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Coronavirus Pandemic

Arrhythmia Risk Profile and Ventricular Repolarization Indices in COVID-19 Patients: A Systematic Review and Meta-Analysis

Alexander Edo Tondas[1,2], Rido Mulawarman[3], Monica Trifitriana[3] , Siti Nurmaini[4], Irfannuddin[3]

[1] *Department of Cardiology and Vascular Medicine, Mohammad Hoesin General Hospital, Palembang, Sumatera Selatan, Indonesia*
[2] *Biomedicine Doctoral Program, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia*
[3] *Faculty of Medicine, Universitas Sriwijaya Palembang, Indonesia*
[4] *Intelligent System Research Group, Universitas Sriwijaya, Palembang, Indonesia*

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) has been associated with cardiac arrhythmias. Several electrocardiographic markers have been used to predict the risk of arrhythmia in patients with COVID-19. We aim to investigate the electrocardiographic (ECG) ventricular repolarization indices in patients with COVID-19.

Methodology: We performed a comprehensive systematic literature search from PubMed, EuropePMC, SCOPUS, Cochrane Central Database, and Google Scholar Preprint Servers. The primary endpoints of this search were: Tp-e (T-peak-to-T-end) interval, QTd (QT dispersion), and Tp-e/QTc ratio in patients with newly diagnosed COVID-19 from inception up until August 2020.

Results: There were a total of 241 patients from 2 studies. Meta-analysis showed that Tp-e/QTc ratio was higher in COVID-19 group (mean difference 0.02 [0.01, 0.02], $p < 0.001$; I^2: 18%,). Tp-e interval was more prolonged in COVID-19 group (mean difference 7.76 [3.11, 12.41], $p < 0.001$; I^2: 80%) compared to control group. QT dispersion (QTd) also was increased in COVID-19 group (mean difference 1.22 [0.61, 1.83], $p < 0.001$; I^2:30%).

Conclusions: Several electrocardiographic markers including Tp-e/QTc, Tp-e interval, and QTd are significantly increased in patients with COVID-19.

Key words: COVID-19; SARS-CoV-2; arrhythmia; ventricular repolarization; ECG; meta-analysis; T-peak-to-T-end.

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Introduction

The COVID-19 pandemic has spread worldwide, affecting 21.2 million and taken a death toll of 761,000 people, by the time this paper was written [1]. 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 [2]. The pathophysiology of COVID-19 myocarditis probably roots from direct viral injury and cardiac injury due to the host's immune response, which is the cytokine storm [3,4]. Previously, ventricular arrhythmias have been reported to be quite frequent in viral myocarditis or pericarditis [5], and a significant rise of its incidence was noted in patients with implantable cardioverter-defibrillators during the influenza epidemics [6]. Arrhythmias were observed in 19% of COVID-19 patients, according to a recent meta-analysis, and their presence was associated with a poorer outcome [7]. Some novel electrocardiography (ECG) markers, such as Tpeak-to-Tend (Tp-e), QT dispersion (QTd), and Tp-e/QT ratio have been shown to reflect transmural ventricular dispersion of repolarization or the repolarization heterogeneity and defined as predictors of risk for ventricular arrhythmias and sudden cardiac death in various clinical settings, including myocarditis [8–10]. This systematic review and meta-analysis aimed to evaluate ventricular repolarization parameters in treatment-naive COVID-19 patients compared to healthy individuals.

Methodology

Search strategy and study selection

A systematic literature search was performed, using PubMed, EuropePMC, SCOPUS, Google Scholar Preprint Servers, and the Cochrane Central Database with the search terms 1) "COVID-19" OR "SARS-CoV-2" AND "arrhythmogenic"; 2) "COVID-19" OR "SARS-CoV2" AND "Repolarization"; 3) "COVID-19" OR "SARS-CoV-2" AND "ECG". After the

removal of duplicates, the abstract for each article was independently screened by three authors (AET, RM, and MT). After eliminating any irrelevant articles, the full texts were then thoroughly assessed according to the criteria for inclusion or exclusion below. The search was finalized on 15 August 2020. This systematic review and meta-analysis are compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study process can be appreciated in Figure 1.

Inclusion and exclusion criteria

All research articles that described adult patients diagnosed with COVID-19, together with information on arrhythmogenic, repolarization, and ECG parameters were included in this study. We excluded articles other than original research, case series with samples below 20, case reports, articles on research in pediatric populations (age ≤17 years), and non-English language articles.

