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Review Article

Comparing of the First Electrocardiographic Variables in Patients with Newly Diagnosed COVID-19 with Healthy Men Volunteer: A Systematic Review and Meta-Analysis

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Abstract

Background: We aimed to report the findings of the first Electrocardiography (ECG), before therapy initiation and receiving medication in COVID-19 patients, and to compare them with the ECG findings of healthy men.

Methods: A comprehensive and regular search was performed through the keywords ("Electrocardiographic" OR "ECG" OR; "COVID-19" OR "Coronavirus Disease 2019") without time and language restrictions in the Web of Science, Scopus, ProQuest, Cochrane Library, Science Direct, Medline, PubMed and Google Scholar. After evaluating the quality and reviewing the biases, 27 studies were finally enrolled.

Results: In 27 studies with a total number of 3994 COVID-19 patients, and mean age of 62.7 yr, 1993 subjects were male. The most common type of arrhythmia in them, especially in severe and critical cases, was 7% based on 10 studies (Atrial Fibrillation); while in 7 studies, QTc interval prolong (≥ 460 msec) was 15% and in 5 studies, QTc interval prolong (≥ 500 msec) was 18%. In COVID-19 patients at the time of admission and healthy men, HR (b per / min) was 85, 61.7 and PR interval (msec) was 285.4, 156 and QRS duration (msec) was 95, 94.3 and QT (msec) was 380. 384.1 and QTc (msec) (Bazett's formula) was 437, 387.1, respectively. In most cases, the variables were higher for COVID-19 patients.

Conclusion: ECG abnormalities at the time of admission and prior to the initiation of medication that cause arrhythmic may have a clinically substantial effect on the course of the disease and confirm the effect of COVID-19 on increased cardiovascular risk in long-term.

Keywords: Electrocardiographic; COVID-19; Arrhythmia; Heart; Meta-analysis

Introduction

Coronavirus Disease 2019 (COVID-19) is a clinical manifestation of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) with a high mortality rate. The clinical course of the infection is characterized by respiratory symptoms including fever, cough, and fatigue, and may progress to pneumonia, Acute Respiratory Distress Syndrome (ARDS), and shock (1). Adverse effects of COVID-19 on cardiovascular disease with acute cardiovascular syndrome have been described as decompensated heart failure, acute coronary syndromes and myocarditis, which increase mortality (2).

Therefore, it is important to identify prognosis-related markers that assist physicians in rapidly triaging and conduct clinical decision-making. Electrocardiography (ECG) is a fully accessible diagnostic test performed quickly without large numbers of personnel being exposed to SARSCoV2. ECG has been shown to increase prognostic value in population-based studies and among patients with a variety of underlying cardiovascular diseases, including hypertension (3). Therefore, it is of special seriousness during the current epidemic.

Therefore, the objective of the present systematic review and meta-analysis was to report the findings of the first ECG, before starting treatment and prior to receiving medication in Covid-19 patients, and to compare them with the ECG findings of healthy men.

Methods

Objective

The objective of the present meta-analysis is to report the findings of the first ECG, prior to treatment initiation and before receiving medication in COVID-19 patients, and to compare them with the ECG findings of healthy men.

The present study was conducted based on the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) (4) and it has the ethics code (IR.SEMUMS.REC.1399.230).

Components of structured question (PICO) were population (P): newly diagnosed patients with COVID-19; and intervention (I): not required; comparison (C): with healthy men; outcome (O): findings of the first ECG before treatment initiation and receiving medication. The results of this meta-analysis in COVD-19 patients were compared to the results of the study in healthy men volunteer (5).

Search Strategy

A comprehensive and regular search was performed with the keywords ("Electrocardiographic" OR "ECG" OR; "COVID-19" OR "Coronavirus Disease 2019") without time and language restrictions in the following databases: Web of Science, Scopus, ProQuest, Cochrane Library, Science Direct, Medline, PubMed and Google Scholar.

Eligible Criteria

Retrospective, prospective, randomized, and nationwide studies reported the first ECG findings of COVID-19 patients before receiving any medication were included in this review; and pediatric studies or studies that did not report the findings of the first ECG prior to treatment in these patients, and case report studies were excluded.

