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Cardiac dysrhythmia in COVID-19 patients; occurrence and risk factors: a retrospective cohort study

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Abstract: **Objective:** In this study, we have evaluated the occurrence and risk factors of cardiac dysrhythmia on admission and during hospitalization in COVID-19 patients.

Methods: This study was conducted as a retrospective cohort in which 893 electrocardiograms (ECGs) taken at the time of admission, and 328 ECGs taken during hospitalization were evaluated. These ECGs were assessed for cardiac dysrhythmias by a cardiologist. Finally, relationships between clinical characteristics and the occurrence of cardiac dysrhythmias in patients were assessed.

Results: Most common cardiac dysrhythmias on admission were sinus tachycardia (64.8%), atrial fibrillation (13.5%), and sinus bradycardia (11.3%). Multivariate regression analysis showed that a history of metformin use (RR=0.83; P=0.042) was independently associated with reduced risk of cardiac dysrhythmias on admission, while male sex (RR=1.16; P=0.018), history of cardiovascular diseases (RR=1.16; P=0.017), history of cancer (RR=1.40; P=0.004) and QT interval prolongation on ECG (RR=1.18; P=0.017) were associated with a higher risk of cardiac dysrhythmias on admission. Also, among the 328 patients that had a second ECG, 185 (56.4%) experienced cardiac dysrhythmias during their hospitalization. Multivariate analysis showed that presence of cardiac dysrhythmias on admission (RR=1.85; 95% CI: 1.49,2.35; P<0.001) was the only independent prognostic factor for the occurrence of cardiac dysrhythmias during hospitalization. No significant relationships were observed between treatment regimens and the incidence of cardiac dysrhythmias.

Conclusion: The present study showed that more than half of COVID-19 patients have cardiac dysrhythmias on admission. Our analyses illustrated that a history of metformin use was associated with a lower risk of cardiac dysrhythmias on admission, while male sex, history of cardiovascular diseases, history of cancer, and QT interval prolongation were associated with a higher rate of cardiac dysrhythmias. Hydroxychloroquine use along with azithromycin and kaletra (lopinavir-ritonavir) had no association with the development of cardiac dysrhythmias during hospitalization.

Keywords: Cardiac Arrhythmia; COVID-19; Electrocardiography

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1. Introduction

Coronavirus disease 2019 (COVID-19) spread from Wuhan, China in December 2019 and the ensuing pandemic caused more than 100 million cases of disease and more than 2 million deaths (1). Since angiotensin converting enzyme 2 (ACE-II) is the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and regarding the extent of its distribution in various tissues, symptoms of COVID-19 range from a mild respiratory infection to cardiac, renal, gastrointestinal, and neurological involvement (2-5). According to previous studies, cardiovascular involvement in COVID-19 can present as myocarditis, cardiomyopathies, ischemic disorders, and cardiac dysrhythmias even without pulmonary involvement (5,6). These complications can be related to direct effects of the virus on the cardiac tissue the follow-

ing inflammation, or can be caused by systemic inflammation, hemostatic instability, and coagulation abnormalities (7). Systemic inflammation and cardiac tissue involvement can cause changes in cardiac muscle tissue and its electrical activity (8). Available evidences show that older age, presence of underlying diseases, and certain medications increase the risk of cardiac dysrhythmias (9,10). Sinus tachycardia, atrial fibrillation (AF), and ventricular tachycardia (VT) are some of the most important cardiac dysrhythmias that are associated with higher rates of mortality in hospitalized COVID-19 patients (11,12).

Previously, it has been shown that age and underlying diseases are associated with severe forms of COVID-19 (13). Also, occurrence of cardiac dysrhythmias and electrocardiographic abnormalities, both as a result of medications or a direct result of SARS-CoV-2 virus invasion, have been reported (14). Therefore, considering that the occurrence of cardiac dysrhythmias is associated with higher rates of COVID-19 related mortality, and due to the fact that factors causing cardiac dysrhythmias are prevalent in severe COVID-19 patients, it is important to assess the risk factors of cardiac dysrhythmias in COVID-19 patients. As there is a paucity of studies on this matter, the current retrospective cohort study evaluates the incidence and independent risk factors of cardiac dysrhythmias in COVID-19 patients on admission and during hospitalization.

