Category: Original Article

Paper Title: Electrocardiographic Changes in Adult Patients with COVID-19 Infection Treated with Hydroxychloroquine / Chloroquine, Azithromycin and Lopinavir / Ritonavir in Metro Manila, Philippines

Electrocardiographic Changes in Adult Patients with COVID-19 Infection Treated with Hydroxychloroquine / Chloroquine, Azithromycin and Lopinavir / Ritonavir in Metro Manila, Philippines

I. Abstract

Background: Hydroxychloroquine/chloroquine, or in combination with azithromycin and lopinavir/ritonavir have shown increasing efficacy for COVID-19. However, the local experience in the usage these medications have not been fully documented.

Objectives: To characterize the risk and degree of QT prolongation in patients with COVID-19 with administration of chloroquine/hydroxychloroquine and azithromycin, as monotherapy or in combination.

Methods: A retrospective single-center cohort study involving reverse transcriptase polymerase chain reaction (RT-PCR) confirmed adult COVID-19 patients who received chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir and were admitted in Makati Medical Center from March 1, 2020 to April 15, 2020. The initial and repeat ECGs during the course of hospital stay were obtained to determine if there were changes in ECG relative to the administration of the said medications.

Results: For QTc interval change, chloroquine/hydroxychloroquine had lower mean of QTc interval of 436.9msec compared to those with azithromycin (corrected QT interval 488.2msec). A change in QTc from baseline was a significant risk factor for mortality. The higher the QTc in the first monitoring (from baseline), the more likely the patient will die. *(p=0.0349). Also, t*he higher average from the first to fifth QTc monitoring *(p=0.0163)* and the higher peak QTc, the higher chances of dying. *(p=0.0301).*

Conclusion: The change in QTc does not significantly vary in the four treatment arms. It also did not significantly affect all-cause mortality and development of arrhythmia. Older age, male sex, CAD, CKD, and high-risk Tisdale scores were predictors of mortality. Any increase QTc from baseline was also a predictor of mortality.

Keywords: *COVID-19, electrocardiogram, QT prolongation*

II. Background

A new strain of the coronavirus called coronavirus disease (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-COV2) emerged last December 2019 had rapidly spread worldwide. The epicenter had been presumed to have come from Hubei province, Wuhan, China.[1] At the time of this study, globally confirmed cases have risen to a staggering 896,450 for the past 4 months. In the Southeast Asian region, a total of 5,324 had been documented. Unfortunately, 56.7% of cases belong in the Philippines with a total of 3,018. With the ever climbing rate of COVID-19 cases, the search for the cure, or at least, to slow down the disease was still ongoing.

Latest pharmacotherapy recommendations involved a variety of drug classes. Of interest, monotherapy of hydroxychloroquine/chloroquine, or in combination with azithromycin have shown increasing efficacy.[3,7-10] In vitro and preliminary clinical research, the aforementioned medications shortened the time to resolution of viral shedding of COVID-19.[3] This lead to multiple randomized trials being initiated. However, hydroxychloroquine, chloroquine, and azithromycin have documented adverse effect of dysrhythmia, specifically QT interval prolongation. This increases the risk of *Torsades de pointes* leading to cardiac arrest with concurrent use of the medications.[4,5,6]

The SARS outbreak last 2003 proved to be challenging, and the need for treatment could not have been more urgent. Antiviral agents available in the market then, such as lopinavir/ritonavir, were then put to the test in combating this disease. In vitro studies showing antiviral activity of lopinavir/ritonavir were demonstrated[11], and in this token, were now used in the treatment of the COVID-19, which was the newest strain of a SARS coronarvirus.[12]

The purpose of this study was to assess patient characteristics and evaluate current recommended therapeutic options in the setting of no existing effective treatment. Therefore, we will be able to identify those who were good candidates for pharmacotherapy with hydroxychloroquine/chloroquine and azithromycin. Also, identification of patients who were at an increased risk for *Torsades de pointes* so that aggressive countermeasures can be done.

III. Methodology and Materials

This was a retrospective cohort study involving reverse transcriptase polymerase chain reaction (RT-PCR) confirmed adult COVID-19 patients admitted in Makati Medical Center from March 1, 2020 to April 15, 2020. Convenience sampling was used for data collection. Included in the study were patients aged 18 years and above, managed as a case of COVID-19 infection, who received treatment with any one or a combination of the following medications: chloroquine, hydroxychloroquine, azithromycin, lopinavir/ ritonavir were included in the study. Excluded patients were those with congenital LQTS, with complete left bundle branch block or other cardiac conduction defect disallowing, QT-interval measurement, with an implanted pacemaker, QTc$\geq$ 500msec. The primary outcome was the all-cause mortality while the secondary outcomes were

QTc prolongation from baseline, QTc interval change, ventricular arrhythmia/ *Torsades de pointes* (TDP), myocardial injury/infarction and septic shock.