Selection Procedure

Out of 589 searches, 149 were excluded due to duplication. Title and abstract of 440 studies were reviewed. Texts that did not contain ECG or COVID-19 related findings in their titles and abstracts were also excluded in 358 cases. Eighty-two full-text articles were reviewed by two researchers based on inclusion and exclusion criteria. Fifty articles were excluded due to lack of detailed reporting of ECG findings and five were excluded due to ECG findings reported after receiving medication. Finally, 27 articles were selected and included in quality evaluation stage (Fig. 1).

Quality Assessment

To evaluate the critical evaluation of studies, a 5-item checklist was used based on JBI Critical Appraisal Checklist for Case Control Studies and longitudinal cohort, or cross-sectional Studies Reporting Prevalence Data (6). The two authors independently reviewed each study based on the criteria in these checklists with the options of "Yes", "No", and "Unclear". For each item "Yes", had a score of two, "Unclear" had a score of one and "No" had no score. Total scores of each study were considered as total scores. Quality classification of studies in this 5-item checklist was high (7-10), Moderate (3-6), and Weak (3>). Figure 2 shows a review of the biases of the reported studies.

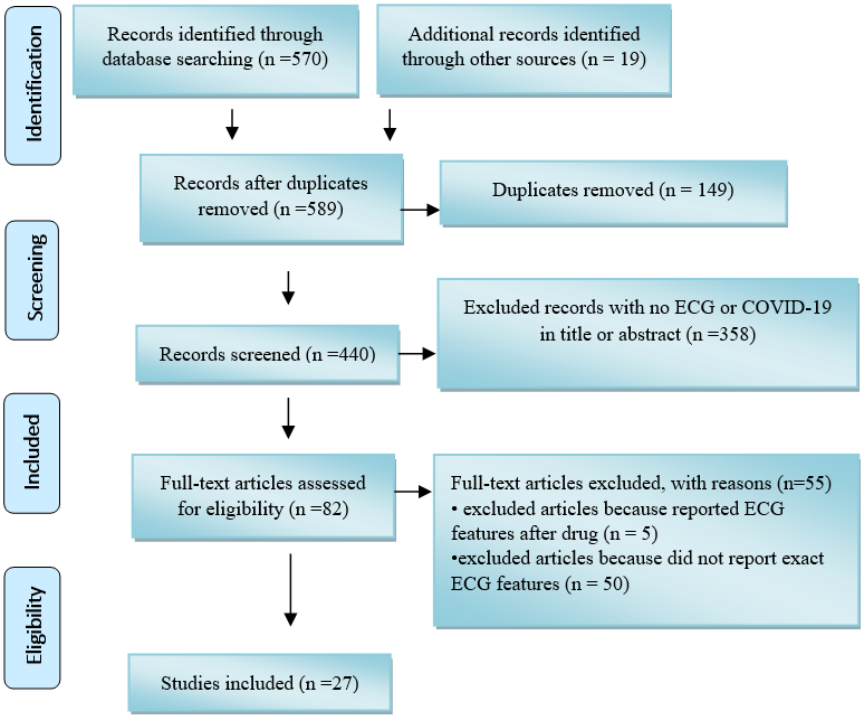

Fig. 1: PRISMA flow diagram

Fig. 2: Review of the biases of the reported studies

Data Extraction

Based on the inclusion and exclusion criteria, the two researchers independently reviewed the title and abstract of the studies. Whenever there was disagreement between them in selecting the articles, the third person, as a judge, resolved the disagreement through discourse. Variables were extracted from the study, including the name of the first author, publication year, age, sample size, BMI, and findings of the first ECG at the time of admission and prior to drug administration.

Data Synthesis and Statistical Analysis

Mean or Prevalence was reported by confidence interval (95% CI). Besides, the randomized model was reported by 95% CI. *P* value < 0.05 was considered statistically significant. The Q statistic and the I^2 index were used to assess the heterogeneity of the studies. The I^2 index was used due to its accuracy to compensate for the lack of power (the Q statistic) in small sample sizes or increase the power in large sample sizes. In the I^2 index, a value of less than 50% indicated low variance between studies and a fixed effect model and the inverse variance method were used. Otherwise I-V heterogeneity method was used (7). Studies data were entered into comprehensive meta-analysis and -5RecMan softwares and data were analyzed. The radar chart was used to compare the ECG findings of COVID-19 patients and healthy men.

