

Assessment of Knowledge, Practice and Perception of Nigerian Medical Practitioners on COVID-19 and Its Treatment Using Antimalarial Drugs

Oluwafunmibi E. Anjorin^{1*}, Olawunmi R. Oyerinde², Ikechukwu A. Orji³, Mercy U. Ikechukwu-Orji³, Ibukun A. Anjorin⁴

¹Department of Pharmacology, Babcock University Teaching Hospital, Ilisan-Remo, Ogun State, Nigeria

²Department. of Zoology, University of Ibadan, Ibadan, Nigeria

³Cardiovascular Research Unit, University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria

⁴Department of Family Medicine, University College Hospital, Ibadan, Nigeria

Abstract

Pharmaceutical interventions are being investigated as possible treatment options for COVID-19. Antimalarial drugs-Hydroxychloroquine and chloroquine are also being investigated in clinical trials due to their antiviral effects though their efficacy in the treatment of COVID-19 is largely inconclusive. This study assessed the knowledge, perception, and practice of prescribing these drugs in the treatment of COVID-19 by practicing medical doctors in Nigeria. The survey was conducted online using Google forms sent via a link on WhatsApp[®] and Facebook[®] through the authors' contacts to medical doctors in the six geo-political zones of Nigeria from April-May 2020. Ethical issues were addressed by ensuring the anonymity of respondents, voluntary participation, and non-incentivized. Descriptive statistics were used to determine the mean and frequencies of data generated using SPSS version 22. Responses were obtained from 145 medical doctors with mean age of 37.78±6.47 years and 10.9±5.58 years of practice experience. All the respondents knew that the virus affects the lungs. Over 48% of the doctors believed in the efficacy of the antimalarial drugs, and more than half of them thought it would be more effective for mild disease presentation. About 46.8% of respondents agreed to prescribe the drug to COVID-19 patients, and most based their decisions on case reports, recommendations of NCDC or WHO. However, 75.9% believed a randomized control trial should be conducted to determine the efficacy and safety of the drugs. Practicing doctors in Nigeria are knowledgeable on COVID-19, and their perceptions and decision to prescribe antimalarial drugs are largely dependent on clinical trial outcomes.

Keywords: Chloroquine, COVID-19, Hydroxychloroquine, Medical doctors, Treatment.

Introduction

The healthcare system in Nigeria and the rest of the world are grappling with the Coronavirus disease (COVID-19), an emerging infectious respiratory disease, with other organ systems involvement [1]. It is currently a pandemic caused by the newly discovered coronavirus (SARS-CoV-2). The initial outbreak of coronavirus in Wuhan, China, spread globally

via international travels, and the World Health Organization (WHO) declared it a pandemic on 11th March, 2020 [2]. As of June 2020, over 9 million people have been infected, and about 500,000 people have died globally from the disease [3], with attendant psychological distress on survivors [4], which, however, according to a recent study, tends to be more prevalent among female survivors than males [5]. COVID-19 is spread by human-to-human

*Corresponding Author: enitaanjorin@yahoo.com

transmission through the droplet, feco-oral, and direct contact and has an incubation period of 2-14 days [6]. The specific pathophysiologic mechanism of COVID-19 is unknown, but there are varying proposed mechanisms of lung injury. Hence, the signs and symptoms are varied, with the commonest being respiratory tract infection-related symptoms like fever, dry cough, and dyspnea. In addition, headache, dizziness, generalized weakness, vomiting, and diarrhea has been observed, while a few others present with anosmia, loss of taste, and a runny nose [7].

The greatest challenge with the global pandemic is the fact that as of June 2020, no drug or vaccine has currently been approved for its treatment. This is probably due to the insufficiency of evidence-based science in the form of randomized control trials to support the use of any pharmaceutical product yet. Therefore, regulatory agencies advise that non-pharmaceutical interventions (NPIs) like social distancing, hand hygiene practices, and the use of face masks serve as means of reducing the spread and impact of the disease [8]. However, there are speculations about the use of emerging old pharmaceuticals as possible treatment options. Some of these are antimalarial drugs like chloroquine (CQ) and hydroxychloroquine (HCQ); old, cheap, and accessible drugs used for many years for prophylaxis, therapy of malaria, and autoimmune diseases. CQ has been shown to have antiviral effects on SARS, MERS, Ebola, and HIV infections, but without data showing clinical effectiveness [9]. Some of the mechanisms proposed to assume CQ/HCQ may be effective for COVID-19 are their ability to counter the process of virion assembly and viral protein synthesis, block viruses from binding to human cells, and get inside them to replicate. They also have the ability to stimulate the immune system [9]. A preliminary report containing limited information noted that in 100 COVID-19 patients in China, CQ

