Empirical treatment with hydroxychloroquine and azithromycin for suspected cases of COVID-19 followed-up by telemedicine

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Abstract

Background: Telemedicine can facilitate patient's assessment with initial flu-like symptoms in the COVID-19 pandemic, moreover it promotes social isolation. Hydroxychloroquine and azithromycin are associated with reduction in COVID-19 patients' viral load. This study aims to assess whether empirical prescription of hydroxychloroquine and azithromycin for patients with suspected COVID-19 is associated with less need for hospitalization **Methods:** A telemedicine team evaluated suspected COVID-19 outpatients with flu-like symptoms, if no contraindications were detected, treatment with hydroxychloroquine and azithromycin was prescribed after consent from subjects. Patients were monitored daily by telemedicine appointments. **Results:** Of the 636 symptomatic outpatients, 412 started treatment with hydroxychloroquine and azithromycin and 224 refused medications (control group). Need for hospitalization was 1.9% in the treatment group and 5.4% in the control group (2.8 times greater) and number needed to treat was 28 (NNT = 28). In those who started treatment before *versus* after the seventh day of symptoms, the need for hospitalization was 1.17% and 3.2%, respectively. **Conclusion:** Empirical treatment with hydroxychloroquine associated with azithromycin for suspected cases of COVID-19 infection reduces the need for hospitalization ($p < 0.001$).

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Keywords: SARS-CoV-2; COVID-19; hydroxychloroquine; azithromycin; telemedicine, pandemic.

1. Background

In the past two decades, severe acute respiratory syndromes have been one of the most critical threats to global health. Coronaviruses (Mers-CoV, SARS-Cov) are virus that may affect humans and cause severe infections and deaths worldwide (1).

In December 2019, a new Beta-coronavirus, named SARS-CoV-2, was associated with a set of respiratory tract infections in Wuhan, Hubei province in China, and spread rapidly across continents (2). According to the World Health Organization (WHO), the outbreak was declared a public health emergency of international interest on January 30, 2020 and on March 11, WHO announced COVID-19 outbreak a pandemic (3).

Patient's clinical characteristics from China revealed that comorbities such as diabetes, hypertension and others cardiovascular diseases were related to poor outcomes and high death rates, with three to four times more chances to be admitted in the intensive care unit and mechanical ventilation, compared to patients free of comorbidities (4).

The infection early stage is characterized mainly by respiratory symptoms, including fever, cough, sore throat and fatigue (4). Later, high viral replication, high inflammatory activity and exacerbated immune response leads to a "cytokine storm", which is responsible for complications, such as severe pneumonia and acute respiratory distress syndrome (5), with increased requirement of ventilatory support and intensive care unit (ICU) admission (1, 6).

Telemedicine has been described as a potential tool for mitigating the impact of disasters, health emergencies and providing public services (7). Countries which health care systems have already implemented telemedicine innovations, such as the United States, may respond better to COVID-19, especially by assessing high

risk outpatients (8). "Direct screening" by telemedicine, described as the classification of patients before they reach the emergency department, promotes social isolation, which is considered of great importance to disease control, protecting both patients and healthcare professionals. Telemedicine to the consumer (or on-demand) is a 21st-century approach that allows patients to be tracked efficiently and possibilities communication between doctors and patients 24/7 through smartphones or webcam-enabled computers (7, 8).

Chloroquine was first synthesized in Germany in 1934 and has been used for decades as first-line drug in the treatment and prophylaxis of malaria. Previews *in vitro* studies had reported that chloroquine has antiviral activity against several RNA-viruses, such as rabies (9), poliovirus (10), Hepatitis A and C viruses (11, 12), Influenza A and B (13, 14), Dengue (15), Zika (16) and recently also against coronavirus (17). Mechanism of action includes blocking cell infection by increasing the endosomal pH and interfering with the glycosylation of the SARS-CoV2 cell receptor (18, 19). According to Chinese reports, approximately 100 patients infected and treated with chloroquine had a faster decline in fever, improved images of pulmonary tomography (CT), with shorter recovery time, and no serious adverse effects were observed (20).