Results

Characteristics of the Included Studies

In 27 studies published in 2020, a total of 3994 COVID-19 patients were studied, of which 1993 were male. The mean age of patients in 26 studies was 62.7 yr with 95% CI: 0.51-0.66, and interquartile range (IQR) was 18.44-23.5. The mean BMI of patients in 13 studies was 28 (Kg/m2), while 95% CI was 27.2-28.7. The sample size of the studies ranged from six to 756. Other information related to selected studies is listed in Table 1.

Table 1: Basic characteristics of the included studies in the meta-analysis

Reference	*Time of patients presented to hospital*	*country*	*Type of study*	*n*	*Age (yr)*		*Sex Male%*
					M	*sd*	
(8)	01/06/2020 to 02/20/2020	China	Retrospective cohort	112	65.0	(49–71)	57(50.9)
(9) All	01/27/2020 to 02/28/2020	China	Cross-sectional	54	57.6	11	36(66)
(9)Severe group				39	56.1	13.5	27 (69.2)
(9)Criticalgroup				15	61.7	9.6	9 (60)
(10)	01/NR/2020 to 12/NR/2020	France	Observational	100	67	7	59(59)
(11)	02/01/2020 to 04/04/2020	USA	Case series	98	62.3	17	60 (61)
(12)	02/13/2020 to 04/05/2020	USA	Observational	105	67	15	58 (55.2)
(13) All	02/30/2020 to 03/30/2020	Iran	Prospective cohort	119	60.52	13.45	78 (65.5)
(13) Survivedgroup				107	59.8	13	71 (66.4)
(13)Diedgroup				12	67.4	16	7 (58.3)
(14)All	02/NR/2020 to 03/NR/2020	Germany	Prospective	123	68	15	77 (62.6)
(14)Survivedgroup				107	67	15	65 (60.7)
(14) Diedgroup				16	73	16	12 (75.0)

(15)	03/01/2020 to 03/23/2020	USA		201	58.5	9.1	115 (57.2)
(16)	03/01/2020 to 04/15/2020	USA	Retrospective cohort	6	57	10.6	2(33.3)
(3)All	03/03/2020 to 04/09/2020	USA	Retrospective cohort	756	63.3	16.0	278(63.2)
(3)Survivedgroup				666	61.1	15.3	418(62.8)
(3) Diedgroup				90	79.3	11.8	60(66.7)
(17)	03/08/2020 to 03/27/2020	Netherlands	Retrospective cohort	95	65	(18–91)	63 (66)
(18)	03/09/2020 to 03/15/2020	Italy		113	68	(61–74)	85 (75)
(19)	03/10/2020 to 04/22/2020	Netherlands	Retrospective cohort	397	67.8	12.5	262 (66)
(20)All	03/13/2020 to 03/31/2020	USA	Retrospective cohort	224	65	7	127(56.7)
(20)ICUgroup				57	67	[58, 76]	31(51)
(20)No ICUgroup				167	65	[51, 77]	96(57.5)
(2)	03/15/2020 to 04/15/2020	Italy	Cross-sectional	50	64	15	36(72.)
(21)	03/17/2020 to 04/30/2020	Indonesia	Observational case series	30	53.9	16.4	16 (53.3)
(22)	03/18/2020 to 03/225/2020	France		50	68	53-81	28(55.2)
(23)Case group	03/20/2020 to 03/10/2020	Turkey	Case-control	75	55.5	17.1	39 (52)
(23)Controlgroup				75	50.2	16.6	41 (54)
(24)	03/23/2020 to 04/05/2020	Brazil	RCT	81	51.1	13.9	61(86.1)
(25)	03/24/2020 to 04/20/2020	France	Prospective observa-tional	73	62	14	49(67)
(26)	03/28/2020 to 04/30/2020	New Haven	Cross-sectional	524	68.2	15.2	64 (62.1)
(27)	03/31/2020 to 04/16/2020	Turkey	Retrospective observa-tional	109	57.3	14.4	48 (44)
(28) Case group	03/NR/2020 to 04/NR/2020	Turkey	Case-control	51	49.2	16.7	29(57)
(28)Controlgroup				40	47.9	14.9	26(65)
(29)Case group	03/NR/2020	Italy	Case-control	22	64	(56–70)	18 (82)
(29)Controlgroup				34	64	(56–70)	18 (82)
(30)	04/NR/2020	USA	Cohort	84			
(31)	04/NR/2020	Italy & USA	Retrospective	251	64	13	188(75)
(32)	05/25/2020 Accepted	Connecticut	Retrospective	91	62.7	15.1	60(56)