2. Methods

2.1. Study design

This retrospective cohort study is conducted on 991 cases of COVID-19 patients that were admitted to Imam Hussein hospital, Tehran, Iran from February 18 to July 20, 2020. The study is approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1399.180).

2.2. Subjects

All confirmed COVID-19 patients with an electrocardiogram (ECG) at the time of admission were included in the present study.

COVID-19 infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in all patients.

Exclusion criteria were the absence of required information in patient profiles and an asystole ECG on admission. In total, 893 patients had an ECG on admission and 328 had a second ECG that was acquired during their hospitalization (Appendix 1).

2.3. Data collection

Baseline and demographic characteristics of the patients were extracted from the hospital database. All ECGs were evaluated by two independent cardiologists and any disagreement between them was resolved by discussion with a third cardiologist. The findings of the first and the second ECGs of patients (if available) were recorded separately in the statistical software.

All ECGs were standard 12 lead electrocardiograms. If an abnormality was present in at least two ECG leads, that was recorded as a definite abnormal finding in the study. Recorded cardiac dysrhythmias, included sinus tachycardia, sinus bradycardia, AF, atrial flutter, atrial tachycardia (AT), multifocal atrial tachycardia (MAT), premature ventricular contractions (PVCs), premature atrial contractions (PACs), and VT.

In order to evaluate the factors influencing the presence of cardiac dysrhythmia on admission, demographic and clinical characteristics of the patients including age, sex, body mass index (BMI) in addition to underlying diseases, drug history, and laboratory findings were recorded. Furthermore, for evaluation of factors affecting the occurrence of cardiac dysrhythmia during hospitalization, prescribed drugs during hospitalization, and presence of cardiac dysrhythmia on admission were analyzed.

2.4. Statistical analysis

The mean (standard deviation) and frequency (percentages) were used to describe continuous and categorical data, respectively.

We checked normality assumption of data by checking kurtosis, skewness, box plot and Q-Q plot. T-test or Mann-Whitney U test (for non-normally distributed variables) were used for comparing the continuous variables in both groups of with and without cardiac dysrhythmia. Categorical variables were analyzed using the chi-squared test, or the Fisher's exact test. A multivariate log binomial regression model was performed to investigate the association between cardiac dysrhythmia on admission and during hospitalization with underlying diseases, drug history, prescribed drugs during hospitalization, and demographic information. Final model was selected according to backward Wald. Findings were reported as relative risk ratio (RR) and its 95% confidence interval (95% CI). Two-sided P-value less than 0.05 was considered statistically significant. Analyses were performed using the STATA 14.0 software.

3. Results

3.1. Epidemiological characteristics and clinical findings

Eight hundred ninety three patients hospitalized with diagnosis of COVID-19 were included in this study. Mean age of the patients was 61.8±17.1 years (10 to 99 years) and 491 (55%) were male. Mean BMI in this population was 26.9±4.9 kg/m^2 (15.5 to 56.1).

Duration of hospitalization had a mean of 7.9±6.8 days (1 to 80). Hypertension (n=369; 41.3%), cardiovascular disease (n=297; 33.3%), diabetes mellitus (n=271; 30.3%), cerebrovascular disease (n=99; 11.1%), chronic kidney disease (n=95;

10.6%), chronic pulmonary disease (n=78; 8.7%) and cancer (n=38; 4.3%) were the most prevalent underlying diseases in the studied population. The medications that were used by the patients before hospitalization were as follows: aspirin (n=187; 20.9%), beta blockers including metoprolol, carvedilol, propranolol, and bisoprolol (n=141; 15.8%), ACE inhibitors and Angiotensin II receptor blockers (ARBs) including enalapril, captopril, and losartan (n=234; 26.2%), metformin (n=162; 18.1%) and atorvastatin (n=155; 17.4%). Medications used for the treatment of COVID-19 in hospital, included dexamethasone (n=257; 28.8%), hydroxychloroquine (n=486; 54.4%), azithromycin (n=266; 29.8%), kaletra (lopinavir / ritonavir) (n=486; 54.4%), interferon (n=339; 38%), remdesivir (n=36; 4%) and favipiravir (n=38; 4.3%). Other drugs that were used during the course of hospitalization were broad spectrum antibiotics including meropenem, cefepime and tazocin (piperacillin / tazobactam) (n=257; 28.8%), aspirin (n=312; 34.9%), ACE inhibitors and ARBs including enalapril, captopril and losartan (n=268; 30%), metformin (n=116; 13%), atorvastatin (n=393; 44%), beta blockers including metoprolol, carvedilol, propranolol and bisoprolol (n=201; 22.5%), and heparin (n=745; 83.1%) (Table 1). All patients had at least one ECG. Also, 328 of the patients had a second ECG during hospitalization. Table 2 summarizes the results of the first and second ECGs of the patients. The characteristics of the group with only one ECG at the time of admission and the group with a second ECG during hospitalization are summarized in appendix 1.

