A STUDY ON

"ASSESSMENT OF PULMONARY FUNCTION IN POST COVID PATIENTS IN A TERTIARY CARE INSTITUTION A PROSPECTIVE OBSERVATIONAL STUDY"

Dissertation submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

In partial fulfilment of the regulations

for the award of the degree of

M.D.BRANCH -I

(GENERAL MEDICINE)

Register number - 201911066

DEPARTMENT OF GENERAL MEDICINE GOVERNMENT STANLEY MEDICAL COLLEGE CHENNAI

MAY 2022

CERTIFICATE

This is to certify that this dissertation entitled **"ASSESSMENT OF PULMONARY FUNCTION IN POST COVID PATIENTS IN A TERTIARY CARE INSTITUTION A PROSPECTIVE OBSERVATIONAL STUDY"** submitted by Dr.T.Mohanavel to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D Degree Branch-I (General Medicine) is a bonafide research work carried out by her under direct supervision and guidance.

GUIDE

Prof.Dr.ROHINI.M.D.,

Unit Chief,

Department of General Medicine,

Stanley Medical College & Hospital,

Chennai.

HOD

Prof. Dr.S.CHANDRASEKAR. M.D

Head of the Department,

Department of General Medicine,

Stanley Medical College & Hospital,

Chennai.

Prof.P.BALAJI M.S.,FRCS.,Ph.D.,FCLS.,

Dean,

Government Stanley Medical College and Hospital,
Chennai.

DECLARATION

I solemnly declare that the dissertation titled **"ASSESSMENT OF PULMONARY FUNCTION IN POST COVID PATIENTS IN A TERTIARY CARE INSTITUTION A PROSPECTIVE OBSERVATIONAL STUDY"** is a bonafide work done by me at Government Stanley Hospital, Chennai between November- 2020 and April - 2021 under the guidance and supervision of Prof.I.Rohini.M.D. I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other university, board either in India or abroad. This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, towards the partial fulfilment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

Dr.T.Mohanavel

Post Graduate student

M.D General Medicine

Government Stanley Medical College

Register number : 201911066

Chennai

Place :chennai

Date

CERTIFICATE – II

This is to certify that this dissertation work titled **"ASSESSMENT OF PULMONARY FUNCTION IN POST COVID PATIENTS IN A TERTIARY CARE INSTITUTION A PROSPECTIVE OBSERVATIONAL STUDY"** the candidate Dr.T.Mohanavel. with Registration Number 201911066 for the award of M.D. DEGREE in the branch of BRANCH-I (GENERAL MEDICINE). I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains, from introduction to conclusion pages and result, shows One percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

SPECIAL ACKNOWLEDGEMENT

I gratefully acknowledge and thank

Prof.**P.BALAJI M.S.,FRCS.,Ph.D.,FCLS.,**

Dean

Government Stanley Medical College and Hospital,

Chennai

For granting me permission to utilize the resources

of this Institution for my study.

ACKNOWLEDGEMENT

"Gratitude is the fairest blossom which springs from the soul"-Henry Ward Beecher

I would like to express my humble gratitude to The Head of the Department **Prof.Chandrasekar M.D.,** sir for guiding and accepting the study.

My sincere thanks to my guide **Prof.I.Rohini.M.D.,** madam, Chief of Medicine for her vital guidance and support for the successful completion of my dissertation.

My sincere thanks to my co guide **Dr. V.Vinodkumar.** sir, Chief of Thoracic Medicine for his vital guidance and support for the successful completion of my dissertation.

My special thanks to my beloved unit Assistant professors **Dr.G.Vijayalakshmi M.D and Dr.B.Uma maheshwari M.D** and and all the faculty of the Department of Medicine for their valuable support throughout the study.

My sincere gratitude to the patients and their attenders for the cooperation aiding in the successful conduct of my study.

Most importantly I am ever so grateful to God and my family for guiding me in all my endeavours and always being my greatest pillar of support. A special thanks to my friends for all their help.

ETHICAL COMMITTEE CERTIFICATE

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

TITLE OF THE WORK	:	"ASSESMENT OF PULMONARY FUNCTION IN POST COVID PATIENTS IN A TERTIARY CARE - A PROSPECTIVE OBSERVATIONAL STUDY"
PRINCIPAL INVESTIGATOR	:	DR. T. MOHANAVEL
DESIGNATION	:	PG IN GENERAL MEDICINE
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

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

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

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

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

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

PLAGIARISM CERTIFICATE

Curiginal

Document Information

Analyzed document	Assessment of Pulmonary Function in Post covid patients in a Tertiary care Institutions A Prospective observational study.docx (D124405171)
Submitted	2022-01-10T06:16:00.0000000
Submitted by	Mohanavel T
Submitter email	vel.mohanavel@gmail.com
Similarity	5%
Analysis address	vel.mohanavel.mgrmu@analysis.urkund.com

Sources included in the report

W	URL: https://www.covid19treatmentguidelines.nih.gov/overview/overview-of-covid-19/ Fetched: 2021-07-26T14:39:11.9070000	3
SA	**Veena Shriram Draft Thesis.pdf** Document Veena Shriram Draft Thesis.pdf (D123798453)	8
SA	**Tamil Nadu Dr. M.G.R. Medical University / deesertation final.docx** Document deesertation final.docx (D31073784) Submitted by: amuthamozhi.p@gmail.com Receiver: amuthamozhi.p.mgrmu@analysis.urkund.com	3

ABBREVATIONS

Ro	Reproduction Number
SARS COVID 19	Severe acute respiratory syndrome covid virus disease
MODS	Multiorgan dysfunction syndrome
CBC	Complete blood count
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
PEFR	Peak Expiratory Flow Rate
CT	Computed Tomography
PFT	Pulmonary Function Test
MERS-CoV	Middle East Respiratory Symptoms corona virus.
DLCO	Diffussing capacity of Lung for Carbon Monoxide
RNA	Ribonucleic acid
RT PCR	RealTime Reverse Transcription Polymerase Chain Reaction
ARDS	Acute Respiratory Distress Syndrome

PEEP	Positive end-expiratory pressure
CPAP	Continuous Positive Airway Pressure
NRM	Non Rebreathing Mask
HFNO	High Flow Nasal Oxygen
MV	mechanical Ventilation
NIV	Non Invasive Ventilation
CORADS	coronavirus disease 2019 Reporting and Data System
DM	Diabetes Mellitus
SHT	Systemic Hypertension
ACE	Angiotensin Converting Enzyme
AKI	Acute Kindney Injury
IL	Interleukin
PPE	Personal Protective Equipment
FiO2	Fraction of inspired oxygen

TABLE OF CONTENTS

INTRODUCTION

As of mid-February 2021, the coronavirus disease 2019 (COVID-19) has been identified in 192 countries/regions world-wide with over 110 million known cases and over 2.4 million global deaths . Many patients have recovered from the initial illness but have had significant morbidity for many months following the infection with ongoing symptoms including fatigue, insomnia, muscle weakness, and dyspnea . Of greater concern is long term lung damage caused by infection with COVID-19

COVID-19 due to SARS-CoV-2 involves multiple organs and lung injury is one of the most common clinical manifestation. Persistent impairment of pulmonary function and exercise capacity have been known to last for months or even years in the recovered survivors from other coronavirus pneumonia like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome

This raised the concerns regarding the assessment of Pulmonary Function in discharged patients who are clinically recovered from Covid-19 is important to anticipate the sequelae of lung injury A recent report portrayed that discharged patients with COVID-19 pneumonia still have residual abnormalities in chest computed tomography (CT) scans, with ground-glass opacity as the most common pattern so complete recovery from severe COVID-19 disease is not proven yet(1)

PFTs are non-invasive tests that are commonly performed in routine assessment and follow-up of patients in the pulmonology units The recommendation of conducting pulmonary function tests (PFTs) from different societies after covid 19 pandemic was rated by the experts of the Turkish Thoracic Society (TTS) and presented as the TTS experts consensus report(2)

Recent studies reveal that the lung is the organ most commonly affected by Coronavirus with pathologies that includes pulmonary consolidation ,diffuse alveolar epithelium destruction, capillary damage or bleeding, hyaline membrane formation and alveolar septal fibrous proliferation[1] Many studies have demonstrated that recovered patients with coronavirus pneumonia can be left with damaged lungs. Impaired lung function was common and could last for months or even years. In the follow-up studies lasting 0.5–2 years in rehabilitating SARS patients impaired DLCO was the most common abnormality[2]. So Pulmonary function tests including Peak Expiratory Flow rate should be considered in routine clinical follow-up for certain recovered survivors, especially in moderate and severe cases. Subsequent pulmonary rehabilitation might be considered as an optional strategy. Long-term studies are needed to address whether these deficits are persistent.

AIM AND OBJECTIVES OF THE STUDY

AIM OF THE STUDY:

To Assess the Pulmonary Function in Clinically Recovered patients affected by COVID-19

OBJECTIVES OF THE STUDY:

To assess the Pulmonary function with Spirometry and Peak Flow meter in routine clinical follow-up for recovered survivors of covid 19

To determine the association between impairment of pulmonary function and severity in COVID-19 patients

REVIEW OF LITERATURE

INTRODUCTION

The current outbreak of the novel coronavirus SARS-CoV-2 (coronavirus disease 2019; previously 2019-nCoV), epi-centred in Hubei Province of the People's Republic of China, has spread to many other countries. On 30. January 2020, the WHO Emergency Committee declared a global health emergency based on growing case notification rates at Chinese and international locations. The case detection rate is changing daily and can be tracked in almost real time on the website provided by Johns Hopkins University 1 and other forums. As of midst of February 2020, China bears the large burden of morbidity and mortality, whereas the incidence in other Asian countries, in Europe and North America remains low so far.

WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020. WHO classified the disease as a pandemic on March 11, 2020.

EPIEMIOLOGY

Five of seven human coronavirus was isolated in this century. Unfortunately, last three of them entered our life with a fear of outbreak, pandemic or death. Last human coronavirus which emerged world from Wuhan China, SARS CoV-2 and its clinical expression, Coronavirus disease (COVID-19) recently taken a significantplace in our daily practice. Initial reports showed that, its origin was bats.

.

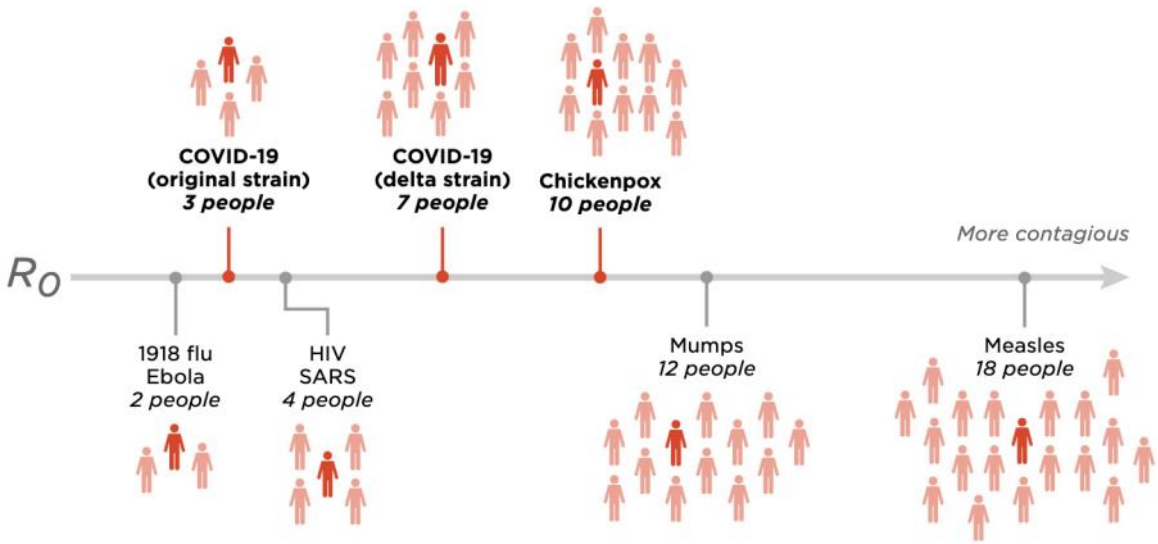


Figure 1 R0 of various communicable disease

It transmitted human to human by droplet and contact routes, but some doubt about airborne, fecal or intrauterine transmission also should be removed Its R0 value is 2.3 but it could be as high as 5.7. Its case fatality rate was 6.3, but it was different in different ages and counties, and it could be over 15%. According to early models total 10-12 weeks is required to control an outbreak in the community

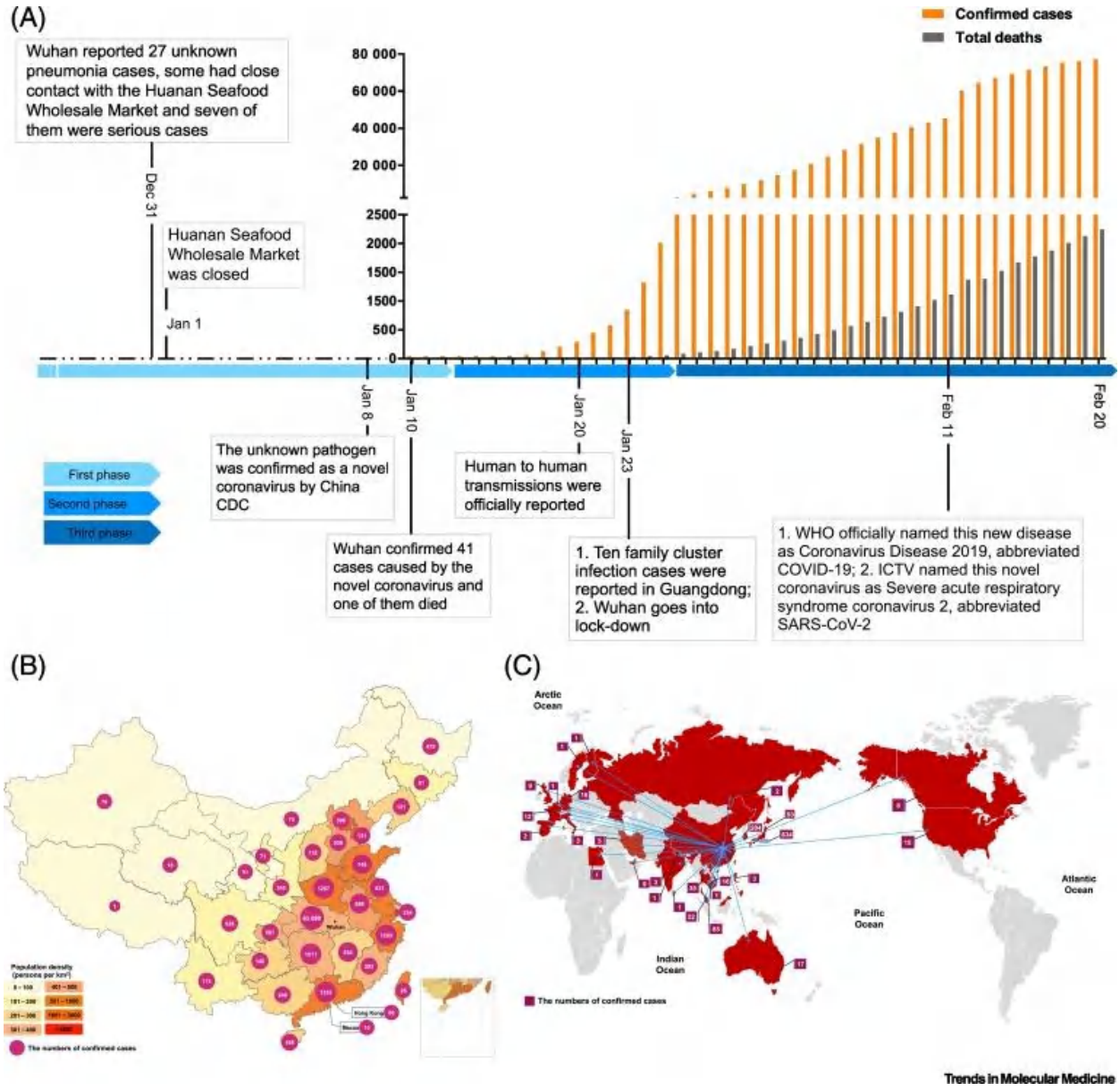


Figure 2 Epidemiology of covid 19

Infectivity ~31–43% attack rate of family members (As per initial data from china) Basic reproduction number (R0): ~ 2–4 (Varies depending on the ability of the virus to be transmitted) . Efforts to prevent the spread of infection (e.g., social distancing, quarantine) decrease the R0, i.e., "flatten the curve" of the number of new cases. Although the total number of cases may not decrease, such actions distribute the number of new cases over a longer period of time, which allows health care facilities (HCFs) to better cope and not become overwhelmed.

It also provides more time to determine if there are effective antiviral treatments and to develop a potential vaccine. Men and women are equally affected. The median age of patients is ~ 47 years Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases of COVID-19 that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.[2] The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of those who were hospitalized was 6 times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, liver disease (especially in patients with cirrhosis), obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19 (3)

VIROLOGY

SARS-CoV-2 is a potentially lethal type of coronavirus, a subfamily of enveloped non-segmented positive-sense RNA viruses that usually cause mild respiratory tract infections.

• Order: NIDOVIRALES

• Family: CORONAVIRIDAE – Belongs to Baltimore class IV (positive sense ssRNA viruses)

- Genus: 4 types (a coronavirus, b coronavirus, g coronavirus, d coronavirus) – 7 coronaviruses cause disease in humans – called as HCoV. All HCoV's belong to a coronavirus and b coronavirus genus. g coronavirus and d coronavirus DO NOT cause disease in humans. High risk groups: Children, elderly and immunocompromised.
- a coronavirus: Have worldwide distribution. Can cause common cold, LRTI (PNA/Bronchiolotis/acute exacerbation of COPD) & GI symptoms (Nausea/Vomiting/diarrhea). HCoV 229E – discovered in the 1960's. Most likely to infect immunocompromised and can cause severe LRTI (e.g., viral pneumonia) HCoV NL63 – Discovered in a lab in 2003 (Netherlands). Second most common CoV that infects humans. Infection can cause croup in susceptible children.
- b coronavirus:
- Lineage A: Worldwide distribution. Can cause common cold, LRTI & GI symptoms as above. HCoV OC43 (most common strain). Discovered in 1967 – in a lab in Maryland, USA. Most severe disease among all HCoV strains.

- Most common Due to its frequent detection in view of clinically significant symptoms/signs. HCoV HKU1 - Discovered in 2005 – in a lab in Hongkong. Associated with febrile seizures.
- Lineage B: SARS-CoV: Discovered in 2002/2003 in Guangdon province in China and expelled from humans in July 2003. Possible origin/transmission by Bat Civet/racoon dogs Humans. Its Clinical features are Fever, Cough, chills, myalgias and ARDS (called as SARS – Severe acute respiratory syndrome). Had a basic R0 of 0.7 – 3. > 8000 cases with 774 deaths & a fatality rate of ~ 9.6%.
- SARS CoV2 (COVID19) – Discovered in late 2019 in Hubei, China. First cases - Dec 16. 2019.

  1. WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020.

  2. WHO classified the disease as a pandemic on March 11, 2020.

  3. Probable origin/transmission: Bats →Pangolin → Humans (? Huanan seafood market – a live animal and seafood market). Shares 96.2 % sequence homology with bat coronavirus (RatG13).

  4. Interestingly, majority can be asymptomatic (unlike the 2003 SARS-CoV).

  5. Basic R0 ~ 2-4 (average: 2.2) and mortality rate ~ 0.5 – 3%.

  6. Epidemic doubles every 7 days in susceptible areas.

  7. SARS-CoV-2 shares 79.5% identity to the SARS-CoV genome.

  8. A population genetic analysis conducted in January 2020 concluded there are two prevalent genotypes of SARS-CoV-2, an L-type (~ 70%) and an S-type (~ 30%), with very minor differences.

It is suggested that S-type was the original type transmitted to humans from the animal host and is less contagious and aggressive. L-type (more prevalent - limited studies – need further research) evolved from the S-type and is somewhat more contagious and aggressive.

9. However, the WHO does not believe the genetic diversity observed in the study means that virus activity is changing. 10. In April 2020, some researchers proposed that mutations of the viral genome of SARS-CoV-2 have led to hundreds of different viral strain

Structure

- Coronaviruses contain structural proteins which
- S- Spike protein (has a receptor binding domain [RBD] that binds to ACE2 receptor)
- E- Envelope protein
- M – Matrix protein
- HE – Hemagglutinin – esterase (introduced to group 2 coronavirus genome by influenza C)
- N – Nucleocapsid

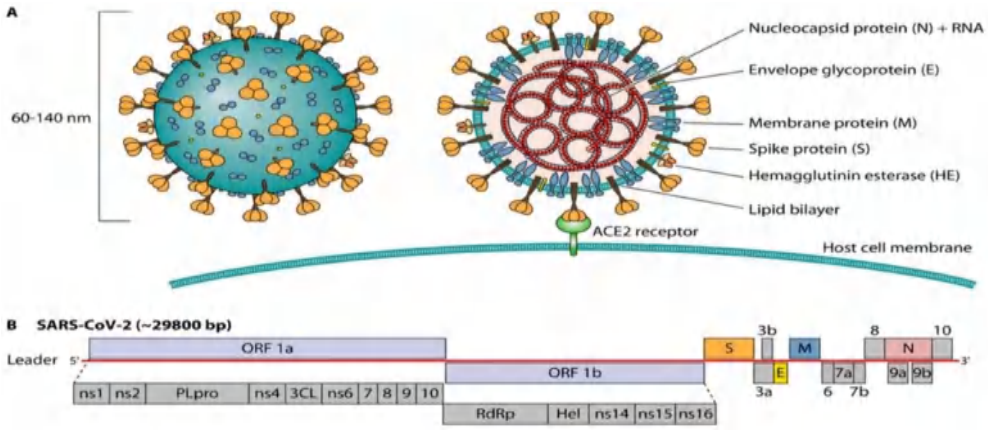


Figure 3 SARS COVID STRUCTURE & GENOME

SARS COVID GENOME

The genome of SARS-CoV-2 is a single-stranded positive-sense RNA of 30kb (29891 nucleotides) encoding 9860 amino acids. The G + C content is 38%. There are 12 functional open reading frames (ORFs) along with a set of nine subgenomic mRNAs carrying a conserved leader sequence, nine transcription-regulatory sequences, and 2 terminal untranslated regions. The genome of this virus lacks the haemagglutinin-esterase gene (since introduced by Influenza C), which is characteristically found in lineage A βCoV. Two-thirds of viral RNA, mainly located in the first ORF translates two polyproteins, pp1a and pp1ab, and encodes 16 non structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins. The 16 non-structural proteins include two viral cysteine proteases [NSP3 (papain-like protease) and NSP5 (main protease)], NSP12 (RNA-dependent RNA polymerase, NSP13 (helicase), and other NSPs which are likely involved in the transcription and replication of the virus q The rest part of the viral genome codes for four structural proteins S, E,M, and N along with a number of accessory proteins that interfere with the host immune response. However, mutations are observed in NSP2 and NSP3 and the spike protein, that play a significant role in infectious capability and differentiation mechanism of SARS-CoV-2

PATHOPHYSIOLOGY

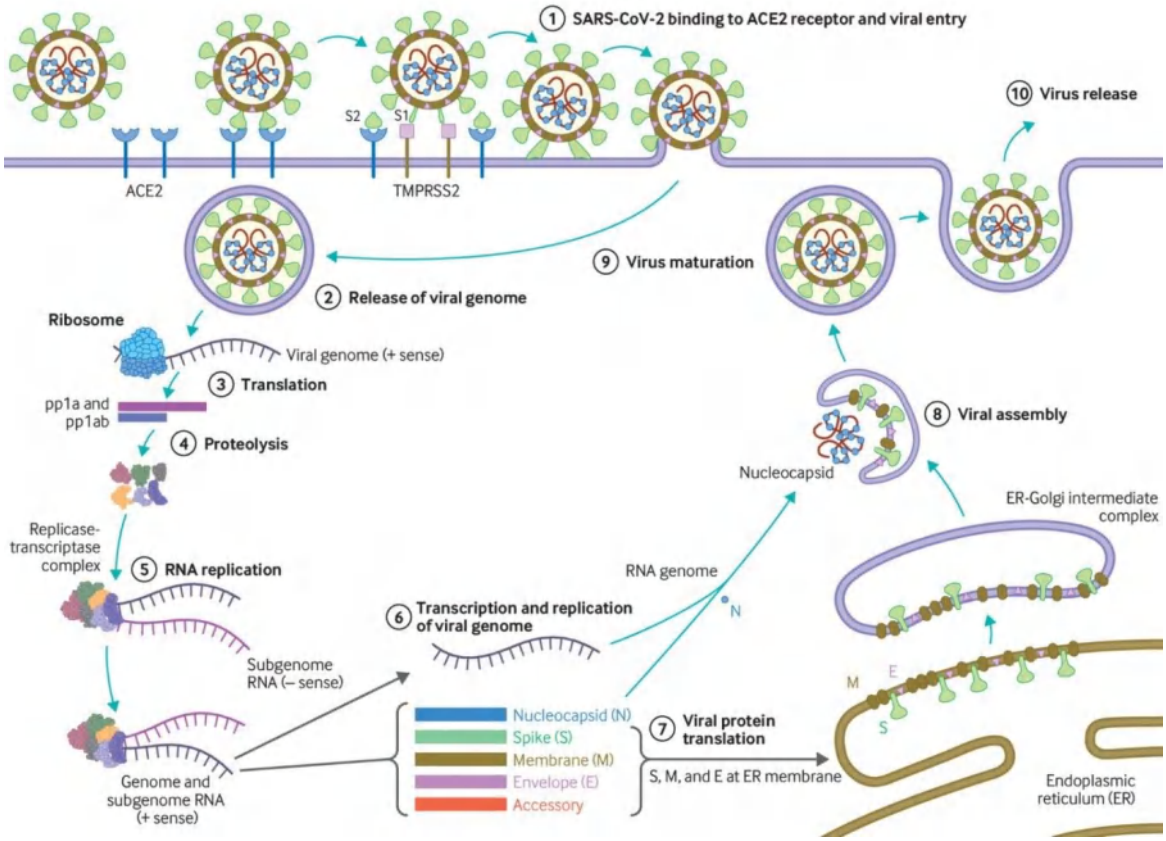


Figure 4 Pathophysiology of virus entry

1. The spike protein is a homotrimer, each trimer consists of

   2 different subunits (S1 and S2). The zoom box shows that S2 is located at the basis and S1 at the top. S1 binds to the membrane protein ACE2 on host cells.

