EVALUATION OF THE LONGTERM EFFECTS OF COVID-19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(GENERAL MEDICINE)

JULY, 2020 **DR. NAJA K**

AIIMS, JODHPUR

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DECLARATION

I hereby declare that the thesis titled **"EVALUATION OF THE LONGTERM EFFECTS OF COVID-19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled "**EVALUATION OF THE LONGTERM EFFECTS OF COVID-19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS**" is the bonafide work of Dr Naja K carried out under our guidance and supervision, in the Department of General Medicine, All India Institute of Medical Sciences, Jodhpur.

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Acknowledgement

"*Alone we can do so little; together we can do so much*"

-Helen Keller

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Last but by far not the least, I express thanks to all my patients without whom this milestone was not possible.

Dedicated to my family and friends

LIST OF ABBREVIATIONS

AIIMS	All India Institute Of Medical Sciences
ANA	Anti Nuclear Antigen
COVID	Corona virus disease
SARS-CoV	Severe Acute Respiratory Distress Syndrome Corona Virus
WHO	World Health Organisation
CNS	Central Nervous System
GIT	Gastro Intestinal System
MERS	Middle East Respiratory Syndrome
DM	Diabetes Mellitus
HTN	Hypertension
CVD	Cardiovascular Disease
COPD	Chronic Obstructive Pulmonary Disease
TB	Tuberculosis
ILD	Interstitial Lung Disease
CBC	Complete Hemogram
RFT	Renal function Test
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
PT-INR	Prothromib Time- International Normalised Ratio
PFT	Pulmonary Function Test

HRCT	High Resolution Computed Tomography
ATS	American Thoracic Society
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in the First Second
FVC	Forced vital capacity
PEF	Peak Expiratory Flow
FEF25–75%	Forced Expiratory Flows at 25 and 75% of FVC
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SD	Standard Deviation
IQR	Interquartile Range
IEC	Institutional Ethics Committee
GCP	Good Clinical Practices
TLC	Total Lung Capacity
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
URTI	Upper Respiratory Tract Infection
PCT	procalcitonin
CRP	C-reactive Protein
GGO	Ground Glass Opacities
NAAT	Nucleic Acid Amplification Test
IgM	Immunoglogulin M
IDSA	Infectious Disease Society Of America
PPCS	Persistent Post Covid Syndrome

PICS	Post Intensive Care Syndrome
VTE	Venous Thrombo Embolism
TSH	Thyroid Stimulating Hormone
ICU	Intensive Care Unit
UAE	United Arab Emirates
6MWT	6 Minute Walk Test
ECMO	Extra Corporeal Membrane Oxygenation
CI	Confidence Interval
SOB	Shortness of Breath
APTT	Activated Partial Thromboplatin Time
LLN	Lower Limit Normal
HCoV	Human Corona Virus
BMJ	British Medical Journal
Kb	Kilo Bytes
RdRp	RNA Dependent RNA Polymerase
RNA	Ribonucleic Acid
ORF	Open Reading Frames
TRS	Transcription Regulatory Sequences
CEACAM	Carcinoembryonic Antigen Related Cell Adhesion Molecule
APN	Aminopeptidase N
CD	Cluster of Differentiation
ACE	Angiotensin Converting Enzyme

CXCL	CXC motif Ligand
IFN	Interferon
IL	Interleukin
MCP	Monocyte Chemoattractant Protein
TNF	Tumor Necrosis Factor
CDC	Centre For Disease Control And Prevention
ARDS	Acute Respiratory Distress Syndrome
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AKI	Acute Kidney Injury
ICMR	Indian Council of Medical Reasearch

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SUMMARY OF THE PROJECT

Background: COVID-19 pandemic which affected all parts of the world can have significant impairment of lung function even after recovery. Studies conducted in post COVID patients have revealed restrictive pattern of pulmonary function and altered diffusing capacity. Recovered patients can also have persistent CT abnormalities. Indian studies on pulmonary function in post COVID patients are limited.

Primary objectives:

1. To evaluate the spectrum of abnormalities in pulmonary function in recovered COVID-19 patients at 3-6 months follow up and 6-12 months follow up.

Secondary objectives:

1. To know the association of impairment of lung function with the severity of COVID-19 infection.
2. Association of the severity of pulmonary function abnormality with radiological severity.

Methods: In this study we prospectively studied recovered COVID-19 patients from January 2021 to July 2022 at All India Institute of Medical Sciences (AIIMS), Jodhpur. Patients were assessed clinically and pulmonary function test was done. HRCT was done if clinically indicated.

Results: 52 post COVID patients were enrolled in the study. Median age of 40(23-75) years, there were 78.8% males and 21.2% females. Fatigue was the most common post COVID symptom and was present in 40.4% participants. Restrictive pattern was seen 20.8% at 3-6 month follow up in our study. There was significant difference between males and females in pulmonary function values at 3-6 months {FEV1(p=0.001), FVC(p=<0.001), PEF(p=<0.001) and FEF25-75%(p=0.006)} and 6-12 months {FEV1(p=0.004), FVC(p=0.005), PEF(p=0.001) and FEF25-755(p=0.022)}. Our study found significant difference in

pulmonary function values at 3-6 month after recovery from COVID-19 disease with different severity at the time of hospitalization. Mean value of FEV1, FVC, PEF and FEF25-75% decreased as the severity increased. FEV1: asymptomatic-3.51±0.83, mild-3.21±0.71, moderate-2.62±0.61 and severe- 2.51±0.72, p=0.02; FVC: asymptomatic-4.11±0.83, mild-3.69±0.81, moderate-3.04±0.71 and severe- 2.93±0.87, p=0.02; PEF: asymptomatic-9.80±1.68, mild- 8.04±1.96, moderate- 5.93±1.75 and severe- 7.58±2.25, p=0.01; FEF25-75%: asymptomatic- 3.86±1.32, mild- 4.09±1.14, moderate- 3.13±0.74 and severe-3.38±0.92, p=0.05. These values were adjusted for age and post adjustment, only difference in PEF and FEF25-75% were significant: p=0.02 and p=0.04 respectively. In our study there was significant difference in pulmonary function values at 3-6 months between patients who required oxygen at the time of hospitalization and who did not require oxygen. The mean values of pulmonary function values were lower in the patients who required oxygen, FEV1: 3.16±0.15 vs 2.66±0.13, p=0.002; FVC:3.63±0.17 vs 3.11±0.16, p=0.003; PEF: 8.16±0.48 vs 6.60±0.44, p=0.013; FEF25-75%: 4.20±0.23 vs 3/25±0.21, p=0.006. This data was adjusted for age and subsequent data is also showing significant difference in FEV1, FVC, PEF and FEF25-75% with p values of 0.025, 0.046, 0.028 and 0.007 respectively.

14 out of 21 (66.67%) had abnormal HRCT findings. Positive correlation of age and HRCT abnormality with a correlation coefficient of 0.522 with p value of 0.015 and positive correlation of LDH and HRCT abnormality with a correlation coefficient of 0.515 with a p value of 0.024 were found. Age> 50 years is an independent predictor of the subsequent development of abnormality on HRCT thorax after 3-6 month follow-up.

Conclusion:

Severe COVID-19 pneumonia patients and patients who required oxygen at the time of hospitalization had a higher rate of abnormal spirometry when compared to patients with mild symptoms and non-severe pneumonia. Follow-up CT scans obtained within 6 months of disease onset showed abnormalities in more than half of patients who survived COVID-19 pneumonia.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in Wuhan province in China in December 2019 and has rapidly evolved into a global pandemic over few months(1). Globally as of 23 December 2022, there have been 651,918,402 confirmed cases of COVID-19, including 6,656,601 deaths, reported to World Health Organization (WHO). The first case of COVID-19 in India was reported on January 30, 2020; the index patient was a student who had returned from Wuhan to Kerala . Since then, it spread all over India to a total of 44,676,678 COVID-19 cases at present with 530,690 deaths till 23 December 2022 (2).

To combat this situation of COVID-19, All India Institute of Medical Sciences Jodhpur is providing optimal care to patients. COVID-19 primarily causes lung pathology and can cause multi organ dysfunction syndrome due to cytokine storm (3). Cases from all around the world reported that COVID-19 can involve all most all organs of body including central nervous system (CNS), gastro-intestinal system (GIT), liver, renal and heart. Even after the severe acute respiratory syndrome (SARS coV-1) outbreak, there was an important question that needed to be answered: will patients recovering from SARS have any further detrimental effect on their health status (4). Studies have been reported that ongoing active alveolitis during the host immune system response to the SARS-CoV-1 antigen might lead to pulmonary fibrosis in some patients after recovery (5). Even long term manifestations were also found in Middle East respiratory syndrome (MERS) infection after 1-year of recovery (6).

According to World Health Organization (WHO), the mortality rate of COVID-19 patients is 3 to 5%, and the remaining affected patients are mostly recovering. Long term follow-up studies are needed to evaluate the effect of COVID-19 on health of recovered patients. This would be helpful to assess any changes in the acquired immune function, blood parameters, psychological factors, biochemical factors, lung, brain, eye, kidney, heart and gastrointestinal (GI) tract functions over the course of time.

Knowledge of possible complications and its after-effect in the recovered patients will be helpful to ascertain the future disease complications. This will also provide more information for the development of vaccines and drugs for these kinds of pandemics in the future. More research is required on the diagnostic and therapeutic approaches to develop vaccines and drugs

Hence, we planned this study to focus on the pulmonary changes which could occur due to SARS-CoV-2 infection in long term.

METHODOLOGY

OBJECTIVES:

Primary objective:

1. To evaluate the spectrum of abnormalities in pulmonary function in recovered COVID-19 patients at 3-6 months follow up and 6-12 months follow up.

Secondary objectives:

3. To know the association of impairment of lung function with the severity of COVID-19 infection.
4. Association of the severity of pulmonary function abnormality with radiological severity.

STUDY SETTING:

Patients who attended the Post COVID-19 clinic of Department of Internal Medicine and Pulmonary Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan.

STUDY DURATION: From January 2021 to July 2022

STUDY DESIGN:

The study was conducted as a prospective observational study after seeking informed written consent from the study participants. On the first visit to the clinic, baseline assessment of various variables was done which included:

1. Socio-demographic: Name, age, gender, occupation.
2. Clinical: Current symptomatology in history and relevant personal history and detailed physical examination.
3. Associated comorbidities like diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD),

tuberculosis (TB), interstitial lung disease (ILD) were noted and relevant drug history was taken.

4. Investigations: All patients underwent the following investigations:
    a. Baseline hematological and biochemical assessment as per routine clinical care including Complete Blood Count (CBC), RFT, LDH, LFT, PT-INR, d-dimer, ferritin, NT-proBNP and CK-MB.
    b. All patients will underwent evaluation for pulmonary function including Pulmonary Function Test (PFT) and High Resolution Computed Tomography (HRCT) Chest (if clinically indicated).
    c. Pulmonary function test was done by spirometry.

Pulmonary function test

All PFT measurements were performed at Pulmonary Function room, department of pulmonary medicine, AIIMS jodhpur, according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (7). Correct performance of PFT measurements was ensured by a qualified pulmonary function technologist.

Each subject was provided with a disposable glove and a surgical mask and are tested separately for a period of 15 min in a well-ventilated and fumigated room. Furthermore, disposable mouth pieces, nose clips, and flow sensors are discarded after each use, filters in the Spirometer are changed for all subject and other high touch surfaces are cleaned using sanitizing wipes. Subjects were instructed before avoid smoking, heavy meal 24 h before the procedure, and use light clothing. The subjects were asked to sit in a chair with lips tightly closed to prevent the air leaks around the mouth piece. They were instructed to take a deep breath in, hold the breath for a few seconds and then exhale as hard as possible into the device. Correct performance was ensured as the procedure is effort dependent and requires adequate subject cooperation. The maneuver was performed 3

times to ensure that the results are reproducible. The variation was <200 ml between the maneuvers for each subject. Spirometer was adequately sterilized before the next use(fig 1).

The parameters measured are: Forced Vital Capacity (FVC), Forced Expiratory Volume in the First Second (FEV1), Forced Expiratory Flows at 25 and 75% of FVC (FEF25%-75%), Peak Expiratory Flow (PEF) and FEV1 /FVC.

1. FVC – Forced vital capacity is the amount of air forcibly expired after a deep inspiration. Normal reference value in Indian males: 3.10 ± 0.48 L(8), normal % predicted value of FVC:>80% (8).

2. FEV1 – is the maximum amount of air expired forcibly in 1 s. Normal value: 2.60 ± 0.42 L/sec(8), normal % predicted value of FVC:>80% (8).

3. FEV1 /FVC% – The percentage of the FVC expired in 1 s. Normal value: >70%

4. FEF25–75% or maximum mid-expiratory flow rate is forced expiratory flow over the middle one half of the FVC. Normal value: 3.23 ± 0.85L/sec (8).

5. PEF – Peak expiratory flow rate is the maximum flow achieved during a forced expiration after maximal lung inflation. Normal value:6.97 ± 1.13L/sec(8).

The severity of acute COVID-19 was defined as mild, moderate or severe with reference to national guidelines for COVID-19 (9). The patients with COVID-19 without evidence of breathlessness or hypoxia (defined as room air oxygen saturation ≥ 94%) during the course of acute illness were categorized as mild COVID-19 disease. Those who had breathlessness and a room air oxygen saturation (SpO2) of ≥ 90% and ≤ 93% were categorized as moderate disease and those with room air SpO2 of < 90% were categorized as severe COVID-19 disease.

Fig 1: Pulmonary function test being performed

Chest CT acquisition

21 follow-up chest CT scans from the 52 included patients were available. All chest CT scans were performed from apices to bases. Slice thickness of 1mm/5mm was obtained on SOMATOM Definition Flash Dual Source Dual Energy 2×128-slice CT scanner. Application of iodine contrast agents was only performed if pulmonary embolism was suspected and/or in case of clinical deterioration. Multiplane reconstructions were performed in axial, coronal and sagittal planes as required.

STUDY PARTICIPANTS

Inclusion criteria:

1. Age >18 Years
2. All patients who were RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) positive and discharged from hospital after recovery presenting to COVID-19 clinic at 3-6 months and 6-12 months.

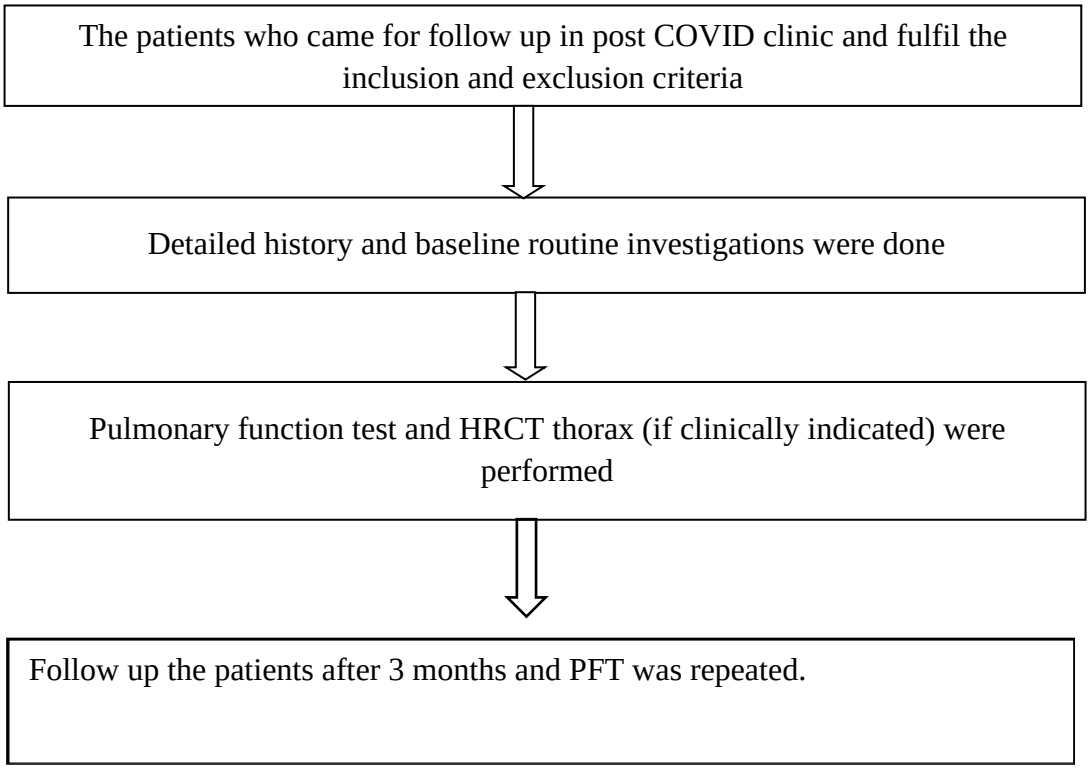
Exclusion criteria:

1. Patients who were not willing to give consent.
2. Pregnant females.

SAMPLING AND SAMPLING SIZE:

It was a time bound study. It enrolled all the patients who were RT PCR positive for COVID-19 and admitted in AIIMS Jodhpur coming in Post COVID-19 clinic for 3-6 months follow up and 6-12 months follow up till July 2022.

METHODOLOGY:



STATISTICAL ANALYSIS:

Continuous variables were described using mean with standard deviation (SD) or median with interquartile range (IQR). Group comparisons were done using unpaired t-test or Mann–Whitney test for data that had normal and non-normal distribution, respectively. Paired t test was used to compare pre and post mean values. The Chi-square test was used to compare the categorical variables. Pearson's correlation was used to test any association between variables. Independent predictors for the presence of impaired pulmonary function were investigated using logistic regression analysis. P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Version 20.0

EXPENDITURE:

No expenditure as all the investigations and management were done under post COVID clinic AIIMS JODHPUR.

ETHICAL CONSIDERATIONS

The thesis work was started and performed with the approval by Institutional Ethics Committee (IEC) [ANNEXURE-1,2] and following good clinical practices (GCP). Informed written consent were taken from the study participants as directed and provided by the institute. (ANNEXURE-3,4).

REVIEW OF LITERATURE

Corona virus 2019 (COVID-19) disease caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first reported in Wuhan in China and spread worldwide to cause more than 6 million deaths and catastrophic effect on global health is the fifth pandemic since 1918 flu pandemic. It is fortunate that the disease has been asymptomatic to mild in the majority (> 80%) of the patients in view of its rapid pandemic spread (10).

A series of pneumonia cases emerged in Wuhan, Hubei, China in December 2019 without any known cause and with clinical presentations resembling viral pneumonia. By Jan 2, 2020, Whole genome sequencing from respiratory samples of 41 patients indicated a novel corona virus, initially designated as 2019-nCoV. 27 (66%) patients had direct exposure to Huanan seafood market where snakes, birds and other animals such as bats were sold. Dec 1, 2019 was the symptom onset date of the first patient identified. No epidemiological link was identified between the first patient and later cases. The first fatal case had continuous exposure to the market, and had symptoms like fever, cough, and dyspnea. After 5 days of onset of illness wife of the first fatal case, a 53-year-old woman who had no known history of exposure to the market, also presented with pneumonia (10).

