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Clinical Profile of COVID-19 Patients and QT Interval Changes with Drugs used for Empirical Treatment: A Case Series from Eastern India

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Abstract: ***Background: Clinical profiling of COVID-19 cases is lacking from the eastern part of India. Also, the risk of QT prolongation with hydroxychloroquine when used empirically, with or without azithromycin, for the treatment of in COVID-19 is a matter of concern in India. We sought to generate a clinical and laboratory profile of confirmed COVID-19 patients and study the issue of QT prolongation. Design: Record based case series. Methods: Study included 55 confirmed COVID-19 patients admitted to a dedicated COVID-19 treatment facility set up in a tertiary care hospital. ECG was recorded at baseline, prior to start of hydroxychloroquine ± azithromycin, and following administration of the drugs for 48 hours. Results: Among 55 COVID-19 patients included in the study, 47 (85.5%) were symptomatic. Patients had mean (standard deviation [SD]) age of 45.8 (17.76) years and 20 (36.37%) were female. Fever and cough were the predominant symptoms on admission. Lymphopenia with or without leukocytosis were the dominant laboratory findings. The mean (SD) baseline QTc was 398.4 (46.96) ms; after starting of hydroxychloroquine ± azithromycin it was 401.8 (45.23) ms. QTc changes were not significant statistically or clinically. Conclusions: The clinical profile of COVID-19 patients seen in this case series is similar to that documented in other studies published till date. The triad of fever-cough-dyspnea are predominant presenting symptoms. Lymphopenia, with or without leukopenia, could be potential laboratory marker. The use of hydroxychloroquine for treatment, with or without azithromycin, did not show significant QTc prolongation at 48 hours.***

Keywords: COVID-19, SARS-CoV-2, India, hydroxychloroquine, azithromycin

1. Introduction

Novel corona virus disease 2019 (COVID-19) outbreak, which emerged from Wuhan, China,[1] has rapidly turned into a pandemic with a global case burden of 5.49 million cases and 349,190 deaths as on May 27, 2020.[2] India had 1,58,333 cases, as on May 28, 2020 and 4531 deaths[3] despite a stringent countrywide lockdown imposed from Mar 24, 2020. The disease has created havoc in several countries, including USA, Brazil, Russia, Italy, Spain, UK, France and Iran, besides China. India's case fatality rate has been relatively low at < 3%.

In the initial phase, majority of cases who tested positive in India either had a history of travel abroad or had come into contact with a person with travel history such as a close family member. The causative organism, a novel member of the human coronavirus family,[1] now officially named as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by International Committee on Taxonomy of Viruses (ICTV), is a new strain of RNA virus that has not been previously identified in humans. Studies have shown that the disease caused by SARS-CoV-2 can induce symptoms like fever, dry cough, dyspnea, myalgia, and fatigue in infected patients. In more severe cases, there may be progression to viral pneumonia that may lead to severe acute respiratory syndrome (SARS) and even death. This is the third coronavirus to emerge among human population through zoonotic spread in the last two decades. The other two were the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012.[4]

In India, the official strategy so far has been to admit all positive patients to dedicated COVID-19 treatment facilities (COVID hospitals) and discharge them after they are clinically cured and have tested negative. Patients requiring intensive care are shifted to dedicated COVID ICU beds in the same or nearby facilities. Fortunately, only a small proportion of patients require intensive care. The objective of this study, conducted in a dedicated COVID hospital in eastern India, was to assess the demographic, clinical, laboratory profile of COVID-19 patients, to assess their potential mode of acquisition of infection and to assess any ECG changes in QT interval following administration of drugs such as hydroxychloroquine, either alone or in combination with azithromycin, for empirical treatment of the infection.

2. Methods

The study was a descriptive observational study conducted in a tertiary care hospital, declared as a dedicated COVID-19 treatment facility by the state in April 2020. Data were captured in a retrospective manner from manual medical records that had been collected over a 15-day period. During this period 55 patients were treated and discharged and the

case records of all were accessed. Institutional ethics committee approval (IPGME&R/IEC/2017/471 dated 01.06.2020) was obtained for a retrospective case series.

