



Meta-analysis: hydroxychloroquine therapy approach with or without azithromycin against covid-19

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Keyword: Azithromycin; Covid-19; Hydroxychloroquine; SARS-CoV-2.

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Keywords: Azithromycin; Covid-19; Hydroxychloroquine; SARS-CoV-2.

1. Introduction

In the last 20 years, the human coronavirus (CoVh) is responsible for virulent epidemic which cause respiratory and enteric diseases, causing a Severe Acute Respiratory Syndrome (SARS). The CoVh is

classified with a prevalent agent etiologic in the acute respiratory infections (IRAs), it should be the principal cause of this respiratory disease or can predispose people to have secondary infections caused by bacteria (LANA et al., 2020).

In 2003, the epidemic of SARS started in Hong Kong China, with lethality near to 10% of them habitants. In 2012, the Middle East Respiratory Syndrome (MERS) emerged in Saudi Arabia, making a mortality level something about of 35% of them population. In December 2019, was detected in Wuhan, China the first behaviour of the new CoVh, denominated SARS-CoV-2, which cause the new disease knowledge like Covid-19 (JUURLINK, 2020). The structure of virus and gene receptor response by the cell link are similar to SARS-CoV. However, SARS-CoV-2 use the receptor of the Angiotensin converting enzyme (ACE2), to try to enter in cell, although the reservoir of SARS-CoV-2 is localized in animals, your stay is still unknown for a long time. furthermore, studies shows the genomic of SARS-CoV-2, revealing the high phylogenetic distance in those CoVh, identified in respiratory human disease, because they shared respectively 50 and 79% of identify with SARS-CoV and MERS-CoV (BESSIÈRE et al., 2020).

The clinical manifestations of Covid-19 in 80% of them, are classified in low cases, generally characterized by fever, dry cough, tiredness. In several cases, 5% of them, the patient will have progressive dyspnoea, pulmonary bleeding, lymphopenia, it's important to say that we still don't know every signs and symptoms of covid-19, knowing that's a new pathology. The severe phases, associated with disease of the low respiratory tract, generally are seeing in people with risk factors, like: cardiopathy, pneumopathy and others chronic conditions like diabetes, obesity and asthma (STRABELLI; UIP, 2020). The laboratory diagnostic is giving using the exam: Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR), that's the gold-pattern for definitive diagnostic of this pathology, with the positive results. However, the absence of a good treatment against the infection caused by coronavirus 2 (SARS-CoV-2) and Severe Acute Respiratory Syndrome predispose the research for drugs known for their effectiveness in others medical conditions (ZHAI et al., 2020).

In this contest, articles shows that the reuse of medicines can find approved drugs which can be used for treatments in diseases with unknown ethology. One of the highlighted drugs is Hydroxychloroquine (HCQ), which showed antivirals properties and immunomodulatory effect. Furthermore, the HCQ is used in control of autoimmune pathologies, like rheumatoid arthritis and systemic lupus erythematosus. In addition, another therapeutic agent used is Azithromycin (AZT) is also defended because this classification as an antibiotic with antiviral activity. Moreover, the typical posology of these drugs is: 5 days using HCQ (400–600mg) and AZT (500mg) in diary doses, that makes a cumulative effect like the administration of 48 hours in patients with chloroquine sensibility (JUURLINK, 2020).

The quickly expansion of the pandemic caused by the new virus of the SARS-CoV-2, recalled a lot of research's around the world, searching for answers for a possible solution for the management of this disease. However, although the advance in researches for treatments, science still haven't found an effective drug against covid-19 (PACHECO et al., 2020). Therefore, every action of a study need a legitimacy recognize about them approaches, mitigating the damage, high transmissibility and complications during the hospitalization in unities of intensive therapy care. In others words, a treatment which provide the reduce the viral charge and promote the clinical cure of the patients in the onset of this disease, may help to limit the transmission of the virus in question. The present research had like focus identify and analyse

the use of HCQ with or without AZT in the fight against Covid-19, using a systematic review with meta-analysis.

2. Method

This study is a systematic review with meta-analysis, tried to identify judiciously the studies which rated the efficacy of HCQ with or without AZT, in patients with the diagnostic of covid-19. The inclusion criteria of the articles was made by two steps, like that: the first one was structured by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), who is based in evidences for reports in systematic reviews and meta-analysis. In the second step, used the strategy of patient, intervention, comparing, outcome (PICO), with the purpose to check the internal value of each study (SADIGURSKY et al., 2019). In the first step, was used PRISMA, with these criteria: 1) qualitative studies, quantitative, clinical trial, season cases studies, technical reports, exploratory studies made by physicians; 2) studies using adults patients (more than 18 years) who received HCQ with or without AZT; 3) studies with control group which did not receive HCQ e AZT; 4) studies write in Portuguese or English; 5) was included randomized and not randomized clinical trials; 6) cohort studies; 6) studies posted in data base in December 2019 until May 2020.