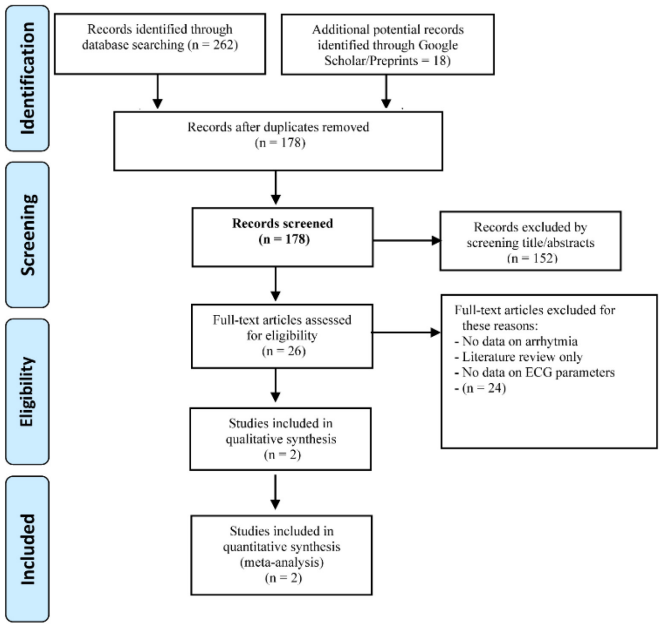
Data extraction

Data were extracted separately by three authors (AET, RM, and MT) using a standardized method to identify the relevant study characteristics and the outcome of interest. Study characteristics included the author, year, study design, age, sex, cardiovascular diseases, hypertension, diabetes mellitus, LVEF, and smoking (former and current).

Statistical analysis

To perform the meta-analysis, we used RevMan version 5.3 software (Cochrane Collaboration). We used the odds ratio (OR) and a 95% CI as a pooled measure for dichotomous data. We used mean difference (MD) and its SD as a pooled measure for the continuous data. The inconsistency index (I^2) test which ranges from 0% to 100% was used to assess heterogeneity across studies. A value above 50% or $p < 0.05$ indicates statistically significant heterogeneity. We used the Mantel-Haenzsel method (for OR), and the Inverse Variance method (for MD) with a fixed-effect model for meta-analysis, and a random effect model was used in case of heterogeneity. All p values were 2-tailed with a statistical significance set at 0.05 or below.

Figure 1. PRISMA flowchart.



Results

Study selection

We found a total of 280 records, of which 178 remained after the removal of duplicates; 152 records were excluded after screening the title/abstracts. After assessing 26 full texts for eligibility, we excluded 24 for the following reasons: 1) no data on arrhythmia; 2) literature review only; 3) no data on ECG parameters. We included 2 studies in the qualitative synthesis and in the meta-analysis, which included a total of 241 patients (Yenerçağ, 2020 and Öztürk, 2020) [11,12].

Study Characteristics

A total of 241 patients from two case-control studies were included. Patients enrolled in these studies have similar gender characteristics with a mean age ranging from 48-56 years old, as seen in Table 1. The control groups from all studies were healthy individuals (not COVID-19), age-matched with the COVID-19 group.

Table 1. Characteristics of the included studies.

Author, year	Study Design	Sample (n)	Age (years)	Gender (male/female)	Hypertension (%)	DM (%)	Smoking (%)	LVEF (%)
Yenerçağ, 2020	cross-sectional, single-centre studies	75 vs 75	55.5 ± 17.1 vs 50.2 ± 16.6 (p = 0.0053)	39/36 vs 41/34 (p = 0.777)	52 vs 54 (p = 0.885)	36 vs 33 (p = 0.273)	37 vs 40 (p = 0.478)	59.9 ± 2 vs 60.9 ± 2.1
Öztürk, 2020	cross-sectional, double-blinded studies	51 vs 40	49.2 ± 16.7 vs 47.9 ± 14.9 (p = 0.39)	29/22 vs 26/14 (p = 0.431)	11.8 vs 10.0 (p = 0.789)	11.7 vs 7.5 (p = 0.951)	19.6 vs 12.5 (p = 0.384)	58.5 ± 5.4 Vs 60 ± 4.3

Table 2. Assessment of publication bias using the Newcastle-Ottawa Scale (NOS).

Study	Selection				Comparability	Exposure			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Yenerçağ et al, 2020	*	*	*	–	*	*	*	*	*******
Ozturk et al, 2020	*	*	–	–	*	*	*	*	******

Figure 2. Tp-e/QTc ratio showed to be higher in COVID-19 patients group.

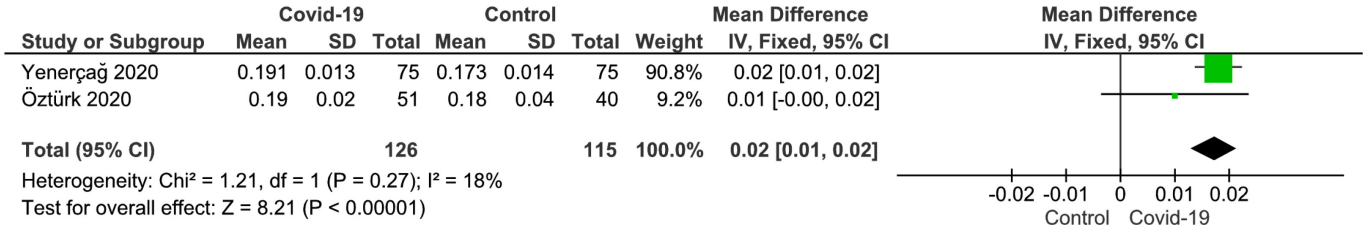


Figure 3. Mean Tp-e interval showed to be longer in COVID-19 patients group.