3.2. Cardiac dysrhythmia on admission

The most common type of cardiac dysrhythmia observed on admission was sinus tachycardia which was present in 315 (64.8%) patients. AF (11.5%), sinus bradycardia (11.3%), PVCs (4.9%), and PACs (4.7%) were the other common cardiac dysrhythmias. 297 of the 893 patients had a history of cardiovascular disease. After breaking down into two groups based on their history, 60.9% of the patients with and 51.2% of patients without history of cardiovascular disease had cardiac dysrhythmia on admission. Table 2 shows the prevalence of cardiac dysrhythmias according to the history of cardiovascular disease.

Univariate analyses showed that cardiac dysrhythmias were present in male COVID-19 patients more than females (RR=1.16; 95% CI: 1.02,1.31; P=0.021). In addition, cardiac dysrhythmia on admission had a significant association with previous history of cardiovascular disease (RR=1.18; 95% CI: 1.05,1.32; P=0.006) and a history of cancer (RR=1.28; 95% CI: 1.01,1.61; P=0.037). There was a possible association between reduced cardiac dysrhythmia on admission and a history of metformin use that was close to significance threshold (RR=0.84; 95% CI: 0.70,1.01; P=0.056). Furthermore, the presence of QT interval prolongation was significantly associated with the presence of cardiac dysrhythmias on admission (RR=1.21; 95% CI: 1.05,1.39; P=0.007).

Multivariate regression analysis was conducted to identify independent risk factors of cardiac dysrhythmia in COVID-19 patients on admission. History of metformin use (RR=0.83; 95% CI: 0.69,0.99; P=0.042) was independently associated with reduced risk of cardiac dysrhythmias on admission, whereas male sex (RR=1.16; 95% CI: 1.02,1.31; P=0.018), underlying cardiovascular disease (RR=1.16; 95% CI: 1.02,1.31; P=0.017), history of cancer (RR=1.40; 95% CI: 1.11,1.77; P=0.004), and presence of QT interval prolongation (RR=1.18; 95% CI: 1.03,1.35; P=0.017) were associated with increased risk of cardiac dysrhythmias on admission (Table 3).

3.3. Cardiac dysrhythmia during hospitalization

Among the 328 patients that had a second ECG, 185 (56.4%) experienced cardiac dysrhythmias during their hospitalization. Sinus tachycardia (54.1%), sinus bradycardia (18.9%), AF (15.7%), PACs (4.9%), PVCs (4.3%), VT (1.1%) and MAT (1.1%) were the most common cardiac dysrhythmias during hospitalization (Table 2).

Univariate analyses showed that older age (RR=1.01; 95% CI: 1.01,1.02; P=0.013) and cardiac dysrhythmia at the time of hospital admission (RR=1.95; 95% CI: 1.15,2.49; P<0.001) had a significant relationship with the occurrence of cardiac dysrhythmia during hospitalization. Combined hydroxychloroquine and azithromycin, combined hydroxychloroquine and kaletra and the use of all three medications combination were not significantly associated with the occurrence of cardiac dysrhythmia during hospitalization. Furthermore, heparin (RR=0.86; 95% CI: 0.68,1.02; P=0.181) or aspirin (RR=1.17; 95% CI: 0.97,1.42; P=0.091) administration was not significantly associated with the occurrence of cardiac dysrhythmias during hospitalization.

Multivariate analysis showed that the presence of cardiac dysrhythmia on admission (RR=1.85; 95% CI: 1.49,2.35; P<0.001) was the only independent risk factor for the occurrence of cardiac dysrhythmia during hospitalization (Table 4).