The second step was based in PICO strategy, to try to check the internal value of these studies. The including criteria was defined, according the description inside the Table 1. The bibliography research was made during January to May de 2020, in Virtual library in Health (BVS), with these data base: PUBMED, MEDLINE, LILACS, BDNF e SCIELO. For the construction of this review, was used terms of research to identify the disease COVID-19 or the agent SARS-CoV-2, after was addicted to research these descriptors: COVID-19, SARS-CoV-2, HCQ and AZT, where was defined using the platform of descriptors in Science of Health (DECS).

Table.1: Table caption above the table.

Definition	Description
Indicators	Founded articles selected by the title and resume according the PRISMA.
Researches	Cohort studies, clinical control group and randomized and non-randomized studies.
Patients or problem	Adults with more than 18 years, without highest age limit, diagnosed with Covid-19.
Intervention	Analyse the posology of HCQ with or without AZT in therapeutic treatment against Covid-19.
Coltroll and effectiviness	Evaluate the therapeutic results of HCQ and AZT according the measuring of RT-PCR and the numbers of deaths/intubation comparing with the experimental group and control.
Outcome	Analyse the therapeutic answers of HCQ with or without AZT, through the negativity of RT-PCR.

Source: PICO Strategy, SADIGURSKY et al., 2019. Adapted by the authors, 2020.

The exclude criteria was composed by the wrong description and when the clinical outcome were not reported by the author. Serial cases, posted experiences, narrative reviews, and systematic reviews weren't considered. Moreover, were exclude as well posts with application made in surgical clinics and obstetric, paediatric and new-born. In addition, reviews with tests made by professionals associated to pharmacologic industry was exclude.

3. Results

The bibliography search results in 7.232 posts, after the selection, 60 articles was founded and selected by the title and resume. After that, with a deeper read and use of PRISMA and PICO strategy, was considered 9 available articles for this systematic review. The figure 1 shows a flux gram and the selected researches, with the researches shared in groups.

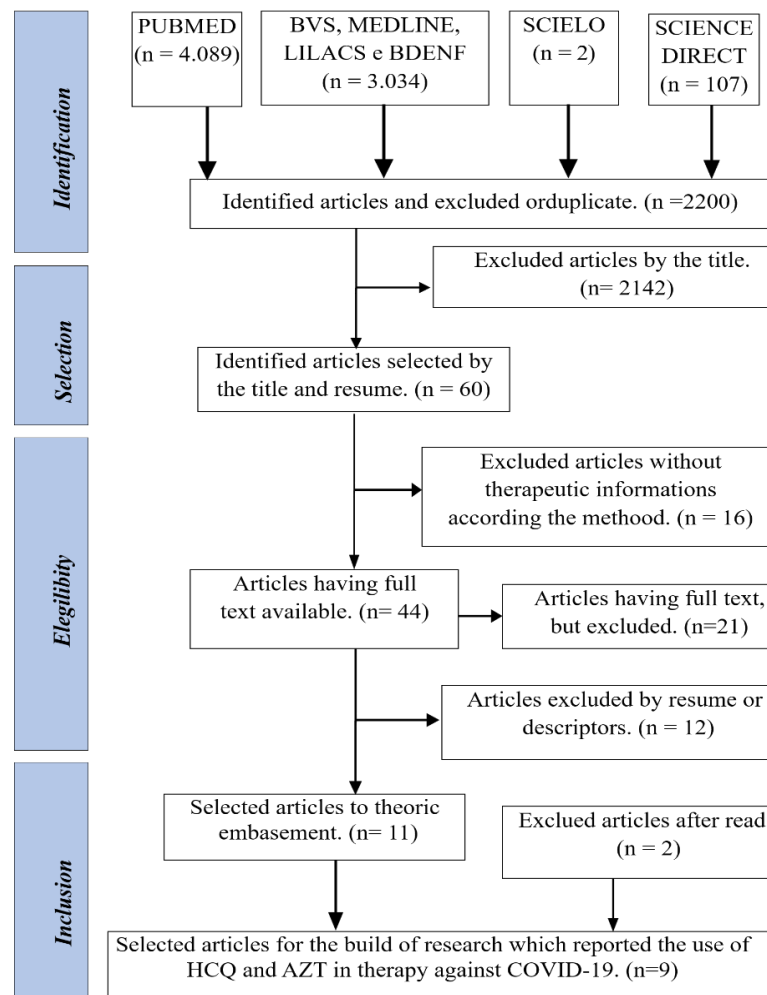


Figure 1: Stages of the procedures of the systematic review, elaborated by the authors.