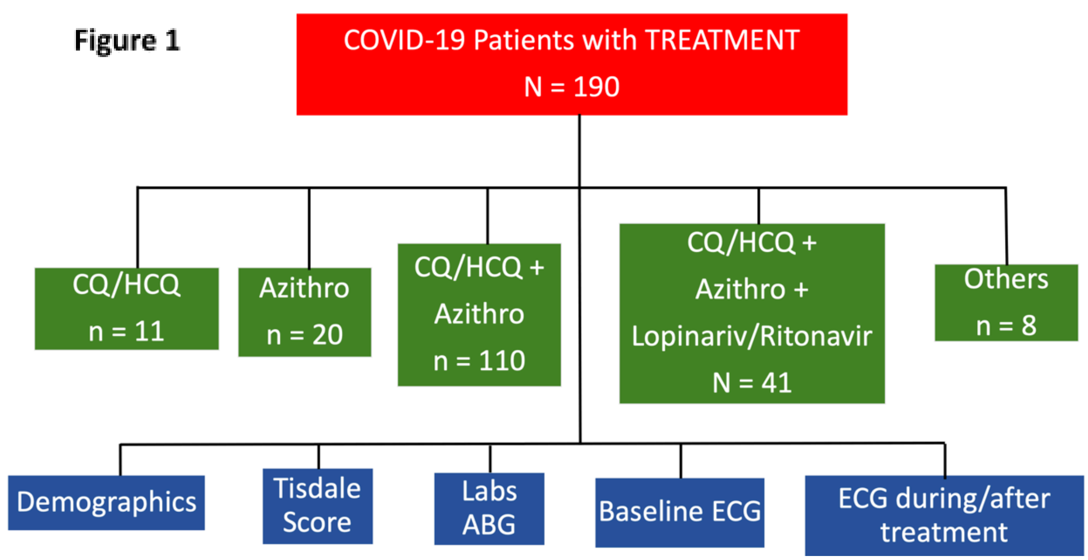
This study involved a chart review for retrospective data collection. The following ECGs were considered for analysis: (1) Baseline 12L-ECG on admission, (2) 12L ECG done from day 2 onwards of treatment. At the beginning of the study, the patients were categorized based only on the initial treatment given and monitored for outcomes as previously described. Treatment categories were noted as follows: (1) chloroquine (CQ)/ hydroxychloroquine (HCQ), (2) azithromycin, (3) chloroquine/hydroxychloroquine plus azithromycin, (4) chloroquine (CQ)/ hydroxychloroquine (HCQ) plus azithromycin plus lopinavir/ritonavir. No additional analysis was done for those patients who crossed over to another treatment arm. ECG interpretation and manual QT-interval measurement was performed by the same cardiologist- electrophysiologist throughout the study, blinded to the patient's demographics, clinical course and outcome. Bazett's formula was used to compute for corrected QT interval. QTc prolongation was defined as a value greater than 450 ms for men and 460 ms for women. Demographic and clinical data were collected from all patients, including cause of admission, co-morbidities, vital signs, blood biochemistry, and Tisdale risk score for QT prolongation. Labs tests included were serum potassium, magnesium, sodium, calcium and creatinine since electrolyte derangements can cause ECG changes such as QT prolongation, PR segment and ST-T wave changes. All medications taken by the patient prior to admission were recorded as well.

Interobserver variability for QTc interval measurement was assessed using a random sample of ten ECGs analyzed by two independent observers (two electrophysiologists). Intra-observer variability was also performed by each electrophysiologist on ten ECGs read on two occasions one week apart. Inter class Correlation Coefficient was used. Data encoding was done using MS Excel for ease of encoding. Completeness, consistency and errors among the answers were checked, edited and analyzed using Medcalc Statistical software. Baseline characteristics at the entry of the study was expressed as frequencies and percentages for categorical variables, mean ± standard deviation (SD) for continuous. One Way ANOVA was used to compare the four treatment groups for the continuous data while chi square test for the categorical. Logistic regression was also utilized to determine the factors affecting mortality. Level of significance was at 5%.