On January 30, 2020, the first positive case was identified in Kerala, and more cases were subsequently reported in other parts of the country. On March 24, 2020, a nationwide lockdown was enacted to curb the spread of COVID (11).

Because it was genetically related to the coronavirus outbreak responsible for the SARS outbreak of 2003, the virus was named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee for Taxonomy of Viruses. Because of its high speed of transmission coronavirus Disease 2019 (COVID-19) was declared as pandemic by the World Health Organization on March 11th, 2020 (12).

Corona viruses

The name "coronavirus," coined in 1968, is derived from the "corona"-like or crown-like morphology observed in the electron microscope. The first description of human coronavirus—a family of viruses that now includes SARS-CoV-2, the cause of the current covid-19 pandemic—was published in *The BMJ* in 1965. Coronaviruses (CoV) (order *Nidovirales*, family *Coronaviridae*, subfamily *Coronavirinae*) are enveloped, positive stranded RNA viruses. The subfamily *Coronavirinae* contains the four genera *Alpha-*, *Beta-*, *Gamma-*, and *Deltacoronavirus*. The alphacoronaviruses include HCoV-NL63 and -229E and the betacoronaviruses include HCoV-OC43, -HKU1, SARS-CoV and MERS-CoV. HCoV-OC43 and -229E were described in 1960s. HCoV-NL63 was discovered in 2004 and HKU1 in 2005. severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV emerged in last two decades and were discovered in 2003 and 2012 respectively (13).

Members in the family *Coronaviridae* are enveloped, single-stranded RNA viruses and are the largest RNA viruses, with genomes ranging from 25 to 32 kb and a virion of 118–136 nm in

diameter. Virions are spherical with large spike (S) glycoprotein extending 16–21 nm from the virus envelope.

Non-structural polyprotein including RNA-dependent RNA polymerase (RdRp) is encoded by two overlapping open reading frames (ORFs 1a and 1b) present in the 5′ two-thirds of the CoV genome. At least six ORFs are present in its genome in a typical CoV. ORF1a and ORF1b contain a frameshift in between which produces two polypeptides: pp1a and pp1ab. These polypeptides are processed into 16 nsps by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro) and one or two papain-like protease. One third of the genome consists of ORFs encoding 4 main structural proteins, spike (S), membrane (M), envelope (E) and the nucleocapsid (N), and some non-structural proteins (nsp), 3a, 3b, 3c, 7a and 7b. Different CoVs encode special structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein apart from these main structural proteins. Transcription regulatory sequences (TRS) are located at 5′-distal position in each mRNA and play an important role in the RNA replication of CoV (14).

Pathogenesis of COVID 19

As we discussed coronaviruses are made up of four structural proteins, spike (S), membrane (M), envelop (E) and nucleocapsid (N) proteins. The S protein which protrudes from the viral surface is the most important one for host attachment and penetration. This protein is composed of two functional subunits (S_1 and S_2). S_1 is for binding to the host cell receptor and S_2 is responsible for fusion of viral and host cellular membranes. During viral infection, target cell proteases cleave the S protein into S1 and S2 subunits. Serine protease TMPRSS2 is used as a protein primer. Cleavage site of SARS-CoV-2 is unknown, although that of SARS-CoV is known (15).

Coronavirus disease-2019 spreads through physical contact and inhalation of infected droplets or air. After the inhalation of virus particles, they bind to cell receptors on the surface of the host cell. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), members of the immunoglobulin superfamily of receptors and zinc metalloprotease aminopeptidase N (APN, CD13) are the receptors used by coronaviruses other than SARS-CoV. The receptor of the SARS-CoV is the angiotensin-converting enzyme 2 (ACE2). ACE-2 receptors are present on pulmonary epithelial cells and act as binding site for S protein which is the initial stage for host invasion. S protein undergoes cleavage by target cell proteases. This is a two-step process. First step involves stabilization of S2 subunit at the attachment site. 2^{nd} step cleavage causes conformational changes leading to activation of S protein and further leading to membrane fusion of virus and host cell (16).

Multiciliated cells in the nasopharynx or trachea, or sustentacular cells in the nasal olfactory mucosa are the first cells targeted by SARS-CoV-2 during natural infection in humans. After the fusion of virus to the membrane it enters the cells and release viral contents inside. Replication and transcription take place inside the host cell resulting in formation of negative strand RNA by the pre-existing single stranded positive RNA through RNA polymerase activity. By translation new proteins are synthesized in the cell cytoplasm (17).

Pathophysiology can be divided into 3 stages/phases:

1) Asymptomatic phase

The SARS-CoV-2 binds to the nasal epithelial cells in the upper respiratory tract which is received via inhalation of respiratory aerosols. ACE-2 which is highly expressed in adult nasal epithelial cells is the main receptor. Primary cells infected in the conducting airways are the ciliated cells. These individuals are infectious although the viral burden is not very high. Nasal swabs can be used for the detection of virus at this stage. There is only a limited immune response at this stage although there is propagation of virus. This stage lasts for 1-2 days (18).

2) Involvement of the upper respiratory tract

Virus migrates from nasal epithelium to upper airway along the conducting airways. This stage involves release of C-X-C motif chemokine ligand 10 (CXCL-10) and interferons (IFN-beta and IFN-gamma) from the virus infected cells resulting in greater immune response. This is the stage when COVID 19 clinically manifests with symptoms of malaise, fever and dry cough. As the immune response against virus is sufficient to control the infection majority of the patients present with symptoms restricting to upper airway tract and do not progress beyond this stage. These patients can be treated with symptomatic management at home (19).

3) Involvement of lower respiratory tract

This stage of disease can be seen in 20% of the patients infected. They develop pulmonary infiltrates and some will develop very severe disease. Fatality varies with age. Initial estimates are around 2%. ACE receptors are used by the virus to invade type 2 alveolar epithelial cells and result in the production of more nucleocapsids by replications. Interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumour necrosis factor-α (TNF-α), IFN-λ and IFN-β, CXCL-10, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) are produced by the virus laden pneumocytes and result in the sequestration of neutrophils, CD4 helper T cells and CD8 cytotoxic T cells. They cause the inflammation and lung injury during the process of fighting against virus. Apoptosis of host cell occurs and the virus infects the adjacent cell. The process of invasion of cell, cytokine storm and apoptosis of host cell happens multiple times resulting in acute respiratory distress syndrome. The pathological result of COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. Diminished immunity in elderly along with their reduced ability to repair the damaged epithelium make them more prone to the injury. Virus can spread in their lungs easily because of their reduced mucociliary clearance (20).

There are many other sites where ACE receptors are present in our body. Virus particles travelling to other organs with ACE2 receptors result in the extra pulmonary manifestations. They include gastroenteritis (small intestine); insomnia, dysgeusia, and headache (brainstem, cerebral cortex, and hypothalamus, respectively), high blood pressure, and tachycardia (heart and blood vessels, respectively), and some skin infections (basal epidermis). ACE2 receptors may be present in the retina and other eye tissues, leading to conjunctivitis (21,22).

Severity of COVID 19 can be determined by many factors. They include viral load, genetic factors, presence of comorbidities, age, sex, use of immune-suppressive agents, and immunity. Because of the ACE2 receptor gene polymorphisms severity of infection can be influenced by the genetic factors (23).

Comorbidities such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease (COPD), chronic lung disease, chronic kidney disease, cancer, and low immunity can make the infected people more prone to serious infection and complications. Many comorbidities lead to defects in ACE2 expression. Obesity also results in increased expression of ACE2 receptors as they are higher in adipose tissue. Obese patients have shown increased risk of respiratory failure and mechanical ventilation. The increased mortality and morbidity in obese people with COVID 19 can also be attributed to their comorbidities like hypertension and diabetes mellitus (24).

Elderly people showed more severe disease in many studies with pulmonary complications like ARDS and multiple organ failure more common in elderly. Reasons for the more severity can be low immunity and comorbidities. Some studies have suggested that ACE2 expression is higher in the lungs of old people than in the lungs of people of other ages (25).

Many studies have shown that due to increased expression of ACE2 receptors in men, men are more affected and having higher mortality compared to women with COVID-19 (26).

Clinical features

All ages of the population are susceptible to SARS-CoV-2 infection with the median age of infection being 50 years. Older men (>60 years old) with co-morbidities are more likely to develop severe respiratory disease that requires hospitalization or even die, whereas most young people and children have only mild diseases (non-pneumonia or mild pneumonia) or are asymptomatic. Evidence of transplacental was reported although risk of disease is not higher in pregnant women (27,28).

Patients can be asymptomatic to severe cases of pneumonia. Severe cases can lead to death. Triad of fever, cough and shortness of breath was the characteristic of COVID 19 and the US Center for Disease Control and Prevention (CDC) later added chills, muscle pain, headache, nausea, vomiting, congestion or runny nose, sore throat, and loss of taste or smell to this list. Most common symptoms are fever, fatigue and dry cough. Studies from china also showed symptoms including sputum production, headache, haemoptysis, diarrhoea, anorexia, sore throat, chest pain, chills and nausea and vomiting. Studies from Italy revealed taste disorders. Most people showed signs of diseases after an incubation period of 1–14 days (most commonly around 5 days), and dyspnea and pneumonia developed within a median time of 8 days from illness onset.

Pulmonary system is the most common organ system affected with studies reporting pulmonary manifestations including cough, shortness of breath, sputum production, respiratory failure, and ARDS (29,30).

Gastrointestinal symptoms including diarrhea can be the initial manifestation of infection. The liver can be affected by SARS-CoV-2 with commonly reported hepatic manifestations including elevations in serum levels of alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin, with decreasing serum albumin levels (31).

Neurological manifestations including ischemic or hemorrhagic stroke, dizziness, headache, musculoskeletal disturbance, altered mental state, Guillain-Barré syndrome, or acute necrotizing encephalopathy can be seen in patients with COVID-19 (10).

Severe infection can have cardiac manifestations including myocarditis and myopericarditis with reduced systolic function, cardiac arrhythmias, heart failure, acute coronary syndrome and pulmonary embolism (32).

Renal system can also be affected with more prevalence of AKI in COVID 19 compared to SARS. Analysis of 51 critically ill COVID-19 patients in Wuhan, China showed AKI in 29% (33).

ocular manifestations such as conjunctival hyperaemia, chemosis, and increased secretions could be present with possibility of SARS-CoV-2 RNA getting detected in tears (22).

Dermatological symptoms like erythematous rash, generalized urticaria have been described in COVID-19 infection. Acral ischemia such as cyanosis of toes, skin blisters, and dry gangrene can also be there in severe infection (34).

Rodrigo et al (35) conducted a systematic review of the literature. 152 publications were included finally with a total of 41,409 individuals from at least 23 countries and 26 different clinical manifestations were reported. In percentage terms, 6 symptoms had a general prevalence greater than or equal to 25%. They were fever (58.66%), cough (54.52%), dyspnea (30.82%), malaise (29.75%), fatigue (28.16%) and sputum/secretion (25.33%). Neurological symptoms (20.82%), dermatological manifestations (20.45%), anorexia (20.26%), myalgia (16.9%), sneezing (14.71%), sore throat (14.41%), rhinitis (14.29%), goosebumps (13.49%), headache (12.17%), chest pain (11.49%) and diarrhea (9.59%) were other common symptoms. Only one study reported dermatological manifestations. The least frequent sign/symptom was hemoptysis (1.65%). In studies with more than 100 patients, the 3 main symptoms were fever (57.93%), cough (54.21%), and dyspnea (30.64%). Dermatological manifestations do not appear among the main symptoms.

Pulmonary manifestations of COVID-19: Pulmonary manifestations in COVID-19 can be mild, moderate, and severe. Mild cases usually present with upper respiratory tract infection (URTI), cough, or sore throat. The moderate type of pulmonary manifestations include pneumonia and fever. Severe presentation is ARDS. Studies also suggested cases of silent hypoxia as a result of silent COVID-19 pneumonia (36).

ARDS in COVID-19 patients can due to 2 pathological mechanisms. Pulmonary surfactant is produced by type 2 pneumocyte and ACE2. ACE2 receptor is located in type 2 pneumocyte. This is the first mechanism, type 2 pneumocyte function can be improved by increased blood flow in the alveoli which can be improved by ACE2. As this virus binds to ACE2 receptors

destruction od alveolar cells take place and will result in decreased production of surfactant resulting in increased surface tension. This will predispose the patient to ARDS. Cytokine storm is the second mechanism of development of ARDS in COVID-19. Excessive inflammatory response due to release of proinflammatory cytokine and interleukins leads to destruction of alveolar cells predisposing to ARDS and multi organ failure. viral overload, genetic roles and ethnicity, presence of comorbidities, age, and sex are some of the factors which can determine the severity of pulmonary manifestations in COVID-19 (37).

Diagnosis of COVID-19

Possibility of COVID infection should be considered in anyone with new onset fever and/or respiratory symptoms.

Routine investigations: In one study, about half of the patients had leucopenia and lymphopenia or thrombocytopenia with increased activated thromboplastin time. C-reactive protein (CRP) levels were increased in most patients, but procalcitonin (PCT) levels were normal. Elevated serum ferritin levels were reported in some patients. Some patients showed increased liver enzymes and glucose levels, and few patients had abnormal muscle enzymes. Liver test abnormality of COVID-19 may be due to liver cell damage or bile duct cell dysfunction and other reasons.

In a study conducted in China in 2019, amongst 1099 COVID-19 patients, lymphocytopenia was present in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. elevated C-reactive protein was a very common finding and other less common findings were elevated alanine aminotransferase, aspartate aminotransferase, creatine kinase and d-dimer. lymphocytopenia and leukopenia were common in severe disease as compared to non-severe disease (29).

Elevation of CRP and reduction of are associated with clinical severity as they are the inflammation indices. Young et al (38) observed an average CRP level of 1.1 mg/dL in patients with normal oxygen saturation and of 6.6 mg/dL in hypoxaemic patients. Ruan et al (39)observed a correlation between CRP and mortality risk. Increased troponin was also reported in 7% of patients who later died because of fulminant myocarditis. Troponin appeared to be a strong prognostic indicator of mortality. Finally, it was noticed that D-dimer and ferritin levels were usually high in hospitalized patients.

Imaging: Chest computed tomography has a role in diagnosis and management of COVID-19 cases. It also aids in the decision making in follow up patients. COVID-19 pneumonia can be suspected in patients with abnormal CT findings although the confirmation of COVID-19 is based on RT-PCR report. COVID-19 cases who were admitted in ICU had subsegmental consolidation and bilateral multiple lobular on admission whereas the non-ICU patients

showed subsegmental consolidation and bilateral ground-glass opacity (GGO) on CT. “white lungs” can be found when most lobes are affected and can be seen in severe disease, other findings in severe disease include heterogeneous consolidation with GGOs in bilateral lungs and bronchiectasis. COVID-19 patients can also have CT findings of intralobular septal thickening and bilateral pleura, interstitial inflammation, extensive consolidation and pleural effusion. High-resolution computed tomography (HRCT) can detect GGOs more easily in the early stage.

Pan et al (40)described 4 stages based on their CT results of 21 RT-PCR confirmed COVID cases (1) early stage (0–4 days):small GGO (2) progressive stage (5–8 days) with involvement of bilateral multi-lobe with diffused GGO, consolidation, and crazy-paving pattern, (3) peak stage (10–13 days) that shows peak involvement of the involved part, including diffused GGO, crazy-paving pattern, residual parenchymal bands, and consolidation, and finally (4) absorption stage which occurs two weeks after the onset of first symptoms and shows the slow absorption of the consolidation. No crazy-paving signs present anymore. Nevertheless, in this step, widespread GGO can be observed as an indication of the consolidation absorption.

In one study, the time period from symptom onset to initial CT scan was evaluated and the authors found that 56% of patients who presented symptoms within 2 days had normal CT images. RT-PCR positive patients had more CT sensitivity. Sensitivity was lower in patients with non-respiratory symptoms and only constitutional symptoms.

Chest X-ray has very low sensitivity and is around 59%. Ultrasound has very low specificity and a sensitivity of 75% and is used as a diagnostic tool only rarely in COVID-19 patients. Ultrasound may play a role in monitoring the progression of the disease through the detection of interstitial lung disease features, such as B lines and subpleural consolidations (41).

Microbiological tests:

1) **RT-PCR:** Most common detection assay used for the detection of SARS-CoV 2 virus is RT-PCR. This molecular technique detects and quantifies the nucleic acid of RNA viruses from the samples isolated from respiratory specimens such as oropharyngeal swabs, sputum, nasopharyngeal aspirate, bronchoalveolar lavage, or deep tracheal aspirate. Studies have reported sensitivity of CT to be more than that of RT-PCR (98% and 71%, respectively). The causes for the low effectiveness of viral nucleic acid measurement include low viral load, inappropriate sample, variation in the diagnosis rate among different kits, and undeveloped technology for detection of the nucleic acid. Detection accuracy can be improved by collecting samples from lower respiratory tract bronchoalveolar lavage fluid, deep tracheal aspirates) and induced sputum as they have high viral load (42).

2) **NAAT**:The gold standard test for microbiological diagnosis, NAAT detects viruses by amplifying the targeted nucleic acids and is used to confirm the presence of viruses that are challenging to grow. Regardless of the test's sensitivity, it can still come out negative if there is not enough nucleic acid. The typical specimen for NAAT is the nasopharynx, however if self-collection is feasible, the nasal vestibule or middle turbinate swab can also be utilised. Although saliva must undergo further processing before NAAT, it is nevertheless often utilised for testing. Patients with a high risk of the disease based on clinical manifestations, such as chronic symptoms with characteristic pulmonary lesions, are advised to use lower respiratory tract specimens (43).

3) **Antigen testing:** The antigen test measures some of the viral proteins and, similar to NAAT, indicates the pathogen presence. Despite the lower sensitivity of the antigen test compared with the PCR method it is used widely. It is a suitable test for low resource setting as it is simple to perform and has a shorter turnaround time than most NAATs (44).

4) **Antibody testing:** There is limited role of antibody testing for definitive diagnosis. IgM levels begin to rise approximately 7 days after the onset of illness and peak at around 14 days after the onset of illness. There are many antibody-testing methods. Immunochromatographic antibody testing because of its possible cross-reactivity with other antibodies and low correlation with neutralizing antibodies is less useful. Enzymatic chemiluminescence immunization and chemiluminescence immunization, which have been shown to correlate with neutralizing antibodies is more useful (45).

