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THE RATE AND CHARACTERISTICS OF DYSRHYTHMIA IN PATIENTS WITH SEVERE COVID-19, A HOLTER STUDY

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ABSTRACT

Background: covid-19 disease caused by the newly emergent corona virus proved to have a myriad of pulmonary and extra-pulmonary manifestations including cardiovascular manifestations through multiple mechanisms and many patients developed different types of cardiac injury and arrhythmia and some of which proved to have a worse outcome in the clinical course of the disease. **Aim of study:** to determine the rate and characteristics of cardiac rhythm abnormality in patients with severe covid-19 infection using a 24 hour-holter monitor. **Methods:** A descriptive cross-sectional study conducted in Al-Yarmouk Teaching Hospital Baghdad, Iraq for a period of six months from 1st December 2020 to 30th June 2021, where 60 patients with severe covid-19 according to WHO criteria for severe disease were enrolled and underwent a 24-hour holter study, echocardiography electrocardiography and biochemical investigations for relevant inflammatory markers of covid19. **Results:** In this study the percentage of patients with significant dysrhythmia during a Holter study was 43.3%(26 patients) and distributed as follows: 20 cases (33.3%) of sinus tachycardia; 17 cases (28.3%) of sinus bradycardia, 9 cases (15%) of paroxysmal AF and 6 cases (10%) of bigeminy; 7 cases (11.6%) of PVC; 6 cases (10%) of NSVT; one case (1.7%) of SVT(some patients had more than one type of arrhythmia during a holter study) while 56% (34 patients) no significant arrhythmia was observed, Patients who had cardiac arrhythmias had significantly higher levels of ferritin, D-Dimer, CRP, and troponin compared to those without cardiac arrhythmias. **Conclusion:** dysrhythmias are common in patients with severe covid-19 disease, and Most of the clinically significant arrhythmia like atrial fibrillation and non-sustained ventricular tachycardia were paroxysmal and detected only during a holter study. patients with High levels of inflammatory marker (CRP, Ferritin, troponin, d-dimer) had significant relation to clinically severe covid-19 and risk of developing significant arrhythmias.

KEYWORDS: covid-19, dysrhythmia, holter, inflammatory markers.

INTRODUCTION

Background

In December 2019, a group of patients with severe pneumonia started to emerge in Hubie province in Wuhan, China, many of those patients were working or visiting the wet fish market in Wuhan city, soon after more people commenced to show symptoms in which a new strain of Coronavirus was recognized by the Chinese CDC[1] and later on spread to the state of Wuhan and to the world.

The international Committee on Taxonomy of Viruses (ICTV) named the new virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the new disease coronavirus disease (COVID-19) by the World health organization (WHO) in its International Classification of Diseases (ICD).[2]

Virology

After full genomic sequencing the new virus was found to belong to the Beta corona family which showed several resemblances to prior outbreaks in 2002 SARS (severe acute respiratory syndrome) caused by SARS-

COV Virus and the successor in 2014 MERS (middle east respiratory syndrome) caused by MERS-COV Virus,[3] the beta corona family is comprised of six strains of viruses that has been documented to infect humans and cause mild flu symptoms and two zoonotic viruses (SARS and MERS viruses).[4]

The new strain acted similarly to SARS and MERS virus in respects of transmissibility through respiratory droplets and fomites but with higher virulence and infectivity.[1]

Covid-19 virus entry is initiated through binding of the S-protein of SARS-COV2 virus with the host angiotensin converting enzyme (ACE) which mediate cell entry, ACE enzyme is highly expressed on pulmonary cardiomyocytes and vascular endothelial cells which may be responsible for the cardiopulmonary manifestations, upon entry the S-protein cleaves the dibasic arginine site by host protease TMPRSS2 to generate the s1/s2 subunits, s2 subunit induces a membrane fusion and viral endocytosis in the cell then viral RNA is released into the cytoplasm where it replicates and produce the virion-containing particle which fuse with the cell membrane to be released and cause a wide spread infection.[5]

Epidemiology

While SARS and MERS had a higher case fatality rate (9.7% for SARS AND 34% for MERS)[6,7] covid-19 pneumonia had a case fatality rate was estimated variably in many reports with variation between countries and time of the year.[8] in a summary of the Chinese center for disease control report (72,314 cases) Case fatality rate was 2.3% in which patients who had hypertension cardiovascular disease and diabetes had a higher case fatality rate compared to those with no comorbidity.[9]

In 11th march 2020, the WHO in its briefing on the new emergent disease declared a worldwide pandemic upon spreading of the virus to 200 countries and cross all continents posing a global health concern, and advised pandemic regulations to limit the spread of the virus through social isolation and wearing masks and restriction of flights after the disease began to gain more and more numbers causing both healthcare and financial burdens especially in countries of higher population and third world countries.[10]

Till the time of writing this research there is as many as 190 million reported cases of COVID and 4 million deaths worldwide, in Iraq 1.6 million reported cases and nearly 19000 deaths.[11]

In Iraq, the first confirmed case of Covid-19 pneumonia was in AL-Najaf governorate in a travelling student and soon the cases began to spread with the first confirmed case in Baghdad was in March 2020, and the first wave of the disease began in April of the same year.[12]

Clinical features and diagnosis

Clinical features ranging from asymptomatic to mild flu-like symptoms to severe pneumonia and adult respiratory distress syndrome (ARDS) while most persons develop fever, cough, fatigue, anorexia, shortness of breath and myalgia. Other non-specific symptoms, such as sore throat, rhinorrhea, episodes of headache, mild to moderate diarrhea, nausea and vomiting, have also been reported. Loss of smell (anosmia) or loss of taste (ageusia) prior to the onset of respiratory symptoms has also been described.[13]

The progression of covid-19 disease has been theorized to go through three overlapping yet distinct stages, upon infection constitutional symptoms develop and stage II develop on entry and replication of the virus in pneumocyte type II causing direct cellular toxicity and activation of inflammatory pathway leading to ARDS and hypoxia and if the immune system was not able to clear the infection then stage III ensues with hyper inflammatory cytokine storm that result in multiorgan dysfunction.[14]