offered superior clinical efficacy than control [10]. Several in vitro studies report antiviral activity of chloroquine and hydroxychloroquine against COVID-19, and over a score in-vivo clinical trials have already been registered to test their use for the treatment of COVID-19 [11]. A small, non-randomized clinical trial conducted in France showed that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients, and its effect is reinforced by co-administration of azithromycin [12]. Various clinical trials are underway to ascertain these claims. The speculations about the efficacy of CQ/HQ for COVID-19 treatment have led to panic buying by the public and health workers alike, leading subsequently to the scarcity of these drugs for the real beneficiaries [13]. Many healthcare workers and the general public in Nigeria are presently hoarding these medications, either for prophylaxis or treatment of COVID-19 in anticipation of an explosion of community transmission.

In view of this, it becomes imperative to understand the perspective of Nigerian medical doctors as regards the use of these antimalarials when managing patients with COVID-19 infection in real practice. The knowledge of physicians as front liners in the management of patients with COVID 19 will influence their perception based on their beliefs and experiences. These can affect the physician's identification and handling of potential COVID-19 patients during the pandemic period as well as their mental well-being [14]. However, the level of knowledge and perceptions of physicians toward COVID-19 and its treatment with antimalarial, which has not been approved for such, remain unclear. In addition, we aimed to assess the readiness of Nigerian health institutions (through their attending physicians) to combat the COVID-19 outbreak.

Materials and Methods

Study Design

The study was designed as a cross-sectional online survey among practicing medical doctors in Nigeria. The questionnaire provided respondent details such as age, years of clinical practice, specialty, type, and location of the workplace. The knowledge and perception of practicing Nigerian medical doctors concerning the use of antimalarial drugs for the treatment of COVID-19 were addressed. Furthermore, the preparedness of their workplaces in combating the ongoing pandemic was evaluated. To ascertain the validity of the questionnaire, it was critically scrutinized and validated by medical practitioners who are experts in the subject matter, and necessary corrections were made. The reliability coefficient of the questionnaire was determined using the Cronbach's Alpha test. A correlation coefficient of 0.7 was obtained.

The Google application[®] Google forms (Mountain View, California, USA) was used for the questionnaire. It was sent via a shared link on WhatsApp[®] and Facebook[®] to individuals and group platforms of practicing medical doctors, and they were asked to forward it to others. The target was to obtain responses from the six geo-political zones of the country by ensuring that there was at least one contact person in each zone. Participation was voluntary, and no respondent was compensated for being part of the survey. More so, the rationale of the study and the issue of anonymity were clearly stated in the survey form. The link was made available online from April 6, 2020, to May 1, 2020. Data received was initially collated on an MS Excel spreadsheet. Ethical approval was obtained from Federal Capital Territory Health Research Ethics Committee (FHREC/2020/01/30/30-04-20).

Inclusion and Exclusion Criteria

Inclusion: All medical doctors who were in

active practice in Nigeria were eligible to participate in the study.

Exclusion: Data from non-medical practitioners or medical doctors practicing outside Nigeria were excluded.

Data Analysis

Data obtained were coded and analyzed using SPSS version 22 (IBM). Frequencies and mean values of variables were determined using descriptive statistics. Pearson Chi-Square was used to test for association between variables.

Results

One hundred and forty-five respondents participated in this study. The survey link was opened on April 6, 2020, when there were less than 40 cases of COVID-19 in Nigeria. The link remained active for about a month, but 96.5% of the total responses were obtained by the end of the second week. Four responses were excluded because they were either not medical doctors or they were practicing outside Nigeria.

