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Clinical Importance of QT Dispersion in Newly Diagnosed Non Cardiac COVID-19 Patients

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ABSTRACT

Background: Although COVID-19 primarily presents with respiratory-related symptoms, there is interplay between COVID-19 and the cardiovascular system. The aim of the present study was to detect QT/QT dispersion in COVID-19 non-cardiac patients.

Methods: These prospective cohort studyincluded patients admitted to isolation department at Zagazig University Hospitals. The data was collected from the pre-treated COVID-19 patientswho diagnosed according to the World Health Organization.Electrocardiogram (ECG), echocardiography forLVEF, presence of wall motion abnormality, E, E/A, ē –TD, E/ē, LA Volume and LAVI were performed.

Results: COVID-19 patients who had DM showed higher incidence of MACE 10.0%(p=0.012), and 18.9% of diabetic patients suffered from MACEs.There was a statistically significant higher value of D dimer, FBS, WBC and neutrophil among COVID19 patients who developed MACEs compared to other COVID19 patients (p<0.05 The best cut-off value of QTc in the prediction of MACEs was ≥443.5 msec Logistic regression analysis identified that independent predictors of MACEs occurrence among COVID-19 patients were increase: temperature, FBS, WBCs, neutrophil, D-dimer,Qtc; odds of having MACEs is 11.2 times greater in presence of diastolic dysfunction, 8 times greater in presence of ECG abnormality as opposed to normal.

Conclusion: We confirmed that there is an increase of QT dispersion (as an ECG predictors) in COVID-19 patients before treatment compared to recovery. There is a good relation between occurrence of MACEs in COVID-19 patients and QTc.

Keywords: COVID-19; QT Dispersion; MACEs; cardiac complications .

INTRODUCTION

In December 2019, the world started to face a new pandemic situation. This new virus (SARS-CoV-2) belongs to the same sever acute respiratory syndrome –coronavirus (SARS-COV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) family. After this virus appeared in Wuhan-China, coronavirus disease 2019 (COVID-19) began to spread rapidly to the world. Although most of the clinical findings of the disease belong to the respiratory system in COVID-19, complications of the cardiovascular system such as myocardial damage, hypoxia, hypotension, increased inflammatory response and proarrhythmic changes have also started to be reported. Studies evaluating COVID-19 patients presenting with increased cardiac involvement show that it is associated with poorer outcomes, and arrhythmic events are not uncommon **(1).**

We defined the pandemic period after 11 March 2020 , according to the World Health Organization (WHO) declaration of the COVID-19 pandemic **(2)**. Its cardiovascular effects include myocardial damage, thromboembolic events, and fatal arrhythmias. In fact, similar viruses have arrhythmogenic potential; there is higher probability of arrhythmia for the disease due to the medications used for COVID-19. Several surface electrocardiographic (ECG) markers like QT interval and QT dispersion (QTd), T wave peak-to-end interval (Tp-e) and Tp-e/ QTc ratio have been used to predict the risk of ventricular arrhythmias **(3).**

Acute myocardial damage, arrhythmia, and cardiogenic shock have been demonstrated in adult COVID-19 infection. Arrhythmias may be the first clinical sign of COVID-19 infection, besides drugs such as hydroxychloroquine (HCQ) and azithromycin which are used to treat the disease may increase the risk of arrhythmia **(4).**

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Ventricular repolarization parameters can be measured in the electrocardiogram (ECG) by the QT interval, QT dispersion and T wave measurements **(5).** Increased dispersion of ventricular repolarization showing heterogeneity of repolarization is an important marker of ventricular arrhythmias **(6).**

The aim of the present study was to detect QT/QT dispersion in COVID-19 non-cardiac patients.

METHODS

This prospective cohort studyincluded 70 patients admitted to isolation department at Zagazig University Hospitals.The data was collected from the pre-treated COVID-19 patients who diagnosed according to the World Health Organization. An informed written consent was obtained from each patient, after approval from our ethical committee.

Including COVID-19 patients above 18 years confirmed diagnosis by RT-PCR or nasopharyngeal swab or COVID-19 highly suspected patients based on history, clinical and imaging finding even in the absence of positive nasopharyngeal swab, who were on cardiac.Patient with recent non Covid-19 infection, pregnant females, Patients with malignancies or inflammatory disease,known coronary artery disease or other cardiac disease and patients using QT interval lengthening drugs,patients with electrolyte disturbance (hypokalemia,hypomagnesemia and hypocalcemia), were excluded from the study.