Hydroxychloroquine, a derivative of chloroquine, has a hydroxyl group at the end of the side chain, having pharmacokinetics similar to chloroquine, with rapid gastrointestinal absorption and renal excretion, in addition to a less toxic profile (21). Hydroxychloroquine also has been demonstrated to inhibit SARS-CoV-2 infection *in vitro (22).* Moreover, Gautret et al (23) in an open-label non-randomized clinical trial with a small sample size have reported that hydroxychloroquine significantly reduced viral carriage on day 6 post-treatment compared to control group. Furthermore,

adding azithromycin to hydroxychloroquine increased treatment's effectiveness. A randomized study from China also found that patients treated with hydroxychloroquine compared to control improved lung imaging findings and had shorter time to clinical recovery (24).

The antiviral and anti-inflammatory activities of chloroquine/hydroxychloroquine may be responsible for its efficacy in COVID-19 treatment (19, 25). Moreover they are well-studied drugs with limited toxicity (26) and generally mild and transient side effects (27). The use of chloroquine for more than 70 years as an antimalarial treatment reinforces its safety for acute administration. Long prescription of hydroxychloroquine for rheumatic disease also has demonstrated the low incidence of adverse events for periods up to five years (26). Furthermore, hydroxychloroquine's low cost makes it a feasible option for massive scale use.

Malaria is a serious public health problem in Brazil. In 2018, there were 190,000 malaria notification cases (28, 29), and up to 99% of all cases were in the Amazonian region (30). In South America, *Plasmodium vivax* is responsible for 71-81% of malaria cases (31) and chloroquine remains the treatment of choice (32). As a result, Brazil has a long and comprehensive experience in treating patients with chloroquine.

In a pandemic scenario, off-label and consented use of drugs with good safety profiles and potential benefits, as demonstrated by preliminary researches, should be considered as treatment options. Assuming that hydroxychloroquine plus azithromycin on early stages of COVID-19 could inhibit viral replication and prevent progression to severe forms of the disease, it is rational to hypothesize that treating patients at the beginning of the viral infection could have potential benefits (23), possible decreasing the need for hospitalization.

Nevertheless, limited supply of tests for detection of COVID-19 and time for diagnosis can pose a serious obstacle for treating patients at the beginning of infection. On the other hand, empirical treatment has been routinely performed in medicine, especially for serious infections when antibiotic therapy must be chosen empirically, despite the lack of knowledge of the etiologic pathogen (33). The strategy of empirical treatment prescription is based on the principle of risk assessment versus benefits for each individual case and the therapeutic safety profile must be considered. Use of hydroxychloroquine and azithromycin for treating patients with suspected COVID-19 fulfill the principles of empirical treatment and may be a reasonable approach to refrain the disease.

In a critical pandemic situation, many people become infected in a short period of time, which can significantly burden the health system. Strategies to improve accessibility to medical appointments through telemedicine can be a fundamental tool for screening patients suspected with COVID-19. Although little data are available, empirical treatment with safe profile drugs that have demonstrated potential benefits could be a pragmatic strategy in controlling the epidemic, as scientific evidence will be gradually established. It is of great importance that patients are followed closely, concerning safety and efficacy of the therapeutic intervention.

Given the points discussed and the urgent situation, this study aims to assess whether the empirical prescription of hydroxychloroquine and azithromycin for patients with suspected COVID-19 is associated with less need for hospitalization.

2. Methods

Study population

Patients enrolled in the study were residents of the city of Sao Paulo, Brazil, after the pandemic was officially declared in this city. Positive epidemiology for COVID-19 was defined as living in a city with more than 100 confirmed cases of COVID-19.

Consecutive outpatients with persistent flu-like symptoms (suspected COVID-19 infection), persisting for a period equal to or greater than 2 days, were first evaluated by the telemedicine team or by the emergency department medical doctor. All physicians had access to medical records of all subjects, such as clinical history, laboratory parameters, images exams and electrocardiograms.

Those who had no immediate need for hospitalization and no contraindications for treatment were invited to participate in the study. Treatment with hydroxychloroquine associated with azithromycin was suggested and prescribed if consented from patient.

The swab laboratory was not mandatory and chest computed tomography was performed according to medical judgment.

