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The Use of 4-Aminoquinolines as Treatment for COVID-19 Infection in PCR-Positive Tested Patients: A Preliminary Study

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Abstract

The advent of SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) respectively, eventually ushered in the impactful SARS-COV2 (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which was first described in December 2019 and therefore procured the name COVID-19. Just before it was declared a pandemic by the WHO in March 2020, Nigeria experienced its first case of COVID-19 on February 27th 2020. However, at the announcement of COVID-19 in December 2019, LiveWell Initiative LWI along with its Research Collaborators, put on its Thinking Cap and designed Study Protocols for COVID-19 Response in Africa. From Mid-March to Mid-April 2020, the organization shared out the study protocols to physicians, virologists, pharmacists and other specialists in the clinical sciences; thus a Hypothesis Testing went on for a month, during which time some physicians has started trying out some of the protocols on themselves and their clients, as a means of repurposing the 4-Aminoquinolines for use in COVID-19.

The Oyo State COVID-19 Isolation Centre eventually decided to embrace the Study Protocols and use them as their Standard Treatment Schedule for COVID-19. Kunle-Ara Pharmacy also used the 4-Aminoquinolines for healthcare worker prophylaxis. In collaboration with LWI, the Oyo State Isolation Centre, ably led by Prof Temitope Alonge, and the Kunle Ara Pharmacy collaborated with the LWI-Chrisland University Alliance and Professional Clinical Researchers in the United States (Prof Dotun Sobande and Dr Bola Olatunji), to run a preliminary study using real-time subjects and real-time scientific inclusion and exclusion criteria while awaiting further research bordering on a double blind placebo controlled clinical trial by NAFDAC. The study was a random Physician – Patient Trials at the discretion of Prescribing Clinicians and Clinical Researchers.

The results were astounding, with 100% positive outcomes stratified against placebo. However, further research is needed to further establish the role of 4-Aminoquinolines in late COVID-19 or acute exacerbations of pre-existing conditions in high risk patients (HRP) who have been successfully managed with the regimen.

Keywords: 4-Amino Quinolines; Healthcare workers (HCWs); Non-healthcare workers (NHCWs); High risk persons (HRPs); Severe acute respiratory syndrome coronavirus 2 (SARS-COV2)

Introduction

Coronavirus-19 (COVID-19) is a viral infectious disease of the respiratory system, first described in Wuhan China in December 2019, and caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Thus it acquired the name COVID-19 (Corona Virus Disease-2019). The outbreak of this infection started out in Wuhan province of China and eventually spread to virtually all the countries of the world. It was declared as a pandemic infection by the World Health Organization WHO on March 11th 2020 [1].

In Nigeria, the first confirmed case in Nigeria was announced on 27 February 2020. There are over 18,000 infections to date, with Lagos State as the Epicenter. As at May 27th 2021, Nigeria has had 166,146 Cases of COVID-19 and 2,071 Deaths [2].

Amid the panic that ensued after the declaration of the pandemic, several treatment options were birthed, ranging from non-pharmaceutical methods to prophylaxis, to the development of new drugs, the repurposing of older drugs, and the rapid development of vaccines.

Non-pharmaceutical method

The use of facemasks, handwashing, the use of hand sanitizers, and the observance of social distancing were initially well accepted non-pharmaceutical methods of containing the pandemic. However, after a while, exacerbated by Lockdowns, with economic, social, and mental health ramifications, defaulters emerged who advocated against the use of facemasks.

Development of new drugs

The development of new drugs like Remdesivir, heralded a new era in the COVID-19 Response, and the new drug was given rapid approvals, as it was believed to reduce the length of stay of COVID-19 Patients from 11 days to 7 days of hospitalization. However, the effect on mortality was not significant enough. Remdesivir is believed to act by stopping the RNA Viral replication; thus diminishing the chances of advancement to severe COVID-19 Infection and reducing the chances of a cytokine storm prevailing [3].