Later, create a table to describe the studies found with the following characteristics: authors, identification of the research, method, study objective, number of patients or hospital beds, posology of

drugs, results of researches and conclusions about the effectiveness of the following medicines: HCQ and AZT for treatment of Covid-19. According the Table 2

Table.2: Description of the articles included in the review about the use of hydroxychloroquine with or without azithromycin.

Author	Identification of research	Method	Objective of research	Number of patients or hospital beds.	Posology of drugs	Drug percentual of effectiveness	Conclusions
ANDREA NI et al., 2020.	In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect.	That's a clinical trial using in vitro system which consist the use of cells culture.	Shows that the combination of HCQ e AZT have a synergic effect in vitro no SARS-CoV-2.	Not relacioned.	The tested drugs concentration was expressed in micromoles per liter (μM), was 1, 2 or 5 μM for HCQ associated with a 5 or 10 μM for AZT.	The combination using AZT and HCQ made a high inhibition in viral replication for the wells having HCQ in 5 μM in combination with AZT in 10 and 5 μM with relative viral inhibition of 97,5% and 99,1%, respectively.	This research shows that the combination using HCQ and AZT have a strong synergic effect in vitro against SARS-CoV-2 in compatible dosage founded in human lung.
CHEN et al., 2020.	A pilot study using hydroxychloroquine in the treatment of common cases of (Covid-19).	Open label trial.	Check the safety and effectiveness of HCQ in treatment of the patients with SARS-CoV-2 (Covid-19).	The patients was randomized 1: 1 in the HCQ group + usual treatment (n=15) and control group (n=15) only usual treatment.	Was use a dosage of HCQ 400mg/ per day for 5 days (n = 15), usual treatment (n = 15).	after 7 days of treatment: Group using HCQ + usual treatment was without viral detection in nasopharyngeal swab in 86,7% (n=13/15) <i>versus</i> 93,3% (n=14/15) control	There was no high difference in virus negativation using swab of nasopharynges comparing with group using usual treatment.

						group (p > 0.05).	
1- GAUTRET et al., 2020.	Hydroxychloroquine and azithromycin as a treatment of Covid-19: results of an open-label non-randomized clinical trial.	It was a clinical randomized trial quantitative, during 6 days.	Check the HCQ and AZT effectiveness in the viral charge of SARS-CoV-2.	36 patients; 20 patients treated with HCQ, 6 of them received AZT and 16 of the control group).	20 patients received 200 mg of orally sulphate of HCQ, during 10 days, three times in diary doses 6 of them received the association with a AZT in the dosage of 500 mg in day 1, after 250 mg per day, for 4 days.	The patients with the association of HCQ plus AZT had the virology cure in 100% in the sixth day, comparing with 70% of the patients treated only with HCQ and 12,5% of control group.	Showed that the treatment with HCQ plus AZT had effectiveness in reduction of the viral charge about Covid-19 disease.
2- GAUTRET et al., 2020.	Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 Covid-19 patients with at least a six-day follow up: A pilot observational study.	That's a cohort research without control, and comparison, using patients treated with the combination: HCQ and AZT. For 3 days or more.	Check with urgency a treatment to use in patients with Covid-19 and reduce the viral transport.	Total of 80 patients with Covid-19.	Received 200 mg of orally HCQ, 3 diary doses for 10 days, with AZT (500 mg) in the first day, after (250 mg of AZT) per day for 4 days.	After the sixth day of treatment, 83% of PCRs was negatives in positive tested patients. In the 8° day 93% the hospitalized ones showed a decrease in the number of infective. After the 5° day of the onset of admission, the virus cultures	Therefore, the combination of HCQ and AZT against Covid-19, showed a potential reduce in the onset. Moreover, this therapy showed a reduction in infectiveness.