Lung injury criteria for COVID-19 were defined as the computed tomography scans with the presence of ground glass opacities in multiple lung lobes with bilateral predominance and peripheral localization (which may evolve to the central region). Definitions of the severity of lung injury according to tomographic aspects were: Mild (<25% of lung involvement), moderate (25% to 50% of lung involvement) and high (>50% of lung involvement).

All patients were part of the same health care provider, with access to the same network of hospitals, outpatient clinics and diagnostic clinics in the city of São Paulo-Brazil.

In case patients needed to be referred to hospital, they were evaluated, admitted and treated by medical staff advised to follow the standard protocol from the institution.

The main hospitalization admission criteria were:

- Worsening general condition
- Oxygen Saturation < 90%

Inclusion criteria

- Patient over 18 years old and flu-like persistent symptoms > 3 days, with a probable diagnosis of COVID-19 and no immediate indication for hospitalization.

Exclusion criteria

- Severe related retinopathy
- Severe liver disease
- Myasthenia Gravis
- Known QT enlargement
- Pregnant
- Severe renal failure

Treatment protocol

Hydroxychloroquine 800mg on the first day and 400mg for another 6 days and azithromycin 500mg once daily for five days.

Clinical outcomes

To evaluate whether the empirical prescription of Hydroxychloroquine plus Azithromycin in outpatients is associated with less need for hospitalization.

To evaluate the difference for hospitalization in patients treated before and after the seventh day of symptoms observation.

Study design and data collection

Consecutive patients with flu-like symptoms with no indication for hospitalization were included and followed up by telemedicine healthcare team. All patients were informed that the efficiency of azithromycin and hydroxychloroquine in treating COVID-19 remains to be determined. They were also informed about the safety profile of the drugs and potential side effects.

The consent form was electronically sent to the patient and signed on line, during telemedicine call or presently when the first evaluation was done in the emergency department. Hydroxychloroquine plus azithromycin were delivered at home to all those who accepted the term and agreed to use the medication. A telemedicine platform, with HIPAA compliance certified system for data security, was used for medical consultations.

All patients were followed daily by telemedicine consultations until the fifth day of symptoms, after that, patients were contacted twice a day until the fourteenth day of initial symptoms.

Breathing pattern was evaluated during videoconference and was an important tool to assess the severity of the disease and guide need for hospitalization.

The dyspnea was defined when the patient referred “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”.

The improvement in dyspnea during follow-up was defined as the total improvement in dyspnea symptoms reported by the patient during follow-up.

All patient data were taken from electronic medical records.

It was defined as the treatment group, patients that accepted the treatment with hydroxychloroquine plus azithromycin.

It was defined as the control group, patients that refused and did not sign the informed consent to use hydroxychloroquine and azithromycin.

Ethics committee approval

All patients provided written informed consent. The Ethics Committee approved the study (CONEP/Plataforma Brasil CAAE: 30586520.9.0000.0008). All procedures were performed in accordance with the Declaration of Helsinki.

Statistical analysis

Values are expressed as mean and standard deviation or median as appropriate. Categorical variables were summarized as counts and percentages. The paired-sample t test and the unpaired-sample t test were used to compare means within the study group or between subgroups. The chi-square and the Fisher exact tests were used for comparison of discrete variables. The number needed to

treat (NNT) was calculated by the inverse of the absolute risk reduction (ARR) expressed as a decimal. Continuous variables without normal distribution were compared using the Mann-Whitney U test, and correlation between such variables using the Spearman rank test. Values of $p < 0.05$ were considered statistically significant. The statistical analysis was conducted using the statistical package SPSS 15 (SPSS, Chicago, IL).

3. Results

From March 26 to April 4, 721 patients with flu-like symptoms were referred to telemedicine service, of these 85 patients were not followed due to difficulties in technical communication and lack of registration. Telemedicine team followed 636 consecutive outpatients who had flu-like symptoms and could be monitored. Of these, 224 patients (35.2%) refused the proposed treatment, making up the control group; 412 (64.7%) consented to start treatment with hydroxychloroquine and azithromycin.