4. Discussion

This study's findings showed that cardiac dysrhythmias are a common phenomenon in COVID-19 patients, that occur even when a history of cardiovascular disease is not present. Cardiac dysrhythmias on admission are more common in male patients, patients with a history of cardiovascular disease or cancer, and patients with a QT interval prolongation on ECG. Moreover, a history of metformin use is associated with a lower risk of cardiac dysrhythmia on admission. It is worth noting that cardiac dysrhythmias are also present during hospitalization in patients with previous cardiac dysrhythmia on admission, and dysrhythmia on admission was the only predictive factor for dysrhythmia during hospitalization.

In line with previous studies, findings of the current study, state that the use of hydroxychloroquine along with other medications used for treatment of COVID-19 is not associ-

Table 1 Baseline characteristics of COVID-19 patients

Variables	Cardiac dysrhythmia on admission				Cardiac dysrhythmia during hospitalization			
	Yes (N=486)	No (N=407)	Total (N=893)	P-value	Yes (N=185)	No (N=143)	Total (N=328)	P-value
Demographics								
Gender (%)								
Male	282 (49)	209 (51)	491 (100)	0.046	103 (58.2)	74 (41.8)	177 (100)	0.405
Female	204 (50.7)	198 (49.3)	402 (100)		82 (54.3)	69 (55.7)	151 (100)	
Age (year)								
Mean ± SD	62.18±17.83	61.30±16.28	61.78±17.13	0.440	65.13±17.98	60.80±16.59	63.24±17.49	0.018
Body mass index (kg / m^2)								
Mean ± SD	27.09 ±5.11	26.87 ±4.60	26.99±4.88	0.499	27.20±5.27	26.89±4.54	27.07±4.96	0.575
Length of stay (day)								
Mean ± SD	8.41±7.79	7.23±5.18	7.87±6.75	0.007	9.59±8.11	9.19±6.47	9.42±7.43	0.607
Medical history								
Hypertension (%)								
Yes	202 (54.7)	167 (45.3)	369 (100)	0.872	83 (53.2)	73 (46.8)	156 (100)	0.324
No	284 (54.2)	240 (45.8)	524 (100)		102 (59.3)	70 (40.7)	172 (100)	
Cardiovascular disease (%)								
Yes	181 (60.9)	116 (39.1)	297 (100)	0.006	84 (62.6)	50 (37.4)	134 (100)	0.042
No	305 (51.2)	291 (48.8)	596 (100)		101 (52)	93 (48)	194 (100)	
Diabetes mellitus (%)								
Yes	142 (52.4)	129 (44.7)	271 (100)		52 (46.8)	59 (53.2)	111 (100)	0.018
No	344 (55.3)	278 (44.7)	622 (100)	0.423	133 (61.3)	84 (38.7)	217 (100)	
Central nervous system diseases (%)								
Yes	62 (62.6)	37 (37.4)	99 (100)		23 (63.8)	13 (36.2)	36 (100)	
No	423 (53.3)	370 (46.7)	793 (100)	0.080	162 (55.4)	130 (44.6)	292 (100)	0.337
Chronic kidney disease (%)								
Yes	48 (50.5)	47 (49.5)	95 (100)		21 (51.2)	20 (48.8)	41 (100)	
No	438 (54.9)	360 (45.1)	798 (100)	0.420	164 (57.1)	123 (42.9)	287 (100)	0.474
Respiratory diseases (%)								
Yes	50 (64.1)	28 (35.9)	78 (100)		20 (62.5)	12 (37.5)	32 (100)	
No	436 (53.5)	379 (46.5)	815 (100)	0.072	165 (55.7)	131 (0.443)	296 (100)	0.446
Cancer (%)								
Yes	27 (71.1)	11 (28.9)	38 (100)		6 (50)	6 (50)	12 (100)	
No	459 (53.7)	396 (46.3)	855 (100)	0.035	179 (56.6)	137 (43.4)	316 (100)	0.649
Drug history								
Aspirin (%)								
Yes	107 (57.2)	80 (42.8)	187 (100)		45 (63.3)	26 (36.7)	71 (100)	
No	379 (53.7)	327 (46.3)	706 (100)	0.388	140 (54.4)	117 (45.6)	257 (100)	0.180
Atorvastatin (%)								
Yes	85 (54.8)	70 (45.2)	155 (100)		35 (59.3)	24 (40.7)	59 (100)	
No	401 (54.3)	337 (45.7)	738 (100)	0.909	150 (55.7)	119 (44.3)	269 (100)	0.618
ARBs and ACEIs (%)								
Yes	121 (51.7)	113 (48.3)	234 (100)	0.332	48 (52.7)	43 (47.3)	91 (100)	0.408
No	365 (55.4)	294 (44.6)	659 (100)		137 (57.8)	100 (42.2)	237 (100)	
Beta blockers (%)								
Yes	80 (56.7)	61 (43.3)	141 (100)		39 (60)	26 (40)	65 (100)	
No	406 (54)	346 (46)	752 (100)	0.548	146 (55.5)	117 (45.5)	263 (100)	0.514
Metformin (%)								
Yes	77 (47.5)	85 (52.5)	162 (100)		34 (52.3)	31 (47.7)	65 (100)	
No	409 (56)	322 (44)	731 (100)	0.052	151 (57.4)	112 (42.6)	263 (100)	0.457
Medication used during hospitalization								
Aspirin (%)								
Yes	-	-	-		91 (61.4)	57 (38.6)	148 (100)	0.092
No	-	-	-		94 (52.2)	86 (47.8)	180 (100)	
Atorvastatin (%)	-	-	-					
Yes	-	-	-		98 (59.7)	66 (40.3)	164 (100)	
No	-	-	-		87 (53)	77 (47)	164 (100)	0.221
ARBs and ACEIs (%)								
Yes	-	-	-		57 (51.8)	53 (48.2)	110 (100)	
No	-	-	-		128 (58.7)	90 (41.3)	218 (100)	0.234