   2. S1 subunit undergoes a hinge-like conformational change to ex pose the receptor-binding domain (RBD) and binds to ACE2.

   3. Activation of spike protein (S protein priming): The membrane protein TMPRSS2 acts as a protease. S protein cleavage at the S1/S2 cleaving site leads to cleavage of S1 (including the RBD). By cleaving the S2'-cleavage site, the fusion peptide of the S2 subunit is exposed.

   4. The fusion peptide of the S2 sub-unit is inserted in the host cell membrane.

5. Membrane fusion: Conformation change of the S2 subunit (folds together to the side, not depicted here). This causes fusion of the viral and the host cell membrane. Un coating of the viral RNA takes place.

Dysregulated immune response Activation of the immune system, which involves the release of cytokines (e.g., tumour necrosis factor, IL-1β, IL-6), can cause an acute inflammatory response. An overshooting immune response through very high levels of cytokines ("cytokine storm") can lead to organ failure and death. While some of these mechanisms are similar to those that occur in sepsis, COVID-19 usually does not lead to hypotension, which is a defining feature of septic shock.

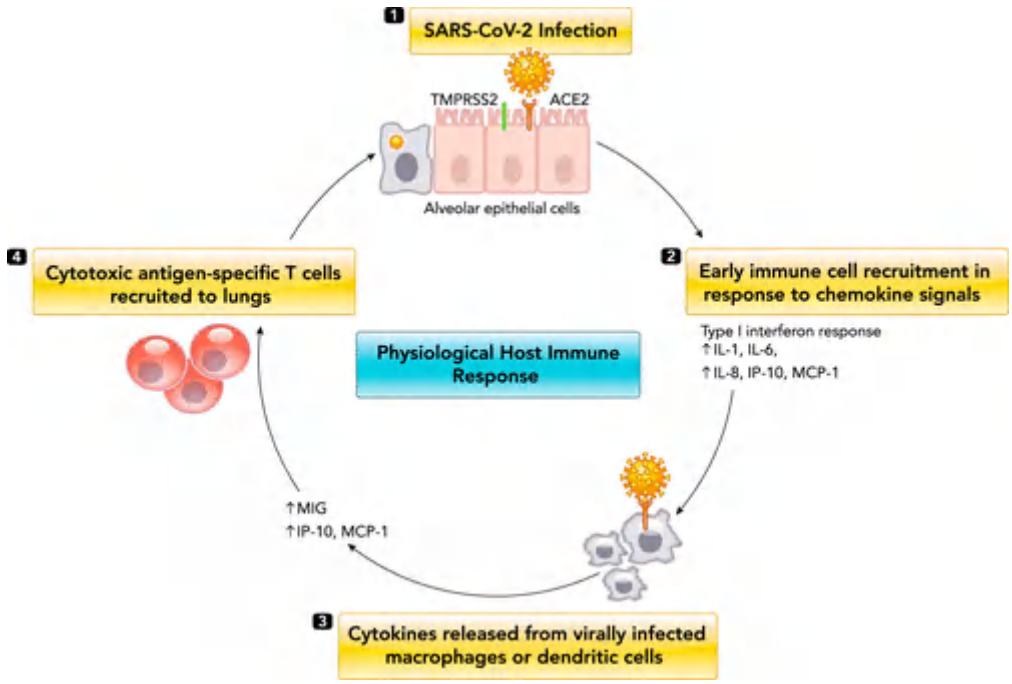


Figure 5 Host immune respone to covid

Autopsy findings in China and European countries showed endothelial damage of pulmonary vasculature, microvascular thrombosis and hemorrhage linked to extensive alveolar and interstitial inflammation that ultimately result in COVID-19 vasculopathy, pulmonary intravascular coagulopathy, hypercoagulability,

ventilation perfusion mismatch, and refractory ARDS. Hypoxemia, secondary to ARDS may also activate the coagulation cascade

TRANSMISSION

- **Respiratory transmission** is the dominant mode of transmission, with proximity and ventilation being the key determinants of transmission risk. Available evidence suggests that transmission between people occurs primarily through direct, indirect, or close contact with infected people through infected secretions such as saliva and respiratory secretions, or through their respiratory droplets, which are expelled when an infected person coughs, sneezes, talks, or sings.
- **Airborne transmission** can occur in healthcare settings during aerosol-generating procedures. There are also some outbreak reports that suggest aerosol transmission is possible in the community under certain conditions; however, these reports relate to enclosed indoor crowded spaces with poor ventilation where the infected person may have been breathing heavily (e.g., restaurants, choir practice, fitness classes). A detailed investigation of these clusters suggests that droplet and fomite transmission could also explain the transmission in these reports. While the air close to, and distant from, patients has been found to frequently be contaminated with SARS-CoV-2 RNA, few of these samples contained viable virus. The risk of transmission is much lower outdoors compared with indoors, with a limited number of studies estimating a transmission rate of <1%. Evidence that nebuliser treatments increase the risk of transmission of coronaviruses similar to SARS-CoV-2 is inconclusive, and there is minimal direct evidence about the risk for transmission of SARS-CoV-2.(4)

- **Fomite transmission** (from direct contact with fomites) may be possible, but there is currently no conclusive evidence for this mode of transmission. In the few cases where fomite transmission has been presumed, respiratory transmission has not been completely excluded.While the majority of studies report identification of the virus on inanimate surfaces, there is a lack of evidence to demonstrate recovery of viable virus.
- **Faecal-oral transmission** (or respiratory transmission through aerosolised faeces) may be possible, but there is only limited circumstantial evidence to support this mode of transmission. The pooled detection rate of faecal SARS-CoV-2 RNA in patients with COVID-19 is approximately 51%, with 64% of samples remaining positive for a mean of 12.5 days (up to 33 days maximum) after respiratory samples became negative.
- **Transmission via other body fluids** (including sexual transmission or bloodborne transmission) has not been reported.[48] While the virus has been detected in blood, cerebrospinal fluid, pericardial fluid, pleural fluid, urine, semen, saliva, ocular tissue including the cornea, tears, and conjunctival secretions, as well as in the middle ear and mastoid, the presence of virus or viral components does not equate with infectivity.(5) While SARS-CoV-2 is not sexually transmitted, it may have an effect on male fertility, although this is yet to be confirmed.
- **Vertical transmission** occurs rarely and transplacental transmission has been documented. There is limited evidence on the extent of vertical transmission and its timing.(6) Overall, 6.3% of infants born to mothers with COVID-19 tested positive for SARS-CoV-2 at birth. Transmission was reported in both preterm and full-term infants. There is also evidence for antibodies against SARS-CoV-2 among infants

born to mothers with COVID-19 who tested negative for SARS-CoV-2. The rate of infection appears to be no greater when the baby is born vaginally, breastfed, or allowed contact with the mother. Viral fragments have been detected in breast milk; however, this finding is uncommon and, when it occurs, has been associated with mild symptoms in infants. Anti-SARS-CoV-2 antibodies are more prevalent in breast milk compared with viral fragments.Vertical transmission is unlikely to occur if correct hygiene precautions are taken.

- **Nosocomial transmission** was reported in 44% of patients in one systematic review; however, this review was limited to case series conducted early in the outbreak in Wuhan before the institution of appropriate infection prevention and control measures. Hospital-acquired infections accounted for approximately 11.3% of infections in the UK between February and August 2020. This peaked at 15.8% in the middle of May. Rates as high as 25% were reported in some areas in October 2020. Rates were notably higher in residential community care hospitals (61.9%) and mental health hospitals (67.5%) compared with acute and general care hospitals (9.7%).Studies of healthcare workers exposed to index cases (not in the presence of aerosol-generating procedures) found little to no nosocomial transmission when contact and droplet precautions were used.(5)

Incubation period: 2–14 days, usually ~ 5 days

COVID-19 can occur if a person touches a surface contaminated with SARS-CoV-2, and then the hands come into direct contact with mucous membranes such as the eyes, nose, or mouth. Thus, sufficient washing of hands with soap and water or hand sanitizers is recommended.

The reported contagion rates from a patient with symptomatic infection vary by location and efficiency of infection control measures. Based on a joint WHO-China report, the rate of secondary COVID-19 infection ranged from one to five percent among tens of thousands of confirmed patients in China(5)

Clinical Features

Often asymptomatic

• Assumed to be more likely in children

• This makes it especially difficult to identify infected individuals for quarantine and facilitates the spread of the virus via stealth transmission.

Symptomatic cases

Most common

• Fever (often not initially!) • Fatigue • Dry cough

Common

• Shortness of breath: an early indicator of rapid deterioration developing

• Loss of smell (sometimes the only symptom!) and/or taste

• Loss of appetite • Myalgia

Less Common

• Diarrhea and abdominal pain: sometimes a presenting symptom and, rarely, the only one

• Sputum production, rhinitis, sore throat, headache, conjunctivitis

• Coagulopathy: Thromboembolic events (e.g., pulmonary embolisms) might be the cause of death in many fatal COVID 19 cases (based on autopsy studies)

• Cardiomyopathy due to COVID19 myocarditis has been described as well

• Multisystem inflammatory syndrome in children (MIS-C), which manifests with similar features to Kawasaki disease or toxic shock syndrome, has been described in children in the context of active and previous infections with SARS-CoV-2.

• Purplish, blue discoloration of the toes (COVID toes) and/or fingers. Also called as pernio-like lesions, pseudo-chill & acute acro-ischemia. More common in children with COVID. blain Mechanism is controversial – some studies suggest endothelial damage vs cytopathic effect as the mechanism behind it whereas some studies suggest that it is completely unrelated to virus !! Surprisingly observed more in European countries than Asian countries.

The classic triad of fever, cough, and dyspnea is only present in ~ 15%.

Course: The disease has a wide spectrum of severity, ranging from mild to critical. It typically starts with mild symptoms that can progress to more severe courses after about 5–7 days.

Mild (~ 80%) Uncomplicated course without dyspnea Lasts 1–2 weeks Severe (~ 15%) Develops ~ 5–7 days after symptom onset Indicates the disease has progressed to pneumonia Signs include dyspnea and hypoxia Lasts 3–6 weeks Critical disease (~ 5%) Signs of severe pneumonia (respiratory failure), acute respiratory distress syndrome (ARDS), coagulopathy, shock, and possibly multiple organ dysfunction syndrome(MODS)

Lasts 3–6 weeks Major risk factors for severe disease are: Age more than 60 years (increasing with age). Underlying non-communicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebro-vascular disease, chronic kidney disease, immune-suppression and cancer

COVID-19 Symptoms at a glance box

Symptoms*	Asymptomatic	Mild	Moderate	Severe
• Fever	✕	+	++	+++
• Cough	✕	+	+	++
• Sore Throat/Throat irritation	✕	+	+/-	+/-
• Body ache/ Headache	✕	+	+	++
• Malaise/Weakness	✕	+	+	++
• Diarrhoea or gastro-intestinal upset	✕	+	+	+
• Anorexia/ Nausea/ Vomiting	✕	+/-	+/-	+/-
• Loss of Smell and/or Taste	✕	+/-	+/-	+/-
• Shortness of breath/breathlessness	✕	✕	++	+++
• Respiratory rate/min	12-16	May be raised but less than 24	24-30	≥ 30/min
• SpO_2 on room air	≥95%	≥ 94%	90%-93%	< 90%

TABLE 1 COVID 19 SYMPTOMS

COVID-19 symptoms in children – at a glance

Common symptoms		
Fever	Sore throat/throat irritation	Diarrhoea
Cough	Body ache/headache	Anorexia/nausea/vomiting
Rhinorrhoea	Malaise/weakness	Loss of sense of smell and/or taste

Differentiating symptoms/signs	Asymptomatic	Mild	Moderate	Severe
Respiratory rate/min	**Normal** with age dependent variation	**Normal** with age dependent variation	**Rapid respiration** (age based) <2 months ≥60/min 2-12 months ≥50/min 1-5 years ≥40/min >5 years ≥30/min	**Rapid respiration** (age based) <2 months ≥60/min 2-12 months ≥50/min 1-5 years ≥40/min >5 years ≥30/min
SpO_2 on room air	≥94%	≥94%	≥90%	<90%
Grunting, severe retraction of chest	✕	✕	✕	+/-
Lethargy, somnolence	✕	✕	✕	+/-
Seizure	✕	✕	✕	+/-

TABLE 2 COVID 19 SYMPTOMS IN CHILDREN

DIFFERENTIAL DIAGNOSIS

Features	COVID19	Influenza	Common cold	Allergic rhinitis
Fever	+++	+++	-	-
Cough	+++	+++	+++	++
Fatigue	+++	+++	+	-
SOB	++	-	-	-
Loss of appetite	++	++	-	-
Myalgia	++	+++	+	-
Anosmia/Ageusia	++	-	++	++
Runny nose	+	+	+++	+++
Sneezing	-	-	+++	+++
Sore throat	+	+	+++	-
Diarrhea	+	+	-	-
Headache	-	+++	++	-
Itchy eyes	-	-	-	+++

TABLE 3 COVID 19 DIFFERENTIAL DIAGNOSIS

RESPIRATORY SYSTEM INVOLVEMENT IN COVID

The most frequent, serious manifestation of COVID-19 infection seems to be pneumonia, which is characterized by cough, fever, dyspnea and bilateral infiltrates displayed on radiographic chest imaging. Unfortunately, there are no specific clinical features that discern COVID-19 from other viral respiratory illnesses. Although most patients will only experience mild symptoms of the disease, some patients will experience rapid progression of their symptoms over the span of a week (Table 3). One study found that 17% of their patients developed Acute Respiratory Distress Syndrome (ARDS) and among these, 65% rapidly worsened and died from multiple organ failure. In a study focusing on the associated risk factors, it was reported that ARDS was greatly associated with older age (>65 years old), diabetes mellitus, and hypertension.

For most cases, bilateral lower zone consolidation (identified through chest x-ray) peaked at 10-12 days from symptom onset.

Clinical severity and assessment parameters

Clinical Severity	Clinical presentation	Clinical parameters	Remarks
Mild	Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache	Without evidence of breathlessness or Hypoxia (normal saturation).	(i) Managed at Covid Care Centre (ii) Managed at home subject to fulfilment of conditions stipulated in guidelines[2]

Acute Respiratory Distress Syndrome

Onset: new or worsening respiratory symptoms within one week of known clinical insult.

Chest imaging (Chest X ray and portable bed side lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. Origin of Pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/ oedema if no risk factor present

Moderate	Pneumonia with no signs of severe disease	**Adolescent or adult** with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute. **Child** with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40	Managed in Dedicated Covid Health Centre (DCHC)
Severe	Severe Pneumonia	**Adolescent or adult**: with clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% on room air. **Child** with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 <90%; severe respiratory distress (e.g. grunting, chest in- drawing); signs of pneumonia with any of the following danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest in drawing, fast breathing (in breaths/min): <2 months ≥60; 2–11 months ≥50; 1–5 years ≥40. The diagnosis is clinical; chest imaging can exclude complications.	Managed in Dedicated Covid Hospital

TABLE 4 COVID 19 SEVEREITY CATEGORY

.

Oxygenation impairment in adults: Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H2O) Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg with PEEP ≥5 cm H2O) Severe ARDS: PaO2/FiO2 ≤ 100 mmHg with PEEP ≥5 cm H2O) When PaO2 is not available, SpO2/FiO2 ≤315 suggests ARDS (including in non- ventilated patients) Oxygenation impairment in Children Note Oxygenation Index (OI) and OSI (Oxygen Saturation Index) Use OI when available.

If PaO2 not available, wean FiO2 to maintain SpO2 < 8 or 5 ≤ OSI < 7.5 Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3

Sepsis

Adults: Acute life-threatening organ dysfunction caused by a dys-regulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia.

Children: suspected or proven infection and ≥2 age based Systemic Inflammatory Response Syndrome (SIRS) criteria, of which one must be abnormal temperature or white blood cell count Septic Shock Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level > 2 mmol/L Children: any hypotension (SBP 2 SD below Page | 8 normal for age) or 2- 3 of the following: altered mental state; bradycardia or tachycardia (HR 160 bpm in infants and HR 150 bpm in children); prolonged capillary refill (>2 sec) or

weak pulse; tachypnea; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output ; hyperthermia or hypothermia(7)

Cardiovascular Involvement of COVID-19

COVID-19 and Pre-Existing Cardiovascular Disease

Patients with existing cardiovascular disease (CVD) are at a greater risk of suffering from severe COVID-19 and having poorer prognosis. A meta-analysis comprising of 46,248 patients with confirmed COVID-19 found that the most common co-morbidities were hypertension (17%), diabetes (8%), and CVD (5%). CVD and hypertension have also been more prevalent in the severe patient group as compared to non-severe cases (odds ratio of 3.42 and 2.36, respectively). Existing CVD is also associated with higher mortality which is summarized in Table 1. On the other hand, it is widely agreed that COVID-19 can also have adverse effects on cardiovascular health itself, causing or aggravating damage to the heart. There are reports of cardiogenic involvement in patients without known CVD[37] as well as cases with solely cardiac presentations.

	Survivors	Nonsurvivors
Coronary heart disease	8%	24%
Hypertension (CVD risk factor)	30%	48%
DM (CVD risk factor)	13.9%	31.4%
Smoking (CVD risk factor)	4.4%	9.3%

CVD, cardiovascular disease; DM, diabetes mellitus.

TABLE 5 Association between CVD and risk of mortality from COVID-19 as reported by Zhou et al(8)

Mechanism of Cardiovascular Involvement

The exact mechanism of cardiovascular involvement in COVID-19 is not yet well understood, however elevated cardiac biomarker levels are commonly seen. In a study by Wang et al, 7.2% of patients had either elevated troponin levels or new electrocardiography or echocardiography abnormalities suggestive of cardiac injury.

ACE2 is highly expressed in the heart, providing opportunity for ACE2-dependent myocardial infection. Cytokine storm from systemic inflammation and the hypoxic state from ARDS inducing excessive extracellular calcium levels leading to myocyte apoptosis are also possible mechanisms of damage Surge in cytokine levels due to hyperinflammatory response or secondary hemophagocytic lymphohistiocytosis and increased myocardial demand in the setting of acute infection can lead to atherosclerotic plaque instability and myocardial injury, increasing the risk of acute myocardial infarction. blood pressure abnormalities can also be seen in response to the illness. Additionally, palpitations due to arrhythmia have been observed. The type of arrhythmias are variable and etiology can be multi-factorial, ranging from hypoxic state due to ARDS to myocarditis. Hu et al and Zeng et al also reported patients with reduced ejection fraction and heart enlargement. Therefore, possible long-term effects of COVID-19 on cardiovascular system such as risk of heart failure should be considered and further investigated.

Renin-Angiotensin-Aldosterone System Inhibitors and COVID-19

Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers on COVID-19 susceptibility and prognosis have been controversial. Some evidence suggests that increasing ACE2 expressions facilitate COVID-19 infection, while others

suggest potential beneficial effects of reducing lung injury.Therefore, changes to their standard indications on the basis of COVID-19 is not currently recommended.

Renal Involvement of COVID-19

Renal Manifestations

Acute kidney injury (AKI) is the abrupt loss of kidney function that develops within 7 days. Its incidence has been observed with SARS and MERS-CoV previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%–90%) mortality rate. Early reports suggested a lower incidence (3%–9%) of AKI in those with COVID-19 infection.

Recent reports, however, have shown higher frequency of renal abnormalities. A study of 59 patients with COVID-19 found that 34% of patients developed massive albuminuria on the first day of admission, and 63% developed proteinuria during their stay in hospital.

Blood urea nitrogen was elevated in 27% overall and in two-thirds of patients who died. Computed tomography scan of the kidneys showed reduced density, suggestive of inflammation and edema. Cheng *et al.*(9)

recently reported that amongst 710 consecutive hospitalized patients with COVID-19, 44% had proteinuria and hematuria and 26.7% had hematuria on admission. The prevalence of elevated serum creatinine and blood urea nitrogen was 15.5% and 14.1%, respectively. AKI was an independent risk factor for patients' in-hospital mortality

Pathogenesis of kidney injury

The exact mechanism of kidney involvement is unclear: postulated mechanisms include sepsis leading to cytokine storm syndrome or direct cellular injury due to the virus. Angiotensin-converting enzyme and dipeptidyl peptidase-4, both expressed on renal

tubular cells, were identified as binding partners for SARS-CoV and MERS-CoV, respectively Viral RNA has been identified in kidney tissue and urine in both infection

Recently, Zhong's lab in Guangzhou successfully isolated SARS-CoV-2 from the urine sample of an infected patient, suggesting the kidney as the target of this novel coronavirus.

Gastrointestinal Involvement of COVID-19

Gastrointestinal Symptoms

A significant number of patients reported GI symptoms such as diarrhea, nausea, vomiting, and abdominal pain, with some reporting these symptoms as their sole presenting complaint.(10) The incidence of GI symptoms, alongside the detection of SARS-CoV-2 RNA in stool samples of infected patients, suggest that ACE2 receptors highly expressed in the GI tract are another target for SARS-CoV-2 infection.

Liver Injury in COVID-19 Patients

Mild and transient liver injury, as well as severe liver damage can occur in COVID-19. Wong et al indicated that 14.8-53.1% of COVID-19 patients had abnormal levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin during the course of the disease, with bilirubin showing the smallest elevation. Furthermore, they reported that severity of liver damage is proportional to that of COVID-19.[32] Gamma-glutamyl transferase was elevated in 54% of patients in 1 cohort study that included 56 COVID-19 patients.(11)

Immune System Response

The immune response is undeniably one of the key determiners of the susceptibility and severity of the disease. While weakened immune system can increase the risk of severe

COVID-19, hyperinflammatory response to the infection can be responsible for the commonly seen complications by causing organ damage.