The average time of symptom onset in which the medication was prescribed was 5.2 ± 3.1 days and the average follow up was 5.0 ± 2.7 days. The clinical and demographic characteristics of the patients are summarized in Table 1. The mean age was 62.5± 15.5 years and 400 (64%) were female. In addition, 85 (13.4%) patients had a diagnosis of type 2 diabetes mellitus, 168 (26.5%) had a history of hypertension, 49 (7.7%) were obese and 17 patients (2.7%) were smokers during the inclusion period of the study. The baseline clinical characteristics were similar between groups except by a higher rate of diabetes and previous stroke in the treatment group (Table 1). The treatment group also had higher prevalence of flu-like

symptoms than the control group, such as fever, cough, dyspnea, diarrhea, myalgia, coryza, and headache. Dyspnea at baseline was more prevalent in the treatment group compared to controls (22.1% versus 16%, p<0.0001) (Table 1). When we evaluated only patients with dyspnea, improvement was greater in the treatment during the follow-up (13.5% versus 5.8%, p<0.0001; Table 1)

Chest CT was performed in 251 (60.9%) subjects in the treatment group and showed that 70.1% had COVID-19 suggestive images; 150 (59.7%) patients had mild lung involvement, 26 (10.4%) moderate and none (0%) showed severe lung compromising. Only 54 (24.1%) chest CT were performed in the control group and of those 40,7% had COVID-19 suggestive images (Table 2). All patients from both groups who needed hospitalization presented COVID-19 pattern at chest CT.

There were no serious side effects in patients treated with hydroxychloroquine plus azithromycin (Table 3). Two patients in the treatment group died during the follow-up; first death was due to acute coronary syndrome and second death due to metastatic cancer.

On the treatment group, 1.9% required hospitalization, compared to the control group, which was 5.4% (p < 0.0001). That is, 2.8 times greater need for hospitalization compared to those without medication (Figure 1). It means an Absolute Risk Reduction (RAR) of 3.5% and a Number Needed to Treat (NNT) of 28 to prevent one hospitalization.

When the treatment group was stratified concerning the day of the symptom on which the drugs were started, we observed that patients treated before *versus* after day 7 of symptoms required less hospitalization (1.17% and 3.2%, respectively

p<0.001). Comparing the early treatment (< 7 days of symptoms) to those without treatment (control group) the NNT was 23 (Figure 2).

4. Discussion

In this prospective study, we observed that early evaluation of suspected COVID-19 patients by telemedicine associated with empirical treatment with hydroxychloroquine and azithromycin is an important strategy that may prevent hospitalization.

Patients treated with hydroxychloroquine and azithromycin compared to untreated patients had 2.8-fold lower need for hospitalization. In addition, need for hospitalization in patients treated before *versus* after the 7th day of symptoms were 1.17% and 3.2%, respectively,, that is a 2.7x lower rate of hospitalization when treatment was started earlier and 4.6x lower rate of hospitalization compared to untreated patients.

Patients hospitalized with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, also described as "cytokine storm" with persistent fever, elevated inflammatory markers and proinflammatory cytokines (interleukin-6 [IL-6], D-dimer, ferritin, troponin). Those findings have been associated to a more severe disease and poor outcome (6, 34). The pathophysiological rationale of our study is that starting treatment empirically, allows hydroxychloroquine and azithromycin to act in a milder phase of the disease, possibly decreasing viral replication and preventing progression to aggressive stages.

To date, there is no robust evidence that prescribing hydroxychloroquine and azithromycin in the early stage of the disease is beneficial. Recently an open-label

non-randomized clinical trial with 20 COVID-19 patients showed that hydroxychloroquine treatment for 6 days is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin. In addition, they showed that hydroxychloroquine is effective in removing viral load in patients with COVID-19 in just three to six days. Moreover, a significant difference was observed between patients treated with hydroxychloroquine and controls, starting even on day 3 after inclusion (23).