Diagnosis is made through polymerase chain reaction (PCR) of nasal swabs[15] in addition to radiological features in chest CT-scan in form of consolidation, septal thickening, reticulation and crazy-paving pattern and ground glass appearance.[16]

Since it's a new strain of the virus and causing a new disease, the academic society began to work to try to better understand the clinical features, complications and prognosis of confirmed cases with many reports demonstrating pulmonary and extra-pulmonary involvement as such one of those manifestations were renal impairment, hepatic impairment and gastrointestinal symptoms, hematological in the form of hypercoagulability and thromboembolism and finally cardiovascular complications.[17]

These associated manifestations of the disease proved to have worse clinical outcomes compared with cases with no extra pulmonary involvement causing mortality in severe cases.[18]

Covid-19 and the cardiovascular system

In regards to the cardiovascular system many reports suggested new cardiovascular events and destabilization of patients with stable coronary artery disease, arrhythmias and heart failure, cardiac complication may occur in covid-19 patients even without pulmonary symptoms.[19]

While the national health commission of China reported cardiovascular symptoms were the first presentation in some patients without respiratory symptoms delaying the diagnosis of covid-19.[20]

Many studies demonstrated cardiac injury in covid-19 patients in the form of elevated cardiac troponins I titers

(higher than the 99th percentile) especially in those with severe disease, one study in China demonstrated 44% of the patient enrolled in the study needing ICU treatment developed cardiac injury while only 16% in those not requiring ICU,[6] indicating the burden of severe disease to the heart, Chen et al study demonstrated that cardiac troponin Ti was an independent risk factor for mortality in covid-19 patients.[21]

Also, Shi et al which was a single center cohort of 416 patients admitted for covid-19 showed cardiac injury in the form of high sensitivity troponin I (hs-cTnI > 99th percentile) on admission with a median 0.19 (0.08-1.12) ug/L and demonstrated that patient with cardiac injury required more non-invasive ventilation (46.3% vs 3.9% P < 0.001) and invasive mechanical ventilation (22% vs 4.2% P < 0.001) and after adjusting for all confounding factors still cardiac injury was a predictor of mortality (HR:4.26:95% CI:1.92-9.49) other studies like Huang et al reached a similar conclusion.[22,23]

Tao guo et al. in their study showed that there is a linear relationship between plasma troponin levels to C-reactive protein (CRP) indicating that myocardial injury may be closely related to an inflammatory pathogenesis.[24]

Explanatory theories regarding covid-19 cardiovascular affection was that it may destabilize a stable CVD due to increased metabolic demands and reduced cardiac reserve caused by the infection and accentuated inflammation and down regulation of ACE receptors in the lung and heart causing damage to the myocardium leading to cardiovascular symptoms.[25]

Since clinical data started to accumulate documenting the cardiovascular implications of Covid-19 its now made clear that there is a cardiac component to the disease itself in presentation and clinical features and prognosis.

Covid-19 and cardiac arrhythmias

As our clinical understanding of covid-19 is still evolving and the sheer number of cases worldwide provided the pportunity to study the disease more and explore the myriad of symptoms that it may present with, and one of those symptoms frequently reported is palpitations, liu k. et al study in China demonstrated 7.3% of patients presented with palpitation as an initial symptom and sometimes causing a delay in the diagnosis of covid19,[26] while other researchers found that arrhythmia were reported frequently in patients with covid19 whether on presentation or in the disease course leading in some cases to a worse prognosis.[27]

It's not clear whether arrhythmogenesis stems from covid-19 itself or being caused by the complications that covid-19 patients develop, but if we looked to previous pandemics specifically the close relatives of covid-19 virus (SARS and MERS corona viruses) they were implicated to pose an arrhythmia risk in patients infected with them, regarding SARS in 2002 a study of 121 patients demonstrated that 71.9% of patients were reported to have tachycardia independent of fever and hypotension while 14.9% were found to have bradycardia.[28]

In 2014 with the MERS epidemic there many reports of even more serious arrhythmias in MERS patients, in one case series 70 patients of MERS, 15.7% developed arrhythmias in form of persistent tachycardia or bradycardia requiring temporary pacing.[29]

As to covid-19 patients arrhythmia has been well documented to develop in the course of the disease or as an initial presenting symptom, in two studies from new York city, a study of 393 patients in two hospitals showed that 7.1% had atrial arrhythmias and 0.3% developed ventricular arrhythmia, while another study highlighted cardiac arrhythmia in patients with severe disease in form of high grade AV blocks, atrial fibrillation, polymorphic ventricular tachycardia, cardiac arrest and pulseless electrical activity,[30,31] from that we may conclude that disease severity plays a major role in arrhythmogenesis and the etiology and mechanism of arrhythmia might be multifaceted.

The taskforce of Italian national institute of health in a recent study showed that 24.5% of 355 non survivors from covid19 had cardiac arrhythmias most commonly atrial fibrillation some of them presented even before the respiratory manifestations had emerged.[32]

Humam et al in their meta-analysis of 1445 patients with covid19 reported an arrythmia incidence was 19.7% (with 95% confidence interval and ranging from 11.7% to 27.6%).[33]

In a recent meta-analysis by Wen W et al showed that covid-19 induced arrhythmias were greater in severe cases than non-severe cases and concluded that covid-19 might be a risk factor for arrhythmias, older age and comorbidities play a role in arrhythmia incidence.[34]

A study by Angeli et al during the outbreak in Italy regarding ECG changes in covid 19 patients concluded that ECG abnormalities in hospitalized patients with covid19 reflected a wide spectrum of cardiovascular complications and sometimes exhibit a late onset in the disease course and doesn't run parallel with pulmonary involvement and may persist beyond negative nasopharyngeal swabs.[35]

Cardiac arrhythmias in covid19 patients appears to be one of the challenging complications of covid19 so a better understanding of covid19 related arrhythmias may allow for a better management and prognosis.