All patients were admitted following a positive nasopharyngeal swab for SARS-CoV-2, detected by reverse transcriptase polymerase chain reaction (RT-PCR) method. Data collected comprised basic demographic information, exposure history, travel history, any associated comorbidities and clinical signs and symptoms. Laboratory data collected included hemoglobin, total leukocyte count, differential leukocyte count and platelet count to assess for anemia, leukocytosis, leukopenia, lymphopenia, and thrombocytopenia. Anemia was defined as hemoglobin less than 11 gm/dL in adult pregnant females, less than 12 gm/dL in adult non pregnant females, and less than 13 gm/dL in adult males. Leukocytosis was defined as total leukocyte count greater than 11,000 cells/microL. Leukopenia was defined as total leukocyte count < 3700 cells/microL. Lymphopenia was defined as peripheral blood lymphocyte count < 1500/microL (or < 2000/microL in children < 6 years age).

ECG was recorded with a digital ECG recorder at baseline, prior to start of hydroxychloroquine ± azithromycin and following administration of hydroxychloroquine ± azithromycin for 48 hours. The QT interval was measured as the time from the start of Q wave to end of T wave in leads II and V5-V6. The corrected QT interval was determined using Bazett's formula which is QT/√RR. QT prolongation was taken as QTc > 500 ms and/or >60 ms increase from baseline. Tisdale score[5] was determined to assess the risk of QT prolongation in which age ≥ 68 years, female sex, loop diuretic use score 1 point each; serum $K^+ \leq 3.5$ mEq/L, admission $QT_c \geq 450$ ms, acute myocardial infarction score 2 points each; sepsis, heart failure, one QT_c-prolonging drug use score 3 points each; and use of ≥ 2 QT_c-prolonging drugs score 3 additional points, with a maximum score of 21. A score of less than 7 has low risk, 7-10 has moderate risk and ≥ 11 has high risk for QT prolongation.

The doses of hydroxychloroquine and azithromycin used by the attending physicians was as per revised Government of India clinical management guidelines for COVID-19.[6] Hydroxychloroquine dose was 400 mg twice daily on first day, followed by 200 mg twice daily for next 4 days. Azithromycin dose was 500 mg once daily for 5 days.

Statistical analysis was done using Medcalc version 15.8 (Mariakerke, Belgium: Medcalc Software bvba; 2015) software. Data were summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables that are normally distributed, median and interquartile range for skewed numerical variables and counts and percentages for categorical variables. Numerical variables were compared between groups by Student's independent samples t test, if normally distributed, or by Mann-Whitney U test, if otherwise. Fisher's exact test or Pearson's Chi-square test was employed for intergroup comparison of categorical variables. Changes in QTc from day 1 to day 3 were assessed for statistical significance by Student's paired *t* test. The cut-off for statistical significance was $p < 0.05$ (two-tailed).

3. Results

Among 55 COVID-19 patients included in the study, 47 (85.5%) were symptomatic and the rest were admitted without symptoms. All were treated and discharged. There were no deaths in this series.

Table 1 summarizes the demographic, clinical and laboratory profiles. The patients had mean (SD) age of 45.8 (17.76) years and 20 (36.37%) were female. Only 3 (5.5%) patients were below 20 years, 18 (32.7%) were in the age group of 21 to 40 years, 25 (45.5%) were between 41 to 60 years and 9 (16.4%) were above 60 years age. Eight (14.5%) patients were hypertensive; 7 (12.7%) had type 2 diabetes, 4 (7.3%) had chronic kidney disease, 2 (3.6%) patients each had chronic obstructive pulmonary disease, coronary vascular disease and hypothyroidism.