In a study of 1014 patients in Wuhan who underwent a polymerase chain reaction with reverse transcription (RT-PCR) and chest computed tomography to assess COVID-19, a "positive" CT for COVID-19 (as determined by a consensus of two radiologists) presented a sensitivity of 97%, using the C-reactive protein (PCR) tests as a reference (35). These aspects strengthen the rationale that early diagnosis should be based more on the clinical-symptomatic presentation associated with radiological manifestations than on laboratory examination, which in itself has low sensitivity (36). In our study, 60.9% of patients in the treatment group underwent chest CT, 70,1% of those had characteristics findings of COVID-19 , suggesting high probability of COVID-19 in our population.

The duration of viral shedding is also variable and may depend on the severity of the disease. In a study with 21 patients with mild disease (without hypoxia), 90% repeatedly tested negative for viral RNA in nasopharyngeal swabs for 10 days after the onset of symptoms; the tests were positive for an extended period in patients with more severe diseases (36) Such data emphasize that initiation of treatment cannot depend on laboratory tests alone, given the high rate of false negatives and the delay in obtaining the result. Swab PCR results can take days until diagnosis, which can be crucial for clinical evolution of the infected patient. Liu et al (36)

demonstrated that the "waiting period" may be critical for patients to entering high inflammatory and immune response phase, which is very difficult to reverse, culminating in high need for hospitalization and mortality rate.

Patients with suspected COVID-19 and mild symptoms who do not need emergency care should be encouraged to stay home and seek a telemedicine appointment before going to a health facility. Clinical status can be assessed during videoconference by tests and evaluation of breathing pattern is decisive to classify severity and support decision-making process.

Therefore, telemedicine is an auspicious tool that can effectively provides patient’s care, reduce emergency unit overcrowding and promotes social isolation, which in turn is not only favorable to prevent the spread of infection in the population, but also among health professionals.

It is important to distress that the proposed treatment protocol, whose medications have potential benefit for COVID-19, and good safety profile, was only carried out in the face of an unprecedented pandemic scenario in recent human history, in which an extremely high mortality among people over 60 is observed throughout the world. We believe that in this extreme situation it is vital to carry out pragmatic studies that can bring rapid responses to the community.

Clinical implications

COVID-19 has caused at least 2 millions confirmed cases and approximately 128,000 deaths worldwide as of April, 15, 2020 (37). Patients with comorbidities are especially at risk. In our study, despite patients in the treatment group had higher

prevalence of diabetes, immunosuppression state and p-trend for history of stroke, the need for hospitalization was smaller.

An efficacious treatment has not yet been determined, but hydroxychloroquine plus azithromycin is one of the most promising alternatives to treat COVID-19. Also, its low cost and safety profile make its reasonable to large-scale use.

In our study, we did not observe any severe side effects related to treatment. A systematic review (31) analyzed the safety of chloroquine treatment for uncomplicated malaria identified three trials (n=1039) that provided sufficient data on adverse events (38-40). Non-serious adverse events, such as vomiting, nausea, headache and abdominal pain, were the most commonly reported and only two cases were considered serious (maculopapular rash and severe pruritus) (38). None of the patients required hospitalization. Hydroxychloroquine is about 40% less toxic than Chloroquine (41) and is considered by the World Health Organization as one of the most efficacious, safe and cost-effective medicines needed in a health system (42) .

Nevertheless, one of the most important therapeutics' challenges includes the right timing to prescribe medication. The initial phase of the disease seems the most rational to start hydroxychloroquine and azithromycin and diagnosis of COVID-19 should not be based on swab collection alone, once it can delay initiation of treatment.

Our study showed a robust decrease in the need for hospitalization when hydroxychloroquine and azithromycin were prescribed in the early days of symptoms. The best results were observed when treatment was prescribed before

day 7 of the initial symptoms, supporting the hypothesis that hydroxychloroquine and azithromycin may act on viral replication, as reported in previous studies (22, 43).

Empirical treatment is performed routinely in several medical illnesses, especially when any delay in the initiation of adequate therapy is potentially harmful. The present study demonstrated that an empirical treatment strategy for COVID-19 pandemic could significantly decrease the number of hospital admissions. Thus it may be used as a potential strategy to control COVID-19 epidemic in the world. In our study, every 23 empirical treatments performed up to 7 days reduced the need for hospitalization of 1 patient.