Clinical Assessment:

All patients were subjected to detailed history taking, thoroughclinical examination, electrocardiogram (ECG), echocardiographic study of (LVEF, presence of wall motion abnormality, mitral E wave velocity by pulsed wave (PW- Doppler) and E/A, average, ē wave velocity by tissue Doppler (ē –TD) and E/ē, estimation of left atrial volume(LAV) and index(LAVI).

Laboratory tests including; complete blood count (CBC), fasting plasma glucose (FBG), ESR, CRP, D-dimer, Serum ferritin, creatinine level, serum electrolytes (K, Ca and Mg)and Troponin I level were done.

Measurement of QT dispersion:

QT and the preceding RR intervals were assessed manually with calipers and mean values were determined in three consecutive cycles. QT intervals were measured in all possible leads from the beginning of the QRS complex to the point of T wave offset, i.e. the point of the return of the T wave to the isoelectric line. In the presence of the U wave interrupting the T wave, the nadir between the T and U waves was used to definethe point of T wave offset.QT dispersion (QTd) in milliseconds was calculated as the difference between the shortest (QTmin) and longest (QTmax) for the mean QT interval in each electrocardiogram. QTd = (QTmax)-(QTmin), Corrected QTd (QTdc) were also measured **(7)**.

Follow up:

All ECG and Echocardiographic parameters were repeated one month after patient recovery (based on improvement of symptoms, investigation and /or negative nasopharyngeal swab) and compared with basal ones.

Statistical analysis:

All data were analyzed using the IBM SPSS (Statistical Package for the social sciences) statistics for windows, version 23.0 IBM Corp., Armonk, NY: USA. Quantitative data were expressed as mean±SD and median (range). A qualitative data were expressed as absolute frequencies (number)and relative frequencies (percentage). Shapiro Walk test, Independent samples Student's t-test, Mann Whitney U test, Wilcoxon Signed Ranks Test, Kruskal Wallis Test, Chi-square test or Fisher's exact test were used. P-value < 0.05 was considered statistically significant (S), p-value <

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0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered statistically insignificant (NS). Receiver operating characteristic (ROC) curve analyses were performed to determine the best cut-off value of QTdc. Logistic regression analysis was performed to identify the independent predictors for occurrence of MACE among studied COVID-19 patients.

RESULTS

The studyincluded 70 patients;mean age 48.443±16.3years old **(Figure 1)**, details of demographic data as shown in **(Table 1)** and vital signs as shown in (Table 2).The QTc for studied patients was shown in **(Figure 2)**.

There was statistically significant higher value of QTd, among COVID-19 patients at admission (pre-treatment) compared to after recovery; p<0.001**(Figure 3)**. Incidence of MACEs among studied COVID-19 patients was 10.0% **(Figure 4)**.

There was a statistically significant relation between MACEs of COVID-19 patients and DM (p=0.012). It is obvious that 18.9% of diabetic patients suffered from MACEs **(Table 3)**.There was a statistically significant higher value of D- dimer, FBS, WBC and neutrophil among COVID19 patients developed MACEs compared to other COVID19 patients p<0.05 **(Table 4)**. There was a statistically significant relation between MACEs of COVID-19 patients and diastolic dysfunction (p=0.014), ECG abnormality (0.018). It is obvious that COVID- 19 patients suffered from diastolic dysfunction, ECG abnormality were more liable to MACEs. Also there was statistically significant higher value of QTc among COVID 19 patients developed MACEs compared to other COVID-19 patients p<0.05 **(Table 5)**.

The best cut-off value of QTc in the prediction of occurrence MACEs among COVID19 patients was ≥443.5 msec using ROC curve; area under curve (AUC) was 0.749. So, QTc at this cutoff could be a good parameter to discriminate MACEs susceptible COVID-19 patients **(Figure5)**. QTc is valid in the prediction of o MACEs among COVID-19 patients**(Table 6)**.

Logistic regression analysis identified that independent predictors of occurrence MACEs among COVID-19 patients were increase: temperature, FBS, WBCs, neutrophil, D-dimer,Qtc all were associated with an increased likelihood of exhibiting MACEs. Also, odds of having MACEs is 11.2 times greater in presence of diastolic dysfunction, 8 times greater in presence of ECG abnormality as opposed to normal **(Table 7)**.