Treatment

Indian government has encouraged the strict practice of social-distancing and implemented complete nation-wide lockdown to contain the spread of virus. In addition, nation-wide complete lockdown has been executed in four phases; (1) March 25-April 14, (2) April 14-May 3, (3) May 4-May 17, and May 18-May 31, 2020 (46).

In January 2022 testing of asymptomatic contacts was stopped based on the ICMR guidelines (47).

Decisions on hospitalization and treatment options are based on the severity of disease. Patients are categorized into 3 groups (9).

1) Mild: Upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia
2) Moderate: Any one of:
    1. Respiratory rate ≥ 24/min, breathlessness
    2. SpO2: 90% to ≤ 93% on room air
3) Severe: Anyone of:
    1. Respiratory rate >30/min, breathlessness
    2. SpO2 < 90% on room air

As the COVID-19 pandemic evolves, more and more scientific data supporting various management and treatment options have been brought to light. The treatment includes antiviral drugs or specific therapy and supportive management of complications, including advanced organ support.

Following drugs have shown benefit in the management of COVID-19 pneumonia:

(i) Hydroxychloroquine/Chloroquine + Azithromycin
(ii) Lopinavir/ritonavir
(iii) Remdesivir
(iv) Favipiravir
(v) Interleukin-6 (IL-6) inhibitors
(vi) Corticosteroids
(vii) Convalescent plasma from COVID-19 survivors
(viii) Famotidine
(ix) Neutralizing Antibodies
(x) Janus Kinase Inhibitors
(xi) Ivermectin
(xii) Fluvoxamine
(xiii) Nirmatrelvir/Ritonavir
(xiv) Molnupiravir
(xv) Colchicine

Infectious disease society of America (IDSA) has recommended/suggested following drugs for the management of COVID-19 (48): Glucocorticoids, Interleukin-6 Inhibitors- tocilizumab, Remdesivir, anti-SARS-CoV-2 monoclonal antibodies, Janus Kinase Inhibitors- tofacitinib & baricitinib, Nirmatrelvir/Ritonavir, Molnupiravir.

Indian council of medical research recommends use of corticosteroids (methylprednisolone and dexamethasone) for moderate and severe disease. Remdesivir and tocilizumab have been recommended but as off label use. Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin is also recommended and there should be no contraindications for the use of anticoagulants.

Oxygen support to maintain target SpO2: 92-96% (88-92% in patients with COPD) with preferred devices for oxygenation- non-rebreathing face mask is recommended in moderate disease patients and in severe patients ICMR recommends use of NIV, HFNC and prioritization of intubation in patients with high work of breathing (47).

Long term effects of COVID-19

The Centre for Disease Control (CDC) has formulated "post-Covid conditions" to describe health issues that persist more than four weeks after being infected with COVID-19 (49). These include

- Long Covid (which consists of a wide range of symptoms that can last weeks to months) or persistent post-Covid syndrome (PPCS)
- Multiorgan effects of COVID-19
- Effects of COVID-19 treatment/hospitalization

The typical clinical symptoms in "long covid" are tiredness, dyspnea, fatigue, brain fogginess, autonomic dysfunction, headache, persistent loss of smell or taste, cough, depression, anxiety, low-grade fevers, palpitations, dizziness, muscle pain, and joint pains.

Multiorgan effects of COVID-19 include clinical manifestations of cardiovascular, pulmonary, renal, and neuropsychiatric organ systems, although the duration of these multiorgan system effects is not clear.

Long-term "effects of COVID-19 treatment or hospitalization" are similar to other severe infections. They include post-intensive care syndrome (PICS), resulting in extreme weakness and posttraumatic stress disorder. Many of the patients with these complications from COVID-19 are getting better with time.

Cardiovascular complications: Cardiac symptoms are common after COVID-19 pneumonia. Carfi et al (50) in their study of 143 post COVID patients found that chest pain was present in 21% of patients 60 days after discharge from the hospital. Palpitations was found in as many as 9% of patients. An increased incidence of postural tachycardia syndrome (POTS) has been reported following infection with SARS-CoV-2. In a large study conducted in young, healthy college athletes myocarditis was found in 2.3% participants with majority of them having subclinical myocarditis. Furthermore, 100 patients discharged with COVID-19 underwent cardiac magnetic resonance imaging and was found ongoing inflammation in 60% of patients with ongoing elevation in high-sensitivity troponin T in as many as 71% of patients (51). Dweck et al (52) reported findings from the first international survey of echocardiography in 1216 patients from 69 countries across six continents with confirmed or suspected COVID-19. Left or right ventricular abnormalities were present in half of all patients with COVID-19 undergoing echocardiography, and these abnormalities were severe in 1 in 7 patients. Non-specific patterns of ventricular dysfunction was present in majority, although new myocardial

infarction, myocarditis, and takotsubo cardiomyopathy were observed in a minority of patients.

Haematological complications: occurrence of thrombotic events is a well-established complication of COVID-19, especially in critically ill patients. The aetiology of this coagulopathy is multifactorial, including increased expression of tissue factors in response to inflammatory cytokines and microvascular dysfunction, as well as the effects of hypoxia on upregulation of hypoxia-inducible transcription factors. The exact duration of hypercoagulability is unknown, but most VTE appears to occur within 2–4 weeks of infection. In retrospective studies, the rates of VTE in patients with COVID-19 who were discharged from the hospital ranged from 0.48% to 1.9%. In a large prospective study designed to better assess various post discharge haematological outcomes in patients with COVID-19, the risks were 1.55% for VTE, 1.71% for arterial thromboembolism, and 1.73% for major bleeds (53). Other haematological complications described are immune thrombocytopenic purpura and aplastic anaemia (54,55).

Renal complications: Acute kidney injury (AKI) is a very common manifestation in acute COVID-19 and renal replacement therapy is required in 5% of all hospitalized patients. AKI could be due to multiple factors including direct viral damage, systemic hypoxia, effects of inflammatory cytokines, and abnormal coagulation. Patients who had AKI during hospital admission may have residual renal dysfunction. In one retrospective research 30% of those who required inpatient dialysis continued to require dialysis after discharge and 35% of patients those with AKI still had impaired renal function at discharge, 36% of individuals with residual kidney disease at discharge had recovered at follow-up in the same study but 14% of those who recovered prior to discharge had recurring renal disease. In another study 13% experienced new-onset renal dysfunction after having had normal kidney function during their initial illness and 35% of survivors of COVID-19 had renal dysfunction after 6 months (56,57).

Gastrointestinal complications: Gastrointestinal symptoms are frequent in acute situation and during recovery. In one systematic review of post-acute COVID-19 manifestations, diarrhoea was among the top 10 most prevalent complaints, with a prevalence of 6%. Other persistent symptoms include nausea, vomiting, abdominal pain, and loss of appetite. SARS-CoV-2 can have prolonged faecal shedding even after respiratory samples become negative. This could be due to continuous viral replication in the GI tract. This can be attributed to the prolonged GI symptoms in post COVID patients. COVID-19 can also alter gut microbiome and can also contribute to the symptoms (58).

COVID-19 infection leading to hepatocellular injury and/or biliary stasis can result in abnormal liver function tests and are seen commonly in acute phase. Direct viral cytotoxicity, particularly in the biliary tree, as well as the effects of systemic inflammation, hypoxia, coagulopathy, and adverse effects of drugs are considered as the causes of hepatocellular injury. Abnormalities in liver function may persist but gradually improve over weeks to months in patients who had liver injury and survived (59).

Neuropsychiatric complications: Various neurological and psychiatric long-term complications have been seen in patients post COVID patients. Fatigue, muscle weakness, sleep difficulties, myalgia, and headache were reported after 2 months of recovery from COVID-19 in a multiple source long term symptom data. Such symptoms have become the hallmark of the long-COVID syndrome. In contrast to other viral infections SARS-CoV-2 infection has also been associated with loss of taste and smell. Follow-up at 2 months found ongoing loss of taste and smell in 11% to 13.1% of patients. Due to the considerable burden of severe life-threatening illness and acute respiratory distress syndrome associated with COVID-19, cognitive disturbances comparable to those shown in ARDS patients in previous studies should be anticipated. Impairments in memory (13%), verbal fluency (16%), and executive function (49%) have been described in ARDS survivors from other causes at 1year of follow-up (60).

One study at 60-day follow-up following hospitalization with COVID-19 reported 23% of patients with anxiety/depression. In a study of 402 patients discharged from the hospital following COVID-19, data suggested prevalence of post-traumatic stress disorder (PTSD) at 28%, depression at 31%, anxiety at 42%, and insomnia at 40% after 1 month follow up.

Dermatological complications: Hair loss was a very commonly reported symptom for patients who recovered from COVID which was reported in 24 of 120 patients (20.0%) in one study. Patients can also have skin rashes as a manifestation of post COVID. However, in the Chinese post-acute COVID-19 study of hospitalized patients, only 47 of 1,655 patients (3%) reported skin rashes 6 months after infection onset (57).

Endocrine complications: COVID-19 has been associated with new-onset hyperglycaemia and acute decompensation of diabetes, including diabetic ketoacidosis in both patients with type 1 and type 2 diabetes. Mechanisms for hyperglycaemia following infection include inflammatory state causing insulin resistance, deficits in insulin secretion from impaired β cells—either due to direct damage by virus or indirect effects and steroid induced hyperglycaemia (61).

Subacute thyroiditis, low T3 and low TSH levels have all been reported in post COVID patients. 64% of the 50 post COVID-19 patients whose thyroid function was reassessed after 3 months after diagnosis were found to have aberrant thyroid function.in comparison to a healthy control group, 56% of them had lower levels of TSH and many also had low T3 levels. No significant differences in thyroxine (T4) levels were found.as documented in earlier studies the degree of the TSH and T3 reduction was positively correlated with the disease severity. Few studies have reported subacute thyroiditis related to COVID-19 (62).

Few clinical cases of COVID-19 related adrenal haemorrhage have been described (63).

Musculoskeletal complications: One of the most common complications in post COVID patients is musculoskeletal complications. These symptoms could be explained by the presence

of ACE2 receptors on skeletal muscles and synovial tissues which predispose them for viral invasion. COVID-19 causes myalgias and arthralgias without inflammatory arthritis (64).

Genitourinary complications: Male infertility is a possible complication after COVID-19 infection. ACE2 receptors are present in male gonads and can result in increased viral invasion. Infected men can have viral mRNA in their semen. Studies have shown pathological signs of testicular inflammation and reduced levels of testosterone and dihydrotestosterone. This can be due to viral orchitis and is reported as high as 19%. In female patients, preterm delivery without the risk of vertical transmission has been suggested , however larger studies are needed to better understand the validity of these hypotheses (65,66).

Pulmonary complications: COVID-19 predominantly is a respiratory illness although it can affect other organs. Many long-term pulmonary complications have been described. They include oxygen dependence, ventilator dependence, dyspnoea, abnormal pulmonary function tests, fibrotic changes in CT. most common symptom in post COVID patients are dyspnoea. Studies showed dyspnoea persisted after 2 months of hospitalization in 22.9%–53% of patients. Oxygen dependence was reported in 6.6% of survivors (67). Ventilator dependence is also seen in patients who had respiratory failure and got tracheostomised. In 1,890 patients requiring a tracheostomy in Spain, weaning from mechanical ventilation at 1 month follow-up was successful in only 48% of patients (68). Pulmonary fibrosis is also a well-known complication in post COVID patients which can manifest with dyspnoea or only abnormalities in pulmonary function tests and HRCT. Other complications include secondary infections, lung function impairment, pulmonary thromboembolic disease (pulmonary embolism, stroke), pulmonary hypertension, bronchiectasis, tracheomalacia, cavitary lesions and small airway disease. Pulmonary function impairment can be most frequently in the form of reduced diffusion capacity and restrictive pattern. The most frequent CT findings are ground-glass opacity and bilateral consolidation with peripheral and diffuse distribution, traction bronchiectasis and reticular patterns (69).

Type 2 alveolar cells that stabilise the epithelial barrier is damaged by viral invasion as they have ACE2 receptors. This results in cell death and increased proinflammatory cytokines. Cytokine storm results in diffuse alveolar damage which can later progress to fibrosis. Pulmonary vasculature is also damaged by SARS-CoV 2 virus with microthrombi. Autopsy studies have shown microthrombi in pulmonary vasculature (70).

1) **Pulmonary fibrosis**: Pulmonary fibrosis can be caused by viral pneumonia. 20% increase in incidence of pulmonary fibrosis was found in studies conducted in patients with viral pneumonia. It was also found that post viral pneumonia pulmonary fibrosis was more common in males and elderly and had severe disease at admission and high inflammatory markers like LDH and CRP. Fabbri et al, suggested that fibrotic changes post-viral infection (SARS-CoV-2 and influenza) can persist for years. Pulmonary fibrosis is estimated to persist in one-third of the survivors of COVID-19 who had severe pneumonia. Pulmonary fibrosis incidence was more in patients who were mechanically ventilated than non-mechanically ventilated patients. Other risk factors

for pulmonary fibrosis post COVID-19 include long intensive care unit (ICU) stay and IMV, smoking, obesity, chronic alcoholism, as well as shorter telomere due to its role in the development of fibrotic ILD. High flow oxygen is also suggested as a contributing factor for pulmonary fibrosis (71).

Patients with mild to moderate COVID-19 pneumonia have less risk of developing post-COVID-19 pulmonary fibrosis. The pathogenesis of pulmonary fibrois is a complex interplay between the virus and the immune response with downstream immune signaling activation, It results from abnormal repair of lung injury caused by various mechanisms including viral infections, inflammation, or idiopathic. In severe forms of lung injury due to COVID-19, destruction of basement membrane ends up with the formation of fibroblastic tissue and scarring, leading to architectural distortion and fibrosis. Although fibrotic phase is one of the pathological features of acute respiratory distress syndrome (ARDS), the exact reason why not all patients develop fibrosis remains unknown. In contrast to idiopathic pulmonary fibrosis fibrosis secondary to ARDS does not have prominent honeycombing and progression over time is not prominent. Therefore the pathological findings in post-COVID-19 fibrosis also seem to differ from that in IPF, the predominant difference being injury to the alveolar epithelial cells rather than to the endothelial cells (72).

2) **Thrombosis**: The risk of arterial and venous thrombosis is more in patients with COVID-19. Complex interplay between excessive inflammation, platelet activation, endothelial dysfunction, and stasis are considered as the factors responsible for increased thrombosis. Intravascular hyperinflammation can lead to microangiopathic endothelial damage and increased thrombosis. In one study pulmonary embolism was found in one third of patients who underwent CT pulmonary angiography suggesting the high prevalence of pulmonary embolism in post COVID patients. An epidemiological study reported thrombotic complications in 23% of COVID-19 patients against only 3.6% in influenza patients at 30 days. These complications were observed more in those who were in ICU during their acute phase. Moreover, a case series of a population cohort from Scotland reported significant increase in risk of myocardial infarction (MI) and ischemic stroke along with VTE(73) in post COVID patients. It was also observed that the risk of developing VTE persisted longer than the arterial thrombotic complications did (74).

3) **Other respiratory complications**: There are various other respiratory complications realted to COVID-19. Bronchiectasis which could be developed either due to the disease itself or secondary to superimposed bacterial infection carries a poor prognosis and has been reported after severe COVID-19. Though the data on bronchiectasis after COVID-19 is very limited it can be expected as the most common cause of bronchiectasis is infection. Studies on survivors of SARS showed that in the small number of patients who developed bronchiectasis, it evolved over long periods of

follow-up. A study from China on 81 post COVID-19 patients, 11% showed evidence of bronchiectasis (75).

Cavitary lung disease is also a complication of COVID-19. Selvaraj et al, reported a case of bilateral lung cavities related to post-COVID-19 where other etiologies were not found. A study from UAE showed that 7% of patients admitted with COVID-19 pneumonia developed cavitation majority being ICU patients. The cavities were either single or multiple with sizes between 3–10 cm with thick smooth walls and fluid level (76).

Pneumothorax is also seen after COVID-19 and has been reported in about 1% of hospitalized COVID-19 patients irrespective of whether they were ventilated or not. The survival rate of those who developed pneumothorax was found to be 63% with age > 70 being a poor prognostic factor. Ufuk et al (77) reported a case of spontaneous pneumothorax in a COVID-19 patient three months after discharge. Four weeks after discharge, another case of delayed recurrent pneumothorax was found. The mechanism for the development of delayed pneumothorax could be related to damage of the alveolar walls due to the ongoing inflammatory process, or the formation of small alveolar blebs although the mechanism is still not fully known. Vigorous cough is also a contributing factor. Management should be according to the guidelines for spontaneous pneumothorax.

Post COVID-19 pulmonary complications – Treatment

There is no effective treatment for post COVID-19 pulmonary fibrosis at the moment. Various therapy methods are being investigated in numerous trials. In a small single-center prospective observational study, prednisone 0.5 mg/kg for three weeks was given to 30 patients who had severe COVID-19 pneumonia and persistent symptoms at six weeks post discharge with impaired PFT and features of organizing pneumonia on CT chest. There was a clear improvement in the dyspnea score with increase in FVC by 9.6% and TLCO by 31.5%. Improvement in the six-minute walk test (6MWT) was also significant. Remarkable improvement was also observed in repeat CT. It is still unclear whether this improvement was due to the steroid treatment or part of the normal recovery of the lung (78).

Three cases of fibrosis due to post H1N1 ARDS were documented by Saha et al (79)Combination of prednisolone, azithromycin and pirfenidone was used to treat these patients for up to one year, and there was improvement in oxygenation, 6 MWT and HRCT changes. Further research is needed to understand the precise mechanisms and the effectiveness of different intervention strategies. Though the best intervention is still not clear the current thinking is that early intervention during severe pneumonia may decrease the post-COVID-19 complications. The two approved antifibrotic medications (pirfenidone and nintedanib) to treat IPF has been shown to decrease lung function decline. The current thinking is to start antifibrotic medications early for post- COVID-19 fibrosis,. However, hepatotoxicity is a

proven side effect of Pirfenidone when used in acute COVID, and the second drug Nintedanib is associated with high risk of bleeding. Ongoing trials are investigating the roles of both drugs in post-COVID-19 pulmonary fibrosis. Phase III NINTECOR (NCT04541680) and phase IV ENDCOV-I trials (NCT04619680) are studying the effects of nintedanib 150 mg twice daily on the changes in post-COVID-19 pulmonary fibrosis patient's FVC. Pirfenidone is undergoing phase II (NCT04607928) and phase III (NCT04282902) trials (80).

Since there is currently no effective treatment for post-COVID-19 pulmonary fibrosis, the preventive measures to limit ventilator associated lung injury such a slung protective ventilation and quitting smoking reduces the development of lung fibrosis. Furthermore, even though there is not much solid proof, rehabilitation may be considered early before discharge as it may improve respiratory function.