This study has the limitation of being carried out during a worldwide COVID-19 pandemic. It is a therapeutic intervention study, which evaluates the practical use of two drugs (hydroxychloroquine and azithromycin) with a well-known safety profile. There are still no randomized, double blind and placebo-controlled studies that prove the effectiveness of these drugs in the treatment of COVID-19. We understand that in an exceptional situation caused by the global pandemic state of COVID-19, conducting a study with drugs that have potential effects against SARS-CoV-2 and a have a good safety adds value to scientific knowledge and public health.

5. Conclusion

According to our study, empirical treatment with hydroxychloroquine associated with azithromycin for suspected cases of COVID-19 infection reduces the need for hospitalization.

Contributors

RBE: protocol development, patient monitoring, statistical analysis, manuscript writing and review; RS: protocol development, patient monitoring; FTCO: protocol development, patient monitoring, manuscript writing and review; MMC: protocol development, patient monitoring; ARF: protocol development; PBBJ: protocol development, manuscript review; SWL: protocol development; CNR: protocol development; RSCF: protocol development; SEBO: patient monitoring; PLR: patient monitoring; VCVM: patient monitoring; PLGE: manuscript writing and review; EFP: protocol development, manuscript review

Declaration of Interests

All authors have no conflict of interest.

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Table 1. Characteristics of the Patients at Baseline

	Total population (n=636)	Treatment group (n=412)	Control group (n=224)	*p-value*
Age (years) *	62.5 (±15,5)	63,6 (±14,9)	61 (±16)	0.5
Female n, (%)	400 (63%)	262 (63.6%)	138 (61.6%)	0.49
Diabetes n, (%)	85 (13.4%)	64 (15.5%)	21(9.4%)	0.043
Hypertension n, (%)	168 (26.5%)	115 (27.9%)	53 (23.6%)	0.16
Obesity n, (%)	49 (7.7%)	30 (7.3%)	19 (8.5%)	0.2
Chronic Obstructive Pulmonary Disease n, (%)	24 (3.7%)	13 (3.2%)	11 (4.9%)	0.058
Asthma n, (%)	30 (4.7%)	21 (5.1%)	9 (4%)	0.99
Stroke n, (%)	10 (1.5%)	9 (2.2%)	1 (0.4%)	0.05
Smoker n, (%)	17 (2.7%)	12 (2.9%)	5 (2.2%)	0.35
Active Oncological Disease n, (%)	6 (0.9%)	5 (1.2%)	1 (0.4%)	0.37
Immunosuppression state n, (%)	6 (0.9%)	6 (1.5%)	0	0.04
Chronic Kidney Disease n, (%)	7 (1.1%)	5 (1.2%)	2 (0.9%)	0.35
Flu-like symptoms:				
Fever n, (%)	42 (6.6%)	32 (7.8%)	10 (4.5%)	<0.0001
Cough n, (%)	277 (43.6%)	219 (53.2%)	58 (25.9%)	<0.0001
Diarrhea n, (%)	58 (9.1%)	53 (12.9%)	5 (2.2%)	<0.0001
Anosmia n, (%)	61 (9.5%)	51 (12.4%)	10 (4.5%)	<0.0001
Coryza n, (%)	54 (8.5%)	40 (9.7%)	14 (6.3%)	<0.0001
Headache n, (%)	50 (7.8%)	43 (10.4%)	7 (3.1%)	<0.0001
Myalgia n, (%)	80 (12.5%)	60 (14.6%)	20 (8.9%)	<0.0001
Dyspnea n, (%)	123 (19.3%)	91 (22.1%)	32 (16%)	<0.0001

* values expressed as mean ± SD

Table 2. Chest computed tomography findings

	Treatment Group (n=251)		Control Group (n=54)	
	N	**%**	N	**%**
Normal CT	75	29.9%	32	59.3%
COVID-19 suggestive CT	176	70.1%	22	40.7%
Severity of lung involvement				
Mild	150	59.7%	17	31.5%
Moderate	26	10.4%	4	7.4%
Severe	0	0%	1	1.8%