The study was conducted in compliance with national and local regulations and guidelines applicable to research involving human subjects and in accordance with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP). The protocol of this study was reviewed and approved by the Makati Medical Center Institutional Review Board (IRB). The privacy and confidentiality of data was maintained. The authors had no conflict of interest in the study.

Conceptual Framework

Figure 1



IV. Results

A total of 183 adult patients with COVID-19 Infection were included in the study where 11 were treated with chloroquine/hydroxychloroquine, 20 were treated with azithromycin, 110 treated with chloroquine/hydroxychloroquine plus azithromycin, and 42 treated with chloroquine/hydroxychloroquine plus azithromycin plus lopinavir/ritonavir.

Table 1.1 showed that the four groups turn out to have significantly different mean age, specifically, those who were treated chloroquine/hydroxychloroquine were significantly younger, 43.4 years old $\pm$12.7 as compared to 57.4 years old $\pm$12.1 for those who were treated with chloroquine/hydroxychloroquine plus azithromycin plus lopinavir/ritonavir. Hospital stay also turned out to be significant (p=.001); patients treated with azithromycin had a mean hospital stay of 7 days which was significantly shorter than 15.5 days for those treated with the combination of chloroquine/hydroxychloroquine plus azithromycin plus lopinavir/ritonavir. Level of risk for QT prolongation based on Tisdale score was also significant (p=.0001) wherein overall results show that 32.9% were classified as low risk, while 54.1% were moderate risk and 13.1% were high risk. Patients treated with single agents such as chloroquine/hydroxychloroquine or azithromycin were mostly classified as low risk, while those on dual or quadruple regimen were mostly the moderate or high risk.

Furthermore, Table 1.2 showed that 19.7% of the total patients were admitted in the intensive care unit and were treated with either dual (chloroquine/hydroxychloroquine plus azithromycin) or quadruple (chloroquine/hydroxychloroquine plus azithromycin plus lopinavir/ritonavir) therapy. Table 1.3 further showed that there was no significant difference among the four treatment groups in terms of mean baseline serum potassium, magnesium, ionized calcium ALT, AST, PT-INR. For the baseline complete blood count, the mean Hgb and WBC were not significantly different across all four groups. However, the mean lymphocyte count and platelet counts were significantly lower in the quadruple treatment group.

Table 1.4 showed the QT interval measurements at baseline and during treatment. There exists a significant difference in the mean first QTc monitoring from baseline, where those who were treated with chloroquine/hydroxychloroquine had significantly lower mean of corrected QT interval of 436.9 msec as compared to those treated with azithromycin showing a corrected QT interval of 488.2 msec. There was no significant difference in the mean change of corrected QT interval measured from baseline to first ECG monitoring among all four treatment groups.

Table two was a univariate analysis comparing the primary and secondary outcome across the four treatment groups. There was no significant difference in terms of occurrence of ventricular tachycardia/arrhythmia (p=0.8775), septic shock (p=0.3016) and all-cause mortality (p=0.1502) in relation to each treatment arm. Overall, there was only 1.6% cases of ventricular tachycardia/arrhythmia while 8.2% experienced septic shock.

Table three obtained the odds ratio for the treatment group on the different patient outcome. Patients treated with either chloroquine/hydroxychloroquine or azithromycin had no cases of ventricular arrhythmia, septic shock and all-cause mortality, thus no odds ratio can be derived. On the other hand, results show that the odds of ventricular arrhythmia, septic shock or all-cause mortality was higher for those treated with chloroquine/hydroxychloroquine plus azithromycin plus lopinavir/ritonavir as compared to chloroquine/hydroxychloroquine plus azithromycin. However, the difference was not significant.

Table four examined factors affecting mortality and results show that the non-survivors were significantly older (64 years old) as compared to those who survived (52 years old). Results also show that male patients were more likely to die as compared to female patients (OR 4.23, 95% CI 1.2 to 14.9, p=0.0250). Patients with CAD were 4.2 (95% CI 1.1 to 18.5) times more likely to die as compared to those without CAD, but the odds ratio was not significantly different from 1.0. However, those with CKD were significantly more likely to die, with odds ratio of 3.93 (95% CI 1.1 to 14.1). Tisdale risk score for QT prolongation was also a significant indictor of mortality based on these results, as those classified as high risk were 19 (95% CI 6.5 to 55.5) times more likely to die as compared to those classified with either low or moderate risk (p=.0001). A change in QTc from baseline was a significant risk factor for mortality. Specifically, the resulting odds ratio of above 1 denotes that the higher was the QTc in the first monitoring (from baseline), the more likely the patient will die. Likewise, the higher was the average from the first to the fifth QTc monitoring was during treatment, compared to baseline, the more likely a patient will die. Lastly, the higher was the peak QTc from baseline, the higher chances of dying.