Lung transplant has become a treatment option for a wide variety of end-stage lung diseases. According to Bharat et al (81) the first two lung transplants in the US that were done on people with COVID-19 related sever fibrosis were successful. According to reports both patients had great outcomes and were able to go without oxygen support 4 to 8 weeks following their transplantation. In addition, a recent case series of 12 patients who underwent bilateral lung transplantations in US, Italy, Austria, and India for post severe COVID-19 ARDS that did not improve despite prolonged ventilation and extracorporeal membrane oxygenation (ECMO), showed that transplantation had comparable survival odds to patients who of survival as in non-COVID-19 patients (82). The risk of a subsequent COVID-19 infection in the transplanted lungs, ventilator associated infections, technical difficulties during surgery, particularly in patients who required pleural procedures and severe deconditioning due to extended ICU stay are the main challenges in transplant surgeries. The possibility that the original lung will eventually recover and outlast the transplanted lung is a final pint that is still unknown.

Pulmonary function test in post COVID-19 patients

The assessments most commonly used to assess the respiratory function of patients with COVID-19 were spirometry, lung volumes and diffusion capacity (83). The British Thoracic Society (BTS) guide recommends the evaluation of PFTs at three months post-discharge, especially at follow-up with patients suspected of having an interstitial disease.

Castro et al (83)studied 7 articles reporting data of 380 patients and altered diffusion capacity, restrictive pattern and obstructive pattern were found in 39%, 15% and 7% of patients, respectively. High prevalence of altered diffusion capacity was found in the study. The most important of the PFTs affected was the diffusion capacity in close to 40% of patients.

Frija-masson et al (84) conducted a retrospective study to assess the pulmonary functional status 1 month after symptom onset in patients with SARS-CoV-2 pneumonia and to correlate

lung function alteration with the severity of pneumonia. Study showed that a majority of patients had mild alterations of lung function 1 month after SARS-CoV-2 infection.

Mo et al (85) recruited 110 discharged cases and among them there were 24 cases of mild illness, 67 cases of pneumonia and 19 cases of severe pneumonia. Anomalies were noted in D_{LCO} % predicted in 51 cases (47.2%), total lung capacity (TLC) % pred in 27 (25.0%), forced expiratory volume in 1 s (FEV_1) % pred in 15 (13.6%), forced vital capacity (FVC) % pred in 10 (9.1%), FEV_1/FVC in five (4.5%), and small airway function in eight (7.3%). According to their research, restrictive ventilatory problems and impairment of diffusion capacity, both of which are related to the severity of the disease are the two most frequent abnormalities of lung function in COVID-19 survivors.

Guler et al (86) conducted a study including 113 COVID-19 survivors (mild/moderate 47, severe/critical 66). They confirmed a number of coexisting conditions as risk factors for serious/Severe/critical disease. After adjustment for potential confounding by age, sex, and BMI, patients after severe/critical COVID-19 had a 20.9 (95% CI 12.4-29.4, p=0.01) lower DLCO %-predicted at follow up. DLCO %-predicted was the strongest independent factor associated with previous severe/critical infection. Mosaic hypoattenuation on chest computed tomography at follow-up was significantly associated with previous severe/critical COVID-19 including adjustment for age and sex (adjusted OR 11.7 [95%CI 1.7- 239), p=0.03).

Zhao et al (87), studied 55 patients and observed that lung function abnormalities in 14 patients (25.45%). TLC was abnormal in 4 patients (7.27%), FEV_1 abnormal in 6 patients (10.91%), FVC abnormal in 6 patients (10.91%), DLCO was abnormal in 9 patients (16.36%), and small airway function abnormalities found in 7 patients (12.73%). Three months after discharge, the degrees of radiological abnormalities were detected in 39 patients (70.91%).

Fumagalli et al (88) studied pulmonary function in 13 patients surviving to COVID-19. The primary aim was to assess pulmonary function at the time of clinical recovery and after 6 weeks. The values and functional vital capacity values were lower at the time of recovery compared to lower limit of normality values with $p = 0.004$, and $p < 0.001$, respectively. Also, FEV1/FVC was higher compared to upper limit of normality values, $p = 0.029$. At 6 weeks, pulmonary function tests improved but FVC was still lower than ULN, $p = 0.014$. Thus, they concluded that COVID-19 pneumonia may result in impairment in pulmonary function with the commonest pattern being restrictive type.

Huang et al (89) did a retrospective study in 57 patients on impact on COVID-19 on PFT in convalescent phase. They assessed lung volumes, spirometry, lung diffusing capacity for carbon monoxide, respiratory muscle strength, (High Resolution Computed Tomography) HRCT thorax and 6 minute walk test. Low respiratory muscle strength, impaired diffusing capacity and, lung imaging abnormalities were found in early convalescent phase.

Huang et al (57)**,** assessed lung function in their study and found that a considerable proportion (22–56% across different severity scales) of participants had a pulmonary diffusion abnormality 6 months after symptom onset. This was in line with the study showing that pulmonary interstitial alteration which resembled the long term lung symptoms of SARS was the most prevalent aberrant CT pattern.

Torres-castro et al (83), conducted a systematic review and data analysis of seven articles reporting on 380 patients. In the sensitivity analysis, they found a prevalence of 0.39 (CI 0.24-0.56, $p < 0.01$, $I^2 = 86\%$), 0.15 (CI 0.09-0.22, $p = 0.03$, $I^2 = 59\%$), and 0.07 (CI 0.04-0.11, $p = 0.31$, $I^2 = 16\%$) for altered diffusion capacity of the lungs for carbon monoxide (DL_{CO}), restrictive pattern and obstructive pattern, respectively.

Zhang et al (90), recruited 21 women and 19 men for their study. At eight months nine (22.5%) patients had different degrees of limitations in daily life. 22 (55.0%) patients had persistent physical and (or) psychological symptoms. Although all patients had normal FVC, one (2.5%), 13 (32.5%), and nine (22.5%) patients had TLC, DLCO, and DLCO/VA below 80% of predicted values, respectively. The chest HRCT of 28 (70.0%) patients were normal whereas the remaining 12 patients had an abnormal CT at eight months after discharge. Most common abnormal CT patterns were ground glass opacity (GGO) (21 cases, 52.5%), irregular lines (19 cases, 47.5%), subpleural line (two cases, 5.0%), and reticular pattern (two cases, 5.0%).

HRCT findings in COVID-19 patients

Numerous COVID-19 CT findings have been described in various studies and the findings vary depending on the severity of disease, stage of the disease and the associated comorbidities. Following are the various CT findings:

Ground glass opacity: Ground glass opacity (GGO) is a nonspecific lug opacification seen on computed tomography or X-ray images that does not obscure bronchial or vascular markings. Partial filling of the lung alveoli by fluid, interstitial thickening, or partial collapse of lung alveoli are the presumed pathology. The most common finding in chest CT in patients with COVID-19 pneumonia is GGO, which is usually described as patchy, peripheral, bilateral, and subpleural.

Consolidation: Consolidation is a region of enhanced attenuation that obscures the bronchial and vascular marks and is brought on by accumulation of blood, fluid, exudates, transudates or cancerous cells in the alveolar spaces. Consolidation in COVID-19 pneumonia can be patchy or segmental, irregular or nodular, and mainly subpleural and peripheral with reported incidence ranging from 2% to 64% depending on the duration of the illness (91).

Reticulations: Reticulations appearing as lineal interlobular or intralobular density are found in COVID-19 patients as a relatively late finding with a reported incidence of 48.5–59%. The appearance of reticulations has correlation with clinical progression of the disease. Lymphocyte infiltration of the interstitial tissues with interlobular and septal thickening is

probably the cause of reticulations. In some studies, the reticular pattern was a relatively common pattern just after GGO and consolidation (91).

Crazy paving sign: The crazy paving signs represent GGO overlaid with thicker interlobular septa. Alveolar edema and interstitial inflammatory reaction are represented by this sign. This results from hyperplasia of interlobular and intralobular interstitia. Interestingly, this sign indicates progression of disease and reaching peak and also is the first CT sign to resolve in the absorptive phase (92).

Nodules: A nodule is an opacity with a diameter of less than 3 cm with regular or irregular outline. In general, viral pneumonitis is characterized by the presence of nodules. 3–13% is the incidence of pulmonary nodules in patients with COVID-19. Appearance of nodules in CT chest is considered as a sign of progressive disease (92).

Subpleural curvilinear line: They are thin linear shadow 1–3 mm in thickness lying parallelly within 1 cm from the pleural surface. These represent edema or fibrosis and is seen in 20% of patients (92).

Halo sign: Ground glass opacity surrounding a nodule or mass is defined as Halo sign. Previously, this sign was thought to be a manifestation of fungus infection, viral pneumonia, or hypervascular metastasis. 26% of patients with COVID-19 pneumonia and 21% of cases with other viral pneumonia were found to have Halo sign and thus they found it a non-helpful sign in differentiating COVID-19 pneumonia from other viral pneumonia (92).

Reverse halo sign or atoll sign: The reversed halo sign represents a region of GGO that is nearly encompassed by a ring of consolidation. an area of GGO encircled by near complete ring of consolidation. In COVID-19 pneumonia this can be seen due to disease progression with development of consolidation around GGO or consolidation with resolution of core area leaving an area of low density. The existence of sign in COVID-19 raises the possibility of development of organising pneumonia (92).

Mediastinal lymphadenopathy: when the short axis diameter is more than 1 cm these lymph nodes are considered to be enlarged. It is an uncommon finding with incidence ranging from 1 to 6%. These are usually considered as a sign of progressive disease or secondary bacterial infection(92).

Pleural changes: In COVID-19 patients pleural thickening and pleural effusion are considered less common findings with incidence of pleural thickening and effusion being 27-32% and 2-5% respectively. Some studies have shown that presence of pleural effusion can be correlated to high viral load and poor prognosis (92).

Vascular enlargement: Patients with COVID-19 frequently have vascular dilatation inside or around the lesions and is correlated to acute inflammatory response induced hyperemia (92).

Air bubble sign or vacuolar sign: A small air containing area with a length of less than 5 mm is referred to as an air bubble sign (vacuolar sign). It is considered as a sign of progressive disease. Dilatation of physiological spaces or transverse section of a bronchus within an area of consolidation could be the causes. It may represent a sign of progressive disease but is also an early sign of consolidation resorption (92).

Spider web sign: Spider web sign represents subpleural triangular area of GGO, with web-like thickening of the interlobular septa and retraction of the adjacent pleura. It is seen commonly in COVID-19 pneumonia (92).

Fibrosis: Patients with COVID-19 have an incidence of 17% for lung fibrosis and fibrous strips. Some experts believe it as a sign of decline in disease severity with a favourable prognosis while others believe it to be a warning sign of the onset of interstitial fibrosis (92).

Pericardial effusion: Pericardial effusion can be found in severe illness and is not a very common finding (92).

Bao et al (93) analysed total of 13 studies. Typical CT signs were ground glass opacities (83.31%), ground glass opacities with mixed consolidation (58.42%), adjacent pleura thickening (52.46%), interlobular septal thickening (48.46%), and air bronchograms (46.46%). Other CT signs included crazy paving pattern (14.81%), pleural effusion (5.88%), bronchiectasis (5.42%), pericardial effusion (4.55%), and lymphadenopathy (3.38%).

Shi et al (91) enrolled 81 patients and the predominant pattern of abnormality observed was bilateral (64 [79%] patients), peripheral (44 [54%]), ill-defined (66 [81%]), and ground-glass opacification (53 [65%]), mainly involving the right lower lobes (225 [27%] of 849 affected segments).

Bernheim et al (41) conducted a reterospective study. In this study, chest CTs of 121 symptomatic patients infected with coronavirus disease-19 (COVID-19) from four centers in China were reviewed. Bilateral and peripheral ground-glass and consolidative pulmonary opacities were found. 20/36 (56%) of early patients had a normal CT. Bilateral lung involvement was observed in 10/36 early patients (28%), 25/33 intermediate patients (76%), and 22/25 late patients (88%).

Wu et al (94) studied CT of 80 patients and found that the most frequent CT abnormalities observed were ground glass opacity (73/80 cases, 91%), consolidation (50/80 cases, 63%), and interlobular septal thickening (47/80, 59%).

RESULTS

Population characteristics:

Total 200 people were screened and 52 people were enrolled in the study(fig.2). Baseline characteristics are given in Table.1. Among 52 participants 41(78.8%) were males and 11(21.2%) were females(fig.3). The median age of the study population was 40 years with interquartile range (IQR) of 29 with age distribution as given below (Fig 4 and 5). Maximum number of participants were from the age group 26-35 years (n=20, 38.5%).

This study included people from different localities. 41(78.8%) people were from urban area and 11(21.2%) were from rural area(fig.6).

Fifty percent (n=26) of the participants required oxygen at the time of hospitalization for COVID-19(fig.8). Out of 52 participants 3(5.8%) were asymptomatic, 23(44.2%) had mild disease severity, 14(26.9%) had moderate disease severity and 12(23.1%) had severe disease at the time of hospital admission(fig.7).

Major symptoms at 3-6 months follow up was cough, shortness of breath, fatigue and chest pain. Cough was present in 12(23.1%) participants. 5(9.6%) people had SOB, 21(40.4%) had fatigue and chest pain was present in 14(26.9%) participants(fig 9).

Fig.2: Patient enrollment and exclusion criteria

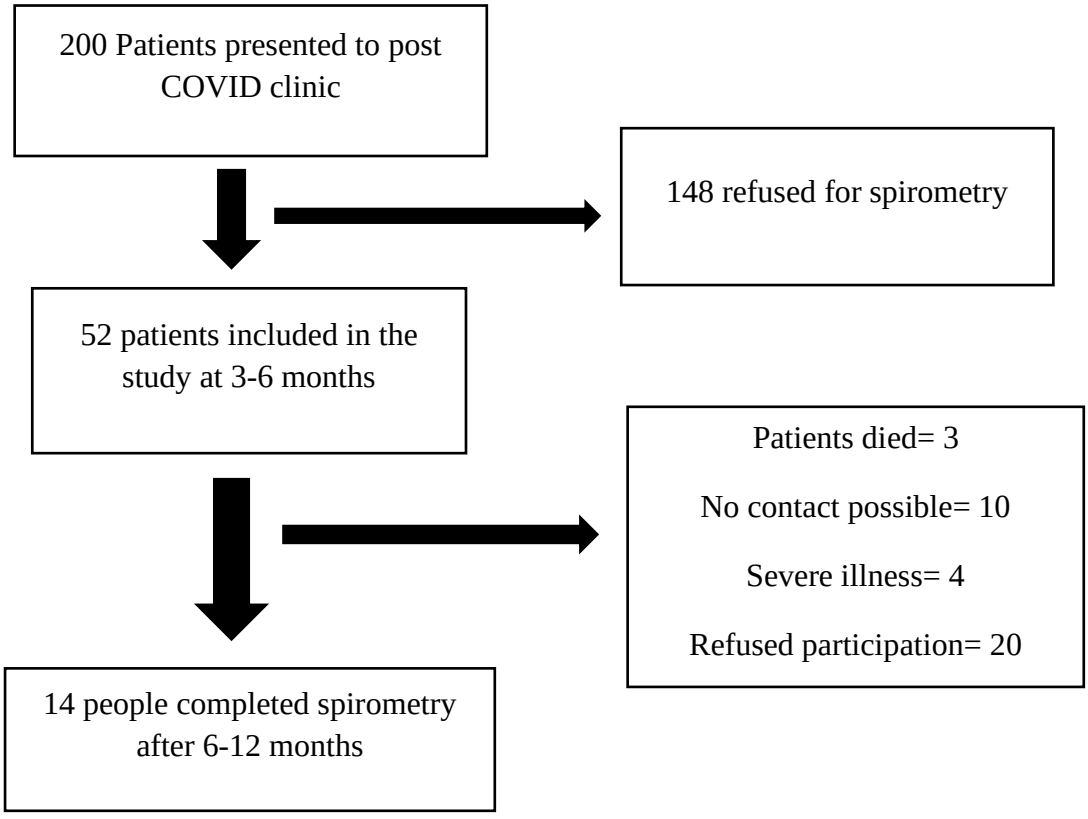
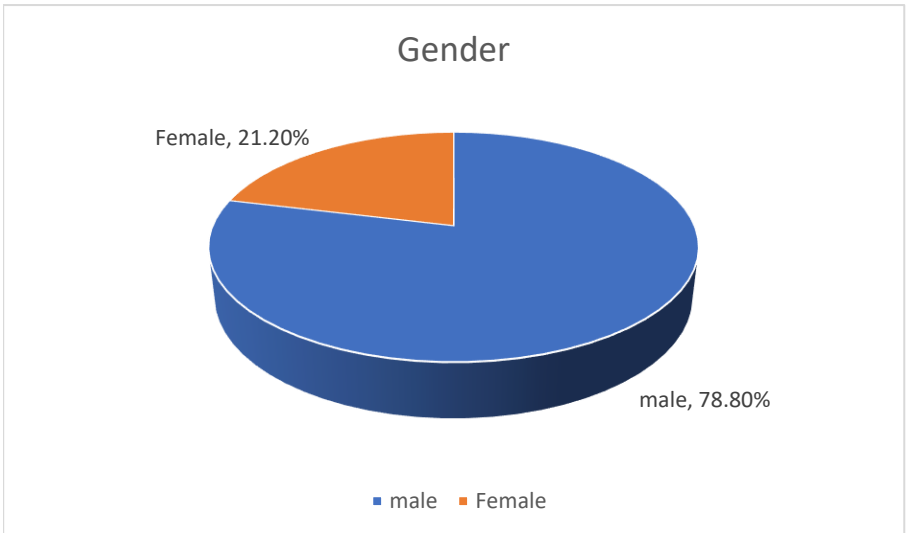


Table 1: Demographical profile of study population (N=52)

Variable	Number (N=52)	Percentage
Gender		
Female	11	21.2%
Male	41	78.8%
Age [Median (IQR)]	39(27)	
<25 years	4	7.7%
26-35 years	20	38.5%
36-45 years	7	13.5%
46-55 years	7	13.5%
56-65 years	9	17.3%
>65 years	5	9.6%
Address		
Rural	11	21.2%
Urban	41	78.8%
Disease severity		
Asymptomatic	3	5.8%
Mild	23	44.2%
Moderate	14	26.9%
Severe	12	23.1%
Oxygen need		
Yes	26	50%
No	26	50%

Fig.3: Gender distribution among study population (N=52)



Symptoms		
Cough	12	23.1%
SOB	5	9.6%
Fatigue	21	40.4%
Chest pain	14	26.9%

Fig 4: Age distribution of study patients (N=52)