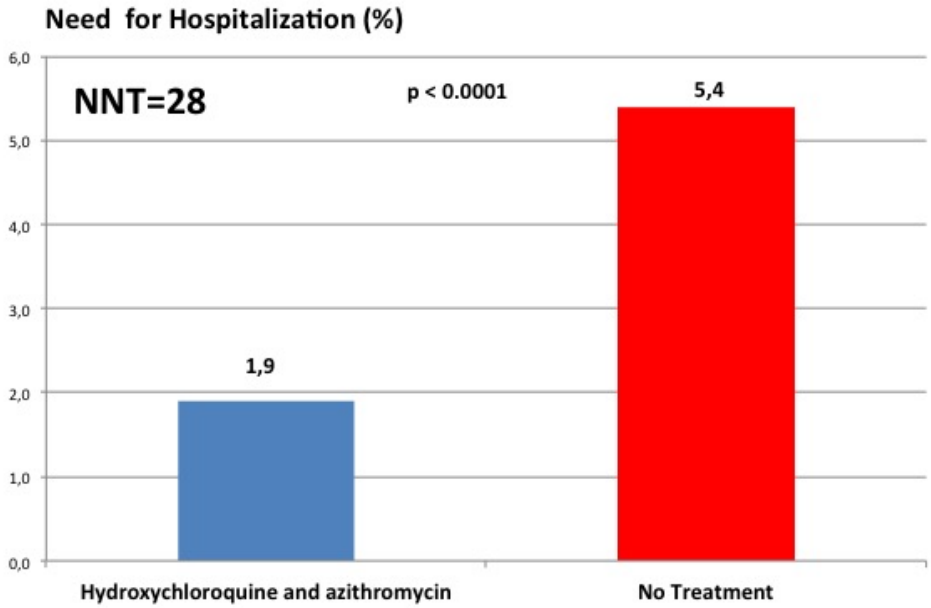
CT: computed tomography

Table 3: Safety Outcomes in the treatment group

Symptoms	**N**	**%**
Dizziness	8	1.94%
Diarrhea	69	16.50%
Nausea	31	7.52%
Vomiting	5	1.21%
Visual Disturbance	1	0.24%
Allergy	4	0.97%

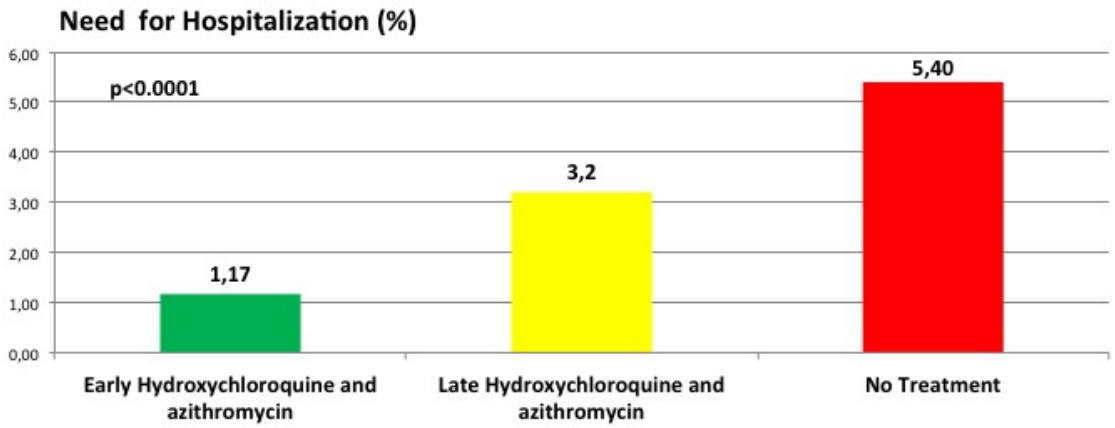
Figures:

Figure 1. Need for hospitalization in patients with suspect COVID-19



NNT =Number Needed to Treat, Qui-square Test.

Figure 2. Need for hospitalization according to treatment strategy (early treatment, late treatment or untreated).



Early treatment (<7 days of symptoms), late treatment (>7days of symptoms). p<0.0001, Qui-square test between all groups. p<0.0001 between early versus late treatment strategy.