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Repurposing of older drugs

In several countries around the world, the repurposing of older drugs which had significant antiviral action, was touted and temporarily approved e.g. USA, France, Italy and a few European countries. In Nigeria, the LiveWell Initiative (LWI), a non-profit healthcare organisation, drew up Study Protocols for COVID-19 Response in Africa, using the 4-Aminoquinolines as reference drugs due to their ionophoric properties as well as several antiviral pathway mechanisms namely, Chloroquine, Hydroxychloroquine, and Quinine [4]. The null hypotheses was tested by physicians, virologists and pharmacists in a 4-week debate, was to test if these drugs could be repurposed for the Treatment, Prophylaxis, or both, for COVID-19. In particular, the organisation posited that the 4-aminoquinilines are zinc ionophores and they have antiviral action along 7 pathways in the viral life cycle; the most prominent action being the anti-haemozoin activity of Quinine, in preventing the cytokine storm. The organisation went further to test the hypothesis, by applying for clinical trials approvals at the National Agency for Food Drugs Administration and Control NAFDAC Nigeria, and at the South African Clinical Trials Registry SACT [5].

Rapid development of vaccines

Initially, the rapid development of vaccines was welcomed, but some skeptics criticized the accelerated testing and approvals. As a result, there has been a significant increase in vaccine hesitancy among people all over the world. Vaccine hesitancy would later emerge as a threat to the success of the COVID-19 vaccines; however, governments around the world, led by the US Government, led in the COVID-19 Vaccine Revolution and have achieved significant success to date [6].

Amid the ongoing COVID-19 hesitancy on the use of vaccines and the difficulty in assimilating the use of masks and adhering to the social distancing protocol, one may wonder what has been the norm of treatment in society as people find it easier to swallow than to be injected with drugs. Several people, especially in the continent of Africa, have settled for Prophylaxis using the daily supplements, especially as vaccines access has been very limited.

Non-vaccine products are said to have a 99.97 percent recovery rate for Coronavirus disease. Furthermore, unlike other conventional vaccines, the primary goal of the vaccine is to suppress the symptoms of COVID-19 infection if it is contracted. While the COVID-19 pandemic has been disrupting lives all over the world for more than a year, with the death toll approaching 3 million people and the origin still shrouded in thick clouds of obscurity, the time has come for us to use the medications that are available and effective [7].

The coronavirus and its infectivity

The first, known as S1, recognizes the virus's target, a protein known as angiotensin-converting enzyme-2 (ACE-2) that is found on the surface of cells that line the human airways. The second, S2, assists the virus in fusing with the cell's membrane once it has been anchored to the cell. The genome is injected into the cell after the virus's outer membrane has fused with that of the infected cell, hijacking its protein-making machinery and forcing it to generate new viruses. However, the invasion cannot begin until the S1 and S2 subunits are separated. They're also right at the S1/S2 junction, which is the furin cleavage site that ensures the spike protein is cleaved in the correct location. The furin cleavage site is a minor component of the virus's anatomy, but it has a significant impact on the virus's infectivity [8].

The infectivity, however, depends on the interferon system, which is the missing link between the innate and adaptive immune system. Type 1 interferons are present in virtually all cells in the body. Upon coming in contact with a virus, the interferon system is stimulated in the cell. Kinase in the cell which facilitates the transfer of phosphate group from ATP is activated by releasing phosphate [9].

The virus then forms a complex with Interferon Regulatory factor three (IRF-3) in the presence of the phosphate, a chemical process called phosphorylation. This complex traverses the nucleus and inspires the interferon β gene to make interferon β protein. Interferon β protein is generated which is transported outside of the cell. Interferonβ protein can signal self-cell, a process called the autocrine response or a neighbouring cell (paracrine response) [10].

The Interferon β protein now outside of the cell interacts with a neighbouring cell called IFNAR (Interferon alpha/beta receptor) which forms a complex with interferon-stimulated gene factor 3 (ISGF3) in the presence of interferon regulatory factor 9 (IFNR-9) which translocates or traverses the nucleus and instructs interferon regulatory factor 7 (IRF-7) gene to make IRF-7 protein which is transported outside of the cell [11].

Now that all of the cells have been inoculated with IRF-7, a sort of internal vaccine system has been established. All of these other cells are primed because the interferon system vaccinates them. When the virus infects this already sensitized cell or another cell, IRF-7 is released to stimulate the cell's machinery to produce not just interferon protein but interferon protein. Interferon and interferon are like supercharged machines that go out and destroy the virus. The interferon protein alerts/signals other cells to the danger, while the virus is knocked out by the interferon protein. Suppressor of cytokine signaling 1 (SOCS1) is a protein that is encoded by the SOCS1 gene in humans and is used to inhibit this process to avoid cytokine storms [12].