Table 1 Baseline characteristics of COVID-19 patients (continued)

Variables	Cardiac dysrhythmia on admission				Cardiac dysrhythmia during hospitalization			
	Yes (N=486)	No (N=407)	Total (N=893)	P-value	Yes (N=185)	No (N=143)	Total (N=328)	P-value
Beta blockers (%)	-	-	-					
Yes	-	-	-		61 (63.5)	35 (36.5)	96 (100)	
No	-	-	-		124 (53.4)	108 (46.5)	232 (100)	0.093
Metformin (%)								
Yes	-	-	-		21 (48.8)	22 (51.2)	43 (100)	
No	-	-	-		164 (57.5)	121 (42.5)	285 (100)	0.283
Heparin (%)	-	-	-					
Yes	-	-	-		148 (54.8)	122 (45.2)	270 (100)	
No	-	-	-		37 (55.1)	21 (44.9)	58 (100)	0.211
Broad spectrum antibiotics (%)								
Yes	-	-	-		80 (64)	45 (36)	125 (100)	
No	-	-	-		105 (51.7)	98 (48.3)	203 (100)	0.029
Medicine for COVID-19 (%)	-	-	-					
Corticosteroids (%)								
Yes	-	-	-		50 (57.4)	37 (42.6)	87 (100)	
No	-	-	-		135 (56)	106 (44)	241 (100)	0.815
Hydroxychloroquine (%)	-	-	-					
Yes	-	-	-		95 (54.2)	80 (45.8)	175 (100)	
No	-	-	-		90 (58.8)	63 (41.2)	153 (100)	0.341
Azithromycin (%)								
Yes	-	-	-		60 (55.5)	48 (44.5)	108 (100)	
No	-	-	-		125 (56.8)	95 (43.2)	220 (100)	0.828
Kaletra (%)	-	-	-					
Yes	-	-	-		93 (56.3)	71 (43.7)	165 (100)	
No	-	-	-		92 (56.4)	72 (43.6)	163 (100)	0.889
Interferons (%)								
Yes	-	-	-		68 (54.8)	56 (45.2)	124 (100)	
No	-	-	-		117 (57.3)	87 (42.7)	204 (100)	0.656
Remdesivir (%)	-	-	-					
Yes	-	-	-		10 (66.6)	5 (33.4)	15 (100)	
No	-	-	-		175 (55.9)	138 (44.1)	313 (100)	0.412
Favipiravir (%)								
Yes	-	-	-		13 (65)	7 (35)	20 (100)	
No	-	-	-		172 (55.8)	136 (44.2)	308 (100)	0.424
Hydroxychloroquine and azithromycin (%)	-	-	-					
Yes	-	-	-		36 (49.3)	37 (50.7)	73 (100)	
No	-	-	-		149 (58.4)	106 (0.416)	255 (100)	0.166
Hydroxychloroquine and kaletra (%)								
Yes	-	-	-		46 (54.7)	38 (45.3)	84 (100)	
No	-	-	-		139 (56.9)	105 (43.1)	244 (74.4)	0.622
Hydroxychloroquine and kaletra and azithromycin (%)								
Yes	-	-	-		10 (43.4)	13 (56.6)	23 (100)	
No	-	-	-		175 (57.3)	130 (42.7)	305 (100)	0.195
In-hospital mortality (%)								
Yes	165 (70)	68 (30)	233 (100)	<0.001	83 (74.1)	29 (25.9)	112 (100)	
No	321 (48)	339 (52)	660 (100)		102 (47.2)	114 (52.8)	216 (100)	<0.001