Electrocardiographic Features of Patients with COVID-19

Table 2 demonstrares the results of pooled mean and prevalence with confidence intervals for the first ECG findings in COVID-19 patients based on a randomized model. Accordingly, the pooled mean for HR (b per / min) in 15 studies was 85.5 (msec) and 95% CI was 90-81; it was 95 (msec) for QRS durationin (msec) in 7 studies with 95% CI of 93-97; while QT (msec) in 5 studies was 380 (msec) with 95% CI of 339-422; QT (msec) according to Bazett's formula in 21 studies was 437 (msec) with 95% CI of 427-447. In seven studies, QTc interval prolong (≥ 460 msec) was 15% with 95% CI of 0.09-0.24; and in 5 studies, QTc interval prolong (≥ 500 msec) was 18% with

95% CI of 0.012-0.8. In four studies, premature beat was 15% and 95% CI was 0.07-0.27. In 10 studies, atrial fibrillation was 7% and 95% CI was 0.05-0.9.

Table 2: Meta-analysis outcomes (random-effects model).[a]

Variable	Number of Studies	Mean (Se) / Prevalence (%)	95%CI	n	Q[b]	I²[c]	t²[d]	Heterogeneity P-value	Egger P-value
Age (yr)	26	62.5 (0.7)	61-64	3910	567	95.5	12.12	<0.001	<0.001
Male	26	0.6	0.51-0.66	1993/3910	489	94.9	0.6	<0.001	0.047
BMI (Kg/m2)	13	28 (0.4)	27.2-28.7	1979	118	90	1.55	<0.001	0.82
HR (b per/min)	15	85.5 (2.3)	81-90	2194	662	98	78.6	<0.001	0.68
PR interval (msec)	5	258.4 (30)	201-315	314	1219	99.6	4181	<0.001	0.049
QRS duration (msec)	7	95 (0.9)	93-97	1000	18.8	68	3.5	<0.001	0.74
QT (msec)	5	380 (21.2)	339-422	857	1377	99.7	2241	<0.001	0.97
QTc(msec) (Bazett's formula)	21	437.39 (5)	427-447	3355	5201	99.6	520	<0.001	0.62
QTc interval Prolong (≥ 460 msec)	7	0.15	0.09-0.24	159/954	29	79.4	0.34	<0.001	0.41
QTc interval Prolong(≥ 500 msec)	5	0.18	0.012-0.8	114/344	124.18	96.78	10.42	<0.001	0.4
Sinus Tachycardia	5	0.34	0.17-0.56	125/408	55	92.55	0.93	<0.001	0.85
Sinus Bradycardia	3	0.05	0.02-0.13	14/264	5.6	64.43	0.52	<0.001	0.22
AF	10	0.07	0.05-0.9	113/1782	16.3	44.82	0.09	<0.001	0.94
VT	2	0.04	0.15-0.09	5/145	1.07	6.6	0.03	0.3	-
Premature beat	4	0.15	0.07-0.27	144/1134	42	93	0.6	<0.001	0.8
PAC	2	0.09	0.06-0.15	73/875	3.2	68.7	0.2	0.07	-
PVC	2	0.08	0.01-0.35	48/875	35.8	97	2.4	<0.001	-
AVB	3	0.02	0.017-0.04	23/929	1.56	0.00	0.00	<0.001	0.71
LBBB	5	0.025	0.013-0.05	27/1312	10.35	61.36	0.33	0.035	0.9
RBBB	7	0.06	0.05-0.08	96/1435	6.8	12.68	0.07	0.33	0.06
LAD	2	0.27	0.08-0.6	24/125	3.2	69.4	0.82	0.07	-
RAD	2	0.07	0.04-0.13	9/125	0.78	0.00	0.00	0.37	-
LAE	2	0.27	0.06-0.7	25/137	11.7	91.5	1.6	0.001	-
RAE	2	0.18	0.12-0.25	25/137	0.7	0.00	0.00	0.4	-
LVH	2	0.14	0.07-0.23	118/774	1.2	17	0.11	0.27	-
RVH	2	0.04	0.028-0.05	31/774	0.11	0.00	0.00	0.73	-