The coronavirus and its infectivity

In general, with the right chemicals, nutrition, and circumstances, the body will interact with the virus and knock it out without producing antibodies. Vitamin D, a part of the innate immune response against the spike protein, is both a hormone and a natural antibiotic. It has been shown to suppress the renin gene and renin, which would otherwise activate RAS and ACE-2. Renin and RAS overexpression is caused by a lack of vitamin D. An ionophore promotes ion transport across the cell membrane. Quercetin acts as a zinc ionophore. Taking quercetin with zinc improves zinc cellular uptake and increases zinc's antiviral activity. Chloroquine, ivermectin, and resveratrol are some other zinc ionophores. Remdesivir, the preferred and preferred drug for COVID-19, only inhibits viral RNA replication and has no effect on viral entry, cell membrane disruption, viral particle assembly, or cytokine storm, despite having palpable adverse effects comparable to Hydroxychloroquine (HCQ) and Chloroquine (CQ).

Focus on the 4-aminoquinolines

Chloroquine (CQ) and Hydroxychhloroquine (HCQ) are ancient chemical substances (with the chemical name, 4-aminoquinolines) recognized for their antimalarial and antiviral properties which from their study on CQ and HCQ as available arsenal to mitigate COVID-19, Colson [13] recognized these drugs for their ability to reduce the life expectancy of COVID-19. In an *in-vitro* antiviral study conducted by Yao [14] it was shown that both CQ and HCQ are effective antiviral agents with inhibitory effects on the secretion of more viruses. However, HCQ was recognized to be more potent for its antiviral property when used before invasion of viral infection when compared to its parent compound, CQ [15]. In their study, it was deduced that

the incubation period of these drugs is directly proportional to their antiviral effects [15]. The mother drug in this class is Quinine (QN), a naturally occurring substance from the bark of the cinchona plant, and, regarded as the mother of the 4-Aminoquinolines.

The immunomodulatory property of these chemical substances enhances their ability to interfere with the multiplication of immune factors; a mechanism that could hinder the progression of COVID-19 disease to become lethal or life threatening if either of CQ/HCQ is administered early [15]; thus early administration of CQ/HCQ will hinder the progression of COVID-19 disease [15].

Mode of action on SARS-COV 2

Vincent [15] study showed that CQ is a potent antiviral agent in averting the spread of SARS coronavirus with its interference property if administered before and after the viral invasion. Thus, could be recognized as a prophylaxis and a therapeutic agent [15]. However, aside from its ability to replicate in SARS coronavirus, its mode of action is still yet to be fully unfold [15].

A diagrammatic representation of the potential mode of action of chloroquine against SARS coronaviruses is shown in Figure 1 below [16,17].

Yao [14] from their *in vitro* study reported that hycroxychloroquine is more efficient than chloroquine in supressing the activity of COVID-19.

CQ/HCQ/QN prevents attachment and penetration of the host cell by altering the pH at the ACE2 Receptor. In addition, it has anti-inflammatory property, it breaks the polymerase chain, is a Hemozoin Inhibitor, and a Zinc Ionophore thus its tissue binding affinity to the viral cell is potentiated in the presence of zinc, prompting enhanced efficacy at lower doses [15].

CQ/HCQ/QN has a broad therapeutic margin and a highly stable safety profile. When used in therapeutic doses CQ/HCQ/QN is very safe. However when used in high doses it prolongs the QT wave leading to cardiovascular outcomes (Figure 1) [17].

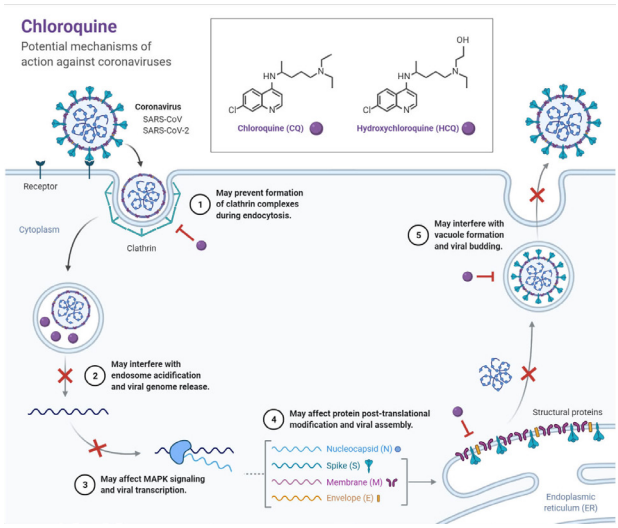

Figure 1: Potential mechanism of action against coronavirus.