SD: Standard deviation; ARBs: Angiotensin II receptor blockers; ACEIs: Angiotensin converting enzyme inhibitors

ated with higher risk of cardiac dysrhythmias, and therefore the use of these drugs does not confer additional risks to cardiac dysrhythmias in COVID-19 patients (15,16).

Previously, metformin was shown to have a protective effect on cardiovascular system, reducing the risk of myocardial infarction, mortality caused by cardiac events and all-cause mortality in patients with a history of coronary artery disease (CAD) (17). Also, there is evidence on metformin's protective effect against the occurrence of atrial cardiac dysrhythmias in diabetic patients (18). Considering that diabetes mellitus, CAD and other cardiovascular diseases are associated with severe forms of COVID-19, and are known as predisposing factors for atrial and ventricular cardiac dysrhythmias, metformin use may have a protective effect against the responsible mechanisms for the occurrence of cardiac dysrhythmias. Although in the current study it was found that cardiac dys-

Table 2 Frequency of type of dysrhythmia according to time of assessment in patients with COVID-19

Dysrhythmia types (%)	Dysrhythmia on admission			Dysrhythmia during hospitalization		
	History of CVD		Total (N=486)	History of CVD		Total (N=185)
	Yes (N=181)	No (N=305)		Yes (N=84)	No (N=101)	
Sinus tachycardia	92 (50.8)	223 (73.1)	315 (64.8)	36 (42.9)	64 (63.4)	100 (54.1)
Sinus bradycardia	20 (11.0)	35 (11.5)	55 (11.3)	13 (15.5)	22 (21.8)	35 (18.9)
Atrial fibrillation	36 (19.9)	20 (6.6)	56 (11.5)	22 (26.2)	7 (6.9)	29 (15.7)
Atrial flutter	2 (1.1)	1 (0.3)	3 (0.6)	—	—	—
Atrial tachycardia	2 (1.1)	1 (0.3)	3 (0.6)	—	—	—
Multifocal atrial tachycardia	1 (0.6)	2 (0.7)	3 (0.6)	1 (1.2)	1 (1.0)	2 (1.1)
Premature ventricular contractions	13 (7.2)	11 (3.6)	24 (4.9)	4 (4.8)	4 (4.0)	8 (4.3)
Premature atrial contractions	13 (7.2)	10 (3.3)	23 (4.7)	7 (8.3)	2 (2.0)	9 (4.9)
Ventricular tachycardia	2 (1.1)	2 (0.7)	4 (0.8)	1 (1.2)	1 (1.0)	2 (1.1)

CVD: Cardiovascular disease

Table 3 Factors associated with dysrhythmia on admission time in hospitalized patients with COVID-19

Variables	Univariate		Multivariate	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Gender			-	-
Female	1		1	-
Male	1.16 (1.02-1.31)	0.021*	1.16 (1.02-1.31)	0.018*
History of cardiovascular disease		-	-	
No	1			
Yes	1.18 (1.05-1.34)	0.006*	1.16 (1.02-1.31)	0.017*
History of cancer				
No	1		-	-
Yes	1.28 (1.01-1.61)	0.037*	1.40 (1.11-1.77)	0.004*
History of using metformin		-	-	
No	1		1	-
Yes	0.84 (0.70 -1.01)	0.056	0.83 (0.69-0.99)	0.042*
Underlying respiratory disorders				
No	1			
Yes	1.08 (0.98-1.42)	0.068	1.18 (0.99-1.40)	0.059
QT interval prolongation		-	-	
No	1		-	-
Yes	1.21(1.05-1.39)	0.007*	1.18 (1.03-1.35)	0.017*

