ingestion of ivermectin in Group A. While there are 154 (77.0%) viral clearance on day 11 and 163 (81.5%) viral clearance at day 12 of hydroxychloroquine ingestion in Group B. Among them, 37 (18.5%) remain CRP positive after 12 days in group B. The P value is 0.000427, which is significant considering the fifth day of viral clearance of the ingestion of ivermectin and the eleventh day of the ingestion of hydroxychloroquine. But considering the sixth day and the twelfth day, the P-value is 0.59, which is not significant.

Mahmud R et al (28) conducted a randomized trial between the 556 patients evaluated, 400 were enrolled and 363 completed the follow-up. The mean age of the patients was 40 years and 59% were men. Median recovery time was 7 (4-10, treatment group) and 9 (5-12, placebo group) days (IR = 0.73, 95% CI = 0.60-0.90). The number of patients with a recovery of 7 days was 61% (treatment group) and 44% (placebo groups) (IR = 0.06, 95% CI = 0.04-0.09). The proportion of patients who remained positive for RT-PCR on day 14 and whose disease did not progress was significantly lower in the treatment group than in the placebo group.

Discussions

In the present systematic review study, 17 studies evaluating the effect of azithromycin, hydroxychloroquine and ivermectin in outpatients and hospitalized patients diagnosed with COVID-19 were identified, where experimental and observational studies were reviewed.

In our report we found results that show that hydroxychloroquine alone or with azithromycin significantly increase mortality in hospitalized patients diagnosed with COVID-19, it was also found that patients received azithromycin alone or with hydroxychloroquine, had a high score of being taken to need mechanical ventilation, finding results that agree from the open randomized trials conducted by Furtado et al (11), Horby et al (15) and Self et al (16). The incidence of transmission of SARS-CoV-2 from infected patients to exposed patients without any protective equipment or medication is high. In our study, it was evidenced that hydroxychloroquine was not associated with a lower incidence of transmission of the SARS-CoV-2 virus, compared to standard care. The results of the randomized trial conducted by Mitja´ O et al (14) are consistent with our results. It was demonstrated in our study that hydroxychloroquine and azithromycin increase hospital stays greater than 21 days in relation to patients with standard care, as is consistent with the trial by Abella and et al (17). However, results were found from a non-randomized, small-sample clinical trial, which concluded that azithromycin and hydroxychloroquine decrease the contagion level and reduce hospital stay (12).

In relation to the adverse events found in our study, it was shown that azithromycin and / or hydroxychloroquine increase mortality in hospitalized patients, as did the various trials (18, 19, 20, 21). Because ivermectin reduces viral levels of SARS-CoV-2 in vitro, but several large sample size trials have not yet been performed to demonstrate its effectiveness. However, our study found results of persistent symptoms and adverse events such as long QTc in outpatients and hospitalized patients with COVID-19, results that are associated with various studies (22, 23, 24, 25, 26).

Study limitations

The limitations of this study were the limited literature found from randomized clinical trials and studies without concluding the results. Another limitation is the sample size bias with respect to age in some randomized trials and the lack of virological or laboratory results.

Conclusion

The quality of evidence on the effectiveness and benefits of azithromycin, hydroxychloroquine, and ivermectin in the treatment of COVID-19 in outpatients and inpatients was limited with no benefit.

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Authors' contribution: The authors carried out the conception and design of the work, data collection, analysis and interpretation, in addition, they wrote and carried out the critical review of the study and approved the final version.

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