For use in COVID-19 CQ/HCQ/QN is required in therapeutic concentrations within the stable therapeutic margin of lower than 5G cumulative loading dose. This lowered efficacious therapeutic effectiveness is further enhanced by ionophoric zinc which bores through the zinc channels in the virus cell and makes a way for CQ/HCQ/QN entry, ensuring enhanced tissue binding affinity and enhanced tissue uptake.

The effect of CQ/HCQ/QN on the SARS-COV2 begins at the entry point of the virus into the host cell, where CQ/HCQ/QN alters the pH, making viral penetration into the host cell more difficult. It also prevents the polymerase chain reaction, breaking the polymerase chain and preventing viral replication. It has anti-inflammatory effects, as well as Haemozoin inhibition properties, hindering the virus from engulfing food vacuoles for its survival.

With its multi-modal intervention CQ/HCQ/QN intervention in COVID-19 is therefore a realistic option which can easily be implemented to Scale, for the generality of the people [18].

The drug has a low clearance rate after metabolism; thus the once-in-a-month cycical weekly prophylaxis regimen is recommended for sustained protection, assured elimination of the drug without systemic accumulation, and, a regular re-dosing schedule for 12 months to build up host immunity [14-16].

The Africa Union Commission AU and the Africa CDC, introduced the 'Test, Trace and Treat' as a way of managing the pandemic on the continent, due to the scarcity of resources and lack of equitable vaccines access and in December 2020 released new guidelines on the use of rapid antigen tests, to enhance affordable testing and easier access to care [19].

Materials and Methods

Study design

Chloroquine (CQ), hydroxychloroquine (HCQ) and quinine (QN), which are known 4-aminoquinolines were repurposed as primary and secondary prophylaxis and treatment for high-risk group of persons. The study was preliminary study of 304 positive tested COVID-19 patients stratified against placebo. The description of persons classified as being high-risk is as listed below:

- PCR Positively Tested Persons inclusive of healthcare workers (HCWs), hospital staff (HS), health system staff (HSS), high risk persons (HRP admitted at the Olodo Isolation Center – Treatment for COVID-19.

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The prophylaxis was administered on a weekly basis to subjects after 4 weeks in the first instance and repeated after every 4-5 weeks, equating to a monthly cyclical repetition of the prophylaxis over a period of 52 weeks. Study participants were recruited across three Southwest states (Lagos, Ogun and Oyo states) in Nigeria.

Study arms

As much as possible, all therapies were administered using Direct Observed Therapy (DOT) protocol.

Pre-exposure prophylaxis (PrEP) study arm: 200 participants received 250 mg/200 mg daily stat dose of Chloroquine (CQ) or Hydroxychloroquine (HCQ) respectively, equivalent to 150 mg of Chloroquine base stat daily for 3 days from the first day of the month. This was administered with 1 gram of vitamin C and 200 mg of zinc, and was repeated after 6-8 weeks from the first day of every subsequent month for a total of 12 months inclusive of the first month. These 200

participants comprised of 100 asymptomatic HCWs, HSS, and HS and 100 HRPs. Symptoms were monitored at start of study, at six months into study and finally at twelfth month of the study.

Post-exposure prophylaxis (PEP) study arm: 200 participants received 500 mg/400 mg daily stat dose of Chloroquine or Hydroxychloroquine respectively, equivalent to 300 mg of Chloroquine base for 5 days from the first day of the month. This was administered with 1 gram of vitamin C and 200 mg of zinc, and repeated after 6-8 weeks from the first day of every subsequent 6-8 week period for a total of 12 months, inclusive of the first month. These 200 participants comprised of 200 symptomatic HCWs, HSS, and HS and 300 HRPs. Total therapy periods was 12 months, after which post-tests were repeated. Symptoms were monitored at start of study, at six months into study and finally at twelfth month of the study.

For recruitment into the study, participants fulfilled any two (2) of the under listed criteria as basic qualification to enter into the pre-exposure prophylaxis clinical trial arm and fulfilled all criteria for inclusion into the post-exposure prophylaxis clinical trial arm. These criteria were:

Body temperature value of less than 36°C or 98.4°F using an infrared thermometer

Pulse oximeter screening to measure oxygen saturation. The acceptable value was ≥ 96% SpO_2 and above for the pre-exposure prophylaxis (PrEP) clinical trial arm, and 94-96% for post-exposure prophylaxis (PEP) arm.

Antigen test (COVID-19 antigenic status) or PCR (Nasopharyngeal Swab).

