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Tisdale score successfully predict outcomes of QT-prolonging treatment in COVID-19 patients

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Abstract

Introduction: Hydroxychloroquine, one of the challenging drugs used for COVID-19, has shown to be beneficial in some studies, although concerns about the side effects of the drug have limited its use. Several electrocardiogram changes have been described in these patients which could be exacerbated using hydroxychloroquine, especially QT-prolongation. Struggles to identify the population at risk of side effects of these drugs result in few scoring systems, one of which is the Tisdale score that showed to have successfully predicted the at-risk population.
Objectives: In this study, we aimed to assess the degree of QT prolongation provoked by hydroxychloroquine, either alone or in combination with azithromycin in association with the treatment outcomes based on their Tisdale score.
Patients and Methods: We conducted a historical cohort study on 659 patients with COVID-19 at Khorshid hospital, Isfahan, Iran from March to April 2020. Tisdale risk score was used for predicting high-risk patients for QT corrected (QTc) interval prolongation.
Results: Mean (SD) of baseline QTc was 390.66 (14.65), 390.74 (16.52), 389.67 (19.51), 390.68 (17.35) for patients who received hydroxychloroquine, hydroxychloroquine plus azithromycin, Kaletra, respectively. QTc was not increased significantly after starting treatment in each group.
Conclusion: Despite that none of our patients have a high Tisdale score, our findings showed the predictive value of this score for treatment outcomes. Individuals with medium Tisdale scores showed much worse outcomes and in-hospital mortality. Tisdale score could be employed as a valuable tool to predict the COVID-19 patients' prognosis after treatment with QT-prolonging drugs.

Introduction

Since late last year, the world has seen a large epidemic of a new strain of the coronavirus family, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has described it as a serious global concern for public health (1,2). Previously, two other viruses in the same family had led to widespread severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) epidemics in 2003 and 2015. The new disease leads to an acute respiratory syndrome called COVID-19 (3).

Although many efforts are being made for controlling the outbreak, due to the very high

Key point

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transmission rate of the virus, it is spreading every day, killing dozens of people (4). According to the WHO statistics (https://covid19.who.int/), the global prevalence of the virus and its mortality as of November 12, 2021, was 253.78 million and 5 million, respectively.

Although to the date of this study, only remdesivir has been approved by the Food and Drug Administration (FDA) for this

respiratory syndrome, there is ample evidence of some medications that have led them to a special place in the treatment of these patients in the current critical situation.

One of the most common medications used is hydroxychloroquine, which was previously used in the treatment of chronic inflammatory conditions like rheumatic diseases. It is beneficial in some studies (5-7), although concerns about the side effects of the drug have limited its use. However, the US FDA has authorized the temporary use of the drug to help people with COVID-19 in this harsh pandemic situation, recent findings doubted the outcomes of treatment with hydroxychloroquine (8). One of the most well-known side effects of this drug is the QT prolongation, especially in the setting of electrolyte disturbance or in combination with other drugs that also prolong the QT interval, such as azithromycin, which is increasingly known for risk of sudden cardiac death and QT prolongation (9-11).

As the virus spread, several cardiovascular complications of COVID-19 were reported. A case report reported myopericarditis and systolic heart disease (12). Evidence of electrocardiogram changes was reported in two other individuals, including ventricular atrial block and elevated ST segment (13). A more recent study reported the observed electrocardiogram changes in COVID-19; including diffuse ST-segment elevation, non-specific ST-segment changes, low voltage in the limb, and premature ventricular contractions (14).

Struggles to identify the population at risk of side effects of these drugs result in few scoring systems, one of which is the Tisdale score that showed to have successfully predicted the at-risk population. This scoring system, first defined by Tisdale et al (15), combine demographic, laboratory, and clinical information of patients to stratify them into three groups (low, medium, and high) regarding the risk for QT prolongation.

Due to the concurrent comorbidities and QT-prolonging drugs, identification of adverse drug events become important, especially in high-risk patients. Patients admitted to intensive care units (ICU), were more susceptible to electrolyte disturbance and therefore, along with cardiovascular complications of COVID19, were at higher risk for prolonged QT and Torsades de pointes (10, 12, 16).

