ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY - AN ANALYTICAL STUDY

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CERTIFICATE - I

This is to certify that this dissertation entitled **"ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY -AN ANALYTICAL STUDY"** submitted by **Dr. SANCHNA DEV S** is a bonafide original work carried out by her under the guidance of Dr. Chandrasekar, Professor, Department of General Medicine, Govt. Stanley Medical College, Chennai towards the partial fulfillment of university regulations for the award of M.D. General Medicine Degree examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in May,2022.

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DECLARATION

I, **Dr. Sanchna Dev S,** solemnly declare that the dissertation titled **"ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY - AN ANALYTICAL STUDY"** is a bonafide work done by me at Government Stanley Hospital, Chennai between November 2020 and May 2021 under the guidance and supervision of **Prof. Dr. R. THILAKAVATHI M.D.,** Professor of Medicine, Government Stanley hospital, Chennai. I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other university, board either in India or abroad. This dissertation is submitted to the Tamil Nadu Dr. M.G.R Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

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CERTIFICATE – II

This is to certify that this dissertation work titled **"ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY -AN ANALYTICAL STUDY"** of the candidate **Dr. Sanchna Dev S** with Registration Number **201911070** for the award of M.D. DEGREE in the branch of BRANCH-I (GENERAL MEDICINE). I personally verified the ouriginal.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains, from introduction to conclusion pages and result shows 2% percentage of plagiarism in the dissertation.

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ABBREVIATIONS

ACE-2	Angiotensin converting enzyme
ACS	Acute Coronary Syndrome
AHA	American Heart Associaton
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
APTT	Activated Partial Thromboplastin time
BMI	Body Mass Index
COVID-19	Corona Virus Disease-19
CK	Creative kinase
CRP	C-reactive protein
DIC	Disseminated Intravascular Coagulation
ESR	Erythrocyte Sedimentation Rate
ESC	European Society of Cardiology
eGFR	Estimated Glomerular Filtration Rate
GBS	Guillain Barre Syndrome
GGO	Ground Glass Opacity
G-CSF	Granulocyte Colony Stimulating Factor
HIV	Human Immunodeficiency Virus
HFNO	High Flow Nasal Oxygen
IL-6	Interleukin-6
INR	International Standardised Ratio
JAK	Janus Kinase
LDH	Lactate Dehydrogenase

MERS	Middle East Respiratory Syndrome
MIS-C	Multi system Inflammatory Syndrome in Children
mRNA	Messenger RNA
PEEP	Positive End Expiratory Pressure
PT	Prothrombin Time
QTc	Corrected QT interval
QTcd	Corrected QT dispersion
QTd	QT dispersion
RT-PCR	Real time polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SARS CoV-2	Severe Acute Respiratory Syndrome corona virus-2
SBECD	Sulfobutylether-beta-cyclodextrin
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard Of Care
SOFA	Sequential Organ Failure Assessment
Tpe	T-peak to end of T wave
VOC	Variants Of Concern
VITT	Vaccine Induced Thrombotic Thrombocytopenia
WHO	World Health Organisation

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Introduction

INTRODUCTION

The global pandemic coronavirus disease-COVID 19, caused by Severe Acute Respiratory Syndrome Coronavirus (SARS CoV-2) was reported first in Wuhan, China. Although lungs are the predominant target of this virus, manifold manifestations of this disease continues to unfold.

An increased risk of cardiac complications namely myocarditis, heart failure, acute coronary syndrome and arrhythmias have been increasingly reported with this novel virus.

Other viruses like Parvo virus B-19, coxsackie virus, adeno virus have also been found to cause myocarditis leading to arrhythmia by various mechanisms. MERS and SARS, the two close relatives of COVID 19 had also caused a significant incidence of cardiac complications.

Due to the plentiful use of many 'off label' drugs in COVID 19, it is especially warranted to do a detailed study on the risk of arrhythmias, so as to avoid or adjust the dose of arrhythmogenic drugs in the treatment of this novel disease.

Aim & Objectives

AIMS AND OBJECTIVES

AIM:

To determine the risk of arrhythmias in COVID 19 patients.

OBJECTIVES:

To assess the risk of arrhythmias in COVID 19 patients by surface ECG markers –

- QT interval,
- Corrected QT interval (QTc),
- QT dispersion (QTd) and corrected QTcd,
- T-wave peak-to end interval(Tpe), Tpe/QT ratio and Tpe/QTc ratio, and
- PR interval.

Review of Literature

REVIEW OF LITERATURE

CURRENT SITUATION OF THE PANDEMIC

We are right in the middle of a battle against a pandemic which has tested the world and its resources to the core. The ongoing COVID-19 pandemic is caused by a coronavirus named SARS-CoV-2(1). As of 12th December, nearly 269 million confirmed cases and nearly 5.3 million deaths have been reported world wide (2).

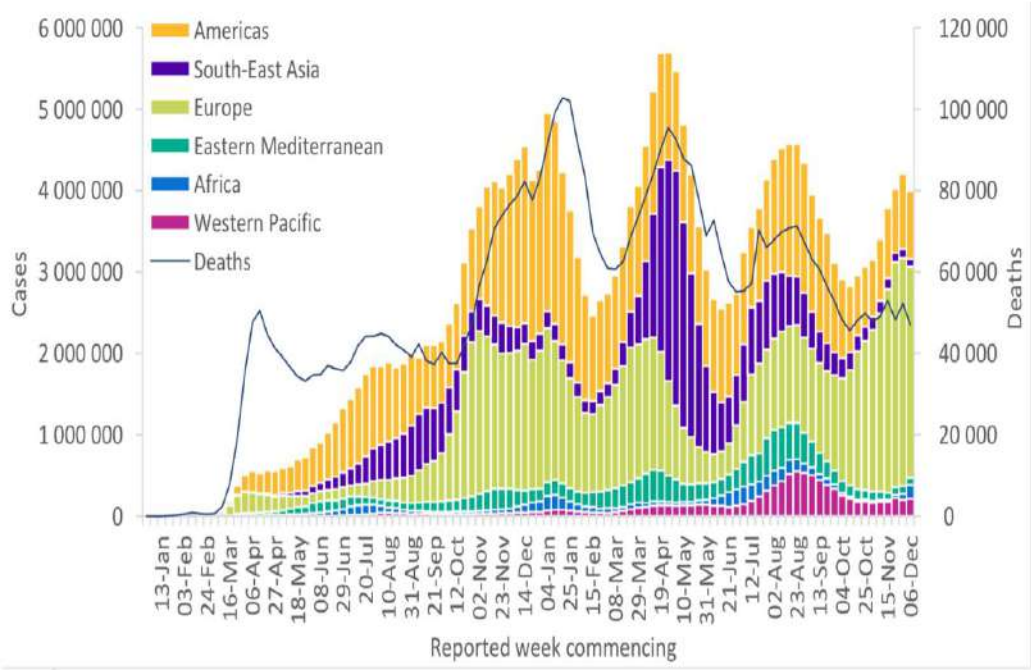


Figure 1 : COVID-19 cases reported weekly by WHO Region, and global deaths, as of 12 December 2021

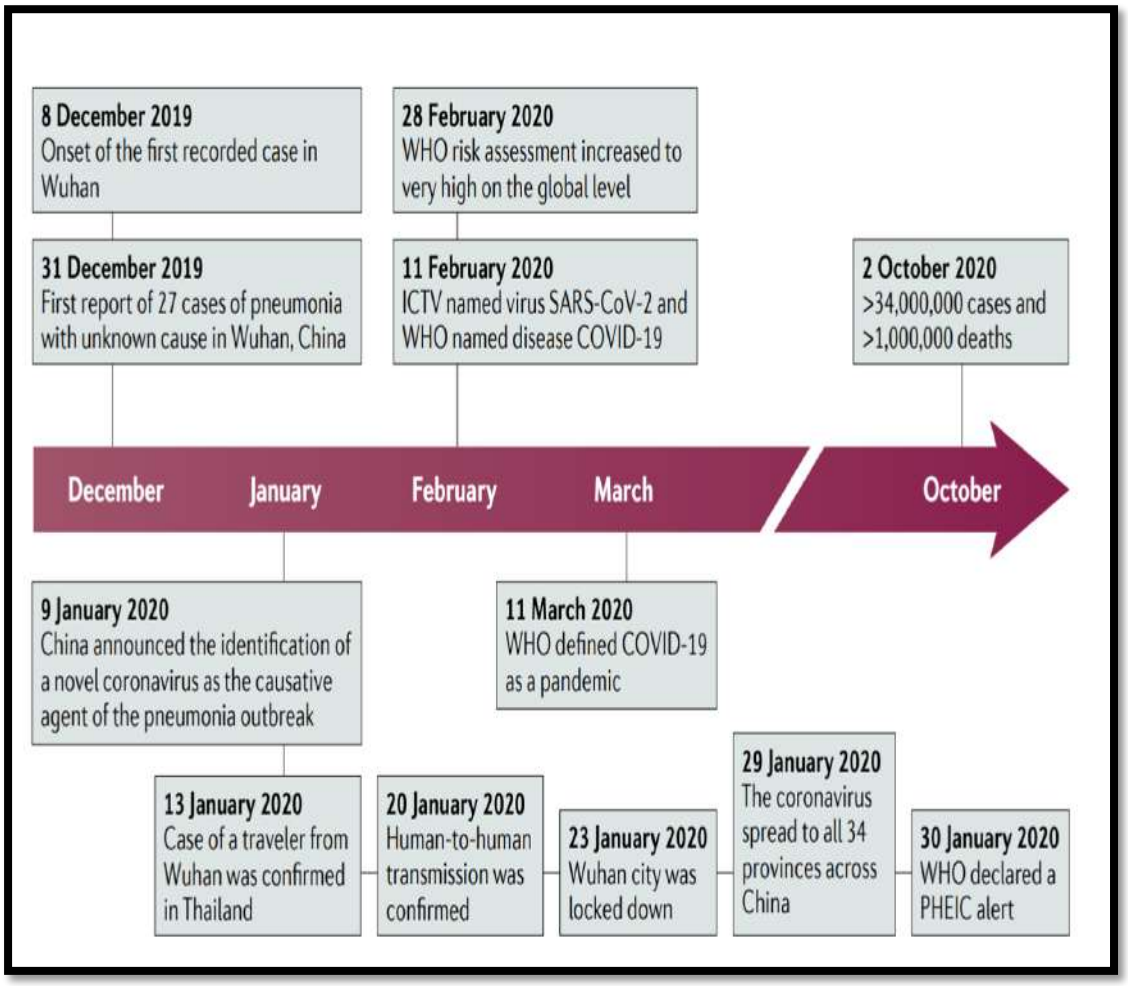
CORONA VIRUSES

Corona viruses(CoVs) belong to the family Coronaviridae and are named so because of the spike projections arising from the virus membrane give the resemblance to a crown, or *corona* in Latin(3). These are enveloped viruses with a single strand,

positive sense RNA genome and are broadly distributed in humans and other mammals, including camels, bats, masked palm civets, mice, dogs, and cats(4). CoVs are divided into 4 genera : alpha-, beta-, gamma and delta-CoV (1). CoVs infecting humans belong to the alpha- or the beta-CoV (1). Even though most human coronavirus cause mild infections, corona viruses have caused two large-scale pandemics in the last two decades (apart from the ongoing one): Severe Acute Respiratory Syndrome (SARS) with a mortality rate of 10%, and Middle East Respiratory Syndrome (MERS) with a mortality rate of 37%, detected for the first time in 2003 and 2012, respectively (1),(4). These CoVs also caused infections in animals viz. SARS-CoV infected civet cats and MERS-CoV was found in dromedary camels corroborating it's zoonotic origin (1).

SARS-CoV-2

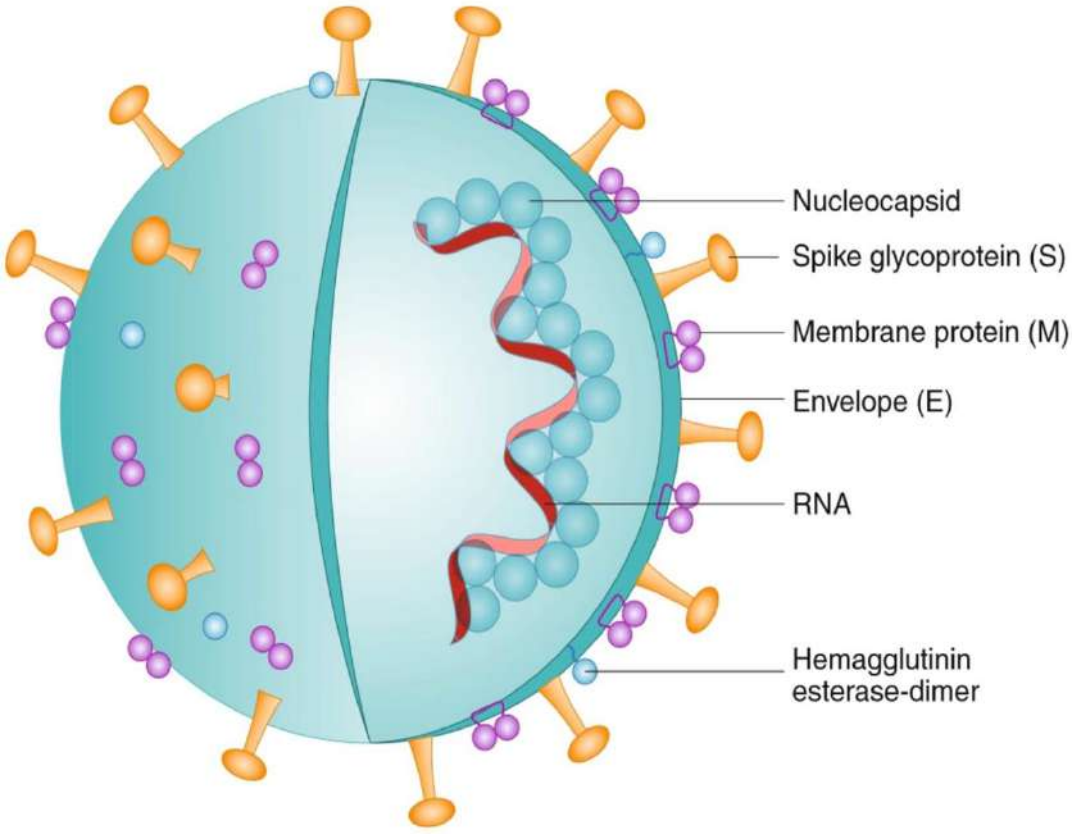
In late December 2019, the city of Wuhan, Hubei province in China became the epicentre of an outbreak of pneumonia of unknown etiology (5). Most of these patients were found to be epidemiologically associated with the Huanan wholesale seafood market in Wuhan, where seafood, wild and farmed animal species were sold (5). By Jan 7, 2020 Chinese scientists had isolated a novel CoV from bronchoalveolar lavage of patients in Wuhan , and the SARS-CoV-2, previously named "2019 novel coronavirus" (2019-nCoV), was identified using metagenomic RNA sequencing(5),(6). The analysis of the published genetic sequences suggests a spillover from an animal source to humans which should have happened during the last few months of 2019 in China (1). Exact animal source of SARS CoV-2 is still not known. However, the closest relative of SARS CoV-2 known till date is a bat coronavirus detected in *Rhinolophus affines* from Yunnan province in China, whose full-length genome sequence is 96.2% identical to that of SARS-CoV-2(7).



The high transmission efficiency of SARS-CoV-2 (the initial estimate of reproduction number was fairly above 1) and the abundance of international travel enabled the explosive global spread of COVID-19 (7). On January 30, 2020, WHO declared COVID-19 epidemic as a public health emergency of international concern (PHEIC) and on 11 March 2020, the WHO officially declared the COVID-19 outbreak as a pandemic (7).

STRUCTURE(8)

SARS-CoV-2 has 79% similarity with the genome sequence of SARS-CoV and 50% with MERS-CoV (7). The viral genome has an initial packaging of capsid formed by the nucleocapsid protein (N) and an envelope which is associated with three structural proteins: membrane protein (M), spike protein (S), and envelope protein (E). This novel betacoronovirus has four structural proteins (S, E, M, and N) and sixteen non-structural proteins (nsp1−16).



Schematic representation of SARS-CoV-2 structure. This is an enveloped, positive-sense RNA virus with four main structural proteins, including spike (S) and membrane (M) glycoproteins, as well as envelope (E) and nucleocapsid (N) proteins.

Figure 2.

VARIANTS OF CONCERN (VOC)

SARS CoV-2 has evolved over time. Certain variants have caught widespread attention because of their rapid emergence within population groups and evidence for rapid transmission or clinical implications.These are labelled as the variants of concern viz.

- **Delta (B.1.617.2 lineage)** – this variant was first identified in India in Dec,2020 and has since become the most prevalent variant globally (9). The delta variant is highly transmissible and with higher risk of severe disease and hospitalisation in comparison with the previously dominant strain i.e **Alpha(B.1.1.7 lineage)** variant (9).

- **Omicron(B.1.1.529 lineage)** – this variant was first reported from Botswana and very soon afterwards from South Africa in Nov 2021 (2). Preliminary data suggests that the Omicron variant has a replication advantage over the delta variant and can evade infection / vaccine induced humoral immunity to a larger extent than previous variants(2). However, reports from South Africa and other countries suggest that disease severity might be less than with other variants (2). India is also seeing rise in the Omicron cases as of Dec 28, 2021.

- **Other variants –Alpha(B.1.1.7 lineage)** – was first identified in the United Kingdom in the later half of 2020 and subsequently became the predominant variety, until the emergence of the Delta variant (9).

- **Beta(B.1.351 lineage)** -was first identified in South Africa in late 2020, further quickly becoming the dominants strain there (9).

-Gamma(P.1 lineage) – was first identified in Japan in 4 travellers from Brazil and later reported from Brazil in Dec, 2020.

PATHOGENESIS(10),(11)

SARS CoV-2 affects both pulmonary and extra pulmonary sites. Because the SARS-CoV-2 spike protein has an affinity for angiotensin-converting enzyme 2 receptors, which facilitate entry of the virus into cells, extra pulmonary manifestations are mostly noted in tissues that express ACE-2 receptors.

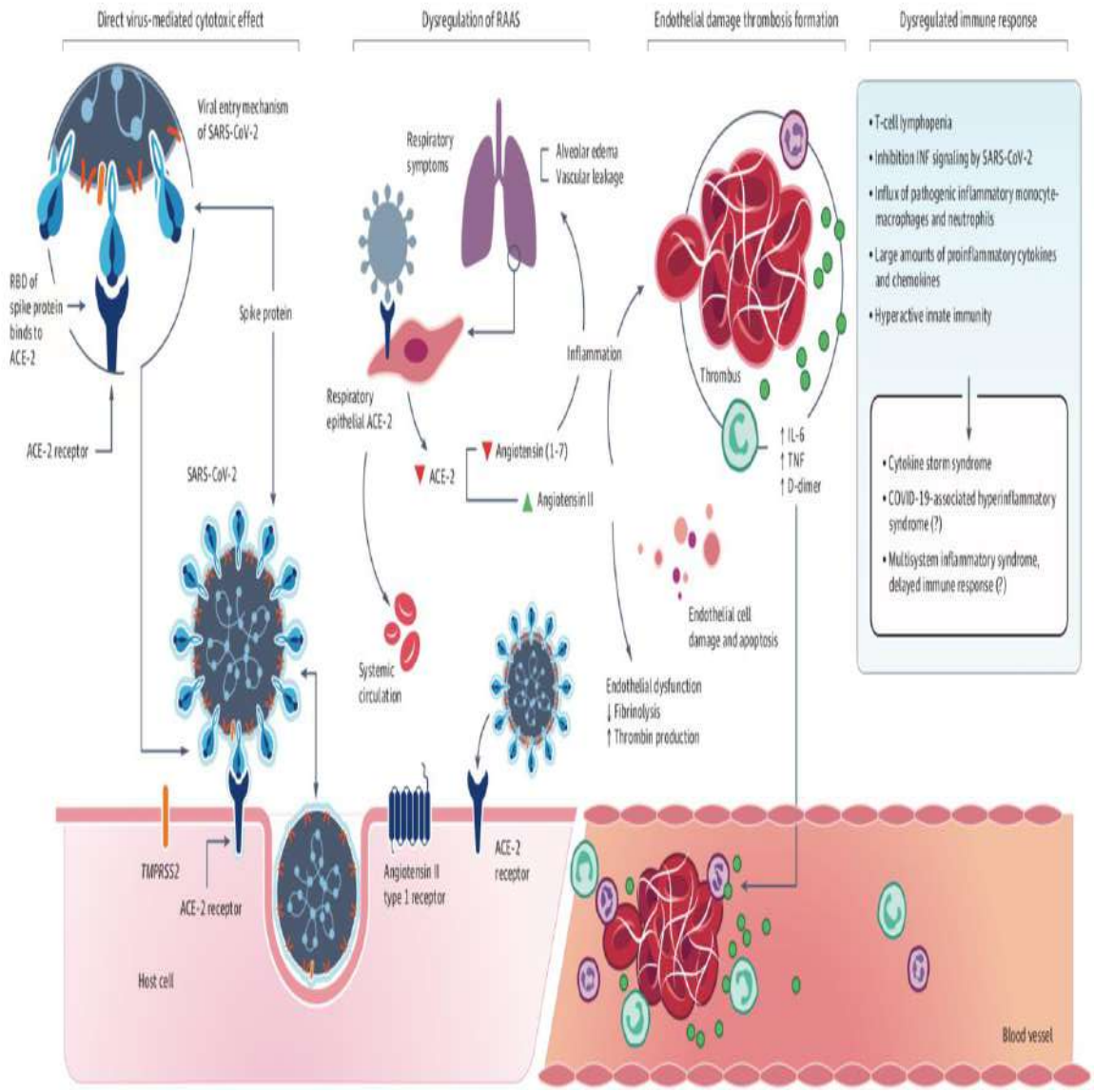


Figure 3. Pathogenesis of SARS coV-2 (46)

The ACE2 receptors are widely expressed in vascular endothelium, alveolar monocytes and macrophages and respiratory epithelium.

Possible mechanisms of injury include:

- direct virus-mediated cytotoxic effects
- dysregulation of the renin-angiotensin-aldosterone system resulting from down regulation of ACE-2 and causing viral-induced inflammation
- endothelial damage and thromboinflammation – (can explain the unusual trend of hypercoagulation)
- dysregulation of the immune response along with hyper inflammation caused by inhibition of interferon, depletion of T lymphocytes, and increased production of pro inflammatory cytokines.

The hyper inflammatory syndrome of COVID-19 shares many similarities with the cytokine storm. Serum cytokine levels are markedly elevated in Covid-19 patients especially those with severe disease. Higher interleukin-6 levels are strongly associated with poor survival. Apart from the elevated systemic cytokine levels and activated immune cells, there's elevation of many inflammatory markers such as C-reactive protein , ferritin and d-dimer level and hypoalbuminemia, renal dysfunction, and effusions, as seen in other cytokine storm disorders . Lab parameters reflecting hyper inflammation and tissue damage were found to predict worse outcomes. However, it is not known whether a failure to resolve the inflammatory response because of ongoing viral replication or immune hyperactivity or immune dysregulation is the underlying pathophysiology in severe cases.

Another hypothesis suggests autoimmunity due to molecular mimicry between SARS-CoV-2 and a self-antigen as a mechanism of injury (11).

SARS CoV-2 is capable of actively replicate in the upper respiratory tract as evidenced by their demonstration of live virus in throat swabs/ detection of mRNA in the cells of the upper respiratory tract cells. The virus shows tropism towards upper respiratory tract tissue and this explains the continuous pharyngeal shedding especially when symptoms are minimal and restricted to the upper respiratory tract (12). However later in the course of the disease, replication of the virus occurs in the lower respiratory tract- this generates the secondary viremia. What follows is an explicit crusade of the organ sites that express ACE2 receptors like the heart, kidney, gastrointestinal tract and distal vasculature. This pattern of viral replication correlates with clinical symptomatology(12).

Many critically ill patients have been reported with a hypercoagulable state characterised by increased levels of D-dimmer, fibrinogen, prolonged prothrombin time and near normal activated partial thromboplastin time, with some of them going for overt disseminated intravascular coagulation (DIC) (12). A study by Tang et al. Showed that 71.4% of non survivors and 0.6% of survivors showed evidence of overt DIC (12). Acro-ischaemia was reported in critically ill patients heralding the onset of overt DIC (12).

Histopathological changes mostly occur in lungs showed bilateral diffused alveolar damage, hyaline membrane formation, desquamation of pneumocytes and fibrin deposits corroborating the pathogenesis(13).

TRANSMISSION(12)

The main route of transmission is direst person-to-person or indirect respiratory exposure. But it’s thought to occur mainly through close range contact of prolonged

exposure (within approx 6 feet for at least 15 minutes) or shorter exposures to individuals who are symptomatic via respiratory particles.

Indirectly, infection might also occur if a person's hands are contaminated by the respiratory secretions or by touching contaminated surfaces (virus appears to persist in high doses on impermeable surfaces like stainless steel, plastic when compared to impermeable surfaces such as cardboard(13). Even up to 3-4 days after inoculation virus has been isolated from impermeable surfaces(13).Viral contamination, especially of hospital rooms have been reported. But rapid decay, within 48-72 hours, occurs of the virus on surfaces.

Transmission over long distance through airborne route is also possible but its not sure how much it has contributed to the spread of the disease. The virus has also been detected in non-respiratory specimens including stool, blood, ocular secretions and semen. However their role in transmission is uncertain.

There's however no evidence of vertical transmission in maternal COVID-19 infections(13).