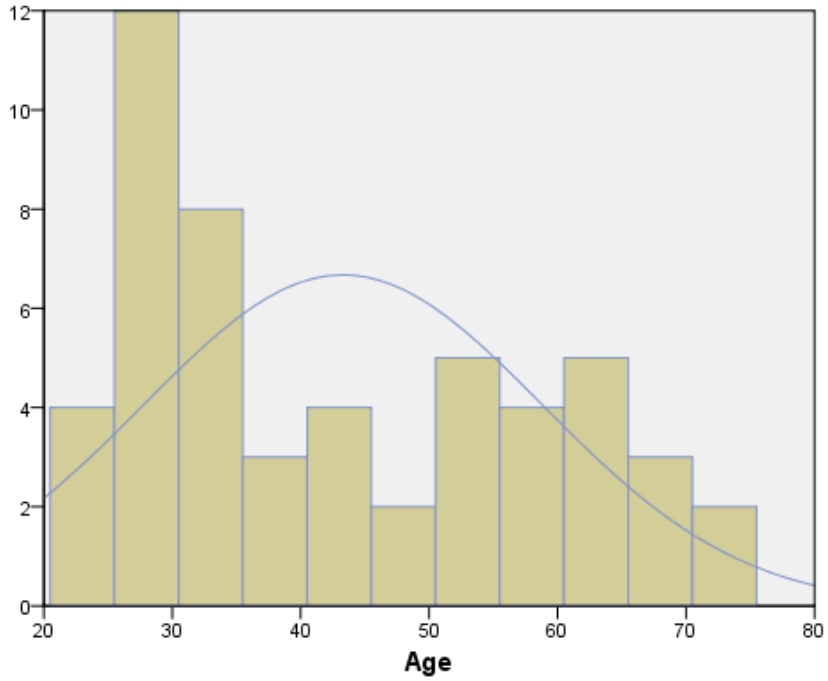


Fig 5: Age distribution of study patients (N=52)

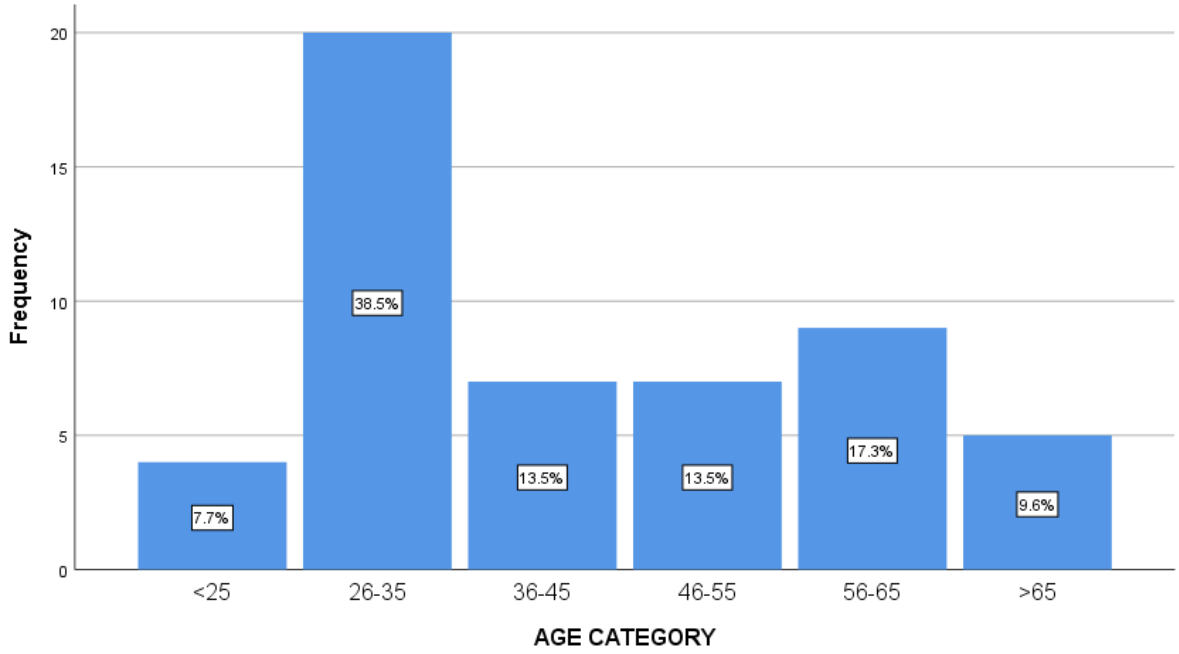


Fig 6: Location distribution of study population (N=52)

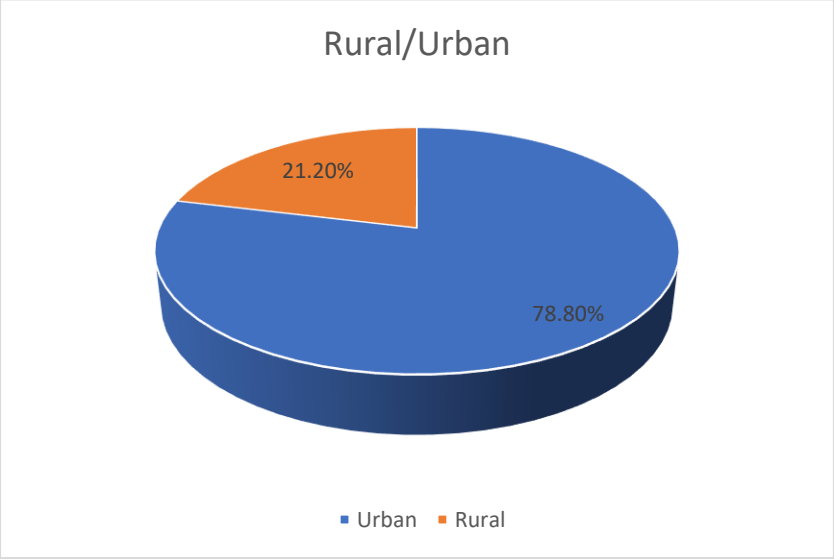


Fig 7: Disease severity of study population during hospitalization (N=52)

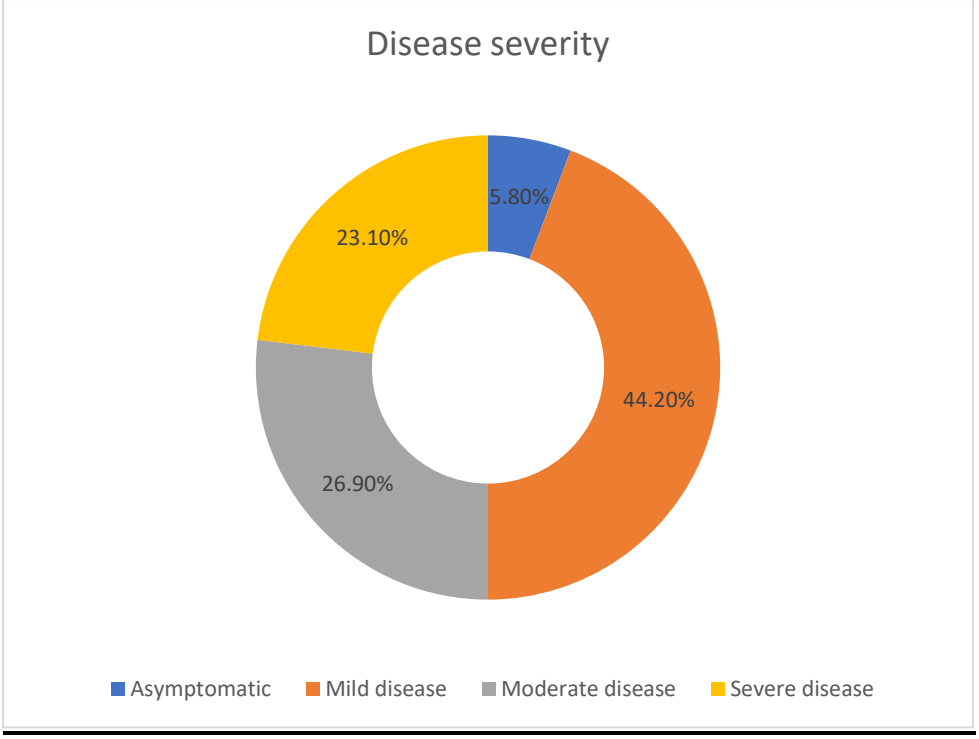


Fig 8: Oxygen requirement during hospitalization in study population (N=52)

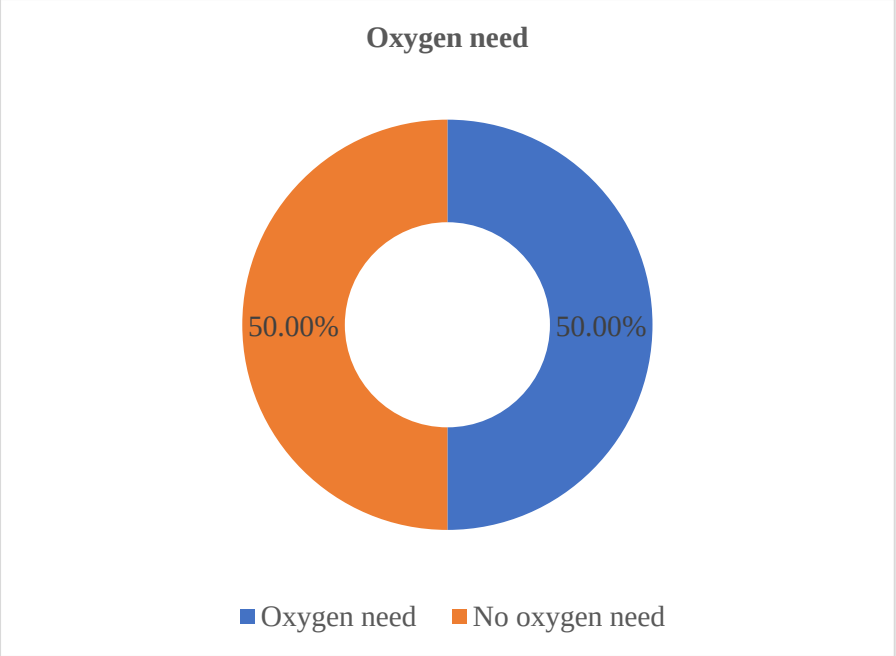
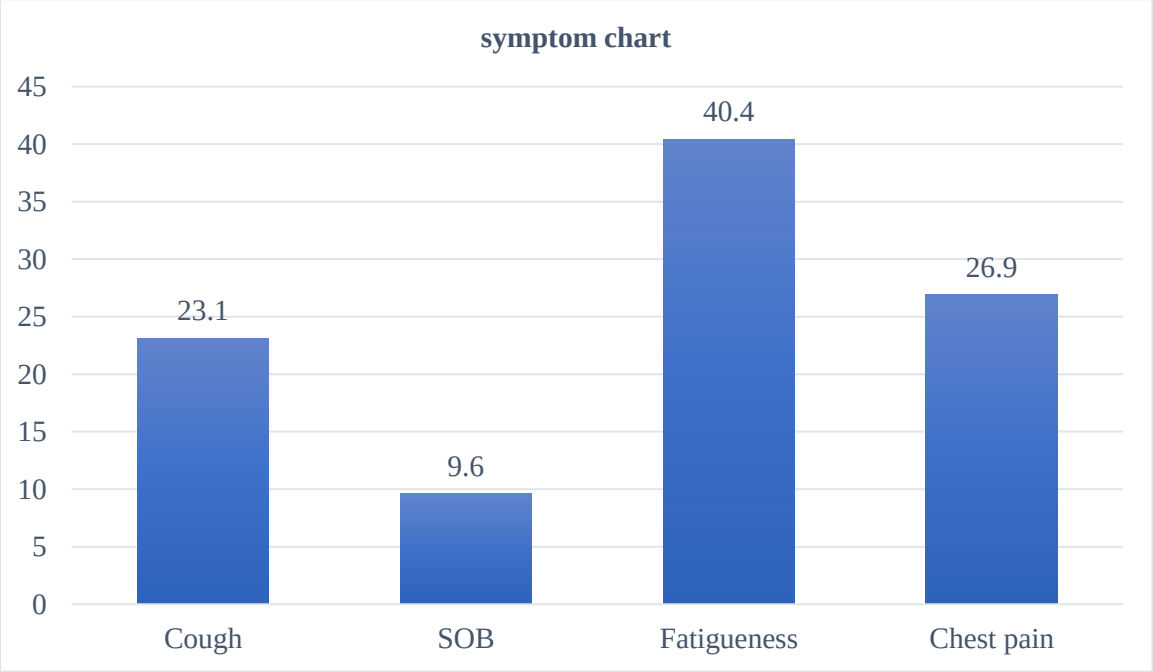


Fig 9: Post COVID-19 symptomatology in 3 to 6 month follow-up in percentage (N=52)



Laboratorical characteristics

Laboratorial characteristics at 3-6 month follow up are depicted in Table 2. Data are express as mean±SD or median(IQR) depending on the normality of the distribution.

Median SGPT was 25.3(11.4), median D-dimer was 0.27(0.13), median LDH was 199(35), median ferritin was 84.77(121.31) and median NTproBNP was38.5(38).

At 3-6 month follow up D-dimer was elevated in 14(26.9%) and was normal in the rest(fig.10). 10(19.2%) had elevated LDH at 3-6 months follow up(fig.11). ANA positivity was present in 7(12.5%) (fig.12).

Table 2: Blood investigations at 3-6 months visit of study population(N=52)

Variables	**At 3-6 months**
Haemoglobin (gm/dl)	13.50±1.78
TLC (10^3 /µL)	7.09(2.44)
Platelets (10^3 /µL)	298.84±87.98
SGPT(IU/L)	25.3(11.4)
SGOT(IU/L)	25.9(14)
Bilirubin(mg/dL)	0.54(0.24)
Albumin(gm/dL)	4.41±0.33
Creatinine(mg/dL)	0.83±0.13
INR	0.94±0.06
APTT(seconds)	22.2(6.7)
D-dimer(µg/ml)	0.27(0.06-3.48)
LDH(IU/L)	200(128-285)
Ferritin(ng/ml)	84(4.25-576.4)
CK-MB(IU/L)	12(7-29)
NT-proBNP(pg/ml)	38.5(35-332)

Fig 10: D-dimer levels in study population at 3-6 months follow up (N=52)

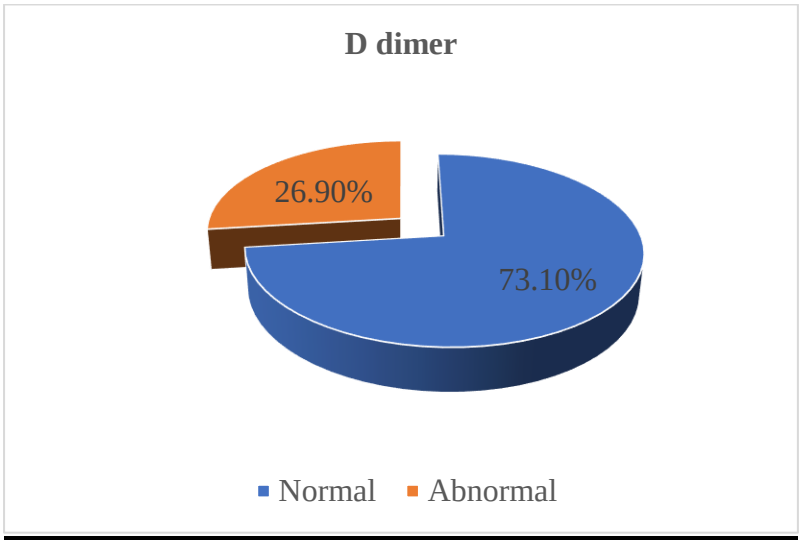


Fig 11: LDH levels in study population at 3-6 months follow up (N=52)

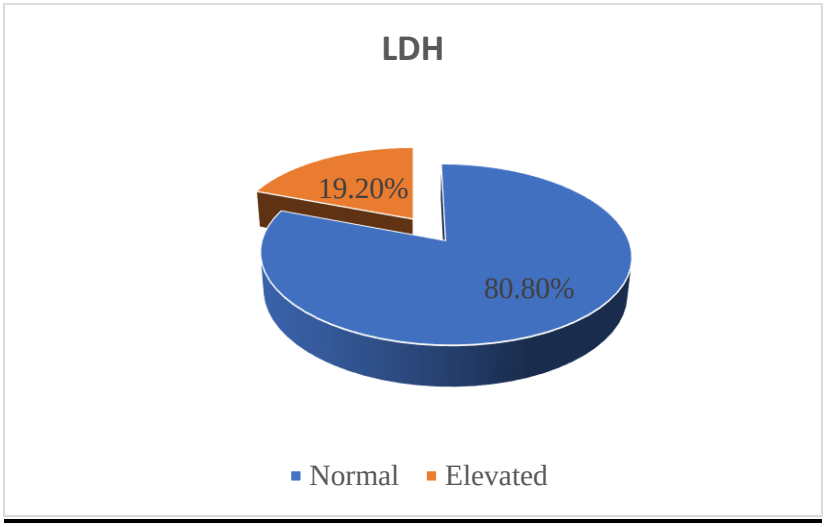
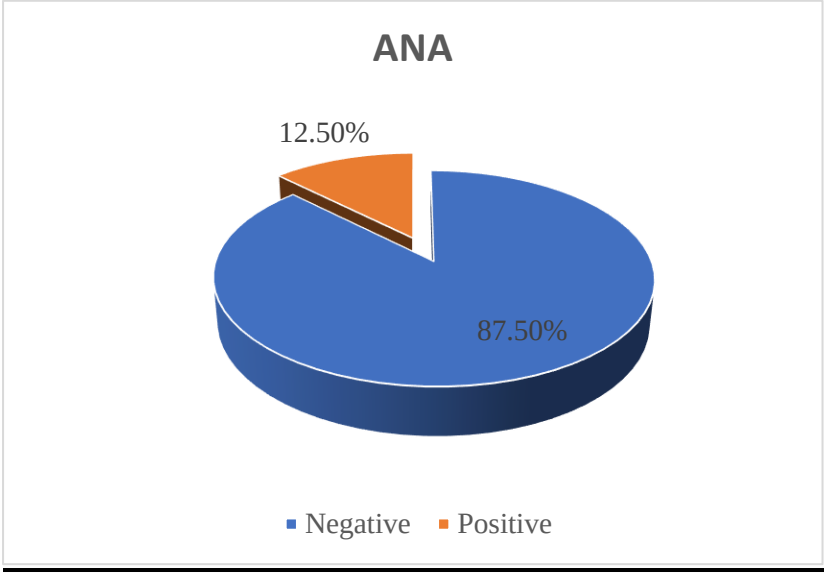


Fig 12: ANA positivity in study population at 3-6 months follow up (N=52)



Pulmonary function test characteristics

Pulmonary function test was done in 52 participants at 3-6 month follow up and 14 participants in 6-12 month follow up. Table 3 depicts the PFT values at 3-6 and 6-12 month follow up expressed in mean±SD or median(IQR).