RR: Relative risk; CI: Confidence interval
* P<0.05 was statistically significant

Table 4 Factors associated with dysrhythmia during hospitalization in patients with COVID-19

Variables	Univariate		Multivariate	
	RR (95% CI)	P-value	RR (95% CI)	P-value
Age	1.01 (1.01-1.02)	0.013*	1.00 (0.99-1.01)	0.101
Cardiac dysrhythmia on admission		-	-	
No	1		1	
Yes	1.95 (1.152-2.49)	<0.001*	1.85 (1.49-2.35)	<0.001*
Using heparin during hospitalization		-	-	
No	1		1	
Yes	0.86 (0.68-1.02)	0.181	0.89 (0.74-1.07)	0.226
Using aspirin during hospitalization		-	-	
No	1		-	-
Yes	1.17 (0.97-1.42)	0.091	1.09 (0.91-1.30)	0.325

RR: Relative risk; CI: Confidence interval

rhythmia on admission was the only prognostic factor for the occurrence of cardiac dysrhythmia during hospitalization, this result should be interpreted with caution. In this study only 328 patients had a second ECG. Routinely, second ECG is acquired when the physician is suspicious of a clinical condition. Therefore, it is possible that the presence of cardiac dysrhythmia on admission had persuaded the physician to order a second ECG which would lead to a falsely increased prognostic role of cardiac dysrhythmia on admission for the re-occurrence of cardiac dysrhythmia during hospitalization.

5. Limitations

Due to study's retrospective nature, the quality control of acquired ECGs from patients was not possible. Moreover, the second ECG was not acquired at the same time interval for all patients. Consequently, some patients could have been in the hospital for a longer period and received more medication, or been in a more severe stage of disease when second ECG was taken. Also, dosage of prescribed medications in patients was not the same, which can be a possible source of bias. Another limitation was the lack of the second ECG in all studied patients. As ECG is usually done only when ordered, and physicians order a second ECG when there is doubt for cardiovascular complications, it is possible that the incidence of cardiac dysrhythmias in patients during hospitalization may be overestimated in this study.

6. Conclusion

Findings of the present study suggest that more than half of the patients with COVID-19 infection have cardiac dysrhythmias on admission. Our analyses suggest that a history of metformin use is associated with a lower risk of cardiac dysrhythmia on admission, whereas male sex, underlying cardiovascular disease, history of cancer and the presence of QT interval prolongation are associated with a higher risk of dysrhythmia occurrence. It is worth noting that using hydroxychloroquine with azithromycin or kaletra for treatment of COVID-19 was not associated with a higher incidence of cardiac dysrhythmias during hospitalization.

7. Declarations

7.1. Acknowledgment

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7.2. Authors' contributions

Study design: MHA, MS, MY; Data gathering: MHA, MS, ZA, AP, FNA, AH, RM, MY; Analysis: AP; Interpretation of results: All authors; Drafting: AT, AMN, MY; Critically revised: All authors;

7.3. Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Appendix 1 Comparison of characteristics between the group with only an ECG at the time of admission and the group who required ECG during hospitalization