Objectives
In this study, we aimed to assess the degree of QT prolongation provoked by hydroxychloroquine, either alone or in combination with azithromycin in association with the treatment outcomes based on their Tisdale score.

Patients and Methods
Study design
We conducted a historical cohort study at Khorshid hospital, Isfahan, Iran from March to April 2020. The inclusion criteria of this study were patients over 18 years of age who were diagnosed with COVID-19 [positive result for SARS-CoV-2 based on PCR (polymerase chain reaction) or clinical findings or chest CT scan] and had been treated with hydroxychloroquine (HCQ), the combination of hydroxychloroquine and azithromycin or Kaletra. According to the available pandemic conditions, the samples of this study were selected as a census of patients referred to Khorshid hospital whose COVID-19 has been approved during this period. We recorded patients' demographic characteristics including age, gender, and body mass index (BMI) comorbidities including hypertension, diabetes, congestive heart failure, renal failure, coronary artery disease (CAD) and atrial fibrillation, and medications including previous use of HCQs and history of loop diuretic used in hospital. Moreover, the electrocardiography findings (at arrival and daily serials) were recorded. In addition to these items, some outcomes such as hospital length of stay, hospital readmission, need for mechanical ventilation, and need for intensive care unit admission were collected.

Tisdale risk score which is calculated based on clinical and laboratory risk factors can be used for predicting high-risk patients regarding QTc interval prolongation. It has been used in several studies for guiding monitoring and treatment decisions (15). In this study, we utilized the Tisdale score to compare the outcomes across different levels of Tisdale score.

The detailed method for the study was published earlier (17). In brief, each patient entered one of the intervention groups, including hydroxychloroquine (hydroxychloroquine diet or hydroxychloroquine and azithromycin diet) or control without hydroxychloroquine (Kaletra diet). In the intervention group, a combination therapy regimen including hydroxychloroquine 400 mg tablets was administered as a stat and 200 mg every 12 hours, and in the control group, other diets lacking hydroxychloroquine were prescribed. Treatment of each patient continued for 7-14 days according to the physician's clinical judgment. To measure the changes in the electrocardiogram in patients, their files are checked and the frequency of changes in the electrocardiogram on the first day and the days after the start of treatment is checked.

Statistical analysis
In this descriptive study, counts and percentages were used to describe categorical variables. Mean and standard deviations (SDs) were used to report quantitative variables. An independent t test was used to compare the quantitative variables with normal distribution. If the variable distribution was not normal according to the distribution curve, the Mann-Whitney U test has been used. The chi-square test was used when comparing categorical variables. In order to investigate the association between demographic and clinical variables with treatment outcomes, we used linear or logistic regression tests. Data

were analyzed using SPSS software version 22 (IBM SPSS Statistics for Windows, version 22.0 Armonk, NY: IBM Crop.). The significance level was considered 0.05 for each test.

Results

In this historical cohort study, 659 patients were diagnosed with COVID-19. The mean age and body mass index of participants was, 57.29 (±15.35) years and, 27.05 (±3.2) kg/m², respectively. The majority of patients were men (n = 405; 61.5%). The most common comorbidities were hypertension (n = 232; 35.2%) and diabetes mellitus (n = 187; 28.4%) (Table 1).

Around 93 (14.1%) of all COVID-19 patients needed ICU care during hospitalization and, 35 (5.3%) of them were mechanically ventilated. 444 patients received hydroxychloroquine, 155 patients received hydroxychloroquine plus azithromycin and 96 patients received Kaletra, as part of their treatment regimen. A baseline ECG was obtained before initiating antiviral therapy. Most patients had sinus rhythm (n = 654; 99.2%). The baseline heart rate for all patients was 90.07 (11.1) per minute (Table 1) .

Baseline QTc (corrected QT interval) was 390.66 (14.65) ms, 390.74 (16.52) ms, 389.67 (19.51) ms, 390.68 (17.35) ms for patients who received hydroxychloroquine, hydroxychloroquine plus azithromycin, Kaletra, respectively. The maximum QTc for patients who received hydroxychloroquine was 392.73 (8.38) ms and for patients who received hydroxychloroquine plus azithromycin was 390.43 (33.79) ms and for patients received Kaletra was 394.74 (15.29) ms. QTc was not increased significantly after starting treatment in each group (Table 1).