Table 3: Pulmonary function test values at follow up visit of study population

Parameter	At 3-6 months(N=52)	At 6-12 months (N=14)
FEV1 pre	2.76±0.72	91.47±17.95
FEV1 post	2.90±0.74	3.00±0.94
FEV1 % predicted pre	92(15.22)	91.47±17.95
FEV1 % predicted post	93(49-121)	94.07±18.07
FVC pre	3.26±0.87	3.41±1.14
FVC post	3.35±0.86	3.46±1.15
FVC % predicted pre	85.08±15.26	89±17.12
FVC % predicted post	89(47-116)	88.57±17.20

FEV1/FVC pre	84.76±4.46	80±5.19
FEV1/FVC post	86.45(70.3-93.4)	87.40±5.13
PEF pre	6.79±2.16	6.85±2.15
PEF post	88.33±19.75	7.56±2.13
PEF % predicted pre	81.22±20.35	82±22.47
PEF % predicted post	88.33±19.75	90.17±19.12
FEF 25-75% pre	3.30±0.98	3.38±1.43
FEF 25-75% post	3.66±1.06	3.79±1.30
FEF 25-75% predicted pre	76(26)	85.40±28.12
FEF 25-75% predicted post	90.27±24.20	94.93±25.11

Pulmonary function abnormalities

Out of 52 participants who did spirometry at 3-6 months follow up 7(13.5%) had abnormal FEV1, 12(23.1%) had abnormal FVC. Abnormal PEF was present in 15(28.8%) while abnormal FEF25-75% was present in 5(9.6%) participants. FEV1/FVC was abnormal only in 1(1.9%) participant (Table 4) (fig.13).

14 people participated in our study at 6-12 month follow up. FEV1 was abnormal in 3(21.4%), FVC was abnormal in 5(35.7%), PEF was abnormal in 3(25%) while 5(9.6%) participants had abnormal FEF25-75% values. FEV1/FVC was normal in all the participants. (Table 5)(fig.14).

In our study most common spirometry pattern at 3-6 month follow up was normal. 40(75.5%) participants had normal spirometry pattern while restrictive pattern was present in 11(20.8%) and obstructive pattern in 1(1.9%) participant(fig.15). At 6-12 month follow up 10(71.4%) had normal and 4(28.5%) had restrictive pattern(fig.16). Out of 11 participants who had restrictive pattern at 3-6 month follow up 3 participants did spirometry at 6-12 months and 2 had restriction. 2 patients who did not have restriction at 3-6 months developed restriction at 6-12 month follow up.

Table 4: Spirometry abnormalities in Post COVID-19 patients at 3-6 month follow-up(N=52)

Parameter	Normal		Abnormal	
	Number	**Percentage(%)**	**Number**	**Percentage (%)**
FEV1 post	45	86.5	7	13.5
FVC post	40	76.9	12	23.1
FEV1/FVC post	51	98.1	1	1.9
PEF post	37	71.2	15	28.8
FEF 25-75% post	47	90.4	5	9.6

Fig 13: Spirometry abnormalities in Post COVID-19 patients at 3-6 month follow-up(N=52)

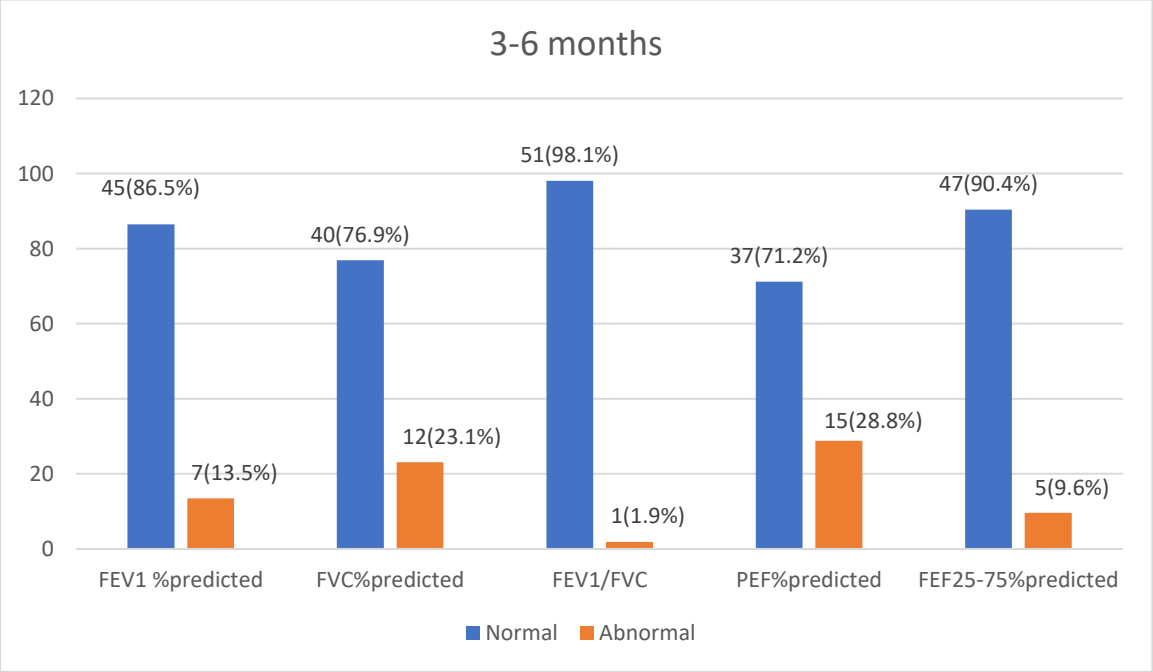


Table 5: Spirometry abnormalities in Post COVID-19 patients at 6-12 month follow-up(N=52)

Parameter	Normal		Abnormal	
	Number	**Percentage(%)**	**Number**	**Percentage (%)**
FEV1 post	11	78.5	3	21.4
FVC post	9	64.2	5	35.7
FEV1/FVC post	14	100	0	0
PEF post	9	75	3	25
FEF 25-75% post	12	85.7	2	14.2

Fig 14: Spirometry abnormalities in Post COVID-19 patients at 6-12 month follow-up(N=52)

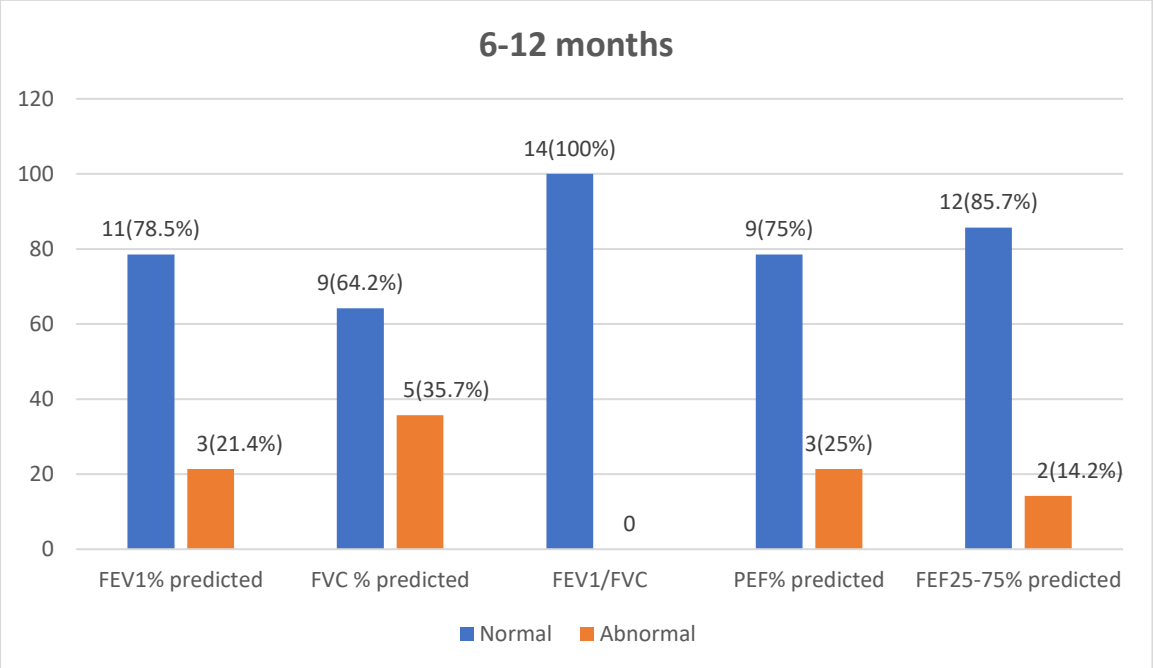


Fig 15: Spirometry patterns in Post COVID-19 patients at 3-6 month follow-up(N=52)

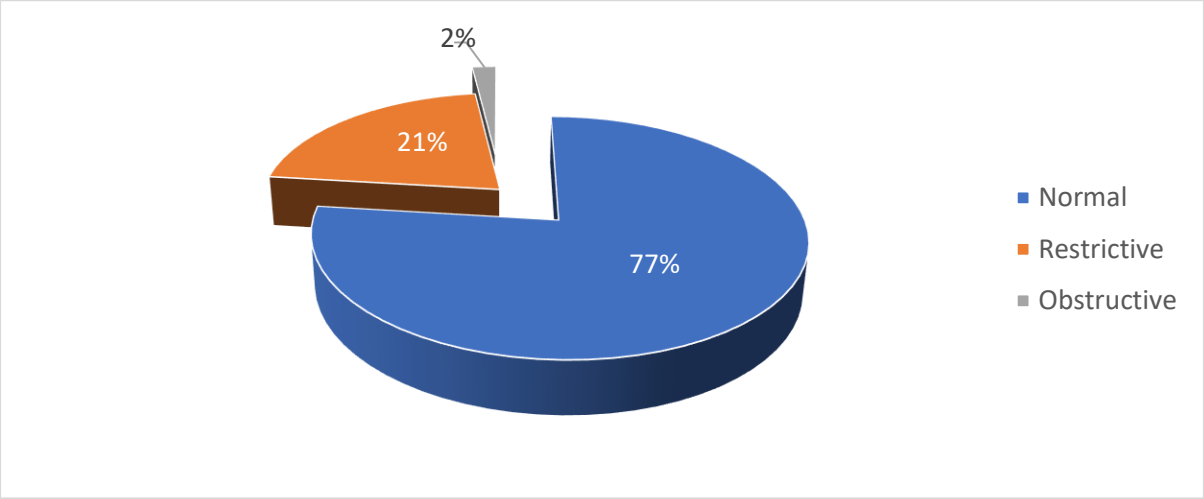
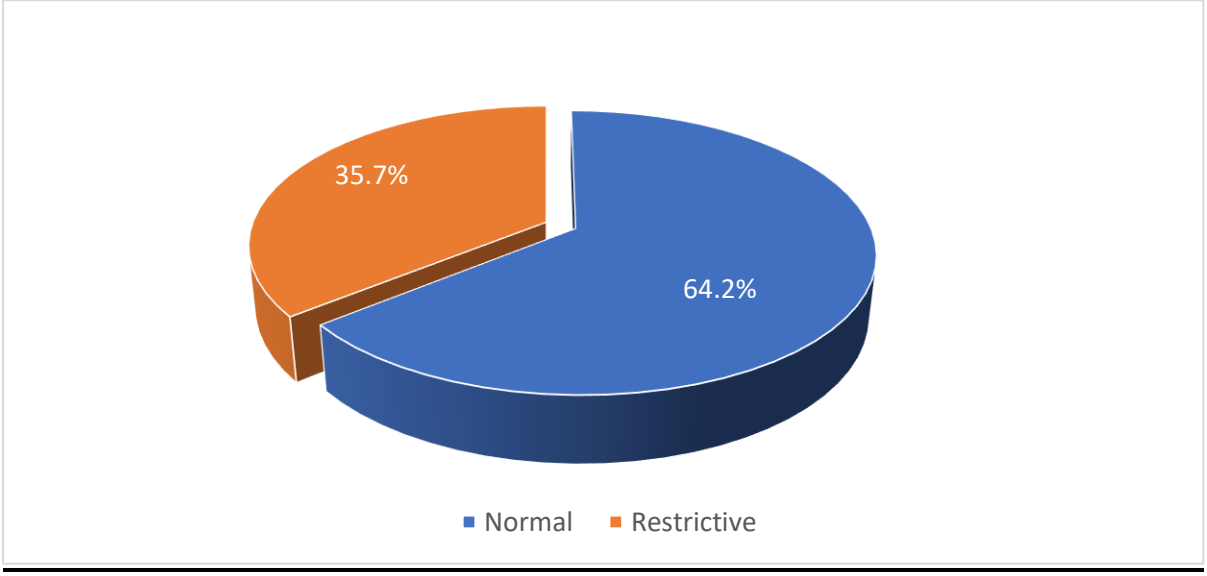


Fig 16: Spirometry patterns in Post COVID-19 patients at 6-12 month follow-up(N=14)



Pulmonary function test in different age categories, gender and location

PFT was assessed in different age categories at 3-6 month follow up and 6-12 month follow up and is depicted in Table 6 and 7. At 3-6 month follow up FEV1 showed decreasing trend as the age increases and it was significant(p=0.019). FVC also showed decreasing trend with significance(p=0.028). FEV and FVC were found to be lowest in the age group 56-65years. PEF and FEF25-75% also showed decreasing trend but with no significance (p=0.351, p=0.158 respectively). 6-12 months follow up did not show significant changes in pulmonary function values among different age groups.

Pulmonary function values in males and females are given table 8 and 9. There was significant difference between males and females at 3-6 month follow up and 6-12 month follow up in FEV1, FVC, PEF and FEF25-75% values.

Our study also compared pulmonary function values in participants from rural area and urban area. There was no significant difference in the PFT at 3-6 month follow up. At 6-12 month follow up all the participants were from urban area.

Table 6: Pulmonary function test values at 3-6 months follow up among different age categories(N=52)

	<25 years	26-35 years	36-45 years	46-55 years	56-65 years	>65 years	p value
FEV1 post	3.06±0.86	3.27±0.70	3.01±0.79	2.62±0.67	2.15±0.38	2.53±0.38	**0.019**
FVC post	3.44±0.93	3.78±0.80	3.57±0.98	3.03±0.81	2.56±0.43	2.91±0.52	**0.028**
FEV1/FVC post	90±4.6	86.1±4.5	83.8±3.6	88.2±5.1	86±9.3	89±9.3	0.282
PEF post	8.45±2.55	7.89±2.11	7.36±2.32	6.69±2.31	5.91±1.97	7.91±1.37	0.351
FEF 25-75% post	3.88±1.08	4.00±1.612	3.47±1.17	3.38±0.90	2.74±0.79	4.06±0.37	0.158

Table 7: Pulmonary function test values at 6-12 months follow up among different age categories(N=14)

	<25 years	26-35 years	36-45 years	46-55 years	56-65 years	>65 years	p value
FEV1 post	-	3.27±0.97	2.30±0.59	-	2.61±1.08	3.77	0.374
FVC post	-	3.76±1.24	2.68±0.65	-	3.05±1.48	4.16	0.518
FEV1/FVC post	-	87.8±9.8	84.4	-	87.4	-	0.892
PEF post	-	7.83±2.29	6.05±1.98	-	8.18±2.15	8.79	0.351
FEF 25-75% post	-	4.15±1.39	2.83±0.96	-	3.20±0.61	5.05	0.336

Table 8: Pulmonary function test values at 3-6 months follow up among different gender categories(N=52)

	Male	Female	P value
FEV1	3.11±0.72	2.28±0.38	**0.001**
FVC	3.62±0.82	2.59±0.43	**<0.001**
FEV1/FVC	85.89±4.25	88.01±2.67	0.129
PEF	8.02±2.00	5.45±1.11	**<0.001**
FEF 25%-75%	3.93±1.07	2.95±0.54	**0.006**

Table 9: Pulmonary function test values at 6-12 months follow up among different gender categories(N=14)

	Male	Female	P value
FEV1	3.54±0.77	2.12±0.44	**0.004**
FVC	4.11±1.01	2.36±0.39	**0.005**

FEV1/FVC	86.68±4.64	89.36±6.60	0.427
PEF	8.63±1.19	5.60±1.16	**0.001**
FEF 25%-75%	4.50±1.19	2.80±0.83	**0.022**

Table 10: Pulmonary function test values at 3-6 months follow up in people from different localities(N=52)

	Urban	Rural	P value
FEV1	2.87±0.75	2.98±0.75	0.691
FVC	3.32±0.90	3.46±0.77	0.651
FEV1/FVC	86.67±3.17	85.63±6.13	0.473
PEF	7.22±2.16	7.84±2.06	0.425
FEF 25%-75%	3.68±1.06	3.67±1.09	0.974

PFT and disease severity

COVID-19 pneumonia disease severity is divided into asymptomatic, mild, moderate and severe based on ICMR guidelines. At 3-6 month follow up based on the severity there was significant difference in FEV1(p=0.02), FVC(p=0.02), PEF(p=0.01) and FEF25-75%(p=0.05). After adjusting for age, it was analysed again and only PEF(p=0.02) and FEF25-75%(p=0.04) were significant. FEV1 and FVC were not significant (p=0.34 and p=0.37 respectively). Table 11 is showing PFT values at 3-6 moths follow up in different severity categories.

At 6-12 month follow up based on the severity there was no significant difference in FEV1(p=0.49), FVC(p=0.48), PEF(p=0.25) and FEF25-75%(p=0.67). Table 12 is showing PFT values at 6-12 month follow up in different severity categories. This data was also adjusted for age and post age adjustment also it was not significant.

Table 11: Pulmonary function test values at 3-6 months follow up in different severity categories(N=52)

	Asymptomatic	Mild	Moderate	Severe	**Unadjusted**	**Adjusted**
					p value*	p value
FEV1 post	3.51±0.83	3.21±0.71	2.62±0.61	2.51±0.72	**0.02**	0.34
FVC post	4.11±0.83	3.69±0.81	3.04±0.71	2.93±0.87	**0.02**	0.37
PEF post	9.80±1.68	8.04±1.96	5.93±1.75	7.58±2.25	**0.01**	**0.02**
FEF 25-75% post	3.86±1.32	4.09±1.14	3.13±0.74	3.38±0.92	**0.05**	**0.04**

Table 12: Pulmonary function test values at 6-12 months follow up in different severity categories(N=14)

	Asymptomatic	Mild	Moderate	Severe	**Unadjusted**	**Adjusted**
					p value*	p value
FEV1 post	4.03	3.26±1.06	2.62±0.55	2.70±1.51	0.49	0.47
FVC post	4.65	3.80±1.32	2.97±0.76	3.05±1.56	0.48	0.46
PEF post	11.5	7.42±2.04	7.46±1.31	6.30±3.52	0.25	0.10
FEF 25-75% post	4.89	4.10±1.60	3.34±0.51	3.47±2.23	0.67	0.62

PFT and oxygen need

Pulmonary function values in participants who needed oxygen at the time of hospitalization was compared with who did not need oxygen. There was significant difference in FEV1(p=0.002), FVC(p=0.003), PEF(p=0.013) and FEF25-75%(p=0.006) among two groups at 3-6 months follow up. After adjusting for age also the difference was significant in FEV1(p=0.025), FVC(p=0.046), PEF(p=0.028) and FEF25-75%(0.007). Table 13 is showing PFT values in two groups without and with age adjustment.
At 6-12 month follow up the difference in two groups were not significant. FEV1(p=0.157), FVC(p=0.139), PEF(p=0.464) and FEF25-75%(p=0.242)(Table 14).