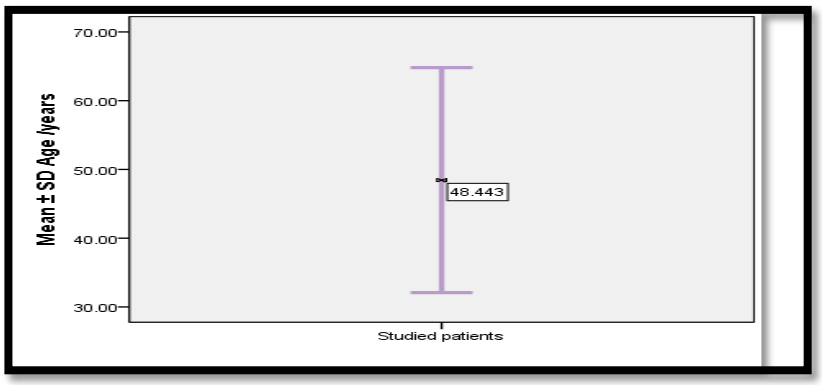

Figure (1):Mean age for the studied patients

Table (1):Demographic, medical data of studied group (n.70):

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Variables		
Age per years Mean ± SD (range)	48.443±16.3 (19-79)	
Gender	n.	%
Females	26	37.1
Males	44	62.9
Risk factors DM HTN	 37 36	 52.9 51.4
Smokers	22	31.4

SD =standard deviation, DM=diabetes mellitus, HTN=hypertention.

Table (2): General examination of studied group (n=70):

Variables	Mean ± SD	Median (range)
BMI	27.29±4.2	26.95(17.5-39.3)
HR	82.77±10.75	(60-99)
Temperature	38.63±0.56	38.5(37.5-40)
Systolic blood pressure	126.36±20.7	120(90-180)
Diastolic blood pressure	76.31±13.3	80(50-100)
O2.saturation	93.21±4.6	95(80-99)

BMI=body mass index, HR=heart rate

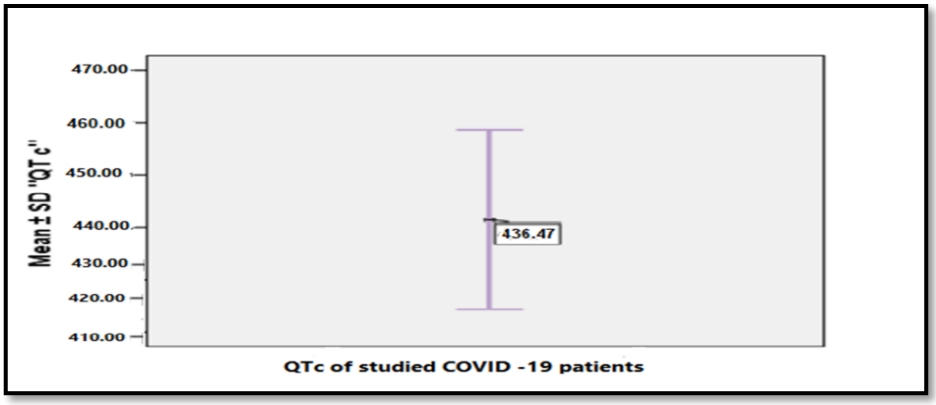

Figure (2): Mean± SD of (QTc) for studied patients

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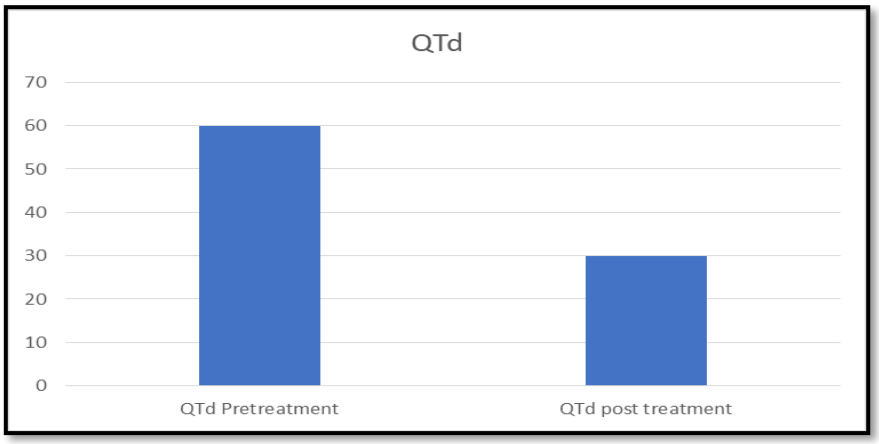

Figure (3) :Comparison of median of QTd of studied group at admission and after recovery of COVID19 patients.