The surge in inflammatory parameters like IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α can be caused by an imbalanced immune response leading to cytokine storm or secondary hemophagocytic lymphohistiocytosis. Along with typical cardinal features like hyperferritinaemia, cytopenia, and unremitting fever; pulmonary and cardiac involvement including ARDS and acute coronary syndrome can also result from hypercytokinaemia(12)

Moreover, accumulating evidence suggests that this hyperinflammatory state can be predictors of morbidity and mortality in a significant subgroup of patients. In a multicenter retrospective study, it was found that ferritin and IL-6 levels were more elevated in the non-survivor group as compared to the survivors. This is also supported by findings of Qin et al who recently discovered that severe cases had higher neutrophil-lymphocyte ratio, lower percentages of basophils, eosinophils, and monocytes, as well as elevated inflammatory biomarkers and cytokines. Additionally, the number of suppressor and helper T cells, B cells, and NK cells were decreased in the severe group.Septic shock is also reported in 4%-8% of patients in several case series.

Therefore, it is paramount for all patients with severe COVID-19 to be screened for hyperinflammation using ferritin levels, platelet count, and erythrocyte sedimentation rate along with the HScore.(12) Once identified, therapeutic approach is to suppress the immune system. However, it is a difficult decision to determine whether anti-inflammatory effects of treatment outweigh the risk of impairing the immune system that is trying to

fight the infection. In addition to the options of steroids and intravenous immunoglobulins, IL-6 receptor antagonist monoclonal antibodies like tocilizumab and sarilumab, anakinra, Janus kinase inhibitor and CC chemokine receptor 5 antagonists are also in the clinical trial stage for treatment of cytokine release syndrome in COVID-19

Other Organ Involvement

The Nervous System

It has been suggested that viral invasion of the central nervous system by SARS-CoV2 is possible by the synapse-connected route observed with other coronaviruses such as SARS-CoV and can lead to several neurological complications including ataxia, seizures, neuralgia, unconsciousness, acute cerebrovascular disease and encephalopathy.(13) Mao et al reported that 36.4% of their cohort had neurologic manifestations, the severe group being more likely to have acute cerebrovascular disease, impaired consciousness and skeletal muscle injury.Furthermore, Li et al proposed that this potential viral invasion might play a partial role in the pathophysiology of acute respiratory failure in COVID-19 patients.

The Coagulation Cascade

Disseminated intravascular coagulation is another common complication of COVID-19 reported in 71.4% of nonsurvivors compared to only 0.6% of survivors. It has also been found that use of anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin improved outcomes in severe cases with coagulopathy

DIAGNOSIS

INVESTIGATION

Sample collection

Preferred sample Throat and nasal swab in viral transport media (VTM) and transported in cold chain. Alternate Nasopharyngeal swab, BAL or endotracheal aspirate which has to be mixed with the viral transport medium and transported in cold chain.

General guidelines

- Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). Maintain proper infection control when collecting specimens
- Restricted entry to visitors or attendants during sample collection
- Complete the requisition form for each specimen submitted
- Proper disposal of all waste generated Apply airborne precautions when performing an aerosol generating procedure Ensure that healthcare workers performing aerosol-generating procedures (i.e. open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95). (The scheduled fit test should not be confused with user seal check before each use.) Whenever possible, use adequately ventilated single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at least 160 liters/second/patient in facilities with natural ventilation. Avoid the presence of unnecessary individuals in the room. Care for the patient in the same type of room after mechanical ventilation commences. Because of uncertainty around the potential for

aerosolization, highflow nasal oxygen (HFNO), NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. There is insufficient evidence to classify nebulizer therapy as an aerosol-generating procedure that is associated with transmission of COVID-19. More research is needed.

Respiratory specimen collection methods:

A. Lower respiratory tract

- Bronchoalveolar lavage, tracheal aspirate, sputum
- Collect 2-3 mL into a sterile, leak-proof, screw-cap sputum collection cup or sterile dry container.

B. Upper respiratory tract

- Nasopharyngeal swab AND oropharyngeal swab Oropharyngeal swab (e.g. throat swab): Tilt patient's head back 70 degrees. Rub swab over both tonsillar pillars and posterior oropharynx and avoid touching the tongue, teeth, and gums. Use only synthetic fiber swabs with plastic shafts. Do not use calcium alginate swabs or swabs with wooden shafts. Place swabs immediately into sterile tubes containing 2-3 ml of viral transport media. Combined nasal & throat swab: Tilt patient's head back 70 degrees. While gently rotating the swab, insert swab less than one inch into nostril (until resistance is met at turbinates). Rotate the swab several times against nasal wall and repeat in other nostril using the same swab. Place tip of the swab into sterile viral transport media tube and cut off the applicator stick. For throat swab, take a second dry polyester swab, insert into mouth, and swab the posterior pharynx and tonsillar areas (avoid the tongue). Place tip of swab into the same tube and cut off the applicator tip. Nasopharyngeal swab: Tilt patient's head back 70 degrees. Insert flexible swab through the nares parallel to the palate (not upwards) until resistance is encountered or the distance is equivalent to that from the ear to the nostril of

the patient. Gently, rub and roll the swab. Leave the swab in place for several seconds to absorb secretions before removing. Clinicians may also collect lower respiratory tract samples when these are readily available (for example, in mechanically ventilated patients). In hospitalized patients in Dedicated Covid Hospitals (severe cases with confirmed COVID - 19 infection, repeat upper respiratory tract samples should be collected to demonstrate viral clearance.

Recommended Test

Real time or Conventional RT-PCR test is recommended for diagnosis. SARS-CoV-2 antibody tests are not recommended for diagnosis of current infection with COVID-19. Dual infections with other respiratory infections (viral, bacterial and fungal) have been found in COVID-19 patients. Depending on local epidemiology and clinical symptoms, test for other potential etiologies (e.g. Influenza, other respiratory viruses, malaria, dengue fever, typhoid fever) as appropriate. For COVID-19 patients with severe disease, also collect blood cultures, ideally prior to initiation of antimicrobial therapy

PULSE OXIMETRY

Clinicians should be aware that patients with COVID-19 can develop ‘silent hypoxia': their oxygen saturations can drop to low levels and precipitate acute respiratory failure without the presence of obvious symptoms of respiratory distress.

Pulse oximetry may be available as part of remote monitoring in the community. Evidence suggests that patients who may benefit most from monitoring are those who are symptomatic and are either over 65 years of age, or are under 65 years years of age and are extremely clinically vulnerable to COVID-19.

The UK National Institute for Health and Care Excellence recommends using oxygen saturation levels below 94% for adults (or below 88% for adults with known type 2 respiratory failure) and below 91% for children in room air at rest to identify people who are seriously ill Pulse oximeters can be used at home to detect hypoxia. Home pulse oximetry requires clinical support (e.g., regular phone contact from a health professional in a virtual ward setting

CHEST X RAY

Approximately 74% of patients have an abnormal chest x-ray at the time of diagnosis. The most common abnormalities are ground-glass opacity (29%) and consolidation (28%). Distribution is generally bilateral, peripheral, and basal zone predominant. Pneumothorax and pleural effusions are rare. There is no single feature on chest x-ray that is diagnostic for COVID-19.

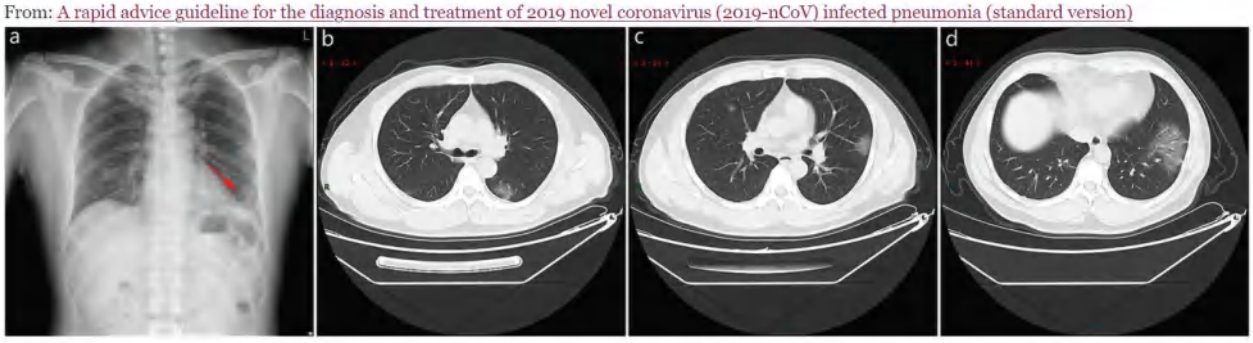
Chest x-ray is moderately sensitive and moderately specific for the diagnosis of COVID-19. Pooled results found that chest x-ray correctly diagnosed COVID-19 in 80.6% of people who had the disease. However, it incorrectly identified COVID-19 in 28.5% of people who did not have the disease.

Although chest x-ray appears to have a lower sensitivity compared with chest CT, it has the advantages of being less resource-intensive, associated with lower radiation doses, easier to repeat sequentially, and portable.

CT CHEST

The imaging features of lesions show: (1) dominant distribution (mainly subpleural, along the bronchial vascular bundles); (2) quantity (often more than three or more lesions, occasional single or double lesions); (3) shape (patchy, large block, nodular, lumpy, honeycomb-like or grid-like, cord-like, etc.); (4) density (mostly uneven, a paving stones-like change mixed with ground glass density and interlobular septal thickening, consolidation and thickened bronchial wall, etc.); and (5) concomitant signs vary (air-bronchogram, rare pleural effusion and mediastinal lymph nodes enlargement, etc.)(14)

From: A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)

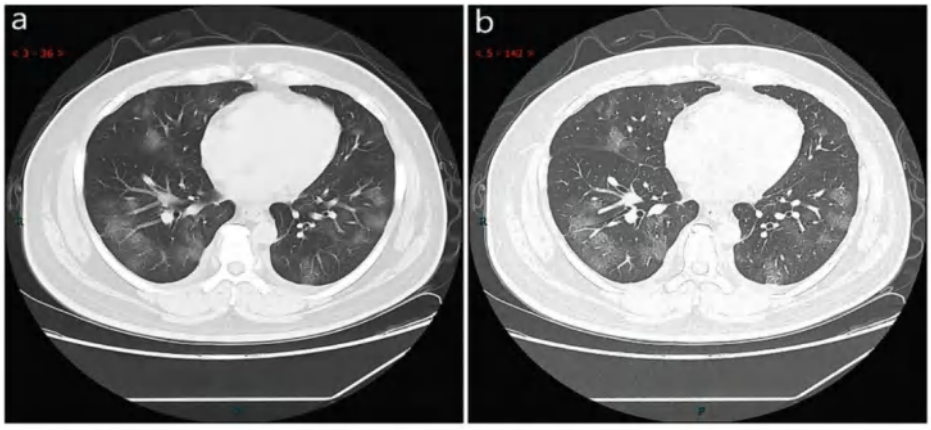


Typical CT / X-ray imaging manifestation (case 2). A 51 years old male with general muscle ache and fatigue for 1 week, fever for 1 day (39.1 °C), anemia. Laboratory test: normal white blood cells (9.24×10^9/L), lymphocytes percentage (5.1%), decreased lymphocytes (0.47×10^9/ L), decreased eosinophil count (0×10^9/L), increased C-reaction protein (170.91 mg/L), increased procalcitonin (0.45 ng/ml), increased erythrocyte sedimentation rate (48 mm/h). Imaging examination: **a** shows patchy shadows in the outer region of the left lower lobe, **b** shows large ground-glass opacity in the left lower lobe, and **c** shows subpleural patchy ground-glass opacity in posterior part of right upper lobe and lower tongue of left upper lobe, **d** shows large ground-glass opacity in the basal segment of the left lower lobe

Figure 6 Radiological findings in COVID 19

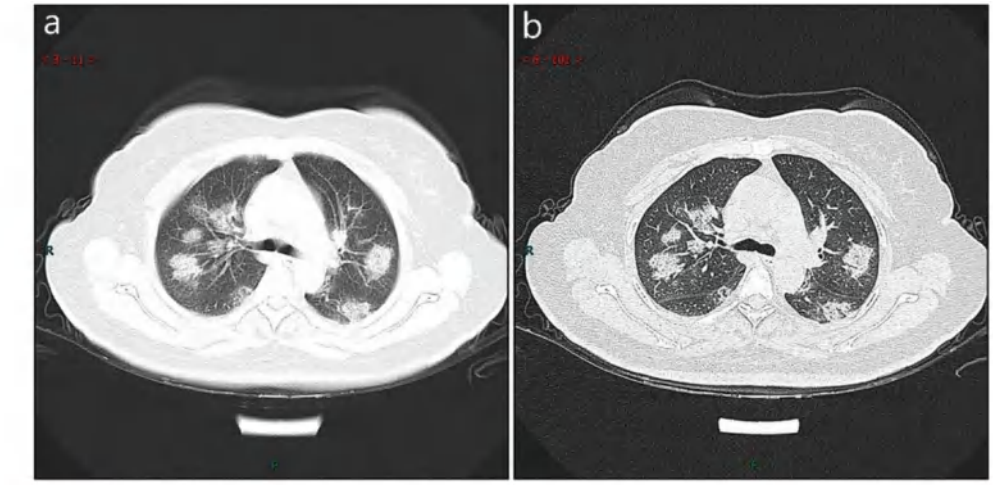
Table 6. Stages of COVID-19 infection based on CT images(14)

Ultra-early	Refers to the stage without clinical manifestations, patients are often asymptomatic, but normally is seen 1-2 weeks after COVID-19 exposure. Main imaging manifestations are single or multifocal GGO, patchy consolidative opacities, pulmonary nodules encircled by GGO and air bronchograms.
Early	Refers to an early symptomatic presentation, 1-3 days after clinical manifestations. This is the most observed stage through radiological imaging (54%). Main imaging manifestations are single or double GGO combined with interlobular septal thickening. Pathological processes during this stage are dilatation and congestion of the alveolar septal capillary, interlobular interstitial edema and exudation of fluid in alveolar cavity.
Rapid progression	Refers to 3-7 days after clinical manifestations, where the pathological features of this stage are accumulation of exudates in the alveolar cavity, vascular expansion and exudation in the interstitium. These pathological features lead to the further aggravation of alveolar and interstitial edema. Fibrous exudation forms bonds between each alveolus through the interstitial space to form a fusion state. Main radiological manifestations are large, light consolidative opacities with air bronchograms.
Consolidation	Refers to the second week after initial symptomatic presentation. Main pathological features are fibrous exudation of the alveolar cavity and the reduction of capillary congestion. CT imaging can show multiple consolidations reducing in size and density, compared to before.
Dissipation	Refers to 2-3 weeks after onset of symptoms. CT imaging can show dispersed, patchy consolidative opacities, reticular opacities, bronchial wall thickening and interlobular septal thickening.



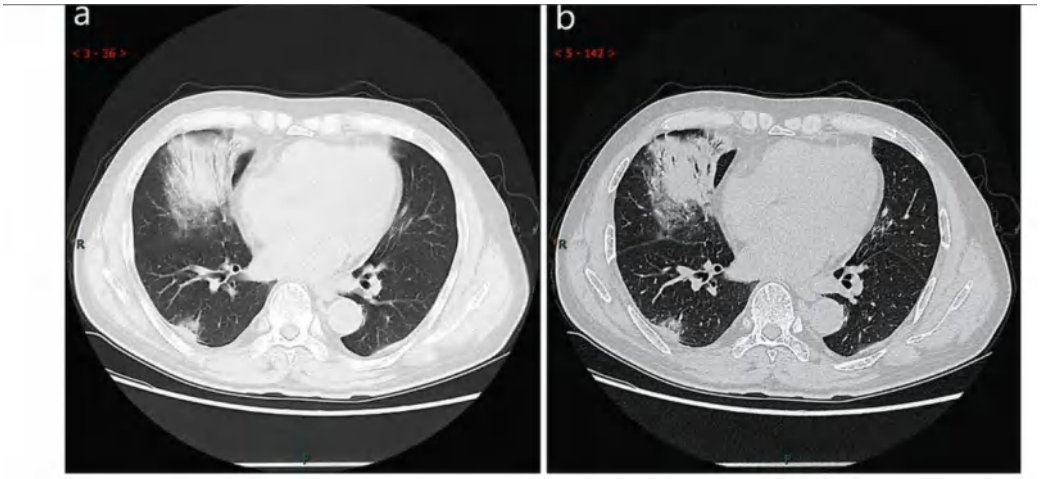
CT imaging of early stage. Male, 38 years old, fever without obvious inducement (39.3 °C), dry cough and shortness of breath for 3 days. Laboratory test: decreased white blood cells (3.01×10^9/L), decreased lymphocytes (0.81×10^9/ L), increased C-reaction protein (60.8 mg/L), increased procalcitonin (0.16 ng/ml). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showed multiple patchy and light consolidation in both lungs and grid-like thickness of interlobular septa

Figure 7 Radiological findings in COVID 19 EARLY STAGE



CT imaging of rapid progression stage. A 50 years old female with anorexia, fatigue, muscle soreness, nasal congestion and runny nose for 1 week, sore and itching throat for 2 days. Laboratory test: increased erythrocyte sedimentation rate (25 mm/h), normal white blood cells (4.08×10^9/L), decreased lymphocytes (0.96×10^9/ L), increased C-reaction protein (60.8 mg/L). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showed multiplepatchy and light consolidation in both lungs and grid-like thickness of interlobular septa

Figure 8 Radiological findings in COVID 19 RAPID POGRESSION STAGE



CT imaging of consolidation stage. A 65 years old male with fever (maximum temperature of 39 ℃). Laboratory test: hypoproteinemia (decreased total protein (62.20 g/L), decreased albumin (35.70 g/L)), abnormal liver function (increased alanine aminotransferase (79 U/L), increased aspartate aminotransferase (72 U/L)), increased procalcitonin (0.10 ng/ml), increased C-reaction protein (53 mg/L), decreased white blood cells (3.72×10^9/L), decreased lymphocytes (0.9×10^9/ L), mildanemia (decreased red blood cells (4.10×10^{12}/L), decreased hemoglobin (131.10 g/L), decreased hematocrit (39.0%). Imaging examination: **a** (thin layer CT) and **b** (high-resolution CT) showedmultiple patchyand large consolidation in right middle lobe, posterior and basal segment of right lower lobe and outer and basal segment of left lower lobe, with air-bronchogram inside

Figure 9 Radiological findings in COVID 19 CONSOLIDATION STAGE

The CORADS score

The CORADS score is a measure of the level of suspicion of a set of CT findings being of a COVID 19 infection etiology. It is not a measure of the severity of the infection. A low score suggests a non COVID 19 etiology and a high CORADS score suggests a COVID 19 etiology. This system of reporting along with a CT severity scoring system (based on either lobar involvement or bronchopulmonary segment involvement) was quickly adopted across the globe and a uniform, reproducible and standardized worldwide reporting system for the CT manifestations of COVID 19 slowly evolved.

The proposers of the CORADS system tested it out initially between eight Radiologists who reported 105 CT scans. It was found that 68% of reports were in complete agreement with each other. It was also noted that 28% reported a 1 category variation in the CORADS score. A difference of more than 2 CORADS categories was noted in only 3.7% of reporters.

A Fleiss Kappa score of the system was then computed. The Fleiss Kappa score is a measure of the reliability of agreement among reporters. It was found to be 0.47 overall. The Fleiss Kappa scores the highest in grade 1 (normal / no pulmonary involvement) and grade 5 (typical findings in COVID 19). This confirmed the high discriminating capacity of the system in ruling out or confirming COVID 19 disease based on CT findings.

The score of the CT findings was graded from 1-5. Scores 1 and 2 were labeled negative (COVID 19 very unlikely). A score of 3 was labeled as indeterminate (COVID 19 etiology possible). A score of 4 or 5 was labeled positive (COVID 19 very likely).

A CORADS score of 6 was subsequently added when classical CT findings were accompanied by a positive RT PCR test.

The CORADS system is based on another similar and successful system of reporting for breast imaging namely the BIRADS system. CT scans in patients with a CORADS score of 4 or 5 were noted even when the RT PCR in these patients was negative suggesting that a CT of the chest could diagnose COVID 19 even when the RT PCR was negative but the clinical index of suspicion is high. These initially negative RT PCRs later became positive as the disease progressed.

The CORADS score is only a measure of the index of suspicion of a CT finding to be due to a COVID 19 infection. It is not a measure of the severity of the lung involvement in COVID 19. It is perfectly possible to have a CORAD score of 5 with a CT severity score of <8 (based on the lobar method of calculation) indicating mild disease. It just means that there is a high chance of the "mild" findings on CT to because of a COVID 19 infection.

The obvious worst case scenario is a CORAD score of 5 or 6 associated with a CT severity score of >15/25 (lobar method of calculation) indicating a high chance of the CT findings being a result of a severe COVID 19 infection.

The CORADS score grading is based on the following findings:

CORADS 0 – incomplete or inadequate scan which cannot be reported (usually due to the patient coughing or breathing during the test)

CORADS 1 – normal CT or presence of findings suggestive of a non infectious etiology such as CHF, emphysema, lung tumors, lung fibrosis.

CORADS 2 – findings consistent with infections other than COVID 19, bronchiolitis, tree in bud appearance, cavitation, thickened bronchi. Minimal alveolar involvement.

CORADS 3 – Unclear if COVID 19 is the etiology, bronchopneumonia, lobar pneumonia, septic emboli, and ground glass opacities.

CORADS 4 – highly suspicious of COVID 19, unilateral or centrilobar / non peripheral ground glass opacities, multifocal consolidation.

CORADS 5 – Typical of COVID 19, multifocal, peripheral ground glass opacities, crazy pavement patterns.

CORADS 6 – CORADS 5 with a positive RT PCR.

CO-RADS* Level of suspicion COVID-19 infection		
		CT findings
CO-RADS 1	No	normal or non-infectious abnormalities
CO-RADS 2	Low	abnormalities consistent with infections other than COVID-19
CO-RADS 3	Indeterminate	unclear whether COVID-19 is present
CO-RADS 4	High	abnormalities suspicious for COVID-19
CO-RADS 5	Very high	typical COVID-19
CO-RADS 6	PCR +	

TABLE 7 CORADS GRADE SYSTEM

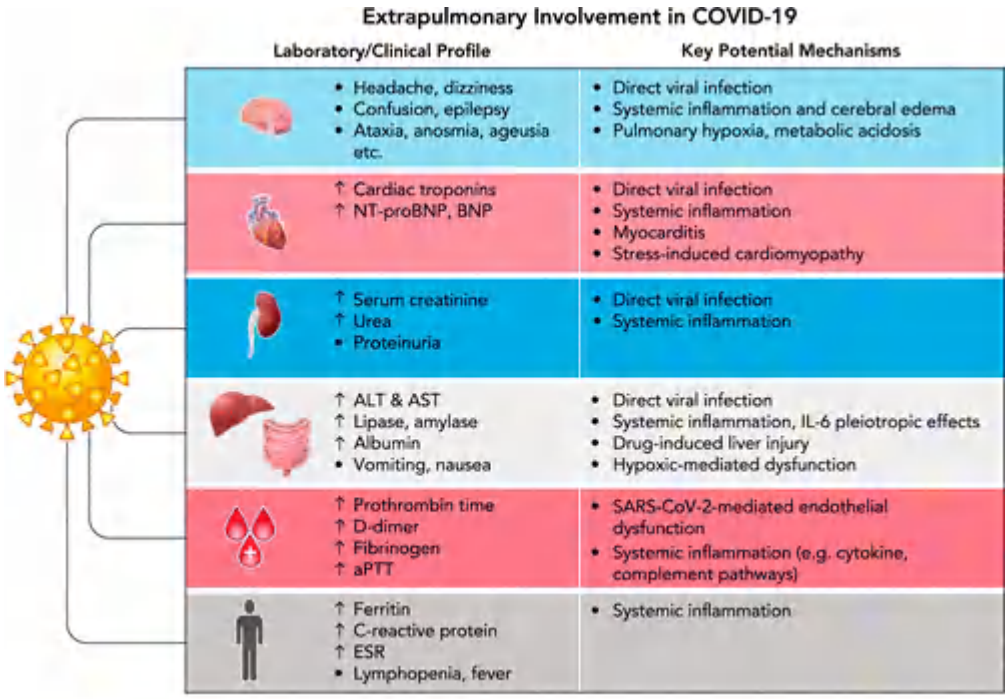


Figure 10 EXTRAPULMONARY INVOLVEMENT IN COVID

MANAGEMENT

KEY RECOMMENDATION

Management predominantly depends on disease severity, and focuses on the following principles: isolation at a suitable location; infection prevention and control measures; symptom management; optimised supportive care; and organ support in severe or critical illness.