Socio-demographic Details

The socio-demographic characteristics of the respondents are shown in Table 1. The mean age of respondents was 37.78 ± 6.47 years, with 43.9% of them within 30-39 years. The majority (61%) of respondents were males. The average number of years of clinical practice was 10.9 ± 5.58 years, and 40.6% of the respondents had a post-qualification practice of 11-15 years. Furthermore, a larger percentage of the respondents were working in a government-owned hospital (78.7%) or a tertiary health facility (74.5%). More than half of the respondents (53.9%) were either a consultant or a senior registrar. Twenty-six percent of the respondents also had a Master's degree or PhD. Responses were obtained from the six geo-political zones, with the highest number from the South-west (66.7%) and the least from the North-east zone (1.4%).

Knowledge of Respondents on COVID-19 and Antimalarial Drugs

Aside fever, most of the medical practitioners identified body aches and pains, headache, fatigue, and myalgia as similar clinical symptoms of COVID-19 and malaria (Figure. 1). All the participants agreed that the virus affects the lungs, and 63.1% believed it also affects the gastro-intestinal tract (Table 2). When asked, “Which antimalarial drug(s) is/are currently being used for the treatment of

COVID-19?” 95% chose hydroxychloroquine (HCQ). The knowledge of chloroquine (CQ) as a drug of choice for COVID-19 treatment was significantly associated with the professional status of the respondents ($\chi^2=8.797$, $p=0.032$). In response to the awareness of adverse reactions (ADRs) to hydroxychloroquine or chloroquine (CQ), 97.9% were affirmative, and more than half selected cardiac toxicity (66.7%) and itching (94.3%) as ADRs to HCQ or CQ (Table 2).

Table 1. Socio-demographic Characteristics of the Participants

Variables	Frequency (n)	Percentage (%)
Age range in years (n=139)		
20-29	19	13.7
30-39	61	43.9
40-49	56	40.3
50-59	3	2.1
Sex (n=141)		
Male	86	61.0
Female	55	39.0
Years of clinical practice (n=128)		
1-5	27	21.1
6-10	27	21.1
11-15	52	40.6
16-20	16	12.5
21-25	6	4.7
Type of Work place (n=141)		
Public	111	78.7
Private	30	21.3
Level of health facility (n=141)		
Primary	6	4.2
Secondary	30	21.3
Tertiary	105	74.5
Current status of respondents		
Consultant	36	25.5
Senior Registrar	40	28.4
Chief Medical Officer	5	3.5
Principal Medical Officer	4	2.8
Senior Medical Officer	7	5.0
Registrar	22	15.6
Medical Officer	19	13.5
House Officer	8	5.7

Other academic qualifications of respondents (n=141)		
None	103	73.1
PGD	1	0.7
MSc or MPH	34	24.1
PhD	3	2.1
Present location of practice (n=141)		
North Central	21	14.9
North East	2	1.4
North West	10	7.1
South East	3	2.1
South South	11	7.8
South West	94	66.7

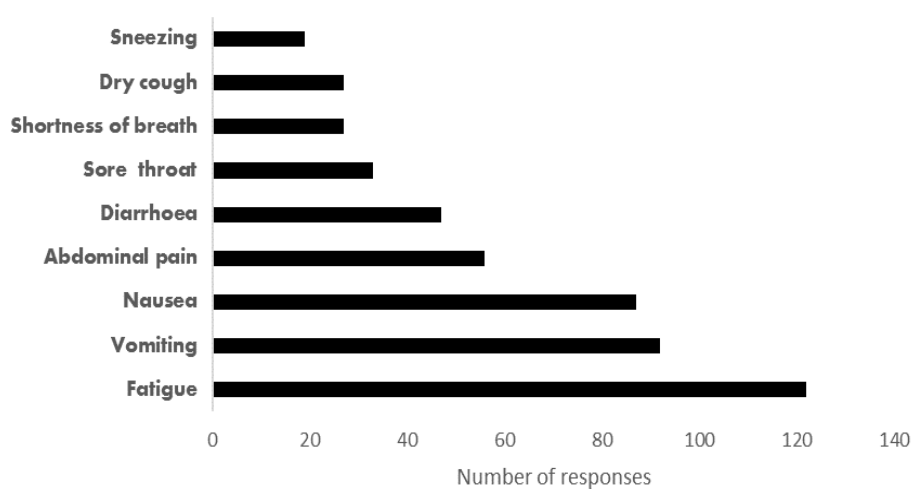


Figure 1. Similar clinical symptoms of COVID-19 and malaria

Table 2. Knowledge of COVID-19 and use of Antimalarial for Treatment among Medical Practitioners

