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Evaluating the possibility that drug-induced arrhythmia may interfere with cardiovascular complications caused by the Covid 19 virus

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Abstract

Porpose: Cardiac arrhythmias are a significant cause of global morbidity and mortality, with inflammation emerging as a key factor in their pathogenesis. Specifically, atrial arrhythmias such as fibrillation, long QT syndrome, tachycardia, and atrial blocks have been linked to inflammatory processes. This study aimed to evaluate arrhythmia occurrence in COVID-19 patients, examining inflammatory markers, laboratory factors, and potential interactions with arrhythmogenic drugs.

Methods: Out of 140 COVID-19 patients, 70 were diagnosed with cardiac arrhythmias via ECG. Blood parameters, inflammatory markers, and medication usage were compared between COVID-19 patients with and without arrhythmia. QT interval and heart rate from EKG were also analyzed using T-TEST.

Results: the findings revealed that COVID-19 patients with arrhythmia exhibited prolonged QT intervals compared to those without, while heart rates were similar in both groups, albeit relatively high. Additionally, inflammatory markers, particularly lymphocyte to neutrophil ratio, were significantly elevated in patients with arrhythmia. Inflammatory factors such as ESR and CRP were markedly higher ($p<0.001$) in COVID-19 patients with arrhythmia compared to those without. Furthermore, a higher proportion of deceased patients with arrhythmia had used azithromycin and hydroxychloroquine alone or in combination.

Conclision: In conclusion, the study highlights the complex relationship between inflammation, COVID-19, and cardiac arrhythmias, underscoring the need for tailored therapeutic approaches to mitigate adverse outcomes in affected patients.

1. Introduction

In light of the widespread prevalence of the new Coronavirus in 205 countries and its importance in combating it, it is essential to pay attention to its effects on all organs. Despite the viral induction of acute respiratory syndrome, we should not ignore its effects on other organs, particularly the cardiovascular system. Coronaviruses rely on the ACE2 receptors for their function in the cardiovascular system[1]. There are many causes of mortality and morbidity associated with cardiac arrhythmias, yet there is still a lack of understanding of the underlying mechanisms [2,3].A variety of arrhythmias have been associated with inflammation, particularly atrial arrhythmias fibrillation, long QT syndrome, tachycardia, and atrial block)) and ascites [3]. A number of inflammatory cytokines have been linked to ascites, which is associated with heart issues and arrhythmia. There is still a great deal of misunderstanding surrounding inflammation in arrhythmia

management, and arrhythmic drugs that target the inflammatory immune system have not yet become standard therapies. The unexpectedly high prevalence of arrhythmic events after COVID-19 has significantly increased interest in this topic. Medical centers have received hundreds of patients with Covid-19 who suffered from systemic inflammation and frequent heart arrhythmias. This rare opportunity to observe how systemic cytokine releases increase arrhythmia risk has been provided by the Covid-19 disease [4,5].

Antiviral and antibiotic treatments used in covid-19 patients can cause arrhythmias as well (5). Therefore, drugs like hydroxychloroquine, which have cardiovascular effects including inducing arrhythmias, should be used with caution. In particular, patients with heart failure, high blood pressure, and diabetes who get infected by this virus are at risk [6]. In accordance with the points mentioned in this plan, the objective is to assess a number of patients with covid-19 disease, as well as the changes in laboratory factors in them, along with the drugs they were using [7,8].

2. Materials and methods

A data bank community was used to extract information about 140 patients infected with the new Corona virus, split into two groups with arrhythmia and without arrhythmia. The EKGs of the patients were assessed to determine if they had arrhythmia. Using the underlying disease of the patient, the drugs received with the potential to induce arrhythmia are then extracted and evaluated. Furthermore, the percentage of patients who recovered or died was compared between groups receiving drugs with and without underlying cardiovascular disease.

It was determined that the data bank in the affected groups contained variables such as age, gender, blood pressure, heart rate, oxygen saturation, antiviral drug used, QT interval, and indicators of disease improvement such as lymphocyte and neutrophil counts. We compared these data among groups with and without arrhythmias, and with underlying diseases and without them. The above variables were compared by using T-TEST.