Consider whether the patient can be managed at home. Generally, patients with asymptomatic or mild disease can be managed at home or in a community facility.

Admit patients with moderate or severe disease to an appropriate healthcare facility. Assess adults for frailty on admission. Patients with critical disease require intensive care; involve the critical care team in discussions about admission to critical care when necessary. Monitor patients closely for signs of disease progression

Provide symptom relief as necessary. This may include treatments for fever, cough, breathlessness, anxiety, delirium, or agitation.

Start supportive care according to the clinical presentation. This might include oxygen therapy, intravenous fluids, venous thromboembolism prophylaxis, high-flow nasal oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Sepsis and septic shock should be managed according to local protocols(15)

Consider empirical antibiotics if there is clinical suspicion of a secondary bacterial infection. Antibiotics may be required in patients with moderate, severe, or critical disease. Give within 1 hour of initial assessment for patients with suspected sepsis or if the patient meets high-risk criteria. Base the regimen on the clinical diagnosis, local epidemiology and susceptibility data, and local treatment guidelines.(16)

Consider systemic corticosteroid therapy for 7 to 10 days in patients with severe or critical disease. Moderate-quality evidence suggests that systemic corticosteroids probably reduce 28-day mortality in patients with severe and critical disease, and probably reduce the need for invasive ventilation

Consider an interleukin-6 inhibitor (tocilizumab or sarilumab) in patients with severe or critical disease. High-certainty evidence suggests that interleukin-6 inhibitors reduce mortality and the need for mechanical ventilation.

Assess whether the patient requires any rehabilitation or follow-up after discharge. Discontinue transmission-based precautions (including isolation) and release patients from the care pathway 10 days after symptom onset plus at least 3 days without fever and respiratory symptoms.

PRONE VENTILATION

Early self-proning in awake, non-intubated patients

- Any COVID-19 patient with respiratory embarrassment severe enough to be admitted to the hospital may be considered for rotation and early self-proning. (17)
- Care must be taken to not disrupt the flow of oxygen during patient rotation
- Typical protocols include 30–120 minutes in prone position, followed by 30–120 minutes in left lateral decubitus, right lateral decubitus, and upright sitting position (Caputo ND, Strayer RJ, Levitan R. Academic Emergency Medicine 2020;27:375–378)

Requirements for safe prone positioning in ARDS

- Preoxygenate the patient with FiO2 1.0
- Secure the endotracheal tube and arterial and central venous catheters
- Adequate number of staff to assist in the turn and to monitor the turn
- Supplies to turn (pads for bed, sheet, protection for the patient)
- Knowledge of how to perform the turn as well as how to supine the patient in case of an emergency Contraindications to prone ventilation
- Spinal instability requires special care
- Intra cranial pressure may increase on turning
- Rapidly return to supine in case of CPR or defibrillation

When to start proning?

- P/F ratio 0.6 and PEEP >5 cm H2O

When to stop proning?

- When P/F exceeds 150 on FiO2 > 0.6 and > 6 PEEP

What portion of the day should patients be kept prone?

- As much as possible (16-18 hours a day)

- Adult patients with severe ARDS receive prone positioning for more than 12 hours per day (strong recommendation, moderate-high confidence in effect estimates)

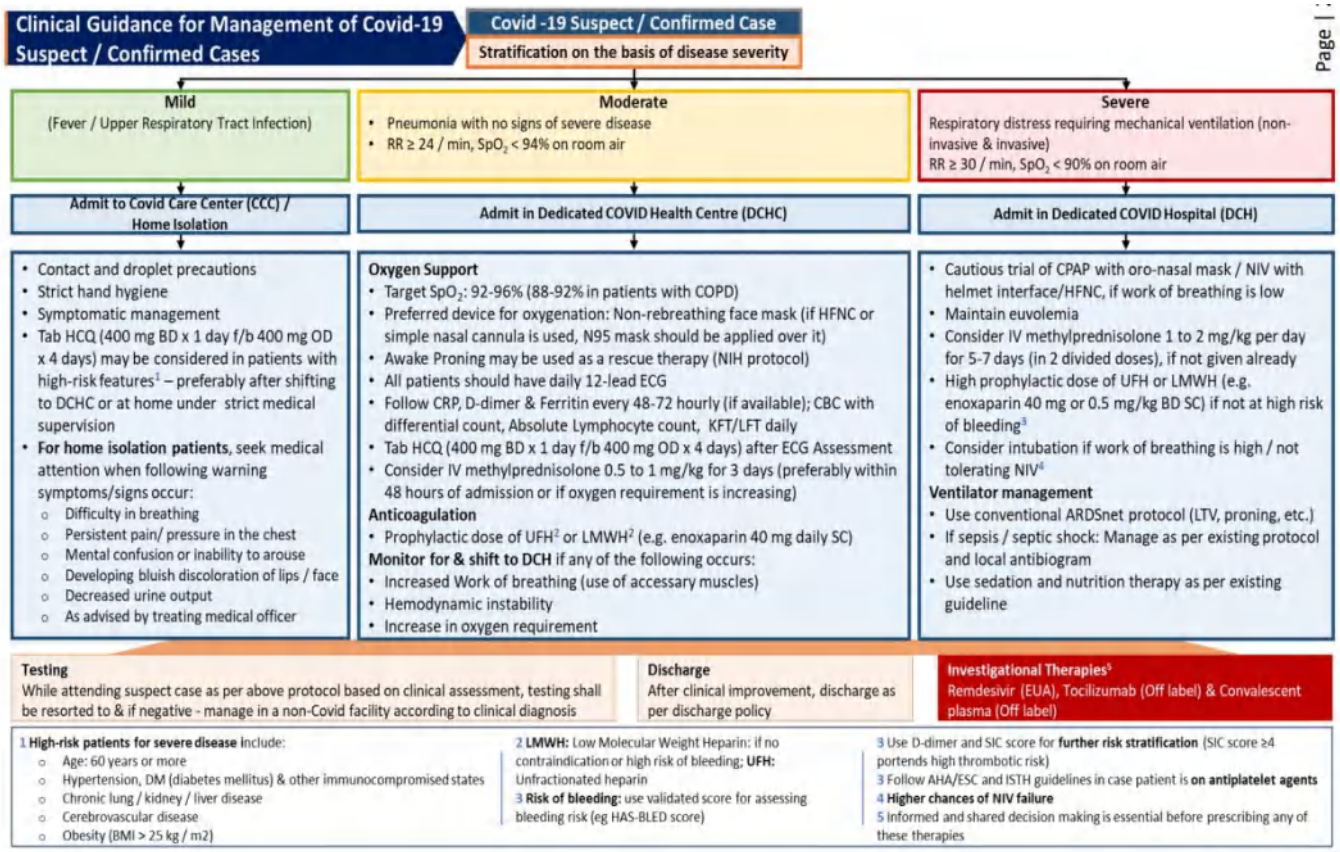
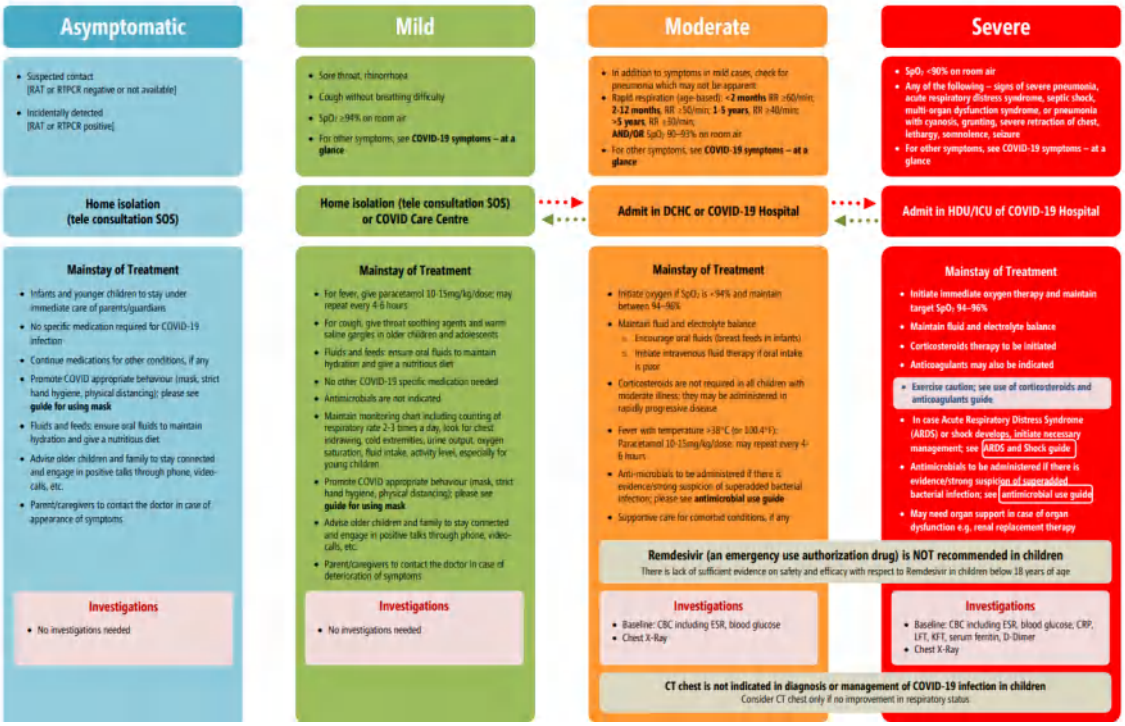
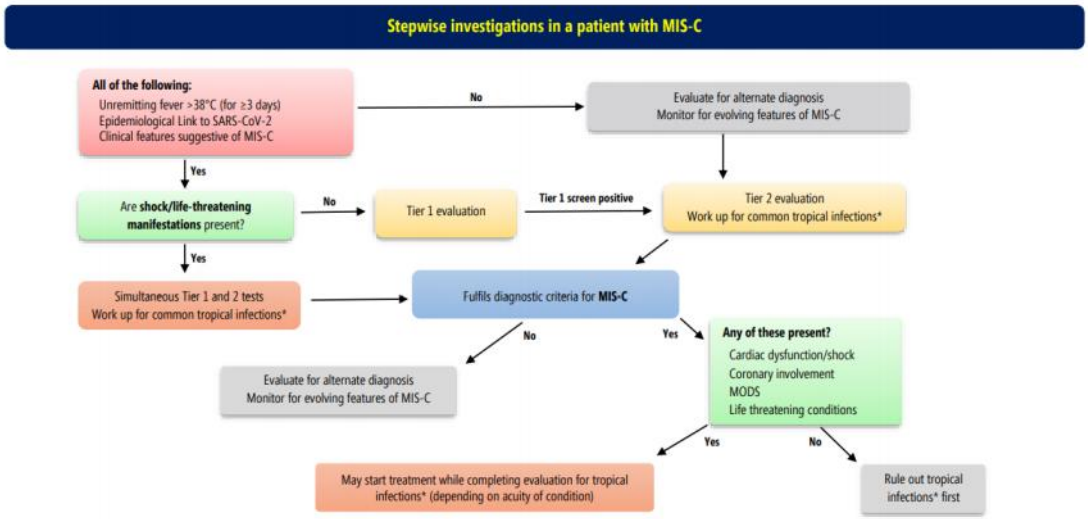


TABLE 8 CLINICAL GUIDANCE FOR MANAGEMENT OF COVID 19 CASES

Guidelines for Management of COVID-19 in Children



Guidelines for Management of COVID-19 in Children



Tier 1 tests (may be done at Covid Care Centre, Dedicated Covid Health Centre): CBC, complete metabolic profile (LFT/KFT/blood gas/glucose), CRP and/or ESR, SARS-CoV-2 serology and/or RT-PCR, blood culture
Positive Tier 1 screen (***both*** of these should be present):

1. CRP >5 mg/L ***and/or*** ESR >40 mm/hour;
2. At least ***one*** of these: ALC <1000/µL, platelet count <150,000/µL, Na <135 mEq/L, neutrophilia, hypoalbuminemia

Tier 2 tests (may be done at Dedicated Covid Hospital): Cardiac (ECG, echocardiogram, BNP, troponin T); inflammatory markers (procalcitonin, ferritin, PT, PTT, D-Dimer, fibrinogen, LDH, triglyceride, cytokine panel); blood smear; SARS-CoV-2 serology
* Common tropical infections include malaria, dengue, enteric fever, rickettsial illness (scrub typhus), etc.

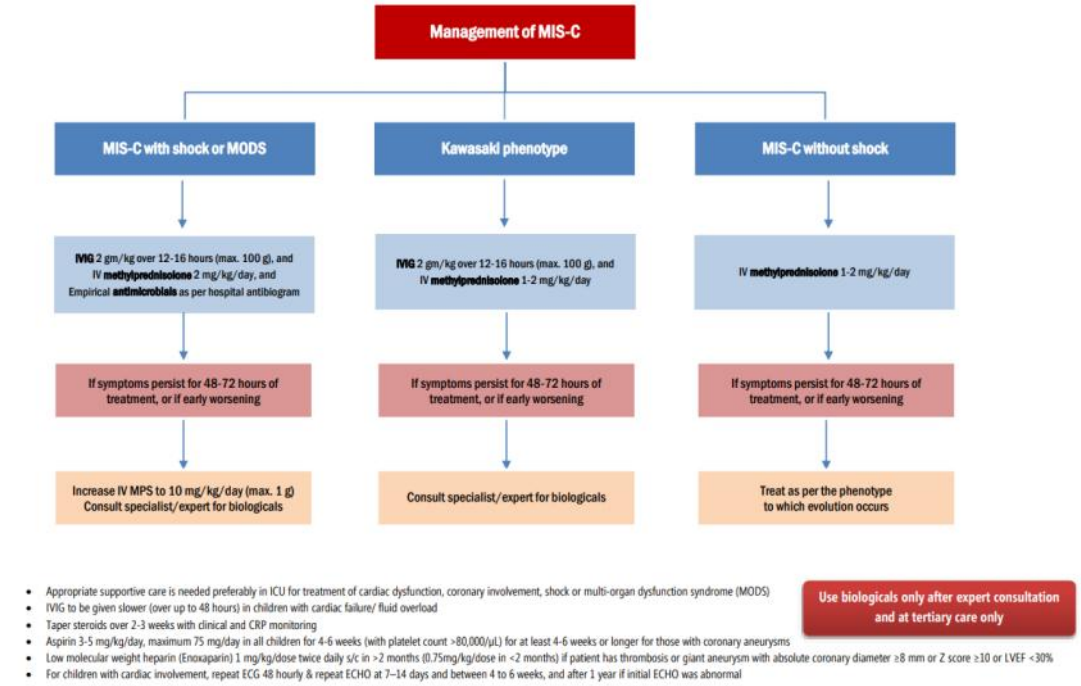


Figure 12 MANAGEMENT OF MIS-C

Directorate General of Health Services, MoHFW, GOI

Comprehensive Guidelines for Management of COVID-19 patients

COVID-19 Treatment/What-to-do at a glance box

Do's/Treatment	Asymptomatic	Mild	Moderate	Severe
Wearing Mask	✓	✓	✓	✓
Physical distancing	✓	✓	✓	✓
Hand hygiene	✓	✓	✓	✓
Cough etiquettes	✓	✓	✓	✓
Anti-pyretic (PCM)	✗	✓	✓	✓
Anti-tussive SOS	✗	✓	✓	✓
Inhalational Budesonide	✗	✓	✗	✗
Oxygen Support#	✗	✓	✓	✓
Anti-inflammatory/ Immunomodulatory therapy#	✗	✗	✓	✓
Anticoagulation#	✗	✗	✓	✓
Monitoring (CXR/ HRCT/ Lab investigations)*#	✗	✗	✓	✓

TABLE 11 COVID 19 TREATMENT

PULMONARY FUNCTION TEST

INTRODUCTION

The assessment of human pulmonary function dates back to the seventeenth century, when the earliest measurements of tidal volume were noted. In 1800, Humphry Davy employed a hydrogen dilution technique to measure his own residual volume (RV) Subsequently, John Hutchinson, in his treatise, On the Capacity of the Lungs and on Respiratory Functions, defined the functional subdivisions of lung volume and reported the results of vital capacity measurements performed in more than 1800 subjects. He related these measurements to the subjects' height, age, and weight, thereby establishing a basis for determining normal values. Progress in development of techniques for pulmonary function testing progressed slowly over the next century. However, in the 1950s, pulmonary physiologists made use of the tools provided by the evolving fields of electronics and computer science. Currently, many techniques exist for assessing both the integrated performance of the cardiovascular and respiratory systems and their individual components.

LUNG VOLUMES AND SUBDIVISIONS

Important quantitative aspects of respiratory function are the changes in lung volume with inspiration and expiration and the absolute volume of air that the lungs hold at various times during the respiratory cycle(18).

Term	Symbol	Definition
Volumes		
Residual volume	RV	Volume of air remaining in the lungs after maximal expiration
Expiratory reserve volume	ERV	Maximal volume of air expired from the resting end-expiratory level
Tidal volume	TV[a]	Volume of air inspired or expired with each breath during quiet breathing
Inspiratory reserve volume	IRV	Maximal volume of air inspired from the resting end-inspiratory level
Capacities		
Inspiratory capacity	IC	Maximal volume of air inspired from the end-expiratory level (the sum of IRV and TV)
Vital capacity	VC	Maximal volume of air expired form the maximal inspiratory level
Inspiratory vital capacity	IVC	Maximal volume of air inspired form the maximal expiratory level
Functional residual capacity	FRC	Volume of air remaining in the lungs at the end-expiratory level (the sum of RV and ERV)
Total lung capacity	TLC	Volume of air in the lungs after maximal inspiration (the sum of all volume compartments)

[a]*The symbol TV is traditionally used for tidal volume to indicate a subdivision of static lung volumes. However, the symbol V_T is used for tidal volume in formulas for gas exchange.*

TABLE 12 LUNG VOLUME & CAPACITIES

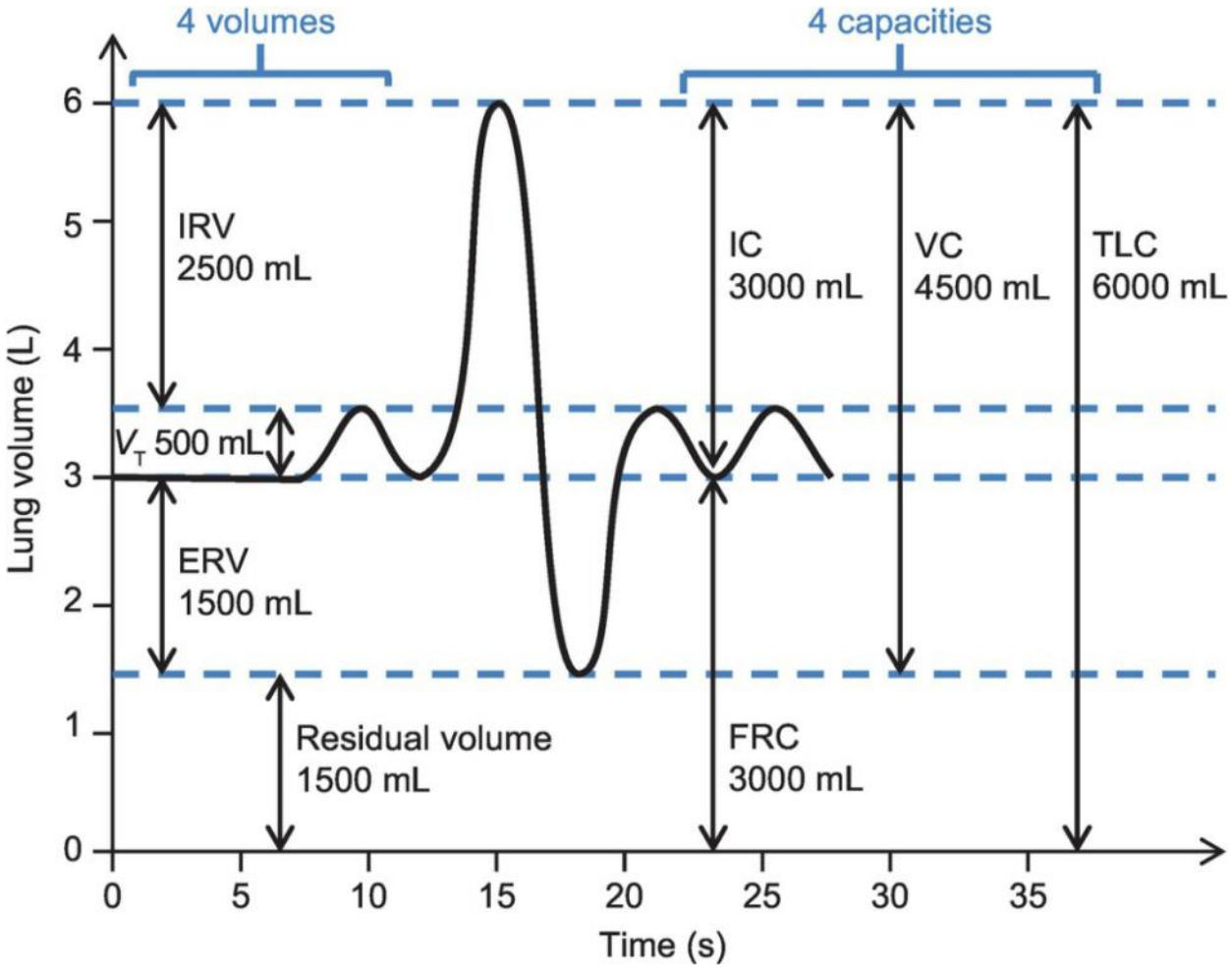


Figure 13 LUNG VOLUME & CAPACITIES

Spirometers that measure volume or change in volume versus time have been used extensively in pulmonary function laboratories. Previously, through manual calculations, or, in modern times, through application of microprocessors, the relationships among volume, flow, and time are generated to provide a measure of the respiratory system's ability to move air

In the water-sealed spirometer, a mouthpiece is attached to a tube through which air passes into a lightweight bell that is inverted over a water bath. Air movement through the mouthpiece into the bell during expiration causes the bell to rise; conversely, as air is withdrawn from the system during inspiration, the bell falls. The change in volume with time can be recorded on a calibrated rotating drum or digitally noted by a computer and displayed on a screen in both graphic and numeric formats. In the dry, rolling-seal spirometer a cylinder with a rolling plastic seal is substituted for the spirometer bell and its water seal. Movement of air through the mouthpiece effects a change in the position of the piston, which is attached to a variable resistor. The resistor, in turn, generates voltage signals proportional to volume changes reflected in displacement of the piston. These signals are processed by a computer to generate graphic and numeric outputs similar to those of the water-sealed spirometer. Currently, most pulmonary function laboratories utilize flow-type spirometers using pneumotachographs or rotating turbines to determine airflow. Two types of pneumotachographs are in general use: hot wire and flow resistive. In the hot-wire type, air flowing past a heated wire cools the wire, thereby altering its resistance in proportion to changes in airflow. Flow-resistive pneumotachographs contain a resistive element composed of parallel tubes a wire mesh, or a fibrous, paperlike element. Airflow through the resistive element results in a pressure gradient across the device,

which can be measured by a very sensitive differential pressure gauge. small-bore tubes maintains a laminar gas flow pattern through the pneumotachograph. As a result, the pressure–flow characteristics of the system can be described by

Poiseuille'LawFormula:

The rate of flow (u) of liquid through a horizontal pipe for steady flow is given by

$$v = \frac{\pi}{8}\frac{pr4}{\eta l}$$

where,

p = pressure difference across the two ends of the tube,

r=radius of the tube,

η = coefficient of viscosity,

l = length of the tube.