Question	Frequency (n)	Percent
Body parts affected by COVID-19 (n=141) – Multiple choice responses		
Lungs	141	100
GIT	89	63.1
Kidneys	46	32.6
Liver	19	13.5
CNS	32	22.7
Antimalarial drug(s) currently being used for the treatment of COVID-19 (n=141) - Multiple choice responses		
Hydroxychloroquine (HCQ)	134	95
Chloroquine (CQ)	96	68.1
Artemisinin based combination therapy (ACT)	1	0.7
Awareness of adverse reactions (ADRs) to CQ/HCQ (n=141)		
Yes	138	97.9
No	2	1.4
Don't know	1	0.7

Known ADRs to CQ and HCQ (n=141) - Multiple choice responses		
Cardiac toxicity	94	66.7
Retinal damage	68	48.2
Cinchonism	57	40.4
Itching	133	94.3
Rashes	65	46.1
Tinnitus	54	38.3
Seizures	17	12.1

Perception of Respondents on the Efficacy of CQ/HCQ

Over 48% (n=69) of the medical practitioners had a positive perception on the ability of antimalarial drugs to cure or prevent COVID-19. Other respondents either exhibited a negative perception (15.6%) or they were uncertain (35.5%). Among those who had a positive perception of the efficacy of antimalarial drugs for the treatment of COVID-19, the majority (65.2%) believed the drugs would be more effective for the mild clinical presentation of the disease (Figure. 2). The mechanism of action of the drug was the main reason given for the option(s) selected. However, a significant proportion (66.7%) of those who were either Consultants, Principal or Chief Medical Officers believed CQ/HCQ will be more effective for severe cases of COVID-19 ($\chi^2=8.242$, $p=0.041$).

A higher fraction of those who believed in the efficacy of CQ/HCQ in the treatment of malaria (n=69) perceived that the antiviral and anti-inflammatory effects of the drugs were responsible for mitigating the effect of COVID-19 (Table 3). Other questions on the perception of the efficacy of antimalarial in the treatment of COVID-19 were addressed to all participants. In response to the question, “Do you think the use of CQ/HCQ amongst the blacks in the past is protective of COVID-19?” 27% chose the likely option (Table 4). About 57% believed the adverse reactions associated with the use of CQ/HCQ would likely occur with its use for COVID-19. When asked, “What are the likely effect of panic buying of CQ for prophylactic use against COVID-19?” 88.7% believed it would increase the incidence of CQ toxicity. In general, 80% had 50-100% certainty that CQ/HCQ will be effective in the treatment of COVID-19 in their environment (Table 4).

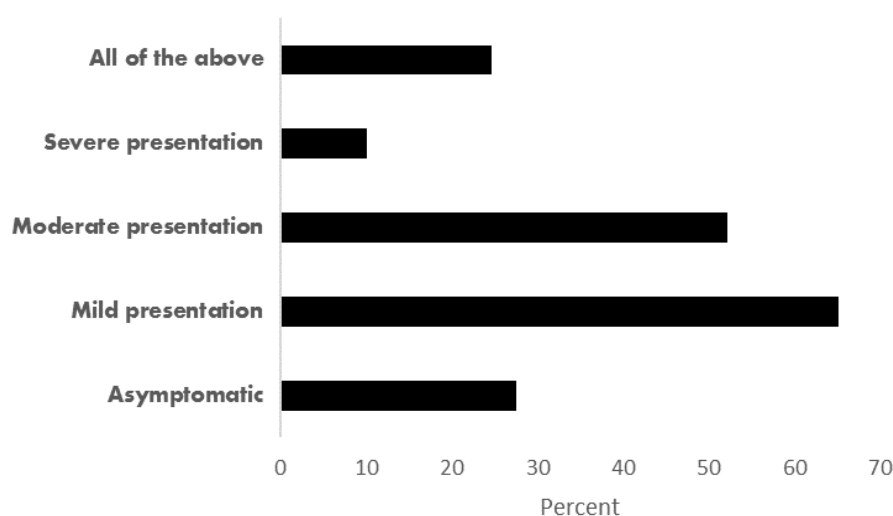


Figure. 2. Respondents' (n=69) Perception on Effectiveness of Antimalarial Drugs at Different Stages of Clinical Presentation