CLINICAL COURSE

The clinical course of COVID-19 disease can be divided into 3 phases (12)

- STAGE l -Viremia(early) phase
- STAGE ll - Acute(pneumonia) phase
- STAGE lll - Severe/recovery phase

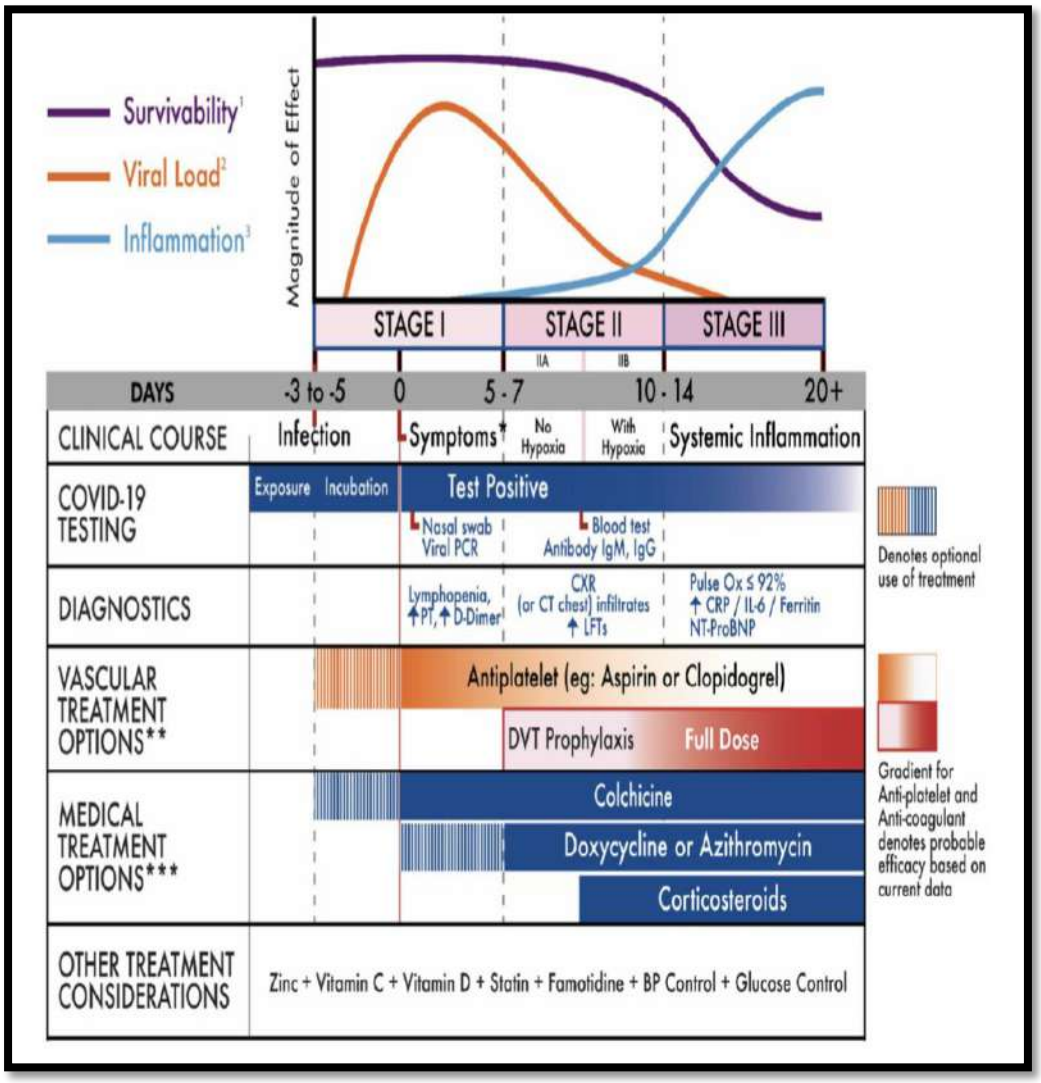


Figure 4. COVID-19 clinical stages and management strategy(47)

SYMPTOMATOLOGY (14)

Presenting signs and symptoms of COVID-19 may differ in patients . The mean incubation period ~ 5 days. The severe disease usually develops ~ 8 days after symptom onset and critical disease and death occurs ~ 16 days.

Most patients experience.

- Fever (83–99%)
- Cough (59–82%)
- Fatigue (44–70%)

- Anorexia (40–84%)
- Shortness of breath (31–40%)
- Myalgia (11–35%)
- Other non-specific symptoms include sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting.
- Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms.
- Neurological manifestations such as dizziness, agitation, weakness, seizures, or stroke.
- Older people and immunosuppressed patients can present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion, and absence of fever.
- Symptoms such as dyspnoea, fever, gastrointestinal (GI) symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events can overlap with symptoms of COVID-19.
- Children may not have fever/cough as frequently reported as adults.

RISK FACTORS ASSOCIATED WITH SEVERE DISEASE(14)

Although severe disease can occur in any individual, most with severe disease have at least one risk factor.

- Increasing age (particularly age >60 years)
- Comorbidities : diabetes mellitus, systemic hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental health disorders, chronic kidney disease, immunosuppression, HIV, obesity, Tuberculosis and cancer.

- Smoking (current or former)
- High sequential organ failure assessment (SOFA) score and D-dimer >1 µg/L on admission were associated with high mortality
- In pregnancy : increasing maternal age, high BMI, non-white ethnicity, chronic conditions and pregnancy specific conditions such as gestational diabetes and pre-eclampsia can overlap with COVID -19 symptoms

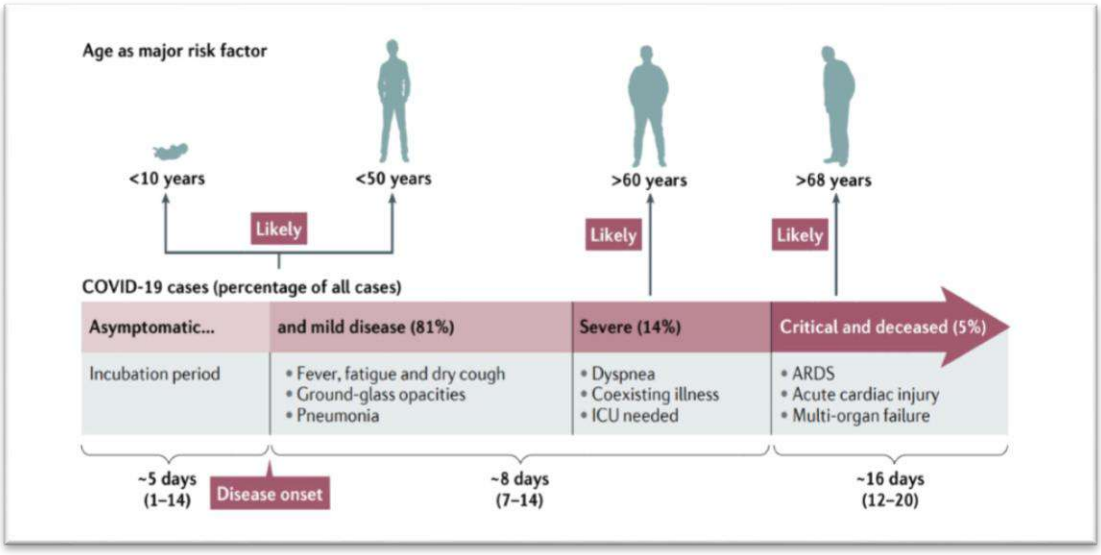


Figure 5. Clinical Features of COVID-19 with age as a major risk factor(7)

CLINICAL SPECTRUM- DISEASE SEVERITY CLASSIFICATION(14)

Based on WHO recommendation of classifying disease severity:

- **Asymptomatic or Pre symptomatic Infection** : Individuals who test positive for SARS-CoV-2 using a virological test (a nucleic acid amplification test [NAAT] or an antigen test) but who are otherwise asymptomatic.
- **Mild disease:** Patients with symptoms of COVID 19, without evidence of viral pneumonia or hypoxia.
- **Moderate disease :**

1. **Adolescent or adult :** clinical signs of pneumonia like, fever, cough, dyspnoea, fast breathing is present. But there are no signs of severe pneumonia like, SpO2 ≥ 90% on room air.

2. **Child :** clinical signs of non-severe pneumonia (cough or difficulty in breathing plus fast breathing and/or chest indrawing) with no signs of severe pneumonia.

Fast breathing (in breaths/min):

- < 2 months: ≥ 60
- 2–11 months: ≥ 50
- 1–5 years: ≥ 40

Although the diagnosis is mostly made on clinical features ; chest imaging studies can also help in the diagnosis .

- **Severe disease :**

1. **Adolescent or adult:** clinical signs of pneumonia like, fever, cough, dyspnoea plus one of the following:
   - respiratory rate > 30 breaths/min
   - severe respiratory distress
   - SpO2 < 90% on room air.

2. **Child**: clinical signs of pneumonia like, cough or difficulty in breathing plus fast breathing or chest wall indrawing plus at least one of the following:
   - SpO2 < 90%,

- Very severe chest wall indrawing, central cyanosis, grunting or presence of any other general danger signs like inability to breastfeed or drink, lethargy or unconsciousness, or convulsions.

- **Critical disease :** Individuals can proceed to have respiratory failure, septic shock, and/or multiple organ dysfunction

- **Acute Respiratory Distress Syndrome (ARDS) :**

  - Onset usually within 1 week of a known clinical insult (like, pneumonia) or new or worsening respiratory symptoms.

  - Chest imaging: (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules.

  - Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload.

  - Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present.

  - Impairment in oxygen is defined as :

a. Mild ARDS : 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5cm

b. Moderate ARDS : 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O)

c. Severe ARDS : PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O).b

- **Sepsis :**

1. **Adults**: Sepsis is defined as an acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status (delirium), difficult or fast breathing, low oxygen saturation, reduced urine output , fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.

2. **Children**: suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count.

- **Septic Shock :**

1. Adults: persistent shock in spite of volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate levels > 2 mmol/L.

2. Children: any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia.

- **Acute thrombosis :** Acute venous thromboembolism (i.e. pulmonary embolism), acute coronary syndrome, acute ischemic stroke.

- **MIS-C :**

Preliminary case definition: children and adolescents 0–19 years of age with fever > 3 days

AND two of the following: rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet); hypotension or shock; features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP); evidence of coagulopathy (by PT, PTT, elevated D-dimers), acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain);

AND elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin

AND no other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes

AND evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

DIAGNOSIS

COVID-19 disease is typically made using polymerase chain reaction testing via nasal swab. But, because of false negative results rates in SARS CoV-2 PCR testing, clinical, laboratory and imaging aids can also be used to make a presumptive diagnosis.

Polymerase Chain Reaction (PCR)(13) - Reverse transcription polymerase chain reaction(RT PCR) for SARS-CoV-2 detection from respiratory tract samples (commonly -nasopharyngeal or oral and quite recently saliva) is by far the most commonly used and reliable test there is. The RNA targets genes commonly used are either one or more of the envelope (env), nucleocapsid (N), spike (S), RNA-dependent RNA polymerase (RdRp), and ORF1 genes (15).The sensitivity of testing varies with time from exposure. One study had estimated sensitivity at 33% ~ 4 days after exposure,

62%~ on the day of symptom onset a nd 80%~ 3 days after the onset of symptom(15) . Many factors contribute to false-negative tests starting with the adequacy of the specimen collection technique, time from exposure to the specimen source. Lower respiratory samples, like bronchoalveolar lavage fluids are more sensitive than upper respiratory samples.

In another study, out of the 1070 specimens collected from 205 patients with COVID-19 disease in China, bronchoalveolar lavage fluid specimens had the highest positive rates of SARS-CoV-2 PCR testing results (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swabs (32%), faeces (29%) and blood (1%). However, none of the urine specimens had tested positive (16). The viral RNA in the nasopharyngeal swab is measured by the cycle threshold (Ct) which is the number of replication cycles required to produce a fluorescent signal, and with lower Ct values representing higher viral RNA loads. A Ct value of less than 40 is clinically reported as PCR test positive (15)

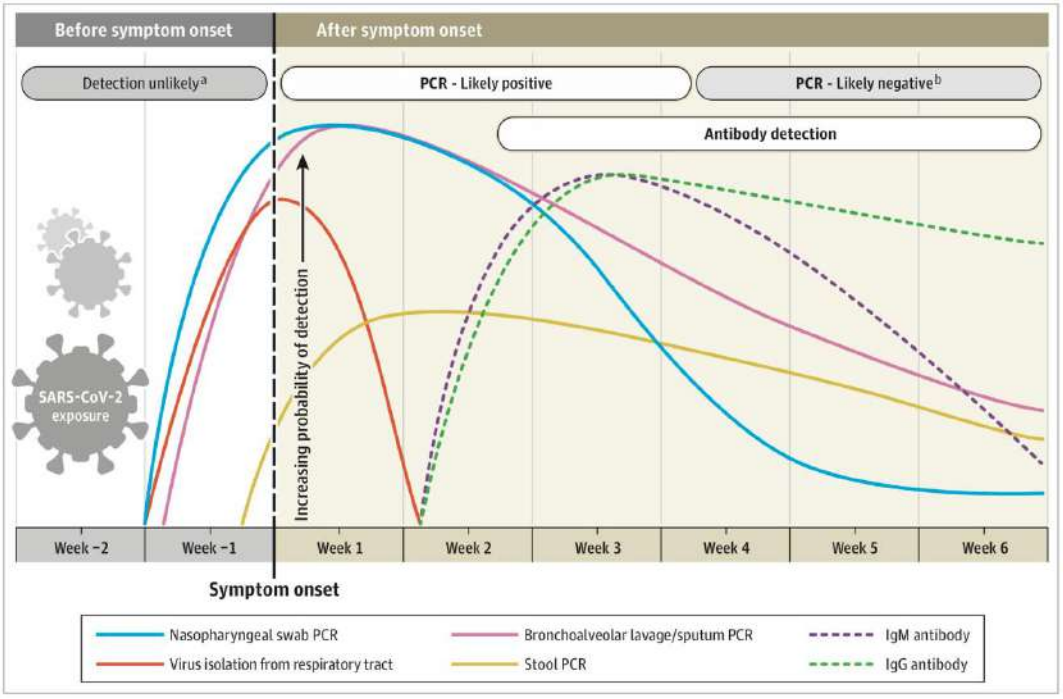


Figure 6. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset(15)

Serological tests

Many serological tests can also aid in the diagnosis and help in the measurement of responses to novel vaccines. However, the presence of antibodies may not confer immunity because not all antibodies produced in response to infection are neutralising. It's not known if or how frequently second infections with SARS-CoV-2 , or if presence of antibody changes susceptibility to subsequent infection or duration of antibody protection lasts. IgM antibodies are detected within 5 days of infection with higher IgM levels seen during weeks 2 to 3 of illness, while an IgG response is first seen approx. 14 days after symptom onset. Therefore, serological tests are not recommended for diagnosis.

Laboratory findings(15)

The major tests that are routinely done for COVID-19 patients are

- complete blood count (CBC)
- coagulation tests (PT,aPTT and D-dimers)
- inflammation-related tests (ESR, CRP, ferritin, procalcitonin, IL-6 levels)

Apart from these, biochemical parameters such as LDH, ALT(SGPT), AST (SGOT), bilirubin, albumin, creatinine kinase(CK) and creatinine are used to assess the functional activities of the vital organs that are commonly affected in COVID-19.

1. COMPLETE BLOOD COUNT

Lymphopenia and mild thrombocytopenia is the most common hematological abnormalities found in COVID-19 patients. Some studies reported neutrophilia in COVID-19 patients.Increased NLR also used as predictor of severe disease.Platelet count less than 1.5 lakhs/mm3 also indicates poor prognosis.

2. COAGULATION TESTS:

It has been reported that PT and APTT levels are elevated in COVID-19 patients. Elevated levels of D-dimer has both diagnostic and prognostic value

3. INFLAMMATION RELATED TESTS:

The most common abnormalities in biochemical parameters include elevated lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels and decreased levels of serum albumin. Creatinine levels are also raised in few patients. These also serves as a marker of poor prognosis. Decrease in the levels of LDH and CK during treatment correspond with viral mRNA elimination. So they probably predict the response to treatment.

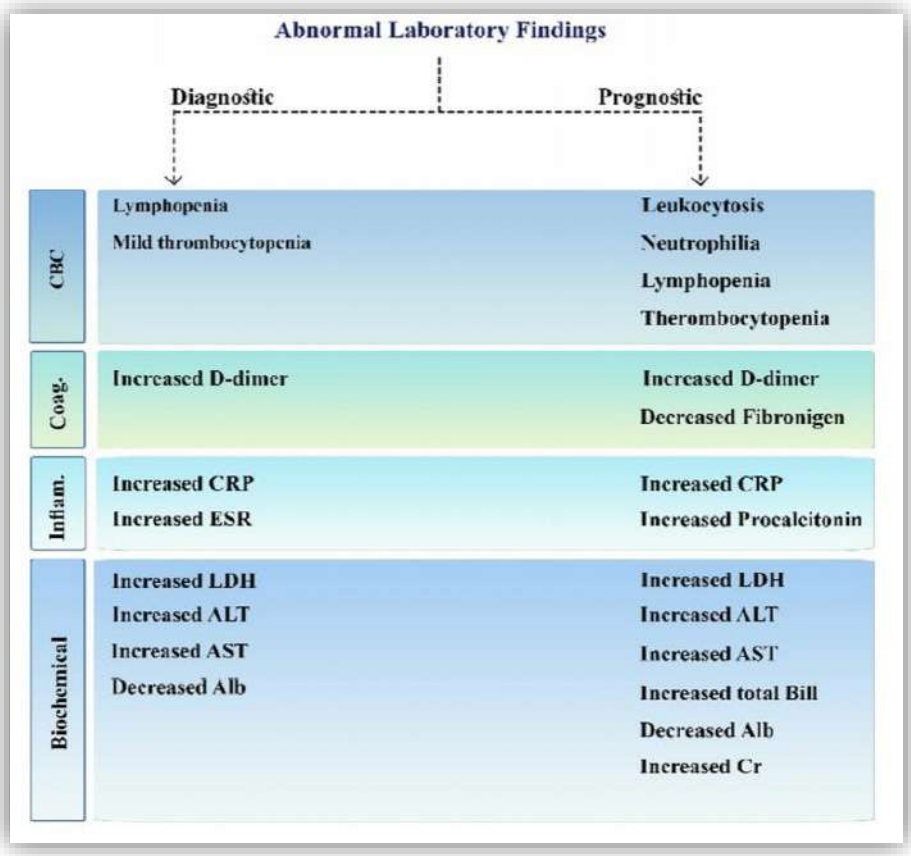
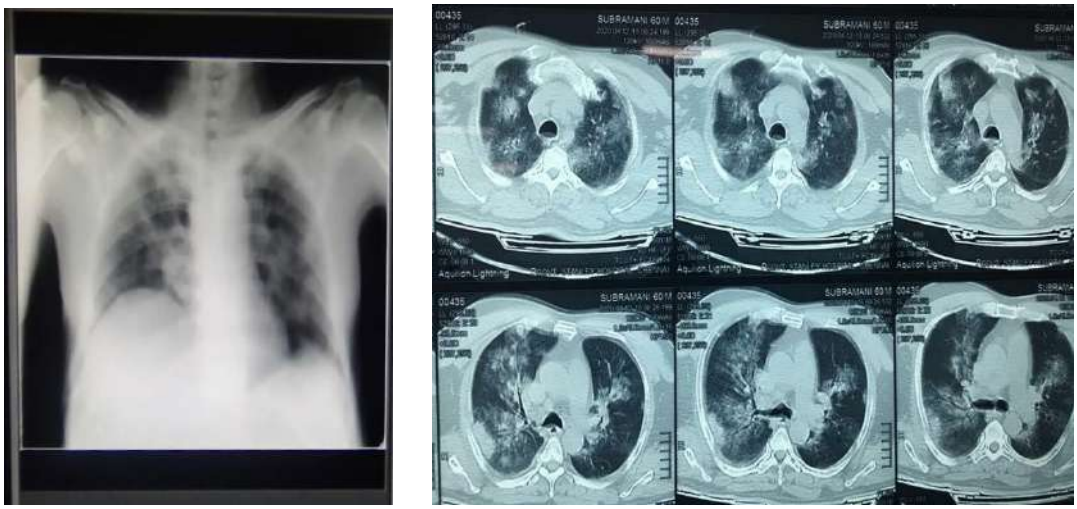


Figure 7. Diagnostic and prognostic lab findings in COVID-19(15)

Imaging studies

Computed tomography of the chest has been widely used to assess the degree of lung involvement in COVID -19 disease. In the early course of the pandemic, CT chest was preferred for imaging as many studies reported that the base line chest X-ray often failed to pick up the ground glass opacities(GGO) – the characteristic finding in COVID-19. However, further studies showed that chest X-ray can be used as a sensitive tool for diagnosis and it did not alter the prognosis. Vancheri et al reported that alterations in imaging such as reticular pattern, ground glass opacities and consolidation occurred in that order often overlapping with each other, predominantly with bilateral and peripheral involvement before central involvement (17) .



(A) **(B)**

Figure 8 - A:A chest x-ray of a 50 yr old male with COVID-19 showing GGO, B: CT chest of a 60 year old male with COVID-19 showing peripheral rounded opacities , GGO and patchy consolidation

TREATMENT

Till date, there are neither any proven effective treatment for COVID-19 nor antivirals that are explicitly effective against SARS-CoV-2, even though some therapies have shown some benefits in studies. As of April 5, 2021 there were about

506 therapeutic drugs in development and 419 in human clinical trial (https://biorender.com/covid-vaccine-tracker).

Oxygen Support

A whooping ~75% of patients hospitalised with COVID-19 require supplemental oxygen therapy(13). For patients who are not responding to conventional oxygen therapy, heated high-flow nasal oxygen (HFNO) can be administered. For patients requiring invasive mechanical ventilation, lung-protective ventilation with low tidal volumes (4-8 mL/kg, predicted body weight) and plateau pressure less than 30 mg Hg with prone positioning, a higher positive end expiratory pressure(PEEP) strategy, and short-term neuromuscular blockade may facilitate oxygenation. The threshold for intubation in COVID-19–related respiratory failure is controversial, as many patients have normal work of breathing but severe hypoxemia. Earlier intubation allows time for a more controlled intubation process. However, hypoxemia in the absence of respiratory distress is well tolerated, and patients may do well without mechanical ventilation. As of now, insufficient evidence exists to make recommendations regarding earlier vs later intubation.

In an observational study by Rawson et al, approximately 8% of in-patients with COVID-19 experience a bacterial or fungal co-infection, but up to 72% are treated with broad-spectrum antibiotics (18). Awaiting further data, it may be advisable to withhold antibacterial drugs in patients with COVID-19 and reserve them for those who present with radiographic findings and/or inflammatory markers compatible with co-infection or who are immunocompromised and/or critically ill(13).

Therapeutics(19)

Based on the pathogenesis of COVID-19, approaches that target the virus itself (eg, antivirals, passive immunity, interferons) are more likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course.

1. Antivirals

These drugs inhibit viral entry viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase. Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses to the hyper inflammatory state that can characterise the later stages of disease including critical illness.

1.1 REMDESIVIR – It is the **only anti-viral drug that is approved** by the Food and Drug Administration for the treatment of COVID-19. Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro activity against SARS-CoV-2. In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.

Clinical trials-

- **ACTT-1** (20)**:** Multinational, Placebo-Controlled, Double-Blind RCT of Remdesivir in Hospitalised Patients With COVID-19 observed reduced time to

recovery compared to placebo(10 days vs 15 days). However, there was no difference in mortality.

- **DisCoVeRy** (21) : Open-Label, Adaptive RCT of Remdesivir in Hospitalised Patients With Moderate or Severe COVID-19 in Europe observed no difference in clinical status between the two arms on Day 15.

- **WHO Solidarity Trial** (22): Multinational, Open-Label, Adaptive RCT of Repurposed Drugs in Hospitalised Patients With COVID-19 reported an in-hospital mortality of 11% with remdesivir vs 11.2% standard of care.

- **GS-US-540-5774 study** (23) : Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared With Standard of Care in Hospitalised Patients With Moderate COVID-19 showed 5 day remdesivir arm had significantly better clinical status at Day 11 than standard of care. However, time to clinical improvement was similar between the two arms.

Adverse effects –

- gastrointestinal symptoms (e.g., nausea),
- elevated transaminase levels
- prothrombin time increase without a change in INR
- hypersensitivity reactions

Therefore, liver function tests and prothrombin time tests should be performed for all patients before starting remdesivir. The drug has to be discontinued if patients ALT level increases >10 times the upper limit of normal. Remdesivir contains a vehicle- sulfobutylether- beta-cyclodextrin sodium (SBECD) that is primarily excreted

through the kidneys.The FDA does not recommend use in patients with eGFR <30ml/min.

Cardiac effects (24)- Post marketing reports of **bradycardia**, including severe bradycardia (some fatal) and sinus bradycardia have been reported in patients receiving remdesivir for SARS-CoV-2. Mechanism is unknown; it has been suggested that the active metabolite of remdesivir, a nucleotide triphosphate derivative, may slow sinoatrial node automaticity due to its similarity with adenosine triphosphate. The onset of bradycardia is varied; a median onset of 2.4 days (range: 1 to 6 days) was observed in an observational study.

1.2 CHLOROQUINE / HYDROXYCHLOROQUINE AND / OR AZITHROMYCIN

Chloroquine is an anti malarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria. Both chloroquine and hydroxychloroquine increase the endososmal pH, which inhibits fusion between SARS-CoV-2 and the host cell membrane. Chloroquine inhibits glycosylation of the cellular ACE2 receptor, which may interfere with the binding of SARS-CoV-2 to the cell receptor. In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of viral genome. Both chloroquine and hydroxychloroquine also have immunomodulatory effects, which have been hypothesised to be another potential mechanism of action for the treatment of COVID-19. Azithromycin has antiviral and anti-inflammatory properties. When used in

combination with hydroxychloroquine, it has been shown to have a synergistic effect on SARS CoV-2 in vitro and in molecular modelling studies.

Clinical trials-

- **Solidarity Trial** (22): Hydroxychloroquine in Hospitalised Patients With COVID-19 observed no significant difference in in-hospital mortality and clinical outcome between HCQ arm and SOC arm and was halted in view of futility.

- Similar observations were seen with **PETAL trial** , and was also stopped for futility

- **RECOVERY trial** (25) : Open-label, randomised controlled platform trial with multiple arms; in 1 arm, hospitalised patients received HCQ reported that HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients who received HCQ had a longer median length of hospital stay, and those who were not on invasive mechanical ventilation at the time of randomisation were more likely to require intubation or die during hospitalisation if they received HCQ. There was also no significant difference in cardiac events in the HCQ arm . In **RECOVERY**, azithromycin alone (without hydroxychloroquine) did not improve survival or other clinical outcomes to the usual SOC.

Adverse effects-

- Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than

chloroquine. **Cardiac adverse events** that have been reported in people who received hydroxychloroquine include **QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths**.

- The use of azithromycin has also been associated with **QTc prolongation**, and using it in combination with hydroxychloroquine has been associated with a higher incidence of QTc prolongation and cardiac adverse events in patients with COVID-19.

Drug interaction-Chloroquine and hydroxychloroquine may decrease the anti viral activity of remdesivir; co-administration of these drugs is not recommended.