In a diagnostic setting, spirometers are used to (1) evaluate symptoms, signs, or abnormal laboratory tests; (2) measure the effect of disease on pulmonary function; (3) screen persons at risk of having pulmonary disease; (4) assess preoperative risk; (5) assess prognosis; and (6) assess health status before enrollment in strenuous physical activity programs. On the other hand, spirometers used for patient monitoring are used to (1) assess therapeutic interventions, including bronchodilator therapy, management of congestive heart failure, etc.; (2) characterize the course of diseases affecting lung function (e.g., obstructive or interstitial lung diseases, congestive heart failure, or neuromuscular diseases); (3) track pulmonary function in persons working in occupations or receiving medications known to affect the lung; (4) evaluate large numbers of people in disability assessments; and (5) provide data as part of epidemiologic surveys. 8 In general, the diagnostic spirometer is used to assess a patient's lung function for purposes of

comparison with values expected in a normal population. The monitoring spirometer, which is less expensive and more portable, is used to evaluate a patient's performance over time and to study large numbers of people for epidemiologic or other purposes.

THE VITAL CAPACITYAND ITS SUBDIVISIONS

Two methods of performing a vital capacity maneuver can be used: closed-circuit and open-circuit methods. In the closed-circuit method, the seated patient, with nose clip in place, breathes quietly into the apparatus. After several breaths to establish the resting end-expiratory level, which serves as a point of reference for all subsequent measurements, the patient is urged to inspire fully and then, after reaching a plateau at maximal inspiration, to expire maximally. This expiration must be performed slowly and evenly; attempts by the patient with obstructive pulmonary disease to maximize flow often reduce expiratory volumes because of dynamic compression of the airways caused by high positive pleural pressur From the record, tidal volume, inspiratory reserve volume, expiratory reserve volume (ERV), vital capacity, and IC are calculated. A similar maneuver in which the subject breathes out as rapidly and forcefully as possible after a maximal inspiration provides a measure of the forced vital capacity (FVC). Other timed measurements of expiratory airflow (e.g., the forced expiratory volume in 1 second, or FEV1) are also determined from this type of record

. In the open-circuit method of determining vital capacity, the patient inspires maximally, inserts the mouthpiece, and then exhales with a slow, constant effort to the point of maximal expiration. With this technique, the resting end-expiratory position is not recorded. Thus, only the vital capacity, not its component volumes, can be measured.

The open-circuit technique offers some advantages. Since the patient inspires from room air before expiring into the apparatus, concern over acquisition of infection from contaminated inspired air is minimized. In addition, the open-circuit method is generally completed in a shorter time, providing a major advantage when epidemiologic studies are being performed on large numbers of subjects.

FUNCTIONAL RESIDUAL CAPACITYAND RESIDUAL VOLUME

One compartment of the TLC that cannot be measured by spirometry is RV, the volume of air remaining in the lungs at the end of a maximal expiration. RV is determined indirectly in three steps: (1) FRC is typically measured using one of the three techniques: closed-circuit helium, open-circuit nitrogen, or total-body plethysmograph. (2) ERV is determined spirometrically. (3) RV is calculated as the difference between FRC and ERV. In principle, it is possible to determine the RV using a dilution technique or body plethysmography after maximal expiration. In practice, however, the resting end-expiratory level is a more reproducible starting point for determining FRC than is the maximal end-expiratory level for determining RV.

Closed-Circuit Helium Method

The closed-circuit helium dilution method for determining FRC is a variation of the hydrogen dilution method first used in the early 19th century. Both methods take advantage of the virtual insolubility of the test gas in body tissues and the law of conservation of mass. The development and simplification of this test were accomplished over a 20-year span in the mid-20th century.

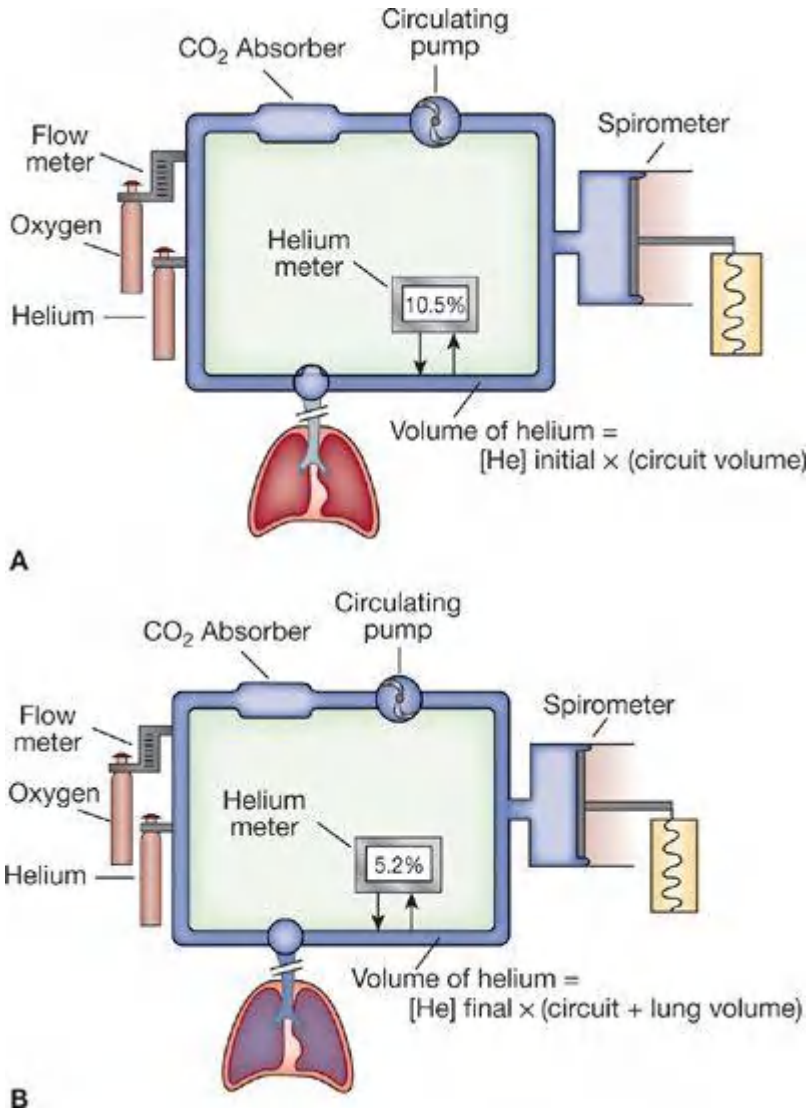


Figure 14 Closed-circuit helium dilution method for measurement of FRC

When a fully manual device is used for measuring FRC, the system is prepared by the addition of about 2 L of air and sufficient helium to achieve an initial helium concentration of approximately 10% in the apparatus. The patient, with nose clip in place, then breathes room air through the mouthpiece (Figure 14 A). After a preliminary period of quiet breathing to familiarize the patient with the mouthpiece, apparatus, and environment, and after the baseline resting end-expiratory level is established, the test begins. At the end of a normal expiration, the valve at the mouthpiece is turned to connect the patient to the

spirometer system (Figure 14 B). As the patient rebreathes from the closed circuit, the blower circulates the gas mixture. The CO2 is absorbed by soda lime (CO2 absorber), while O2 is added through a valve and flowmeter at a rate corresponding to the subject's O2 consumption. As the helium, which was at first contained entirely within the apparatus, mixes with air contained in the lungs, its concentration, as monitored by the helium analyzer, falls. Stabilization of the helium concentration, indicated by a rate of change in concentration of less than 0.02% over a 30-second interval, signals the point at which the helium concentration has equilibrated throughout the lung-breathing circuit system; equilibration, the end- point of the test, occurs within 7 minutes in normal persons.

The initial volume of the system is the volume of the spirometer and circuit tubing, whereas the final volume consists of the initial volume plus FRC. The latter value is the only unknown in the preceding equation. Corrections are usually made for the small amount of helium dissolved in body tissues during the test and for slight volume changes caused by a respiratory exchange ratio that is not equal to 1.0. 9 Although the method described here is based on a manually operated device, the same principles hold when all the mechanical and computational steps are accomplished with a computer-controlled system.

Nitrogen Washout Method

Conceptually, the nitrogen washout method is similar to the helium dilution method described previously; however, it relies on an open circuit rather than the closed circuit used in the helium dilution method. The open-circuit nitrogen washout method for determining FRC. requires that the subject breathe 100% O2 for 7 minutes; during this

period, the concentration of N2 in expired gas is monitored. When the expired N2 concentration falls to zero, all the N2 present in the lungs at the start of O2 breathing has been "washed out." The total volume of gas expired and the concentration of N2 in the expired gas are measured. The calculation of FRC is based on the reasonable assumption that the volume of N2 in the lungs at the start of the test (i.e., the product of lung volume and the concentration of N2 in the lungs) is the same as the total volume of N2 expired and collected during the period of the test – that is, the product of the total volume of gas expired and the concentration of N2 in the expired gas: Since the test is started at the end of a quiet expiration, the volume of gas in the lungs is FRC. This volume is calculated by substituting into the above equation the initial concentration of N2 in the lungs, estimated at 0.81 in fasting and 0.79 to 0.80 in nonfasting subjects, and the measured values for volume and N2 concentration of expired gas.

Body Plethysmography

The word plethysmography is derived from the Greek plethysmos, meaning "enlargement." Although the concept of measuring FRC by recording changes in the volume of the body during "enlargement" of the chest was described in 1882, not until 1956 did DuBois and coworkers introduce a practical plethysmographic technique, based on Boyle's law, for determining thoracic gas volume (TGV).

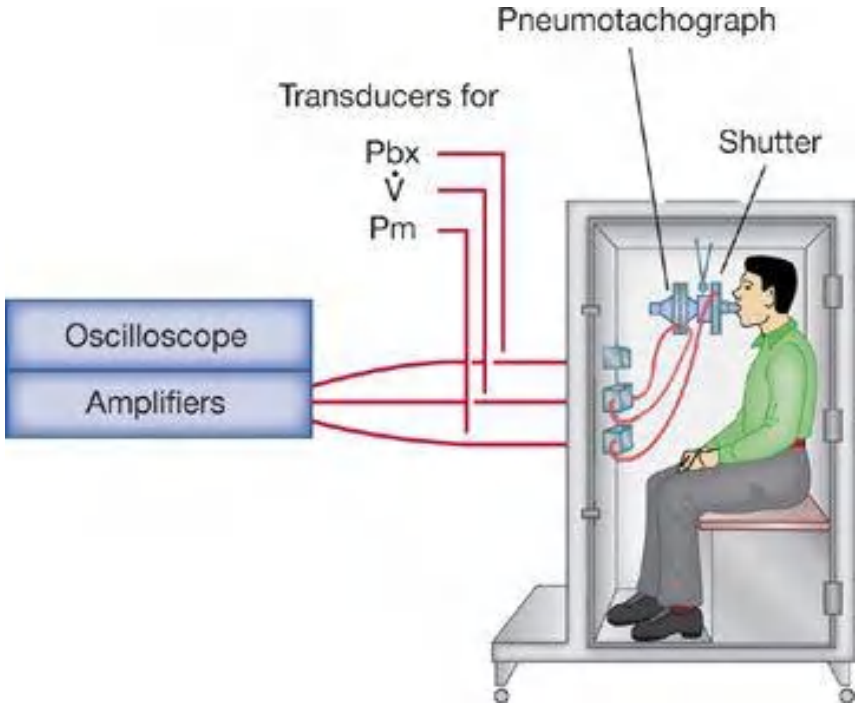


Figure 15 Constant-volume, variable-pressure plethysmograph used for measuring functional residual capacity and airway resistance

Any of three types of body plethysmographs can be used: (1) the pressure plethysmograph, in which pressure during breathing varies while volume remains constant; (2) the volume plethysmograph, in which volume varies during breathing while pressure remains constant; and (3) the pressure-corrected flow plethysmograph, which couples the pressure plethysmograph's fidelity of response to high-speed events with the volume plethysmograph's ability to follow large changes in volume. Since the conceptual basis for all three devices is similar, only the most popular one – the pressure plethysmograph – will be described. The pressure plethysmograph (Fig. 33-5) contains a pneumotachograph and transducer for measuring flow and volume, and two strain-gauge transducers, one for sensing pressure at the mouth (Pm) and the other for sensing pressure in the box (Pbx). A solenoid-operated shutter mechanism is situated between the mouthpiece and the

pneumotachograph. The three transducers are connected to an amplifying and monitoring system so that box pressure (or lung volume) and mouth pressure are displayed simultaneously on the X and Y axes, respectively, of an oscilloscope

STATIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Static compliance describes pulmonary compliance when there is no airflow, like an inspiratory pause. Pressure-volume curves are common schemes to express the relationship of dynamic and static compliance where the slope is compliance.[14]

$C = V/P$

- C: Compliance (ml/mmHg)
- V: Volume (mL)
- P: Pressure (mm Hg)

Lung compliance is the change in volume in the lungs for a given change in transpulmonary or transmural pressure. The transmural pressure (PTM) is the difference between intrapleural pressure(PA) and alveolar pressure (Pa), [PTM= PA – Pa]. If the intrapleural pressure is more negative, the lungs increase in volume to expand. However, if the intrapleural pressure is positive, the lungs will collapse, which decreases lung volume. During expiration, the lung volume is higher for a given intrapleural pressure, and, therefore, compliance is higher in expiration compared to inspiration. Lung compliance is

nversely related to elastance, which is also known as elastic resistance or elastic recoil. So, a patient with low lung compliance will have a relatively stiff lung and, therefore, higher elastance.

Two important factors of lung compliance are elastic fibers and surface tension. More elastic fibers in the tissue lead to ease in expandability and, therefore, compliance. Surface tension within the alveoli is decreased by the production of surfactant to prevent collapse. Compliance is more easily achieved by decreasing surface tension.(19)

The lung and chest wall, together, form a combined compliance system. Independently each lung and chest wall measures higher compliance than the lung-chest wall system combined. In addition to lung compliance, the combined system factors in the opposing force of the chest wall muscles and diaphragm. These muscles provide the necessary pressure difference for air movement. The combined lung-chest wall system is at equilibrium (no inclination toward collapse or expansion) when lung volume is at functional residual capacity (FRC), which is the remaining lung volume after tidal volume is expired. The negative intrapleural pressure is set by the two opposing forces of the chest and lungs.

DYNAMIC MECHANICAL PROPERTIES OF THE RESPIRATORY SYSTEM

Dynamic compliance describes the compliance measured during breathing, which involves a combination of lung compliance and airway resistance.(20)

FORCED VITAL CAPACITY

Both expiratory and inspiratory measurements of the FVC are routinely made in pulmonary function laboratories. Unless otherwise specified, FVC refers to the forced expiratory maneuver.

Forced Expiratory Vital Capacity

The forced expiratory vital capacity is measured during expiration. The maneuver entails two steps: a full inspiration to TLC, followed by a rapid, forceful, maximal expiration (to RV) into a spirometer. The forced expiratory vital capacity (FVC) is normally equal to the relaxed or slow vital capacity (VC). However, a discrepancy between FVC and VC appears in obstructive disease of the airways: the FVC is less than the VC. The relationship between expired volume and time during an FVC maneuver is used to determine airflow during expiration and the volume of air expired within designated intervals; these values provide an indirect measure of the flow-resistive properties of the lung. The FVC is displayed in one of the two ways: expired volume plotted against time (Figure 16) or airflow plotted against lung volume – that is, an expiratory "flow–volume curve" (see below). The normal volume–time display of the FVC consists of a smooth curve with a gradually and progressively decreasing slope. Irregularities in the curve suggest either a failure of coordination or a suboptimal effort. At times, the onset of the forced expiration is unclear (Fig. 33-15) because of hesitation on the part of the patient. When this occurs, the start of expiration ("zero time") is determined with the "back extrapolation" method (Fig. 33-15). 8 A tangent taken through the part of the curve with the steepest slope is extrapolated back to the maximal inspiratory volume; the point of intersection is considered to be the time of onset of expiration

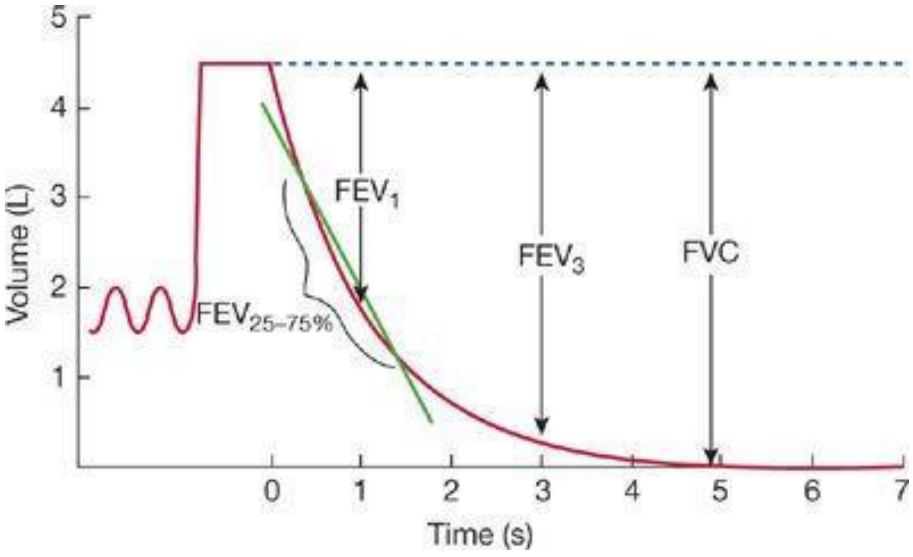


Figure 16 Forced expiratory vital capacity maneuver

After an initial period of tidal volume breathing, the patient inspires maximally to TLC and then exhales as rapidly and as forcefully as possible into a spirometer. Shown on the left of the tracing are a series of tidal volume breaths and the maximal inspiration to TLC. The forced expiration begins at time 0. Nearly all the volume is exhaled in the first 3 seconds of the maneuver. The values for FVC, FEV1 , and FEV3 are measured from the maximal inspiratory level. The FEF25–75% is the slope of the line connecting the points on the volume–time trace that correspond to 25% and 75% of the FVC.

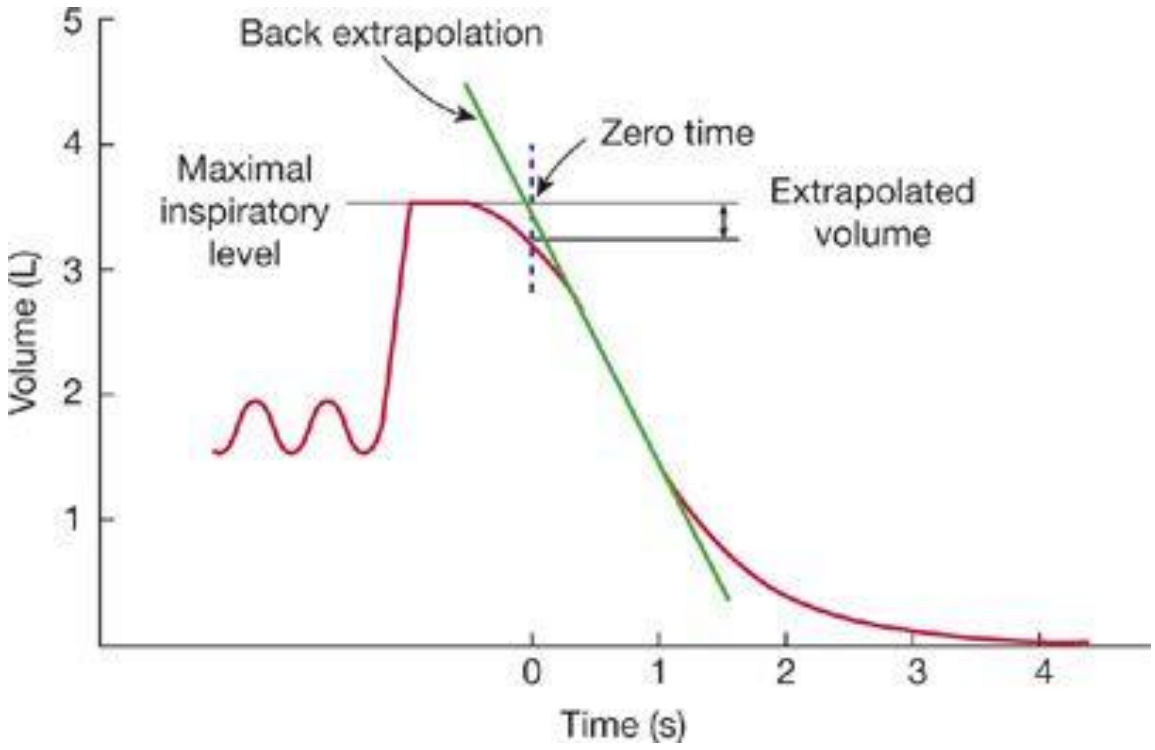


Figure 17 Technique of back extrapolation for determining the zero time in calculation of FEV1 .Zero time is determined as the point of intersection of a tangent drawn through the steepest portion of the spirogram and a line drawn horizontally through the maximal inspiratory level.

Several values are commonly determined from the volume–time plot of the FVC (Table 13, Fig. 16): (1) the volume expired in the first second, expressed either as an absolute volume (FEV1) or as a percentage of the FVC (FEV1 /FVC%); (2) the volume expired in the first 3 seconds, expressed either as an absolute volume (FEV3) or as a percentage of the FVC (FEV3 /FVC%); and (3) the forced midexpiratory flow rate (FEF25–75%). The FEF25–75% is determined by locating the points on the volume– time curve corresponding to 25% and 75% of the FVC and then calculating the slope of a straight line passing through those two points. The slope of this line represents the average airflow over the midportion of the FVC.

FVC (BTPS) (L)	Forced vital capacity; the total volume expired
FEV_1 (BTPS) (L)	Volume of air expired in the first second
FEV_1/FVC%	Volume of air expired in the first second, expressed as percent of the FVC
FEV_3/FVC%	Volume of air expired in the first 3 s, expressed as percent of the FVC
$FEF_{25–75\%}$ (BTPS) (L/s)	Forced midexpiratory airflow

Note: BTPS, body temperature and pressure, saturated with water vapor.