Table 13: Pulmonary function test values at 3-6 months follow up based on oxygen requirement(N=52)

	No oxygen requirement	Oxygen requirement	**Unadjusted**	**Adjusted**
			P value	P value
FEV1	3.16±0.15	2.66±0.13	**0.002**	**0.025**
FVC	3.63±0.17	3.11±0.16	**0.003**	**0.046**
PEF	8.16±0.48	6.60±0.44	**0.013**	**0.028**
FEF 25%-75%	4.20±0.23	3.25±0.21	**0.006**	**0.007**

Table 14: Pulmonary function test values at 6-12 months follow up based on oxygen requirement(N=14)

	No oxygen requirement	Oxygen requirement	**Unadjusted**	**Adjusted**
			P value	P value
FEV1	3.37±1.01	2.64±0.76	0.157	0.14
FVC	3.92±1.25	2.99±0.89	0.139	0.13
PEF	8.00±2.41	7.13±1.88	0.464	0.21
FEF 25%-75%	4.22±1.49	3.37±1.00	0.242	0.03

Correlation of PFT with laboratory parameters

Correlation of pulmonary function values and laboratory parameters like SGPT, APTT, Ferritin, D-dimer, CK-MB, NTproBNP and LDH were assessed and there was no correlation (Table 15).

Table 15: Correlation of some PFT parameters with laboratory parameters at 3-6 month follow up(N=52)

		APTT	SGPT	Ferritin	NTproBNP	CK-MB	D dimer	LDH
FEV1	**r**	0.058	0.282	0.010	-0.306	-0.153	-0.298	0.054
	p	0.721	0.063	0.952	0.055	0.334	0.061	0.733
FVC	**r**	0.064	0.310	0.056	-0.273	-0.167	-0.261	0.048
	p	0.697	0.043	0.724	0.093	0.297	0.109	0.764

Correlation of PFT with symptomatology

Correlation of PFT values with symptomatology at 3-6 month follow up was assessed, there was no correlation found (Table 16).

Table 16: Correlation of some PFT parameters with symptomatology at 3-6 month follow up(N=52)

		Cough	SOB	Fatigue	Chest pain
FEV1	**r**	-0.043	-0.046	0.045	0.116
	p	0.774	0.763	0.769	0.444
FVC	**r**	-0.061	-0.018	-0.061	0.114
	p	0.691	0.904	0.693	0.455

Correlation of oxygen need and symptomatology

Correlation of oxygen need at the time of hospitalization with symptomatology at 3-6 month follow up was checked, no correlation found (Table 17).

Table 17: Correlation of oxygen need at the time of hospitalization with symptomatology at 3-6 month follow up(N=52)

		Cough	SOB	Fatigue	Chest pain
Oxygen need	**r**	0.091	0.065	0.118	0.087
	p	0.521	0.646	0.406	0.541

Comparison of PFTs at 2 visits

PFT values in 6-12 month follow up were more than that of 3-6 month. But the difference was not significant (Table 18).

Table 18: Comparison of pulmonary function tests at 3-6 month follow up and 6-12 month follow up

	3-6 months	6-12 months	P value
FEV1	2.92±0.94	2.97±0.97	0.59
FVC	3.36±1.10	3.43±1.23	0.50
FEV1/FVC	86.61±3.93	87.79±5.12	0.36
PEF	7.24±2.19	7.40±2.12	0.56
FEF 25%-75%	3.78±1.44	3.81±1.35	0.89

HRCT findings

Out of 52 participants, HRCT was done for 21 participants. Out of 21, 7(33.34%) had normal CT findings and 14(66.67%) had abnormal findings(fig.17). Among abnormal findings, ground glass opacity was the most common finding which was present in 8(38%). 2(9.5%) participants had fibrosis. Reticular opacity, pulmonary embolism and nodularity were other findings which was present in 1(4.7%) participant each. Fig.18 is showing the HRCT abnormalities.

Fig 17: HRCT findings in Post COVID-19 patients at 3-6 month follow-up(N=21)

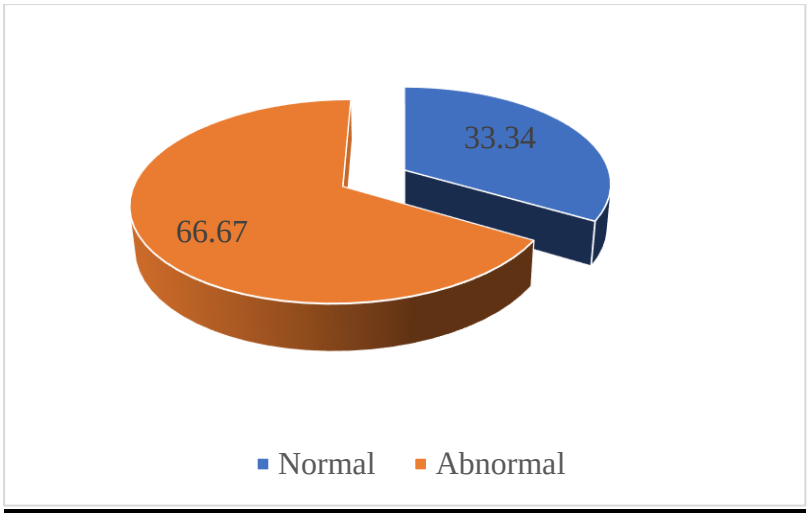
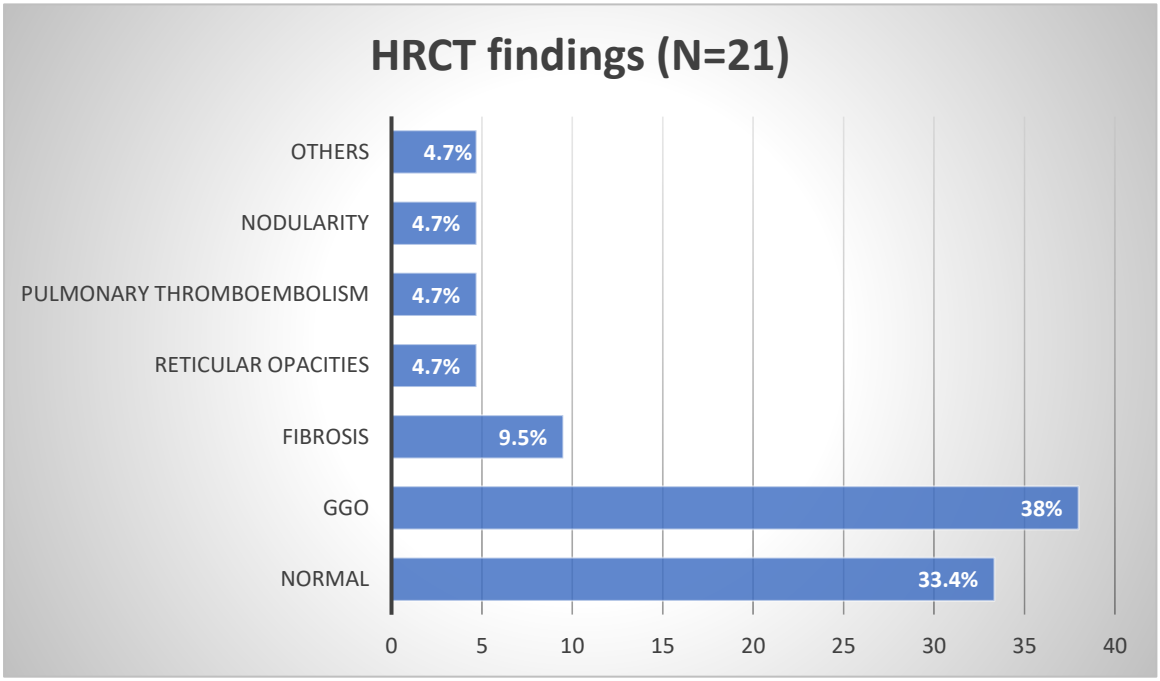


Fig 18: Abnormalities in HRCT in Post COVID-19 patients at 3-6 month follow-up(N=21)



Predictors of abnormality on HRCT thorax

Correlation of HRCT abnormality with some factors was assessed using pearson correlation coefficient. There was a positive correlation of age and HRCT abnormality with a correlation coefficient of 0.522 with p value of 0.015. Similarly, there was a positive correlation of LDH and HRCT abnormality with a correlation coefficient of 0.515 with a p value of 0.024 (Table 19).

Univariable linear regression analysis was done to study the association between age and HRCT abnormality & LDH and HRCT abnormality. We found that age>50 years ([OR]: 0.555; 95% CI: 0.15, 0.92; P = .009), was an independent predictor of the subsequent development of abnormality on HRCT thorax after 3-6 month follow-up (Table 20).

Table 19: Correlation of HRCT abnormality with some factors at 3-6 month follow up(N=21)

		HRCT abnormality
Age	**r**	0.522
	p	**0.015**
Sex	**r**	0.171
	p	0.457
D dimer	**r**	0.193
	p	0.414
LDH	**r**	0.515
	p	**0.024**
FEV1 post	**r**	-0.358
	p	0.133
FVC post	**r**	-0.302
	p	0.223
Cough	**r**	-0.073
	p	0.733
SOB	**r**	0.086
	p	0.712

Table 20: Univariable regression analysis for predictors of abnormalities in post COVID patients on HRCT thorax (n=21)

Dependent Variable	Standard coefficient(beta)	P value	Confidence interval (95%)	
			Lower	Higher
Age>50 years	0.555	**0.009**	0.151	0.926

LDH	0.224	0.330	-0.255	0.722

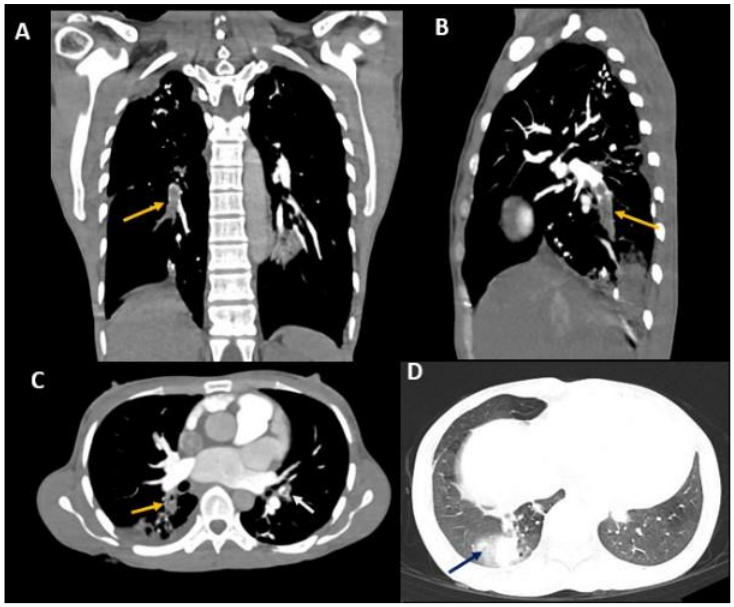


Fig 19: CT pulmonary angiography of a 32-year-old post COVID female patient shows pulmonary thromboembolism in segmental branches of right descending pulmonary artery (yellow arrow) with an associated pulmonary infarct (blue arrow) and partial thrombosis in segmental branch of left descending pulmonary artery (white arrow).

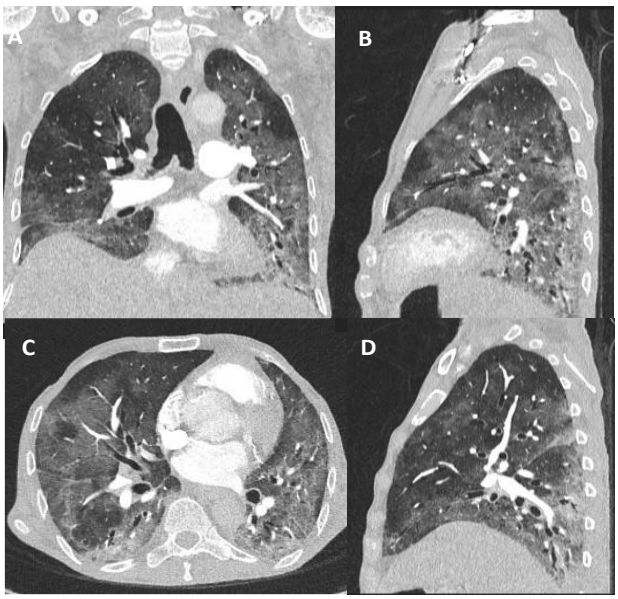


Fig 20: Coronal, Sagittal and Axial HRCT lung images of a 46 year old male who was positive for COVID-19 pneumonia show extensive ground glass opacities scattered throughout bilateral lungs with relative sparing of apices.

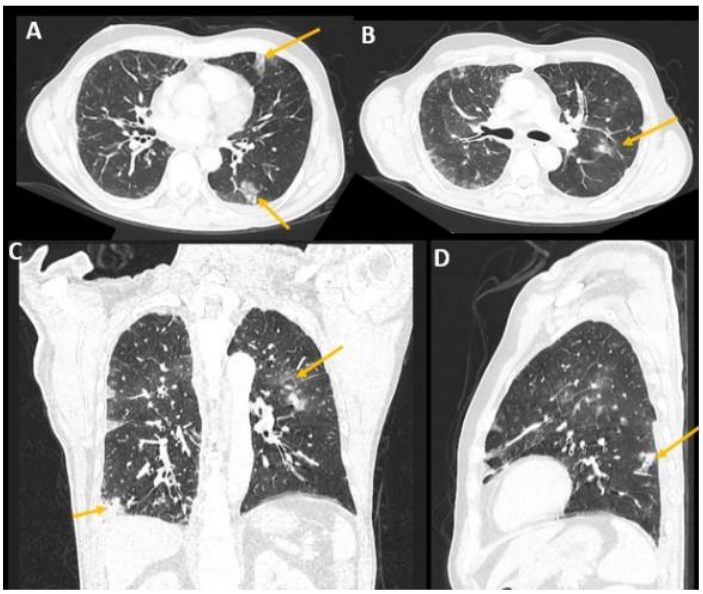


Fig 21: Axial (A and B), Coronal (C) and Sagittal (D) HRCT images of a 60 year old male positive for COVID 19 show patchy peripheral predominant ground glass opacities scattered in bilateral lungs (arrows).

DISCUSSION

COVID-19 pandemic which affected all parts of the world can have significant impairment of lung function even after recovery. Post COVID sequelae can have several manifestations both pulmonary and extra pulmonary.

Baseline characteristics

Our study included 52 recovered COVID-19 patients with a median age of 40(23-75) years which was comparable to previous studies (87,95). Out of this there were 78.8% males and 21.2% females. It was comparable to previous studies (96). Our study had more participants from urban area (78.8%). Similar studies from India did not have mention about the locality.

The reason for more participants from urban can be attributed to the easy accessibility of urban population to the study setting.

Participants were divided into asymptomatic, mild, moderate and severe disease groups with reference to national guidelines for COVID-19. Out of 52 participants, maximum had mild disease severity (44.2%). Prevalence of mild disease severity was comparable to study done by Eksombatchai et al (95)which had 51% mild cases. Naik et al (97) studied recovered COVID-19 patients and their study had 85.8% mild cases, 10.9% moderate cases and 3.3% severe cases. L.lewis et al (98) divided patients into mild, moderate severe and critical groups and there were 48.8%, 26.3%, 20% and 5% respectively in each group.

Proportion of patients who required oxygen at the time of hospital admission for COVID-19 is 50% in our study. This was much more compared to previous study by naik et al (97).

Symptomatology at 3-6 month follow up

Our study reported cough, shortness of breath, chest pain and fatigue at 3-6 months follow up. Fatigue was the most common post COVID symptom and was present in 40.4% participants. Cough was present in 23.1% participants. 9.6% patients had shortness of breath. Chest pain was present in 26.9%. Naik et al (97) reported fatigue in 5.5%, shortness of breath in 6.1%, cough in 2.1% and chest pain in 1.2%. Karoli et al (99)reported fatigue and poor exercise tolerance in 72%, dyspnea in 60% and reduced sleep in 30% participants after 3 months follow up.

On applying pearson correlation, no correlation was found between symptoms at 3-6 months and oxygen need at the of hospitalization. Our finding was in contrast to the Naik et al (97) who reported increased prevalence of long COVID symptoms in moderate/sever group compared to mild group. We did not find correlation between symptomatology and FEV1 and FVC.

Laboratory characteristics

We found elevated D-dimer at 3-6 month follow up in 26.9% with median value of 0.27(0.06-3.48). Townsend et al (100) reported elevated D-dimer in 25.3% patients in convalescent phase up to 4 months with median of 0.32(0.22-0.50). Persistence of elevated D-dimer may explain the predisposition to thrombosis in post COVID patients.

ANA was found positive in 12.5% participants. Peker et al (101) reported ANA positivity in 18% COVID-19 patients. Chang et al (102)detected ANA positivity in 21.3%. But these two studies were done in acute COVID-19 patients. Studies showing ANA positivity in long term post COVID-19 infection is limited. The presence of ANA positivity at 3-6 months follow up may indicate persistence of autoantibodies after the acute infection phase.

On applying Pearson correlation, no correlation was found between D-dimer, LDH, APTT, Ferritin, NT-proBNP, CK-MB and pulmonary function values. Salem et al (103) observed elevated D-dimer value at admission for those who showed a restrictive pattern on PFT, though it did not reach a level of significance.

Pulmonary function

Post bronchodilator values of FEV1, FVC, FVC/FEV1, PEF and FEF25-75% were used for the analysis. % Predicted values of FEV1, FVC, PEF and FEF25-75% were used. At 3-6 month follow up, median FEV1 was 93(49-121). Median FVC was 89(47-116). Median FEV1/FVC was 86.45(70.3-93.4). Mean PEF was 88.33±19.75. Mean FEF25-75% was 90.27±24.2. Our study had lower values as compared to study done by Eksombatchai et al (95)who reported mean FEV1 of 99.5±13.4, mean FVC 98±13.7, mean FEV1/FVC 85.8±6.4, mean PEF 109.3±17.5 and mean FEF25-75% 100.5±27.1 at 60 days follow up. Salem et al (103) had mean values of FEV1, FVC, FEV1/FVC,PEF and FEF25-75% as 90.30±12.78, 83.30±13.34, 82.55±5.82, 85.50±23.18 and 95.35±18.63 respectively. Mean time of assessment after discharge in this study was 166.52 (102–283). Except FEF25-75% all other values were lower than that in our study. In our study at 6-12 month follow up mean FEV1 was 94.7±18.07, mean FVC was 88.57±17.20, mean FEV1/FVC was 87.40±5.13, mean PEF 90.17±19.12 and FEF25-75% 94.93±25.11.