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against the use of chloroquine or hydroxychloroquine and/or azithromycin for the treatment of COVID-19** in hospitalised patients and in non-hospitalised patients.

1.3 INTERFERONS

Interferons are a family of cytokines with in vitro and in vivo antiviral properties. Many of the early studies that evaluated the use of systemic interferons were conducted in early 2020, before the widespread use remdesivir and corticosteroids.

The COVID-19 Treatment Guidelines Panel **recommends against** the use of systemic interferon beta or alfa or lambda for the treatment of hospitalised patients with COVID-19.

1.4 IVERMECTIN

Ivermectin is a Food and Drug Administration (FDA)-approved anti-parasitic drug that is used to treat several neglected tropical diseases. Ivermectin is not approved by the FDA for the treatment of any viral infection.

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host's importin alpha/beta-1 nuclear transport proteins, which are part of a major intracellular transport process that viruses hijack to enhance infection by suppressing the host's response to virus. In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane. Some studies have also reported potential anti-inflammatory properties that may be beneficial to people with COVID-19.

There is **insufficient evidence** for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19.

Adverse effects- dizziness, pruritis, nausea,diarrhoea.

1.5 LOPINAVIR / RITONAVIR and other HIV protease inhibitors

The replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase. The two proteases responsible for this cleavage: 3-chymotrypsin-like protease and papain-like protease.

Clinical trials-

- **RECOVERY trial** (25) - Lopinavir/ritonavir did not decrease 28-day all-cause mortality when compared to the usual standard of care in hospitalised patients.

Participants who received lopinavir/ritonavir and those who received standard of care only had similar median lengths of hospital stay. Among the patients who were not on invasive mechanical ventilation at the time of randomisation, those who received lopinavir/ritonavir were as likely to require intubation or die during hospitalisation as those who received standard of care.

- **Solidarity trial** (22) -Among hospitalised patients, lopinavir/ritonavir did not decrease in-hospital mortality or the number of patients who progressed to mechanical ventilation compared to standard of care.

Adverse effects –

- Nausea, vomiting, diarrhoea (common)
- **QTc prolongation**
- Hepatotoxicity

The COVID-19 Treatment Guidelines Panel **recommends against** the use of lopinavir/ritonavir and other HIV protease inhibitors for the treatment of COVID-19 in hospitalised patients and non hospitalised patients.

1.6 NITAZOXANIDE

Nitazoxanide is a broad-spectrum thiazolide anti-parasitic agent. But the COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of nitazoxanide for the treatment of COVID-19, except in a clinical trial.

2. Anti-SARS-CoV-2 Antibody Products

2.1 ANTI-SARS-COV-2 MONOCLONAL ANTIBODIES

The COVID-19 Treatment Guidelines Panel recommends using 1 of the following anti-SARS-CoV-2 mAb products to treat non hospitalised patients with mild to moderate COVID-19 who are at high risk of clinical progression .

- Bamlanivimab 700 mg plus etesevimab 1,400 mg administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low.

- Casirivimab 600 mg plus imdevimab 600 mg administered as an IV infusion or as subcutaneous (SQ) injections

- Sotrovimab 500 mg administered as an IV infusion

Adverse effects- Hypersensitivity, including anaphylaxis and infusion-related reactions.

2.2 CONVALESCENT PLASMA

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication. In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorisation (EUA) for convalescent plasma for the treatment of hospitalised patients with COVID-19. On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorisation to high-titre COVID-19 convalescent plasma and only for the treatment of hospitalised patients with COVID-19 early in their disease course or hospitalised patients who have impaired humoral immunity.

Adverse effects- transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile non-haemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, haemolytic reactions, hypothermia, metabolic complications, and post-transfusion purpura.

2.3 IMMUNOGLOBULINS (SARS-COV-2 SPECIFIC)

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response.

There is **insufficient evidence** for the COVID-19 Treatment Guidelines Panel to recommend either for or against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins for the treatment of COVID-19.

3. CELL- BASED THERAPY

It is hypothesised that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2. The COVID-19 Treatment Guidelines Panel **recommends against** the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial.

4. IMMUNOMODULATORS

4.1 COLCHICINE

Colchicine is an anti-inflammatory drug that is used in the treatment of gout, recurrent pericarditis and familial Mediterranean fever. The anti-inflammatory properties coupled with the drug's limited immunosuppressive potential, favourable

safety profile, and widespread availability have prompted investigation of colchicine for the treatment of COVID-19. However, the panel **recommends against** the use of colchicine for the treatment of non hospitalised/ hospitalised patients with COVID-19, except in a clinical trial.

4.2 CORTICOSTEROIDS

Multiple randomised trials have reported that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalised patients with COVID-19 who require supplemental oxygen, presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multi-system organ dysfunction. There is no observed benefit of systemic corticosteroids in hospitalised patients with COVID-19 who do not require supplemental oxygen.

The Panel **recommends** the use of corticosteroids in hospitalised patients with COVID-19.

Clinical trials-

- **RECOVERY trial** -28 day mortality was lower among the patients who received dexamethasone than those who received SOC.
- **CoDEX trial** -the study report supports the RECOVERY trial findings.

Adverse effects- hyperglycaemia, secondary infections, psychiatric effects, avascular necrosis.

4.3 FLUVOXAMINE

There's insufficient evidence for using the anti-inflammatory effect of fluvoxamine to recommend either for or against the use in treatment of COVID-19.

4.4 GRANULOCYTE-MACROPHAGE COLONY- STIMULATING FACTOR INHIBITORS

There is **insufficient evidence** for the panel to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalised patients with COVID-19.

4.5 IMMUNOGLOBULINS (NON-SARS-COV-2 SPECIFIC)

The COVID-19 Treatment Guidelines Panel recommends against the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific intravenous immunoglobulin (IVIG) for the treatment of acute COVID-19, except in a clinical trial. This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

4.6 INTERLEUKIN-1 INHIBITORS

Endogenous interleukin (IL)-1 is elevated in patients with COVID-19. SARS-CoV-2 infection causes epithelial damage that leads to the release of IL-1, which recruits inflammatory cells and induces the release of IL-1in monocytes. This in turn leads to the release of more IL-1 to recruit and activate additional innate immune cells. Drugs that block the IL-1 receptor like **Anakinra** or drugs that block IL-1 signalling like **canakinumab** can potentially interrupt this auto-inflammatory loop.

These drugs are being investigated as potential treatments for COVID-19. However there's **insufficient evidence** for recommendation.

4.7INTERLEUKIN-6 INHIBITORS

Interleukin (IL)-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells. COVID-19-associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin. It is hypothesised that modulating IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., **sarilumab, tocilizumab)** and anti-IL-6 mAbs (i.e., siltuximab). The panel **recommends** the use of IL-6 receptor inhibitors (e.g., sarilumab, tocilizumab) in hospitalised patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation.However, the panel **recommends against** the use of anti-IL-6 mAb therapy (i.e., siltuximab) for the treatment of COVID-19, except in a clinical trial. Like other immunomodulators, secondary infection is a serious problem and therefore they should be used with caution.

4.7 KINASE INHIBITORS

4.7.1 JAK KINASE INHIBITORS

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins that are involved in vital

cellular functions, including signalling, growth, and survival. These kinase inhibitors were proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation. Immunosuppression induced by JAK inhibitors could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing SARS-CoV-2 from entering and infecting susceptible cells.

The panel **recommends** the use of **baricitinib** and **tofacitinib** for certain hospitalised patients who require oxygen supplementation (based on data from **ACTT-2** (20)**, COV-BARRIER** and **STOP-COVID** clinical trials).

4.7.2 BRUTON'S TYROSINE KINASE INHIBITORS

Bruton's tyrosine kinase (BTK) is a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways. The Panel recommends against the use of BTK inhibitors (like acalabrutinib, ibrutinib, zanubritinib) for the treatment of COVID-19, except in a clinical trial.

5. ANTI THROMBOTIC THERAPY

Infection with SARS-CoV-2 have been associated with inflammation and a prothrombotic state. A number of studies have observed varying incidences of venous thromboembolism (VTE) in patients with COVID-19.There's insufficient evidence to support starting prophylactic anticoagulants based on lab parameters. However, therapeutic doses have to used in the event of a thromboembolic event.

6. SUPPLEMENTS

Supplements like vitamin C,D and zinc are widely used in the treatment of COVID-19. However, there's insufficient evidence to support their therapeutic effect.

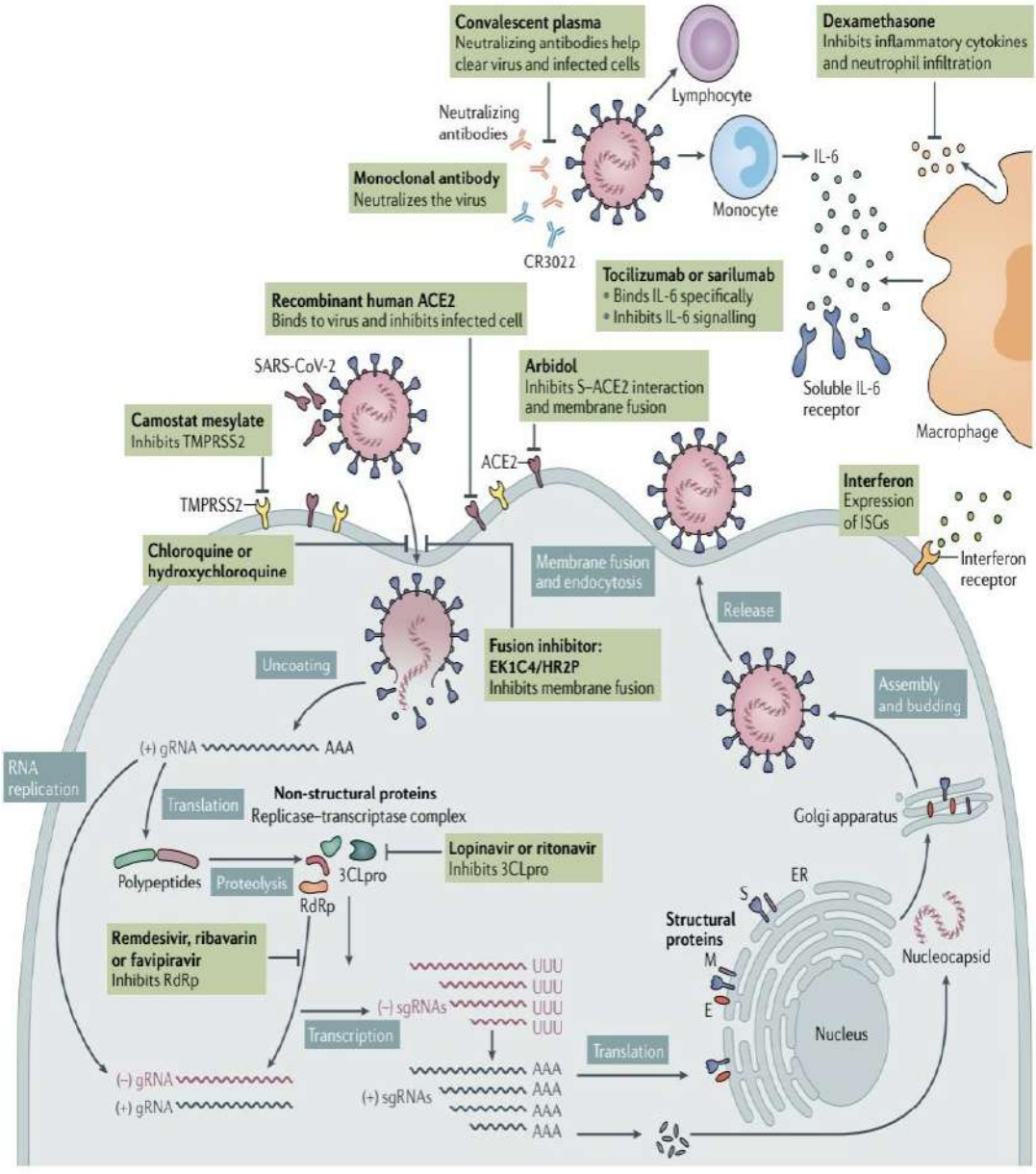


Figure 9- Mechanism of action of various therapeutic agents.

VACCINES

Vaccines to prevent SARS-CoV-2 infection are considered the most promising approach for curbing the pandemic and are being vigorously pursued. COVID-19 vaccines are being developed using several different platforms.

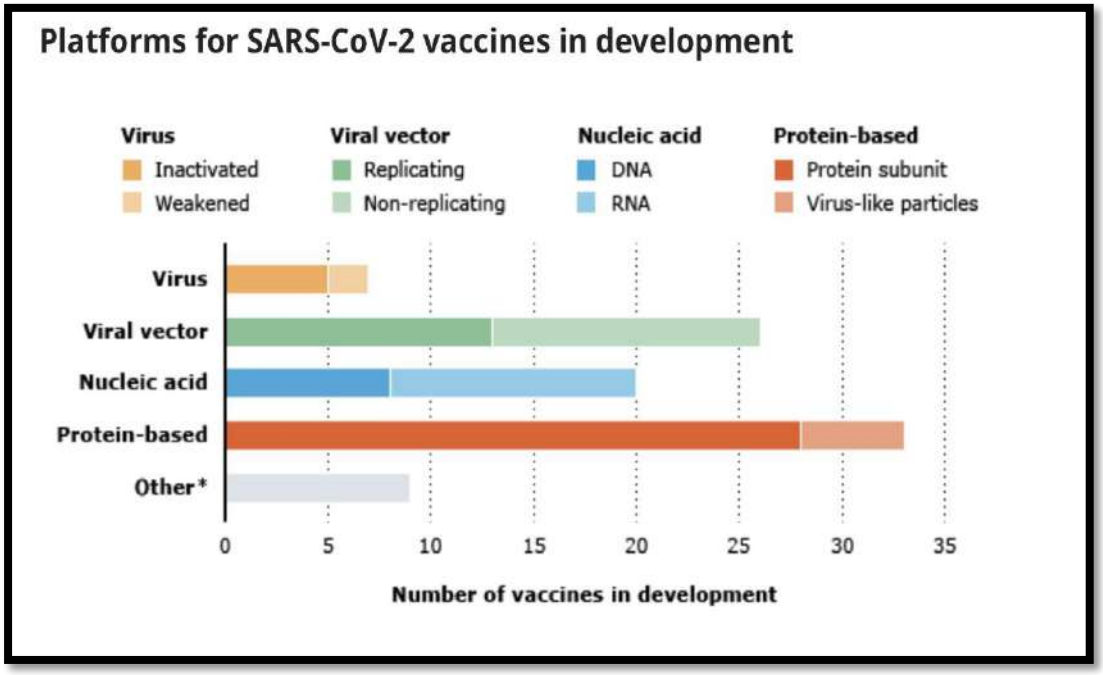


Figure 10-Platforms of SARS-CoV-2 vaccines in development as of late Dec, 2020

The widely used vaccines are

- BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) -mRNA vaccine
- mRNA-1273 (Moderna COVID-19 vaccine) -mRNA vaccine
- Ad26.COV2.S (Janssen COVID-19 vaccine, also called as the Johnson & Johnson vaccine) - replication incompetent adenovirus vector vaccine
- ChAdOx1nCoV-19/AZD1222 (AstraZeneca/University of Oxford/Serum Institute of India) -replication incompetent chimpanzee adenovirus vector
- Ad5-based COVID-19 vaccine (CanSino Biologics) -replication incompetent adenovirus 5 vector vaccine
- WIV04 and HB02 (Sinopharm) - inactivated, whole-virus vaccine

- Gam-COVID-Vac/Sputnik V (Gamaleya Institute) - uses two replication-incompetent adenovirus vectors
- CoronaVac (Sinovac) -inactivated COVID-19 vaccine
- Covaxin (Bharat Biotech/Indian Council of Medical Research) -inactivated COVID-19 vaccine (also called BBV152)
- ZyCoV-D (Zydus Cadilla) -first DNA COVID-19 vaccine ,first authorised in India
- NVX-CoV2373 (Novavax) -recombinant protein nanoparticle vaccine

Side effects-

- Common side effects- local injection site reactions, systemic symptoms (fever, chills, fatigue, myalgias, headache)
- Rare adverse effects-
  - Anaphylaxis
  - **myocarditis/pericarditis** – reported with Pfizer/BioNTech and Moderna vaccines
  - **Thrombotic complication associated with thrombocytopenia (VITT)** - observed with Johnson & Johnson and AstraZeneca.
  - Giuliano Barre syndrome – observed with the latter two vaccines

    Breakthrough infections after vaccination are expected. However, they occur much less frequently and less severely when compared to unvaccinated individuals.

OUTCOMES (26)

- **Immunological**

Immunological changes were extensively reported during the acute phase of illness, such as lymphopenia, reduced peripheral blood T cells and elevated pro inflammatory cytokines.

- **Guillain-Barré syndrome and MIS-C (Multisystem Inflammatory Syndrome-Children)** – further epidemiological studies are needed to establish causal relationship.

- **Haematological**

The incidence of venous thromboembolism in patients with severe COVID-19 was observed to be 25% in a study conducted in China (27) and 31% in another study from the Netherlands(28). Disseminated intravascular coagulation (DIC) and pulmonary embolism were highly prevalent in COVID-19, and DIC has been observed in 71.4% of non-survivors(29) . The phenotype of pulmonary embolism in COVID-19 is observed to be different from conventional thromboembolism, and postulated to represent in situ immunothrombosis.

- **Respiratory**

The major brunt of the illness is borne by the lungs, manifesting as pneumonia and respiratory failure. The long term consequences include post-viral lung fibrosis, pulmonary thromboembolism and residual functional impairment.

- **Gastrointestinal and renal**

Gastrointestinal symptoms ,such as diarrhoea, nausea and vomiting, and abdominal pain, are also found in COVID-19 patients. Liver injury with transient

elevation in liver enzymes have been reported. Acute kidney injury (AKI) have also been observed and often associated with severity of the disease.

- **Neurological**

Loss of smell and loss of taste have frequently been observed in COVID-19. However, rare neurological events such as stroke ,GBS and encephalitis and encephalopathy have also been observed. But its causal relationship or association is yet to be proven by epidemiological studies.

- **Dermatological**

The cutaneous manifestations reported include erythematous rash, pseudo-chilblain, urticaria lesions, vesicular lesions, livedo-reticularis, necrosis, oral ulcers and blisters.

CARDIOVASCULAR SYSTEM AND COVID-19 (30)(31)

UNDERLYING CARDIOVASCULAR COMORBIDITIES

Cardiovascular disease(CVD) is a common comorbidity seen in patients admitted with COVID-19. In a study conducted in Wuhan, among the 46 percent who had comorbidities, 31% had hypertension, 15 % had other cardiovascular diseases and 10% had diabetes . Comorbidities especially cardiovascular diseases were commonly seen in those requiring intensive care. The overall case fatality rate of COVID-19 as reported by the Chinese Centre for Disease Control and Prevention, as of 11 February 2020 was 2.3%.The individual case fatality rate of patients with CVD was 10.5% (highest among those with any comorbidities, including chronic respiratory disease(6.3%) or cancer (5.6%)), the case fatality rate of patients with diabetes was 7.3% and that of patients with hypertension was 6.0%.

CARDIOVASCULAR MANIFESTATIONS- The most common clinical manifestation of COVID-19 is viral pneumonia. However, it has been reported to cause cardiovascular diseases such as myocardial injury, arrhythmias, acute coronary syndrome and thromboembolism. Some patients can present with cardiac symptoms as the first clinical presentation. Myocardial injury is found independently associated with high mortality. Multi system inflammatory syndrome in children has been linked with COVID-19 as well.

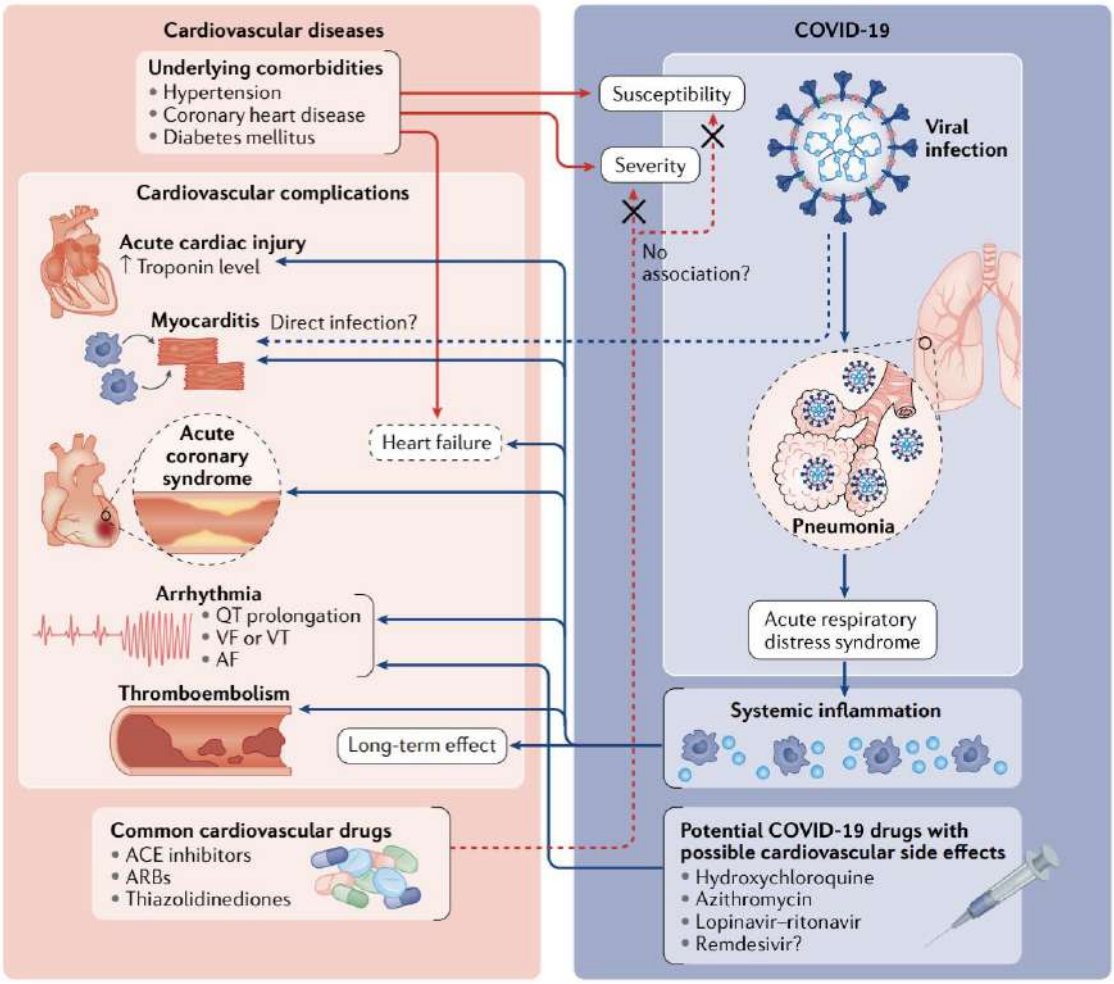


Figure 11- Bidirectional interaction between cardiovascular diseases and COVID-19

1. MYOCARDIAL INJURY/ MYOCARDITIS

Acute myocardial injury, evidenced by elevated levels of cardiac markers or electrocardiogram abnormalities was reported in 7-20% of COVID-19 patients in studies conducted in China. The presence of myocardial injury was associated was associated with a worse prognosis and increased in hospital mortality.. In a multi-centre cohort study conducted in patients with COVID-19, 17% had acute cardiac injury, of whom 32 died. In a subsequent study of 416 patients hospitalised with COVID-19, 82 patients (20%) had evidence of cardiac injury, which was associated with a 5-fold increase in the need for invasive mechanical ventilation and an 11-fold increase in mortality. Another study reported that the rate of death in patients with elevated levels of cardiac troponin T was 37.5%, whereas, in patients with underlying cardiovascular comorbidities plus elevated levels of cardiac troponin T, it was almost double (69.4%). Furthermore, another study demonstrated that markers of myocardial injury were predictive of the risk of in-hospital mortality in patients with severe COVID-19. However, the earlier studies did not include echocardiography or MRI data, so it's unclear whether typical clinical features of myocarditis were present in patients with elevated troponin. In a cohort study involving 112 patients with COVID-19, the 14 patients with myocardial injury who had elevated levels of cardiac troponin along with abnormalities on echocardiography and/or ECG did not have typical signs of myocarditis such as segmental wall motion abnormality or reduced left ventricular ejection fraction. This goes o to suggest that myocardial injury was caused secondary to systemic causes rather than a result of direct viral infection of the heart.

However, some case reports have shown typical signs of myocarditis in patients with COVID-19. A case report of a 53 year old woman with myocardial injury, with elevated levels of cardiac biomarkers and diffuse ST segment elevation on the

electrocardiogram, had diffuse biventricular hypokinesia on cardiac MRI, especially in the apical segments, in addition to severe LV dysfunction.. MRI data also revealed marked biventricular interstitial edema, diffuse late gadolinium enhancement and circumferential pericardial effusion, features that are consistent with acute myocarditis. In another case- a man aged 37 years with chest pain and ST segment elevation, echocardiography revealed an dilated heart with severe LV dysfunction. This patient was diagnosed with COVID-19-induced fulminant myocarditis and treated with methylprednisolone. The cardiac size and function became normal after 1 week.

Histological evidence of myocardial injury or myocarditis in COVID-19 is very limited. An autopsy of a patient with COVID-19 and ARDS who died of a sudden cardiac arrest showed no evidence of myocardial structural involvement, suggesting that COVID-19 did not directly impair the heart. In contrast, another case reported a patient with low grade myocardial inflammation and myocardial localisation of coronavirus particles, as measured by endomyocardial biopsy, suggesting that SARS-CoV-2 can infect the myocardium directly. SARS-CoV-2 gains access to host cells through ACE2 receptors, which are expressed in abundance in cardiac cells.In a report that described autopsy samples from ten Canadian patients with COVID-19, the viral RNA of SARS-CoV was detected in 35% of the heart samples, but the infected cell types were not known. A marked increase in macrophage infiltration with evidence of myocardial damage was also seen, suggesting that SARS-CoV-2 can infect the heart directly.

To sum it up, all the findings suggest that myocardial injury is not only a common manifestation of COVID-19, but also a risk factor for grave prognosis. At present, there’s insufficient data to understand the mechanisms underlying COVID-19-related myocardial injury. However, on the basis of the available clinical material,

myocardial injury seems to be largely attributable to advanced systemic inflammation. SARS-CoV-2 may also infect the myocardium directly, resulting in viral myocarditis in a small fraction of patients.