Table 13 Values Obtained from Forced Expiratory Volume–Time Curves

Although the relaxed or slow vital capacity (VC) may be normal or only modestly reduced in patients with obstructive disease of the airways, the volume–time relationship of the FVC maneuver is usually distinctly abnormal in such patients (Fig. 18 A and B). Most obvious is a flattening of the slope of the curve at any given lung volume, reflecting the reduced airflow. In addition, the duration of the forced expiratory maneuver is prolonged. Normally, expiration is complete within 6 seconds; in obstructive airway disease, expiratory airflow may continue for 10 to 12 seconds. These changes in the expiratory airflow reduce the FEV1 and FEV3 , the FEV1 /FVC%, the FEV3 /FVC%, and the FEF25–75%

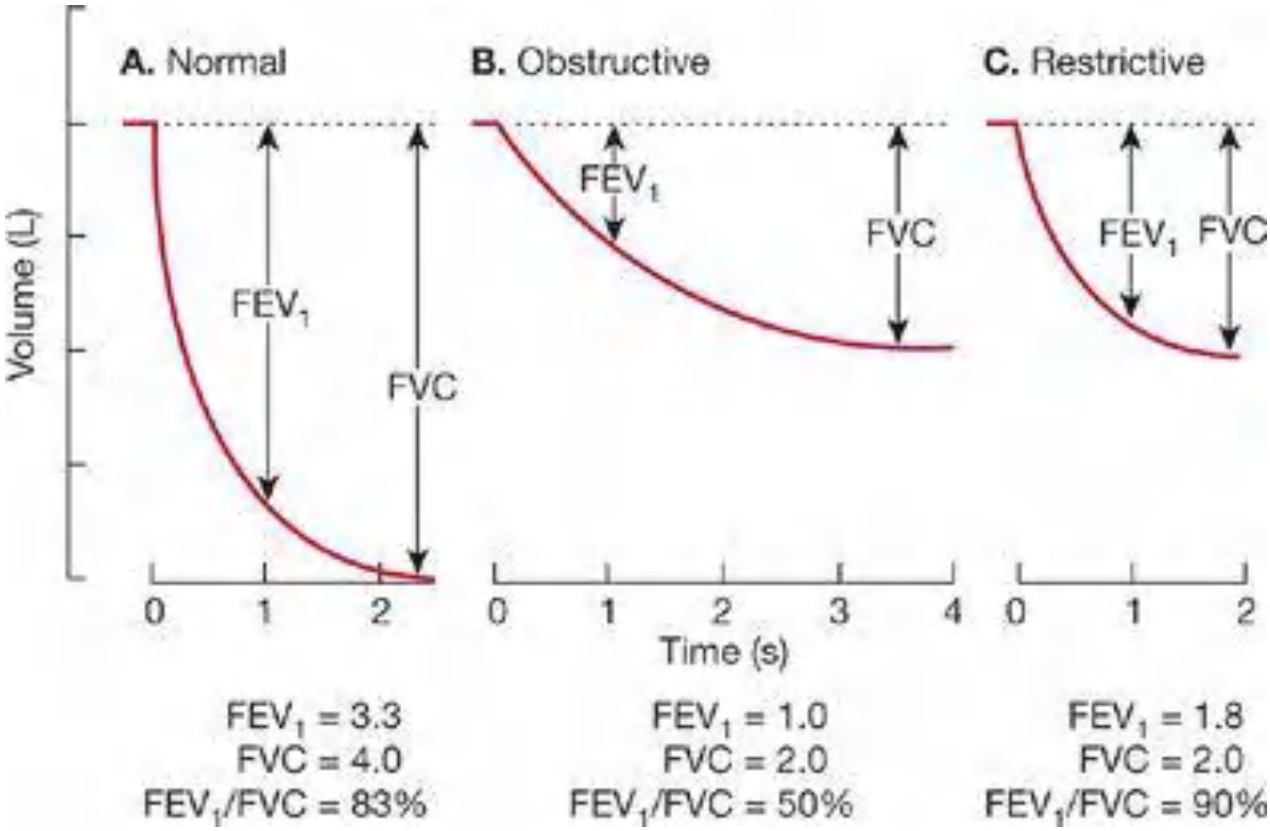


Figure 18 Representative spirograms from a normal subject (A), a patient with obstructive lung disease (B), and a patient with restrictive lung disease (C), obtained during a forced expiratory vital capacity maneuver

In the normal subject, expiration is completed within 3 seconds, and 83% of the volume is expired in the first second (FEV1 /FVC% = 83). In the patient with obstructive disease, expiration is prolonged, and only half the volume is expired in the first second (FEV1 /FVC% = 50). In the patient with restrictive disease, although the magnitude of the reduction in exhaled volume is the same as in the obstructed patient, most of the volume is exhaled within the first second (FEV1 /FVC% = 90). Restrictive lung disorders reduce the slow vital capacity. However, the configuration of the volume– time relationship may not be abnormal (Fig. 33-16C). Although the FEV1 and FEV3 are reduced because of the reduced vital capacity, the FEV1 /FVC% and

FEV3 /FVC% remain normal or even exceed normal values. Often, because of the reduced vital capacity, the FEF25–75% is also less than predicted.

Forced Inspiratory Vital Capacity

Measurement of the forced inspiratory vital capacity (FIVC) consists of two steps: (1) full expiration to RV, followed by (2) a rapid maximal inspiratory effort (Fig. 19). The rate of airflow over the middle half of the forced inspiratory vital capacity (FIF25–75%) is determined using a procedure similar to that described previously for the FEF25–75%.

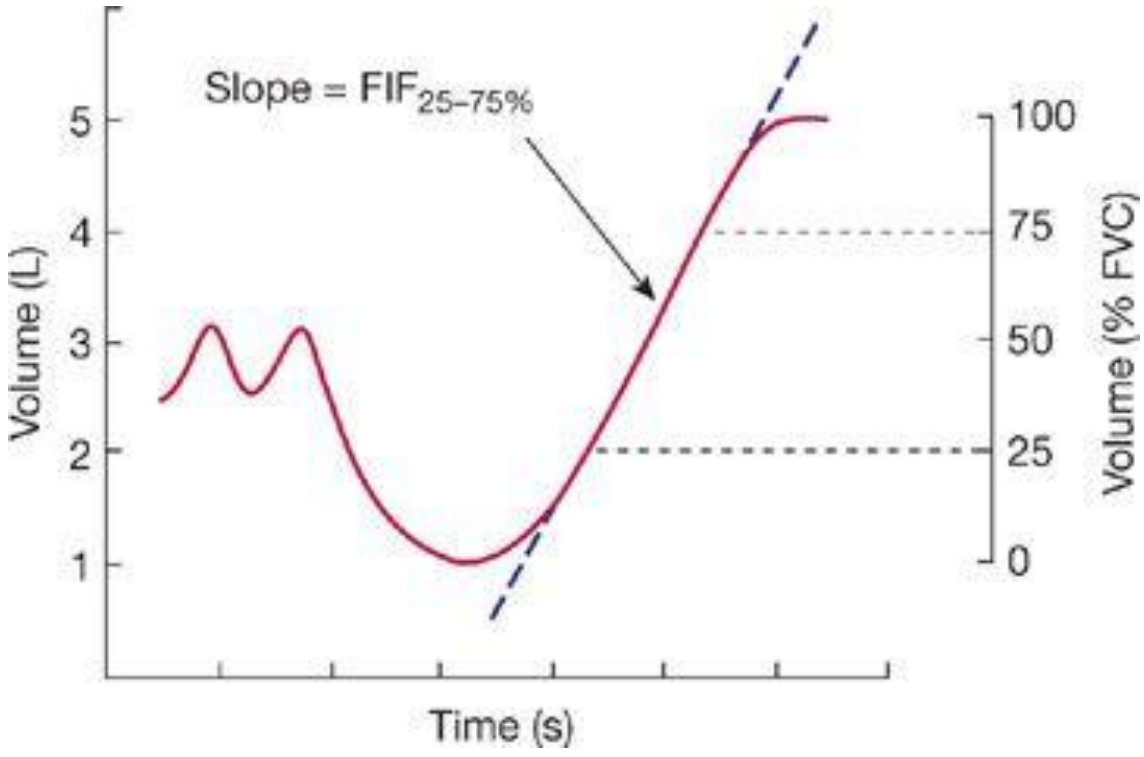
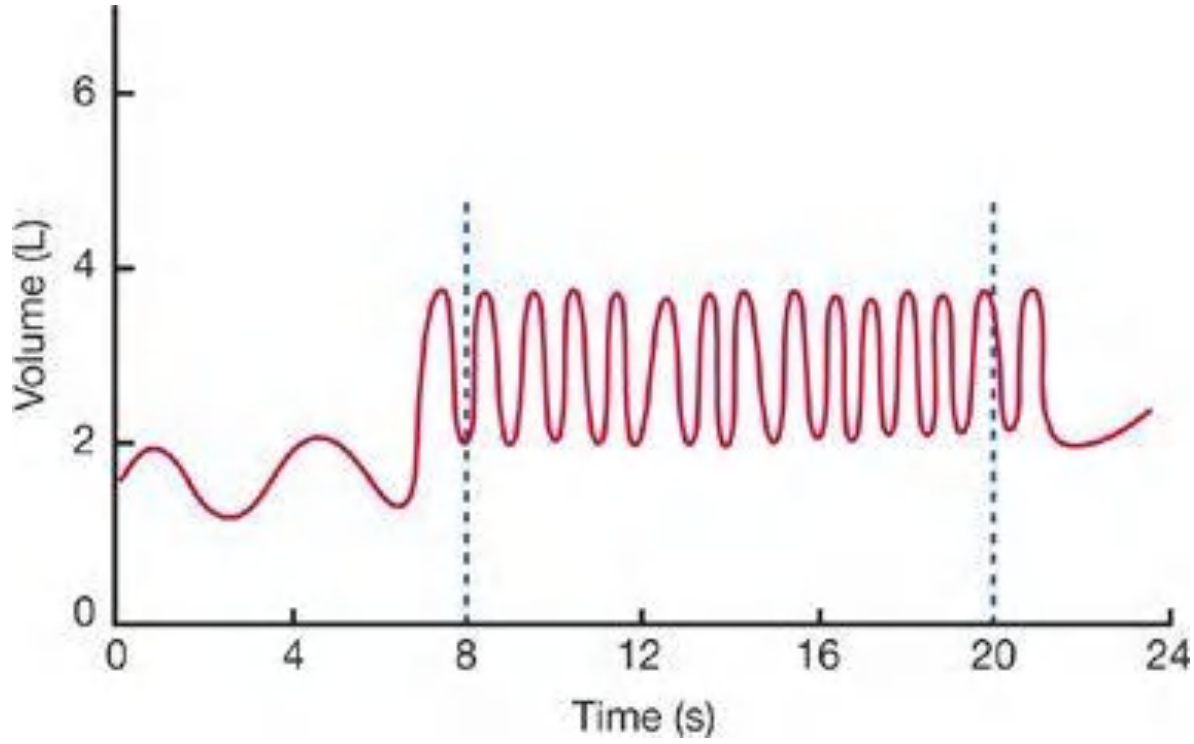


Figure 19 Forced inspiratory volume–time curve. The $FIF_{25–75\%}$ is the slope of a line between the points on the trace corresponding to 25% and 75% of the inspired volume

MAXIMAL VOLUNTARYVENTILATION

The previous considerations of dynamic lung function focus on a single timed maximal expiratory or inspiratory maneuver. In contrast, the MVV depends on the movement of air into and out of the lungs during continued maximal effort throughout a preset interval (Fig. 20). The MVV is a simple, informative test that provides an overall assessment of effort, coordination, and the elastic and flow resistive properties of the respiratory system.



Figue 20 Maximal voluntary ventilation (MVV)

After a period of relaxed breathing, the subject breathes rapidly and as forcefully as possible. The total volume of air inspired over 12 seconds and expressed in L/min is the MVV. In performing the test, the patient is urged to breathe as hard and as fast as possible. As a rule, the patient automatically adjusts frequency and tidal volume for optimal performance. However, extremes of frequency or tidal volume are to be

avoided, since neither panting nor slow deep breathing leads to the highest possible values. The total volume that is expired during a 12-second interval, expressed in liters per minute (BTPS), is the MVV. In some patients the test cannot be done because of an inability to continue the necessary effort for 12 seconds. A normal value for MVV indicates that the overall integrated performance of the respiratory system is intact, thereby excluding moderate to severe restrictive or obstructive disease. In addition, a normal value suggests that the elastic and flow-resistive properties of the respiratory system, respiratory muscle strength, coordination of respiratory performance, and motivation of the patient are all normal. Although this test is very useful in detecting overall disturbances in integrated performance and diffuse tracheobronchial and pulmonary parenchymal diseases, other tests are required to pinpoint specific disorders. The difference between the MVV and the resting minute ventilation is the breathing reserve. At one time, a low breathing reserve was correlated with the breathlessness in lung diseases.

QUALITY CONTROL IN THE PULMONARY FUNCTION LABORATORY

Meaningful interpretation of pulmonary function tests requires confidence in the accuracy and reproducibility of results provided by the pulmonary function laboratory. Previously, it was tacitly assumed that all data from all laboratories, especially when reported as "percent predicted," were equally reliable. In recent years, the fallacy of this assumption has been explicitly recognized, and steps have been taken to standardize equipment and procedures and to ensure accuracy, reproducibility, and uniformity in testing and reporting. To accomplish this goal, both analytical and nonanalytical factors must be taken into account

.

NONANALYTICAL FACTORS IN QUALITYCONTROL

A familiar example of a confounding influence that may distort test results is the anxious patient who pauses outside the laboratory door to “calm the nerves” by smoking one or more cigarettes before undergoing pulmonary function testing. Cigarette smoking before the diffusing capacity of the lungs is determined can generate enough carboxyhemoglobin to reduce a normal value to subnormal levels. Another example of a nonanalytical factor is the failure to achieve patient understanding and comfort for tests that usually require patient cooperation. Unfortunately, a preliminary explanation before the patient arrives at the laboratory or prior exposure of the patient to the laboratory and its personnel is usually impractical. Use of explanatory sheets or descriptive brochures may prove helpful. If such materials are not available, laboratory personnel are obligated to make the patient comfortable and even perform “practice runs” before undertaking final testing. When the patient arrives at the pulmonary function laboratory, an assessment should be made of his or her prior experiences. Did the patient undergo other tests or procedures that could alter the outcome of the pulmonary function tests in question? Is the patient fatigued or in pain? Should a period of rest precede the tests in order to ensure optimal performance? If delay is impractical, the test report should include the fact that the patient was fatigued or in pain. Medication use before pulmonary function testing can seriously affect the results. For example, selfadministration of bronchodilators before testing can artificially enhance tests of airflow. If medications have been taken before the patient arrives at the laboratory, the time of administration should be part of the record. Also, a request for pulmonary function test results for patients who regularly take bronchodilators should indicate whether the tests are to be done without interruption of the regular schedule of

medications, whether bronchodilators are to be discontinued before the test is done, or whether regular bronchodilators are to be discontinued so that the effects of bronchodilation can be tested. Appropriate comments about bronchodilators are part of the report. A major nonanalytical cause of misinterpreting results is the inappropriate application of predicted normal values to the patient population by the laboratory (see Approach to Interpreting Commonly Performed Pulmonary Function Tests). For example, normal values based on data obtained using physically fit hospital personnel do not necessarily apply to those who have a sedentary existence. Noncomparable race, as well as lifestyle, may complicate comparisons. Anthropologic differences among control and test populations are not easily reconciled. Extraordinary height, weight, or age cannot be easily extrapolated if corresponding subjects are not represented in the control group. Using patientreported height, rather than making measurement of patient height, may introduce an error in the selection of appropriate normal values. 84 Comparison of control and test results at different altitudes can be invalid if due regard is not paid to the influence of hypoxia on certain measurements (e.g., diffusing capacity).

ANALYTICAL FACTORS IN QUALITY CONTROL

Performance of pulmonary function tests is replete with opportunities for error. The equipment, techniques, use of control values, and calculations are potential sources of error. In an attempt to minimize errors, standardization of techniques has been advocated. For example, with respect to performing the FVC maneuver, guidelines have been established for the number of attempts required, acceptable variability between efforts, and methods for selecting test data in order to arrive at acceptable results. To avoid misuse of spirometers, criteria have been set for minimal performance

with respect to capacity, accuracy, and frequency response of various spirometers; in addition, standards have been developed for determining the single-breath diffusing capacity. Potential sources of discrepancies – such as breathholding time, concentration of hemoglobin, dead space of the equipment and the patient, FIO2 , volume of the alveolar sample, number of tests, and acceptable variability in results – are taken into account.

QUALITYCONTROL OF TEST RESULTS

Guidelines for standardization play a major role in reducing discrepancies between laboratories. However, measures are also required to ensure accuracy and reproducibility within any given laboratory. Among the elements of control that merit consideration are calibration, validation of calibration, and performance of a control measurement. Calibration is the adjustment of an instrument's output so that it validly reflects a known input. Verification of calibration entails introduction of the same known input and demonstration that the correct output is reproduced. Performance of a control measurement refers to the testing of a substrate that has known properties, similar to those usually tested, to prove the accuracy of the instrumentation. One example of the application of these principles is blood gas analysis. Use of control measurements derived from tonometered blood or commercially prepared buffer solutions is now widespread. Another example is assessment of diffusing capacity 85 and routine incorporation of simulator testing in its measurement. 86 Unfortunately, similar controls do not exist for pulmonary function tests.

Therefore, laboratory technologists have the responsibility for continuing to be alert, not only with respect to faithful observance of guidelines for standardization, but also to detect in-house sources of error – for example, a leak in the system, malfunction of gas analyzers, faulty analog-to-digital converters, and faulty electronics that reduce frequency response.

RESPONSIBILITY AND COST IN QUALITY CONTROL

All who work in the laboratory must be concerned with quality control 87 and resist the frequent temptation to cut corners. Time has to be set aside for the technologist to care for and calibrate equipment, to establish proper control values for the laboratory, to search for inconsistencies in the data and interpretation, and to keep up with changing standards. Also, equipment and supplies, including calibrating syringes and calibrating gases, are expensive. However, when put into the balance, the cost and waste of producing erroneous results exceed, by far, the expense of practicing quality control.

INFECTION CONTROL

Given the relatively close contact between patients and technical staff during performance of pulmonary function tests, the issue of infection control is one that must be carefully considered. To date, the role of pulmonary function equipment in transmission of disease appears to be minimal. Although the presence of potential pathogens on laboratory mouthpieces, valves, and tubing has been well documented, implication of these organisms in the transmission of disease has not been established. Nevertheless, the potential hazards should be recognized and appropriate care exercised. Infection control begins with practice of the basic principles of hygiene. Hand washing between patients and use of protective gloves by staff when they are handling potentially contaminated equipment are important considerations. Care must

be taken in working with mouthpieces, nose clips, and any other implements that come in contact with mucosal surfaces. These devices, if reused, should be disinfected or sterilized after each use. Other equipment – manifolds, tubing, etc. – should be sterilized on a regular basis. In fact, guidelines from the ATS call for the disinfection or sterilization before reuse of any equipment surface with visible condensation from expired air. (21) Because of recent growing concern over cross-contamination among patients and laboratory personnel, manufacturers now produce a variety of in-line filters and disposable pneumotachographs. Care should be taken, however, to assure that response characteristics of the test equipment are not driven to unacceptable levels by use of these devices. Current literature on this topic should be consulted regularly.

APPROACH TO INTERPRETING COMMONLY PERFORMED PULMONARY FUNCTION TESTS

A standard battery of pulmonary function tests is commonly used to identify and quantify abnormalities in the performance of the respiratory system. An organized approach to interpreting these studies is critical. Once a patient's baseline values are established, the tests are valuable in tracking the course of the disorder and its response to treatment. Results of pulmonary function tests are interpreted by comparing individual patient data with reference or predicted values for normal subjects.(21) Ideally, predicted values should be generated from large groups of well-defined, normal or healthy subjects with proper distribution of anthropometric characteristics such as sex, age and height, and ethnic background. Despite dedicated attempts to improve prediction formulas, however, many still fail to take into account important sources of discrepancy, such as the racial and ethnic backgrounds of the patients and the control population, the effects of altitude and exposure to air pollution, and effects of inordinate

body size or old age. As a result, not all sets of predicted normals are applicable in pulmonary function laboratories outside the immediate vicinity of the patient populations from whom the data were collected. Extrapolation beyond the characteristics of the reference population should be avoided. Published guidelines from a joint Task Force of the ATS and ERS recommended that in the United States, ethnically appropriate reference equations from the National Health and Nutrition Examination Survey (NHANES) III be used for individuals aged 8 to 80 years. The Task Force did not recommend any specific set of reference equations for laboratories in Europe, but it suggested the need for an investigation conducted throughout Europe to derive contemporary equations for prediction of normal lung function. The same ATS/ERS Task Force recommended that each pulmonary function test result falling below the fifth percentile of the frequency distribution of values measured in the reference population be considered abnormal. If normal test results fall in a normal distribution, values below the fifth percentile can be estimated using Gaussian statistics. If the distribution of normal values is non-Gaussian, the lower limit of normal is estimated using a nonparametric technique, for example, the 95th percentile method. Traditionally, but without a sound statistical basis, most laboratories have used an arbitrary cut-off of 80% predicted to define normal. While this method may be reasonable in children, errors may arise if it is applied to adult test results.

INTERPRETATION SCHEME AND CLASSIFICATION OF ABNORMAL PATTERNS

A variety of schemes have been proposed for sorting out abnormalities in pulmonary function test results. Many are based on initial categorization of findings reflective of one of the four basic patterns described in the following paragraphs. An obstructive

pattern stems from narrowing of any portion of the airways – from upper airway to bronchioles less than 2 mm in diameter – that results in a reduction of maximal airflow in relation to maximal volume. A restrictive pattern is elicited by diseases of the lung, chest wall, pleural space, or neuromuscular respiratory apparatus that reduce lung volumes, particularly TLC, and vital capacity. A combined obstructive–restrictive pattern results from pathologic processes that reduce lung volumes, vital capacity, and airflow, and that also include an element of airway narrowing. Finally, abnormal gas transfer may be noted as part of one of the aforementioned patterns or in isolation and reflects an abnormality in the alveolar capillary membrane, impairing oxygen uptake from alveolar gas to pulmonary capillary blood. Overlap among categories is not uncommon. For example, widespread interstitial disease, as in idiopathic pulmonary fibrosis, often shows a pattern that indicates important components of both restrictive disease and abnormal gas transfer. One useful sequence recommended by the ATS/ERS Task Force for analyzing a conventional battery of pulmonary function test results is illustrated in Figure 21

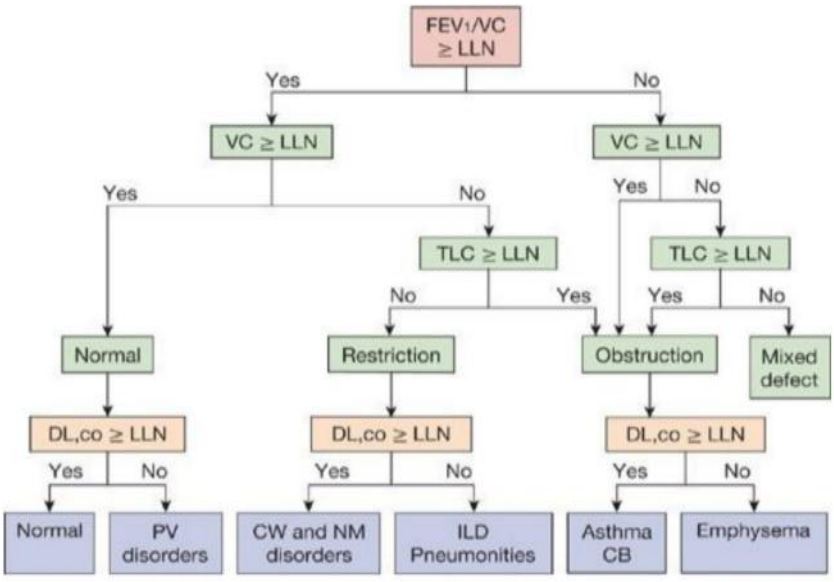


Figure 20 Proposed sequence of test review in the interpretation of pulmonary function tests. See text for discussion. LLN, lower limit of normal; PV, pulmonary vascular; CW, chest wall; NM, neuromuscular; ILD, interstitial lung disease; CB, chronic bronchitis

Analysis begins with evaluation of the ratio of FEV1 to VC. While, historically, the ratio of FEV1 to FVC (FEV1 /FVC%) served as the basis for distinguishing obstructive disorders from normality or restrictive disease, the ATS/ERS Task Force currently recommends using as the denominator the FVC, or the VC ("slow" VC or SVC), or the FIVC, whichever is greatest. If the ratio is less than the lower limit of normal (i.e., below the fifth percentile) and the VC (defining VC as any of the three previously noted vital capacity measurements) is at or above the lower limit of normal, the pattern is obstructive. If TLC is not at or above the lower limit of normal, a mixed obstructive–restrictive pattern is suggested. Distinction between asthma and chronic bronchitis on the one hand, and emphysema on the other, is based upon whether the DLCO is normal (asthma or chronic bronchitis) or reduced (emphysema). The previous practice of using a value for FEV1 /FVC% of less than 70% to define obstruction results in misdiagnosis of airway obstruction in men over 40 years and women over 50 years of age, as well as overdiagnosis of COPD in elderly, asymptomatic nonsmokers. If FEV1 /VC and VC are each equal to or greater than the respective lower limits of normal, spirometry is considered normal; measurement of the DLCO can then help distinguish between normal pulmonary function and pulmonary vascular disorders. If VC is below the lower limit of normal, a reduced TLC supports a diagnosis of restriction, while a normal TLC indicates an obstructive pattern. Once again, in the setting of a restrictive pattern, measurement of DLCO can be used to distinguish between pulmonary parenchymal

disorders and disorders of the chest wall or respiratory muscles. Note that according to these guidelines, an obstructive pattern may be diagnosed in the setting of a normal FEV1 /VC, if VC is reduced and TLC is normal or elevated. Once the predominant abnormality is defined with initial pulmonary function testing, the whole battery may not be necessary in following the course of the disease or in assessing its response to treatment. For example, particular determinations, such as spirometry, may suffice in patients with airway diseases. Notably, according to the ATS/ERS guidelines, the severity of the abnormality in each of the obstructive, restrictive, or mixed patterns is expressed on the basis of the FEV1 (Table 14). Standards have been established for defining significant changes in results over time: A 15% or greater change in FVC or in FEV1 , or a greater than 10% change in DLCO is considered significant.(22)

Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1)		
In patients with $FEV_1/FVC < 0.70$:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

Table 14 COPD severity courtesy:Global strategy for the diagnosis management and prevention of COPD Report 2017

Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) is the volume of air forcefully expelled from the lungs in one quick exhalation, and is a reliable indicator of ventilation adequacy as well as airflow obstruction. The normal peak flow value can range from person to person and is dependent upon factors such as sex, age and height. PEFR is typically higher in males than females and higher in taller patients. After expected increases through

childhood and adolescence, PEFR decreases with age from 30-40 years onwards (see Figure 21)

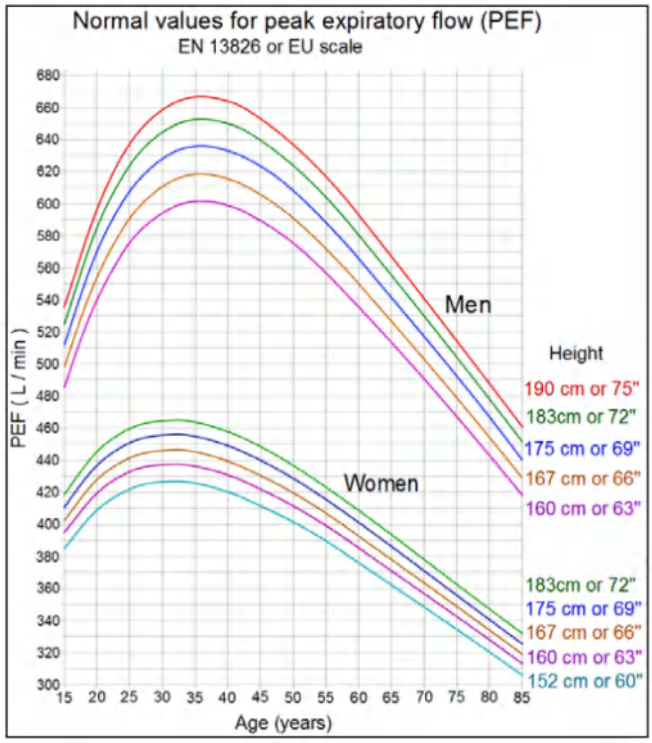


Figure 21 Normal values for PEFR

Asthma is the most common condition that affects peak flow. However, other conditions such as Chronic Obstructive Pulmonary Disease (COPD) that cause airway obstruction can also affect PEFR. Peak Flow and Metered Dose Inhalers Peak Flow Chart Peak Flow Chart Image Source: http://en.wikipedia.org/wiki/Peak_expiratory_flow Asthma is a chronic condition characterised by exacerbations of airway hypersensitivity, bronchoconstriction, mucus secretion and inflammation of the lower airways. An exacerbation of asthma caused by a trigger (for example cold air) results in the narrowing of the lower airways, trapping air and resulting in the individual struggling to exhale. This can lead to a ventilation/perfusion mismatch, hypoxia, hypercapnia and acid-base imbalances, each of which can lead to further potentially life-threatening complications if not treated in a

timely manner. Peak expiratory flow is a simple and easy, yet essential diagnostic tool used to assess asthma severity. Peak flow is also an important measure of the effectiveness of treatment with bronchodilator therapy. Peak flow meters (EU/EN ISO standard) are handheld devices used to measure PEFR in the ambulatory setting. The differences between Peak Flow Meters and Spirometry are shown in Figure 22

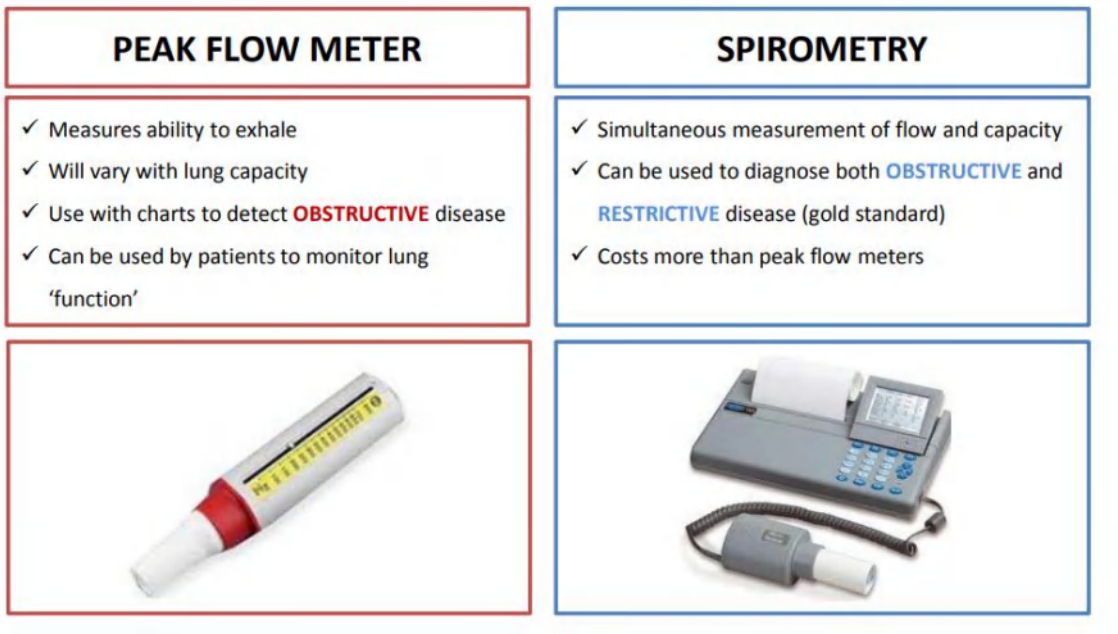


Figure 22 The differences between Peak Flow Meters and Spirometry

Clinical Indications

Indications for Peak Flow In the pre-hospital setting, peak flow can be used to assess the severity of an asthma exacerbation). It is also indicated to assess the effects of therapy post nebulisation

Contra-indications: Patients who are severely short of breath and unable to achieve full inspiration may not tolerate a peak flow, and in situations where the patient is in severe respiratory distress, attempting a peak flow may quicken deterioration of their breathing

Peak Flow and Metered Dose Inhalers

Patients diagnosed with asthma may already have a peak flow meter and undertake daily readings, logging these on their own personalised charts. Peak flow readings can change throughout the day therefore patients are advised to record their readings both morning and evening. It is important to ascertain what an individual's normal and best PEFR values are and compare current readings along with the normal values chart(23)

Performing the Procedure

Peak Flow and Metered Dose Inhalers Procedure

Introduce, EXPLAIN, consent

- Ask the patient to: Slide the marker down as far as it will go. This sets the meter at zero
- Stand up
- Breathe out fully
- Take a deep breath in with their mouth open
- Place the meter in their mouth with their lips forming a tight seal around the mouthpiece
- Keep their fingers away from the markings
- Blow out once as hard and fast as they can
- Repeat two more times (resetting the marker to zero each time)
- Their peak flow is the HIGHEST of these 3 reading

Figure 23 PERFORMING PRFR PROCEDURE

Clinical implications and patient management

During an exacerbation of asthma, air becomes trapped due to bronchoconstriction and inflammation and therefore limits the volume of air exhaled during each breath. This can present with differing levels of severity which can affect peak flow values

Asthma Severity

- Mild/moderate :PEFR >50-75% best or predicted
- Acute severe : Adults: PEFR 33-50% best or predicted

  Paediatrics 1 year and over: PEFR 33-50% best or predicted
- Life threatening • Adults: PEFR <33%best or predicted

  Paediatrics 1 year and over: PEFR <33-50%best or predicted

METHODOLOGY

Materials and Methods

Study area – Govt. Stanley Medical College and Hospital

Study population – Moderate and severe COVID positive patients admitted in Stanley COVID ICU and COVID wards and discharged after clinical recovery who came for follow up to Post covid Follow up OPD in Stanley after 3 months

Sample size-100

Sampling – Convenient sampling

Study design – Prospective observational study

Study duration – November 2020 to April 2021

Inclusion criteria

- COVID-19 RT PCR positive patients
- SpO2<94% in room air on admission
- Respiratory rate>24/min on admission
- CT chest suggestive of CORADS 5
- Lab investigations supporting moderate/ severe COVID-19

Exclusion criteria

- Asymptomatic, Mild and moderate cases of COVID-19.
- Pregnant women
- Past History of Lung disease

Data collection: Demographic, risk factors and clinical features, laboratory and radiological data, treatment and mortality rates will be registered.

STATISTICAL ANALYSIS:

From the reference study done by Fumagalli et al, Germany

Formula:

$n=Z_{a/2}^2\ SD^2\ /d^2$

where n=Sample size

$Z_{a/2}$ = 1.96 (Statistically significant constant for 95% CI)

Sd= 0.86 (Standard deviation of Forced Vital Capacity among ppost COVID19 patients from previous study.)

d = 10 % relative precision (ie 10% of 2.07 = 0.2)

On substituting this in the above formula

n=3.84 x 0.9 x 0.9 /0.04

n =79

Adding 20% non response rate (ie 20% of 79 = 16)

n=95 (Minimum sample size)

Therefore **n = 100 (1 group).**

STUDY TOOLS:

- Questionnaire with Basic demographic details of the patient such as name, etc.
- Spirometer ,PEFR flow meter.

DATA COLLECTION:

After getting permission from Institutional Ethical Committee information regarding the study will be explained to the patients with. Written and informed consent will be obtained from them.

ANALYSIS:

- After collecting the data will be compiled and entered in Microsoft Excel sheet.
- All continuous variables will be done using Statistical software version 16.
- All continuous variables will be expressed as Mean Standard Deviation.
- P value of <0.05 is taken as significant.

INFORMED CONSENT:

Consent form was prepared in both English and Tamil for obtaining patient permission. Further the study was explained orally to the patients in their own language and consent was obtained from the participants. Absolute confidentiality will be always maintained.

ETHICAL CONSIDERATION:

Patients will be given a Patient Information sheet and informed consent form that will be verbally explained to the patients orally in a language they understand. Confidentiality will be maintained.

CONFLICT OF INTEREST: None to declare

FINANCIAL DISCLOSURE: None to declare

PERMISSION: Written permission will be obtained from the Heads of Department of General Medicine, Nephrology and Biochemistry.

STATISTICAL ANALYSIS

Results and Observations:

The collected data were analysed with IBM SPSS Statistics for Windows, Version 23.0.(Armonk, NY: IBM Corp).To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. To predict the influencing factors for the severity of the disease the Binary logistic regression with enter method was used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In all the above statistical tools the probability value .05 is considered as significant level.

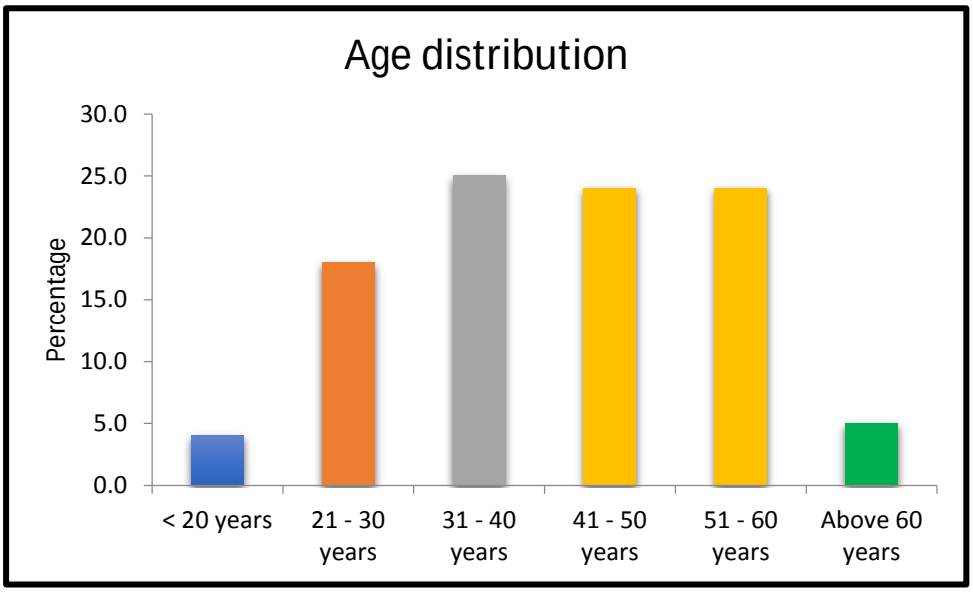


Figure 1

Table 1: Age distribution

Age distribution		
	Frequency	Percent
< 20 years	4	4.0
21 - 30 years	18	18.0
31 - 40 years	25	25.0
41 - 50 years	24	24.0
51 - 60 years	24	24.0
Above 60 years	5	5.0
Total	100	100.0

The above table shows Age distribution were <20 years is 4.0%, 21-30 years is 18.0%, 31-40 years is 25.0%, 41-50 years is 24.0%, 51-60 years is 24.0%, >60 years is 5.0%.

Table 2: Gender distribution

Gender distribution		
	Frequency	Percent
Male	51	51.0
Female	49	49.0
Total	100	100.0

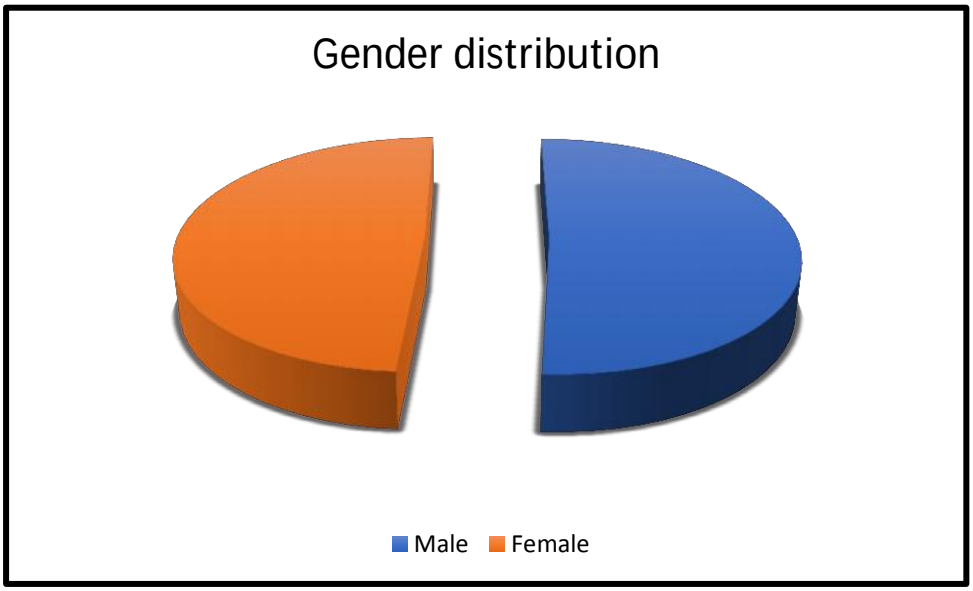


Figure 2

The above table shows Gender distribution were Female is 49.0%, Male is 51.0%.

Table 3: Distribution of Co morbidities

Co morbidities		
	Frequency	Percent
Not known	68	68.0
Present	32	32.0
Total	100	100.0

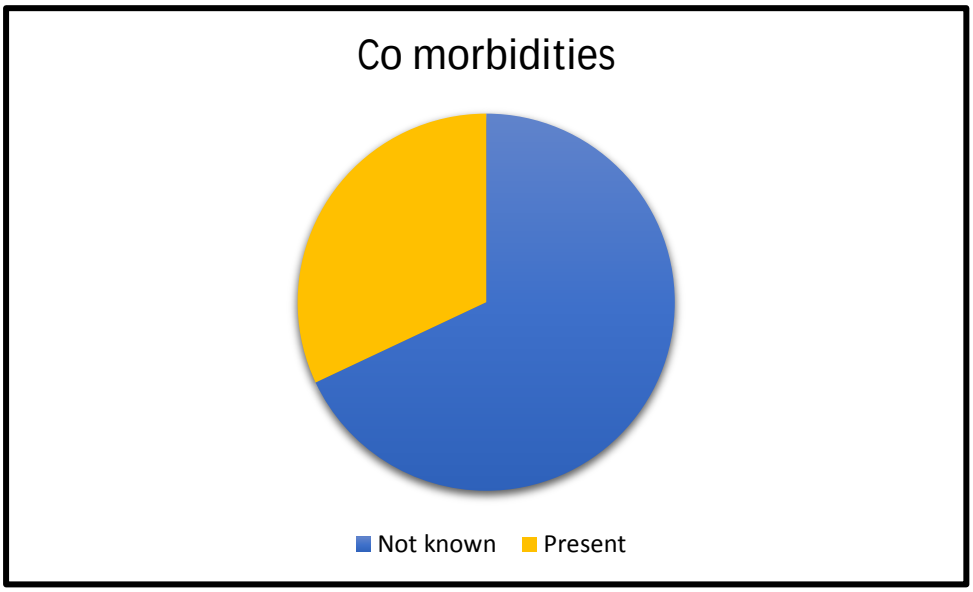


Figure 3

The above table shows Co morbidities distribution were not known is 68.0%, Present is 32.0%.

Table 4: Distribution of Smoking habit

Smoking habit		
	Frequency	Percent
Absent	83	83.0
Present	17	17.0
Total	100	100.0

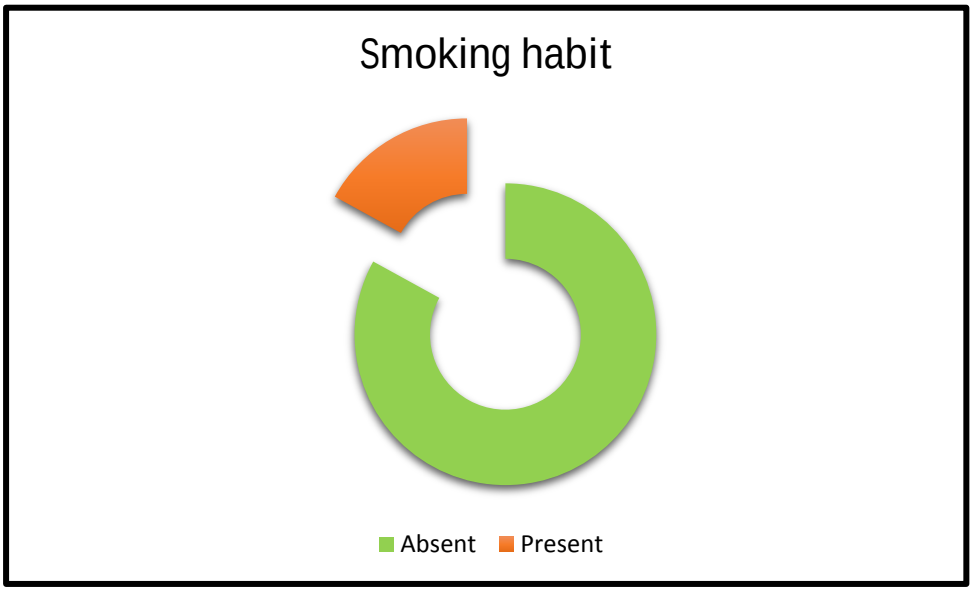


Figure 4

The above table shows Smoking habit distribution were absent is 83.0%, present is 17.0%.

Table 5: Distribution of BMI

BMI		
	Frequency	Percent
< 17.5	8	8.0
17.5 - 22.9	18	18.0
23 - 27.4	24	24.0
27.5 - 32.4	25	25.0
32.5 - 37.4	24	24.0
> 37.5	1	1.0
Total	100	100.0

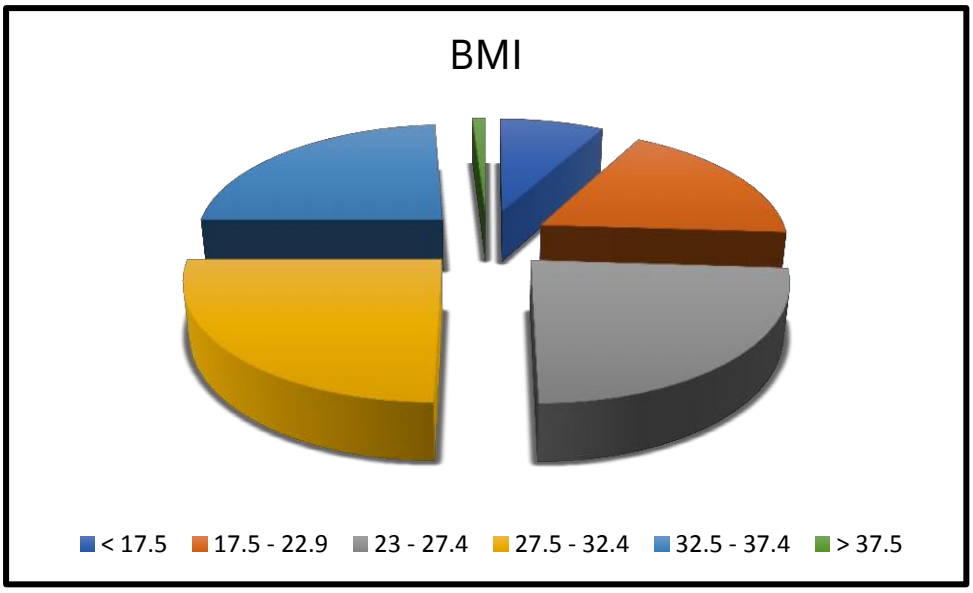


Figure 5

The above table shows BMI distribution were < 17.5 is 8.0%, 17.5 - 22.9 is 18.0%, 23 - 27.4 is 24.0%, 27.5 - 32.4 is 25.0%, 32.5 - 37.4 is 24.0%, > 37.5 is 1.0%.

Table 6: Distribution of Severity of the disease

Severity of the disease		
	Frequency	Percent
Moderate	72	72.0
Severe	28	28.0
Total	100	100.0

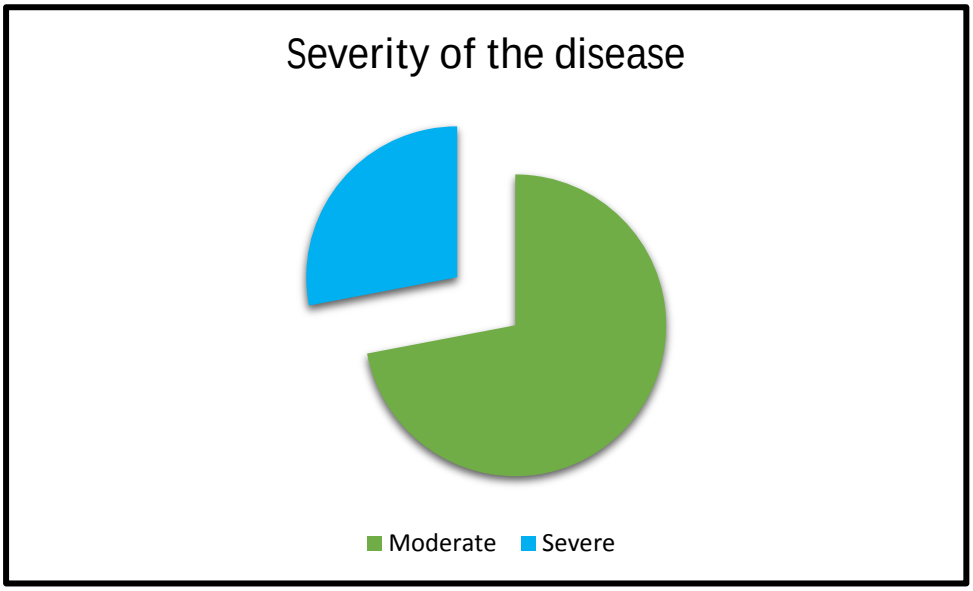


Figure 6

The above table shows Severity of the disease distribution were Moderate is 72.0%, Severe is 28.0%.