Only 1 (1.8%) subject had history of travel to other state within India, 13 (23.6%) had positive history of contact with COVID-19 patient and 10 (18.2%) were healthcare workers. No subject in our study had taken hydroxychloroquine chemoprophylaxis prior to admission.

Fever and cough were the predominant symptoms on admission, affecting 26 (47.3%) patients, though sputum production was seen in only 12 (21.8%) and sore throat in 14 (25.5%) patients. The other symptoms at admission were dyspnea (29.1%), myalgia (29.1%), headache (23.6%), dysgeusia (9.1%), anosmia (7.3%) and chest pain (3.6%). Diarrhea (23.6%) was the most prominent new symptom after administration of hydroxychloroquine. Bilateral patchy opacities in both lower lobes or the periphery (29%) was the most common radiological finding.

Investigations revealed mean (SD) hemoglobin of 12 (2.03) g/dL and median (IQR) total leukocyte count of 7800 (6125 to 10000). Sixteen subjects (29.1%) had leukopenia and 6 (10.9%) had leukocytosis; 18 (32.7%) had lymphopenia and 7 (12.7%) thrombocytopenia. The mean (SD) SpO_2 was 98.8% (2.19).

Subgroups comparisons between symptomatic and asymptomatic patients did not reveal any significant differences in age, evolving clinical features and laboratory findings.

In our series, 16.4% patients received hydroxychloroquine, 65.5% received hydroxychloroquine with azithromycin, 14.5% received hydroxychloroquine in combination with azithromycin and oseltamivir and 3.6% patients received other drugs. Other than diarrhea (none of severe intensity) in 13 (23.6%) subjects, no other significant suspected adverse drug reaction was recorded.

Table 2 and **Figure 1** depict the QTc interval changes. The mean (SD) baseline QTc was 398.4 (46.96) ms; after starting of hydroxychloroquine it was 401.8 (45.23). Thus, in the hydroxychloroquine receiving group (n = 54), the mean QTc increase was only 3.4 ms from baseline to 48 hours whereas in the group receiving dual QTc prolonging drugs (n = 44), hydroxychloroquine plus azithromycin, this difference was

4.6 ms. None of these QTc changes were statistically or clinically significant.

Applying Tisdale scoring system, 63.6% patients had a low risk of QT prolongation whereas 36.4% patients had moderate risk. Only 1 patient had prolonged QTc > 500 ms and in this case the hydroxychloroquine ± azithromycin was discontinued. No other serious adverse drug reactions and no incidence of torsades de pointes or other significant arrhythmias were recorded.

4. Discussion

This present study on 55 patients represents the descriptive profiling of COVID-19 patients, from a dedicated COVID-19 hospital in eastern India.

Nearly two-thirds of the COVID-19 patients were male which figure is in close proximity to that reported by Bhandari et al,[7] Huang et al[8] and Chen et al[9] but higher than that reported by Wang et al (54.3%)[10]. This male predominance may reflect more travel by male persons for occupational or educational purposes, rather than greater susceptibility to infection for males. The median age of 48 years in our case series is similar to that reported by Guan et al[11] where the median age of patients was 47 years and Bhandari et al[7] where median age was 43.5 years. In all these series there were very few patients below 20 years of age which might reflect less travel in this age group and therefore less risk of coming in contact with positive individuals. It is also possible that physiologically children and adolescents may be less susceptible to COVID-19 infection.

In our study 18.2% patients were healthcare workers which is in contrast to 3.8% for Guan et al[11]. It is a moot point whether this marked contrast is the result of lack of chemoprophylaxis with hydroxychloroquine in our case and the question will have to be probed through studies specifically designed to assess the effectiveness of chemoprophylaxis. It is noteworthy that in India, the National Task Force on COVID-19 under the aegis of the Indian Council of Medical Research (ICMR) has recommended 400 mg weekly hydroxychloroquine prophylaxis, after an initial loading does of 800 mg (split into two equal doses 12 hours apart) on the first day, for all frontline healthcare workers[12].