1. ACUTE CORONARY SYNDROME (ACS)

Like other infectious agents, COVID-19 can also trigger ACS. In studies from China, a small proportion of patients with COVID-19 presented with chest pain on admission to hospital, but the features of the chest pain were not accurately described . In another case series from New York involving 18 patients with COVID-19 and ST segment elevation, indicative of acute myocardial infarction, five out of the six patients with myocardial infarction required percutaneous coronary intervention. In another case series from Italy involving 28 patients with COVID-19 and ST segment elevation myocardial infarction, assessment by coronary angiography showed that 17 patients had evidence of a culprit artery involvement that required revascularisation. ST segment elevation myocardial infarction was the first clinical manifestation of COVID-19 in 24 of these 28 patients who had not yet received a positive test result for COVID-19 at the time of coronary angiography.

These observations suggest that COVID-19 can cause ACS even in the absence of significant systemic inflammation. However, the incidence of ACS in patients with COVID-19 is still not known. Considering the overwhelmed health-care facilities of many cities during the COVID-19 outbreak, the number of cases of acute myocardial infarction among patients with COVID-19 might be underestimated in previous studies. The mechanisms underlying COVID-19-induced ACS may involve plaque rupture, coronary spasm or micro thrombi owing to systemic inflammation or cytokine storm. For instance, activated macrophages secrete enzymes like collagenases that degrade

collagen, a major constituent of the fibrous cap on atherosclerotic plaques, which can lead to plaque rupture. Activated macrophages also secrete tissue factor, a potent procoagulant that triggers thrombus formation when the plaque ruptures. Direct endothelial or vascular injury by SARS-CoV-2 infection may also increase the risk of thrombus formation and acute coronary syndrome. The number of reported cases of ACS globally have fallen during the COVID period, in spite of the potential of SARS-CoV-2 to induce ACS. However, the incidence of out of hospital cardiac arrest has also spiked during the COVID-19 outbreak in Italy. This was strongly associated with cumulative incidence of COVID-19. This observation is in accordance with the finding that the number of patients with myocardial infarction seeking urgent inpatient care declined by more than 50% during the peak of the COVID-19 outbreak, as reported in the global survey by the ESC.

2. HEART FAILURE

Heart failure is one of the most commonly reported complication of COVID-19 with a reported incidence of 24% in all patients and 49% in patients who died. Increased levels of amino-terminal pro-B-type natriuretic peptide were identified in 49% of all patients (85% of those who died). The cause of acute heart failure in COVID -19 not yet known. Those patients who are affected with COVID-19 are likely to be older and to have pre-existing comorbidities such as coronary artery disease, hypertension and diabetes, heart failure may be the result of an exacerbation of these pre-existing conditions, whether already diagnosed or unknown, or the uncovering of subclinical cardiac dysfunction. Especially, elderly patients with reduced diastolic function may develop heart failure with preserved EF during the course of the disease, which can be triggered by high fever, tachycardia, excessive hydration and impaired renal function. In patients with heart failure with preserved ejection fraction, cardiac MRI may help to

detect changes induced by the virus.. Acute myocardial injury and ACS triggered by COVID-19 can also aggravate pre-existing heart disease or trigger systolic dysfunction. In the advanced stages of the disease, the response of the immune system to infection might trigger the development of stress-induced cardiomyopathy or cytokine storm related myocardial dysfunction, as also sepsis associated cardiac dysfunction. As COVID-19 primarily causes respiratory symptoms and viral pneumonia, the pulmonary edema that is observed in these patients, which is usually accompanied by ARDS, is mainly regarded as non cardiogenic. Particularly, approximately 25% of patients hospitalised with COVID-19 develop heart failure, the potential contribution of pulmonary congestion by heart failure should also be taken into consideration.

3. COAGULATION ABNORMALITIES

COVID-19 has been associated with coagulation abnormalities which can cause thromboembolic events. As described earlier, elevated levels of D-dimer, slightly increased prothrombin and modestly reduced platelet counts have been observed with COVID -19 patients. The levels of fibrinogen and factor VIII were also elevated in such patients, indicating a hypercoagulable state.

A significant proportion of patients with COVID-19 have coagulation abnormalities that typically do not meet the criteria of disseminated intravascular coagulation but nevertheless may contribute to the development of the various cardiovascular manifestations of the disease. Clinical observations of increased thromboembolic events in patients with COVID-19 suggest the presence of a hypercoagulable state. It has been observed that venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is a common complication in critically ill patients with COVID-19. Another autopsy study reported that deep vein thrombosis

was present in 7 of 12 patients who died with COVID-19 in whom venous thromboembolism was not suspected before death, whereas pulmonary embolism was identified in 4 of the 12 patients. Arterial thrombotic events have also been reported. A case series from New York described five patients aged ≤50 years who presented to the same hospital with large-vessel ischaemic stroke and who all tested positive for SARS-CoV-2 infection.

Further, acute limb ischaemia was also reported in 20 patients infected with SARS-CoV-2 in a case series from Italy. All 20 patients were diagnosed with COVID-19-related pneumonia before acute limb ischaemia was detected. The underlying mechanism of hypercoagulable state is still not clear. One plausible mechanism is that the severe inflammatory response and endothelial damage caused by COVID-19 in combination with underlying comorbidities may predispose patients to a hypercoagulable state. Also, certain antiviral medications and investigational therapeutics given to the patients may promote thrombosis or bleeding events through interactions with anti platelet agents and anticoagulants.

4. ARRHYTHMIAS AND SUDDEN CARDIAC ARREST

Arrhythmias and sudden cardiac arrest are common manifestations of COVID-19. Cardiac palpitations have been reported in some COVID-19 patients. In a cohort study of 138 patients infected with SARS-CoV-2 in China, the presence of cardiac arrhythmia was reported in 17% of all patients (44% of patients in the ICU), but the types of arrhythmia were not recorded. In another study in Wuhan involving 187 patients, those with elevated levels of troponin T were more likely to develop malignant arrhythmias, such as ventricular tachycardia and fibrillation, than those with normal levels of troponin T (12% compared to 5%). Sudden cardiac arrests have also

been reported in patients with COVID-19. However, the actual contribution of this corona virus to cardiac arrhythmias remains uncertain given that arrhythmias, such as atrial and ventricular tachycardia and fibrillation, can be triggered by myocardial injury or other systemic causes such as fever, sepsis, hypoxia and electrolyte abnormalities. Furthermore, patients with advanced COVID-19 are often treated with antiviral medications and antibiotics that are known to induce arrhythmias in some patients.

5. DRUG-DISEASE INTERACTIONS

A lot of research has been done under this heading. Foremost, whether antihypertensive agents such as ACE inhibitors and angiotensin II receptor blockers (ARBs) are involved in the progression or prevention of COVID-19 is unknown. Second, some of the antiviral drugs used to treat patients with COVID-19 are known to induce cardiac toxicity.

a. Effect of RAAS inhibitors on COVID-19

SARS-CoV-2 gains access to host cells through ACE2 receptor. ACEi and ARBs have shown to cause an increase in the expression of ACE2 receptors in animal models. The question was whether to continue the use of ACEi and ARBs (in patients already taking these drugs) in patients infected with COVID-19. Most importantly, indiscriminate withdrawal of these drugs can cause harm to high risk patients. The AHA, ESC and Heart Failure Society of America have all recommended the continuation of these drugs in patients already on them. Studies have shown that the use of RAAS inhibitors was not associated with increased susceptibility to SARS-CoV-2 infection. Also, the use of these drugs was not associated with an increase in the severity of the disease.

b. Cardiovascular effects of antiviral drugs

Drug repurposing, wherein already existing medications approved for other diseases are tested for a new disease, is currently the main approach in finding new drugs for COVID-19.

1. Hydroxychloroquine and Azithromycin - associated with QT prolongation more when combined than alone. A retrospective cohort study among hospitalised patients with COVID-19 observed that cardiac arrest was more likely in patients receiving both drugs than in patients receiving neither drugs.

2. Remdesivir – not much cardiovascular effects have been reported so far; post marketing reports of sinus bradycardia has been reported.

3. Lopinavir-ritonavir – drug interaction with common cardiovascular drugs is possible; QTc prolongation also.

SURFACE ELECTROCARDIOGRAPHIC MARKERS OF ARRHYTHMIA

Several 12 lead-ECG parameters have been suggested as potential markers of malignant arrhythmia. These include QT interval, QTc interval (corrected QT interval), QTd (QT dispersion), QTcd (corrected QT dispersion), Tp-e interval, corrected Tp-e Tp-e/QT ratio , Tp-e/QTc ratios and PR interval.

1. QTc interval (32,33)

The QT interval has been used widely, primarily because prolongation of this interval can predispose to potentially fatal ventricular arrhythmia like torsades de pointes. QT interval on surface ECG is measured from the beginning of the QRS complex to the end of T wave. Thus, it represents the electrocardiographic

manifestation of ventricular depolarisation and repolarisation. This is brought about by channels, complex molecular structures within the myocardial cell membrane which regulates the flow of ions across the cardiac cells.the rapid influx of positively charged ions (viz. sodium and calcium) cause normal myocardial depolarisation. When this influx is exceeded by outflow of potassium ions , myocardial repolarisation occurs. Malfunctioning of the ion channels leads to an intracellular excess of positively charged ions either by inadequate outflow of potassium ions or excess influx of sodium ions. This intracellular excess of positively charged ions extends ventricular repolarisation and results in QT interval prolongation. U waves possibly correspond to late repolarisation of cells in the mid myocardium and included in the measurement only if they are large enough to seem to merge with T wave.

There is significant variability in the measurement of the QT interval resulting from biological factors , like diurnal variation , difference in autonomic tone , electrolytes and drugs; other factors like the environment, the processing of the recording and intra observer and inter observer variability which results from variations in T-wave morphology, noisy baseline and the presence of U waves. In the measurement of QT interval , the determination of T offset is troublesome and there are different methods for the same.The slope methods determine the T offset as an intercept between the slope of the descending part of the T wave and the isoelectric line or a threshold line above it. Therefore, the shape of the descending part of the T wave affect the measured values of QT interval.

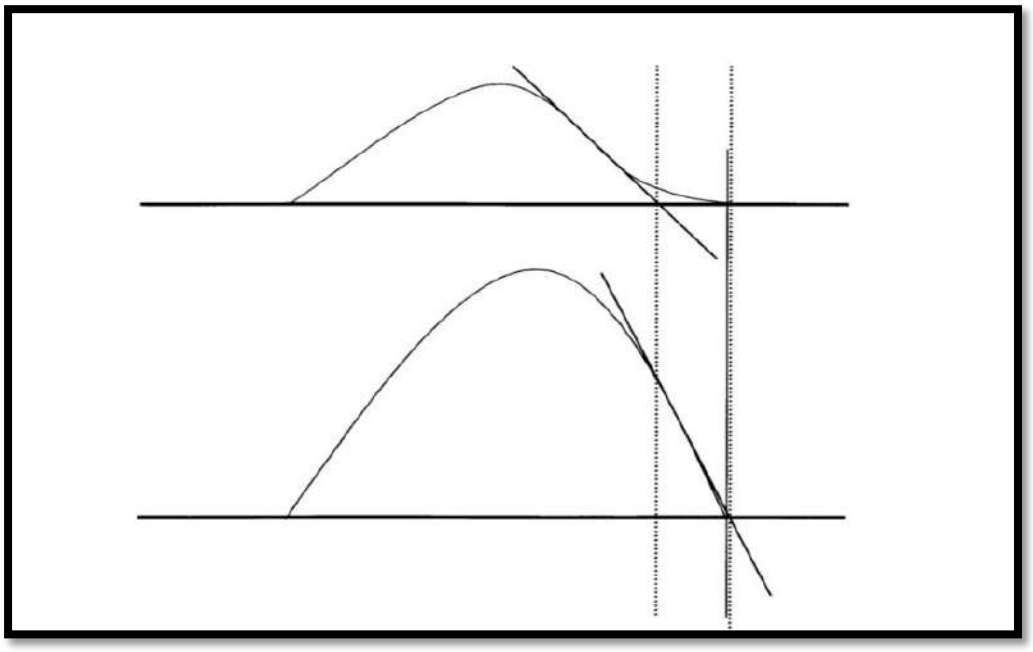


Figure 12 – effect of the shape of the descending part of the T wave on the QT interval measured with a tangent method

The QT interval is prolonged at slower heart rates and reduced at faster heart rates . Therefore, many formulas have been proposed to correct the variation due to heart rate viz. Bazett formula, Fridericia cube-root correction, Framingham linear regression equation and Hodges equation.

Fridericia	$QTc = QT/\sqrt[3]{RR}$
Framingham	$QTc = QT + 0.154\,(1 - RR)$
Hodges	$QTc = QT + 1.75(HR - 60)$
Bazett	$QTc = QT/\sqrt{RR}$

The normal QT interval is 0.36-0.44 sec.

Normal QTc (sec)			Borderline QTc (sec)			Prolonged (sec)		
Male	**Female**	**Age 1-15yrs**	**Male**	**Female**	**Age 1-15yrs**	**Male**	**Female**	**Age 1-15yrs**
<0.43	<0.45	<0.44	0.431-0.45	0.451-0.47	0.441-0.446	>0.45	>0.47	>0.46

Factors that affect the QT interval – QT prolongation can be caused due to congenital or acquired abnormalities. Several forms of congenital LQTS have been reported and 3 forms (LQT1, LQT2 and LQT3) have been well characterised in previous studies. When exposed to QT-prolonging medications, individuals without life-long QT prolongation may develop QT prolongation either with or without torsades de pointes or may even not develop QT prolongation. These may be governed by many risk factors

Patient risk factors for Torsade de pointes with drug induced QT prolongation	
Non-modifiable	**Potentially modifiable**
Congenital long QT syndrome	Bradycardia
Structural heart diseases such as heart failure (Low ventricular ejection fraction), left ventricular hypertrophy , and myocardial infarction)	Dyselectrolemia -hypokalemia, hypomagnesemia, hypocalcemia
Thyroid disease- more common with hypothyroidism	Recent cardio version with a QT prolonging drugs
Impaired hepatic or renal function	
Female sex	
Age >65 years	

DRUGS CAUSING QT PROLONGATION	
HIGH RISK	SOME RISK
Antiarrhythmics class Ia- (ajmaline, cibenzoline, disopyramide, hydroquinidine, procainamide, quinidine)	Amisulpride Anagrelide Bedaquiline Bosutinib Cabozanitib Ranolazine
Antiarrhythmics class III (amiodarone, azimilide, cibenzoline, dofetilide, dronedarone, ibutilide, sotalol, vernakalant)	Chlorpromazine Citalopram Crizotinib
Arsenic trioxide	Dasatinib Delamanid Domperidone
Artemisinin derivatives-(artemisinin, artemether/lumefantrine, artenimol)	Dolasetron Droperidol Efavirenz Eribulin Escitalopram Fluconazole
Halofantrine	Gatifloxacin Hydroxyzine Iloperidone Lapatinib
Haloperidol	Levomepromazine
Ketanserin	Ondansetron
Mesoridazine	Methadone
Panobinostat	Moxifloxacin
Pimozide	Nilotinib

Ribociclib	Paliperidone
Sertindole	Pasireotide
Thioridazine	Pazopanib
Vandetanib	Quinine

Drug interactions can increase the risk of QT prolongation. There are 3 mechanisms by which interaction can occur –

- Pharmacodynamic interaction- when 2 or more drugs that prolong QT interval are co-prescribed, which can lead to an additive or potential in effect.
- Pharmacokinetic interactions, when a drug that does not prolong the QT interval itself but reduces the clearance or is metabolised by the same hepatic enzymes, resulting in increased concentrations of the QT-prolonging drug.
- Drug-induced electrolyte imbalances, such as hypokalaemia and hypomagnesaemia, which can increase the risk of QT prolongation.

  There are many **tools that assess and predict the risk of QT prolongation/TdP** like

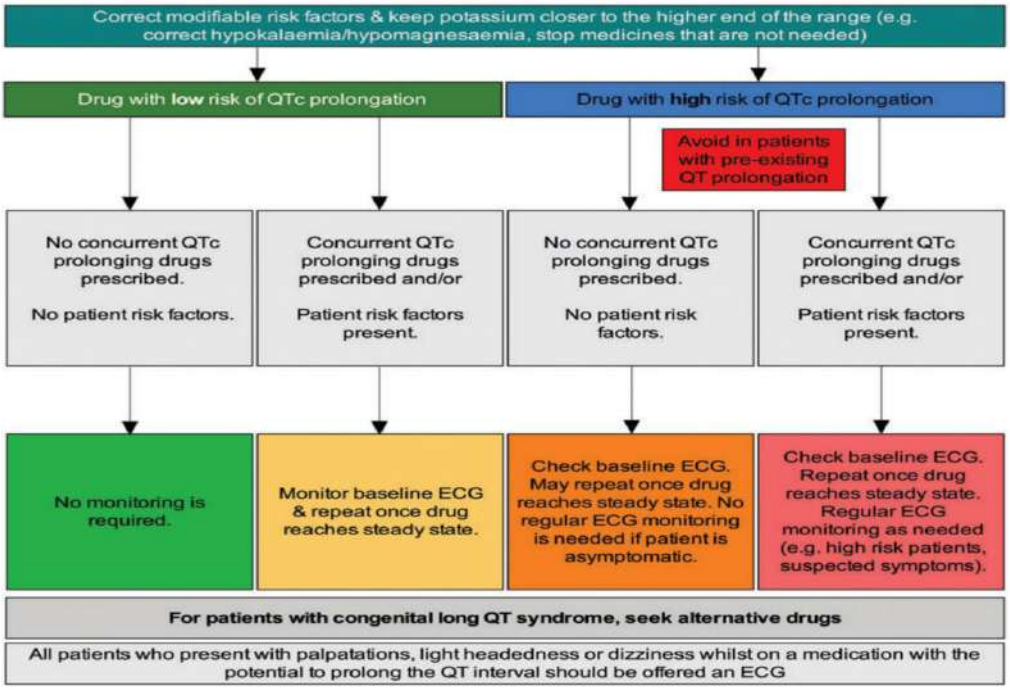
- Tisdale risk score- The tool was developed using patients admitted to ICU and hence generalisability to broader populations may be limited.
- MedSafety Scan (MSS) QT prolongation risk score- It includes the risk factors in the Tisdale tool and additional risk factors, such as drug interactions and other cardiac risk factors. It is more comprehensive than the Tisdale tool. It provides advice on drug interactions
- Risk of QT drug–drug interactions assessment tool - A tool enabling the identification of patients with an increased risk of QTc prolongation when using two or more QTc-prolonging drugs with a known risk of TdP

- Sharma clinical decision support system - A clinical decision support system to prevent the use of QT-prolonging medications in the hospital setting
- Hincapie-Castillo predictive model for drug associated QT prolongation
- Bindraban risk model for predicting QTc interval prolongation in patients using QTc-prolonging drugs

Monitoring – it's not practical to do an ECG every time a QT prolonging drug is administered

- a baseline ECG is done when drug levels are likely to be at steady state 9 generally after 4-5 $t_{1/2}$
- Repeat ECG after dose change
- If there is significant change in QTc (eg , an increase of >50ms or an absolute value >500ms) -one should correct any electrolyte imbalances; if QTc prolongation is not resolved, further dose reduction or cessation should be considered.

The QT- prolonging drug management algorithm



2. QT dispersion(34)(35)

A report by the group of the late Professor Campbell revived an old idea of the inter-lead differences in the QT interval duration. This inter-lead differences in the QT termed “QT dispersion” was proposed as an index of the spatial dispersion of the ventricular recovery times.

It was proposed that the different ECG leads magnify the ECG signal of different myocardial regions and that, consequently, QT dispersion is an almost direct measure of the heterogeneity of myocardial repolarisation. However, further studies have refuted the initial claims and although the standard 12-lead ECG contains information about regional electrical phenomena, this information cannot be extracted by such a simple technique as QT dispersion assessment.

Some studies had showed that QT dispersion could predict inducibility of ventricular arrhythmias during electrophysiology study, whereas other studies failed to observe this. The manual determination of the T wave offset is very unreliable -this proves to be the main source of error for both human observers and computers.

Measurement – simultaneous 12-lead recordings have been proposed as the gold standard for QT dispersion measurement, in order to avoid QT dynamicity due to heart rate change. The difference between QTc max and min is the corrected QT dispersion (QTcd).

The normal range of QTd is 0.01-0.071 sec. QTd is considered abnormal, if it’s >0.1 sec; QTcd is abnormal if >0.058 sec.

3. Tpe interval and Tpe/QTc ratio(36–38)

In the heart, the ventricular myocardium depolarisation occurs from the endocardial region to the epicardial region. Ventricular repolarization occurs immediately following depolarisation. Dispersion occurs between the endocardial and epicardial region during ventricular repolarisation. The interval between the T wave peak and the end of T wave is called the Tpe interval, which is associated with transmural ventricular repolarisation. The Tpe interval and the ratio of this interval to the QT interval have been shown to be associated with arrhythmic clinical conditions in many cardiac pathological conditions, and pose a high risk for sudden cardiac death(SCD). Dispersion at repolarisation between epicardial and endocardial regions of myocardium causes slow transmission in these two anatomical regions, and this situation causes an increase, especially in re-entry related arrhythmia. This is the most common cause postulated for the association of the increased Tpe interval and Tpe/QT ratio with arrhythmia and SCD.

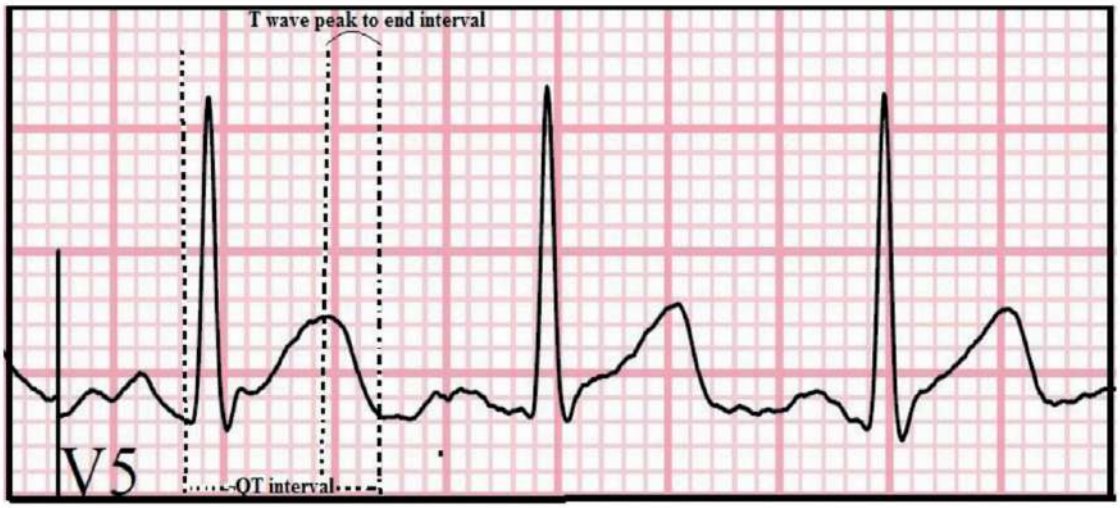


Figure 13– Measurement of Tpe (T wave peak to end interval)

ECG markers	Normal range
Tpe	0.05-0.09 sec
Tpe/QT	0.139-0.252
Tpe/QTc	0.128-0.237

Prolongation of the Tpe or dispersion of ventricular repolarisation is associated with ventricular tachycardia and ventricular fibrillation, which are the most severe forms of ventricular arrhythmias. In the literature, it has been reported that Tpe interval increases in coronary artery disease, Brugada syndrome, heart failure, Short QT, catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy, and brain death from non cardiac diseases, gastroesophageal reflux, anorexia nervosa, hypothyroidism, obesity and primary aldosteronism and this has both diagnostic and prognostic significance.

4. PR interval(39)

The PQ or PR interval on the electrocardiogram is defined as the time needed for an electrical impulse to be transmitted from the sinus node through the atrioventricular node to the Purkinje fibers, and therefore, it represents the atrioventricular conduction. The normal PR interval is 0.12-0.2s. The first-degree atrioventricular block or prolonged PR interval is defined as a duration longer than 200 ms. This prolongation can be a result of conduction retardation in the atrial myocardium, the AV node and the His bundle or at multiple sites. PR interval prolongation without structural heart disease or additional conduction disturbances has been considered as a benign entity. However, recent studies have shown that there is an association between PR prolongation and the incidence of AF. It has also been showed

that PR interval prolongation is related to other adverse events such as pacemaker implantation, thromboembolism, and an increased mortality. Paradoxically, it had been shown that the short PR interval (<120 ms) can also be a predictor for AF. This could be explained by a different P wave duration (as a part of PR interval).

These surface ECG markers OF arrhythmia require further studies to fully understand their potential and use in successfully predicting the arrhythmogenic risk in an individual , in particular those with COVID-19.

Methodology

METHODOLOGY

Study Design- Analytical study

Study Area -COVID and General Medical wards , Government Stanley Hospital and Medical College, Chennai

Study Duration -November 1, 2020 to May 31, 2021

Study Participants - COVID-19 patients admitted in COVID wards and patients admitted in General medical wards in Government Stanley hospital were approached by the principal investigator and the study was explained. Those who gave consent and fulfilled the inclusion criteria were included in the study.

Inclusion Criteria:

Patients admitted in COVID-19 wards in Govt Stanley Hospital and Medical College with SARS-CoV-2 virus detected by nasopharyngeal swab RT PCR test.

Patients with moderate to severe COVID-19 disease defined by

- respiratory rate >24/min **and/or**
- SpO_2 <94 % , for study subjects.

Patients admitted in General medical wards matched for age and gender with the study subjects, for non COVID controls.

Exclusion Criteria:

Patients with preexisting arrhythmias like presence of atrial fibrillation or frequent ventricular premature beats or bundle branch blocks.

Patients on beta blockers, calcium channel blockers, anti-arrhythmic, anti- psychiatric drugs, recent use of azithromycin or hydroxychloroquine or antivirals .

Patients with coronary artery disease, structural heart disease, chronic kidney failure, chronic liver failure, malignancies, inflammatory diseases or hypothyroidism.

Pregnant women.

Sample Size: Based on the reference study done by Ozturk et al, Turkey (40), the sample size was calculated as following:

$n = 2(Z_a+Z_B)^2Sd^2/(M_1-M_2)^2$

Where $Z_a = 1.96$ (statistical significant constant for 95% CI)

$Z_B = 0.84$ (80% power)

Sd =24.5 (Standard deviation of QTc interval on electrocardiography among COVID 19 patients.)