Postulated mechanisms of covid-19 associated arrhythmias

The exact cause of arrhythmias in covid-19 is still unclear however a proposed mechanism might be related to covid-19 induced cardiac injury, hypoxia, drugs, electrolytes disturbances and inflammatory or immune response to covid-19 virus through abnormality of impulse formation, abnormality of impulse conduction, or combinations of both.[36]

Cardiac injury: Many studies since the earliest days of the pandemic demonstrated cardiac injury in form of elevated cardiac enzymes specifically troponin TI (>99th percentile) indicating that cardiac injury might be a cause for arrhythmogenesis, through myocarditis or ischemia either destabilizing an already stable coronary artery disease or even new insult.[22]

Myocardial injury may also stem from the loss of the protective role of angiotensin (1-7) Due to the loss of function of the angiotensin converting enzyme as it is utilized by the virus to internalize and shed into the cells thus reducing angiotensin (1-7) and tumbling their protective effect on the myocardium and vasculature on the other hand the increase in angiotensin II may promote hypertrophy, vasoconstriction, tissue fibrosis and oxidative stress potentially causing arrhythmias.[37]

Loss of angiotensin converting enzyme function has been linked to epicardial adipose tissue inflammation and pericarditis and pericardial effusion.[38]

Other postulated mechanism of cardiac injury is vasculitis and endothelitis which may be triggered by viral entry into the cardiac vasculature causing a hypersensitivity reaction and causing damage and myocardial injury.[39]

Myocardial injury may also stem from hypercoagulability that Covid-19 produces through developing arterial and venous thromboembolism, the incidence of thrombotic complications in covid19 patients is high among hospitalized patients so it may propose a possible mechanism through development of pulmonary embolism related arrhythmias or even acute coronary syndrome.[40-42]

Hypoxia: Covid-19 virus is known to have a predilection to replicate inside pneumocytes type II causing pneumonia and ARDS leading to hypoxia, its theorized that hypoxia might affect the myocardium through promoting myocyte cell death on a cellular level and affect the function of ion channels leading to action potential prolongation and\or repolarization through reduction of pH and increased cytosolic calcium facilitating early and late repolarization.[43]

Hypoxia might also downregulate the HERG (Human ether-a-go-go-related gene) encoding pore-forming subunits of the fast activated delayed rectifier potassium channels which results in an increase of a protein called Calopresin which act on the rapid delayed rectifier potassium (IKR) channels possibly leading to prolongation of ventricular repolarization thus causing arrhythmias.[44]

Hypoxia may also result in a shortening of repolarization though its effect on the small conductance calcium activated potassium channels leading to a proarrhythmic effect through shortening of the effective refractory periods leading to arrhythmias.[45]

Pro-inflammatory cytokines: Covid-19 has been documented to trigger an intense immune by the imbalance between t-helper (th1) and t-helper 2 (th2) leading to the release of a myriad of pro-inflammatory cytokines namely (IL6, IL1B, IL2, IL8, GM-CSF, TNFα).[46]

Studies have shown that high levels of IL6 can lead to a surge of L-type calcium current density and an increase in the amplitude and duration of calcium transits in ventricular myocytes.[47]

IL6 may also downregulate the atrial junction protein S causing atrial electrical remodeling leading to a disturbance in the sinoatrial nodal firing and conduction.[48]

IL6 is also linked to proatherogenic effects due to stimulation of vascular smooth muscle proliferation and endothelial cell activation and platelets activation.[49]

A multicentric study showed that the increase in IL6 in non survivors of covid-19 compared to survivors suggest an increased mortality which might be mediated by the hyperimmune response potentially causing increased susceptibility to arrhythmias.[50,51]

Proinflammatory cytokines may also result in endothelial dysfunction particularly impaired nitric oxide depended vasodilation,[52] also impaired handling of oxidative stress which is linked to atrial electrical remodeling, Other pro-inflammatory cytokines may also play a role in arrhythmogenesis yet to be studied.[53.54]

Electrolyte disturbance

Covid19 may cause electrolyte disturbance through its gastrointestinal symptoms namely diarrhea and may also lead to constitutional symptoms like fever sweating and decreased oral intake, or Kidney injury may also contribute to electrolyte disturbance and intravascular volume imbalance,[55,56] electrolytes has been known to cause arrhythmia through different mechanisms affecting the electrical conduction system in the heart.[57]

in one study of 416 covid19 patients it was found that 7.2% had electrolytes disturbance mostly hypo and hyperkalemia and hypomagnesemia.[22]

Drugs: some drugs that was used early in the pandemic like hydroxychloroquine has been reported to cause prolongation of the QT interval.[58] Azithromycin also has been reported to cause arrhythmias especially when combined with hydroxychloroquine.[59,60]

Abnormal sympathetic tone

Covid19 has been theorized to cause an abnormal sympathetic response in form of exaggerated catecholamine spill over and reduced neurovagal inflammatory reflex possibly due to abnormal cytokine response leading to dyshomeostasis and abnormal stress response resulting in transient or long-term orthostatic intolerance syndromes in form of postural orthostatic tachycardia syndrome.[61]

Severe inflammation may also activate the sympathetic nervous system (SNS) leading to calcium influx into the cardio myocytes resulting in delayed after depolarization and triggered action potentials promoting arrhythmias.