In this series fever and cough (47.3%) were the prominent symptoms which is in similar to the study by Gupta et al[13] (42.9%) and Guan et al[11] (43.8%) but in contrast to Bhandari et al[7] where fever was 78.57% and cough was 85.71%. In this case series 14.4% patients were asymptomatic whereas 33.33% patients were asymptomatic in case of Bhandari et al[7] and 42.9% for Gupta et al[13]. This difference might be due to inclusion of further symptoms such as myalgia, chest pain, anosmia, dysgeusia and diarrhea which has therefore increased the proportion of symptomatic patients in this study. With respect to proportion of patients with myalgia and dyspnea in our case (each 29.1%), our study is comparable to 34.8% with myalgia and 31.25% with dyspnea for Wang et al[10]. Regarding comorbidities, nearly a third of our patients had at least one other significant medical problem at admission. Comorbidity figures vary widely, 23.7% for Guan et al[11] but 46.4% for Wang et al[10]. The extent of comorbidity may be related to age of the patients but could also mean increased susceptibility to viral infection. This question will need to be addressed by future studies.

In various studies such as Bhandari et al[7], Guan et al[11], Zhang et al[14], lymphocytopenia has been documented as a predominant laboratory finding apart from eosinopenia and thrombocytopenia but in our study lymphopenia was documented in 32.7% patients. The other noteworthy findings were leucopenia (29.1%), thrombocytopenia (12.7%) and even the others being leukocytosis (10.9%). In case of Bhandari et al[7] 52.38% patients had lymphopenia and for Gupta et al[13] only one patient had leucopenia. For Guan et al[11] 83.2% had lymphopenia, 36.2% had thrombocytopenia and 33.7% patients had leucopenia. Therefore, lymphopenia either alone or in combination with leucopenia can be a potential marker for SARS-CoV-2 infection.

The drug hydroxychloroquine has long history of use as disease modifying agent in rheumatoid arthritis but poses risk for cardiac patients. Hydroxychloroquine is structurally and mechanistically similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, prolonging the QT interval and increasing the risk of torsades de pointes and sudden cardiac death. Azithromycin also has been implicated in QTc prolongation and proarrhythmic events; its Food and Drug Administration label highlights the dose dependent elevation in QTc when combined with chloroquine. Therefore, the use of hydroxychloroquine, particularly in combination with azithromycin is debatable in critically ill patients and in fact, recently published studies suggest that it should not be used[15,16].

However, in our series, the patients were not critically ill (none were ICU admitted) and majority received hydroxychloroquine with or without azithromycin without statistically significant change in corrected QT interval after 48 hours. This contrasts with the report by Mercuro et al[15] where 23% patients treated with hydroxychloroquine or hydroxychloroquine plus azithromycin had either significant QTc prolongation or increase from baseline of 60 ms or greater. It is to be noted that COVID-19-associated stress cardiomyopathy or myocarditis itself may lead to QTc prolongation and, therefore, QTc prolonging drugs may not be solely responsible.

Apart from the relatively small sample size, our study has certain limitations. Varying patient profiles and varying aggressiveness of SARS-CoV-2 strains circulating in different regions makes it difficult to generalize findings to national and international level. Logistical limitations prevented us from doing repeat QTc assessment for all patients after 48 hours whereas effects of hydroxychloroquine and azithromycin are likely to persist longer. Finally, our patients were not critically ill so that our study does not reflect profiling in severe COVID-19 disease.

Despite these limitations, we can say that our study has shown that the clinical profile of COVID-19 patients, who are not severely ill, is in general similar to that documented in other studies published till date. The triad of fever-cough-dyspnea are predominant presenting symptoms with myalgia, headache, sore throat and diarrhea being other common accompaniments. Thus, in public surveillance programs, it is appropriate to screen patients for influenza-like illness, in addition to severe acute respiratory infection. Lymphopenia, with or without leukopenia, could be potential laboratory marker. The use of hydroxychloroquine for treatment, with or without azithromycin, did not show significant QTc prolongation at 48 hours though some patients did have hypertension and coronary artery disease.