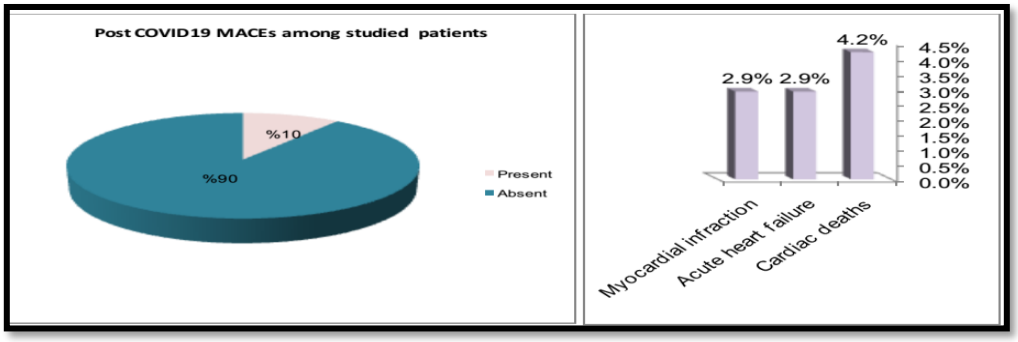

Figure (4): Incidence of MACEs and its types among studied COVID19 patients

Table (3): Relation between MACEs among COVID19 patients with their demographic and medical history:

Variables	MACEs				p-value
	Yes		No		
Age per years Mean ±SD	58.85±17.2		47.28±15.9		0.076
BMI Mean ±SD	30.02±5.5		26.99±3.9		0.070
	No.	%	No.	%	
Sex					
Males	5	11.4	39	88.6	0.99
Females	2	7.7	24	92.3	
DM	-	-	-	-	
Yes	7	18.9	30	81.1	0.012
No	0	0	33	100.0	(S)
HTN	-	-	-	-	
Yes	4	11.1	32	88.9	0.99
No	3	8.8	31	91.2	
Smoker	-	-	-	-	
Yes	3	13.6	19	86.4	0.67
No	4	8.3	44	91.7	

Table (4): Relation between MACEs among COVID19 patients with their laboratory finding:

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	MACEs		t/u	p-value
	Yes	No		
D dimer	2.3(0.2-4.3)	0.4(0-4.9)	3.043	0.002 (S)
CRP	115(10.2-296)	48(1.57-317.3)	0.106	0.269
ESR first hour	76(10-95)	30(5-98)	1.67	0.095
ESR2second hour	92(15-107)	58(12-115)	1.55	0.119
FBS	292(140-400)	118(85-405)	3.241	0.001 (S)
Ferritin	906(363-1602)	583.7(6.2-3491)	1.38	0.167
Creatinine	0.8(0.6-1.72)	0.8(0.3-3.05)	0.167	0.867
K	3.88±0.69	4.02±0.48	0.7	0.486
Ca	8.41±0.59	8.68±1.06	0.67	0.505
Mg	2.03(1.4-2.6)	2.03(1.03-13.9)	0.382	0.702
WBC	14.8(9-29.8)	10.6(3.2-33.9)	2.173	0.03(S)
Mono	0.6(0.2-1.3)	0.6(0.1-9.3)	0.069	0.945
LYM	1.3(.7-3.1)	0.9(0.2-4.4)	1.398	0.162
Neutrophil	13.4(5.3-27.8)	8.6(1.9-31.3)	2.193	.028 (S)
Hb	12.17±3.05	13.01±1.8	0.713	0.501
PLT	216(164-354)	223(49-514)	0.323	0.747

t= test u=Mann whitnney u test, insignificant p>0.05 (S)=significant p<0.05 normally distributed data expressed as mean ± SD , abnormally distributed data expressed as median (Range)

Table (5): Relation between MACEs among COVID19 patients with their ECG finding:

	MACEs				p-value
	Yes		No		
	No.	%	No.	%	
pathological arrhythmia	2	18.2	9	81.8	0.3
Sinus Tachycardia	5	8.5	54	91.5	
Diastolic dysfunction	6	21.4	22	78.6	0.014
Diastolic Normal	1	2.4	41	97.6	(S)
ECG Abnormality	5	25.0	15	75.0	0.018(S)
Normal ECG	2	4.0	48	96.0	
HR (mean ± SD)	97.71±11.7		89.38±16.2		0.191
RR (mean ± SD)	15.5±1.8		17.16±2.7		0.124
QT1 Ms (on admission) median (range)	60(40-80)		60.(20-100)		0.545
QT2 Ms (after recovery) median (range)	40(20-60)		30.(20-60)		0.753
QTc mean ± SD	458.7±29.1		434±23.4		0.012(S)

Insignificant p>0.05, (S)=significant p<0.05

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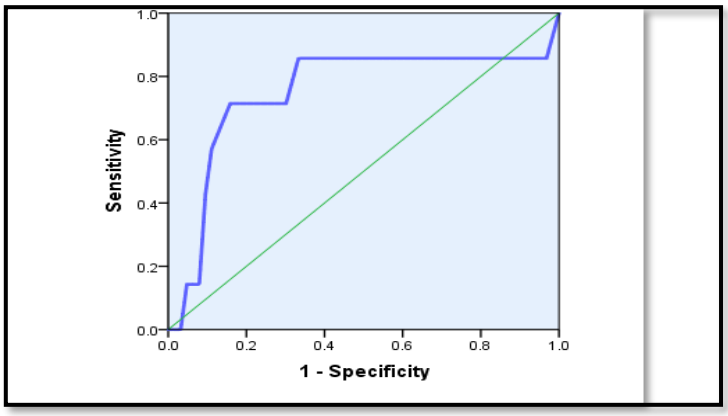

Figure (5): ROC Curve forQTc among COVID19 patients.

Table (6): Validity of QTc value in the prediction of occurrence MACEs among COVID19 patients

Cut off	Sensitivity	specificity	PPV	NPV	Accuracy	AUC
QTc≥ 443.5	85.71%	66.67%	22.22%	97.67 %	68.57%	0.749

Table (7): Logistic regression of the predictors for occurrence MACEs among COVID19 patients

Variables	P	odds ratio	95%CI	
			Lower limit	upper limit
Temperature	0.043	3.817	1.040	14.005
FBS	0.002	1.013	1.005	1.022
WBCs	0.016	1.141	1.025	1.270
Neutrophil	0.011	1.155	1.034	1.289
D-dimer	0.006	2.524	1.310	4.864
Diastolic dysfunction	0.030	11.12	1.265	98.864
Qtc	0.021	1.040	1.006	1.076
ECG abnormality	0.019	8.000	1.405	45.547

DISCUSSION

The World Health Organization (WHO) officially announced corona virus disease 2019 (COVID-19) as a pandemic in March 2020.Although the new virus (SARS-CoV-2) is mostly associated with respiratory symptoms, a recent paper has highlighted the role of cardiac injury in mortality and critically ill pneumonia in COVID-19 patients **(8).**

The pathophysiology of COVID-19 myocarditis probably roots from direct cardiac injury due to the host's immune response cytokine storm **(9).** Arrhythmias were observed in 19%

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of COVID-19 patients, according to a recent meta-analysis, and their presence was associated with a poorer outcome (**10).**

Our study included non cardiac COVID-19 patients who evaluated before treatment.We aimed in this study to detect QT/QT dispersion in Covid-19 non-cardiac patient.

In this study, longer QT ratios were detected before treatment started in COVID-19 patient. This is the first study to evaluate the clinical importance of QT Dispersion in Newly Diagnosed Non Cardiac COVID-19 Patient. Study reported changes in repolarization parameters in non cardiac patients infected with COVID-19. This came in agreement with **Yenerçağ, et al (6)** who found the same results. **Öztürk F, et al (11)** have found that potential ECG arrhythmia markers, QTc, QTd, were significantly increased in COVID -19 patients.