All HRPs still underwent further pre-testing in accordance with their health status at the beginning of the study, at six months and at the twelfth month of the study.

Sample size determination

With an assumption of 50,000 people across several of the country's 36 states, a 95% confidence interval, a 5% margin of error, and a 25% sample proportion, we needed about 287 people to participate in the study. As a result, a convenient figure of 300-400 enrollees per study arm was proposed, resulting in a total of 704 (304 Cases controlled against 400 placebo) study participants for the study.

Inclusion criteria

Adult male or female healthcare worker aged 18 to 75 years

All frontline healthcare workers irrespective of his/her role in the health system

All health system or hospital workers who are not working at the frontlines. These were identified as HCWs, HS, and HSS.

All high risk persons suffering from chronic disease states with or without co-morbidities. These includes all persons suffering from heart disease including hypertension, other cardiovascular or renovascular disorders including diabetes mellitus, all persons with a history of or ongoing oncogenecity, all persons with history of or ongoing treatment for asthma, COPD, emphysema or other chronic airway diseases, or other ongoing medical treatment or recent multiple visits to the health system as well as all persons aged above 65 years old.

Pre-surgical patients as well as in-patients on non-COVID hospital admissions

Exclusion criteria

Persons with known hypersensitivity to chloroquine or hydroxychloroquine (CQ/HCQ) or any of the 4-aminoquinolines. However, if the benefit of prophylaxis outweighs the risk of an allergic response, the physician may manage the subject symptomatically using appropriate anti-allergic medication. Loratidine is the anti-allergen of choice due to its pharmacokinetic and pharmacodynamic properties in attenuating the release of histamine thus reducing chloroquine-induced pruritus. It is also a non-sedating antihistamine

Severely ill patients who may not tolerate the CQ/HCQ or 4-aminoquinolines without on toward side effects shall be excluded from the trials

Participation in other investigational clinical trials for the treatment or prevention of SARS-COV-2 infection within 30 days

Prior history of blood disorders like aplastic anemia, agranulocytosis, leukopenia or thrombocytopenia.

Prior history of G6PD deficiency

History of viral hepatitis or HIV/AIDS

History of dermatitis, psoriasis or porphyria

History of allergy to aminoquinolones

Pre-existing retinopathy of the eye

Pregnant women or actively breastfeeding mothers

Known history of prolonged QTc syndrome or history of additional risk factors for torsades de pointes e.g. hypokalemia, hypomagnesemia or use of concomitant drugs that prolong QTc interval.

Data collection and instrument

Inpatient Data was used at the Isolation Center. For PrEP and PEP (Placebo), Data were collected using a pre-tested, interviewer-administered, structured questionnaire.

Ethical consideration

This study was approved by Oyo State HREC. The respondents were fully informed about the research and their consent to participate in the study was obtained. There are no known disclosures. The research is not a sponsored work.

Results and Findings: Desciptive Analysis COVID 19-Olodo Center

Background

Table 1 shows the frequency distribution of patients from four different characteristics namely Age, Gender, Job Category and Comorbidity factor, from the Age category, Ages thirty (30) years to Forty Nine (49) years had the highest number of admission at the Isolation Centre with 126 people out of a total sample of 304 representing 41.4%, this means 2 out of every 5 people admitted, followed by Ages ten (10) years to twenty nine (29) years, with approximately 30% that is One (1) out of every three (3) (Figure 1). About 203 people admitted were of male gender which represents two-third of the total admission compare to 101 female admissions; one in every three is a female (Figure 2).

Characteristic	Frequency	Percent (%)	Cumulative Percentage (%)
Age category (`years)			
<10	7	2.3	2.3
10-29	91	29.9	32.1
30-49	126	41.4	73.5
50-69	64	21.1	94.6
69+	16	5.4	100
Gender			
Male	203	66.8	66.8
Female	101	33.2	100
Job category			
Non-Health Care Worker	274	90.4	90.4
Health Care Worker	29	9.6	100
Comorbidity			
Absent	242	79.6	79.6
Present	62	20.4	100

Table 1: Frequency distribution of patients' characteristics (N=304).