IL6 release also cause SNS hyper activation through hypothalamic and left stellate ganglia activation pathways.[62]

Anxiety and stress that covid19 patients may suffer also drives the SNS activation leading to tachycardia and potentially arrhythmias.[63]

Arrhythmia in covid-19 appears to be related to disease severity being more common in cases that are severe and require assisted ventilation, in a cohort study during the New York city outbreak, (393 patients with covid19) the rates of atrial arrhythmias were significantly higher in mechanically ventilated patients (17.7%) compared with 1.9% in non-invasive ventilation group.[64]

Colon et al found that atrial fibrillation atrial flutter and atrial tachycardia was seen in (16.5%) all of which were admitted to the ICU while no atrial arrhythmia was detected in patients who only required medical ward admission.[65]

Reports of ventricular arrhythmias and torsade de pointes were seen especially in patients who received hydroxychloroquine and azithromycin combination than either drug alone.[66]

The wide variety of arrhythmias that covid19 patients may develop is not only exclusive to tachyarrhythmia, but Brady arrhythmia are also reported in many studies, Kir et al a case of high-grade AV block in a patient with normal echocardiography and cardiac biomarkers and negative past history of cardiac disease, while Peigh et al. reported two cases of sinus nodal dysfunction in which the patients presented with bradycardia and followed by episodes of accelerated idioventricular rhythm and interestingly bradycardia lasted more than two weeks after negative nasopharyngeal swabs.[67,68] Inflammatory markers like serum ferritin, C-reactive protein D-dimer and LDH are documented to be elevated in concordance with disease severity and associated with higher mortality and worse prognosis.[69-72]

In regards to the cardiovascular diseases in covid-19 patients the European society of cardiology updated their recommendations on the diagnosis and management of such patients, and as far as arrhythmias is concerned a similar treatments of arrhythmias with the exception of some caution on beta blockers in patients with severe respiratory distress as to avoid bronchospasm and avoidance of drug-drug interactions, Anticoagulation for the prevention of AF-related stroke or systemic embolism should be guided by the CHA2DS2-VASc score and Therapeutic anticoagulation should be considered in male and female patients with CHA2DS2-VASc score $\geq 1$and ≥ 2, respectively.[73]

Aim of study

to determine the rate and characteristics of cardiac rhythm abnormality in patients with severe covid-19 infection using a 24 hour-holter monitor and determine the correlation of the rhythm abnormality with specific inflammatory markers related to covid-19 and patients comorbidities and other biometric data.

PATIENTS AND METHODS

2.1. Study design, Setting and Data collection time

A descriptive cross-sectional study conducted in Al-Yarmouk Teaching Hospital Baghdad.

2.2. Ethical considerations

Verbal permission was obtained from the patients after explanation of the procedure and patients' data were confidential and names replaced with identification numbers and data kept in a password protected laptop and used for research purposes only.

2.3. Administrative approvals were granted from the following

1. The Council of Arab Board of Medical Specialization.
2. Approval of the Department of Internal Medicine in Al-Yarmouk Teaching Hospital.

2.4. Study patients and Sample size

Sixty patients with severe covid-19 were enrolled in the study who had a positive nasal swab PCR and chest CT scan consistent with covid19 pneumonia and according to the WHO criteria for severe covid-19 and underwent a 24hrs Holter study, bedside transthoracic echocardiography and blood sample was taken for lab work.

Inclusion criteria

- Adult patients with severe covid-19 pneumonia who had a positive PCR and chest CT-scan and severity defined according to the WHO criteria.

WHO criteria for severe covid-19

Severe COVID-19 – Defined by any of:

- Oxygen saturation <90% on room air;
- Respiratory rate > 30 breaths/min in adults
- Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).[74]

Exclusion criteria

- Patients with known ischemic heart disease.
- Hypotension (from patient observation chart).
- Previous documented arrhythmia.
- Valvular heart disease and congestive heart failure (by transthoracic Echocardiograph).
- Thyroid disease.
- Renal impairment.
- Chronic liver disease.
- Electrolyte disturbance (potassium calcium and magnesium).
- Critically ill patients and those in need of mechanical ventilation.
- Use of anti-arrhythmic drugs (beta blockers amiodarone, or any arrythmogenic drugs).

Out of ninety patients were interviewed in the ward, 15 patients had previous ischemic heart disease and another 5 of them had electrolytes disturbance in form of hypokalemia and 7 had congestive heart failure and 3 had renal impairment all were excluded from the study.

2.5. Devices or equipment used

- **Holter device:** General Electric healthcare SEER.
- **Echocardiography device**: General Electric healthcare VSCAN EXTEND.
- Portable three-channel Holter monitoring systems (GE Healthcare) were used for the 24-hour ECG recording in al-Yarmouk teaching hospital covid19 isolation ward and the analysis was performed at the Al-Yarmouk Holter department.
- Bedside echocardiography was performed to exclude heart failure or wall motion abnormalities and valvular heart disease.
- Personal protective equipment and sanitary precautions were followed during patient interview and echocardiography and Holter device placement.
- Echocardiography and Holter analysis were performed by a certified cardiovascular physician and according to the current guidelines.

Holter finding criteria for significant arrhythmia

- Significant sinus tachycardia was defined as sinus heart rhythm with rate more than 100 bpm more than 25% of the study time or mean heart rate above 90bpm.
- Significant bradycardia was defined as sinus heart rhythm with rate under 50 bpm and more that 25% of study time and not during sleep hours.
- PVCs was defined as premature occurrence of a QRS complex that is abnormal in shape and has a duration usually exceeding the dominant QRS complex generally longer than 120 milliseconds with full compensatory pause following the PVC, more than 10% of the 24hr to be count as abnormal.
- Ventricular bigeminy defined as sinus beat followed by premature ventricular complex recurring in 1:1 patterns deemed significant if more than 10% of the study.
- Ventricular tachycardia (VT) was defined as a sequence of ≥ 3 beats at a rate of > 100 beats/minute which were ventricular in origin.
- VT which lasted < 30 seconds was termed NSVT, and VT lasting ≥ 30 seconds was termed Sustained VT.
- Supraventricular tachycardia was defined as ≥3 consecutive supraventricular complexes at a rate >100 bpm of regular narrow QRS complex without a p wave.
- Patients may have had more than one abnormality during the 24-hour Holter monitoring period.[75]
- QT interval was measured from the beginning of q wave to the end of t wave and corrected to heart rate according to Bazett's formula.[76]
- All biochemical investigations (renal function test and electrolytes and thyroid function, ferritin lactate dehydrogenase troponin and d-dimer.) were done in AL-Yarmouk teaching hospital central lab department and under standard methods.