						tested as negative in 97,5% of patients.	
GELERIS et al., 2020.	Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19.	This is a randomized clinical trial research made in Hospital of Columbia University Irving Medical Centre, localized in the north of Manhattan, during the hospitalization in march 7 until April 25 of 2020.	Check up the using of HCQ in respiratory insufficiency in a big medical centre which helps a substantial number of patients with Covid-19 in New York City.	1446 patients were checked, 70 had intubation, they dead and was excluded of the research, having 1376 patients in total.	The dosage suggested was one dose of HCQ 600 mg twice in 1/D, after that 400 mg per day during more 4/D. AZT 500 mg was given in 1/D, after that 250 mg per day for more 4/D combination using with HCQ was a optional therapeutic	In the 1376 of patients Admitted in hospital with Covid-19. The patients who received HCQ with or without combination had intubation or came to death 232/811 (28,6%), and who didn't use these drugs 84/565 (14.9%).	This observational study about HCQ showed that there is no high association about using HCQ and evolution to intubation or death. Therefore, more controlled randomised researches are necessary, because that's the best way to prove the benefits in a therapy.
MILLION et al., 2020.	Early treatment of 1061 Covid-19 patients with hydroxychloroquine and azithromycin, Marseille, France.	That's a randomized clinical trial, in cohort, the average age was 43,6 years and 46,4% of the patients was men.	Check the safety and effectiveness in the use of HCQ and AZT in Covid-19.	This research was made with 1061 patients with Covid-19 during 9 days.	200 mg HCQ three times per day + AZT (500 mg day 1 after 250 mg per day for more 4 days).	The virology cure was seen in 91,7% of patients in 10 days. The result was unsatisfactory in 46 patients (4,3%).	The precocious use of HCQ + AZT is safe and effective against Covid-19.
MOLINA et al., 2020.	No evidence of rapid antiviral clearance or clinical benefit with the combination of	Observational, prospective study realized in France during 10	Evaluate the viral mitigating or clinical benefit about using	Sampling had 11 persons made by 7 men and 4 woman's. 8	HCQ (200mg per each 8/8 hours and AZT 500mg in	This research showed that 80% (n=8/10) was still	There was no evidence of antiviral activity about using HCQ plus AZT.

	hydroxychloroquine and azithromycin in patients with severe COVID-19 infection.	days.	HCQ and AZT in critical patients with COVID-19.	of them had several comorbidities. During 5 days 1 patient died.	D1, after that 250mg in the 2-5 day).	tested positive in viral charge using swab nasopharyngeal after 5 and 6 days after the onset of treatment.	Moreover, others biggest clinical trials had not proved the effective or damage in the use of these drugs.
ROSENBERG et al., 2020.	Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients With Covid-19 in New York State.	Multicentre cohort retrospective study using patients in a aleatory sampling about all admitted patients with Covid-19 confirmed by labs in 25 hospitals in New York City.	Describe the association of using HCQ, with or without AZT, and the clinical results in hospitalized patients diagnosed with de Covid-19.	Sampling using 7914 patients having Covid-19. A total of 2362 registers was selected randomly and 1438 was included in the analysis of medical treatment.	The dosage of HCQ was made in 3 steps, with 200mg, 400mg, 600mg. In addition the dosage of AZT was given in 200mg, 400mg e 500mg.	The study showed that the mortality level was 20,3%. In the experimental group using HCQ + AZT was 25,7%, 19,9% with isolated HCQ, 10,0% with the association using AZT. In the control group was 12,7%.	The treatment using HCQ and AZT made no high difference in the levels of hospital mortality. However, this founds should be limited by the observational draw.
TANG et al., 2020.	Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial.	That's a multicentre opened randomized clinical trial about the use of HCQ in patients admitted in hospitals having Covid-19.	Check the effective and safety about the use of HCQ associated with the usual. Comparing with the usual treatment.	150 patients admitted in hospital having covid-19. 75 patients received HCQ plus usual treatment and 75 only using the usual one.	Started dose of 1200mg/per day still the thirty day. After that, using the maintenance dose of 800mg/per day of HCQ during two or three weeks.	The probability of negative conversion of SARS-CoV-2 in these patients who used usual treatment plus HCQ, was 85,4% in 28 days. Similar than who used only the usual one (81,3%) with perceptual difference of pattern in 4,1%.	The use of HCQ in the usual treatment did not change the probability of negativation in results of SARS-CoV-2 comparing with group using only usual treatment.

Source: HCQ (hydroxychloroquine), AZT (azithromycin), D (day), MG (milligram), SADIGURSKY et al., 2019. With adaption in the authors, 2020.

4. Discussion

After the evaluation, it's possible to identify three non-randomized clinical trials, three randomized trials, one multicentre clinical trial, one experimental clinical trial in vitro and one cohort study. Of The 9 studies, only eight had approach with humans, a total of 4182 patients. In this way, the selected articles was chose and organized by alphabetic order for discussion.