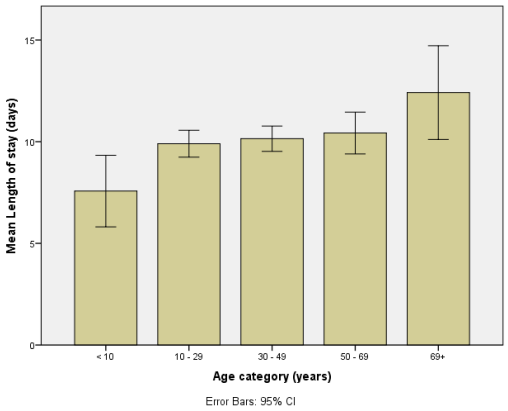

Figure 2: Mean bar plot of length of stay vs. age category.

Job category was split into Non-Healthcare workers and Health Care workers, 90% of people admitted were non-healthcare workers while Healthcare workers represent 10%. 64 people out of 304 had comorbidity factors, this represents 20%, that is one (1) in every five admission has at least an underlining factor.

Table 2 represents the descriptive statistics of the summary of Age and Length of Stay at the Isolation Centre, from the 304 patients the mean age is 39 years with a standard deviation of 16 years, with the youngest admission at Two (2) years old and the oldest at ninety-five (95) years old. The shortest stay before discharge at the facility is Two (2) days while Twenty-one (21) days was recorded as the maximum length of stay at the isolation centre, the average length of stay at the facility was 10 days, 4 hours with a standard deviation of 3 days 11 hour (Figure 3).

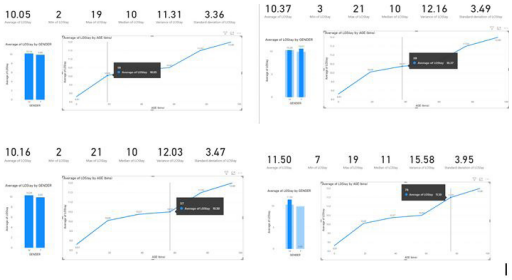

Figure 3: Descriptive statistics of the summary of age and length of stay.

Variable	N	Minimum	Maximum	Mean	SD
Age (years)	304	2	95	38.73	16.3
Length of stay (days)	285	2	21	10.16	3.47

Table 2: Descriptive statistics of the summary of age and length of stay.

Table 3 represents the descriptive statistics of the gender distribution against Age category of patients. This summary shows that the average age of female admitted during this period was 35 years old compared to 39 years old for the male gender, the oldest male on admission was 95 years while the oldest female was 71 years old. The youngest male was a 2 year old Baby and the youngest female was a 3 year old Baby (Figure 4).

Gender	Mean_AGE	Max_AGE	Min AGE	Sd AGE
Male	39.4	95	2	16.6
Female	35.4	71	3	14.4

Table 3: Descriptive statistics of the gender distribution against age category of patients.

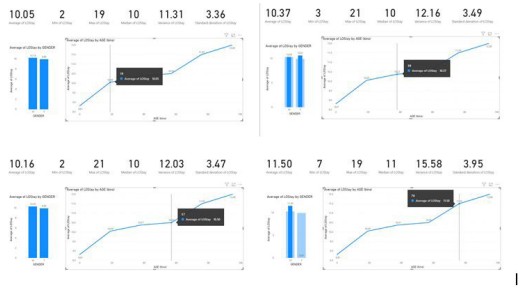

Figure 4: Descriptive statistics of the gender distribution against age category of patients.

The data shows that the older people were more likely to present with comorbidity (Table 4).

Comorbidity	mean_AGE	max_AGE	min_AGE	sd_AGE
None	35.8	95	2	15.2
Present	47.6	83	9	16.1

Table 4: Descriptive statistics of the comorbidity status against age category of patients.

The data shows Descriptive statistics of Job category against age category of patients (Table 5).

Job category	mean_AGE	max_AGE	min_AGE	sd_AGE
Health Care Worker	42.7	63	21	13.3
Non-Health Care Worker	37.6	95	2	16.3

Table 5: Descriptive statistics of job category against age category of patients.

The table shows that the males had longer length of stay than the females (Table 6).

Gender	mean_LOStay	max_ LOStay	min_ LOStay	sd_ LOStay
Male	10.3	21	2	3.67
Female	9.9	16	3	3.04

Table 6: Descriptive statistics of gender against the length of stay of patients.

Pearson's product-moment correlation for length of stay and gender

The correlation coefficient between Length of Stay and Gender are -0.05180542, the t-test statistics value -0.87267 and degrees of freedom of 283, the p value are 0.3836, from the Pearson's product-moment correlation at 95 percent confidence interval. With Alpha=0.05, our p-Value is greater than alpha as a result we fail to reject the null hypothesis and there is NO relationship between Length of Stay and Gender (Table 7 and Figure 5).