T inverted	5	0.15	0.09-0.25	151/1221	37	89.2	0.4	<0.001	0.5
ST depression	4	0.04	0.009-0.2	26/465	24.44	87.72	2.36	<0.001	0.19
ST elevation	4	0.02	0.007-0.06	15/1098	12.7	76.55	0.98	0.005	0.85
ST-T abnormalities (%)	7	0.22	0.11-0.38	218/1314	119.5	95	0.98	<0.001	0.47

a 95% CI : 95% confidence interval- Se:Standard error- ICU: intensive care unit- yr-old. BMI:Body mass index, kg/m2- HR: Heart rate (beats per minute)- AT: Atrial Fibrillation- VT: Ventricular- PAC: Premature Atrial Contraction Tachycardia- PVC: Premature Ventricular Contraction- AVB: Atrio Ventricular Block- LBBB: Left Bundle Branch Block- RBBB: Right Bundle Branch Block- LAD: Left Axis Deviation- RAD: Right Axis Deviation- LAE: Left Atrial Enlargement- RAE: Right Atrial Enlargement - LVH: Left Ventricular Hypertrophy - RVH: Right Ventricular Hypertrophy-
b Cochran's Q statistic for heterogeneity
c I^2 Index for the degree of heterogeneity
d Tau-squared measure of heterogeneity

In 7 studies QTc interval prolong (≥ 460 msec) was 15% and 95% CI was 0.09-0.24. In 5 studies, QTc interval prolong (≥ 500 msec) was 18% and 95% CI was 0.012-0.8. In 5 studies, Sinus Tachycardia was 34% and 95% CI was 0.17-0.56. In 5 studies, T inverted was 15% and 95% CI was 0.09-0.25. In 7 studies, ST-T abnormalities was 22% and 95% CI was 0.11-0.38. In 7 studies, RBBB was 6% and 95% CI was 0.05-0.08. In 5 studies, LBBB was 2.5% and 95% CI was 0.013-0.05. Figure 3 depicts the details of pooled mean scores and graphical funnel plot for QTc (msec) based on Bazett's formula in COVID-19 patients before therapy initiation.