3.Results

laboratory factors

According to the results, patients with covid with arrhythmia had a significant increase in NLR (the ratio of lymphocytes to neutrophils), which is normally between 0.78 and 3.5. As compared to this ratio in patients without arrhythmia, this value reached 9.6 ($p<0.0001$) in those with covid and arrhythmia (table 1).

Moreover, the results showed that the values of WBC, RBC, HB, MCV, and BUN increased significantly ($P<0.0001$). There was also a significant increase in creatinine factors, liver enzymes and a significant increase in blood pressure in patients with cardiac arrhythmia compared to patients without cardiac arrhythmia. A significant increase in potassium (from 4.18 to 18.23) was observed in patients with arrhythmia.

The table 2 also shows blood factors among people with arrhythmia who died and those who did not die. As a result, WBC, MCV, POLY, BS, and sodium were significantly higher in deceased people compared to non-deceased individuals, but RBC, HB, HCT, Creatinine, SGPT, CPK, and potassium were significantly lower.

QT period and HR changes

In this section, it was shown that covid patients with arrhythmia had an average QT period of 402.7± 10.38, while covid patients without arrhythmia had an average QT period of 347.36± 6.1. While no significant difference was observed in heart rate between groups with or without arrhythmias, the group with arrhythmias had a longer QT period than other patients ($P<0.001$) (Figure 1).

Mortality rates

Among 72 people with arrhythmia, 20% of the deaths occurred after receiving hydroxychloroquine. Azithromycin was associated with about 17% of deaths, while both drugs were associated with 16.7% (Table 3).

4. Discussion

An EKG analysis of patients with covid-19 and cardiac arrhythmia indicated a long QT interval, compared to patients without cardiac arrhythmia, this length was significant, but their heart rates were not significantly different. Both groups, however , had a heart rate of 95 beats per minute on average.

The following indicators are used by medical experts to diagnose arrhythmia: changes in P-P intervals (from the beginning of the P wave to the beginning of the next P wave),

The table 2 also shows blood factors among people with arrhythmia who died and those who did not die. As a result, WBC, MCV, POLY, BS, and sodium were significantly higher in deceased people compared to non-deceased individuals, but RBC, HB, HCT, Creatinine, SGPT, CPK, and potassium were significantly lower.

	group	Mean	Std. Error Mean
NLR	non-arythmia	4.7424	.42142
	arythmia	5.7309*	.33138
WBC	non-arythmia	6.2302	.28664
	arythmia	5.8192***	.28682
RBC	non-arythmia	5.0327	.08747
	arythmia	10.8125***	.59047
HB	non-arythmia	14.5719	.22468
	arythmia	31.3500***	1.76247
MCV	non-arythmia	84.9222	.95836
	arythmia	49.1407***	3.42986
MCHC	non-arythmia	34.3175	.17091
	arythmia	123.7437***	11.69495
Plateletes	non-arythmia	186.1714	9.67706
	arythmia	85.5121***	14.83437
Poly	non-arythmia	73.6860	1.63383
	arythmia	40.0390***	3.53285
Lymph	non-arythmia	21.1597	1.18899
	arythmia	14.2550***	1.01359
ESR	non-arythmia	41.1786	3.26791
	arythmia	94.1190***	10.59020
BloodUreaNitrogen	non-arythmia	14.8730	1.02123
	arythmia	7.5268	1.36240
Creatinine	non-arythmia	1.0413	.05111
	arythmia	19.7700	3.47273
SGOT	non-arythmia	41.5882	3.40428
	arythmia	62.8500	12.50434
SGPT	non-arythmia	42.2745	4.64656
	arythmia	139.4103***	14.57253
ALK	non-arythmia	194.0392	10.99595
	arythmia	176.3889	24.34968
CPK	non-arythmia	194.0333	24.89961
	arythmia	444.1622***	45.29240
SGPT	non-arythmia	194.0333	24.89961
	arythmia	444.1622***	45.29240
Na	non-arythmia	136.4762	.45581
	arythmia	56.4127***	8.72963
PotassiumK	non-arythmia	4.1794	.05753
	arythmia	23.6531***	4.41808
CRP	non-arythmia	27.7661	3.75157
	arythmia	21.6667	5.60431