Table 3. Likely effect(s) of HCQ/CQ Responsible for Mitigating the Effect of COVID-19

CQ Effect (n=69)	Frequency (n)	Percent
Antiviral	43	62.3
Anti-inflammatory	32	46.4
Antipyretic	22	31.9
Analgesic	8	11.6
Antibiotic	5	7.2

Table 4. Perception of Medical Practitioners on Efficacy of CQ/HCQ

Question	Frequency (n)	Percent
Use of CQ/HCQ among the blacks is protective of COVID-19 (n=141)		
Most likely	9	6.4
Likely	38	27.0
Not likely	51	36.1
Never	1	0.7
Don't know	42	29.8
Occurrence of ADRs with use for COVID-19 treatment (n=141)		
Most likely	45	31.9
Likely	80	56.7
Not likely	5	3.6
Don't know	11	7.8
Likely effects of panic buying of CQ (n=141) – Multiple choice responses		
It can cause therapeutic failure for its other uses	83	58.9
It can result in scarcity for treatment of autoimmune disease	96	68.1
It can further worsen resistance to <i>Plasmodium falciparum</i>	92	65.2
It can lead to its renewed efficacy for malaria	6	4.3
Increased incidence of CQ toxicity	125	88.7
More expensive	65	46.1
Treatment by quacks	65	46.1
Certainty of CQ/HCQ being effective for COVID-19 treatment (n=141)		
100%	6	4.3
75%	30	21.3
50%	64	45.4
25%	24	17.0
0%	17	12.0

Practice of Respondents and the Preparedness of the Health Facilities in Response to COVID-19 Pandemic

In this study, 66 (46.8%) respondents affirmed that they would prescribe CQ/HCQ if confronted with a COVID-19 case. More than 50% of these positive respondents based their decision to treat on case reports and recommendations from the Federal Ministry of

Health (FMOH) or National Centre for Disease Control (NCDC) or World Health Organization (WHO) as shown in Table 5. However, 75.9% of all respondents believed a randomized control trial (RCT) should be conducted before the decision to administer CQ/HCQ for COVID-19 treatment. This was strongly associated with the respondent's age group (30-45 years, $\chi^2=6.177$, $p=0.046$) and years of

practice (≥ 11 years, $\chi^2=4.172$, $p=0.041$). When asked the open-ended question, “If you administer CQ/HCQ to a patient with COVID-19 and he/she develops any of the ADRs you listed, what will you do?” 116 participants responded. 44.8% responded that they would discontinue the drug, while 57.8% would treat

the ADRs. In response to the readiness of their centre or practice to attend to a COVID-19 case, only 17.7% agreed they were prepared (Table 5). The majority (68%) of these centres were in the Southwest zone. However, almost all the doctors identified the basic requirements needed for COVID-19 management.

Table 5. Responses to Practice and Preparedness of Health Facilities

Question	Frequency (n)	Percent
Prescription of CQ/ HCQ if confronted with a COVID-19 case (n=141)		
Yes	66	46.8
No	27	19.2
Not sure	48	34.0
Informed decision to prescribe (n=66) – Multiple choice responses		
Randomized Control Trials (RCT) findings	28	42.4
Social media findings	3	4.5
Intuition	5	7.6
Case reports	44	66.7
Recommendation by FMOH/NCDC	34	51.5
Recommendation by WHO	34	51.5
Mainstream media reports from USA	12	18.2
RCT before decision to administer CQ//HCQ (n=141)		
Yes	107	75.9
No	22	15.6
Not sure	12	8.5
Readiness of centre or practice for a COVID-19 case (n=141)		
Yes	25	17.7
No	87	61.7
Not sure	26	18.5
Don't want to disclose	3	2.1
Levels of preparedness – Multiple choice responses		
Adequate testing kits and well-equipped laboratories	121	85.8
Adequate Personal protective equipment (PPE)	126	89.4
Adequate ventilators	110	78
Well-equipped isolation centers	123	87.2
Adequate well trained infectious disease team of health workers	124	87.9
Adequate supply of oxygen	110	78
Provision of treatment guidelines/Standard operating procedure (SOP)	121	85.8
Disease surveillance	88	62.4
Adequate funding	58	41.1
Adequate contact tracing	65	46.1
Case definition and triaging	62	44
Improved welfare of frontline workers	40	28.4