M_1 =410 (Mean QTc interval on electrocardiography among COVID 19 patients)

M_2 =395 (Mean QTc interval on electrocardiography among non COVID controls)

$(M_1-M_2)^2 = 225$ (15 x 15)

On substituting in the formula

n = 15.6 x 24.5 x 24.5 / 225 ;n = 43

Adding 10% non response rate (ie 10% of 43 = 4)

n = 47 (minimum sample size)

Therefore Sample size n = 50 (1 group) ,n = 100 (2 groups)

50 participants in each group were taken.

Data Collection

Patients were screened by the Principal investigator for the presence of any exclusion criteria. Demographic details, anthropometric measurements (height, weight, BMI) and symptoms (asymptomatic, Influenza like illness(ILI), severe acute respiratory illness(SARI) on oxygen support ,non invasive ventilation (NIV), invasive ventilation, multi organ dysfunction syndrome/complications or atypical presentations), vitals(pulse rate, systolic/diastolic blood pressure, respiratory rate) and baseline investigations(serum glutamic-oxaloacetic transaminase(SGOT), serum glutamic pyruvic transaminase(SGPT), C-reactive protein(CRP), haemoglobin(Hb), total WBC count, differential count, neutrophil lymphocyte ratio (NLR), fasting and prandial blood sugars)) at presentation was collected. The 12 lead ECGs was recorded at the time of hospitalisation, and the following days. Admission day ECGs of the cases were compared with the admission day ECGs of the non covid control group. Standard 12-lead ECG records (25mm/s, 10mm/mV) was used. The participants having U wave in their ECGs was not be included in the study.

QT interval was measured from the beginning of the QRS complex to the end of the T wave (using slope method) and corrected QT interval was calculated using Bazetts formula (QTc =QT $\sqrt{}$(R−R interval)). The QT interval and QTc interval of all 12 leads were measured. The average QT and QTc intervals were then calculated.

The normal QT interval was taken as 0.36-0.44 sec. The reference range of QTc is given below:

Normal QTc (sec)			Borderline QTc (sec)			Prolonged (sec)		
Male	**Female**	**Age 1-15yrs**	**Male**	**Female**	**Age 1-15yrs**	**Male**	**Female**	**Age 1-15yrs**
<0.43	<0.45	<0.44	0.431-0.45	0.451-0.47	0.441-0.446	>0.45	>0.47	>0.46

The QT dispersion (QTd) was taken as the difference between the maximum and minimum QT intervals in 12 leads. Normal values of QT dispersion vary in a very wide range from 0.01 to 0.071 sec. QTd is considered abnormal, if it was >0.1 sec; QTcd was abnormal if >0.058 sec.

The Tp-e interval is defined as the duration from the peak of the T wave to the end of the T wave. Tp-e interval was measured from precordial leads. Tpe/QT and Tpe/QTc ratio was calculated.

ECG markers	Normal range
Tpe	0.05-0.09 sec
Tpe/QT	0.139-0.252
Tpe/QTc	0.128-0.237

The PR interval is defined as the distance from the start of the P wave to the Q wave. Prolonged PR interval is defined as >200ms.

Statistical Analysis:

The data from the pro forma was compiled and entered in Microsoft Excel spreadsheet and was analysed using Statistical Packages for Social Sciences (SPSS) software. All continuous variables were expressed as mean and standard deviation. All

categorical variables were expressed as percentages and proportions.univariate analysis were done to explore the relationship of various risk factors and the outcome. Chi-square analysis was used to test for difference in proportions of categorical variables between the two groups. The level $P<0.05$ was considered as the cut off value for significance at 95% confidence interval.

Results

RESULTS

A total of 50 patients with COVID-19 disease and 50 patients without the disease, both satisfying the inclusion and exclusion criteria for case and control subjects respectively, were enrolled in the study.

Age and gender distribution

The mean age of the cases was 51. 9 years (S.D=14.2) while the mean age of the controls is 47.4 years (S.D=17.9). Age distribution was more or less comparable between the two groups.

Age	Covid cases	Non covid controls
<20	1	4
20-40	11	13
40-60	25	21
>60	13	12

Table 1: Age distribution of COVID and non COVID groups

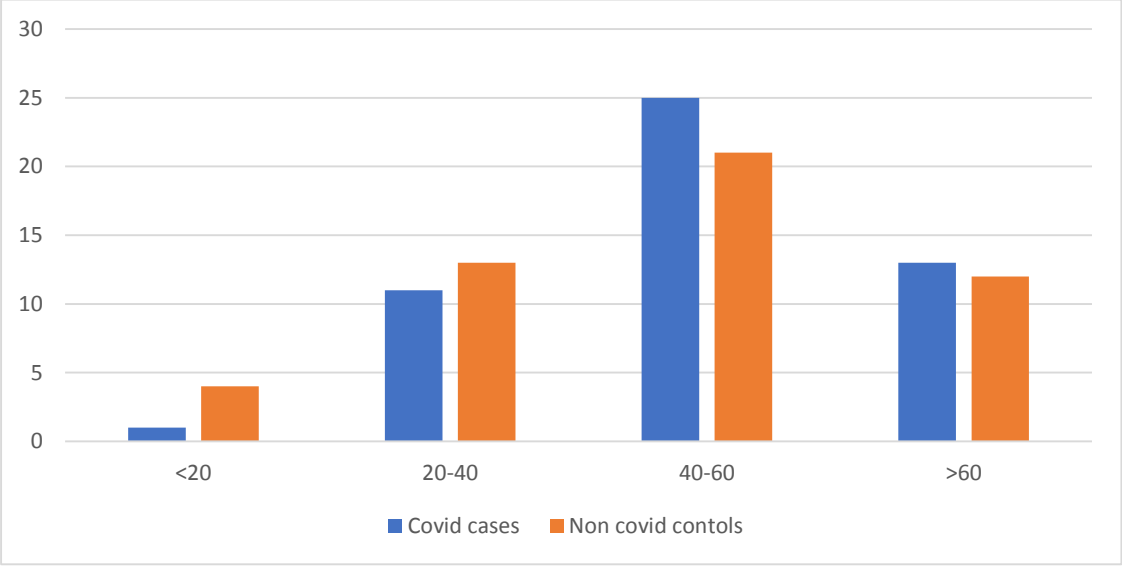


Figure 14 : Age distribution of COVID and non COVID groups

In COVID cases, there were 37 males and 13 females. In non COVID controls, there were 24 males and 26 females.

		Cases/Control	
		COVID cases	Non COVID controls
Gender	Female	13	26
	Male	37	24
Total		50	50

Table 2: Gender distribution of the participants

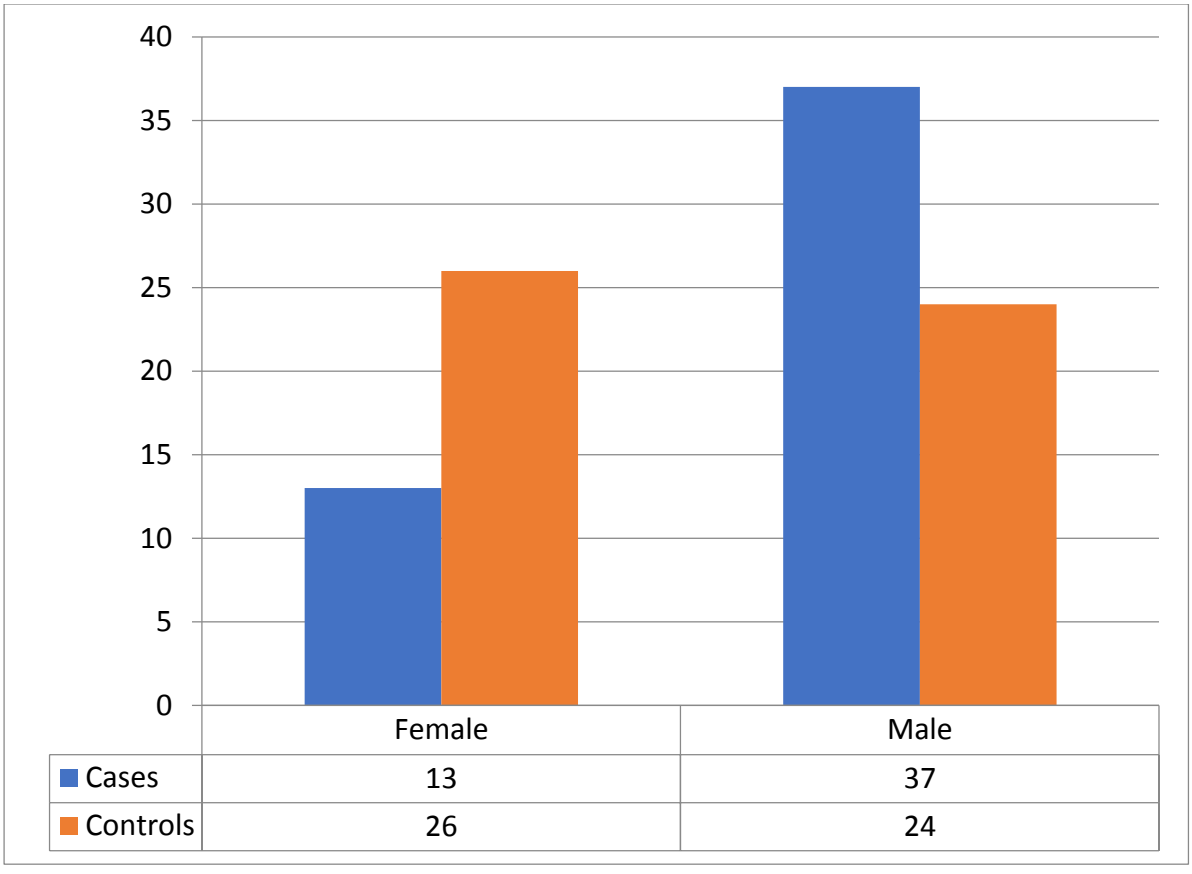


Figure 15: Gender distribution of the participants

Anthropometric distribution

The mean BMI of the COVID group was significantly more than the non COVID controls ($p<0.05$). The mean BMI of the COVID group (27.1) falls under the overweight category whereas that of non COVID controls (23.3) falls in the normal range for Indian population.

Cases/Control	COVID cases		Non COVID controls		t-test
	Mean	SD	Mean	SD	p value
Weight(kg)	74.8	9.3	62.8	9.1	**<0.05**
Height(cm)	166.2	9.4	163.7	6.0	>0.05
BMI	27.1	2.6	23.3	2.6	**<0.05**

Table 3: Anthropometric distribution of the two groups

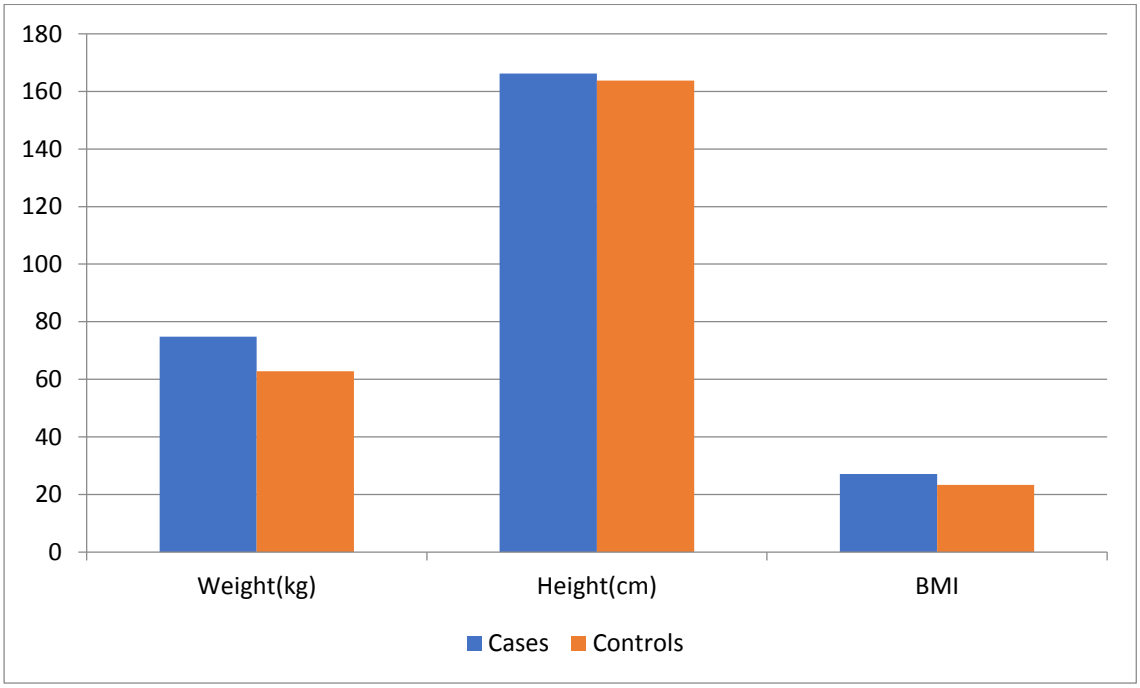


Figure 16- Anthropometric distribution of participants

Prevalence of comorbidities

The majority of participants had no comorbidities in both groups. The prevalence of comorbidities viz. diabetes mellitus (DM) and systemic hypertension (SHTN) or their combination was no different between the two groups.

		Cases/controls	
		COVID cases	Non COVID controls
Co-morbidities	No comorbidities	29	33
	DM	11	10
	SHTN	4	5
	DM+SHTN	6	2
Total		50	50

Table 4: Prevalence of comorbidities in the participants

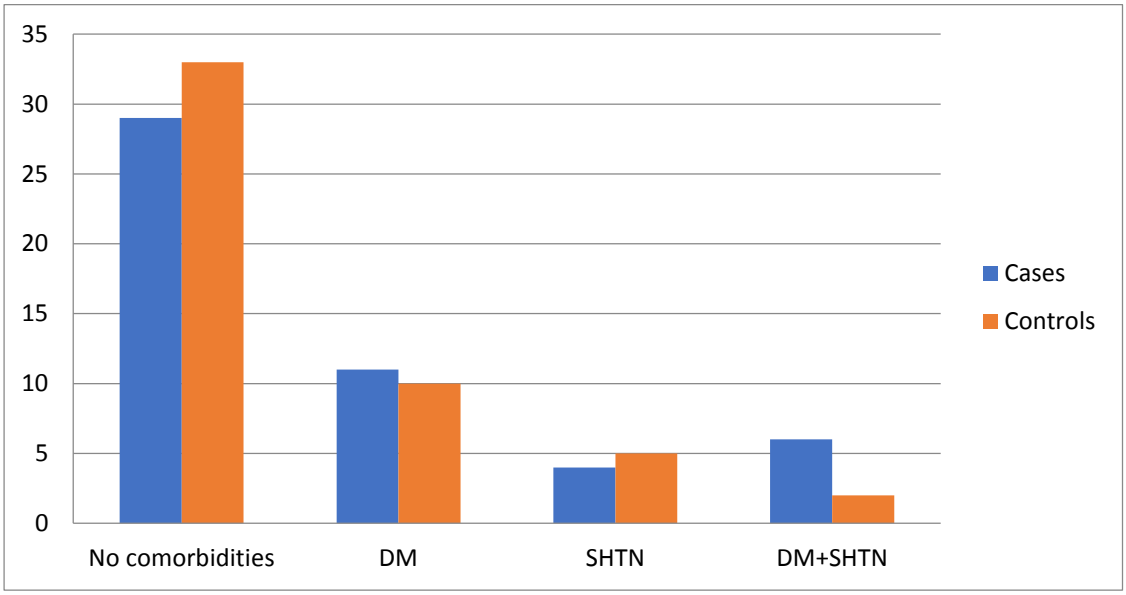


Figure – 17 : prevalence of comorbidities in the participants

Symptoms at presentation

In the COVID group, 2 patients had influenza like illness, 38 patients required oxygen support and 10 required NIV at the time of presentation. The non COVID group did not have any ILI/SARI.

		Cases/Controls	
		Covid cases	Non COVID controls
Symptoms at presentation	Asymptomatic	0	50
	ILI	2	0
	SARI on Oxygen support	38	0
	SARI on NIV	10	0

Table 5: Symptoms at presentation of participants

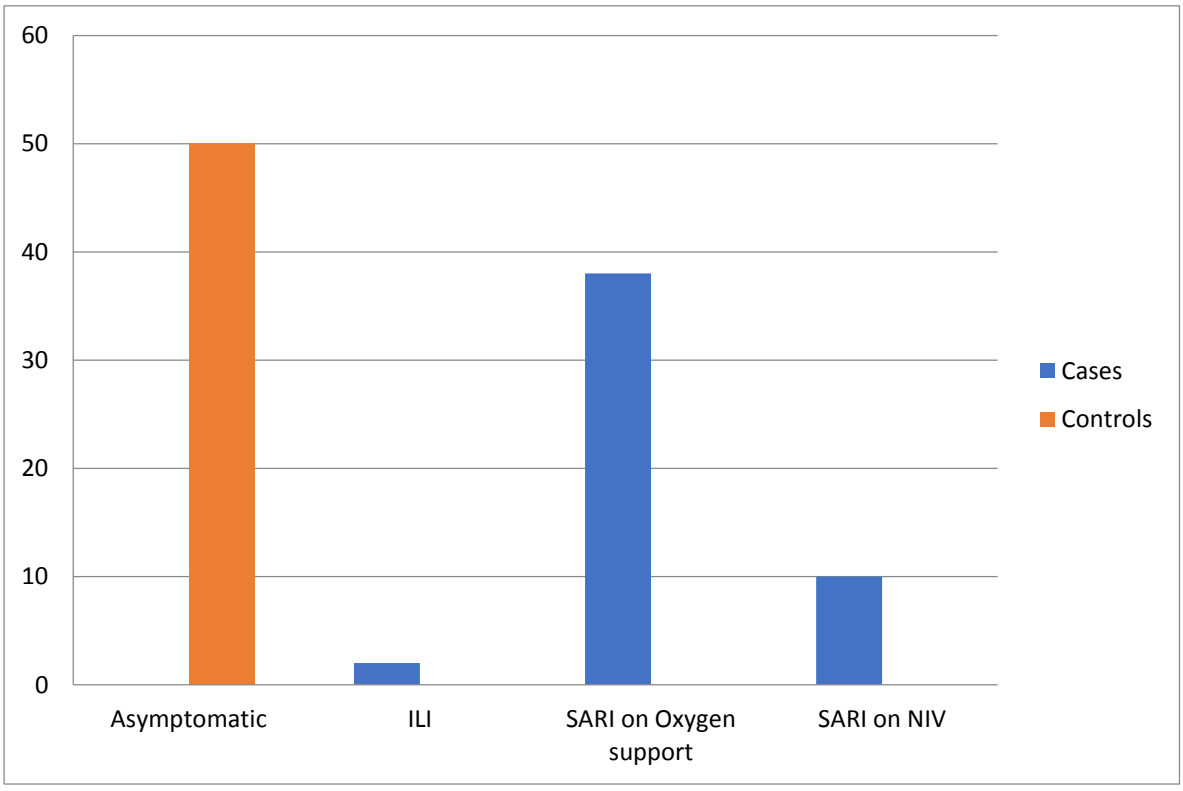


Figure -18 symptoms at presentation of participants

Vitals measurement

The mean SpO2 of COVID cases was 80.6 and the mean respirate rate was 27.1, and was significantly reduced and elevated respectively, from the controls. However, the pulse rate and systolic and diastolic blood pressures were comparable in both groups.

Vitals	COVID cases		Non COVID controls		t-test
	Mean	SD	Mean	SD	
PR	99.9	14.4	95.3	14.4	>0.05
SBP	123.3	17.0	125.7	13.6	>0.05
DBP	76.8	11.2	75.2	8.8	>0.05
RR	27.1	5.0	15.2	1.1	**<0.05**
SpO2	80.6	13.4	98.4	0.7	**<0.05**

Table 6: Comparison of vital parameters between the two groups

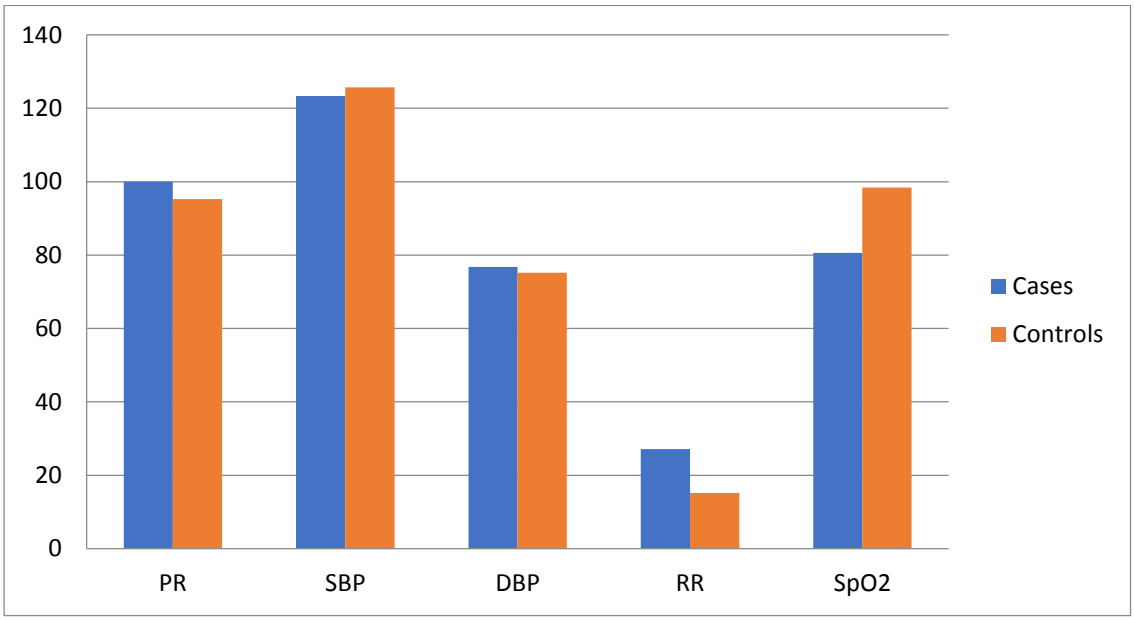


Figure - 19 : comparison of vitals between two groups

Baseline Investigations

The mean values of SGOT/SGPT, CRP, TC, DC-N, NLR, FBS and PPBS were significantly elevated in COVID cases ($p<0.05$) when compared to the non COVID control group.

Lab parameters	COVID cases		Non COVID controls		T-test
	Mean	SD	Mean	SD	
SGOT	62.96	65.31	29.44	6.18	**P<0.05**
SGPT	59.04	69.71	25.34	5.08	**P<0.05**
CRP	77.04	48.22	1.36	0.45	**P<0.05**
HB	13.02	2.17	12.63	1.93	**P<0.05**
TC	10214.00	4340.93	8458	2173.22	**P<0.05**
DC-N	75.96	14.36	56.94	8.52	**P<0.05**
DC-L	16.19	10.10	38.98	7.51	**P<0.05**
DC-M	7.61	6.40	4.00	1.80	**P<0.05**
PLATELET	2.61	1.33	2.86	0.45	P>0.05
NLR	7.62	7.14	1.58	0.68	**P<0.05**
FBS	166.52	76.16	98.80	24.57	**P<0.05**
PPBS	264.36	119.34	141.10	58.42	**P<0.05**

Table 7 -comparison of baseline investigations between the two groups

SGOT and SGPT, and blood sugars, (p value <0.05) at the time of admission was significantly higher in COVID group than the control non COVID group. The

neutrophil lymphocyte ratio, a prognostic marker in COVID-19 was also considerably elevated in the case group. (NLR was 7.6 ± 7.14 in the COVID group compared to 1.58 ±0.68 , in the non COVID group).

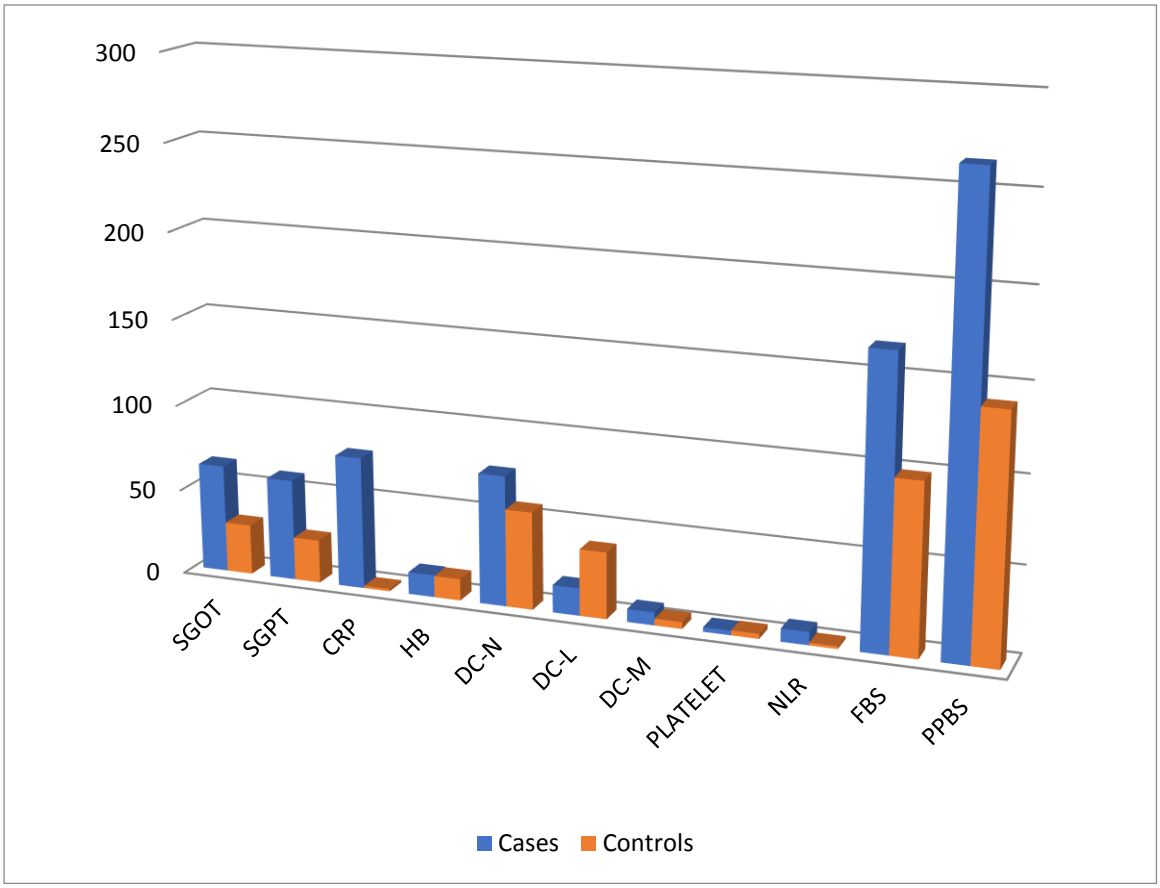


Figure 20 - comparison of baseline investigations between the two groups

ECG markers

The heart rate calculated was no different in both groups. The mean QT interval was 0.344 in cases and 0.342 in non COVID subjects. The mean values of QTc , Tpe, Tpe/QT, Tpe/QTc and PR interval were comparable between the groups. The mean value of QTd though significantly greater than the non COVID group, still remained within the normal limits. However, QTcd was abnormally and significantly elevated in the COVID group in comparison to the non covid group.