BMI = Weight (Kg) / Square height (m^2).[77]

Participants were classified according to BMI as:

- Under weight (<18.5 kg/m^2).
- Normal (18.5-24.99 kg/m^2).
- Overweight (25 - 29.99 kg/m^2)
- Obese (≥ 30 and <35 kg/m^2)
- Very obese (≥35 and <40kg/m^2)
- Morbid obesity (≥40 kg/m^2)

2.6. Data collection tool

A questionnaire consisting of patient age, sex, past medical history and drug history and physical examination (including vital signs and BMI) and laboratory work up including serum ferritin, CRP, LDH and serum potassium and s calcium (corrected to albumin) and thyroid function test (TFT), renal function test and chest CT and 24hrs Holter monitor findings.

2.7. Statistical analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 26. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Chi square test was used to assess the association between provisional diagnosis and certain information, while fisher exact test was used instead

when the expected frequency was less than 5. A level of P – value less than 0.05 was considered significant.

RESULTS

A total of sixty patients with severe COVID-19 were enrolled in this study. All of them were underwent a history and physical examination with biochemical investigation and ECG and echocardiography with a 24hr Holter monitor to diagnose different types of cardiac dysrhythmias.

3.1. Demographic and clinical characteristics

Patients' age ranged from 34 to 75 years with a mean of 59.21 years and standard deviation (SD) of ± 9.23 years, and 26 patients (43.3%) were found in the age group of (60 – 69) years (Figure 3.1). Regarding gender, proportion of males was higher than females (60% versus 40%) with male to female ratio of 1.50:1. The calculated BMI had a mean of 28.30 ± 2.38 kg/m^2, 32 (53.3%) were overweight, 22 (36.7%) were obese, and the remaining 6 (10%) had normal weight. Symptoms of palpitation were reported among 18 (30%) of the enrolled patients. Concerning chronic medical conditions, diabetes reported in 20 patients (33.3%), hypertension in 8 (13.3%), while 31 (51.7%) of patients had both diabetes and hypertension. Lung involvement was ≥ 50% in 41 (68.3%), while SPO_2 saturation was < 90% in 41 (68.3%) of cases. Based on ECG, rhythm disturbance was detected in 34 (56.6%) of patients; sinus tachycardia in 32 (53.3%) and sinus bradycardia in 2 (3.4%), while the remaining 26 (43.3%) had normal rhythm. (Table 3.1).

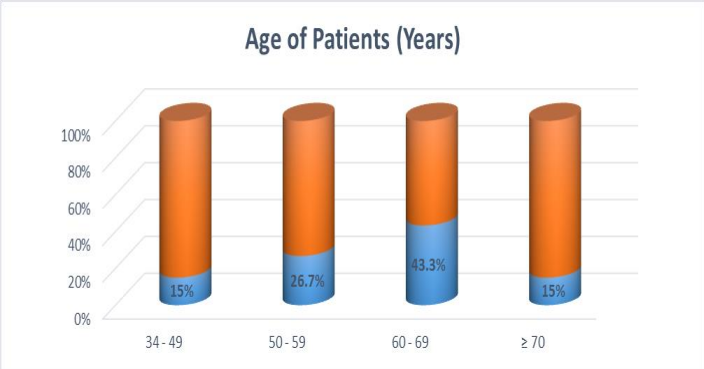

Figure 3.1: Distribution of the study patients by age.

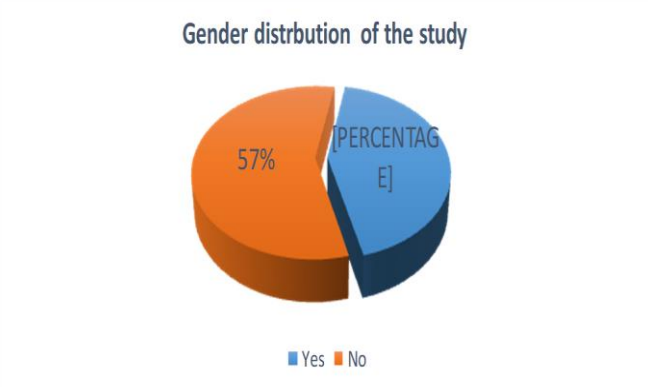

Figure 3.2: distribution of the study patients by gender.

Table 3.1: Distribution of patients by certain demographic and clinical characteristics.

Demographic and Clinical Characteristics	No. (n= 60)	Percentage (%)
Gender		
Male	36	60.0
Female	24	40.0
BMI		
Normal	6	10.0
Overweight	32	53.3
Obese	22	36.7
Symptoms of Palpitation		
Yes	18	30.0
No	42	70.0

Comorbidities		
No	1	1.7
DM	20	33.3
HTN	8	13.3
DM & HTN	31	51.7
Lung Involvement (%)		
< 50	19	31.7
≥ 50	41	68.3
SPO_2 (%)		
< 90	41	68.3
≥ 90	19	31.7
ECG Findings		
Normal	26	43.3
Sinus Tachycardia	32	53.3
Sinus Bradycardia	2	3.4

3.2. Results of Holter monitor

According to Holter monitoring, a significant cardiac arrhythmia was detected in 26 cases, with incidence of 43.3% (Figure 3.2).

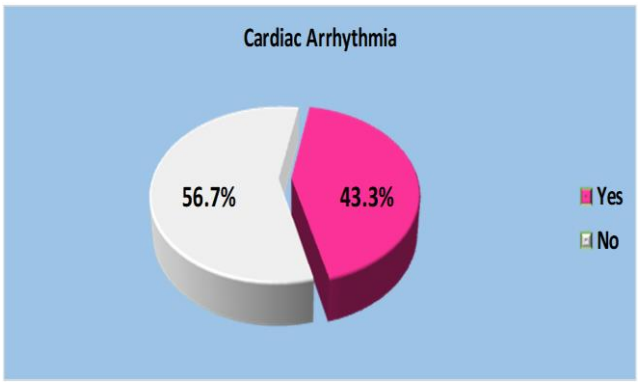

Figure 3.2: Prevalence of cardiac arrhythmias among the study patients in 24 hour holter study.