Disclaimers: None

5. Conflict of interest

The authors declare that they have no conflict of interest with this study either financial or otherwise.

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References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al : A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.

[2] Coronavirus disease (COVID-19) pandemic. Update from World Health Organization. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjwq832BRA5EiwACvCWsYcNvuIBnFuGtaWycqZaaIETGGmUteG-HII_yF4QlgSvBBCjhmCkzRoCiH8QAvD_BwE. Accessed on 2020, May 27.

[3] Government of India. Covid-19 Dashboard. Available from: https://www.mygov.in/covid-19/. Accessed on 2020, May 28.

[4] De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 523-34.

[5] Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict QT interval prolongation in hospitalized patients. Circ Cardiovasc Qual Outcomes 2013; 6: 479-87.

[6] Government of India, Ministry of Health & Family Welfare, Directorate General of Health Services (EMR Division). Revised guidelines on clinical management of COVID-19. Dated 2020, Mar 31. Available from: https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelinefor COVID1931032020.pdf. Accessed on 2020, May 27.

[7] Bhandari S, Bhargava A, Sharma S, Keshwani P, Sharma R, Banerjee S, et al Clinical profile of Covid-19 infected patients admitted in a tertiary care hospital in North India. J Assoc Phys India 2020; 68. Available from: http://apiindia.org/wp-content/uploads/pdf/corona-virus/covid-19-publication-03.pdf. Accessed on May 28, 2020.

[8] Huang C. Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

[9] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-13.

[10] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 hospitalized patients with 2019 novel coronavirus infected-pneumonia in Wuhan,China. J Am Med Assoc 2020; 323: 1061-9.

[11] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med 2020; 382: 1708-20.

[12] Indian Council of Medical Research. Revised advisory on the use of Hydroxychloroquine (HCQ) as prophylaxis for SARS-CoV-2 infection; dated 22nd May, 2020 (in supersession of previous advisory dated 23rd March, 2020). Available from: https://www.icmr.gov.in/pdf/covid/techdoc/V5_Revised_advisory_on_the_use_of_HCQ_SARS_CoV2_infection.pdf. Accessed on May 28, 2020.

[13] Gupta N, Agrawal S, Ish P, Mishra S, Gaind R, Usha G, et al. Clinical and epidemiologic profile of the initial COVID-19 patients at a tertiary care centre in India. Monaldi Arch Chest Dis 2020 Apr 10; 90(1). doi: 10.4081/monaldi.2020.1294.

[14] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print, 2020 Feb 19]. Allergy. 2020;10.1111/all.14238. doi:10.1111/all.14238.

[15] Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). [published online ahead of print, 2020 May 1] JAMA Cardiol 2020; e201834. doi: 10.1001/jamacardio.2020.1834.

[16] Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hirpcsak G, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19 [published online ahead of print, 2020 May 7]. N Engl J Med 2020; NEJMoa2012410. doi:10.1056/NEJMoa2012410.

Table 1: Summary of demographic, clinical and laboratory features of COVID-19 patients