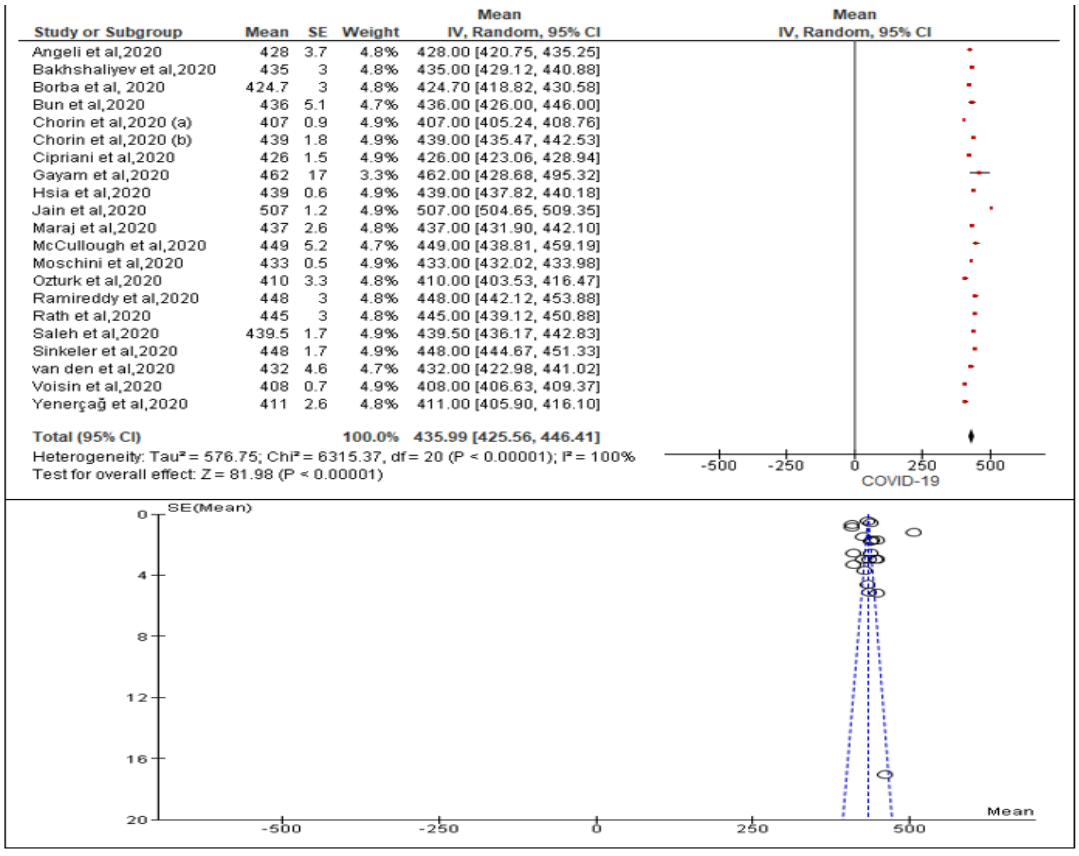

Fig. 3: Impact of COVID-19 on QTc (msec) before initiation of therapy (Forest plot & Funnel plot)

Electrocardiographic Features of COVID-19 Patients and Outcome

The radar chart (Fig. 4) compares the findings of the first ECG of COVID-19 patients before therapy initiation with the findings of a meta-analysis related to the ECG findings of healthy male volunteers before receiving any intervention. The most changes were related to PR interval (msec), QTc (msec) (Bazett's formula) and HR (b per / min).

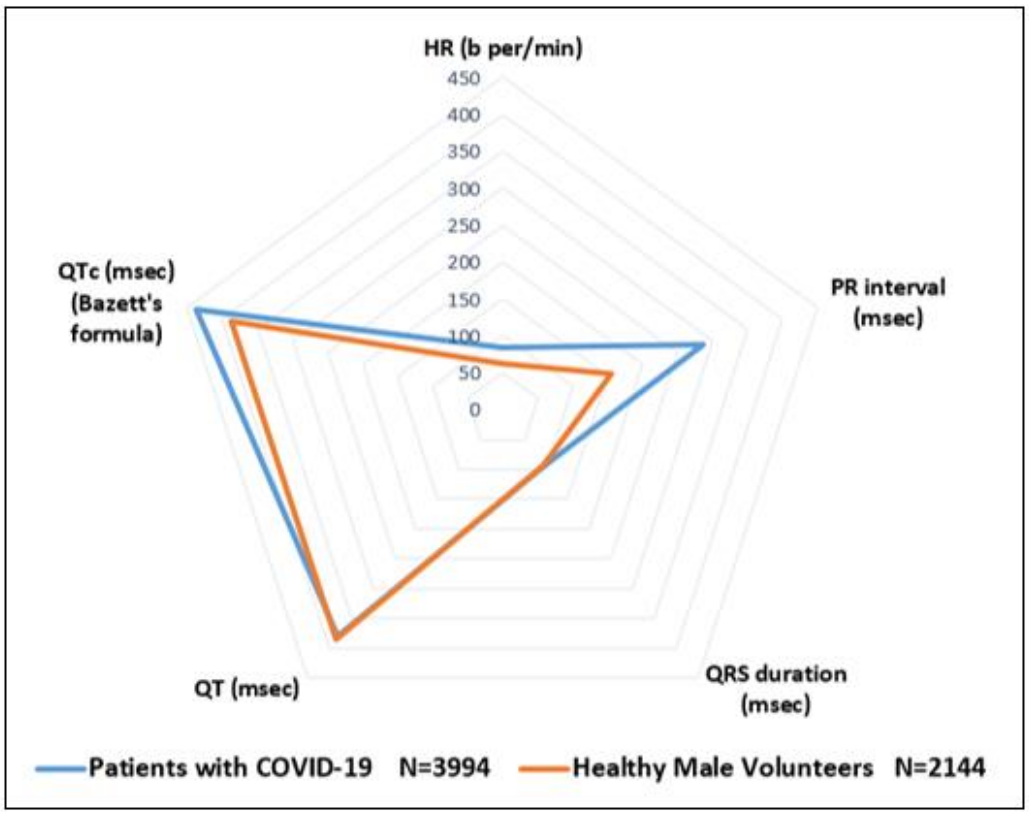

Fig. 4: Use of radar chart to compare the ECG featuresin patients with COVID-19 with healthy male volunteers