Table five shows no significant inter and intra-observer variability in the ECG interpretation and corrected QT interval measurements were observed.

Table 1.1 Demographics, Comorbidities, Tisdale Risk Stratification According to Treatment Group

	Total n = 183	**CQ/HCQ n = 11**	**AZI n = 20**	**CQ/HQ+AZI n = 110**	**CQ/HCQ + AZI+ lopinavir-ritonavir n = 42**	**p value**
Age (years), mean ± sd	53.5 ± 15.4	43.4 ± 12.7	50.9± 18.7	53.5 ± 15.8	57.4± 12.1	0.0450
Gender, n, %						
Male	113 (61.7)	7 (63.6)	15 (75)	61 (55.5)	30 (73.2)	0.1707
Female	70 (38.3)	4 (36.4)	5 (25)	49 (44.5)	12 (29.3)	
Hypertension	101 (55.2)	7 (63.6)	8 (40)	57 (51.8)	29 (69)	0.114

Diabetes Mellitus	52 (28.4)	2 (18.20	6 (30)	28 (25.5)	16 (38.1)	0.3917
CHF	3 (1.6)	0 (0.0)	0 (0.0)	1 (.9)	2 (4.8)	0.3313
CAD	8 (4.4)	0 (0.0)	0 (0.0)	5 (4.5)	3 (7)	0.5326
Tisdale Score, n, %						
Low	60 (32.9)	11 (100)	13 (65)	31 (28.2)	5 (11.9)	0.0001
Moderate	99 (54.1)	0 (0.0)	6 (30)	64 (58.2)	29 (69.0)	
High	24 (13.1)	0 (0.0)	1 (5)	15 (13.6)	8 (19.0)	

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; AZI, azithromycin; sd, standard deviation

Table 1.2 ICU Admission and Mean Hospital Stay According to Treatment Group

	Total n = 183	**CQ/HCQ n = 11**	**AZI n = 20**	**CQ/HQ+AZI n = 110**	**CQ/HCQ + AZI+ lopinavir-ritonavir n = 42**	**p value**
ICU admission, n, %	36 (19.7)	0 (0.0)	0 (0.0)	23 (12.6)	13 (7.1)	0.0113 *
Hospital stay, mean ± sd	11.7 ± 6.9	15.4 ± 8.9	7 ± 4.9	10.9 ± 6.5	15.5 ± 6.4	0.0010 *

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; AZI, azithromycin; sd, standard deviation

Table 1.3 Baseline Laboratories According to Treatment Group

Parameters	**Total n = 183**	**CQ/HCQ n = 11**	**AZI n = 20**	**CQ/HQ+AZI n = 110**	**CQ/HCQ + AZI+ lopinavir-ritonavir n = 42**	**p value**
Potassium	3.8 ± 0.5	4 ± 0.4	3.9 ± 0.6	3.8 ± 0.5	3.9 ± 0.5	0.6710
Creatinine	1.2 ± 1.4	1.4 ± 2	1.3 ± 2	1.1 ± 1.5	1.1 ± 0.4	0.8310
Magnesium	2.1 ± 0.3	2.2 ± 0.2	2 ± 0.2	2.1 ± 0.3	2 ± 0.3	0.6940
Ionized Calcium	1.5 ± 1.3	1.3 ± 0	1.1 ± 0.1	1.4 ± 1.2	1.6 ± 1.7	0.8540
Hemoglobin	14 ± 1.7	14.7 ± 1.5	14.5 ± 1.9	13.8 ± 1.6	14.2 ± 1.7	0.7240
WBC	8.4 ± 7.5	8.3 ± 3.2	6.3 ± 2.5	8.5 ± 7.8	9.4 ± 8.7	0.4910
Lymphocyte	22 ± 10.4	23.7 ± 9.1	26.2 ± 11.3	22.5 ± 10.7	18.2 ± 8.5	0.0230
Segmenters	67.9 ± 12.5	65.9 ± 9.5	63.4 ± 13.1	67.7 ± 12.6	71 ± 12.1	0.5220
Monocytes	9 ± 5.4	8.7 ± 1.8	9.2 ± 3.5	8.5 ± 3.1	10.4 ± 9.7	0.3190
Platelets	241.9 ± 97.2	301.5 ± 146	203.3 ± 71.4	254.8 ± 99.5	211.2 ± 70.4	0.0030
ALT	53 ± 41.9	59.1 ± 42.7	43.7 ± 22.9	52.6 ± 45.8	55.5 ± 36.7	0.8390
AST	62 ± 115.3	43.2 ± 22.1	45.5 ± 22.3	68.4 ± 147.3	57.4 ± 25.7	0.8870
PT - INR	1.1 ± 0.1	1.1 ± 0.1	1.1	1.1 ± 0.1	1.2 ± 0.2	0.4620