Variables	Only ECG on admission (N= 565)	Requiring second ECG (N=328)	P-value
Demographics			
Gender (%)			
Male	315 (64.2)	176 (35.8)	0.544
Female	250 (62.2)	152 (37.8)	
Age			
(mean ± SD)	61.01±16.8	63.299±17.3	0.064
Body mass index (kg / m^2)			
(mean ± SD)	26.94±4.83	27.06±4.96	0.505
Medical history			
Hypertension (%)			
Yes	214 (58.0)	155 (42.0)	0.006
No	351 (67.0)	173 (33.0)	
Cardiovascular disease (%)			
Yes	164 (55.2)	133 (44.8)	<0.0001
No	401 (67.3)	195 (32.7)	
Diabetes mellitus (%)			
Yes	161 (59.4)	110 (40.6)	0.114
No	404 (65.0)	218 (35.0)	
Central nervous system diseases (%)			
Yes	63 (63.6)	36 (36.4)	0.929
No	501 (63.2)	292 (36.8)	
Chronic kidney disease (%)			
Yes	54 (56.8)	41 (43.2)	0.169
No	511 (64.0)	287 (36.0)	
Respiratory diseases (%)			
Yes	46 (59.0)	32 (41.0)	0.410
No	519 (63.7)	296 (36.3)	
Cancer (%)			
Yes	26 (68.4)	12 (31.6)	0.501
No	539 (63.0)	316 (37.0)	
Drug history			
Aspirin (%)			
Yes	116 (62.0)	71 (38.0)	0.693
No	449 (53.6)	257 (36.4)	
Atorvastatin (%)			
Yes	96 (61.9)	59 (38.1)	0.705
No	469 (63.6)	269 (36.4)	
ARBs and ACEIs (%)			
Yes	143 (61.1)	91 (38.9)	0.425
No	422 (64.0)	237 (36.0)	
Beta blockers (%)			
Yes	76 (53.9)	65 (46.1)	0.012
No	489 (65.0)	263 (35.0)	
Metformin (%)			
Yes	97 (59.9)	65 (40.1)	0.322
No	468 (64.0)	263 (36.0)	
Medication used during hospitalization			
Aspirin (%)			
Yes	164 (52.6)	148 (47.4)	<0.0001
No	401 (69.0)	180 (31.0)	

Appendix 1 Comparison of characteristics between the group with only an ECG at the time of admission and the group who required ECG during hospitalization (continued)

Variables	Only ECG on admission (N= 565)	Requiring second ECG (N=328)	P-value
Atorvastatin (%)			
Yes	336 (67.2)	164 (32.8)	0.006
No	229 (58.3)	164 (41.7)	
ARBs and ACEIs (%)			
Yes	158 (59.0)	110 (41.0)	0.080
No	407 (65.1)	218 (34.9)	
Beta blockers (%)			
Yes	105 (52.2)	96 (47.8)	<0.0001
No	460 (66.5)	232 (33.5)	
Metformin (%)			
Yes	73 (62.9)	43 (37.1)	0.935
No	492 (63.3)	285 (36.7)	
Heparin (%)			
Yes	472 (63.6)	270 (36.4)	0.638
No	93 (61.6)	58 (38.4)	
Broad spectrum antibiotics (%)			
Yes	132 (51.4)	125 (48.6)	<0.0001
No	433 (68.1)	203 (31.9)	
Medication for COVID-19 (%)			
Corticosteroids (%)			
Yes	170 (66.1)	87 (33.9)	0.257
No	395 (62.1)	241 (37.9)	
Hydroxychloroquine (%)			
Yes	310 (63.8)	176 (36.2)	0.727
No	255 (62.7)	152 (37.3)	
Azithromycin (%)			
Yes	158 (59.4)	108 (40.6)	0.118
No	407 (64.9)	220 (35.1)	
Kaletra (%)			
Yes	320 (65.8)	166 (34.2)	0.081
No	245 (60.2)	162 (39.8)	
Interferons (%)			
Yes	215 (63.4)	124 (36.6)	0.941
No	350 (63.2)	204 (36.8)	
Remdesivir (%)			
Yes	21 (58.3)	15 (41.7)	0.531
No	544 (63.5)	313 (36.5)	
Favipiravir (%)			
Yes	18 (47.4)	20 (52.6)	0.038
No	547 (64.0)	308 (36.0)	
Hydroxychloroquine and azithromycin (%)			
Yes	118 (63.7)	73 (36.3)	0.630
No	447 (61.8)	255 (38.2)	
Hydroxychloroquine and kaletra (%)			
Yes	181 (68.0)	85 (32.0)	0.054
No	384 (61.2)	243 (38.8)	
Hydroxychloroquine and kaletra and azithromycin (%)			
Yes	63 (73.3)	23 (26.7)	0.043
No	502 (62.2)	305 (37.8)	

Appendix 1 Comparison of characteristics between the group with only an ECG at the time of admission and the group who required ECG during hospitalization (continued)

Variables	Only ECG on admission (N= 565)	Requiring second ECG (N=328)	P-value
In-hospital mortality (%)			
Yes	122 (52.6)	110 (47.4)	<0.0001
No	443 (67.0)	218 (33.0)	
Length of stay			
(mean ± SD)	6.98±6.17	9.37±7.36	<0.0001

ECG: Electrocardiogram; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; SD: Standard deviation