In two studies, there was no significant difference between the survived and died groups in the standardized mean QTc (msec) (P = 0.36) with 95% CI of -0.30, 0.11. In three studies, there was no significant difference between the survived and died groups in the standardized mean HR (b per / min) (P = 0.92) with 95% CI of -0.31, 0.27 (Fig. 5-A). In three case-control studies, there was no significant difference between the control group and COVID-19 group in the standardized mean QTc (msec) (P = 0.08) with 95% CI of -0.09, 1.67 and HR (b per / min) (P = 0.15) with 95% CI of -0.48, 3.06 (Fig. 5-B).

Publication Bias Assessment

In the present study, publication bias was reported by the Egger test and the results are shown in Table 2. Moreover, graphical funnel plots were symmetrical in most zones and did not show bias. Funnel plot for QTc (msec) is shown in Fig. 3.

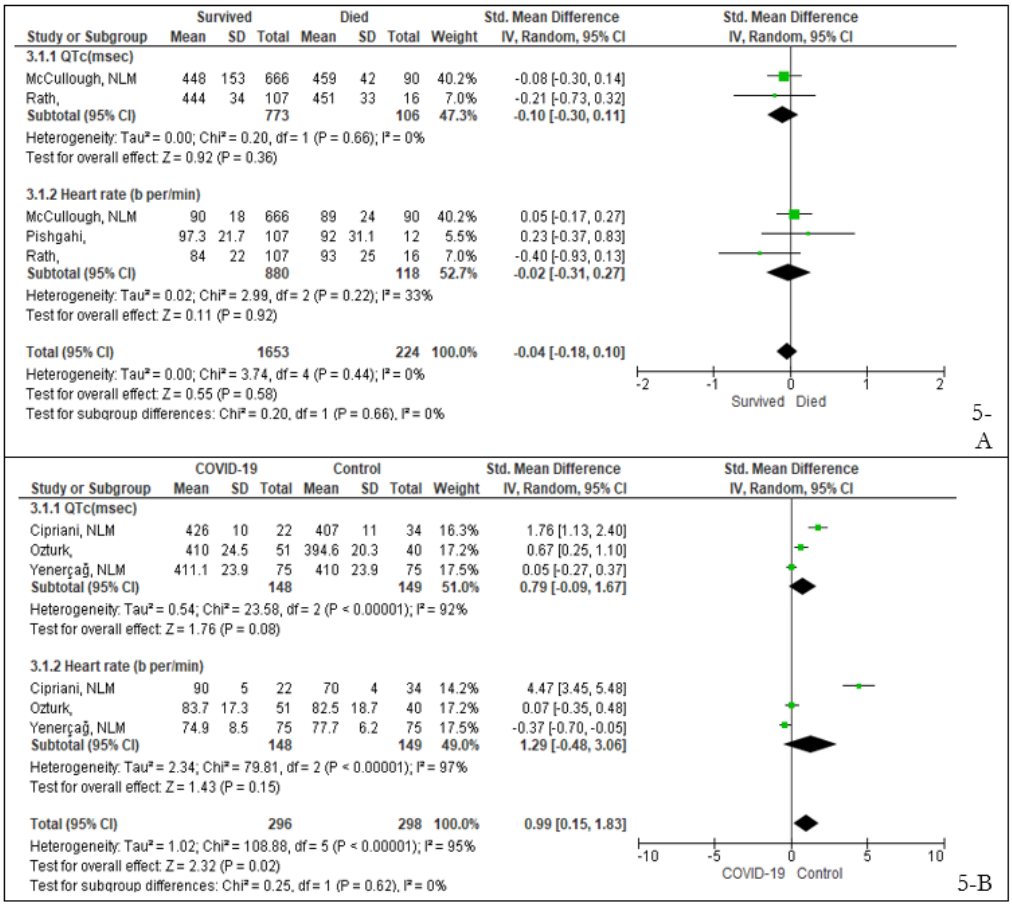

Fig. 5: 5-A: Forest plot of pooled mean of HR and QTC between survived and died patients with COVID-19. 5-B: Forest plot of pooled mean of HR and QTC between patients with COVID-19 and control group

Discussion

Despite the important role of the ECG in diagnosing the complications of COVID-19 in the acute phase, unfortunately there is no detailed study on the characteristics of the ECG and their changes during the hospitalization of COVID-19 patients before starting pharmacotherapy. In this regard, the researchers of the present study analyzed the data of 27 studies on the findings of the first ECG of COVID-19 patients who were hospitalized and had not yet received medical treatment. Finally, they have provided some of the key issues that are worth mentioning.