To evaluate the result of in vitro evidences, the research made by Andreani et al., (2020), used the HCQ isolate or associated with AZT, resulting in a high reduce in viral replication of SARS-CoV-2, showing synergic effects. Therefore, in this controlled clinical trial using wells having HCQ (5 μ M), in association with AZT (10 and 5 μ M) cause viral relative reduction of 97,5% and 99,1% in the viral replication. Although can be possible to have this dosage in compatible levels founded in lung tissue, this research translates the difficult situation about reproducing clinically, because the high possibility to have adverse effects in these dosages. Moreover, the results founded in works using in vitro projects in pharmacology opened space to search more answers in clinical trials controlled in vivo.

In addition, in a Chinese randomized clinical trial, Chen et al., (2020), which tried to check the safety about using HCQ in moderate cases showed their results and have not showed high difference in the detection of viral charge using nasopharyngeal and oral swab, in the group using HCQ with usual treatment, evaluated during 28 days. In this way, the results without viral detection using HCQ plus usual treatment was 86,7% (n=13/15) versus 93,3% (n=14/15) about control group (usual treatment) ($p > 0.05$). So, for the authors, science needs more studies to found better outcomes about the use of HCQ against Covid-19.

In this context, the study realized by the French Gautret et al., (2020), presented some clinical trials about the use of HCQ with AZT. One of them had an important reduction in the viral charge after 6 days of treatment comparing with control group (n=16). A total of 36 persons was analysed (100%), 55% of them (n=20) just used only HCQ e 17% (n=6) or the combination addiction with AZT, resting for the control group 44% (n=16) of persons. After the analyse, in the sixth day after the started of treatment 100% of the patients having the combination of HCQ and AZT, was cured virologically, comparing with 57,1% of patients using only HCQ e and inside control group the cure level was 12,5%. However, another researched posted by Gautret et al., (2020), reproduced the same results seeing before, but with a biggest sampling of cases (80 patients), non-comparative e non-randomized, used doses with 200 mg of orally HCQ (three times per day for ten days), addicting the AZT (500 mg in D1, after 250 mg per day during four days). This article did not show against indications about using these drugs, did not putted critical situations and addicted a cephalosporin of third generation in therapy.

In this way, researches made by de Gautret et al., (2020) reinforced that after the sixth day of treatment, a the virological cure was seen in 83% of PCRs and negative in patients in the 8 $^{\circ}$ day of admission (93%). However, was a decrease in the number of infective patients after the 3 $^{\circ}$ day of the onset of admission, proved using viral cultures using respiratory specimen, where was negatives in 97,5% of the cases in the

5-day no. Therefore, the both studies bring relevant data about effectiveness of these medicines using precociously, however, showed with limitations, not only because the low number of patients analysed, but also the absence of a better strict in the randomization presents.

Another different article produced in France founded the same conclusion, showed by Gautret et al., (2020). Approach using 1061 patients, the author Million et al., (2020) concluded that the precocious use of HCQ and AZT against SARS-CoV-2 is safe and effective, having low levels mortality. An Observational and retrospective study was realized, which saw the virology cure in 973 patients in 10 days (91,7%); by the other side, a bad clinical result happened in 46 patients (4,3%), with 8 deaths (74-95 years). So, the association of HCQ plus AZT used precociously, is related with an interesting reduce of viral charge with a good clinical result, preventing possible complications, also should be considered in this sampling, that something about 95% of the patients have not reported complications, classified like low cases in the admission.

This trials gained prominence around the world like possible drugs in the treatment against SARS-CoV-2. After that, others studies was developed to try to reproduce the clinical results founded before. In a prospective study, made in France, the authors Molina et al., (2020), used the same posology used by the study of Gautret et al., (2020) to analyse these drugs in patients in several cases, having comorbidities, to prove as well the effectiveness of this study in the reduce of viral charge. However, the results of these authors, founded different results comparing with the production of Gautret et al., (2020), In these ones, there was no evidence of clinical success in the association use of HCQ e AZT to several patients infected by this virus, because 80% (n=8) of the patients still had positive results for SARS-CoV-2 after 5-6 days of treating, against drastically with the results showed by Gautret et al., (2020) which had a significantly reduce in viral charge after sixth day of treatment.

The study of Geleris et al., (2020), exposed a total of 1446 patients, after the hospital admission, was excluded from analyse 70 patients who were intubated, dead or had hospital discharge after 24 hours of admission. Were included 1376 patients in analyse, 811 (58,9%) received HCQ (600 mg twice in first day, after 400 mg per day during 5 days), the controlled group was 565 (41,1%) who have not received HCQ. During something about 22 days, patients treated with HCQ was hardly sick in the started than others who have not received HCQ). Having like first outcome the respiratory insufficiency in 346 patients (25,1%); a total of 180 patients was intubated, 66 of them dead after, and 166 dead without intubation. In this analyse non adjusted, the patients who used HCQ had more chance to face complications during the admission comparing with the patients who have not used HCQ (risk level, 2,37; IC95%, 1,84 a 3,02).

