

Comments: Dear Authors, Thank you for conducting this study entitled "Conduction system disorders and electrocardiographic findings in COVID-19 mortality patients in 2021, Shiraz, Iran" for possible publication in the esteemed journal "World Journal of Cardiology". I have a few points that need to be revised as I mentioned them in the main manuscript file.

● **Conduction system disorders and electrocardiographic findings in COVID-19 deceased patients in Shiraz, Iran**

Background: Many cardiac conduction disorders and electrocardiography (ECG) changes occur as a manifestation of Coronavirus disease 2019 (COVID-19), especially in severe cases.

● **Keywords:** COVID-19, Conduction system disorder, ECG, Atrioventricular block, cross-sectional, electrocardiography

● caused by a novel coronavirus, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that triggered the respiratory infection, Coronavirus disease 2019 (COVID-19). Due to the rapid transmission rate of COVID-19, WHO declared a pandemic on March 11th, 2020 [1].

批注 [RV1]: Title was changed accordingly and we added a running title.

批注 [J12]: Please separate the background from the aim of the study.

批注 [RV3]: Thank you, done

批注 [J14]: Please add another two keywords to be six in number as per journal style.

批注 [RV5]: Thank you, done.

批注 [J16]: Write the full term of the abbreviation.

批注 [RV7]: Thank you, done

● All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM corp.), for windows. Categorical variables were shown as frequency and percentages, and continuous variables as mean (SD). Chi-square test was performed to assess the relationships between ECG parameters and patients' medical conditions with conduction system disease. The presence of conduction system disorders was considered the outcome variable, and ECG parameters were regarded as dependent variables. Then, the association of conduction system disorders and ECG parameters was calculated using logistic regression, and adjusted odds ratios were reported for univariate analysis and multivariate analysis after adjustment for the presence of other ECG parameters, sex, age, and underlying diseases. A two-sided P-value less than 0.05 was considered statistically significant.

● Among the 432 demised patients, 261 (60.4%) were male, with a mean age of 67.02 (± 14.44) and age range of 28 to 96. The most prevalent comorbid diseases were hypertension (47.9% - 207 cases), diabetes mellitus (36.3% - 157 cases) and cardiac diseases (35.2% - 158 cases). The prevalence of other co-morbidities in order of frequency is as follow: coronary disease (18.5% - 80 cases), hyperlipidemia (12.5% - 54 cases), pulmonary disease (8.6% - 37 cases), chronic kidney disease (6.3% - 27 cases). Evaluating the association between patients' past medical conditions and conduction system disorders in patients who died of COVID-19 revealed that conduction disorders were not related to any underlying medical condition. A summary of demographic and comorbid diseases can be seen in table 1.

Regarding heart rate and rhythm, sinus tachycardia ($HR > 100$) and bradycardia ($HR < 60$) were noticed in 100 (23.1%) and 9 (2.3%) patients, respectively. Abnormal rhythms were noted in 66 (15.2%) patients. The most prevalent arrhythmia was atrial fibrillation (12.5%). Reviewing

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electrocardiographic findings, AVB was found in 40 (9.3%) patients. 28 (6.5%) of the patients suffered from 1st degree AVB, and 12 (2.8%) suffered from CHB. Changes in ST-T wave compatible with myocardial infarction or localized myocarditis appeared in 189 (59.0%) patients. Other abnormal conduction system findings were bundle branch blocks. Left bundle branch block was seen in 25 (5.8%) patients, and right bundle branch block was seen in 50 (11.6%) patients. Moreover, the prevalence of findings compatible with pulmonary diseases such as S1Q3T3, poor R progression, axis deviations, and low voltage ECG were 14.4% (62 patients), 41.0% (177 patients), 21.7% (94 patients), and 11.3 (49 patients), respectively. Findings compatible with myocardial injury, such as fragmented QRS, and prolonged QTc, were assessed with prevalence of 21.1% (91 patients), 6.5% (28 patients). Primary electrical cardiac diseases such as prominent J wave, Brugada pattern, and early repolarization were observed in 4.4% (19 patients), 1.2% (5 patients), and 4.2% (18 patients).