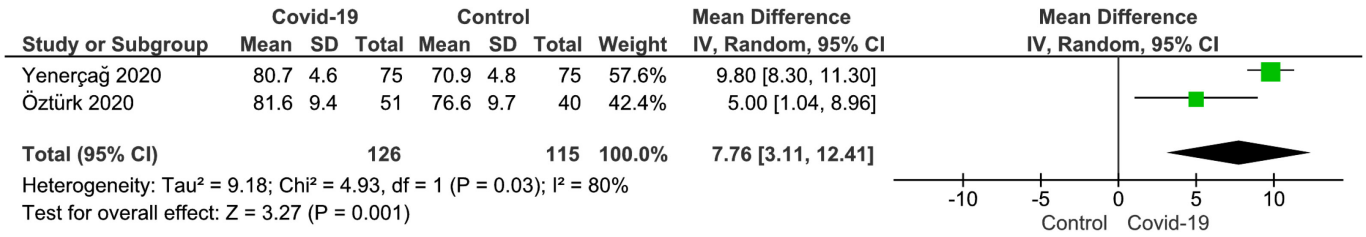
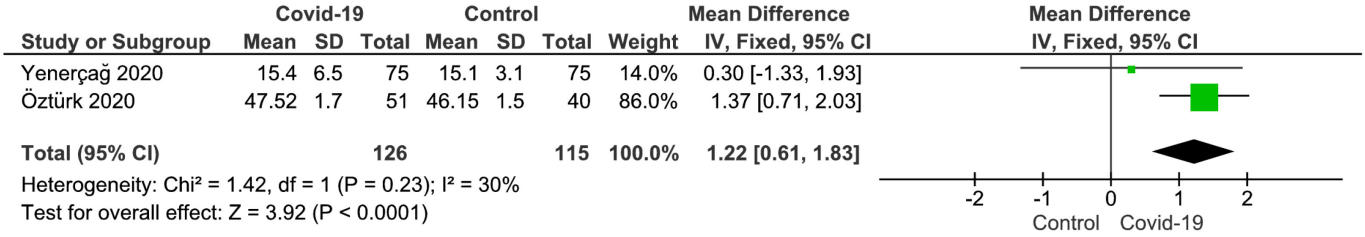


Figure 4. QTd was found to be longer in the COVID-19 patients' group.



The studies reported comorbidities such as hypertension, diabetes mellitus, and smoking history, which are proportionally similar in the COVID-19 group and control group. The mean values of left ventricular ejection fraction (LVEF) were similar in COVID-19 groups and control groups. All included studies reported baseline ventricular repolarization parameters relevant to arrhythmogenic risk: Tp-e/QTc ratio, Tp-e interval, and QTd. Polymerase chain reaction (PCT) testing was used in both studies for establishing the diagnosis of COVID-19.

Tp-e/QTc Ratio and COVID-19

Pooled analysis of the electrocardiographic measurement showed increased Tp-e/QTc ratio in COVID-19 group compared to control group with mean difference of 0.02 [95% CI 0.01-0.02], $p < 0.001$; I^2:18%, $p = 0.27$ (Figure 2).

Tp-e interval and Covid-19

Both studies from Yenerçağ *et al* and Öztürk *et al* found that the mean Tp-e interval to be significantly longer in the COVID-19 group with a mean difference of 7.76 milliseconds [95% CI 3.11-12.41], $p < 0.001$; I^2: 80%, $p = 0.03$. (Figure 3)

QTd and Covid-19

Meta-analysis showed that prolongation of QTd interval was associated with the COVID-19 group. Standardized mean difference was 1.22 milliseconds [95% CI 0.61-1.83], $p < 0.001$; I^2:30%, $p = 0.23$. (Figure 4).

Publication Bias

We used the Newcastle-Ottawa Scale (NOS) for case-control studies to assess publication bias (Table 2). All of the included studies have 6-7 stars, indicating high-quality papers with a low risk of publication bias.