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; AZI, azithromycin; sd, standard deviation

Table 1.4 QT Interval Measurements According to Treatment Group

	Total n = 183	CQ/HCQ n = 11	AZI n = 20	CQ/HQ+AZI n = 110	CQ/HCQ + AZI+ lopinavir-ritonavir n = 42	p value
Baseline QT	439.9 ± 40.8	423.8 ± 33.1	456.8 ± 36.2	436.3 ± 39.9	458.6 ± 47.5	0.0520
QT 1st monitoring	459.6 ± 43.8	436.9 ± 57.3	488.2 ± 33.7	457.4 ± 42.4	466.6 ± 42.9	0.0440
Peak monitoring	482.5 ± 50.1	451.3 ± 49.6	503.9 ± 45.2	481.4 ± 47.7	493.1 ± 61.4	0.0830
Baseline – 1st QTc (Change)	-19.7 ± 47.8	-13.1 ± 62.7	-31.4 ± 23.9	-21.2 ± 48.8	-8 ± 46.7	0.5900
Baseline - peak (Change)	-42.6 ± 53.9	-27.6 ± 55.6	-47.1 ± 33.1	-45.1 ± 54.7	-34.6 ± 62.8	0.7060
Baseline - average (Change)	-24.6 ± 44.0	-8.4 ± 45.8	-35.6 ± 29.6	-26.2 ± 44.0	-18.4 ± 50.3	0.4740

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; AZI, azithromycin; sd, standard deviation

Table 2. Summary of Patient Outcomes based on Treatment

	Total n = 183	CQ/HCQ n = 11	AZI n = 20	CQ/HQ+ AZI n = 110	CQ/HCQ + AZI+ lopinavir-ritonavir n = 42	p value
Ventricular tachycardia	3 (1.6)	0 (0)	0 (0)	2 (1.1%)	1 (0.5%)	0.8775
Myocardial ischemia/ infarction	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Septic shock	15 (8.2)	0 (0)	0 (0)	10 (5.5%)	5 (2.7%)	0.3016
All-cause mortality	20 (10.9)	0 (0)	0 (0)	13 (7.1%)	7 (3.8%)	0.1502

Abbreviations: CQ, chloroquine; HCQ, hydroxychloroquine; AZI, azithromycin; sd, standard deviation

Table 3. Odds Ratio of Each Treatment for the Patient Outcome

	Odds Ratio	95% CI	p value
Ventricular Tachycardia			
CQ/HCQ (n=11)	-	-	-
AZI (n=20)	-	-	-
CQ/HQ+AZI n=110(dual)	1.64	0.14 to 18.62	0.6914
CQ/HCQ+AZI+lopinavir/ritonavir n=42		**Reference**	
Septic Shock			
CQ/HCQ (n=11)	-	-	-
AZI (n=20)	-	-	-
CQ/HQ+AZI n=110	1.72	0.55 to 5.45	0.3534
CQ/HCQ+AZI+lopinavir/ritonavir n=42		**Reference**	
All-cause Mortality			

CQ/HCQ (n=11)	-	-	-
AZI (n=20)	-	-	-
CQ/HQ+AZI n=110	1.93	0.70 to 5.33	0.2017
CQ/HCQ+AZI+lopinavir/ritonavir n=42		**Reference**	