Table 2. The comparison of blood factors between dead and nondead patients with arrhythmia in COVID

	group	Mean	Std. Error Mean
NLR	dead	6.4995	1.75332
	nondead	5.6274	.30207
WBC	dead	7.5763*	1.22642
	nondead	5.5488	.25943
RBC	dead	7.7675*	1.71030
	nondead	11.2810	.60939
HB	dead	21.0000*	4.90550
	nondead	32.9423	1.80705
HCT	dead	51.1450**	7.13432
	nondead	73.2312	2.94683
MCV	dead	68.3450*	8.70899
	nondead	46.1862	3.58019
MCHC	dead	59.7325	17.28760
	nondead	133.5915	12.72777
Plateletes	dead	148.8375*	38.34488
	nondead	75.3800	15.75269
Poly	dead	56.8000*	10.67407
	nondead	37.4098	3.63694
Lymph	dead	17.4125*	3.16078
	nondead	13.7692	1.06100
ESR	dead	83.5000	21.68064
	nondead	95.8889	11.89356
BS	dead	171.33*	26.692
	nondead	123.58	9.071
FBS	dead	11.5000	3.50000
	nondead	17.1290	1.53297
BloodUreaNitro-gen	dead	12.9125	2.89059
	nondead	6.6292	1.48549
Creatinine	dead	8.1900*	4.65124
	nondead	22.2079	3.99624
SGOT	dead	59.1429	18.46545
	nondead	63.6364	14.74151
SGPT	dead	58.1429*	20.83887
	nondead	157.1875	15.55858
ALK	dead	175.8571	48.53150
	nondead	176.5172	28.25241
CPK	dead	214.1429	60.93143
	nondead	497.8333	49.36093
Na	dead	102.4625*	21.41952
	nondead	48.5745	9.14444
Potassium K	dead	18.59	13.987
	nondead	24.50	4.666
CRP	dead	28.20	11.269
	nondead	19.01	6.511
	nondead	1.0375	.01292
troponin	dead	.12	.108
	nondead	.18	.162

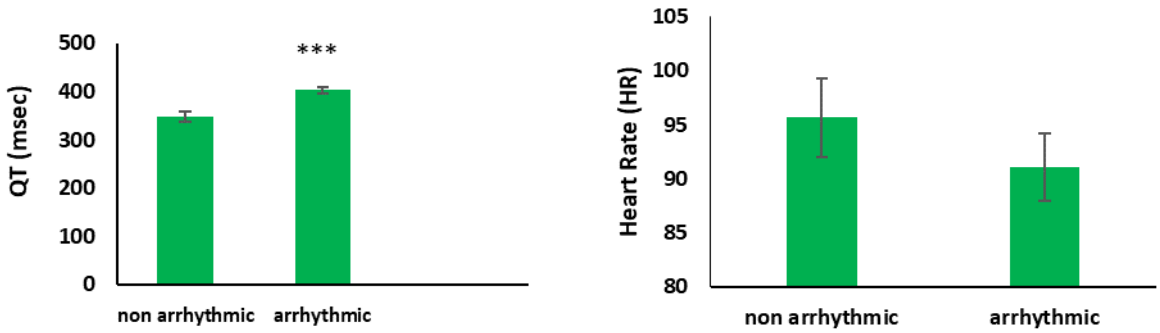

Figure 1. Changes in heart rate and QT interval in covid patients with and without arrhythmias

Table 3. Mortality rate among patients with arrhythmias and without heart problems receiving arrhythmogenic drugs.

Patients with arrhythmia	Hydroxychloroquine	Azithromycin	both drugs
the dead 11.59%	20%	17.85%	16.7%
the undead 88.4%	80%	1%82.14	83.4%
Patients without heart problems	Hydroxychloroquine	Azithromycin	both drugs
the dead 8.69%	8.19%	10.52%	10.81%
the undead 91.3%	90.16%	89.47%	89.18%

lengthening of the QT time, heart rate and P-P interval, narrow QRS complex, wide QRS complex, atrial fibrillation, irregular rhythm, and elimination of P waves. Arrhythmia was confirmed by the long QT parameter in the selected group (9,10).

In terms of inflammation factors, the group with arrhythmia has a significantly higher ESR than the group without arrhythmia and heart disease. As a result of the high standard deviation in this variable, the CRP factor did not show a significant difference between the two groups, but the NLR factor also showed a significant difference in the arrhythmia group.