ECG markers	COVID cases		Non COVID controls		T-test
	Mean	SD	Mean	SD	
HR	91.400	15.911	95.297	14.399	>0.05
QT	0.344	0.030	0.342	0.031	>0.05
QTc	0.423	0.032	0.428	0.029	>0.05
PR interval	0.152	0.026	0.144	0.024	>0.05
Tpe	0.083	0.018	0.077	0.018	>0.05
Tpe/QT	0.242	0.046	0.225	0.056	>0.05
Tpe/QTC	0.197	0.043	0.178	0.046	>0.05
QTd	0.058	0.023	0.041	0.024	**<0.05**
QTcd	**0.073**	0.030	0.051	0.029	**<0.05**

Table 8– comparison of ECG markers between two groups

Prolonged ECG markers

The abnormally elevated values of almost all ECG markers were seen more commonly in COVID cases than with the non COVID controls (with the exception of QTd and PR interval, wherein it was more or less similar). However, only QTcd and Tpe/QTc ratio were significantly higher ($p<0.005$) in the COVID cases when compared to the non COVID controls. Out of the 50 COVID cases, 26 had QTcd prolongation while only 11 in the non COVID group showed the same. The number of cases with Tpe/QTc ratio increased was 10, and only 3 in the non COVID group.

ECG parameter prolonged	COVID cases	Non COVID controls	p-value
QTc prolongation	10	8	>0.05
QTd prolongation	1	1	>0.05
QTcd prolongation	26	11	**<0.005**
Tpe prolongation	15	12	>0.05
Tpe/QT prolongation	20	15	>0.05
Tpe/QTc prolongation	10	3	**<0.005**
PR prolongation	1	2	>0.05

Table 9: Comparison of prolonged ECG parameters between the two groups

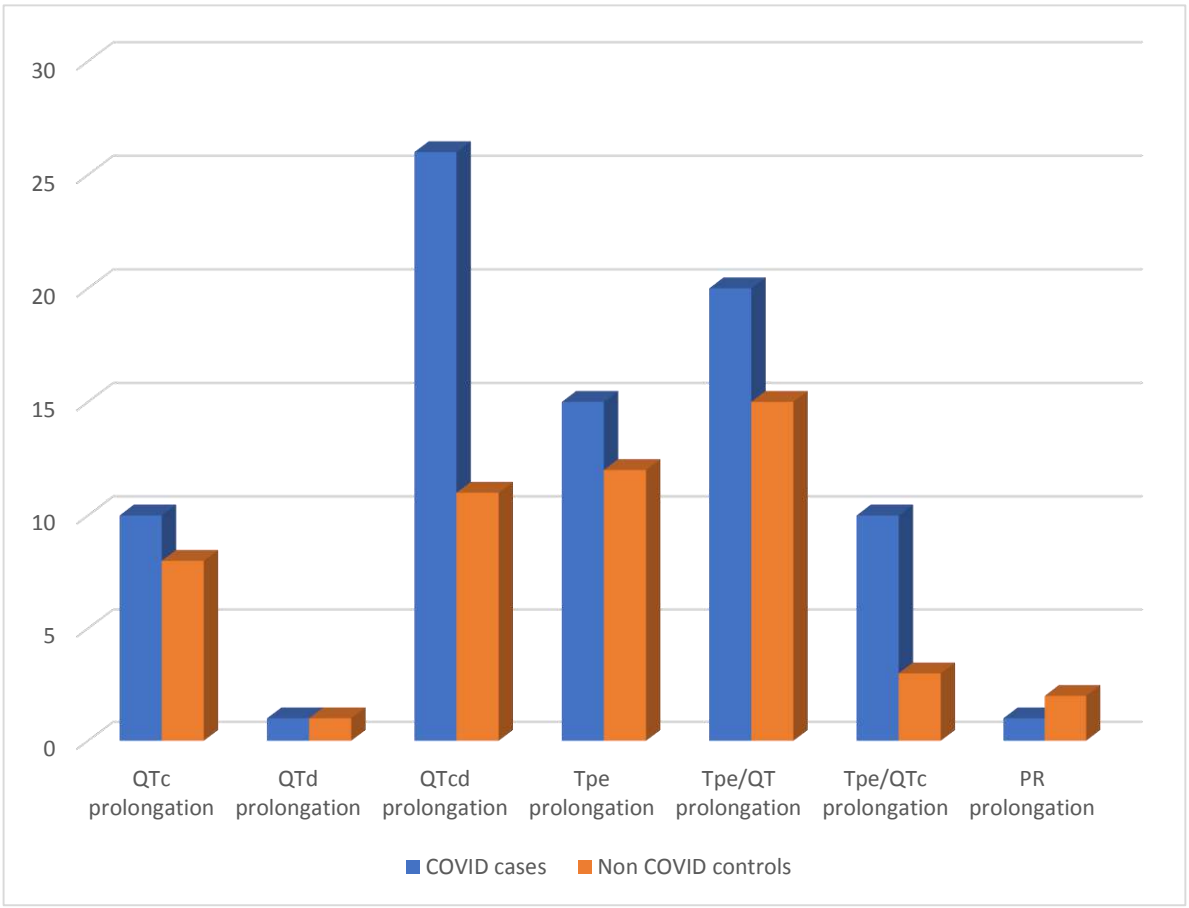


Figure 21 : Comparison of ECG markers between two groups

Borderline QTc was seen in 10 patients in the COVID group vs 5 patients in non COVID group, although not significant.

	COVID cases	Non covid group
Normal QTc	30	37
Borderline QTc	10	5
Prolonged QTc	10	8

Table10 – comparison of QTc between the two groups

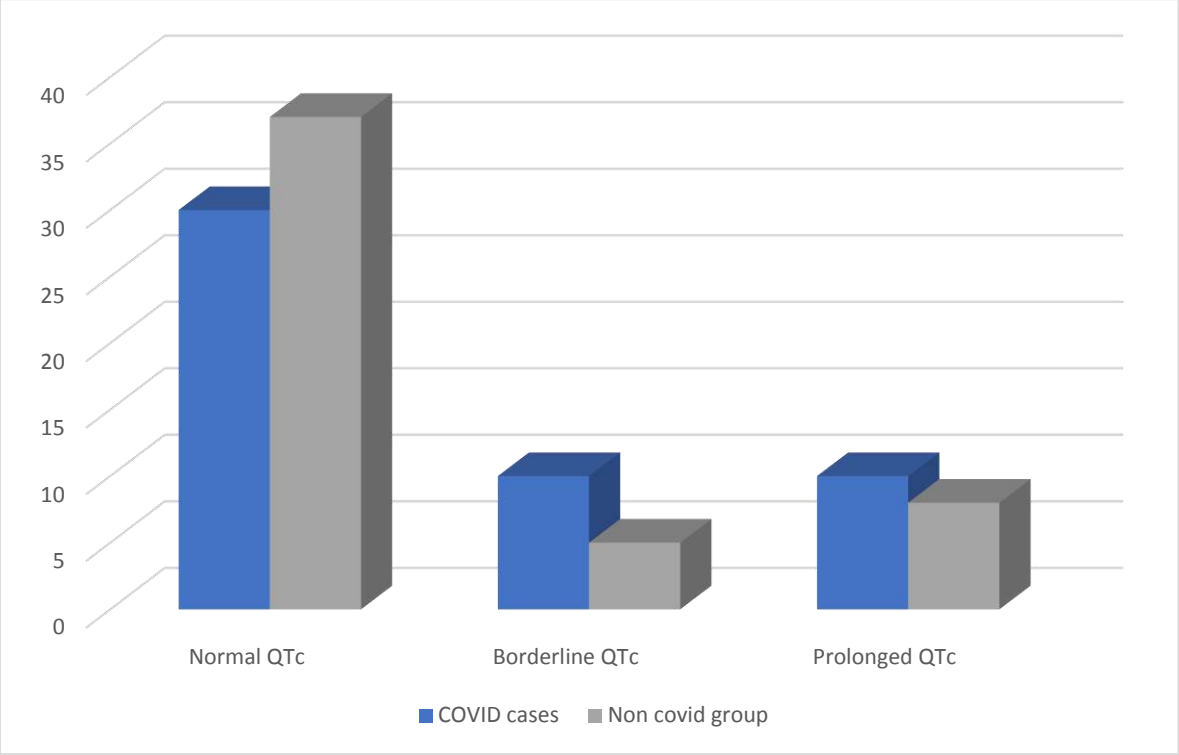


Figure 22 : Comparison of QTc between the two groups

Comparison of various parameters between subjects who had QTcd prolongation among the COVID cases-and those who did not, showed that SGPT and neutrophil lymphocyte ratio was elevated significantly ($p<0.05$).

QTcd prolongation	Normal		Prolonged		
	Mean	SD	Mean	SD	
Age	54.1	9.6	52.9	17.5	p>0.05
BMI	27.1	2.2	27.3	3.2	p>0.05
PR	97.1	12.8	101.1	12.4	p>0.05
SBP	125.8	17.6	123.7	19.4	p>0.05
DBP	75.7	10.9	78.1	13.3	p>0.05
RR	24.9	3.5	28.9	5.9	p>0.05
SpO2	84.4	7.6	76.3	17.9	p>0.05
SGOT	46.4	34.2	84.9	91.6	p>0.05
SGPT	35.2	16.1	87.2	99.7	**P<0.05**
CRP	86.4	53.3	79.1	46.7	p>0.05
HB	12.3	2.6	13.2	1.8	p>0.05
TC	9488.2	3927.9	10633.3	3635.6	p>0.05
DC-N	74.0	11.9	78.5	16.7	p>0.05
DC-L	19.0	10.3	13.5	10.5	p>0.05
DC-M	7.1	3.7	7.4	8.3	p>0.05
PLATELET	2.5	0.8	2.5	1.4	p>0.05
FBS	160.7	68.6	185.2	92.2	p>0.05
PPBS	269.2	107.4	284.5	136.1	p>0.05
HR	87.8	17.7	93.6	11.2	p>0.05
NLR	5.2	3.0	10.3	9.6	**P<0.05**

Table 11- comparison of baseline parameters between cases who had QTcd prolongation and those who did not.

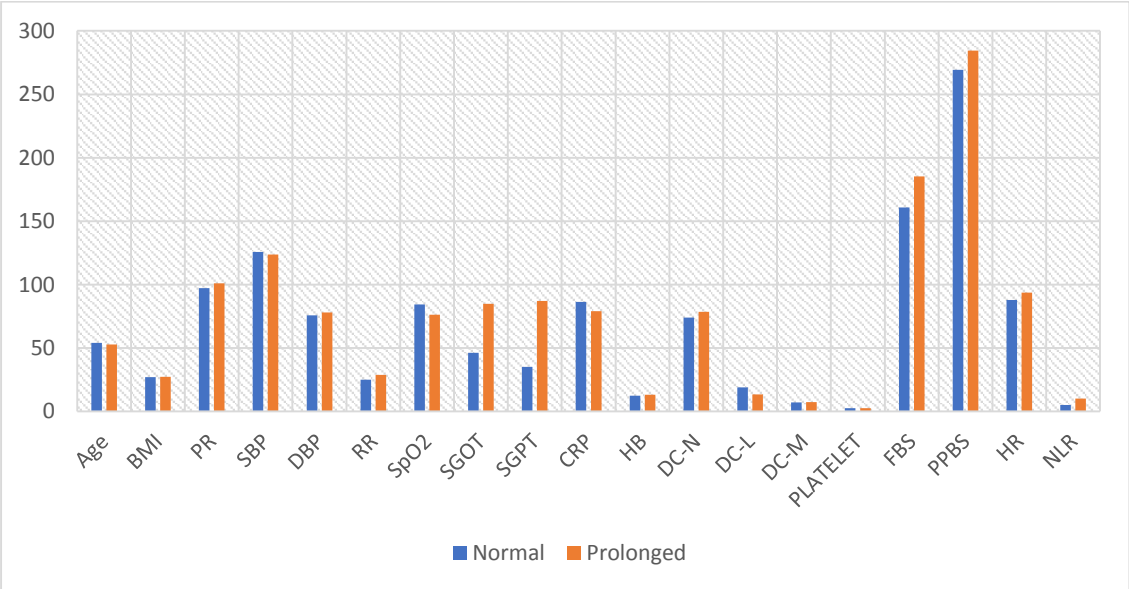


Figure - 23 -comparison of baseline characteristics between cases who had QTcd prolongation and those who did not

Comparison of various parameters between subjects who had Tpe/QTc prolongation and those who did not, showed that neither the demographic details nor the baseline investigations showed any significant difference.

Tpe/QTc prolongation	Normal		Prolonged		
	Mean	Std. Deviation	Mean	Std. Deviation	p>0.05
Age	52.1	14.9	57.0	12.6	p>0.05
BMI	27.0	2.9	27.9	2.1	p>0.05
PR	101.6	12.6	92.8	10.1	**<0.05**
SBP	124.9	19.2	123.8	17.0	p>0.05
DBP	77.9	12.6	74.6	11.3	p>0.05
RR	27.7	5.6	25.5	4.1	p>0.05
SpO2	78.0	16.0	85.3	8.4	p>0.05
SGOT	61.8	36.5	84.3	133.8	p>0.05
SGPT	59.6	62.4	76.1	116.1	p>0.05
CRP	86.9	53.6	69.8	33.2	p>0.05
HB	12.6	2.5	13.4	0.9	p>0.05
TC	9910.7	3813.7	10710.0	3743.6	p>0.05
DC-N	74.9	16.4	81.0	7.3	p>0.05
DC-L	17.1	11.9	12.8	5.1	p>0.05
DC-M	7.7	7.4	6.1	3.4	p>0.05
PLATELET	2.3	0.6	3.1	1.9	p>0.05
FBS	171.5	75.7	181.8	103.0	p>0.05
PPBS	275.2	115.9	284.6	146.7	p>0.05
HR	94.9	13.1	80.2	13.4	**<0.05**
NLR	8.1	8.8	7.5	3.4	p>0.05

Table 12: Comparison of various parameters between COVID cases who had Tpe/QTc prolongation and those who did not

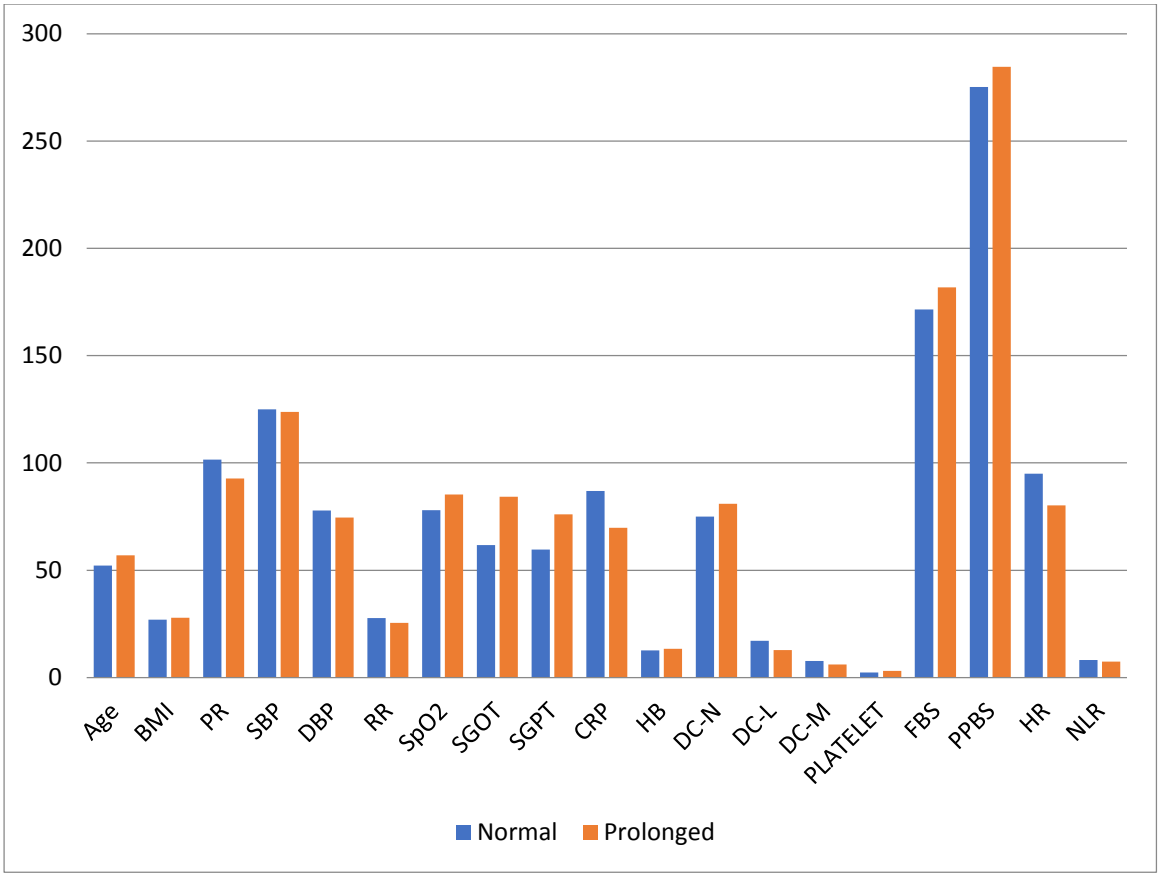


Figure-24 : comparison of various parameters between COVID cases who had Tpe/QTc prolongation and those who did not

During the course of the study, one subject under the COVID group developed narrow complex tachycardia- paroxysmal supraventricular tachycardia on day 3 of admission which was transient and self limiting. The ECGs are given in figure-15. For this patient, day 1 ECG showed prolonged QTc, Tpe and TPe/QT ratios. However, he did not develop any malignant ventricular arrhythmias. He had no comorbidities and was overweight (BMI-25.2).

PR (/min)	104	CRP	112
BP (mmHg)	120/80	SGOT/SGPT	94/37
RR (/min)	26	Hb (g/dL)	8.9
SpO2 (%)	84	Platelet	1.56

TC (cells/mm3)	19300	DC (cells/mm3)	88/8/2
NLR	11	FBS/PPBS	146/298

PR interval	0.12	Tpe/QT	0.315
QTc	0.457	Tpe/QTc	0.219
QTcd	0.057	Tpe	0.1

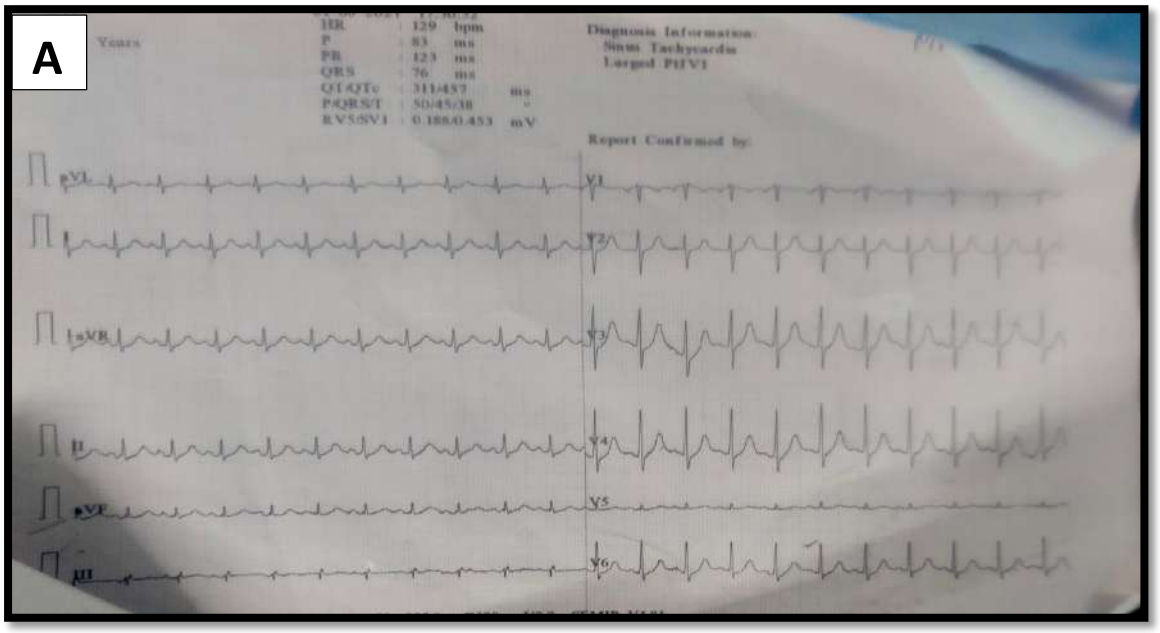


Figure- 25: A- Day 1 of ECG of 38 year old male patient suffering from severe COVID -19.

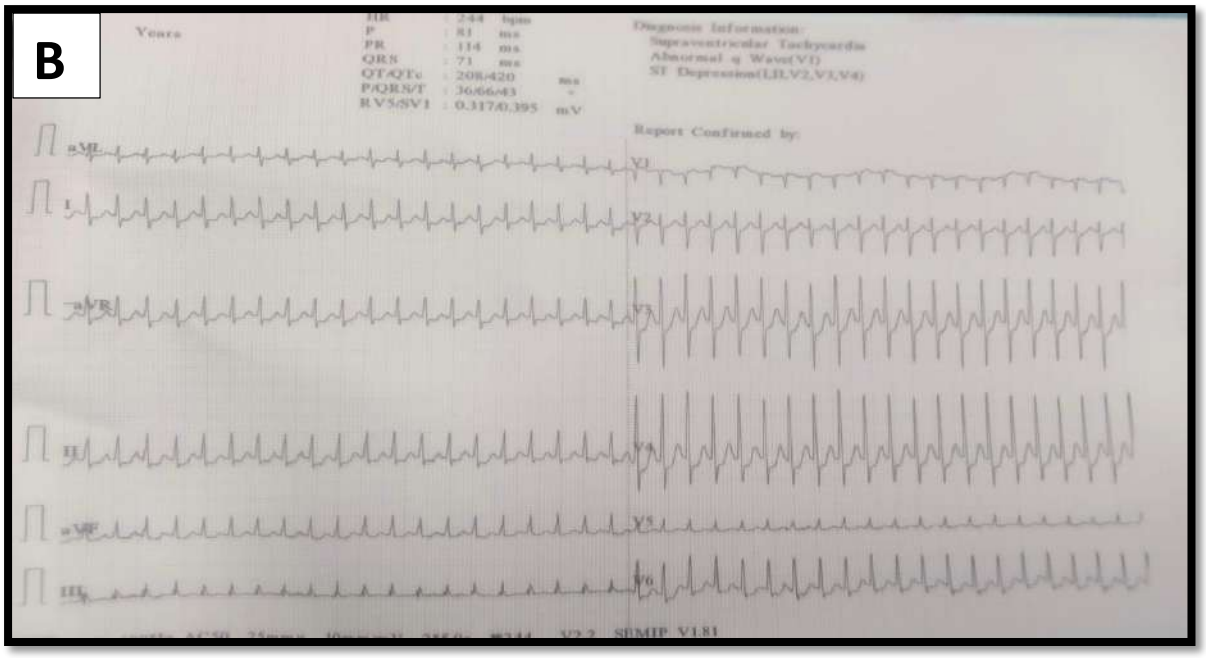


Figure 25 : B -Day 3 ECG of the same patient showing paroxysmal supra ventricular tachycardia (PSVT)

Discussion

DISCUSSION

Our understanding of complications of arrhythmia in COVID-19 is still in infancy. Many cases of different arrhythmia complications have been reported and the number is still growing. However, there is a big lacunae in literature for studies specifically aiming at pathogenesis of arrhythmias in COVID-19 patients.

In the cohort study by Shaobo Shi et al. (40) in Wuhan, China, among 416 consecutive COVID-19 patients, cardiac injury occurred in 19.7% of patients during hospitalisation and it was also an independent risk factor for in-hospital mortality. A retrospective, single-centre case series of the 138 consecutive hospitalised patients with COVID-19 in Wuhan, China, in the patients transferred to ICU(26.1%) 44.4% of the patients developed arrhythmia(42).

According to a series of case reports, one of the most common arrhythmias discussed in relation to COVID-19 is sinus bradycardia(43). However, as of now only case reports of sinus bradycardia and intermittent high degree AV block seen in COVID-19 patients exists. Peigh et al. reported sinus node dysfunction in two cases of COVID-19(44). They reported that these patients presented with sinus bradycardia followed by episodes of accelerated idioventricular rhythm. In particular, the patients remained in sinus bradycardia for 2 weeks following the onset of sinus node dysfunction. The potential mechanisms for sinus node dysfunction in patients with COVID-19 include myocardial inflammation or direct viral infiltration.

In a cohort study of 393 patients with COVID-19 patients in New York, rates of atrial arrhythmias were higher among patients requiring mechanical ventilation reporting 17.7% in mechanically ventilated patients compared with 1.9% in patients

requiring non-invasive ventilation. Atrial fibrillation was the most common cardiac arrhythmia observed in patients with COVID-19 infection according to a survey. According to a Danish study, following a national lockdown in Denmark , a 47% drop in registration of new onset atrial fibrillation cases was observed. The investigators conclude that the risk of undiagnosed atrial fibrillation patients with complications could have lead to worse outcomes in patients with atrial fibrillation in the COVID-19 pandemic(45).