Discussion

COVID-19, SARS-CoV-2, and Coronavirus would definitely emerge as the most used words in the year 2020 as a pandemic that brought the world to a standstill. It is the most discussed subject globally, and this is essentially so because there is yet to be an identified, acceptable, and approved protocol for its management. Finding an appropriate treatment for COVID-19 seems difficult probably because of its indefinite pathophysiologic mechanism, despite frantic efforts by researchers and scientists from all over the world. There are many speculations and unproven claims for the use of certain chemotherapeutic agents, inclusive of antimalarials like chloroquine (CQ) and hydroxychloroquine (HCQ). These are cheap and readily available in Nigeria. Many individuals, especially medical practitioners in Nigeria, have started buying and using these medications either for prophylaxis or treatment of the disease leading to many unwanted adverse reactions, some of which are deadlier than the initial disease itself. It was for these reasons that we investigated the knowledge and perception of practicing medical doctors in Nigeria to COVID-19 and the use of antimalarial for treatment of COVID-19 when confronted with infected patients in real-life settings.

In this survey that was available online for a month, one hundred and forty-five medical doctors participated. In general, most of our respondents had a good knowledge of the symptoms of COVID-19 and those that are similar to malaria. While all respondents had a good knowledge of the lungs as the primary target, about 63% had knowledge of the effect on the GIT and other organ systems by the disease. This is quite expected because it has been well established from the beginning that SARS-CoV-2 causes respiratory disease and that the lungs are primarily affected. However, the involvement of other organs has been reported in recent literature as described in a

subgroup of COVID-19 patients with mild disease severity but marked GIT involvement [15]. These sets of patients were observed to have a longer duration of symptoms onset and viral clearance and more likely to test positive for viral RNA in stool samples. Viral nucleic acid has also been detected in the stools of 50% of patients with COVID-19 [16] and in some cases where their respiratory samples test negative to viral RNA [17]. We also recorded 32% of our respondents who had knowledge of kidney involvement in COVID-19. It is pertinent to note that an association between kidney disease and mortality in hospitalized COVID-19 patients was initially recognized by Cheng and colleagues as a major complication and a significant risk factor of death [18]. Another study went further to show that about 75% of Chinese patients in a retrospective study presented with renal complications, and those patients with renal involvement had higher overall mortality [19]. Although Wang et al. reported that Acute Kidney Injury (AKI) was uncommon among COVID-19 patients and SARS-CoV-2 does not result in AKI [20], a more recent study has now confirmed with direct evidence the invasion of SARS-CoV-2 into kidney tissue [21]. Liver injury is another consequence of COVID-19 that has been documented. Only 19% of our respondents demonstrated knowledge of liver involvement. In a systematic review and meta-analysis, a pooled prevalence of abnormal liver functions of 19% from 12 studies accounting for 1,267 COVID-19 patients was reported [22]. Their reports show that abnormalities in liver function are not uncommon with COVID-19. Our findings suggest that many medical practitioners in Nigeria may not be actively following current trends in COVID-19 research, especially with respect to its pathophysiology. This might be because peer-reviewed research articles may not be their primary source of information on COVID-19 updates.

Most of the physicians were aware of the probable use of HCQ and CQ. This position is

supported by studies that found CQ to have treatment potential against COVID 19 [23, 24]. Many of the respondents were affirmative of the adverse drug reactions (ADRs) to CQ, such as itching, which was commonly experienced in Nigerians who used CQ for treatment of malaria when it was the drug of choice [25]. The other ADRs commonly known to more than half of the respondents are cardiac toxicity and retinal damage, while cinchonism which is almost pathognomonic of CQ toxicity, was readily known by most physicians. These ADRs had been reported to be associated with chloroquine toxicity in recent publications [26, 27, 28]. For the reason of the potential clinical effect of chloroquine and hydroxychloroquine against COVID-19, about a quarter of the respondents thought blacks are immune from COVID-19 because of their previous exposure to CQ as an antimalarial. However, there had not been any study linking the previous use of these antimalarials to immunity against COVID-19.