In the group with arrhythmia, the amount of CPK increased significantly, indicating that the activity of this enzyme correlates with heart hemodynamics, according to the research of the researchers. Patients with arrhythmia also have a significant increase in hemoglobin and hematocrit.

These patients' heart activity can be severely weakened by a combination of a severe decrease in sodium ions and a significant increase in potassium ions.

Although cytokines were not directly measured in this study, they can be linked to other evidences. Several mechanisms, including direct cardiac activity and indirect systemic changes, play a role in the arrhythmogenic effects of inflammatory cytokines, especially TNF, IL-1, and IL-6. Among the direct effects are structural and electrical changes in the heart. As well as stimulating structural remodeling (over weeks or months),

cytokines can also stimulate cardiac fibrosis in a myofibroblast-driven manner. Action potential durations (QTc) are prolonged by these phenomena, aberrant firing is increased, and electrical impulse propagation through myocardium is slow or heterogeneous.

As a result, tachyarrhythmias, bradyarrhythmias, and conduction disturbances become more common.).(,11,12,13

This study found that 11.59 % of people with cardiac arrhythmia died, of whom 20% took hydroxychloroquine, 17.85% azithromycin, and 16.7% both. There were 69.8% deaths in the group without underlying heart disease, 19.8% received hydroxychloroquine, 10.5% received azithromycin, and 10.8% received both drugs.

There are evidences that mortality and arrhythmias associated with covid-19 are more likely to be caused by disease-specific mechanisms such as direct viral invasion of the heart or "off-label" drugs, especially antihypertensive drugs, that have an electrophysiological effect. Azithromycin and protease inhibitors are the treatments for malaria. The virus, however, is causing only a small number of patients to suffer direct heart damage. Additionally, even though the above-mentioned drugs were gradually withdrawn due to their ineffectiveness, the risk of arrhythmia was still high. As a result of these observations, attention was focused on other arrhythmogenic factors, such as tissue hypoxia resulting from lung injury and systemic high-grade inflammation (14,15).

A study conducted in Wuhan with 187 patients hospitalized with Covid-19 revealed that patients with high troponin levels had a greater risk of developing malignant arrhythmias like ventricular tachycardia and fibrillation than patients with normal troponin levels. However, in this study, troponin levels were found to be 0.12 to 0.18 (ng/ml) in arrhythmia patients (13,16).

The anti-malarial drugs chloroquine and hydroxychloroquine inhibit lysosome function by increasing pH, and interfere with nucleic acid replication and viral protein glycosylation to prevent virus infection. According to the treatment section, this drug was widely used at the beginning of the covid pandemic, but the main concern in evaluating its toxicity in covid-19 is the prolongation of the QT interval (17,18).

The combination of azithromycin and hydroxychloroquine has also been evaluated. A study enrolled 80 patients with covid-19 and gave them 200 mg of hydroxychloroquine three times a day for ten days, followed by 500 mg azithromycin on day 1 and 250 mg on day 4. As a result, on day 8, a significant reduction in viral load was observed in the nasopharynx. In contrast to this finding, in a clinical trial of 504 patients with mild-to-moderate covid-19, compared with standard care, no improvement in the clinical condition was observed in those receiving hydroxychloroquine (400 mg, twice daily) alone or azithromycin (500 mg, once a day) (19).

An additional clinical study conducted by a Chinese team of 6 compared 2 patients' fever recovery time and cough duration to standard treatments after taking 400 mg of hydroxychloroquine for five days. Nonetheless, a systematic review and meta-analysis of 12 observational and randomized trials found that hydroxychloroquine and chloroquine did not significantly improve clinical outcomes in patients with COVID-19, although these drugs reduced mortality and morbidity. Death does not occur to them. Lastly, the FDA determined on June 15, 2020 that hydroxychloroquine and chloroquine are not useful in treating Covid-19 (11,13)

5. Conclusion

Inconclusion, this study showed that the death rate of covid patients who have arrhythmia was higher than the death rate of covid patients without cardiac disorders. Patients who died and had arrhythmia had a higher concentration of hydroxychloroquine and azithromycin used alone and together. Meanwhile, it has been observed that the death rate of covid patients with arrhythmias is higher than that of patients without cardiac disorders.

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