Our study aimed to assess the risk of arrhythmias in COVID-19 patients through potential surface ECG markers. These surface ECG markers viz. QTc, QTcd,Tpe, Tpe/QTc, are easy, safe and non invasive methods, by which one can predict the risk of life threatening malignant arrhythmias. It has increasingly been used by physicians and cardiologists alike especially during the current pandemic. In the search for an effective treatment against COVID-19, there was a rapid surge in drug repurposing like the use of hydroxychloroquine , azithromycin and other antivirals.Some of these drugs can cause QTc prolongation. QTc prolongation as a harbinger of sudden cardiac deaths due to ventricular arrhythmias have been established in many previous studies. Therefore, there is a renewed interest in these markers to help predict arrhythmia in the current scenario.

In our study, the ECG markers namely QTcd and Tpe/QTc were significantly elevated among COVID-19 group, suggesting an increased risk of arrhythmias in COVID -19 patients. This correlates well with a similar analytical study, conducted in Turkey by Fatih et al. (40), in which mean QTc (410.8 ± 24.3 msec vs. 394.6 ± 20.3 msec), Tpe/QTc (0.19 ± 0.02 vs. 0.18 ± 0.04), and median QTd(47.52 vs. 46.5) were significantly elevated in COVID-19 patients. However, our study did not show a

significant increase in QTc or Tpe among the COVID group. Furthermore, in our study a 38 year old male with no known comorbidities developed supraventricular tachycardia. The exact cause was not identified.

In COVID-19, arrhythmias could be secondary to medication side effects, hypoxia and pulmonary disease, activated protein kinase C, direct oxidised Ca2+/calmodulin dependent protein kinase 2 activity , and myocarditis. So the exact mechanism in any patient as of now can only be postulated . It could be due to an interplay of all these factors as well. This study was aimed to prove the risk of arrhythmias in COVID-19 that can be picked up easily by physicians by using a simple tool -ECG.

Conclusion

CONCLUSION

The COVID-19 pandemic is changing our lives in unprecedented ways. The capacity of health-care systems globally has been severely tested (and in some countries completely overwhelmed), and the effect of this pandemic on social interactions, health-care delivery and the global economy continues to increase. Physical inactivity owing to lockdown measures may now contribute to poor control of cardiovascular risk factors.To meet the urgent need for effective treatment and preventative strategies, a concerted effort must be made by researchers globally to investigate and integrate biological and clinical findings related to COVID-19.

Arrhythmias have been associated with viral infections causing viral myocarditis and existing evidence suggests this may be at play in patients infected with COVID-19 as well. The current literature has a lacuna of detailed primary studies on arrhythmias and their possible mechanisms. This makes it difficult to distinguish between arrhythmias caused by hypoxemia, metabolic abnormalities, inflammatory syndrome, comorbidities, and medications as opposed to direct effect of virus on the heart. In order to firmly establish this relationship and to determine long-term consequences, further research is needed in the area.

Limitations

LIMITATION

The following limitations were noted in our study

1. This was a single centre study.
2. The small sample size is one of the most important limitation of the study.
3. The risk of arrhythmia was assessed based on ECG alone. Lack of echocardiography, coronary angiogram and cardiac markers for the study subjects did not help in ruling out underlying structural heart diseases, coronary artery diseases, which are independent risk factors of developing arrhythmia.
4. Long term effects of the risk of arrhythmia in COVID-19 patients was not assessed.
5. Association of increased risk of arrhythmias with disease severity has not been established.
6. The strain of COVID-19 in each study subject has not been determined. Hence association of any particular strain with increased risk of arrhythmias is not established.

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Annexures

ANNEXURE-1 ETHICAL COMMITTEE CERTIFICATE

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL,CHENNAI -01
INSTITUTIONAL ETHICS COMMITTEE

TITLE OF THE WORK	:	"ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY - A ANALYTICAL STUDY"
PRINCIPAL INVESTIGATOR	:	DR. S. SANCHNA DEV,
DESIGNATION	:	PG IN GENERAL MEDICINE,
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 03.11.2020 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

ANNEXURE-2. PROFORMA

Demographic details

Name :
Age :
Sex :
Hospital Number :
Co- morbidities :

Anthropometric Parameters

Parameters	Values
Weight(in kg)	
Height (in cm)	
BMI (kg/m2)	

Symptoms At presentation

Symptoms	Yes/No
Asymptomatic	
ILI	
SARI on Oxygen support	
SARI on NIV	
SARI on Invasive ventilation	
MODS/ Complications	
Atypical presentation(Neuro/others)(Specify)	

Baseline Parameters

Vitals

Vitals	Values
Heart rate(/min)	
Systolic BP (mm of Hg)	
Diastolic BP (mm of Hg)	
Respiratory rate(/min)	
SpO2 (%)	

Investigations

Investigation	**Values**
SGOT (U/L)	
SGPT(U/L)	
CRP(mg/L)	
Hb(mg/dL)	
Total count (/mcL)	
Differential count(%)	
Platelet (/mcL)	
Neutrophil lymphocyte ratio(NLR)	
FBS(mg/dL)	
PPBS(mg/dL)	

ECG Parameter

ECG Parameters	
Heart rate(bpm)	
QT interval(msec)	
QTc interval(msec)	
PR interval(msec)	
T p-e interval(msec)	
T p-e /QT ratio	
T p-e/QTc ratio	
QT_{max}(msec)	
QT min (msec)	
QTd (msec)	
QTcd(msec)	

ANNEXURE-3 CONSENT FORM- ENGLISH

ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY -AN ANALYTICAL STUDY

Place of study: Govt. Stanley Hospital, Chennai- 600001

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

CONSENT FORM-TAMIL

ARRHYTHMOGENIC RISK ASSESSMENT IN COVID 19 PATIENTS THROUGH ELECTROCARDIOGRAPHY -AN ANALYTICAL STUDY

Place of study: Govt. Stanley Hospital, Chennai- 600001

நான் ……,இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றிநான் அறிந்துள்ளேன்.

நான் எந்தவொருவேளையிலும் ஆய்வில் இருந்து திரும்பமுடியும், அதன்பின்னர், நான் வழக்கம் போல் மருத்துவசிகிச்சை பெறமுடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்குஎடுத்து பணம் எதையும் பெறமுடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை,

என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்ககூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்யபோகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர் பெயர் மற்றும் முகவரி

சாட்சி பெயர் மற்றும் முகவரி

கையொப்பம் / விரல்ரேகை:

கையொப்பம் /விரல்ரேகை:

தேதி

ஆராய்ச்சியாளராக கையொப்பம் மற்றும் தேதி

Cases/Control	Age	Sex no	Sex	Hospital Number	Co-morbidities	Weight(kg)	Height(cm)	HEIGHT(M)	BMI	Symptoms at presentation	PR	SBP	DBP	RR	SpO2	SGOT	SGPT	CRP	HB	TC	DC-N	DC-L	DC-M	PLATELET	NLR	FBS	PPBS	HR	QTmean	QTC mean	PRint	TPE	TPE/QT
Cases	65	2	F	2156748	1	65	150	1.5	28.9	3	86	130	90	28	85	43	23	54	11.6	7100	81	14.3	4.5	2.42	5.7	304	429	93.7	0.27	0.345	0.2	0.06	0.22
Cases	57	1	M	2156736	1	80	176	1.76	25.8	3	82	130	80	28	81	68	35	178	13.3	7700	85	12	3	2.09	7.1	134	368	78.9	0.336	0.386	0.16	0.08	0.238
Cases	26	1	M	2153911	1	65	170	1.7	22.5	3	92	140	80	30	84	70	94	89	13.5	8800	100	0	0	2.04	HIGH	100	214	93.75	0.36	0.45	0.18	0.1	0.27
Cases	67	2	F	2143937	1	80	161	1.61	30.9	3	86	150	90	24	85	143	78	214	12.5	7400	76	20	4	1.1	3.8	200	404	88.2	0.332	0.404	0.16	0.06	0.181
Cases	58	2	F	2151065	1	70	150	1.5	31.1	3	102	120	80	20	90	144	225	230	13	15400	88	5.3	6.4	1.42	16.6	186	258	115.4	0.32	0.44	0.2	0.05	0.156
Cases	27	1	M	2156234	1	94	172	1.72	31.8	4	112	100	60	36	39	98	100	48	12.2	11700	81	16	3	1.7	5.1	113	140	93.7	0.31	0.388	0.12	0.06	0.194
Cases	45	2	F	2156268	2	64	150	1.5	28.4	3	96	110	60	28	88	39	30	67	5.8	6100	69	22	9	2	3.1	233	305	100	0.32	0.4	0.22	0.06	0.188
Cases	17	1	M	2156245	1	60	148	1.48	27.4	4	92	100	70	38	35	80	43	72	9.8	7300	70	27	3	2.4	2.6	110	156	100	0.358	0.465	0.18	0.08	0.223
Cases	45	1	M	2156318	1	70	168	1.68	24.8	4	120	150	100	40	55	52	42	125	17.3	9500	46	20	34	1.8	2.3	167	222	107	0.32	0.434	0.18	0.05	0.156
Cases	39	2	F	2153704	1	72	164	1.64	26.8	4	112	120	70	40	45	70	27	26	11.6	11600	85	9	5	2.13	9.4	99	136	83.3	0.34	0.402	0.16	0.06	0.176
Cases	70	1	M	2156523	1	80	177	1.77	25.5	3	88	130	90	26	85	40	25	42	11.6	7600	81.3	10.2	8.5	2.04	8.0	82	156	75	0.378	0.425	0.2	0.07	0.185
Cases	80	1	M	2156621	4	82	181	1.81	25.0	3	92	160	60	20	94	49	29	65	12.4	6800	82	15	2	1.73	5.5	123	236	83.3	0.338	0.398	0.12	0.1	0.296
Cases	54	1	M	2156260	4	88	168	1.68	31.2	3	98	130	80	28	95	80	64	88	13.2	7800	84	15	1	2.2	5.6	260	422	76.9	0.37	0.462	0.16	0.12	0.32
Cases	51	1	M	2157321	2	81	178	1.78	25.6	3	86	130	90	30	74	59.6	57	48	12.7	9000	84	11	5	2	7.6	230	404	75	0.385	0.433	0.16	0.12	0.311
Cases	56	1	M	2161004	2	76	166	1.66	27.6	2	79	110	70	18	93	32	34	64	12.1	8600	72	18	11	3.1	4.0	160	225	88.2	0.337	0.409	0.16	0.06	0.178
Cases	57	1	M	2153566	2	73	161	1.61	28.2	4	129	130	80	32	80	24	34	86	14	12000	96.4	2.4	1.2	1.61	40.2	166	284	88.2	0.388	0.471	0.12	0.09	0.232
Cases	75	1	M	2156488	4	92	181	1.81	28.1	3	89	120	90	27	70	461	403	117	11.7	10900	89	6	5	2	14.8	404	522	88.2	0.328	0.398	0.14	0.1	0.305
Cases	63	1	M	2162334	2	84	173	1.73	28.1	3	108	120	70	28	84	26	22	30	14	7800	81	11	8	1.95	7.4	201	322	75	0.355	0.397	0.12	0.1	0.282
Cases	52	1	M	2163333	1	92	174	1.74	30.4	3	112	130	70	24	90	20	18	12	13	7300	70	20	10	2.8	3.5	98	149	88.2	0.34	0.412	0.16	0.1	0.294
Cases	52	1	M	2127548	3	88	171	1.71	30.1	3	84	100	70	28	86	56	33	94	14.5	18200	86	10	4	8.1	8.6	101	164	103.4	0.35	0.461	0.16	0.11	0.314
Cases	62	1	M	2085300	1	86	178	1.78	27.1	3	92	130	80	20	93	58	73	14	15.7	6500	50	37	11	3.3	1.4	110	166	93.8	0.313	0.392	0.2	0.08	0.256
Cases	61	1	M	2157661	1	70	168	1.68	24.8	3	110	110	70	24	80	25	49	48	13.8	8300	80	20	0	3.1	4.0	86	180	93.8	0.318	0.398	0.14	0.08	0.252
Cases	50	1	M	2085171	2	72	166	1.66	26.1	3	106	120	90	28	85	141	301	69.7	12	14700	84	12	2	2.43	7.0	389	592	100	0.345	0.483	0.14	0.1	0.29
Cases	38	1	M	2158552	1	78	176	1.76	25.2	3	104	120	80	26	84	94	37	112	8.9	19300	88	8	2	1.56	11.0	146	298	125	0.317	0.457	0.12	0.1	0.315
Cases	54	1	M	2127126	1	70	160	1.6	27.3	3	82	100	60	20	92	38	62	95	14.6	14300	83	8.8	7.7	2.99	9.4	98	119	51.7	0.423	0.396	0.16	0.12	0.284
Cases	78	1	M	2126454	3	69	166	1.66	25.0	3	104	100	70	26	84	20	20	13.6	14.9	17400	91	4.2	4.7	1.93	21.7	164	332	75	0.41	0.458	0.1	0.08	0.195
Cases	58	2	F	2127333	4	68	150	1.5	30.2	3	112	130	70	28	88	33	21	156	14.9	13600	82	14	4	2.65	5.9	209	404	111.1	0.315	0.429	0.12	0.08	0.254
Cases	59	1	M	2085306	1	65	159	1.59	25.7	3	96	120	70	26	80	22	29	62	12.8	11000	56	42	6	2.6	1.3	126	203	75	0.356	0.399	0.16	0.08	0.225
Cases	58	2	F	2127364	4	62	158	1.58	24.8	3	90	150	80	28	60	24	18	97.9	8.3	8500	79	17	5	2.5	4.6	330	418	88.2	0.368	0.445	0.14	0.09	0.245
Cases	48	2	F	2085079	1	58	154	1.54	24.5	3	90	120	70	24	82	66	53	92	12.3	13200	88	4	7	2.1	22.0	95	107	88.2	0.35	0.424	0.12	0.1	0.286
Cases	37	2	F	2137487	1	62	152	1.52	26.8	3	88	122	70	20	88	20	27	56	13.6	11100	66	22	12	4.5	3.0	76	116	75	0.33	0.373	0.16	0.09	0.27
Cases	39	1	M	2800391	2	66	169	1.69	23.1	3	119	110	70	26	84	96	41	67	15.8	5100	61	27	11	2.02	2.3	198	324	115.4	0.316	0.439	0.16	0.08	0.253
Cases	75	1	M	2157631	1	67	168	1.68	23.7	4	112	100	60	32	73	56	49	112	15.9	7100	56	21	21	2.58	2.7	189	291	93.75	0.316	0.396	0.12	0.09	0.285
Cases	52	1	M	2184236	2	71	164	1.64	26.4	3	89	126	86	30	80	33	46	92.5	14	13900	85	9	6	2.4	9.4	227	392	85.7	0.307	0.365	0.18	0.1	0.326
Cases	45	2	F	2169998	1	64	152	1.52	27.7	3	110	110	70	26	85	68	49	43.7	12.8	5500	39	39	21	3.21	1.0	126	161	107	0.338	0.451	0.16	0.07	0.207
Cases	38	1	M	2154985	1	65	166	1.66	23.6	3	104	168	110	28	80	50	82	87	15	10800	81	10	8	3.21	8.1	241	338	100	0.322	0.415	0.16	0.08	0.248
Cases	53	1	M	2179962	3	92	178	1.78	29.0	2	110	170	100	20	92	35	27	75	10.3	3700	44	42	13	3.5	1.0	128	194	78.9	0.33	0.382	0.16	0.08	0.242
Cases	68	2	F	2136418	2	85	156	1.56	34.9	3	110	120	70	26	89	38	31	88	11	12000	88	5	7	2.2	17.6	212	401	107	0.33	0.441	0.14	0.08	0.242
Cases	45	2	F	2173212	3	70	162	1.62	26.7	3	120	130	70	22	88	59	93	83.6	10.7	11600	75.2	18.1	6.7	6.25	4.2	156	288	111.1	0.346	0.471	0.14	0.08	0.231
Cases	52	1	M	2179961	1	66	166	1.66	24.0	3	77	110	76	26	90	51	37	156	13	9000	56	22	20	3.2	2.5	87	112	100	0.337	0.434	0.16	0.1	0.296
Cases	31	1	M	2085318	1	73	179	1.79	22.8	3	88	120	70	20	87	101	61	90	14.1	5000	48.5	31.1	20.4	1.92	1.6	76	92	75	0.332	0.371	0.12	0.06	0.181
Cases	70	1	M	2143089	4	80	176	1.76	25.8	4	78	120	80	30	72	39	17	35.8	12.1	8500	78	18	4	2.3	4.3	212	304	78.9	0.39	0.447	0.14	0.1	0.256
Cases	37	1	M	2154397	1	75	168	1.68	26.6	4	115	100	70	32	73	43	70	20	15.1	13400	90.8	7.2	2	3.12	12.6	90	127	62.5	0.381	0.389	0.14	0.08	0.21
Cases	30	1	M	2127671	1	72	165	1.65	26.4	3	80	110	70	24	85	34	21	18.1	14.8	7300	74	18	8	1.7	4.1	156	212	78.9	0.368	0.422	0.12	0.08	0.217
Cases	55	1	M	2127499	2	80	166	1.66	29.0	3	110	120	76	26	89	39	35	102	14.7	12900	92	5	3	1.3	18.4	185	309	96.7	0.359	0.456	0.16	0.08	0.223
Cases	33	1	M	2155033	1	84	182	1.82	25.4	4	126	140	90	33	76	10	28	12	15.5	27500	86.9	7	6.1	7.06	12.4	146	288	90.9	0.345	0.426	0.16	0.08	0.232
Cases	46	2	F	2155294	1	76	156	1.56	31.2	4	112	120	70	28	70	52	58	69	10.6	10800	85.6	9	5.4	2.4	9.5	88	98	93.7	0.37	0.462	0.13	0.09	0.242
Cases	57	1	M	2075839	1	78	171	1.71	26.7	3	80	120	70	26	92	42.7	28	48.9	12.9	5100	62.1	28.8	9.1	2.17	2.2	151	203	75	0.393	0.442	0.17	0.08	0.204

TPE/QTC	QTMAX	QTMIN	QTD	QTCMAX	QTCMIN	QTCD	QT1	QT2	QT3	QTavr	QTavl	QTavf	QTv1	QTv2	QTv3	QTv4	QTv5	QTv6	QT Prolongation	QTc prolongation	QTd prolongation	QTcd prongation	Tpe prolongation	Tpe/QT prolongation	Tpe/QTc prongation	PR prolongation
0.17	0.36	0.24	0.12	0.45	0.3	0.15	0.28	0.32	0.32	0.24	0.24	0.24	0.34	0.36	0.36	0.32	0.32	0.36	1	1	3	3	1	1	1	1
0.207	0.4	0.36	0.04	0.459	0.413	0.045	0.36	0.36	0.36	0.36	0.4	0.32	0.36	0.36	0.4	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.22	0.4	0.32	0.08	0.5	0.4	0.1	0.36	0.4	0.32	0.36	0.36	0.36	0.4	0.36	0.36	0.36	0.36	0.36	1	2	1	3	3	3	1	1
0.14	0.36	0.32	0.04	0.404	0.39	0.049	0.34	0.34	0.32	0.32	0.32	0.36	0.34	0.32	0.32	0.32	0.32	0.36	1	1	1	1	1	1	1	1
0.11	0.36	0.28	0.08	0.5	0.38	0.11	0.32	0.32	0.3	0.36	0.32	0.32	0.32	0.28	0.32	0.28	0.34	0.36	1	1	1	3	1	1	1	1
0.154	0.34	0.28	0.06	0.425	0.35	0.075	0.3	0.32	0.32	0.3	0.28	0.32	0.32	0.32	0.32	0.28	0.3	0.34	1	1	1	3	1	1	1	1
0.15	0.36	0.32	0.04	0.45	0.4	0.05	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.36	0.32	0.32	0.34	0.34	1	1	1	1	1	1	1	3
0.172	0.4	0.32	0.08	0.519	0.415	0.1	0.36	0.32	0.32	0.32	0.36	0.32	0.36	0.36	0.4	0.4	0.4	0.36	1	3	1	3	1	1	1	1
0.115	0.38	0.28	0.1	0.51	0.37	0.14	0.3	0.32	0.32	0.32	0.3	0.32	0.36	0.32	0.32	0.28	0.38	0.32	1	2	1	3	1	1	1	1
0.14	0.4	0.3	0.1	0.47	0.35	0.12	0.32	0.32	0.33	0.3	0.32	0.36	0.34	0.4	0.4	0.32	0.36	0.32	1	1	1	3	1	1	1	1
0.165	0.4	0.36	0.04	0.449	0.404	0.045	0.36	0.38	0.38	0.38	0.37	0.38	0.4	0.37	0.37	0.39	0.38	0.4	1	1	1	1	1	1	1	1
0.251	0.38	0.28	0.1	0.448	0.329	0.12	0.33	0.33	0.36	0.33	0.37	0.34	0.38	0.33	0.35	0.34	0.28	0.32	1	1	1	3	3	3	3	1
0.259	0.4	0.36	0.04	0.5	0.4	0.1	0.36	0.4	0.36	0.36	0.36	0.36	0.36	0.36	0.4	0.36	0.36	0.36	1	3	1	3	3	3	3	1
0.277	0.44	0.36	0.08	0.494	0.404	0.09	0.36	0.36	0.34	0.4	0.36	0.4	0.36	0.4	0.4	0.4	0.44	0.4	1	2	1	3	3	3	3	1
0.147	0.36	0.32	0.04	0.436	0.32	0.048	0.32	0.36	0.36	0.36	0.32	0.36	0.36	0.32	0.32	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.191	0.4	0.34	0.06	0.485	0.412	0.073	0.34	0.36	0.32	0.36	0.32	0.36	0.36	0.36	0.36	0.4	0.4	0.36	1	3	1	3	1	1	1	1
0.251	0.36	0.31	0.05	0.436	0.376	0.061	0.32	0.32	0.32	0.36	0.32	0.36	0.32	0.32	0.32	0.32	0.34	0.34	1	1	1	3	3	3	3	1
0.252	0.37	0.32	0.05	0.413	0.358	0.056	0.36	0.36	0.36	0.37	0.33	0.36	0.37	0.32	0.35	0.36	0.36	0.36	1	1	1	1	3	3	3	1
0.243	0.36	0.32	0.04	0.436	0.387	0.048	0.36	0.36	0.32	0.32	0.32	0.32	0.36	0.36	0.32	0.32	0.36	0.36	1	1	1	1	3	3	3	1
0.239	0.4	0.32	0.08	0.526	0.421	0.105	0.4	0.32	0.36	0.36	0.32	0.36	0.32	0.36	0.36	0.36	0.32	0.36	1	3	1	3	3	3	3	1
0.204	0.36	0.28	0.08	0.45	0.35	0.1	0.32	0.28	0.3	0.36	0.32	0.28	0.28	0.34	0.32	0.32	0.32	0.32	1	1	1	3	1	3	1	1
0.201	0.34	0.3	0.04	0.425	0.375	0.05	0.32	0.32	0.32	0.34	0.32	0.32	0.3	0.3	0.3	0.32	0.32	0.34	1	1	1	1	1	1	1	1
0.207	0.4	0.32	0.08	0.516	0.413	0.103	0.34	0.4	0.36	0.32	0.36	0.34	0.36	0.36	0.34	0.32	0.32	0.32	1	3	1	3	3	3	1	1
0.219	0.34	0.3	0.04	0.49	0.433	0.057	0.3	0.32	0.3	0.32	0.34	0.32	0.32	0.32	0.32	0.32	0.32	0.3	1	3	1	1	3	3	1	1
0.303	0.44	0.4	0.04	0.411	0.374	0.037	0.4	0.4	0.44	0.44	0.44	0.44	0.44	0.4	0.44	0.44	0.4	0.4	1	1	1	1	3	3	3	1
0.175	0.44	0.36	0.08	0.492	0.402	0.089	0.36	0.4	0.44	0.4	0.4	0.44	0.4	0.44	0.44	0.4	0.36	0.4	1	3	1	3	1	1	1	1
0.186	0.32	0.28	0.04	0.435	0.381	0.054	0.32	0.31	0.32	0.32	0.28	0.3	0.32	0.32	0.33	0.32	0.32	0.32	1	1	1	1	1	3	1	1
0.201	0.36	0.32	0.04	0.403	0.358	0.045	0.36	0.38	0.36	0.36	0.36	0.38	0.34	0.32	0.34	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.202	0.4	0.36	0.04	0.485	0.436	0.049	0.36	0.36	0.4	0.36	0.4	0.4	0.36	0.4	0.4	0.4	0.36	0.36	1	1	1	1	1	1	1	1
0.236	0.4	0.32	0.08	0.485	0.388	0.097	0.32	0.36	0.32	0.36	0.32	0.36	0.32	0.36	0.34	0.36	0.4	0.38	1	1	1	3	3	3	1	1
0.241	0.36	0.32	0.04	0.403	0.357	0.045	0.32	0.32	0.34	0.32	0.32	0.36	0.36	0.32	0.32	0.32	0.34	0.36	1	1	1	1	1	3	3	1
0.182	0.36	0.32	0.04	0.5	0.44	0.05	0.32	0.28	0.32	0.3	0.28	0.36	0.28	0.28	0.36	0.36	0.34	0.36	1	2	1	1	1	3	1	1
0.227	0.36	0.28	0.08	0.45	0.35	0.1	0.32	0.28	0.3	0.32	0.28	0.32	0.36	0.36	0.32	0.32	0.32	0.3	1	1	1	3	1	3	1	1
0.274	0.32	0.28	0.04	0.381	0.33	0.05	0.28	0.32	0.32	0.28	0.28	0.28	0.32	0.32	0.32	0.32	0.32	0.32	1	1	1	1	3	3	3	1
0.155	0.36	0.3	0.06	0.48	0.4	0.08	0.32	0.36	0.3	0.36	0.36	0.36	0.36	0.32	0.32	0.32	0.32	0.36	1	2	1	3	1	1	1	1
0.193	0.36	0.3	0.06	0.465	0.387	0.077	0.32	0.36	0.32	0.36	0.3	0.32	0.32	0.32	0.32	0.32	0.3	0.3	1	1	1	3	1	1	1	1
0.209	0.36	0.32	0.04	0.413	0.367	0.045	0.32	0.32	0.32	0.34	0.34	0.36	0.34	0.32	0.36	0.34	0.32	0.32	1	1	1	1	1	1	1	1
0.181	0.36	0.28	0.08	0.481	0.374	0.107	0.34	0.34	0.36	0.36	0.28	0.32	0.32	0.32	0.32	0.28	0.36	0.36	1	1	1	3	1	1	1	1
0.169	0.36	0.34	0.02	0.489	0.462	0.027	0.34	0.36	0.34	0.34	0.36	0.34	0.34	0.34	0.34	0.36	0.34	0.36	1	3	1	1	1	1	1	1
0.23	0.36	0.32	0.04	0.465	0.413	0.05	0.32	0.32	0.34	0.36	0.32	0.32	0.34	0.34	0.34	0.36	0.34	0.34	1	2	1	1	3	3	1	1
0.162	0.36	0.32	0.04	0.403	0.358	0.05	0.32	0.32	0.32	0.32	0.32	0.32	0.34	0.36	0.32	0.36	0.34	0.34	1	1	1	1	1	1	1	1
0.224	0.4	0.36	0.04	0.459	0.412	0.046	0.36	0.38	0.4	0.38	0.38	0.4	0.38	0.38	0.38	0.4	0.4	0.4	1	2	1	1	3	3	1	1
0.21	0.44	0.34	0.1	0.449	0.347	0.1	0.34	0.4	0.4	0.36	0.36	0.4	0.36	0.36	0.36	0.44	0.44	0.4	1	1	1	3	1	1	1	1
0.19	0.4	0.36	0.04	0.459	0.413	0.046	0.36	0.36	0.36	0.4	0.36	0.38	0.36	0.36	0.36	0.38	0.38	0.36	1	1	1	1	1	1	1	1
0.175	0.4	0.32	0.08	0.508	0.407	0.102	0.34	0.32	0.34	0.34	0.34	0.36	0.36	0.36	0.35	0.4	0.4	0.4	1	3	1	3	1	1	1	1
0.188	0.38	0.32	0.06	0.467	0.394	0.073	0.35	0.35	0.35	0.38	0.36	0.32	0.34	0.36	0.36	0.34	0.34	0.32	1	1	1	3	1	1	1	1
0.195	0.4	0.34	0.06	0.5	0.425	0.075	0.38	0.36	0.4	0.38	0.4	0.36	0.38	0.34	0.34	0.36	0.36	0.38	1	2	1	3	1	1	1	1
0.181	0.4	0.37	0.03	0.449	0.416	0.03	0.38	0.4	0.4	0.4	0.4	0.4	0.4	0.38	0.37	0.4	0.4	0.39	1	2	1	1	1	1	1	1