Amidst the misconceptions about CQ and HCQ being wonder drugs for the treatment of COVID-19, close to half of the respondents had a positive perception of the ability of antimalarial drugs to cure or prevent COVID-19 and they thought it would be effective for mild cases. They attributed the possibility of CQ as a cure to its anti-inflammatory and antiviral properties, which assertion is in line with the findings of Jixin et al. [24]. Most of the respondents are aware of the danger of panic buying being the toxicities to the medications.

Strengths and Limitations of the Study

This study reinforces the significance of the knowledge base of medical practitioners and how this may influence clinical practice in the face of an epidemic. One of the limitations of the study was that there were few respondents from some geo-political zones of the country. Hence, the data may not be fully representative of the medical practitioners in Nigeria.

Conclusion

Nigerian medical practitioners have a good knowledge of the symptoms of COVID-19. The perception and practice of these doctors on the treatment of COVID-19 patients showed that the majority would likely administer the drug in the mild presentation of the disease. However, the majority of the doctors acknowledged the need for more randomized clinical trials to ascertain these beliefs.

Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Concept/design – All authors, Data analysis/interpretation – ORO and MUI, Drafting article – OEA and ORO, Critical revision and approval of article – All authors

Acknowledgements

The authors acknowledge the contribution of Mr. S. A. Ibemgbo in search of literature and writing assistance.

- [1] Greenland JR, Michelow MD, Wang L, London MJ. COVID-19 Infection: Implications for Perioperative and Critical Care Physicians. *Anesthesiology*. 2020 Jun; 132(6):1346–61. <https://doi.org/10.1097/ALN.0000000000003303> PMID:32195698.
- [2] Mani Mishra P, Uversky VN, Nandi CK. Serum albumin-mediated strategy for the effective targeting of SARS-CoV-2. *Med Hypotheses*. 2020 Apr; 140:109790. <https://doi.org/10.1016/j.mehy.2020.109790> PMID:32353740.
- [3] World Health Organization. Novel Coronavirus (COVID-19) Situation. WHO (June 11). 2020.
- [4] Marzo, R. R., Ismail, Z., Htay, M. N. N., Bahari, R., Ismail, R., Villanueva III, E. Q., & Su, T. T. (2021). Psychological distress during pandemic Covid-19 among adult general population: Result across 13 countries. *Clinical Epidemiology and Global Health*, 10, 100708. <https://doi.org/10.1016/j.cegh.2021.100708>.
- [5] Marzo, R. R., Singh, A., & Mukti, R. F. (2021). A survey of psychological distress among Bangladeshi people during the COVID-19 pandemic. *Clinical epidemiology and global health*, 10, 100693. <https://doi.org/10.1016/j.cegh.2020.100693>.
- [6] Bhagavathula A, Aldhaleei W, Rahmani J, Mahabadi M, Bandari D. (2020). Novel Coronavirus (COVID-19) Knowledge and Perceptions: A Survey of Healthcare Workers (Preprint). <https://doi.org/10.1101/2020.03.09.20033381>.
- [7] Li L quan, Huang T, Wang Y qing, Wang Z ping, Liang Y, Huang T bi, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. *Journal of Medical Virology*. 2020.
- [8] Nonpharmaceutical Interventions (NPIs) | CDC [Internet]. [cited 2020 Jun 24]. Available from: <https://www.cdc.gov/nonpharmaceutical-interventions/index.html>.
- [9] Cortegiani A, Ippolito M, Ingoglia G, Einav S. Chloroquine for COVID-19: rationale, facts, hopes. *Crit Care*. 2020 May; 24(1):210.

[10]Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends. 2020 Mar; 14(1):72–3. <https://doi.org/10.5582/bst.2020.01047> PMID:32074550.

[11]Hashem AM, Alghamdi BS, Algaissi AA, Alshehri FS, Bukhari A, Alfaleh MA, et al. Therapeutic use of chloroquine and hydroxychloroquine in COVID-19 and other viral infections: A narrative review. Travel Med Infect Dis. 2020 May - Jun; 35:101735. <https://doi.org/10.1016/j.tmaid.2020.101735> PMID:32387694.