Moreover, this research analysed the principal multivariate with pondering of reverse probability, exposing that there was not association about using HCQ and intubation and death (risk reason: 1,04; IC95%, 0,82 a 1,32) and emphasized that the association with AZT also haven't increase in the final compose (level of risk 1,03; IC95%, 0,81 a 1,31). The last analyse was made in April 25, totalizing 232 deaths and 114 still were hospitalized (only 24 wasn't have intubation). So, the observational article tried to exam the association about using HCQ and respiratory insufficiency, although this huge research, is notorious the incoherence about the data organization about deaths and intubation, predisposing questions about this theme. As well, the authors mentioned the limitations about this study, including low data's for some variants.

In this same context, the same results also happen in other research scene, according to Rosenberg et al., (2020) realized in United States of America. The studied group of the cohort multicentre study was guide for a aleatory sampling about every cases of patients admitted with suspect of da Covid-19 and conformed by labs 25 hospitals. Article showed that 88,2% of patients with Covid-19 was from the metropolitan area of New York, which approached 1438 hospitalized patients. 735 (51,1%) of these patients received HCQ + AZT, 271 (18,8%) received HCQ isolated, 211 (14,7%) received AZT isolated e 221 (15,4%) have not received any drug. The dosages of HCQ occurred in 3 steps: first with 200mg, after 400mg and 600mg. The dosages of AZT were: 200mg, 400mg e 500mg. The hospital mortality was 20,3% (IC 95%, 18,2% -22,4%). The probability of death in patients using HCQ + AZT was 189/735 (25,7% [IC95%, 22,3% -28,9%]), HCQ isolated, 54/271 (19,9% [IC95%, 15,2% -24,7%]). AZT isolated, 21/211 (10,0% [IC 95%, 5,9% -14,0%]) and none drug 28/221 (12,7% [IC 95%, 8,3% -17,1%]).

Furthermore, the approach of the research of Rosenberg et al. (2020), posted the proportional risk models of Cox adjusted, comparing to patients who have not received any drug, there was not high differences in mortality of the patients who received HCQ + AZT (HR, 1,35 [IC 95%, 0,76-2,40]), HCQ isolated (HR, 1,08 [95 % IC, 0,63-1,85]) or AZT alone (HR, 0,56 [IC 95%, 0,26-1,21]). In the hospitalized patients in New York city having Covid-19, the therapy with HCQ with or without AZT, comparing to the group who haven't use these drugs, there is no difference in association about mortality.

Another open-multicentre trial with randomized clinical approach, used 150 persons diagnosed with Covid-19, most of them are classified in low and moderate persistent cases, c Tang et al., (2020), this trial search the probability about negative conversion of SARS-CoV-2 using extraction and amplifying the total RNA in RT-PCR removed by the patients seeing for 28 days, sharing them in 2 groups: one group with HCQ and usual treatment and the other with control group, using only usual treatment. Therefore, the outcomes of these studies about HCQ showed a negativation at virus SARS-Cov-2 in 85,4%, evidencing a probability similar than a viral elimination, comparing to the usual treatment 81,3%. As well, more gastric and enteric effects was reported inside the group using HCQ, comparing to control. No geral, tais estudos não apoiam o uso do fármaco HCQ em pacientes de leve a moderado com covid-19.

In these 9 articles, 4 were excluded because the absence of comparison with control groups. PICO strategy selected retrospectives cohort researches, clinical controlled trials and randomized and non-randomized. 5 articles were included in this meta-analyse, 3 of them for the experimental group and for control one, 2 for evaluate the number of deaths/intubated. These data's was putted, analysed and projected by the forest plots with informatics software called Rstudio to help them, using these packs: Openxlsx, meta e Office 2016. The graphycs is showing in the figures 2 and 3.

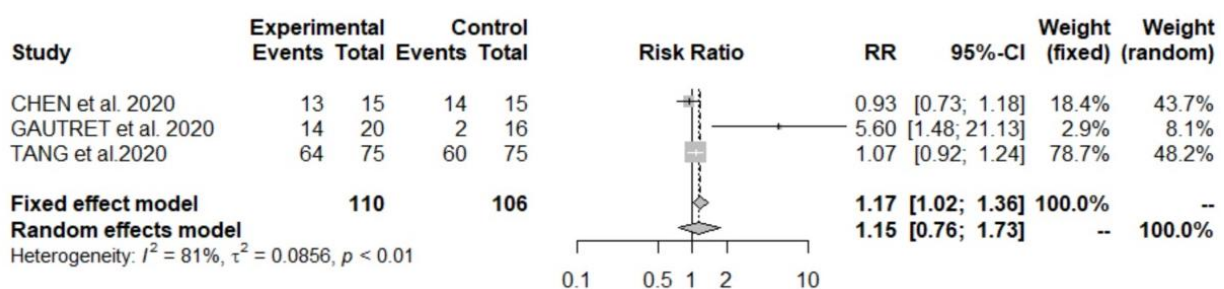


Figure 2: Authors, 2020. Graphic of forest plots which compare the use HCQ with or without AZT with

control group gainst Covid-19.