Cases/Control	Age	Sex no	Sex	Hospital Number	Co-morbidities	Weight(kg)	Height(cm)	HEIGHT(M)	BMI	Symptoms at presentation	PR	SBP	DBP	RR	SpO2	SGOT	SGPT	CRP	HB	TC	DC-N	DC-L	DC-M	PLATELET	NLR	FBS	PPBS	HR	QTmean	QTC mean	PRint	TPE	TPE/QT
Cases	45	1	M	2075781	1	84	168	1.68	29.8	3	126	130	90	30	80	56	44	30.4	16.5	7300	71	21	8	1.72	3.4	156	222	136.3	0.294	0.443	0.14	0.07	0.238
Cases	66	1	M	2145266	2	78	171	1.71	26.7	3	112	110	80	28	93	49.6	28.9	56	14.6	7700	70	18	12	2	3.9	202	411	111.1	0.33	0.453	0.14	0.06	0.18
Controls	23	2	F	2185923	1	48	156	1.56	19.7	1	71	110	60	16	99	23	22	1.2	12	8700	81	18	1	3.2	4.5	88	104	71.4	0.343	0.374	0.2	0.12	0.349
Controls	13	2	F	2185931	1	45	159	1.59	17.8	1	111	120	80	14	99	25	23	1	11	6600	65	33	2	2.8	2.0	156	202	111.1	0.32	0.435	0.13	0.1	0.31
Controls	50	1	M	2185943	2	66	160	1.6	25.8	1	97	100	80	15	98	33	26	1.5	13	8400	54	40	6	1.9	1.4	144	322	96.7	0.33	0.424	0.15	0.08	0.242
Controls	53	2	F	2187504	1	65	169	1.69	22.8	1	88	120	70	12	99	32	29	1.3	12	9800	61	36	3	2.7	1.7	88	110	88.2	0.329	0.399	0.14	0.1	0.304
Controls	50	1	M	2189389	2	65	169	1.69	22.8	1	111	100	60	16	99	21	20	2.2	14.5	7800	71	24	4	3.5	3.0	129	211	111.1	0.332	0.45	0.14	0.08	0.241
Controls	47	1	M	2189363	1	69	170	1.7	23.9	1	82	130	70	16	99	29	25	2.4	14.6	12000	49	47	4	3.8	1.0	100	160	82.3	0.358	0.422	0.14	0.06	0.168
Controls	28	2	F	2189405	1	58	158	1.58	23.2	1	65	110	80	14	99	25	24	1.5	10.3	6800	60	34	6	2.5	1.8	87	99	65.2	0.375	0.391	0.16	0.06	0.16
Controls	16	2	F	2189404	1	44	152	1.52	19.0	1	103	140	70	15	99	22	30	1.6	11	4600	67	30	3	2.1	2.2	79	112	103.4	0.322	0.422	0.1	0.06	0.186
Controls	37	1	M	2189397	1	52	166	1.66	18.9	1	111	130	80	16	98	27	21	1	15	5500	53	39	8	3.3	1.4	78	104	111	0.296	0.403	0.13	0.06	0.2
Controls	62	1	M	2189359	1	70	159	1.59	27.7	1	88	110	70	14	99	28	23	1	14.3	9600	62	36	2	2.9	1.7	87	109	88.2	0.321	0.389	0.16	0.08	0.249
Controls	60	1	M	2187517	2	59	165	1.65	21.7	1	94	120	80	16	98	33	29	1.5	13.5	10400	73	32	4	2.7	2.3	140	199	93.75	0.335	0.418	0.16	0.1	0.299
Controls	26	1	M	2187537	1	70	176	1.76	22.6	1	94	130	70	14	98	34	30	3.1	14	7800	45	50	5	3.4	0.9	89	121	93.75	0.326	0.408	0.16	0.08	0.245
Controls	65	2	F	2188901	3	72	160	1.6	28.1	1	100	160	90	13	99	36	32	1.2	15	10800	58	39	3	2.8	1.5	102	136	100	0.324	0.418	0.16	0.06	0.185
Controls	38	2	F	2188967	1	56	157	1.57	22.7	1	67	130	88	14	99	21	20	1.1	8	9900	51	45	4	2.9	1.1	78	106	66.7	0.424	0.446	0.16	0.07	0.165
Controls	60	2	F	2188936	2	72	160	1.6	28.1	1	120	120	78	16	99	22	20	1	10.4	9400	48	47	5	3.4	1.0	134	212	120	0.336	0.475	0.14	0.08	0.238
Controls	65	2	F	2188935	1	70	164	1.64	26.0	1	88	110	70	16	99	27	26	1	11.2	8300	62	34	4	2	1.8	98	128	88.2	0.36	0.436	0.18	0.08	0.22
Controls	45	2	F	2187105	1	62	158	1.58	24.8	1	107	120	72	14	98	25	21	1.6	11.8	7200	72	25	3	2.5	2.9	86	99	107.1	0.318	0.425	0.12	0.1	0.314
Controls	42	2	F	2187424	1	62	156	1.56	25.5	1	94	140	68	16	98	39	21	1.9	11.1	16000	66	29	5	3.1	2.3	76	109	93.75	0.318	0.397	0.14	0.08	0.25
Controls	50	2	F	2186788	1	58	148	1.48	26.5	1	88	130	66	17	98	40	19	2.2	10.8	5200	45	50	5	2.9	0.9	68	110	88.2	0.362	0.438	0.13	0.08	0.22
Controls	23	1	M	2188149	1	66	169	1.69	23.1	1	88	126	72	15	97	31	24	1.1	13	8300	56	41	3	3.5	1.4	89	102	88.2	0.335	0.406	0.16	0.09	0.269
Controls	38	1	M	2187167	1	73	165	1.65	26.8	1	103	140	78	16	96	33	28	1	14	9600	54	43	3	2.8	1.3	91	119	103.4	0.373	0.489	0.12	0.1	0.268
Controls	56	1	M	2187081	1	68	169	1.69	23.8	1	75	130	84	16	98	34	19	1	14.4	10300	50	46	4	2.5	1.1	85	104	75	0.378	0.425	0.21	0.1	0.265
Controls	78	1	M	2188745	4	72	169	1.69	25.2	1	91	140	90	14	98	36	27	1.3	13	9800	53	39	8	3.1	1.4	120	220	90.9	0.36	0.44	0.13	0.1	0.28
Controls	24	1	M	2187845	1	55	166	1.66	20.0	1	107	150	90	16	98	27	28	1	9.8	7600	49	46	5	2.5	1.1	82	115	107.1	0.353	0.471	0.15	0.1	0.283
Controls	52	1	M	2186584	2	66	167	1.67	23.7	1	107	120	72	15	99	28	39	1.4	16.6	5800	51	46	3	2.6	1.1	101	136	107.1	0.308	0.412	0.14	0.08	0.259
Controls	42	1	M	2189203	3	68	165	1.65	25.0	1	88	130	80	16	98	39	33	1.6	15.4	6400	46	44	10	3.1	1.0	72	98	88.2	0.34	0.412	0.12	0.08	0.235
Controls	49	1	M	2180744	1	56	164	1.64	20.8	1	115	116	70	17	98	32	41	1.3	14.8	7300	62	36	2	2.4	1.7	76	104	115.3	0.316	0.438	0.16	0.1	0.316

TPE/QTC	QTMAX	QTMIN	QTD	QTCMAX	QTCMIN	QTCD	QT1	QT2	QT3	QTavr	QTavl	QTavf	QTv1	QTv2	QTv3	QTv4	QTv5	QTv6	QT Prolongation	QTc prolongation	QTd prolongation	QTcd prongation	Tpe prolongation	Tpe/QT prolongation	Tpe/QTc prongation	PR prolongation
0.158	0.32	0.28	0.04	0.483	0.422	0.06	0.28	0.3	0.28	0.29	0.3	0.3	0.3	0.28	0.28	0.3	0.32	0.3	1	2	1	3	1	1	1	1
0.132	0.36	0.32	0.04	0.489	0.435	0.05	0.36	0.36	0.32	0.36	0.36	0.32	0.32	0.32	0.32	0.32	0.32	0.32	1	3	1	1	1	1	1	1
0.321	0.4	0.32	0.08	0.436	0.349	0.087	0.36	0.32	0.3	0.36	0.34	0.34	0.36	0.32	0.34	0.34	0.34	0.4	1	1	1	3	3	3	3	1
0.23	0.32	0.3	0.02	0.435	0.408	0.03	0.32	0.32	0.32	0.32	0.3	0.32	0.32	0.32	0.32	0.32	0.32	0.32	1	1	1	1	3	3	1	1
0.102	0.36	0.32	0.04	0.457	0.407	0.05	0.32	0.36	0.34	0.32	0.32	0.32	0.36	0.32	0.34	0.34	0.34	0.32	1	1	1	1	1	1	1	1
0.251	0.36	0.32	0.04	0.436	0.387	0.05	0.32	0.33	0.32	0.34	0.32	0.32	0.32	0.36	0.34	0.32	0.33	0.33	1	1	1	1	3	3	3	1
0.178	0.36	0.32	0.04	0.49	0.435	0.05	0.32	0.36	0.32	0.36	0.36	0.34	0.32	0.32	0.32	0.32	0.32	0.32	1	2	1	1	1	1	1	1
0.142	0.36	0.34	0.02	0.424	0.401	0.02	0.36	0.34	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.153	0.44	0.36	0.08	0.459	0.375	0.083	0.36	0.36	0.36	0.4	0.36	0.38	0.36	0.36	0.36	0.44	0.4	0.36	1	1	1	3	1	1	1	1
0.142	0.34	0.3	0.04	0.446	0.393	0.05	0.32	0.34	0.32	0.34	0.34	0.32	0.32	0.3	0.3	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.15	0.3	0.28	0.02	0.408	0.381	0.027	0.3	0.3	0.3	0.3	0.3	0.3	0.29	0.29	0.3	0.28	0.29	0.3	1	1	1	1	1	1	1	1
0.206	0.33	0.32	0.01	0.4	0.387	0.012	0.32	0.32	0.32	0.33	0.32	0.32	0.33	0.32	0.32	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.24	0.36	0.32	0.04	0.45	0.4	0.05	0.32	0.32	0.32	0.32	0.32	0.34	0.36	0.36	0.36	0.32	0.34	0.34	1	1	1	1	3	3	3	1
0.196	0.36	0.3	0.06	0.45	0.375	0.075	0.3	0.32	0.32	0.32	0.36	0.34	0.36	0.32	0.32	0.32	0.32	0.32	1	1	1	3	1	1	1	1
0.143	0.34	0.3	0.04	0.439	0.387	0.05	0.32	0.32	0.33	0.3	0.32	0.32	0.32	0.34	0.34	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.157	0.44	0.4	0.04	0.463	0.421	0.042	0.4	0.4	0.41	0.44	0.41	0.44	0.44	0.44	0.41	0.44	0.42	0.44	1	1	1	1	1	1	1	1
0.168	0.36	0.3	0.06	0.509	0.424	0.08	0.3	0.32	0.36	0.32	0.36	0.32	0.32	0.36	0.36	0.36	0.32	0.34	1	3	1	3	1	1	1	1
0.183	0.36	0.34	0.02	0.436	0.412	0.024	0.36	0.36	0.36	0.34	0.36	0.34	0.36	0.36	0.36	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.235	0.32	0.3	0.02	0.427	0.41	0.025	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	1	1	1	1	3	3	1	1
0.202	0.34	0.3	0.04	0.425	0.375	0.05	0.3	0.32	0.3	0.32	0.32	0.32	0.3	0.32	0.34	0.32	0.32	0.34	1	1	1	1	1	1	1	1
0.183	0.38	0.36	0.02	0.461	0.436	0.025	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.38	0.36	0.36	1	1	1	1	1	1	1	1
0.22	0.34	0.32	0.02	0.412	0.388	0.024	0.34	0.32	0.34	0.32	0.32	0.34	0.34	0.34	0.34	0.34	0.34	0.34	1	1	1	1	1	3	1	1
0.205	0.4	0.36	0.04	0.523	0.472	0.05	0.36	0.4	0.36	0.4	0.36	0.36	0.36	0.36	0.36	0.4	0.36	0.4	1	3	1	1	3	3	1	1
0.235	0.44	0.36	0.08	0.494	0.405	0.09	0.44	0.4	0.36	0.36	0.4	0.36	0.38	0.36	0.38	0.37	0.36	0.36	1	1	1	3	3	3	1	3
0.23	0.37	0.34	0.03	0.457	0.419	0.04	0.37	0.37	0.36	0.36	0.36	0.36	0.36	0.34	0.36	0.36	0.36	0.36	1	2	1	1	3	3	1	1
0.212	0.36	0.32	0.04	0.481	0.427	0.05	0.34	0.34	0.32	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	1	3	1	1	3	3	1	1
0.194	0.32	0.3	0.02	0.427	0.401	0.025	0.3	0.32	0.32	0.3	0.3	0.3	0.32	0.3	0.32	0.3	0.32	0.3	1	1	1	1	1	3	1	1
0.194	0.36	0.32	0.04	0.436	0.387	0.048	0.36	0.34	0.34	0.35	0.32	0.36	0.34	0.32	0.34	0.34	0.34	0.34	1	1	1	1	1	1	1	1
0.228	0.36	0.28	0.08	0.499	0.388	0.11	0.32	0.36	0.36	0.32	0.32	0.34	0.28	0.28	0.28	0.3	0.32	0.32	1	2	1	3	3	3	1	1

Cases/Control	Age	Sex no	Sex	Hospital Number	Co-morbidities	Weight(kg)	Height(cm)	HEIGHT(M)	BMI	Symptoms at presentation	PR	SBP	DBP	RR	SpO2	SGOT	SGPT	CRP	HB	TC	DC-N	DC-L	DC-M	PLATELET	NLR	FBS	PPBS	HR	QTmean	QTC mean	PRint	TPE	TPE/QT
Controls	85	1	M	2189170	2	60	166	1.66	21.8	1	115	122	60	15	98	33	23	1.4	13.6	7500	53	41	6	3.1	1.3	125	256	115.4	0.336	0.466	0.16	0.08	0.23
Controls	52	1	M	2189045	1	65	167	1.67	23.3	1	111	120	70	15	98	23	26	1.7	14.2	9200	48	49	3	2.5	1.0	78	99	111.1	0.341	0.464	0.1	0.07	0.205
Controls	60	1	M	2189176	3	69	168	1.68	24.4	1	100	140	90	14	99	28	28	2	16	10800	68	30	2	2.9	2.3	79	102	100	0.323	0.417	0.12	0.07	0.217
Controls	54	1	M	2189160	2	72	169	1.69	25.2	1	88	130	70	16	98	24	26	1	15.4	8200	48	39	4	3.1	1.2	140	260	88.2	0.342	0.415	0.16	0.06	0.175
Controls	38	1	M	2189000	1	75	170	1.7	26.0	1	103	100	60	17	99	34	22	1	13.9	10200	58	38	4	2.8	1.5	81	104	103.4	0.313	0.411	0.14	0.08	0.256
Controls	56	2	F	2185953	1	59	164	1.64	21.9	1	107	120	70	15	99	38	24	1	12.1	9800	48	46	6	3.3	1.0	83	99	107.1	0.337	0.451	0.13	0.04	0.119
Controls	68	2	F	2188933	1	65	165	1.65	23.9	1	111	110	70	14	98	33	21	1.6	10.6	9700	59	38	3	2.9	1.6	96	100	111.1	0.35	0.476	0.16	0.06	0.171
Controls	72	2	F	2188952	1	48	158	1.58	19.2	1	73	120	78	16	98	25	28	1.2	9.6	5200	54	42	4	2.7	1.3	91	112	73	0.44	0.486	0.21	0.1	0.227
Controls	42	2	F	2187040	2	59	162	1.62	22.5	1	91	140	80	16	99	37	22	1	10.2	4900	50	45	5	3.5	1.1	156	219	90.9	0.358	0.441	0.12	0.06	0.168
Controls	18	2	F	2187207	1	50	158	1.58	20.0	1	91	136	80	16	100	47	33	1.2	11.1	5400	57	40	3	2.2	1.4	69	94	90.9	0.304	0.377	0.14	0.06	0.197
Controls	28	2	F	2188009	1	47	155	1.55	19.6	1	94	120	70	14	99	21	34	1	12	7800	52	42	4	2.8	1.2	91	110	93.8	0.322	0.403	0.14	0.05	0.155
Controls	19	2	F	2187842	1	45	157	1.57	18.3	1	115	130	80	16	98	23	19	1.2	12.5	5600	51	44	5	3.1	1.2	87	118	115.4	0.299	0.414	0.16	0.04	0.133
Controls	48	2	F	2188004	3	60	162	1.62	22.9	1	100	140	86	15	99	24	20	1.3	13.6	12100	69	29	2	2.7	2.4	109	139	100	0.343	0.443	0.16	0.08	0.233
Controls	33	2	F	2188345	1	54	160	1.6	21.1	1	100	132	80	14	99	33	28	1	11	9800	62	36	2	2.4	1.7	87	100	100	0.367	0.474	0.12	0.06	0.163
Controls	28	2	F	2189405	1	52	154	1.54	21.9	1	68	130	80	14	98	21	20	1	10.9	9900	53	41	6	3.1	1.3	98	124	68.1	0.415	0.442	0.16	0.06	0.145
Controls	64	2	F	2189492	1	66	165	1.65	24.2	1	115	120	68	14	99	36	24	1	10.5	8700	48	49	3	2.5	1.0	88	109	115.4	0.322	0.447	0.14	0.1	0.31
Controls	73	2	F	2179151	1	68	167	1.67	24.4	1	83	112	70	15	99	23	20	1	11.3	8500	51	48	1	2.7	1.1	92	128	83.3	0.4	0.47	0.1	0.04	0.1
Controls	75	2	F	2189111	2	72	170	1.7	24.9	1	94	120	80	16	98	19	21	1	11	7800	65	33	2	2.8	2.0	148	256	93.8	0.337	0.421	0.12	0.08	0.237
Controls	55	2	F	2190547	1	68	169	1.69	23.8	1	88	120	70	17	98	31	26	1.5	12	6400	54	40	6	1.9	1.4	89	120	88.2	0.358	0.434	0.15	0.06	0.168
Controls	50	1	M	2190667	3	72	172	1.72	24.3	1	107	160	90	17	98	27	29	2.1	15	7200	61	36	3	2.7	1.7	92	118	107.1	0.31	0.414	0.15	0.08	0.258
Controls	64	1	M	2191662	2	76	171	1.71	26.0	1	100	130	70	16	98	28	21	1.5	13.4	8100	71	24	4	3.5	3.0	93	127	100	0.295	0.381	0.13	0.06	0.203
Controls	28	1	M	2191445	1	71	169	1.69	24.9	1	65	110	60	16	98	33	24	1.3	13.3	10400	49	47	4	3.8	1.0	89	108	65.2	0.362	0.377	0.12	0.08	0.221
Controls	68	1	M	2191223	4	78	173	1.73	26.1	1	88	140	90	14	98	29	28	1	13.6	9800	54	43	3	3.1	1.3	156	302	88.2	0.342	0.415	0.12	0.08	0.234

TPE/QTC	QTMAX	QTMIN	QTD	QTCMAX	QTCMIN	QTCD	QT1	QT2	QT3	QTavr	QTavl	QTavf	QTv1	QTv2	QTv3	QTv4	QTv5	QTv6	QT Prolongation	QTc prolongation	QTd prolongation	QTcd prongation	Tpe prolongation	Tpe/QT prolongation	Tpe/QTc prongation	PR prolongation
0.172	0.4	0.3	0.1	0.556	0.416	0.139	0.3	0.32	0.32	0.34	0.34	0.34	0.34	0.32	0.4	0.34	0.32	0.34	1	3	1	3	1	1	1	1
0.151	0.36	0.33	0.03	0.489	0.449	0.04	0.34	0.34	0.36	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.33	0.34	1	3	1	1	1	1	1	1
0.168	0.36	0.32	0.04	0.465	0.413	0.05	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.36	1	1	1	1	1	1	1	1
0.145	0.36	0.32	0.04	0.436	0.388	0.048	0.35	0.36	0.32	0.36	0.36	0.34	0.36	0.36	0.34	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.195	0.36	0.3	0.06	0.472	0.394	0.078	0.3	0.3	0.3	0.3	0.3	0.32	0.3	0.32	0.32	0.32	0.36	0.32	1	1	1	3	1	3	1	1
0.089	0.34	0.32	0.02	0.455	0.428	0.03	0.32	0.32	0.34	0.36	0.34	0.34	0.32	0.34	0.34	0.34	0.34	0.34	1	2	1	1	1	1	1	1
0.126	0.38	0.34	0.04	0.517	0.463	0.054	0.36	0.36	0.36	0.38	0.38	0.32	0.32	0.34	0.34	0.34	0.36	0.34	1	3	1	1	1	1	1	1
0.206	0.46	0.42	0.04	0.508	0.464	0.044	0.44	0.44	0.46	0.44	0.44	0.46	0.44	0.42	0.44	0.44	0.42	0.44	1	3	1	1	3	1	1	3
0.136	0.38	0.34	0.04	0.468	0.419	0.049	0.38	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.34	0.36	0.34	1	1	1	1	1	1	1	1
0.16	0.32	0.3	0.02	0.394	0.369	0.025	0.31	0.3	0.3	0.32	0.3	0.3	0.3	0.3	0.3	0.32	0.3	0.3	1	1	1	1	1	1	1	1
0.124	0.34	0.3	0.04	0.425	0.375	0.05	0.32	0.32	0.32	0.34	0.3	0.32	0.34	0.32	0.32	0.32	0.32	0.32	1	1	1	1	1	1	1	1
0.097	0.3	0.29	0.01	0.416	0.402	0.014	0.3	0.3	0.3	0.3	0.29	0.3	0.3	0.3	0.3	0.3	0.3	0.3	1	1	1	1	1	1	1	1
0.181	0.36	0.32	0.04	0.465	0.413	0.052	0.32	0.32	0.32	0.36	0.34	0.36	0.34	0.34	0.34	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.127	0.4	0.32	0.08	0.516	0.413	0.103	0.36	0.36	0.36	0.34	0.32	0.34	0.4	0.4	0.4	0.4	0.36	0.36	1	3	1	3	1	1	1	1
0.136	0.44	0.38	0.06	0.469	0.405	0.064	0.4	0.44	0.44	0.4	0.44	0.44	0.4	0.4	0.38	0.44	0.4	0.4	1	1	1	3	1	1	1	1
0.224	0.34	0.32	0.02	0.472	0.444	0.028	0.32	0.32	0.32	0.32	0.32	0.34	0.32	0.32	0.32	0.32	0.32	0.32	1	1	1	1	3	3	1	1
0.085	0.44	0.32	0.12	0.517	0.376	0.14	0.44	0.4	0.4	0.4	0.32	0.44	0.36	0.44	0.4	0.4	0.4	0.4	1	2	3	3	1	1	1	1
0.19	0.36	0.32	0.04	0.45	0.4	0.05	0.32	0.34	0.32	0.34	0.34	0.34	0.34	0.34	0.34	0.36	0.34	0.32	1	1	1	1	1	1	1	1
0.138	0.36	0.34	0.02	0.436	0.412	0.024	0.36	0.36	0.36	0.36	0.36	0.36	0.34	0.36	0.36	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.193	0.32	0.3	0.02	0.428	0.401	0.027	0.32	0.3	0.32	0.3	0.3	0.3	0.32	0.32	0.32	0.32	0.3	0.3	1	1	1	1	1	3	1	1
0.157	0.32	0.28	0.04	0.413	0.36	0.05	0.31	0.32	0.3	0.31	0.3	0.28	0.28	0.28	28	0.28	0.3	0.3	1	1	1	1	1	1	1	1
0.212	0.38	0.36	0.02	0.396	0.375	0.021	0.36	0.36	0.38	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	0.36	1	1	1	1	1	1	1	1
0.193	0.36	0.32	0.04	0.436	0.388	0.048	0.34	0.34	0.34	0.34	0.34	0.34	0.34	0.36	0.32	0.36	0.34	0.34	1	1	1	1	1	1	1	1

KEYS

SAP=SYMPTOM AT PRESENTATION

Symptoms	
Asymptomatic	1
ILI	2
SARI on Oxygen support	3
SARI on NIV	4
SARI on Invasive ventilation	5
MODS/ Complications	6
Atypical presentation(Neuro/others)(Specify)	7

Comorbidities	
No comorbidities	1
DM	2
SHTN	3
DM+SHTN	4