TseG, et al (12) found that one of the risk factors that can increase malignant arrhythmia is a prolonged QT interval, which depends on variation in ventricular repolarization. Additionally, QTd also plays a role in prediction of ventricular repolarization abnormalities and ventricular arrhythmias **(13)**. Increased QT and QTd values have been accused for sudden cardiac death caused by cardiac arrhythmias **(14).**

In the present study, there was statistically significant higher value of QTd, among COVID 19 patients at admission (pre-treatment) compared with those after recovery, this came in agreement with **Öztürk F, et al (11)**, who found that QTc and QTd that was higher at admission shows us that the virus might also affect ventricular repolarization.

In our result the incidence of MACEs among studied COVID-19 patients was 10.0% (myocardial infarction 2.9%, acute heart failure 2.9% and cardiac deaths 4.2%). Hypotension, tachycardia, bradycardia, arrhythmia, or even sudden cardiac death are common in patients with SARS disease **(15).** In the largest published clinical cohort of COVID-19 to date, acute cardiac injury, shock, and arrhythmia were present in 7.2%, 8.7%, and 16.7% of patients, respectively **(16).**

Our results show that cardiac involvement may be associated with poor results in patients with COVID-19 and arrhythmias are not uncommon. Cardiac arrhythmias can occur due to myocardial ischemia, heart failure, increased catecholamine exposure, electrolyte disturbances, scar formation, hypoxia, autonomic dysfunction and inflammation, the re-entry and acquired automaticity may initiate arrhythmogenesis at the cellular level **(17).**

Our study showed statistically significant relation between MACEs of COVID19 patients and DM. It is obvious that 18.9% of diabetic patients suffered from MACEs. Also, our study showed statistically significant relation between MACEs of COVID19 patients and diastolic dysfunction ($p=0.014$), and the occurrence of ECG abnormality (0.018) who are more liable to MACEs. Also there was statistically significant higher value of QTc, among COVID- 19 patients developed MACEs compared to other COVID-19 patients $p<0.05$. **Öztürk F, et al was** in agreement with our study **(11), they** have found that two of three died patients also had hypertension and diabetes mellitus disease. Their ages were 69 and 74, respectively. All three dead patients were men. When the ECG values of died patients were analyzed, their QTC values were high, but they were not at a level to cause malignant arrhythmia.

In the current study the studied patients ages ranged between 19 and 79 years, with mean± SD was 48.443±16.3years, 62.9% of studied patients were males and 37.1% were female. Patients suffering from following diseases; 52.9% DM, 51.4% HTN. Finally 31.4% of patients were smokers, These finding are in concordance with **Yenerçağ et al. (6)** who found that studied COVID-19 patients ages mean± SD was 55.5 ± 17.1 years, 52% of studied patients were males. Patients suffering from following diseases; 36 % DM, 52 % HTN, and 37 % of patients were smokers.

BMI of studied patients ranged between 17.5 and 39.3, with mean± SD was 27.29±4.2, and their mean ± SD of vital signs as HR was 82.77±10.75, body temperature was 38.63±0.56, SBP was126.36±20.7, DBP was 76.31±13.3, and O2 saturation was 93.21±4.6. These finding higher than the finding of **Yenerçağ et al. (6)** who found that the studied COVID-19 patients mean± SD heart rate

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was 74.9 ± 8.5 and BMI was 24.1 ± 3.5. While **Ece et al. (18)** found that SBP was 104.5 ± 10.9, DBP was 62.3 ± 7.03, and **Bianco et al. (19)** found that O2 saturation was 91.7 ± 6.6.

In the present study, there was increase in inflammatory markers including total WBCs and its differential count, CRP, ESR, ferritin and an increase in D-dimer. There was statistically significant higher value of WBC, neutrophil, among COVID19 patients developed MACEs compared to other COVID-19 patients. This came in agreement with **Yenerçağ, et al (6)** who found that CRP and WBCs were higher in Covid-19 patients.

Logistic regression analysis identified that increase temperature, FBS, WBCs, neutrophil, D-dimer, QTc were associated with an increased likelihood of exhibiting MACEs. Also, odds of having MACEs is 11.2 times greater in presenceof diastolic dysfunction, 8 times greater in presence of ECG abnormality patients as opposed to normal. We found that we are the first to study these relation by this method.

CONCLUSION:

We confirmed that there is an increase of QT dispersion (as an ECG predictors) in COVID-19 patients before treatment compared to recovery. There is a good relation between occurrence of MACEs in COVID-19 patients and QTc.

No Conflict of Interest to declare.

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