ECG abnormalities at the time of hospitalization due to COVID-19 entailed a wide range of cardiovascular complications including acute coronary syndrome, arrhythmic disorders and ST-T ischemic changes, so that based on the data analysis from five studies T inverted was 15% and according to data analysis in seven studies ST-T abnormalities was 22%. Cardiac arrhythmias in COVID-19 patients were similar to those in SARS patients in 2003 (33). Analysis of five studies showed that Sinus Tachycardia with 34% is the most common type of arrhythmia in COVID-19 patients, especially in severe and critical cases. In ten studies, atrial fibrillation was 7%. Thus, it is possible that atrial fibrillation in COVID-19 is associated with increased systemic

inflammation, fever, hypoxia, and adrenergic tone (2). However, involvement of epicardial adipose tissue during SARS-CoV-2 infection is associated with atrial electrical regeneration and the progression of atrial fibrillation (34). In four studies, premature beat was 15%. Given the before therapy reviews, the inflammatory response caused by COVID-19 may be more effective on the higher prevalence of premature atrial and ventricular beats than on medications (29).

Altogether, these findings reinforce the recommendation to accurately reassess and evaluate therapy options of anticoagulants, balancing the risk of thromboembolic and bleeding risk.

In COVID-19 patients, hydroxychloroquine and azithromycin are at risk for QT prolongation. However, the present study analyzed the ECG findings before starting treatment, according to which in seven studies, QTc interval prolong (≥ 460 msec) was 15% and in five studies, QTc interval prolong (≥ 500 msec) was 18%. Due to the lack of medication use before ECG, QT prolongation may be due to monogenetic stress or other undetected hereditary lesions (35); and in several studies, the main reason for the prolongation of QT has been mentioned to be the use of arrhythmogenic drugs. However, since the initial ECG of COVID-19 patient shows a relative QT prolongation, further studies are needed to assess the interval. In some previous studies, the details of the time of diagnosis before hospitalization were not specified, and just the first ECG was recorded at the time of admission for the patients diagnosed with COVID-19. The lack of details of detection time may have led to some details of the treatment not being reported, and patients may have been taking medication before being admitted to the hospital, but this has not been mentioned in the articles.

Data analysis showed that in COVID-19 patients at the admission time and in healthy men, HR (b per / min) was 85, 61.7; PR interval (msec) was 285.4, 156; QRS duration (msec) was 95, 94.3; QT (msec) was 380, 384.1; and QTc (msec) (Bazett's formula) was 437, 387.1, respectively. In most cases for COVID-19 patients, the variables were higher, possibly due to changes in autonomic tone, cardiopulmonary or peripheral deconditioning, and myocardial injury. Cardiac arrhythmias and ECG changes in COVID-19 patients before treatment compared to healthy men can occur due to myocardial ischemia, heart failure, increased catecholamine exposure, electrolyte disturbances, scar formation, hypoxia, autonomic dysfunction, and inflammation. Re-entry and acquired automaticity may initiate arrhythmogenesis at the cellular level (36). Systemic inflammation has significant effects on arrhythmogenesis. Systemic inflammation plays a key role in the development of arrhythmias by reducing the arrhythmogenic threshold in patients prone to arrhythmias.

Conclusion

In particular, COVID-19 is associated with complete heart block, acute coronary syndromes, myocarditis, decompensated heart failure, and pulmonary embolism. These findings support the notion that ECG abnormalities at the time of admission and prior to the initiation of arrhythmic medication may have a clinically substantial effect on the course of the disease and confirm the effect of COVID-19 on increased cardiovascular risk in long run.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

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Conflict of interest

The authors declare that there is no conflict of interest.

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