Our study reported several spirometry abnormalities. At 3-6 months follow up 13.5% had FEV1<80%, 23.1% had FVC<80%. PEF<80% was present in 28.8% while FEF25-75%<65% was present in 9.6% participants. FEV1/FVC was abnormal (<70%) only in 1.9% participants. Eksombatchai et al (95) in their study which was conducted in 87 patients in Thailand reported abnormal FEV1 in 5.7%, FVC in 8%, FEV1/FVC in 5.7%, PEF in 5.7% and FEF25-75% in 11.5% at 60 days follow up. Our study reported more prevalence of abnormal FEV1, FVC and PEF. But abnormal FEV1/FVC and FEF25-75% were more in their study. Zhao et al (87)conducted study in 55 post COVID patients at 3 months and reported 10.9% abnormal FEV1, 10.9% abnormal FVC and 7% abnormal FEF25-75%. Our participants had more PFT abnormalities compared to this study.

Out of 14 people who participated in our study at 6-12 month follow up, FEV1 was abnormal in 21.4%, FVC was abnormal in 35.7%, PEF was abnormal in 25% while 9.6% participants had abnormal FEF25-75% values. FEV1/FVC was normal in all the participants. As compared

to values at 3-6 month follow up, the proportion of people with abnormal FEV1 and FVC is more at the 6-12 month follow up. Tarraso et al (104)studied 284 recovered patients at 2,6 and 12 months and reported 14.3%, 9.3% and 6.7% abnormal FVC at 2,6 and 12 months respectively showing decreasing number of patients as the time increases. Our study was not comparable to this. This could be explained by the smaller number of people in the second visit. We consider this as the major limitation of our study.

In our study most common spirometry pattern at 3-6 month follow up was normal. 40(75.5%) participants had normal spirometry pattern while restrictive pattern was present in 11(20.8%) and obstructive pattern in 1(1.9%) participant. At 6-12 month follow up 10(71.4%) had normal and 4(28.5%) had restrictive pattern.

Restrictive pattern was seen 20.8% at 3-6 month follow up in our study. Salem et al (103)reported restrictive pattern in 50% post COVID patients which was much more than our study. Their median time of assessment was 166.52 (102-283) while our study was done at 90 days to 180 days. Similarly fumagalli et al (88)also reported a high prevalence of restrictive pattern in their study i.e 10(76%) out of 13 patients. Their time of assessment was 6 weeks. The high prevalence of restrictive disease in this study could be due to the small number of participants. Torres castro et al (83) compared 7 articles reporting on 380 patients and reported restrictive pattern in 15% and was comparable to our study. Our study reported 4 out of 11(28.5%) at 6-12 month follow up. Tarraso et al (104) compared PFT and had 14.3%(54/377), 9.3%(29/312) and 6.7%(19/284) restrictive disease at 2, 6 and 12 months respectively. According to their study there was a decrease in prevalence of restrictive lung disease as the time increase which was not in line with our study where we reported 20.8%(11/52) and 28.5%(4/14) at 3-6 month and 6-12 month respectively. This result can be attributed to the smaller number of participants in follow up study. Out of 11 participants who had restrictive pattern at 3-6 month follow up 3 participants did spirometry at 6-12 months and 2 had restriction, thus confirming improvement in the pulmonary function after 6 months. 2 patients who did not have restriction at 3-6 months developed restriction at 6-12 month follow up. This could be due to delayed development of restrictive lung disease due to COVID-19 or restrictive lung related to some other pathologies. These patients require to be kept under close clinical follow up along with periodic spirometry and repeat imaging to assess progression.

Our study found obstructive lung disease in only 1(1.9%) participant at 3-6 month follow up. Our study did not collect data on comorbidities and this we consider a major limitation of our study. Presence of obstructive finding could be due to comorbidities.

Altered diffusion capacity was the most common pulmonary function abnormality found by most of the studies. Torres-castro et al (83) reported abnormal diffusion capacity in 39% which was more than restrictive pattern (15%). Salem et al reported diffusion capacity abnormality in 15% and Zhao et al (87) in 15.5% participants. We did not perform diffusion capacity in our patients and we consider this as a limitation of our study.

The current guidelines suggest a restrictive pattern if the FEV1/FVC ratio ≥ lower limit normal (LLN) and the FVC is < LLN, which should be confirmed by evaluating the TLC (7). We did not perform plethysmography in our study. This is also a limitation of our study.

We found a declining trend in FEV1 and FVC with ageing with p value of 0.019 and 0.028 respectively at 3-6 month follow up. But 6-12 month follow up did not show significant decline in pulmonary function with ageing. The reason for this abnormality could be lung dysfunction related to COVID-19. Sharma et al (105) in their study in 180 healthy individuals reported that younger population had a high value for FEV_1 and PEFR showed a rise among age groups: 11-20, 21-30 and 31-40 years, reaching up to 7.23±1.75 (L/sec), and then declining to reach 3.93±0.98 (L/sec) for the age group: >60 years.

We found significant difference between males and females in pulmonary function values at 3-6 months {FEV1(p=0.001), FVC(p=<0.001), PEF(p=<0.001) and FEF25-75%(p=0.006)} and 6-12 months {FEV1(p=0.004), FVC(p=0.005), PEF(p=0.001) and FEF25-755(p=0.022)}. The mean values for FEV_1, FVC, PEF and FEF25-75% were higher in males compared to females: 3.11±0.72 vs. 2.28±0.38, 3.62±0.82 vs. 2.59±0.43, 8.02±2.00 vs. 5.45±1.11, and 3.93±1.07 vs. 2.95±0.54 respectively at 3-6 months and 3.54±0.77 vs. 2.12±0.44, 4.11±1.01 vs. 2.36±0.39, 8.63±1.19 vs. 5.60±1.16, and 4.50±1.19 vs. 2.80±0.83 respectively at 6-12 months. However, the mean values for FEV_1/FVC ratio between males and females were not significantly different. This finding of our study was in agreement with the study done by Zakariya et al (106) who in their study reported significant differences in the mean values for forced vital capacity (FVC)% predicted ($p < 0.001$, 95% CI: 6.42–20.67), forced expiratory volume in 1 second (FEV_1)% predicted ($p = 0.007$, 95% CI: 3.14–19.17) and peak expiratory flow (PEF) ($p < 0.001$, 95% CI: 0.99–2.17).

Our study found significant difference in pulmonary function values at 3-6 month after recovery from COVID-19 disease with different severity at the time of hospitalization. Mean value of FEV1, FVC, PEF and FEF25-75% decreased as the severity increased. FEV1: asymptomatic-3.51±0.83, mild-3.21±0.71, moderate-2.62±0.61 and severe- 2.51±0.72, p=0.02; FVC: asymptomatic-4.11±0.83, mild-3.69±0.81, moderate-3.04±0.71 and severe-2.93±0.87, p=0.02; PEF: asymptomatic- 9.80±1.68, mild- 8.04±1.96, moderate- 5.93±1.75 and severe- 7.58±2.25, p=0.01; FEF25-75%: asymptomatic- 3.86±1.32, mild- 4.09±1.14, moderate- 3.13±0.74 and severe-3.38±0.92, p=0.05. These values were adjusted for age and post adjustment, only difference in PEF and FEF25-75% were significant: p=0.02 and p=0.04 respectively. Previous studies had varied result on the relationship between severity of COVID-19 and worsening of pulmonary function. Lewis et al (98)reported no difference in FEV1, FVC and FEV1/FVC based on the COVID-19 severity. However Eksombatchai et al (95) reported lower FVC in the severe pneumonia group than in the other groups. Guler et al (86)demonstrated lower lung volumes (TLC, FVC, and FEV1) in patients after severe/critical COVID-19. The major limitation we observed in these studies is lack of adjustment for age.

We did not find any significant difference in pulmonary function values at 6-12 months between groups based on the severity. This suggests that pulmonary function at 6-12 month has no relationship with the disease severity. Possible reason could be the returning of lung function to baseline.

In our study there was significant difference in pulmonary function values at 3-6 months between patients who required oxygen at the time of hospitalization and who did not require oxygen. The mean values of pulmonary function values were lower in the patients who required oxygen, FEV1: 3.16±0.15 vs 2.66±0.13, p=0.002; FVC:3.63±0.17 vs 3.11±0.16, p=0.003; PEF: 8.16±0.48 vs 6.60±0.44, p=0.013; FEF25-75%: 4.20±0.23 vs 3/25±0.21, p=0.006. This data was adjusted for age and subsequent data is also showing significant difference in FEV1, FVC, PEF and FEF25-75% with p values of 0.025, 0.046, 0.028 and 0.007 respectively. At 6-12 month follow up there was no significant difference in the pulmonary function values, suggesting improvement in lung function after 6 months and reversibility of lung changes due to COVID-19. Previous studies have compared mean values of pulmonary function based on the disease severity. Based on oxygen requirement, data is limited.

We found improvement in lung function (FEV1, FVC, PEF, FEF25-75%) on 6-12 month follow up compared to 3-6 month follow up but was not statistically significant. Tarraso et al (104) in their study, which compared PFT at 2,6 and 12 months reported mean FVC (% of predicted) as 99 (17.9), 100.8 (16.5) and 104.2, at 2, 6 and 12 months [$p < 0.001$].

HRCT findings

Out of 52 participants, HRCT was done for 21 participants in our study. Out of 21, 7(33.34%) had normal CT findings and 14(66.67%) had abnormal findings. Among abnormal findings, ground glass opacity was the most common finding which was present in 8(38%). 2(9.5%) participants had fibrosis. Reticular opacity, pulmonary embolism and nodularity were other findings which was present in 1(4.7%) participant each. Guler et al (86) did HRCT after four months of the initial diagnosis and the predominant finding in their severe/critical subcohort was a mosaic attenuation pattern. Han et al (107) studied 114 post COVID patients after 6 months, evidence of fibrotic-like changes was observed on follow-up in 40 of the 114 participants (35%); 38 of those 40 participants (95%) had de novo fibrotic abnormalities. The remaining 74 participants (65%) showed either complete radiologic resolution (43 of 114, 38%) or residual GGO or interstitial thickening (31 of 114, 27%). In their study, Alarcón-Rodríguez et al (108)reported CT findings and most common findings were bronchial dilation and parenchymal bands (78%), Other findings identified in more than half of the cases were: 1) coarse subpleural reticulation but with no honeycombing, which we have called subpleural interstitial involvement without honeycombing (66%); 2) areas of ground-glass opacity (58%) and 3) a mosaic pattern due to air trapping demonstrated in the expiratory phase of the scan (51%). In 14% of the patients, they demonstrated the existence of pneumatoceles and the least common finding was honeycombing (4%).

Predictors of abnormalities on HRCT thorax

Our study revealed a positive correlation of age and HRCT abnormality with a correlation coefficient of 0.522 with p value of 0.015. Similarly, there was a positive correlation of LDH and HRCT abnormality with a correlation coefficient of 0.515 with a p value of 0.024. Univariable linear regression analysis was done to study the association between age and HRCT abnormality & LDH and HRCT abnormality. We found that age>50 years ([OR]: 0.555; 95% CI: 0.15, 0.92; P = .009), was an independent predictor of the subsequent development of abnormality on HRCT thorax after 3-6month follow-up. This was in line with the finding of study done by Han et al (107)who also found age>50 years as an independent factor predicting HRCT abnormality at 6 months. There was no correlation between radiological abnormality and abnormal PFT in our study.

Limitations

Our study has several limitations. Firstly, data on pulmonary function tests and CT scans prior to admission were not available for assessment of longitudinal changes. Secondly, DLCO and plethysmography were not done in our study. DLCO is the most common PFT abnormality after COVID infection. TLC calculation is needed to divide patients into normal, restrictive and obstructive group. Another important limitation has been the loss of patients due to pandemic-related restrictions and security measures.

CONCLUSION

Post COVID sequelae can have several manifestations both pulmonary and extra pulmonary. Even after recovery these patients can have significant pulmonary function impairment. Impact of COVID-19 pneumonia on lung function in recovered patients can be in the form of abnormality in FEV1, FVC, PEF and FEF25-75%. Most common spirometry abnormality found was restrictive pattern. Severe COVID-19 pneumonia patients and patients who required oxygen despite of having moderate disease at the time of hospitalization had more impairment in spirometry when compared to patients with mild symptoms and non-severe pneumonia. Improvement of pulmonary function after 6 month of initial assessment suggests possibility of recovery.

Follow-up CT scans obtained within 6 months of disease onset showed abnormalities in more than half of patients who survived COVID-19 pneumonia. There was no correlation between pulmonary function derangement and HRCT abnormality.

Long term follow up is recommended in the recovered patients to assess the progression and recovery of pulmonary function and to device rehabilitation measures.

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IEC certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/ 3541 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3376**

Project title: **"Evaluation of the longterm effects of COVID-19 on pulmonary function in recovered patients"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Naja K**
Guide:	**Dr. M.K.Garg**
Co-Guide:	**Dr. Deepak Kumar & Dr. Naveen Dutt**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

APPENDIX-1

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of Thesis/Dissertation: EVALUATION OF THE LONGTERM EFFECTS OF COVID 19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS.

Name of PG Student : Dr. NAJA K 9968969339

Patient/Volunteer Identification No.: _____

I,_____S/o or D/o_____

R/o_____give my full, free, voluntary consent to be a part of the study "EVALUATION OF THE LONGTERM EFFECTS OF COVID 19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS", the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individual from _____ (Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date : _____ _____

Place : _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date : _____ _____

Place : _____ Signature of PG Student

Witness 1 Witness 2

Signature Signature

Name: _____ Name: _____

Address : _____ Address : _____

APPENDIX-2

All India Institute of Medical Sciences

Jodhpur, Rajasthan

<u>सूचित सहमति प्रपत्र</u>

थीसिस / शोध प्रबंध का शीर्षक: **"EVALUATION OF THE LONGTERM EFFECTS OF COVID** 19 **ON PULMONARY FUNCTION IN RECOVERED PATIENTS"**
पीजी छात्र का नाम: डॉ नजा के**:** 9968969339
रोगी / स्वयंसेवक पहचान संख्या: _____
मैं,_____पुत्र/पुत्री_____
निवासी_____मेरी पूर्ण, नि: शुल्क, स्वैच्छिक सहमतिदेताहुनिम्नलिखित अध्ययन का हिस्सा बनने के लिए ।
अध्ययन के एक भाग के रूप में "पुनर्निर्मित मरीजों में सहकर्मियों के सहयोग पर 19 वर्षों का लंबा प्रदर्शन**,"** की प्रक्रिया और प्रकृति**,** मुझे अपनी पूर्ण संतुष्टि के लिए अपनी भाषा में मुझे समझाया गया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।
मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और बिना किसी कारण के किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।
मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारी को _____**(**कंपनी का नाम) या नियामक अधिकारियों के जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

दिनांक : _____ _____
जगह: _____ हस्ताक्षर / बाएं अंगूठे का निशान

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त हुई है।

दिनांक : _____ _____
स्थान: _____ पीजी छात्र के हस्ताक्षर
साक्षी 1 साक्षी 2

हस्ताक्षर हस्ताक्षर
नाम _____ नाम: _____
पता _____ पता: _____

APPENDIX-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID:**

EVALUATION OF THE LONGTERM EFFECTS OF COVID 19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS

1. You are participating in a study to understand the effects of COVID-19 on lung function.
2. We will be collecting information regarding your age, gender, duration of your disease and the treatment you have received.
3. Study procedure: We will be collecting your blood sample to do your routine tests as well as 2 new tests, which are done as part of our study. You will be asked to participate in a lung function test which will decide if you need a CT scan of chest. Following this you will be offered the investigation. The CT scan of chest will expose you to minimum radiation (0.98 mSv) but the benefits of doing the scan will outweigh the risks.
4. Likely benefit: If you have an underlying lung disease, we can treat it early which will be of benefit to you.
5. Confidentiality: All the data collected from you will be kept highly confidential.
6. Risk**:** Enrollment in above study poses no substantial risk to you. You can withdraw from the study at any point of time without any consequences to yourself.

For further information / questions, the following personnel can be contacted:

Dr Naja K, Junior Resident, Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan. Ph: 9968969339

APPENDIX-4

रोगी सूचना पत्र

रोगी का नाम: **रोगी आईडी:**

EVALUATION OF THE LONGTERM EFFECTS OF COVID 19 ON PULMONARY FUNCTION IN RECOVERED PATIENTS

1. आप फेफड़ों के कामकाज पर **COVID 19** संक्रमण के प्रभाव को समझने के लिए एक अध्ययन में भाग ले रहे हैं।

2. हम आपकी उम्र, लिंग, आपकी बीमारी की अवधि और आपके द्वारा प्राप्त उपचार के बारे में जानकारी एकत्र करेंगे।

3. अध्ययन प्रक्रिया: हम आपके नियमित परीक्षण के साथ-साथ **2** नए परीक्षणों, जो हमारे अध्ययन के भाग के रूप में किए जाते हैं, करने के लिए आपके रक्त के नमूने को एकत्रित करेंगे। आपको एक फेफड़े के कार्य परीक्षण में भाग लेने के लिए कहा जाएगा जो यह तय करेगा कि आपको छाती के सीटी स्कैन की आवश्यकता है या नहीं। इसके बाद आपको जांच की पेशकश की जाएगी। छाती का सीटी स्कैन आपको न्यूनतम विकिरण (**0.98 mSv)** तक पहुंचा देगा, लेकिन स्कैन करने के लाभ जोखिमों को कम कर देंगे।

4. संभावित लाभ: यदि आपके पास एक अंतर्निहित फेफड़ों की बीमारी है, तो हम इसका जल्द इलाज कर सकते हैं जो आपके लिए लाभकारी होगा।

5. गोपनीयता: आपके द्वारा एकत्र किए गए सभी डेटा को अत्यधिक गोपनीय रखा जाएगा।

6. जोखिम: उपरोक्त अध्ययन में नामांकन आपके लिए कोई बड़ा जोखिम नहीं है। आप बिना किसी परिणाम के किसी भी समय अध्ययन से पीछे हट सकते हैं।

अधिक जानकारी / प्रश्नों के लिए, निम्नलिखित कर्मियों से संपर्क किया जा सकता है:

डॉ। नजा के, जूनियर रेजिडेंट, आंतरिक चिकित्सा विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान। **Ph: 9968969339**