Parameter	Range or Count (%)	Mean ± SD or Median (IQR)
Age (year)	9 – 95	45.8 ± 17.76
Male : Female	35 : 20 (63.63% : 36.37%)	
Comorbidities		
Hypertension	8 (14.5%)	
Diabetes	7 (12.7%)	
Chronic kidney disease	4 (7.35)	
Cardiovascular disease	2 (3.6%)	
COPD	2 (3.6%)	
Hypothyroidism	2 (3.6%)	
Symptomatic	47 (85.5%	
Symptoms		
Fever	26 (47.3%)	
Cough	26 (47.3%)	
Diarrhea	25 (45.5%)	
Dyspnea	16 (29.1%)	
Myalgia	16 (29.1%)	
Sore throat	14 (25.5%)	
Headache	13 (23.6%)	
Sputum expectoration	12 (21.8%)	
Dysgeusia	5 (9.1%)	
Anosmia	4 (7.3%)	
Chest pain	2 (3.6%)	
History of travel	1 (1.8%)	
History of COVID-19 contact	13 (23.6%)	
Hemoglobin (g/dL)	7.2 – 16.5	12.7 ± 2.05
Total leukocyte count (/microL)	3400-28000	7800 (6125 – 10000)
ANC (/microL)	1666 – 16800	4482 (3517.5- 5787.5)
ALC (/microL)	630 – 5400	2080 (1408.5-3115.5)
Urea (mg/dL)	14.0 – 102.0	20.0 (18.0 – 22.8)
Creatinine (mg/dL)	0.5 – 9.03	0.9 (0.7 – 1.1)
SpO_2 (%)	92.0 – 100.0	100.0 (98.3 – 100.0)
Tisdale Score	3.0 – 9.0	6.0 ± 1.53

- Abbreviations: ALC = absolute lymphocyte count; ANC = absolute neutrophil count; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SD = standard deviation; SpO_2 = peripheral oxygen saturation
- Mean ± SD has been depicted for normally distributed numerical variables; median (IQR) for skewed numerical variables.

Table 2: Summary of QTc interval on the electrocardiogram for patients receiving hydroxychloroquine, with or without azithromycin, for empirical COVID-19 treatment

Cohort	QTc interval at baseline [Range] [Mean ± SD]	QTc interval after 48 h [Range] [Mean ± SD]	*p* value
Whole cohort (n = 55)	302.0 – 497.0 398.3 ± 46.53	294.0 – 506.0 401.3 ± 44.92	0.166
Those receiving hydroxychloroquine (n = 54)	302.0 – 497.0 398.4 ± 46.96	294.0 – 506.0 401.8 ± 45.23	0.134
Those receiving hydroxychloroquine plus azithromycin (n = 44)	302.0 – 497.0 398.0 ± 49.13	294.0 – 506.0 402.6 ± 46.59	0.070

- *P* value in the last column is from Student's paired *t* test.

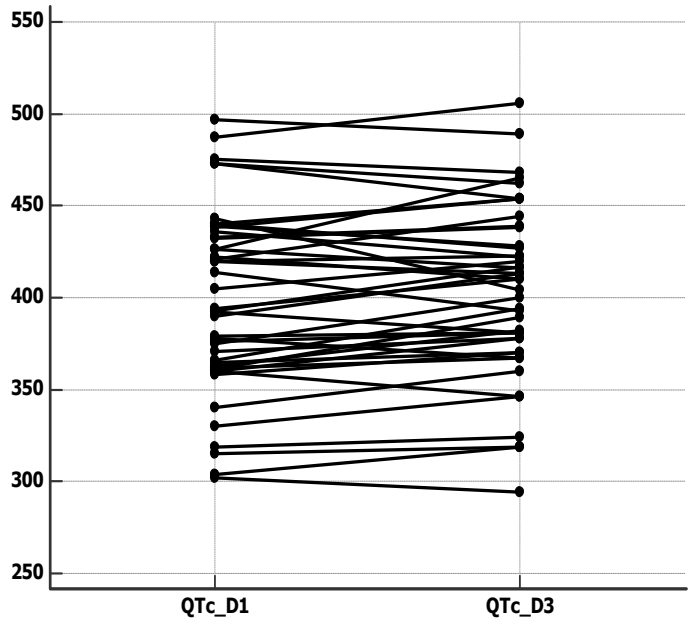

Figure 1: Dot-and-line diagram to indicate corrected QT interval changes in 44 subjects receiving hydroxychloroquine plus azithromycin. Note that although overall QTc range has increased somewhat, changes are small or non-existent in individual subjects. QTc has exceeded 500 ms in only one instance.