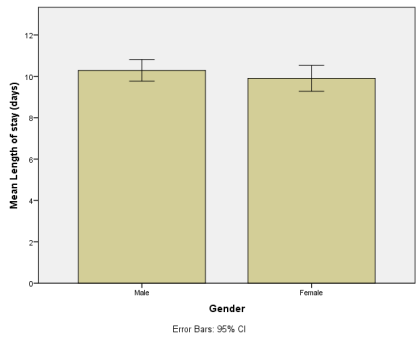

Figure 5: Mean bar plot of length of stay vs. gender, males had a slightly longer length of stay than the females.

Job category	mean_LOStay	max_ LOStay	min_ LOStay	sd_ LOStay
Health Care Worker	9.48	17	2	3.96
Non-Health Care Worker	10.2	21	3	3.43

Table 7: Descriptive statistics of job category against length of stay of patients.

Pearson's product-moment correlation for length of stay and job category

The correlation coefficient between Length of Stay and Job Category are 0.0663413, the t-test statistics value 1.1185 and degrees of freedom of 283, the p value is 0.2643, from the Pearson's product-moment correlation at 95 percent confidence interval. With Alpha=0.05, our p-Value is greater than alpha as a result we fail to reject the null hypothesis and there is NO relationship between Length of Stay and Job Category (Table 8).

Comobidity	Mean_lostay	Max_ lostay	Min_ lostay	Sd_ lostay
None	9.91	20	2	3.24
Present	11.2	21	3	4.2

Table 8: Descriptive statistics of comorbidity status against length of stay of patients.

The correlation coefficient between x and y are 0.1464299, the t-test statistics value 2.4902 and degrees of freedom of 283, the p value is 0.01334, from the Pearson's product-moment correlation at 95 percent confidence interval. With Alpha=0.05, our p Value is less than alpha as a result we reject the null hypothesis and there is relationship between Length of Stay and Comorbidity factor (Figure 6).

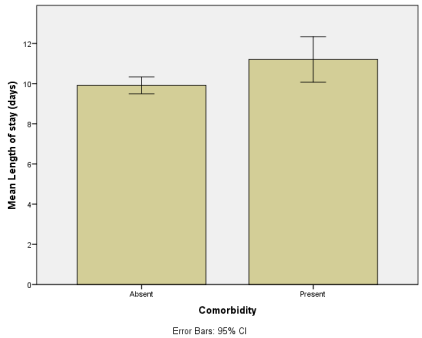

Figure 6: Mean bar plot of length of stay vs. comorbidity, the presence of comorbidity affects the length of stay.

Patients' characteristics

A total of 304 patients were included in the analysis. The mean age of the patients was 38.7 ± 16.3 years (median: 35 years, range: 2 – 95 years). Table 9 shows the frequency distribution of the patients' characteristics. Majority (83.6%) of the patients belonged to age group 18 – 59 years. About 20% of the patients had comorbidities.

Characteristic	Frequency	Percentage (%)
Age category (years)		
<18	13	4.3
18-59	254	83.6
≥ 60	37	12.2
Gender		
Male	203	66.8
Female	101	33.2
Job category		
Non-Health Care Worker	274	90.4
Health Care Worker	29	9.6
Comorbidity		
Absent	242	79.6
Present	62	20.4

Table 9: Frequency distribution of patients' characteristics (N=304).

Length of hospital stay

The mean length of hospital stay was 10.2 ± 3.5 days (median: 10 days, range: 2 – 21 days). More than half (56.8%) of the patients had short length of hospital stay (≤ 10 days).

Determinants of length of hospital stay

Bivariate analysis : Table 10 shows the results of Chi-square analysis of respondents' characteristics and length of hospital stay. Only comorbidity was significantly associated with length of hospital stay (p=0.028). However, age category was included in the multivariate analysis in addition to comorbidity because it met the inclusion criteria of p<0.2.

Characteristic	Length of hospital stay		X2	P-value
	Short [n=162 (56.8%)]	Long [n=123 (43.2%)]		
Age category (years)			5.81	0.055
<18	11 (84.6)	2 (15.4)		
18-59	137 (56.8)	104 (43.2)		
≥ 60	14 (45.2)	17 (54.8)		
Gender			0.08	0.772
Male	108 (56.3)	84 (43.8)		
Female	54 (58.1)	39 (41.9)		
Job category			0.02	0.9
Non-Health Care Worker	146 (56.8)	111 (43.2)		
Health Care Worker	15 (55.6)	12 (44.4)		
Comorbidity			4.85	0.028
Absent	138 (60.0)	92 (40.0)		
Present	24 (43.6)	31 (56.4)		

Table 10: Results of Chi-square analysis of respondents' characteristics and length of hospital stay.