[12]Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Jul; 56(1):105949. <https://doi.org/10.1016/j.ijantimicag.2020.105949> PMID:32205204.

[13]Ria V, Palmeira A, Braga Costa L, Giandoni Perez L, Ribeiro VT, Lanza K, et al. Do we have enough evidence to use chloroquine/hydroxychloroquine as a public health panacea for COVID-19? Simões e Silva 0 0 0 0-0 0 0 0-0 0 0 0-0 0 0 0 *. [cited 2020 Jun 24]; Available from: <https://doi.org/10.1590/0037-8682-0155-2020>.

[14]Htay MNN, Marzo RR, AlRifai A, Kamberi F, El-Abasiri RA, Nyamache JM, Hlaing HA, Hassanein M, Moe S, Su TT, Abas AL. Immediate impact of COVID-19 on mental health and its associated factors among healthcare workers: A global perspective across 31 countries. J Glob Health. 2020 Dec; 10(2):020381. doi: 10.7189/jogh.10.020381. PMID: 33214890; PMCID: PMC7649521.

[15]Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, et al. Digestive Symptoms in COVID-19 Patients with Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. Am J Gastroenterol. 2020 Jun; 115(6):916–23.

<https://doi.org/10.14309/ajg.0000000000000664>
PMID:3230176113.

[16] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology*. 2020 May; 158(6):1831-1833.e3.

<https://doi.org/10.1053/j.gastro.2020.02.055>
PMID:32142773.

[17] Chen L, Lou J, Bai Y, Wang M. COVID-19 disease with positive fecal and negative pharyngeal and sputum viral tests. *Am J Gastroenterol*. 2020 May; 115(5):790.
<https://doi.org/10.14309/ajg.0000000000000610>
PMID:32205644.

[18] Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int*. 2020 May; 97(5):829–38.
<https://doi.org/10.1016/j.kint.2020.03.005>
PMID:32247631.

[19] Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. *J Am Soc Nephrol*. 2020 Jun; 31(6):1157–65.
<https://doi.org/10.1681/ASN.2020030276>
PMID:32345702.

[20] Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. *Am J Nephrol*. 2020;51(5):343–8.
<https://doi.org/10.1159/000507471> PMID:32229732.

[21] Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020 Jul;98(1):219–27.
<https://doi.org/10.1016/j.kint.2020.04.003>
PMID:32327202.

[22] Mao R, Qiu Y, He JS, Tan JY, Li XH, Liang J,

et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020 Jul; 5(7):667–78.
[https://doi.org/10.1016/S2468-1253\(20\)30126-6](https://doi.org/10.1016/S2468-1253(20)30126-6) PMID:32405603.

[23] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020 Mar; 30(3):269–71.
<https://doi.org/10.1038/s41422-020-0282-0> PMID:32020029.

[24] Jixin Z, Jungen T, Cong Y, Lingli D. The immunology of COVID 19; Is immune modulation an option for treatment? *The Lancet*. 2020 May; doi; [https://doi.org/10.1016/s2665-9913\(20\)30120-X](https://doi.org/10.1016/s2665-9913(20)30120-X).

[25] Aghahowa SE, Obianwu HO, Isah AO, Arhewoh IM. Chloroquine-induced Pruritus. *Indian J Pharm Sci*. 2010 May; 72(3):283–9.
<https://doi.org/10.4103/0250-474X.70471>
PMID:21188034.

[26] Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. *Drug Saf*. 2018 Oct; 41(10):919–31.
<https://doi.org/10.1007/s40264-018-0689-4> PMID:29858838.

[27] Stokkermans TJ, Goyal A, Bansal P, Trichonas G. Chloroquine and Hydroxychloroquine Toxicity [Updated 2020 Jul 4] Stat Pearls [Internet] Treasure Island (FL): Stat Pearls Publishing; 2020 Jan., Available from <https://www.ncbi.nlm.nih.gov/books/NBK537086/>.

[28] Bykowski A, Logan TD. Cinchonism [Updated 2020 Jun 16] Stat Pearls [Internet] Treasure Island (FL): Stat Pearls Publishing; 2020 Jan., Available from <https://www.ncbi.nlm.nih.gov/books/NBK559319/>.