Then, we categorized the patients by baseline Tisdale score. Most patients have low Tisdale scores (n=650, 98.6%). Note that Tisdale scores less than 7 were classified as low, 7-10 was classified as medium, and greater than 10 was classified as high, in each group before starting treatment. We did not have any patients with high Tisdale scores in any of the groups before starting treatment (Table 1).

The average length of stay for all patients was 6.57 (±5.77) days. 28 (6.3%) of patients in the hydroxychloroquine group died along with their hospitalization, while seven of them had medium Tisdale score at initiating treatment and for hydroxychloroquine plus azithromycin, group was 9 (5.8%), while two of them had medium Tisdale score at initiating treatment. About 17 (17.7%) patients in the Kaletra group died in the hospital, while one of them had a medium Tisdale score at initiating treatment. Moreover, 23 (5.2%) patients who received hydroxychloroquine were re-admitted to the hospital, seven of which had medium Tisdale score at initiating treatment. This rate for patients who received hydroxychloroquine plus azithromycin was 12 (7.7%), that two of them had medium Tisdale score at initiating treatment and for patients received Kaletra

was 12 (12.5%), which only one of them had a medium Tisdale score at initiating treatment. After treatment, changes in QTc (ΔQTc) of 5 patients were more than 60 ms, surprisingly, all of them had low Tisdale score before starting treatment (Table 2).

When controlling for the confounding factors including gender, age, BMI, marriage status, baseline Tisdale score, and primary QTc, the association between receiving Kaletra as part of treatment with mortality and length of hospitalization were significant (P = 0.001, OR=0.27, CI:0130.56; β: 0.40, P = 0.001 respectively). Accordingly, the association between the rate of readmission and receiving Kaletra or hydroxychloroquine in the patient's antiviral regimen was significant (P = 0.03, OR: 0.45; P = 0.001, OR = 2.86, respectively) (Table 3).

Discussion

In this study, we evaluate the role of utilizing the Tisdale score, for clinical decisions about prescribing drugs for COVID-19. While we found no patient with a high Tisdale score in this study, other studies reported different results. The distribution of Tisdale score across the population was strongly related to the selected population. A study for validation of Tisdale score in 2013 on hospitalized patients reported 14%, 35%, and 21% for high, moderate, and low Tisdale scores, respectively (15). This discrepancy could be due to different patients' selection, especially that all of our patients were diagnosed with COVID-19.

Despite that none of our patients have a high Tisdale score, the findings of this study showed the predictive value of this score for treatment outcomes. Individuals with medium Tisdale scores showed much worse outcomes including hospital length of stay, need for readmission, need for intubation, need for intensive care unit, and in-hospital mortality. There was no obvious difference between drug regimen used except length of stay for patients using hydroxychloroquine and azithromycin. It seems that high Tisdale scores correspond to a worse prognosis, especially when accompanied by the use of QT-prolonging drugs.

Several studies evaluated the efficacy and safety of hydroxychloroquine, Kaletra, and azithromycin in the treatment of COVID-19 (18,19). However, these reports have stressed the non-superiority of these drugs for the treatment of COVID-19, some evidence showed the effectiveness of prophylactic and early prescribed use of these drugs, especially hydroxychloroquine (20,21). The decision of whether to treat patients with hydroxychloroquine and other QT-prolonging drugs should be made based on the patients' clinical, laboratory, and disease-associated characteristics. In another word, previous studies have shown that QT-prolonging drugs, did not equally induce side effects in individuals (15,22).

Our findings also showed that the rate of QT-prolongation was not considerable. Considering all of the recruited patients, QTc was slightly increased after