The frequency and patterns of Holter findings were as follows: 20 cases (33.3%) of sinus tachycardia; 17 cases (28.3%) of bradycardia, 9 cases (15%) of paroxysmal AF and 6 cases(10%) of bigeminy; 7 cases (11.6%) of PVC; 6 cases (10%) of NSVT; one case (1.7%) of SVT while 56.7 %(34) didn't have a significant arrhythmia during holter study.

Many patients had more than one type of arrhythmia during holter study (Table 3.2) and figure 3.4

Table 3.2: Distribution of the study patients according to Holter findings.

Holter Findings	No. (n= 60)	Percentage (%)
Sinus Tachycardia	20	33.3
Sinus Bradycardia	17	28.3
Paroxysmal AF	9	15.0
Bigeminy	6	10.0
PVC	7	11.6
NSVT	6	10.0
SVT	1	1.7

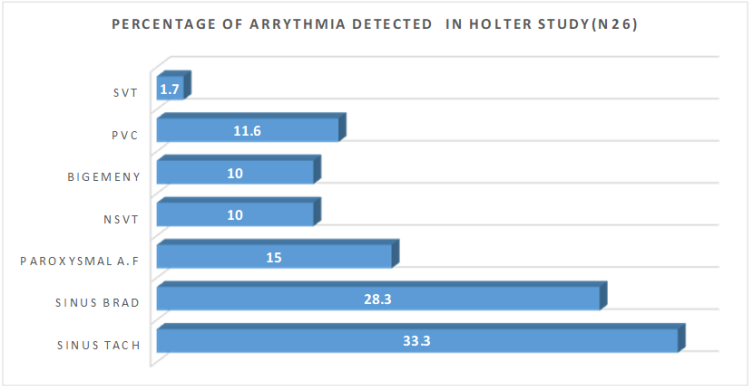

Figure 3.4: Percentage and types of dysrrythmia detected in holter monitor

3.3. Biomarker profile

The comparison in mean levels of certain laboratory parameters according to results of Holter monitoring showed that there was a statistically significant difference in means of ferritin, D-Dimer, and CRP. Patients who had cardiac arrhythmias were with significantly higher levels of ferritin, D-Dimer, and CRP compared to those without cardiac arrhythmias (1281.1 ng/mL vs 986.1 ng/mL, P= 0.001; 3479.9 mg/l versus 1976.9 mg/l, P= 0.007; and 108.1 mg/l versus 77.2 mg/l, respectively). Also, there was a difference in levels of LDH but this difference was not significant (P= 0.335). Level of troponin I was significantly different (P= 0.001) according to the results of Holter study as shown in table (3.3).

Table 3.3: Comparison in mean levels of certain biochemical markers by Holter diagnosis.

Laboratory Parameters	Holter Diagnosis		P – Value
	Arrhythmia Mean ± SD	Normal Rhythm Mean ± SD	
Ferritin ng/ml	1281.1 ± 317.8	986.1 ± 285.2	**0.001**
D-Dimer mg/l	3479.9 ± 2806	1976.9 ± 1230	**0.007**
LDH U/l	565.2 ± 83.2	537.7 ± 129.4	**0.355**
CRP mg/l	108.1 ± 62.3	77.2 ± 37.6	**0.021**
Troponin I no. (%) no. (%)			
Positive	9 (100.0)	0 (0)	**0.001**
Negative	17 (33.3)	34 (66.7)	

The distribution of study patients by Holter diagnosis and certain demographic and clinical characteristics showed that there was a statistically significant association between cardiac arrhythmias and symptoms of palpitation, lung involvement, and ECG findings. The prevalence of cardiac arrhythmias was significantly higher among patients who had symptoms of palpitations (77.8%, P= 0.001), patients with lung involvement of ≥ 50% (53.7%, P= 0.025), and those who had sinus bradycardia (100%, P= 0.034). Other variables showed no significant association with cardiac arrhythmias (Table 3.4).

Table 3.4: Distribution of the study patients by Holter diagnosis and certain demographic and clinical characteristics.

Demographic Clinical Characteristics	Holter Diagnosis		Total (%) n= 60	P – Value
	Arrhythmia (%) n= 26	Normal Rhythm (%) n= 34		
Age (Years)				
34 – 49	3 (33.3)	6 (66.7)	9 (15)	**0.751**
50 – 59	6 (37.5)	10 (62.5)	16 (26.7)	
60 – 69	12 (46.2)	14 (53.8)	26 (43.3)	
≥ 70	5 (55.6)	4 (44.4)	9 (15.0)	
Gender				
Male	13 (36.1)	23 (63.9)	36 (60)	**0.167**
Female	13 (54.2)	11 (45.8)	24 (40)	
BMI level				
Normal	2 (33.3)	4 (66.7)	6 (10.0)	**0.482**
Overweight	12 (37.5)	20 (62.5)	32 (53.3)	

Obese	12 (54.5)	10 (45.5)	22 (36.7)	
Symptoms of palpitation				
Yes	14 (77.8)	4 (22.2)	18 (30.0)	**0.001**
No	12 (28.6)	30 (71.4)	42 (70.0)	
DM				
Yes	21 (41.2)	30 (58.8)	51 (85.0)	**0.422**
No	5 (55.6)	4 (44.4)	9 (15.0)	
HTN				
Yes	19 (48.7)	20 (51.3)	39 (65.0)	**0.251**
No	7 (33.3)	14 (66.7)	21 (35.0)	
Lung involvement (%)				
< 50	4 (21.1)	15 (78.9)	19 (31.7)	**0.025**
≥ 50	22 (53.7)	19 (46.3)	41 (68.3)	
SPO_2 (%)				
< 90	20 (48.8)	21 (51.2)	41 (68.3)	**0.211**
≥ 90	6 (31.6)	13 (68.4)	19 (31.7)	
ECG findings				
Normal	7 (26.9)	19 (73.1)	26 (43.3)	**0.034**
Sinus Tachycardia	17 (53.1)	15 (46.9)	32 (53.3)	
Sinus Bradycardia	2 (100.0)	0 (0)	2 (3.3)	