The meta-analysis of 3 clinical trials (RR: 1.15; IC95%, 0.76 a 1.73), did not found high differences when evaluated in a common outcome about negativation of PCR in patients using HCQ with or without AZT, comparing to control group who haven't used the therapy, a total of 216 persons in the research.

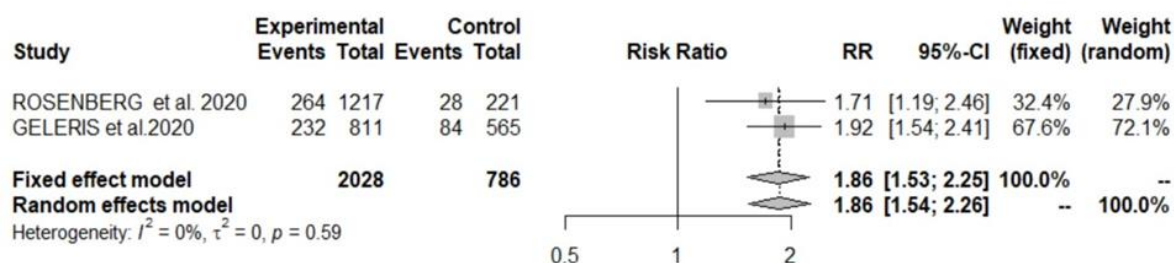


Figure 3: Source: Authors, 2020. Graphic of forest plots which compare the number of deaths about using HCQ with or without AZT, with control group who have not used the medicines.

Figure 3, shows a meta-analysis referent two articles, approaching 2814 patients, where checked up the number of deaths or people who needs to be intubated, in comparative groups: the experimental use of HCQ and control. Therefore, although this research shows a weak result (RR:1.86; IC: 95%, 1.54 a 2.26) should be considered a higher chance to death or intubation in patients who had HCQ in the therapy.

4. Conclusion

According with results, there is no highest difference about using HCQ with or without AZT about the final outcomes which evaluated the relationship with the control group. In this way, it's not possible to prove the effectiveness of these drugs in the fight against SARS-CoV-2, not only for the poor number of controlled clinical trials, but also for the limited sampling, evaluated without scientific rigor. Therefore, the necessity to improve the scientific production used to qualify the real power about using HCQ with or without AZT against covid-19 is more than necessary.

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References

[1] A.C.D. Lima, D.A. Cunha, R.C. Albuquerque, R.N.A. Costa, H.J. Silva, Alterações sensoriais em respiradores orais: revisão sistemática baseada no método prisma. Revista Paulista de Pediatria, 37(1), 97-103, 2019.