Table 1. Characteristics of enrolled COVID-19 patients

Characteristics		HCQ (n=444)	P	HCQ + AZ (n=155)	P	Kaletra (n=96)	P	Total
Gender[a]	Male	281 (63.3%)	0.18	94 (60.6%)	0.82	64 (66.7%)	0.25	405 (61.5%)
	Female	163 (36.7%)		61 (39.4%)		32 (33.3%)		254 (38.5%)
Age[b]		56.79 (15.50)	0.22	60.55 (14.77)	0.02	60.30 (15.37)	0.04	57.29 (15.35)
BMI		27.01 (3.26)	0.40	27.38 (4.86)	0.21	27.44 (4.31)	0.32	27.05 (3.2)
Comorbidities								
Hypertension	Yes	151 (34.0%)	0.35	64 (41.3%)	0.07	37 (38.5%)	0.45	232 (35.2%)
Diabetes	Yes	124 (27.9%)	0.74	56 (36.1%)	0.01	28 (29.2%)	0.85	187 (28.4%)
Congestive heart failure	Yes	3 (0.7%)	0.02	1 (0.6%)	0.33	1 (1%)	0.68	10 (1.5%)
Renal failure (ESRD)	Yes	13 (2.9%)	0.40	5 (3.2%)	0.92	4 (4.2%)	0.62	22 (3.3%)
Coronary artery disease	Yes	82 (18.5%)	0.24	46 (29.7%)	0.00	24 (25%)	0.14	130 (19.7%)
Atrial fibrillation	Yes	3 (0.7%)	0.72	1 (0.6%)	0.85	1 (1%)	0.73	5 (0.8%)
COPD or asthma	Yes	11 (2.5%)	0.14	4 (2.6%)	0.62	96 (100%)	0.99	21 (3.2%)
Medication								
Previous usage of HCQ	Yes	10 (2.3%)	0.46	5 (3.2%)	0.20	1 (1%)	0.48	13 (2%)
History of loop diuretic use in hospital (Furosemide)	Yes	8 (1.8%)	0.04	4 (2.6%)	0.89	96 (100%)	0.99	12 (2.7%)
Electrocardiograms								
Baseline heart rate		90.18 (12.20)	0.68	91.14 (14.31)	0.26	91.12 (11.64)	0.32	90.07 (11.16)
QTc before the start of antivirals		390.74 (16.52)	0.81	389.67 (19.51)	0.33	390.68 (17.35)	0.99	390.66 (14.65)
ΔQTc		1.98 (17.70)	0.80	0.75 (35.92)	0.02	4.06 (18.9)	0.93	1.77 (22.24)
Maximum QTc		392.73 (8.38)	0.57	390.43 (33.79)	0.13	394.74 (15.29)	0.12	392.44 (18.97)
Outcomes								
Length of stay (hospitalization duration)		6.56 (4.88)	0.94	7.8 (5.00)	0.001	12.43 (7.28)	0.00	6.57 (5.77)
Need for ICU admission	Yes	53 (11.9%)	0.02	23 (14.8%)	0.76	37 (38.5%)	0.00	93 (14.1%)
Mechanically ventilated (intubation status)	Yes	21 (4.7%)	0.34	8 (5.2%)	0.92	15 (15.6%)	0.00	35 (5.3%)
Hospital readmission	Yes	23 (5.2%)		12 (7.7%)		12 (12.5%)		
Tisdale score at treatment Initiation	Low (<7)	437 (98.4%)	0.02	153 (98.7%)	0.22	95 (99%)	0.88	650 (98.6%)
	Medium (7-10)	7 (1.6%)		2 (1.3%)		1 (1%)		9 (1.4%)

Abbreviations: HCQ: hydroxychloroquine; AZ: azithromycin, BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); ESRD: end-stage renal disease; QTc: corrected QT interval; ΔQTc: change in corrected QT interval; ICU: intensive care unit; COPD, Chronic obstructive pulmonary disease

[a] Data are expressed as qualitative data, shown by No. (%).

[b] Data are expressed as quantitative data, shown by mean (standard deviation).

In each test, the corresponding group was compared against the rest of the population.

Table 2. Comparison of treatment outcome based on different Tisdale score levels

Treatment		Primary Tisdale score					
		Low			Medium		
		HY	HY+AZ	Kaletra	HY	HY+AZ	Kaletra
ΔQTc	>60 ms	2 (0.5%)	1 (0.7%)	2 (2.1%)	-	-	-
	≤60 ms	435 (99.5%)	152 (99.3%)	93 (97.9%)	7 (100%)	2 (100%)	1 (100%)
In-hospital Mortality		28 (6.4%)	9 (5.9%)	17 (17.9%)	7 (100%)	2 (100%)	1 (100%)
Length of stay		6.51 (4.81)	7.87 (5.03%)	12.29 (7.18%)	9.71 (7.84%)	6 (2.82%)	2 (100%)
Need for ICU admission (for non-severe cases)		52 (11.2%)	23 (15%)	36 (37.9%)	1 (14.3%)	2 (100%)	1 (100%)
Need for intubation (for severe cases)		21 (4.8%)	8 (5.2%)	15 (15.8%)	7 (100%)	2 (100%)	1 (100%)
Hospital Re-admission		23 (5.3%)	12 (7.8%)	12 (12.6%)	7 (100%)	2 (100%)	1 (100%)