DISCUSSION

4.1. Overview

Human coronavirus is a virus of positive-sense ribonucleic acid (RNA). Several mechanisms such as hypoxia, myocarditis, myocardial ischemia, or abnormal host immune response, which induce cardiac arrhythmias, have been described.[78,79] A number of vaccines using different methods have been developed against human coronavirus SARS-CoV-2. Antiviral targets against human coronaviruses have also been identified such as viral proteases, polymerases, and entry proteins. Drugs are in development which target different steps of viral replication.[80] COVID-19 can significantly affect cardiac function and cause cardiac injury. It is associated with increased disease severity and fatal outcomes.[21] Early studies suggest that COVID-19 is associated with a high incidence of cardiac arrhythmias. Severe acute respiratory syndrome coronavirus infection may cause injury to cardiac myocytes and increase arrhythmia risk.[81] Previous work has identified that ARDS (20%), arrhythmias (17%), shock (9%), and acute cardiac injury (7%) are common compilations in COVID-19. A variety of pro-inflammatory mediators play a key role in the pathophysiology of cardiac complications. Therefore, a better understanding of cardiovascular effects in SARS-CoV-2 is essential.[13] In the current study, 60 hospitalized patients with severe COVID-19 were enrolled, all of them were underwent a 24-hour Holter monitor to diagnose cardiac arrhythmias.

4.2. Demographic and clinical characteristics

In the present work, mean and SD of age was 59.21 ± 9.23 years, ranged from 34 to 75 years, 43.3% of patients were found in age group of (60 – 69) years. Regarding gender, proportion of males was higher than females (60%) with male to female ratio of 1.50:1. The calculated BMI had a mean of 28.30 ± 2.38 kg/m^2, and more than half of patients (53.3%) were overweight.

By comparison to other studies, a comparable results found in Kong et al study in 2020, in which a total of 40 COVID-19 patients were enrolled in their study, with a mean and SD of age was 47.7 ± 13.4 years, also male predominance notice in that they represented 65% of them with male to female ratio was 1.85:1.[82] Another comparable results found in Hammadi et al study in 2021, in which mean and SD of age of patients was 50.4 + 15.1 years. Majority of patients were Males, as they represented 59.2%, male to female ratio was 1.4:1.[83] Another study, conducted by Chen and colleagues in 2020, on 99 patients confirmed to had COVID-19 disease found that the age group were ranged from 21-82 years and higher percentage (30%) were patients between 50-59 years old and as with other studies most of them were men (68%).[84]

In this study, symptoms of palpitation were observed in 30%. Moreover, diabetes reported in 33.3% of patients, hypertension in 13.3%, while 51.7% of patients had both diabetes and hypertension. Lung involvement ≥ 50% was found in 68.3%, while SPO_2 saturation < 94% was in 68.3% of cases.

In comparison to Mesquita et al study in 2021, in which 79.7% of patients had associated comorbidities. Arterial hypertension was the most prevalent comorbidity, in 64.1% of patients, 36% of patients had dyslipidemia, 34.4% were diabetic and 29.7% of patients had previously diagnosed atrial fibrillation.[85] In Coromilas et al study in 2021, cardiac comorbidities were common in patients with arrhythmia: 69% had hypertension, 42% DM, 30% had heart failure, and 24% had coronary artery disease. Most had no prior history of arrhythmia.[86]

A variety of factors can explain the differences observed among above studies, of these are socioeconomic, educational factors, moreover, it was obvious that elderly

people are more vulnerable to severe pattern of COVID-19 disease than people younger than 50 years; this probably because of health issues and comorbidities in that population group. Additionally, male predominance in many studies is explained by the higher chance of infection that linked to the occupational risk factors for men in markets, being socially active and work in crowded areas.[87]

4.3. Results of Holter monitor

According to Holter monitoring in this study, cardiac arrhythmia was detected in 43.3% of cases enrolled. Of which; 33.3% of them had sinus tachycardia and 28.3% had sinus bradycardia.

In comparison to other studies, a close results observed in Parwani et al study in 2021, in which out of 113 patients, 50patients had sinus tachycardia (44%), 30 patients (26.5%) had relevant bradycardic events. Of those, 15 patients (13.3%) had sinus bradycardia (heart rate < 40 bpm).[88] In Bhatla et al study in 2020, throughout hospitalization, there were 53 arrhythmic events, of which 9 clinically significant brady-arrhythmias (16.9%) reported.[81] In Mesquita et al study in 2021, Twenty hospitals participated, reporting 692 hospitalized patients. An arrhythmic episode occurred in 81 (11.7%) and 64 (79%) had detailed information on these episodes, in which five patients (7.8%) sinus bradycardia.[85]

Holter monitoring in this study revealed that 15% had paroxysmal AF, As compared to Parwani et al study in 2021, a lower finding reported, in which out of 113 patients enrolled, 5 patients (4.4%) showed atrial fibrillation (AF) with slow conduction to the ventricle (heart rate < 40 bmp).[88] In Bhatla et al study in 2020, there were 53 arrhythmic cases after COVID-19, of which there were 25 incident AF events that required pharmacological management with amiodarone and diltiazem (47.1%).[81] A higher results published in Mesquita et al study in 2021, including 64 patients with detailed information on arrhythmic episodes. They observed that 40 patients had atrial fibrillation or flutter (62.5%).[85]

The current study reported, according to Holter monitoring, that 10% of patients presented with NSVT; 11.6% had PVC; 10% bigemny and SVT were noted in 1.7%.

a close results observed in Bhatla et al study in 2020, in which 10 of 53 patients with arrhythmic events, had NSVT (18.8%). They did not observe any cases of sustained VT, or VF in patients with COVID-19.[81] On the same concern, In Mesquita et al study in 2021, of 64 patients with arrhythmic events. Two patients (3.1%) had VT, and 17 (26.6%) paroxysmal supraventricular tachycardia.[85]

The differences might have explained by different sample size or different study design, demographic and clinical differences such as underlying cardiovascular risk factors and disease, different type of management, since the combination treatment with hydroxychloroquine and azithromycin-medications that result in QT prolongation and independently increase the risk of cardiac arrest.[89]

Despite a high number of asymptomatic cases, the course of the COVID-19 can be serious or even fatal. The affection of the myocardium, called myocardial injury, is the result of multiple triggers. The occurrence of cardiac arrhythmias in COVID-19 patients with myocardial involvement and a critical course is common. Several mechanisms induce cardiac arrhythmias, have been described (as hypoxia, myocarditis, and myocardial ischemia).