Discussion

With this meta-analysis, we can show incremental changes in some electrocardiographic parameters of ventricular repolarization indices, which may become a plausible explanation for the increased incidence of arrhythmias in previous reports [13–15]. The systemic inflammatory response in SARS-CoV2 infection and the accompanying cytokine release by the host immune system, particularly interleukin-6 (IL-6) may exert a direct electrophysiological effect on the myocardium. IL-6 by itself directly inhibits the hERG-K^+ channel, prolonging ventricular action potential duration (APD), and together with IL-1 and tumor necrosis factor (TNF)-α, it can modulate cardiomyocyte K^+ and Ca^{2+} ion channels, causing the so-called inflammatory cardiac channelopathies [16].

Reentrant ventricular arrhythmias are the main contributors to sudden cardiac death (SCD) and mortality in susceptible patients. One of the proposed mechanisms for reentry is transmural dispersion of repolarization (TDR) between three myocardial cell layers: endocardial, epicardial, and mid-myocardial M cells, which have the longest APD, prone to further prolongation by external factors. This phenomenon can be extrapolated to the surface electrocardiogram (ECG), where repolarization of the epicardial layer ends at peak of the T-wave but repolarization of the M cells continues until the end of T wave. Thus, measuring the time between the peak and the end of the T wave reflects TDR, and the Tp-e interval has been defined as a novel ECG marker for arrhythmia and SCD vulnerability, beyond the QT interval only [9,17]. The optimal method to measure the Tp-e interval is to derive it from the precordial ECG leads [18], which has been implemented in the two included studies.

Tp-e and Tp-e/QT ratios have been used as event predictors in numerous clinical scenarios, such as heart failure, Brugada syndrome, hypertrophic cardiomyopathy, bradyarrhythmia, and even in the general population [10,19–21]. In our study, both the Tp-e interval and Tp-e/QT ratio were significantly higher in the COVID-19 group compared to the control. Even so, the values were still less than 100 milliseconds, which is the cut-off for higher risk in heart failure and myocardial infarction population [22].

Prolongation of QT interval is the classic ECG marker for predisposition to the occurrence of *torsades de pointes* (TdP) or malignant arrhythmias and its monitoring can be simplified for COVID-19 patients by using handheld devices [23], especially for those who received QT-prolonging drugs for SARS-CoV-2, such as hydroxychloroquine or azithromycin [24]. However, unlike Tp-e, the QT interval is dependent on the heart rate and still has to be corrected [9], thus variations exist in manual measurements [25]. Tp-e interval and Tp-e/QT ratio were higher in patients with acquired QT prolongation suffering from *torsade de pointes* compared to those who did not, therefore providing additional predictive value for identifying high-risk patients [26].

QT dispersion (QTd) is defined as the difference between the longest and shortest QT on a standard 12-lead ECG [27–31] Subjects with QTc dispersion > 60 ms had a twofold risk for cardiac death or sudden death and a 40% increased mortality risk when compared to

those subjects with a QTc dispersion < 30 ms [32]. The normal values of QTd in the general population is controversial [33], explaining the wide gap of baseline values of QTd in the two studies in this meta-analysis. The corrected Tp-e interval and Tp-e/QT ratio were found to be more accurate measurements of TDR compared to the QT, QTd, and Tp-e intervals in patients with chronic inflammatory fever [34].

Limitations

This systematic review and meta-analysis have several limitations. First, the studies were mostly case-control and did not show a direct correlation of repolarization indices with the incidence of arrhythmias afterward. This is, however, quite a challenge, since the COVID-19 pandemic has created a reluctance to monitor the patient for a longer period, for instance using ambulatory ECG (AECGs) or Holter monitors, therefore the true occurrence of arrhythmias may be missed in most studies on this subject. Second, although the risk of publication bias is low as shown by the Newcastle-Ottawa Scale, the studies are quite heterogenous, especially for the analysis of mean Tp-e interval (I^2>50%, $p < 0.05$). Probably this is due to the small number of studies included in this manuscript. Third, the studies did not report electrolyte levels, which can be a confounding factor for repolarization changes. Fourth, the population of studies are limited to Turkish, and may not be generalizable to other populations. Lastly, this study has not answered the arrhythmogenic risk related to atrial arrhythmias, including atrial fibrillation, which comprised more than 90% of all arrhythmias documented in COVID-19 patients [35]. Future studies should also be directed to assess atrial repolarization indices. Nevertheless, our study provided new insights on the potential of using ventricular repolarization indices for risk stratification and adding contemporary modalities to previously known subclinical severity assessment in COVID-19 patients [36,37].

Conclusions

Arrhythmogenic risk is higher in confirmed COVID-19 patients, compared to the healthy population, as reflected by the incremental change in electrocardiographic markers such as Tp-e interval, QTd, and Tp-e/QT ratio.

Acknowledgements

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Corresponding author
Alexander Edo Tondas MD
Department of Cardiology & Vascular Medicine, Mohammad Hoesin General Hospital, Palembang
Tel : +6281373011090 (A.E.T)
E-mail: edotondas@fk.unsri.ac.id

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