Table 4. Univariate Analysis on Factors Affecting Mortality

	Non-Survivors	**Survivors**	**OR**	**95% CI**	**p value**
Age (years), mean ± sd	64.1 ± 13.2	52.2 ± 15.2	1.06	1.0 - 1.1	0.0015 *
Gender, n, %					
Male	18 (85.7)	95 (58.6)	4.23	1.2 - 14.9	0.0250 *
Female	3 (14.3)	67 (41.4)			
Hypertension, n, %	13 (61.9)	88 (54.3)	1.5	0.6 - 4.0	0.4142
CAD, n, %	3 (14.3)	6 (3.7)	4.2	1.0 - 18.5	0.0536
Diabetes Mellitus, n, %	4 (19.0)	48 (29.6)	0.54	0.2 - 1.7	0.2957
COPD, n, %	1 (4.8)	1 (0.6)	7.9	0.5 - 131.3	0.1495
CKD, n %	4 (19.0)	9 (5.6)	3.92	1.1 - 14.1	0.0364 *
CA, n %	1 (4.8)	2 (1.2)	3.93	0.3 - 45.3	0.2731
Tisdale Score, n, %					
Low	1 (4.8)	60 (37.0)	***Reference***		
Moderate	7 (33.3)	94 (58.0)	4.5	0.5 - 37.2	0.1664
High	13 (61.9)	8 (4.9)	97.5	11.2 - 848.5	0.0001 *
Tisdale Score, n, %					
Low - Moderate	8 (38.1)	154 (95.1)	***Reference***		
High	13 (61.9)	8 (4.9)	19	6.5 - 55.5	0.0001 *
Potassium (K)	3.7 ± 0.6	3.8 ± 0.5	0.6	0.2 - 1.6	0.3165
Creatinine	1.3 ± 0.9	1.1 ± 1.5	1.07	0.8 - 1.4	0.6203
Ica	1.2 ± 0.05	1.5± 1.3	0.01	0.0 - 12.9	0.1927

Change 1st QTc from Baseline	-13.3 ± 73.9	22.2 ± 44.8	1.01	1.00 - 1.03	0.0349 *
Change Average QTc from Baseline	-13.4 ± 76.3	27.3 ± 39.8	1.02	1.00 - 1.03	0.0163 *
Change Peak QTc from Baseline	3.8 ± 84.6	45.5 ± 50.3	1.01	1.00 - 1.03	0.0301 *

Table 5. Inter Rater

File	ICC	Interpretation
1st File	1.00	Excellent Agreement
2nd File	1.00	Excellent Agreement

V. Discussion

Our study had demonstrated that all the agents used to treat COVID 19 patients do prolong the QT interval, singly or in combination with each other. The researchers, however, cannot establish that L/P cannot prolong the QT interval independently since this agent was given in combination with other the afore-mentioned drugs. Among the four treatment groups, azithromycin had the most QT prolongation noted from baseline, followed by the CQ/HCQ group. In contrast, the study of Mercuro et al showed a significant QTc change with combination therapy of HCQ and azithromycin. The increase of the QT from baseline was not statistically significant among the four groups, showing that other factors can be implicated in the ECG changes.

No mortalities were seen in the singe agent groups of azithromycin and CQ/HCQ, as compared to that of the dual and quadruple therapy arms. We can infer from the univariate analysis that the patients in the dual and quadruple arms were critically ill; but as demonstrated, the QT interval increase, risk of developing mortality, ventricular tachycardia and shock was not significant between the dual and quadruple arm. Factors other than the drugs can be attributable in the demise of the patients in the dual and quadruple arms. It was postulated that the SaRS COV virus had particular tropism to the respiratory and cardiac tissue via the ACE 2 receptor, and as such, contribute to the development of inflammation, pushing the heart and lungs into myocarditis and fibrosis. This can contribute to the development of ventricular arrhythmias, secondary bacterial infections and death. [17]

In the treatment of COVID-19 patients, aside from antimalarial drugs and macrolides known to prolong the QT interval, a number of confounders should also be considered such as electrolyte imbalances, administration of concomitant drugs with the potential to prolong the QT interval, renal insufficiency, heart failure and myocardial ischemia. These findings may not be generalizable for all COVID-19 positive patients and that ECG monitoring should be individualized.

VI. **Limitations**

The research was a purely descriptive and retrospective study using convenience sampling method which accounts for the unequal distribution of patients per treatment arm. Due to the nature of the study, the timing of administration of medications and the number of ECG monitoring done per patient were not standardized. Since lopinavir- ritonavir was given in combination with hydroxychloroquine/chloroquine and azithromycin, we cannot independently assess its arrhythmogenic risk.

VII. Conclusion

There were demonstrable changes in the QTc interval across all treatment groups. The change in QTc does not significantly vary in relation to the number of agents given**.** The four treatment arms included in this study did not significantly affect all-cause mortality and development of ventricular tachycardia. Older age, male sex, CAD, CKD, and high-risk Tisdale scores were predictors of mortality. Any increase QTc from baseline was also a predictor of mortality.

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