The effect of QT-prolonging drugs on cardiac arrhythmias has become mitigated, as these medications are no longer recommended. Acute management of cardiac arrhythmias in COVID-19 patients is affected by the reduction of exposure of health care personnel.[79]

4.4. Biomarker profile

The current study revealed that patients with cardiac arrhythmias had significantly high levels of ferritin, D-Dimer, Troponin-I and CRP ($P<0.05$). Also, there was a difference in levels of LDH but this difference was not significant ($P= 0.335$).

As compared to Zylla et al study in 2021, a different results observed, with regard to peak levels of cardiac and inflammatory biomarkers assessed during hospitalization, patients with arrhythmia displayed higher levels of high-sensitive troponin (hsTnT).

Moreover, a more pronounced significant increase in IL-6 and LDH could be detected in the arrhythmia subgroup ($P<0.05$), whereas there was no statistically significant difference in peak levels of CRP between groups ($P>0.05$).[90] In the same accordance, Salbach and colleagues in a study done in 2021 revealed that cardiac troponin values gradually increased across different stages of severity of myocardial injury after COVID-19, and the primary endpoints raised in parallel across classes of injury severity, cardiac troponin, and D-dimer values. It is also noteworthy that an increased cardiac troponin value is indeed associated with worse cumulative outcome, but also correlates with a variety of adverse secondary endpoints.[91]

Moreover, this study found that arrhythmias was significantly higher in patients had symptoms of palpitations, patients with lung involvement of ≥ 50%, and those with sinus tachycardia ($P<0.05$). Other variables (age, gender, BMI, Comorbidities, and SPO_2) showed no significant association with cardiac arrhythmias.

In comparison to Bhatla et al study in 2020, a close finding reported, in which among the assessment of selected variables that included age, sex, race, BMI, history of heart failure, CHD, diabetes, hypertension, CKD, and ICU status on admission, only ICU status emerged as having an association with each arrhythmia category (P<0.05).[81] Differently, Zylla and colleagues in 2021, reported a different result, in which arrhythmia was significantly observed in elderly and those with cardiovascular diseases, (P<0.05). Also, gender, hypertension, DM, and BMI were not related to the arrhythmia (P>0.05).[90]

The discrepancies reported above can related to different sample size, in addition to differences in mechanisms of care, burden of illness in the community, and timing of the peak infection rate. This changes may also point to an association between the degree of inflammatory state caused by COVID-19 and susceptibility to arrhythmia.

A wide array of cardiac manifestations is associated with the interaction between COVID-19 and the cardiovascular system. Cardiac-specific biomarkers provide a useful prognostic tool in helping identify patients with the severe disease early and allowing for escalation of treatment in a timely fashion. In fact, a Significant concerns relating to COVID-19 and the cardiovascular system have been highlighted, with COVID-19 inducing multiple cytokines and chemokines resulting in vascular inflammation, plaque instability, and myocardial inflammation.[92] "

Arrhythmias should be considered as one of the main complications of COVID-19. Mechanically, a variety of ion channels can be adversely affected, causing an alteration in cardiac conduction and/or repolarization properties, in addition to calcium handling, which can predispose to cardiac arrhythmogenesis. Furthermore, many antimicrobials currently used as potential therapeutic agents for COVID-19, like chloroquine, hydroxychloroquine and azithromycin, have uncertain benefit, and yet may cause electrocardiographic QT-prolongation with potential ventricular pro-arrhythmic effects.[93] This inflammatory state may increase the risk of thromboembolic complications, especially when AF is present. Future studies will need to evaluate the most effective and safest strategies for long-term anticoagulation and rhythm management in this 81population.[81]

4.5 Limitations

- The sample size was comparatively smaller than other studies and Short duration of holter monitoring due to unavailability of proper monitoring stations and device limitations.

CONCLUSION AND RECOMMENDATION

5.2. CONCLUSION

- dysrhythmias are common in patients with severe covid-19 disease.
- Most of the clinically significant arrhythmia like atrial fibrillation and non-sustained ventricular tachycardia were paroxysmal may not be detected during a routine ECG prompting the need for holter testing and use of telemetry monitoring.
- High levels of inflammatory marker (CRP, Ferritin, troponin, d-dimer) had significant relation to clinically severe covid-19 and risk of developing significant arrhythmias.

5.3. Recommendations

- Multi-centric larger studies with a larger sample done in isolation centers for covid-19 with longer test time for holter studies.
- Use of telemetry data or holter study to monitor patients with severe covid-19 and especially those with high inflammatory markers.
- Prompt diagnosis and treatment of arrhythmias early in the course of the disease.

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APPENDIX

Patient Questionnaire ( )

Patient ID#

Age

GENDER

BMI kg\m2

Symptoms of Palpitation yes( ) no( )

Any episodes of documented arrhythmia in hospitalization yes( ) no( )

PAST MEDICAL HISTORY DM ( ) HTN ( ) HEART DISEASE ( ) others ( )

Nasal swab

Ct chest percentage:

Markers of severity:

ferritin ( )

LDH ( )

d-dimer ( )

crp ( )

troponins positive ( ) negative ( )

Serum electrolytes K( ) CA ( ) NA ( ) B.UREA ( ) S.CREATININE ( )LFTS( )

THYTORID FUNCTION: normal ( ) hypothyroid ( ) hyperthyroid ( )

ECHO LVEF ( ) %

ECG FINDINGS : sinus tachycardia ( ) normal ( ) sinus bradycardia ( )

Arrhythmia ( )

qtc ms( )

HOLTER MONITOR FINDINGS

Average heart rate

Max hr rate **tachy%**

Min heart rate **brady%**

SVT

Atrial fibrillation

Atrial flutter

Non sustained vt

Bradycardia **avblocks**