Multivariate analysis : After multivariate adjustment, neither age category nor comorbidity was significantly associated with length of hospital stay (Table 11). However, the wide confidence intervals for the adjusted odds ratios (Figure 7) suggested that a larger sample size might be needed to achieve statistical significance.

Characteristic	AOR*	95% CI**	P-value
Age category (years)			
<18	1	-	
18-59	3.97	1.03-26.09	0.078
≥ 60	5.65	1.23-40.99	0.043
Comorbidity			
Absent	1	-	
Present	1.79	0.98-3.31	0.059
*Adjusted Odds Ratio **95% Confidence Interval			

Table 11: Results of logistic regression analysis of respondents' characteristics and length of hospital stay.

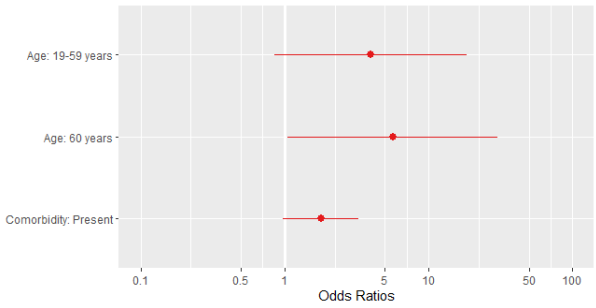

Figure 7: Plot of adjusted odds ratios from logistic regression analysis.

Discussion

In this large multicenter real-world study, we found that using Chloroquine/Hydroxychloroquine with ionophores and vitamin C early after COVID-19 diagnosis resulted in a 100 percent improvement in hospital outcomes. Each drug combination containing vitamin C and zinc sulphate was associated with a faster recovery and a shorter hospital stay.

The use of Hydroxychloroquine (HCQ) or Chloroquine (CQ) in COVID-19 is based on a large number of small uncontrolled studies that found that combining HCQ with ionophores was effective in clearing replication, preventing viral entry, and suppressing cytokine storm [20].

If clinical trial access was unavailable, the FDA issued an emergency use authorization (EUR) for these drugs in patients on March 28, 2020 [21]. China, for example, has issued guidelines allowing the use of CQ in COVID-19 [22].

An observational study of 181 patients from France found that using HCQ at a dose of 600 mg per day did not result in measurable clinical benefits in patients with COVID-19 Pneumonia [23]. Our findings contradict this report because HCQ works better with ionophores like zinc, quercetin, and resveratrol, which are conspicuously absent in the above study. Furthermore, vitamin C, which is known to prevent cytokine storms, was conspicuously absent in the study.

It has been reported that CQ and HCQ are linked to endovascular toxicity, owing to their known relationship with electrical instability, which is characterized by QT interval prolongation (The time taken for ventricular depolarisation and repolarization). This mechanism is related to hERG potassium channel blockade [24], which prolongs ventricular repolarization and the duration of ventricular action potentials. However, with a daily maximum dose of 4G, this mechanism is unlikely to occur, owing to the significant improvement in our patients treated with the guidelines presented here.

CQ or HCQ in combination with macrolide is intended to use their antimicrobial properties synergistically [25]. Macrolide antibiotics, such as azithromycin and clarithromycin, have immunomodulatory and anti-inflammatory properties [26].

Conclusion

From the results, a 100% positive outcome was attained stratified against pacebo which were untested and asymptomatic persons.

The strong association between age and length of stay, and between comorbidity and length of stay, further emphasize the higher infectivity of COVID-19 among older persons and among persons with lower immune status.

The 4–Aminoquinolines have proven effective in surpressing viral load and preventing progression to the cytokine storm in COVID-19, as this study shows surpression and no incident of progression to cytokine storm, even in a patient aged above 90 years who was hospitalized for over 20 days but recovered without progressing into the storm.

The 4-Aminoquinolines present a realistic and affordable option for the treatment of COVID-19 especially in low resource settings.

Further studies are however necessary to further assert their effectiveness if any, in advanced COVID-19 or in late diagnosis of COVID-19 or acute exacerbations of pre-existing conditions in HRPs.

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