● Discussion

This is a single-center study conducted retrospectively. The small sample size of a single-center could result in less generalizability. Unfortunately, assessing the presence of myocarditis was not possible due to the absence of data on serum markers and echocardiographic examination for most of our enrolled patients. This descriptive study aims only to report the incidence of ECG abnormalities and their relationship with conduction system disorders in COVID-19 mortality patients; to determine which conduction disorders are independently associated with mortality, case-control or cohort studies are recommended.

- The mechanism responsible for the development of arrhythmias in COVID-19 has not been specified. However, potential reported triggers are as follows [21]. First, electrolyte

批注 [J110]: This information is without mentioning the tables.

批注 [RV11]: Thank you. we added a sentence referencing table 1

批注 [J112]: The limitations of the study should proceed the conclusion.

批注 [RV13]: Thank you, the limitation paragraph is moved here

imbalance caused by COVID-19 symptoms such as diarrhea and complications such as acute kidney injury or severe sepsis is a notable cause [22]. Second, SARS-CoV-2-induced myocardial injury due to the upregulation of angiotensin-converting enzyme 2 (ACE2) receptor during viral invasion and severe hypoxia-induced myocyte necrosis are other potential causes of arrhythmias [23]. Besides, acute myocardial infarction due to demand/supply imbalance and arterial thrombotic events secondary to hypercoagulable state can cause acute arrhythmias [24, 25]. In addition, stress and cytokine storm in relation to sepsis and high inflammatory state is another potential mechanism [21]. Moreover, prolonged QTc-induced malignant ventricular arrhythmias and channelopathies induced by off-label medical therapy and antiviral therapy could be introduced as direct triggers of arrhythmias [26].

批注 [RV14]: Write its full term.

批注 [RV15]: Thank you added.

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批注 [RV16]: Should follow the style of the journal.

批注 [RV17]: Thank you reference styling changed per journal's guidelines

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Table 1. Association of patients' past medical conditions and conduction system disorder in COVID-19 mortality patients

Medical condition		Patients without conduction system disorder (N=317)	Patients with conduction system disorder (N=108)	P value
Sex	Female	125 (73.1)	46 (26.9)	0.654
	Male	196 (75.1)	65 (24.9)	
Age	<=50	46 (79.3)	12 (20.7)	0.147
	51-60	65 (81.3)	15 (18.8)	
	61-70	82 (75.2)	27 (24.8)	
	>70	128 (69.2)	57 (30.8)	
IHD	Yes	57 (71.3)	23 (28.8)	0.477
	No	260 (75.4)	85 (24.6)	
DM	Yes	113 (72.0)	44 (28.0)	0.357
	No	204 (76.1)	64 (23.9)	
Renal disease	Yes	42 (79.2)	11 (20.8)	0.501
	No	275 (73.9)	97 (26.1)	
Pulmonary disease	Yes	23 (62.2)	14 (37.8)	0.078
	No	292 (75.6)	94 (24.4)	
Hyperlipidemia	Yes	38 (70.4)	16 (29.6)	0.503
	No	279 (75.2)	92 (24.8)	
CKD	Yes	19 (70.4)	8 (29.6)	0.648
	No	298 (74.9)	100 (25.1)	
HTN	Yes	151 (72.9)	56 (27.1)	0.504
	No	165 (76.0)	52 (24.0)	

HTN: hypertension, DM: diabetes mellitus, IHD: ischemic heart disease, HLP: hyperlipidemia, CKD: chronic kidney disease.

批注 [RJ 118]: I think it is better to split this table into 2 tables, one for the association of conduction system disorder and demographic data (age groups and gender) and the other table with patients' past medical conditions.

批注 [RV19]: Thank you for your proposition. However we think a concise table like this is more informative. We added age groups in the table.

Table 2. ECG parameters in conduction system disease in COVID-19 mortality patients