- [2] D. Sadigurskya, M.D. Sousa, Y.G.L. Cajaíba, R.R. Martins, D.M.V. Lobão. Profilaxia infecciosa com aplicação local de vancomicina em pó em cirurgias ortopédicas: revisão sistemática com metanálise. *Revista brasileira de ortopedia*, 54(6), 617-626, 13, 2019.
- [3] D.N. Juurlink, Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of sars-cov-2 infection. *Can. Med. Association journal*, 2020; 192: 450-453, 2020.
- [4] E.S. Rosenberge, E.M. Dufort, T. Udo, L.A. Wilberschied, J. Kumar, J. Tesoriero, P. Weinberg, J. Kirkwood, A. Muse, J. DeHovitz, D.S. Blog, B. Hutton, David R Holtgrave, H.A. Zucker. association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with covid-19 in new york state, *jama*, e208630, 2020.
- [5] F. R. Bessière, H. Rocca, A. Delinière. Assessment of qt intervals in a case series of patients with coronavirus disease 2019 (covid-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *Jama cardiol*, e201787. *Cognition*. (2008). In *Oxford reference online premium dictionary*, 2020.
- [6] J. Andreani, M. Bideau, I. Dufлот, P. Jardot, C. Rolland, M. Boxberger, N. WurtzabIn, J.M. Rolain, P. Colson. B.L. Scola, D. Raoult. vitro testing of combined hydroxychloroquine and azithromycin on sars-cov-2 shows synergistic effect. *Microbial pathogenesis*, v.145, p.1-4, 2020.
- [7] J. Chean, D. Liu, L. Liu, P. Liu, Q. Xu, L. Xia, Y. Ling, D. Huang, S. Song, D. Zhang, Z. Qian, T. Li, Y. Shen, H. Lu, A pilot study of hydroxychloroquine in the treatment of patients with common coronavirus-19 disease (covid-19), *Zhejiang da xue xue bao.Yi xue ban, Journal of Zhejiang University. Medical sciences*, 49(2), 215–21, 2020.
- [8] J. Geleris. Y. Sun, J. Platt, J. Zucker, M. Baldwin, G. Hripcsak, A. Labella, D.K. Manson, C. Kubin, R.G. Barr, M.E. Sobieszczyk, N.W. Schluger. Observational study of hydroxychloroquine in hospitalized patients with covid-19. *The new england journal of medicine*, 2012410. Advance online publication, 2020.
- [9] J. Molina, C. Delaugerre, J. Le Goff, B. Mela-Lima, D. Ponscarne, L. Goldwirt, N. Castro. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Medecine et maladies infectieuses*, 50(4), 384, 2020.
- [10] M. Million, J.C. Lagier, P. Gautret, P. Colson, P.E. Fournier, S. Amrane, M. Hocquart, M. Mailhe, V. Esteves-Vieira, B. Doudier, C. Aubry, F. Correard, A. Giraud-Gatineau, Y. Roussel, C. Berenger, N. Cassir, P. Seng, C. Zandotti, C. Dhiver, I. Ravaux,... D. Raoult. Early treatment of 1061 covid-19 patients with hydroxychloroquine and azithromycin, marseille, France. *Travel medicine and*

infectious disease, 101738, 2020.

- [11] P. Gautret., J.C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, J. Sevestre, M. Mailhe, B. Doudier, C. Aubry, S. Amrane, P. Seng, M. Hocquart, C. Eldin, J. Finance, V. E. Vieira, H. T. Tissot-Dupont, S. S. Honoré, A. Million, M. Colson, D. Raoult, Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 covid-19 patients with at least a six-day follow up: a pilot observational study. *Travel medicine and infectious disease, travel med infect dis*, v.34 (101663): p.1-7, 2020.
- [12] P. Gautret., J.C. Lagier, P. Parola, V.T. Hoang, L. Meddeb, J. Sevestre, M. Mailhe, B. Doudier, C. Aubry, S. Amrane, P. Seng, M. Hocquart, C. Eldin, J. Finance, V. E. Vieira, H. T. Tissot-Dupont, S. S. Honoré, A. Million, P., Chabrière, E., La Scola, B., Rolain, J. M., Brouqui, P.D. Raoult, Hydroxychloroquine and azithromycin as a treatment of covid-19: results of an open-label non-randomized clinical trial, *international journal of antimicrobial agents*, v.20 (105949): 1-24, 2020.
- [13] P. Zhai., Y.X. Ding, J. Long, Y. Zhong, Y. Li. The epidemiology, diagnosis and treatment of COVID-19. *International journal of antimicrobial agents*, 55(5), 105955, 2020.
- [14] R.M. Lana, F.C. Coelho, M.F.C. Gomes, O.G. Cruz, L.S. Bastos, D.A.M. Villela, C.T. Codeço. Emergência do novo coronavírus (sars-cov-2) e o papel de uma vítima nacional em saúde e efetiva. *Cafajeste. Saúde pública*. 36 (3): 1-3, 2020.
- [15] S. J. S. Pacheco, S. Kong, P. P. Santacruz, R.W. Murphy, L. Kubatko. Median-joining network analysis of SARS-CoV-2 genomes is neither phylogenetic nor evolutionary. *Proceedings of the National Academy of Sciences of the United States of America*, 117(23), 12518–12519, 2020.
- [16] T. Strabelli, D.E. Uip. COVID-19 and the Heart. COVID-19 e o Coração. *Arquivos brasileiros de cardiologia*, 114(4), 598–600, 2020.
- [17] W. Tang, Z. Cao, M. Han, Z. Wang, J. Chen, W. Sun, Y. Wu, W. Xiao, S. Liu, E. Chen, W. Chen, X. Wang, J. Yang, J. Lin, Q. Zhao, Y. Yan, Z. Xie, D. Li, Y. Yang, L. Liu, J. Qu, G. Ning, G Shi, Q. Xie. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *The BMJ (Clinical research ed.)*, 369: m1849, 2020.