Table 3. Odds ratio of treatment outcomes, controlling for demographic, primary QTc, and initial Tisdale score

Treatment	Dependent: Mortality (death status)			Dependent: Length of stay (hospitalization duration)			Dependent: Rate of re-admission (Rehospitalization)		
	OR	95% CI	P	Standardized B	B (SD)	P	OR	95% CI	P
HCQ	1.49	(0.73, 3.03)	0.26	-0.014	-0.17(0.4)	0.71	2.86	(1.51, 5.42)	0.001
HCQ + AZ	1.60	(0.68, 3.80)	0.28	0.060	0.81(0.5)	0.11	0.76	(0.35, 1.64)	0.49
Kaletra	0.27	(0.13, 0.56)	0.001	0.40	6.63(0.5)	0.00	0.45	(0.22,0.94)	0.03
Primary QTc	1.007	(0.98, 1.03)	0.56	0.008	0.003(0.1)	0.82	1.00	(0.97, 1.02)	0.98
Gender	1.07	(0.51, 2.24)	0.84	-0.063	-0.74(0.4)	0.90	0.99	(0.53, 1.86)	0.99
Age	0.93	(0.91, 0.96)	0.00	0.14	0.05(0.1)	0.00	0.99	(0.97, 1.01)	0.50
BMI	1.04	(0.93, 1.17)	0.42	0.003	0.005(0.6)	0.93	1.05	(0.96, 1.15)	0.24
Marital status	1.12	(0.10, 2.12)	0.92	-0.012	-0.31(1.0)	0.75	1.63	(0.44, 5.9)	0.46
Primary Tisdale score	1.11	(0.91, 1.36)	0.28	0.012	0.36(0.1)	0.76	0.86	(0.73, 1.01)	0.07

Abbreviations: HCQ: hydroxychloroquine; AZ: azithromycin, BMI: body mass index; OR, odds ratio.

treatment. Similarly, there were a few patients who had QT-prolongation longer than 60ms. On the other hand, other studies evaluating QT interval in COVID-19 patients reported a higher increase in QT interval during treatment (10, 23). Due to much less QTc interval before initiation of treatment between our study and others, the possible underlying factors seem to be the difference in population selection, and different COVID-19 management guidelines, which result in different characteristics of hospitalized patients. It seems that the guideline that had been using in Iran, was much more conservative than others, which hospitalized patients had much better clinical status than hospitalized patients used in other countries. In line with this demonstration was the lower rate of need for intubation, ICU care, and mechanical ventilation in our study, representing more stable patients (10,23,24).

Conclusion
Tisdale score could be used as a valuable tool to predict the COVID-19 patients' prognosis after treatment with QT-prolonging drugs. Patients who have higher Tisdale score would considerably show worst outcomes when treated with QT-prolonging drugs, therefore use of these drugs should be prevented in these patients.

Limitations of the study
Our study's major limitation was the overlapping of study groups, in which some patients received a combination of drugs, which makes it hard to statistically compare the groups. The major strength of this study was that to the best of our knowledge, this is the first study of its kind that utilized the Tisdale score in decision making for the treatment of COVID-19.

Authors' contribution
ZN, MTR and VM were the principal investigators of the study. ZN, MTR, VM and SE were included in preparing the concept and design. HH, KD, MN, SS contributed to the study implementation and measurements. MM and NS participated in analyzing the data. KD and VM contributed to drafting the manuscript. MTR, HH and SS revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest
Authors declare no conflict of interests.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The institutional ethical committee at Isfahan University of Medical Sciences approved all study protocols (IR.MUI.MED.REC.1399.400). Accordingly, written informed consent was taken from all participants before any intervention. Additionally, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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