ECG parameters prevalence		Patients without conduction system disorder (N=317)	Patients with conduction system disorder (N=108)	Univariate OR (95% CI for OR)	P value	Adjusted odds ratio (95% CI for OR)	
Fragmented QRS	Yes	53 (58.2)	38 (41.8)	2.63 (1.61-4.30)	<0.001	2.27 (1.41-3.61)	
	No	268 (78.6)	73 (21.4)	1	-	1	
ST-T change	Yes	125 (66.1)	64 (33.9)	2.14 (1.38-3.31)	0.001	1.81 (1.15-2.85)	
	No	196 (80.7)	47 (19.3)	1	-	1	
Rhythm	Sinus rhythm	279 (76.2)	87 (23.8)	1	-	1	
	AF	34 (63.0)	20 (37.0)	1.89 (1.03-3.45)	0.039	1.70 (0.78-3.71)	0.179
	others	8 (66.7)	4 (33.3)	1.60 (0.47-5.45)	0.450	0.75 (0.15, 3.62)	0.700
	Bradycardia (HR<60)	5 (55.6)	4 (44.4)	2.10 (0.55-8.01)	0.279	1.67 (0.31-9.06)	0.554
Rate	Normal (60<HR<100)	234 (72.4)	89 (27.6)	1	-	1	
	Tachycardia (HR>100)	82 (82.0)	18 (18.0)	0.58 (0.33-1.02)	0.057	0.55 (0.27, 1.09)	0.086
	Axis deviation	Normal	283 (83.7)	55 (16.3)	1	-	1
	Left	14 (48.3)	15 (51.7)	5.51 (2.52-12.07)	<0.001	3.74 (1.50-9.33)	0.005
	Right	24 (36.9)	41 (63.1)	8.79 (4.92-15.71)	<0.001	7.67 (3.95-14.88)	<0.001
QTc 1	<500	211 (75.1)	70 (24.9)	1	-	1	
	>500	110 (73.3)	40 (26.7)	1.10 (0.70-1.72)	0.691	0.94 (0.53, 1.66)	0.819
QTc 2	Male <=440 and Female <=460	300 (74.4)	103 (25.6)	1	-	Not included due to collinearity with the above variable	
	Male >440 Female >460	21 (75.0)	9 (25.0)	0.97 (0.40-2.35)	0.948		
QTd	<40	45 (81.8)	10 (18.2)	1	-	1	
	>=40	276 (73.2)	101 (26.8)	1.65 (0.80-3.39)	0.176	1.42 (0.58-3.47)	0.446
J wave	Yes	13 (68.4)	6 (31.6)	1.35 (0.50-3.65)	0.550	0.98 (0.28-3.49)	0.978
	No	308 (74.6)	105 (25.4)	1	-	1	
U wave	Yes	32 (71.1)	13 (28.9)	1.20 (0.60-2.38)	0.605	1.10 (0.47, 2.63)	0.815
	No	289 (74.7)	98 (25.3)	1	-	1	
Early repolarization	Yes	15 (83.3)	108 (26.1)	0.57 (0.16-2.00)	0.377	1.00 (0.26-3.93)	0.998
	No	306 (73.9)	108 (26.1)	1	-	1	
T slope	<30	12 (75.0)	4 (25.0)	1	-	1	
	30-60	302 (74.6)	103 (25.4)	1.02 (0.32-3.24)	0.969	0.79 (0.21, 2.98)	0.728
	>60	7 (63.6)	4 (36.4)	1.71 (0.32-9.11)	0.527	1.87 (0.249-14.01)	0.551
SIQ3T3	Yes	38 (61.3)	24 (38.7)	2.05 (1.17-3.61)	0.012	1.83 (0.92-3.64)	0.086
	No	283 (76.5)	87 (23.5)	1	-	1	
Low voltage QRS	Yes	42 (85.7)	7 (14.3)	0.45 (0.20-1.03)	0.058	0.38 (0.14-1.05)	0.063
	No	279 (72.8)	104 (27.2)	1	-	1	
PRP	Yes	121 (68.4)	56 (31.6)	1.68 (1.09-2.60)	0.019	1.32 (0.77-2.26)	0.317
	No	200 (78.4)	55 (21.6)	1	-	1	

批注 [RV20]: We have revised this table extensively. Firstly the result from multivariate logistic regression was missing which is now added. Secondly, QTd (QT dispersion) row was edited reported inversely, which is now corrected

Abbreviations: AF: atrial fibrillation, MI: Myocardial Infarction, AVB: Atrioventricular block, LVH: left ventricular hypertrophy, RVH: right ventricular hypertrophy, RBBB: right bundle branch block, LBBB: left bundle branch block, QTc: corrected Q-T interval, QTd: Q-T interval dispersion, T slope: T-wave terminal slope, PRP: Poor R wave Progression.

*Adjusted for age, sex, underlying diseases, and other ECG findings.