Table 7: Distribution of Abnormality

Abnormality		
	Frequency	Percent
Restrictive	33	33.0
Obstructive	14	14.0
Normal	53	53.0
Total	100	100.0

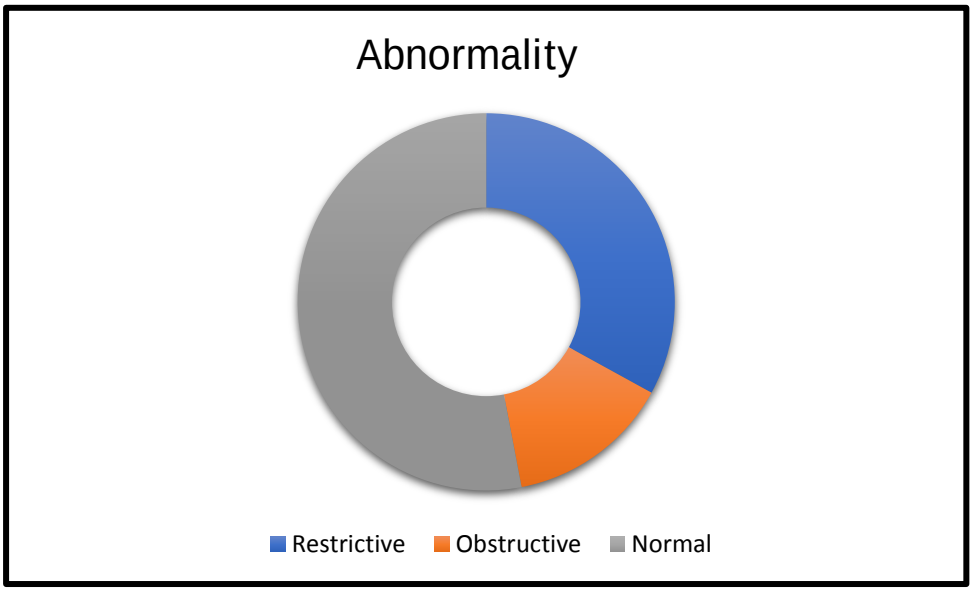


Figure 7

The above table shows Abnormality distribution were Restrictive is 33.0%, Obstructive is 14.0%, Normal is 53.0%.

Table 8: Comparison of Age between Severity by Pearson's Chi-Square test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
Age	< 20 years	Count	4	0	4	13.244	0.021*
		%	5.6%	0.0%	4.0%		
	21 - 30 years	Count	18	0	18		
		%	25.0%	0.0%	18.0%		
	31 - 40 years	Count	18	7	25		
		%	25.0%	25.0%	25.0%		
	41 - 50 years	Count	15	9	24		
		%	20.8%	32.1%	24.0%		
	51 - 60 years	Count	15	9	24		
		%	20.8%	32.1%	24.0%		
	Above 60 years	Count	2	3	5		
		%	2.8%	10.7%	5.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
* Statistical Significance at p < 0.05 level							

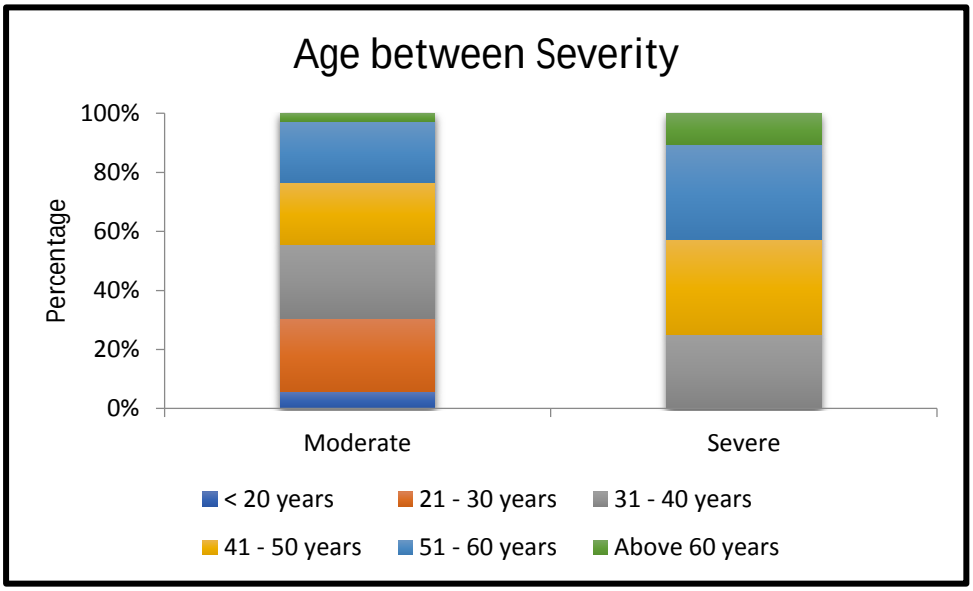


Figure 8

The above table shows comparison of Age between Severity by Pearson's Chi-Square test were □2=13.244, p=0.021<0.05 which shows statistical significance between Age and Severity.

Table 9: Comparison of Gender between Severity by Pearson's Chi-Square test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
Gender	Male	Count	43	8	51	7.828	0.005 **
		%	59.7%	28.6%	51.0%		
	Female	Count	29	20	49		
		%	40.3%	71.4%	49.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
** Highly Statistical Significance at p < 0.01 level							

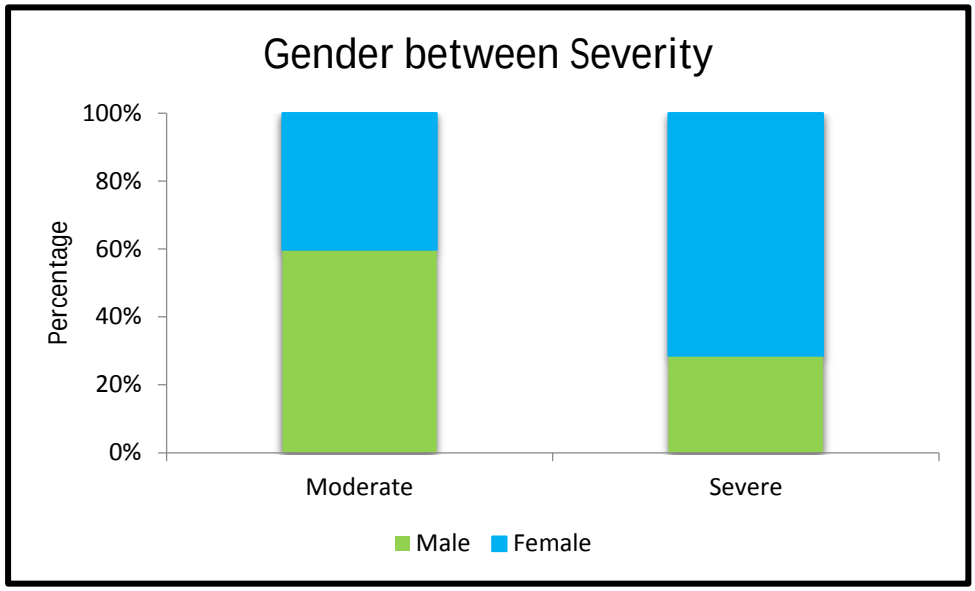


Figure 9

The above table shows comparison of Gender between Severity by Pearson's Chi-Square test were □2=7.828, p=0.005<0.01 which shows highly statistical significance between Gender and Severity.

Table 10: Comparison of Co morbidities between Severity by Pearson's Chi-Square test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
Co morbidities	Not known	Count	55	13	68	8.316	0.004 **
		%	76.4%	46.4%	68.0%		
	Present	Count	17	15	32		
		%	23.6%	53.6%	32.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
** Highly Statistical Significance at p < 0.01 level							

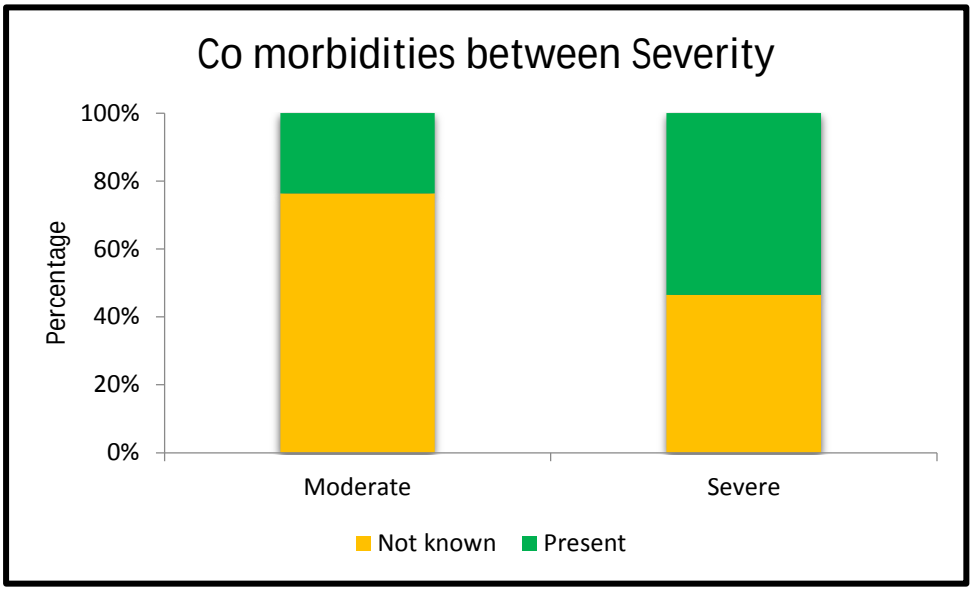


Figure 10

The above table shows comparison of Co morbidities between Severity by Pearson's Chi-Square test were □2=8.316, p=0.004<0.01 which shows highly statistical significance between Co morbidities and Severity.

Table 11: Comparison of Smoking between Severity by Fisher's Exact test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
Smoking	Absent	Count	59	24	83	0.203	0.773 #
		%	81.9%	85.7%	83.0%		
	Present	Count	13	4	17		
		%	18.1%	14.3%	17.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
# No Statistical Significance at p > 0.05 level							

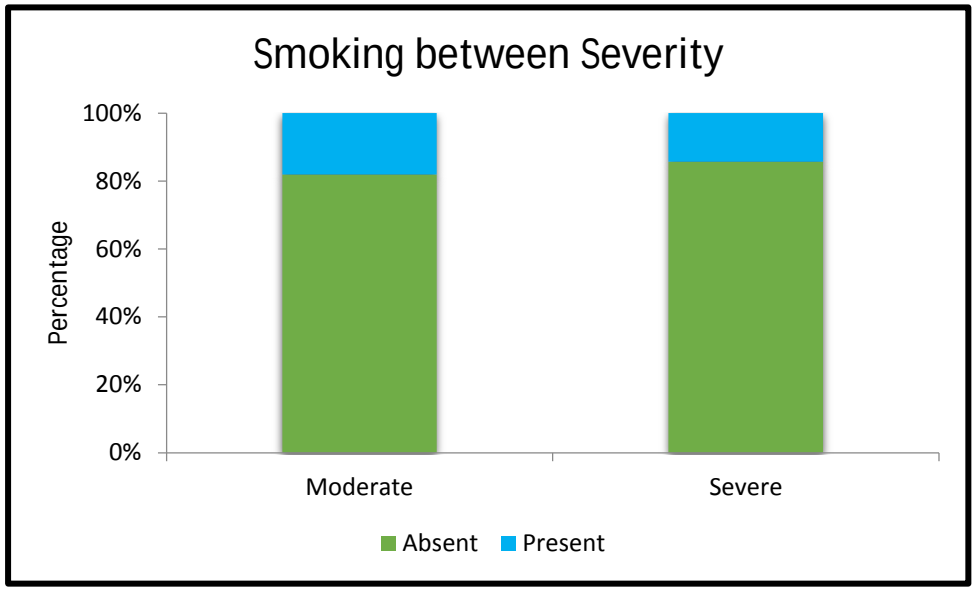


Figure 11

The above table shows comparison of Smoking between Severity by Fisher's Exact test were □2=0.203, p=0.773>0.05 which shows no statistical significance between Smoking and Severity.

Table 12: Comparison of BMI between Severity by Pearson's Chi-Square test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
BMI	< 17.5	Count	7	1	8	11.453	0.043*
		%	9.7%	3.6%	8.0%		
	17.5 - 22.9	Count	13	5	18		
		%	18.1%	17.9%	18.0%		
	23 - 27.4	Count	18	6	24		
		%	25.0%	21.4%	24.0%		
	27.5 - 32.4	Count	12	13	25		
		%	16.7%	46.4%	25.0%		

	32.5 - 37.4	Count	21	3	24		
		%	29.2%	10.7%	24.0%		
	> 37.5	Count	1	0	1		
		%	1.4%	0.0%	1.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
* Statistical Significance at p < 0.05 level							

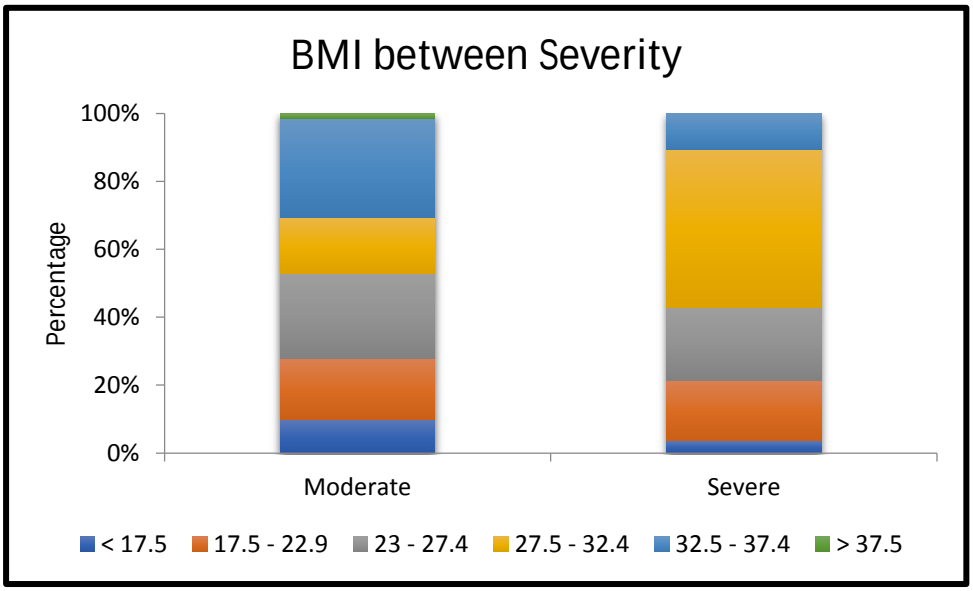


Figure 12

The above table shows comparison of BMI between Severity by Pearson's Chi-Square test were χ^2=11.453, p=0.043<0.05 which shows statistical significance between BMI and Severity.

Table 13: Comparison of Abnormality between Severity by Pearson's Chi-Square test

			Severity		Total	□ 2 - value	p-value
			Moderate	Severe			
Abnormality	Restrictive	Count	16	17	33	19.646	0.0005 **
		%	22.2%	60.7%	33.0%		
	Obstructive	Count	8	6	14		
		%	11.1%	21.4%	14.0%		
	Normal	Count	48	5	53		
		%	66.7%	17.9%	53.0%		
Total		Count	72	28	100		
		%	100.0%	100.0%	100.0%		
** Highly Statistical Significance at p < 0.01 level							

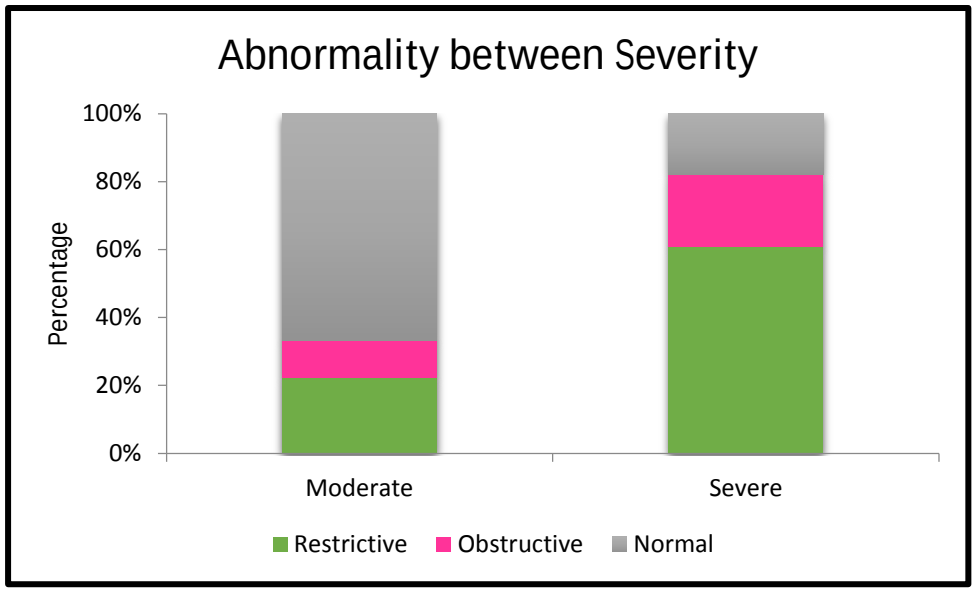


Figure 13

The above table shows comparison of Abnormality between Severity by Pearson's Chi-Square test were □2=19.646, p=0.0005<0.01 which shows highly statistical significance between Abnormality and Severity.

Table 14: Comparison of FEV1/FVC % between Severity by Unpaired sample t-test

Variable	Severity	N	Mean	SD	t-value	p-value
FEV1/FVC %	Moderate	72	86.8	9.3	1.121	0.265 #
	Severe	28	84.3	10.9		
# No Statistical Significance at p > 0.05 level						

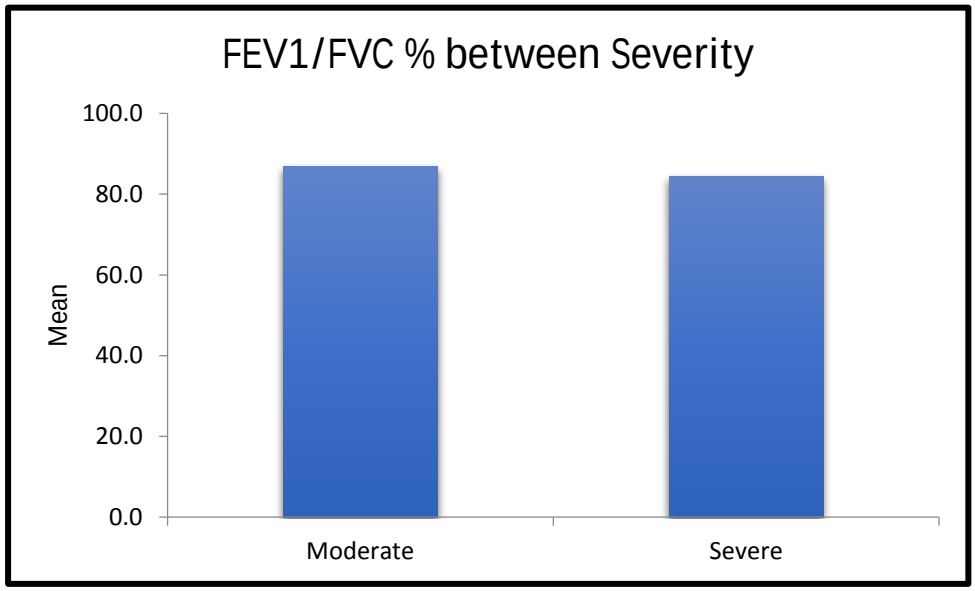


Figure 14

The above table shows comparison of FEV1/FVC % between Severity by Unpaired t-test were t-value=1.121, p-value=0.265>0.05 which shows no statistical significance difference at p > 0.05 level.

Table 15: Comparison of FEV1 % between Severity by Unpaired sample t-test

Variable	Severity	N	Mean	SD	t-value	p-value
FEV1 %	Moderate	72	93.5	9.4	7.184	0.0005 **
	Severe	28	81.3	6.8		
** Highly Statistical Significance at p < 0.01 level						

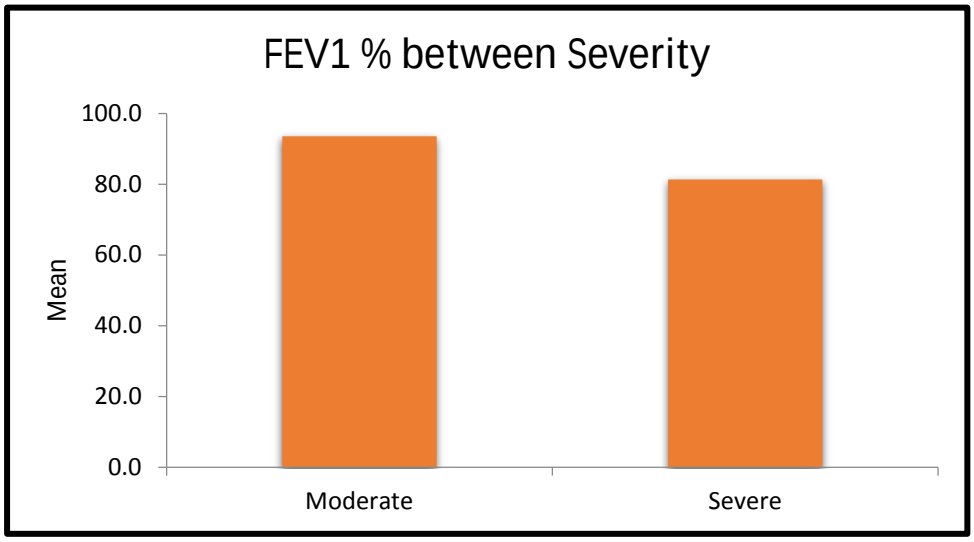


Figure 15

The above table shows comparison of FEV1 % between Severity by Unpaired t-test were t-value=7.184, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.

Table 16: Comparison of FVC % between Severity by Unpaired sample t-test

Variable	Severity	N	Mean	SD	t-value	p-value
FVC %	Moderate	72	90.2	11.1	6.644	0.0005 **
	Severe	28	78.4	6.3		
** Highly Statistical Significance at p < 0.01 level						

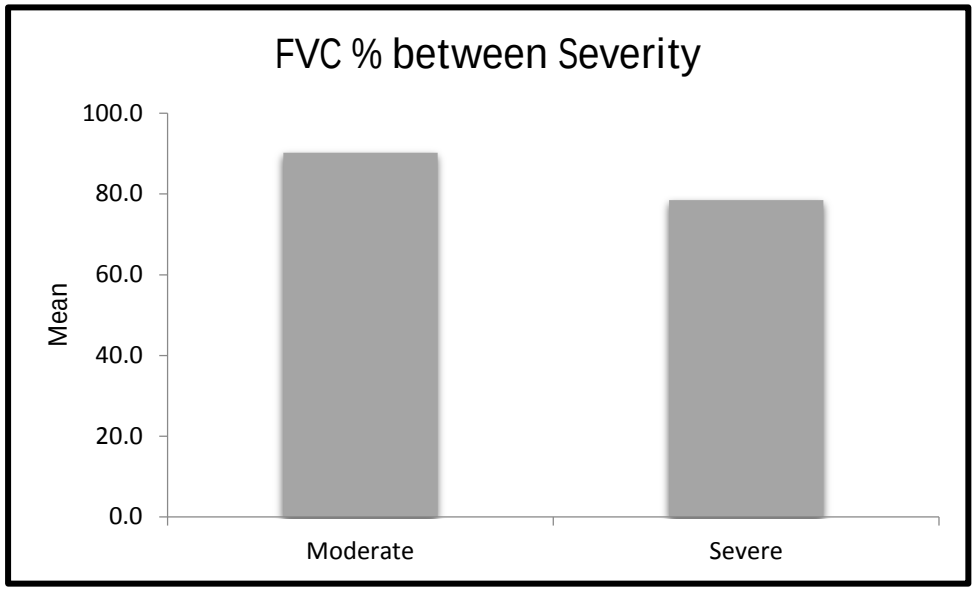


Figure 16

The above table shows comparison of FVC % between Severity by Unpaired t-test were t-value=6.644, p-value=0.0005<0.01 which shows highly statistical significance difference at $p < 0.01$ level.

Table 17: Comparison of PEFR % between Severity by Unpaired sample t-test

Variable	Severity	N	Mean	SD	t-value	p-value
PEFR %	Moderate	72	89.0	6.9	0.813	0.418 #
	Severe	28	87.6	8.2		
# No Statistical Significance at p > 0.05 level						

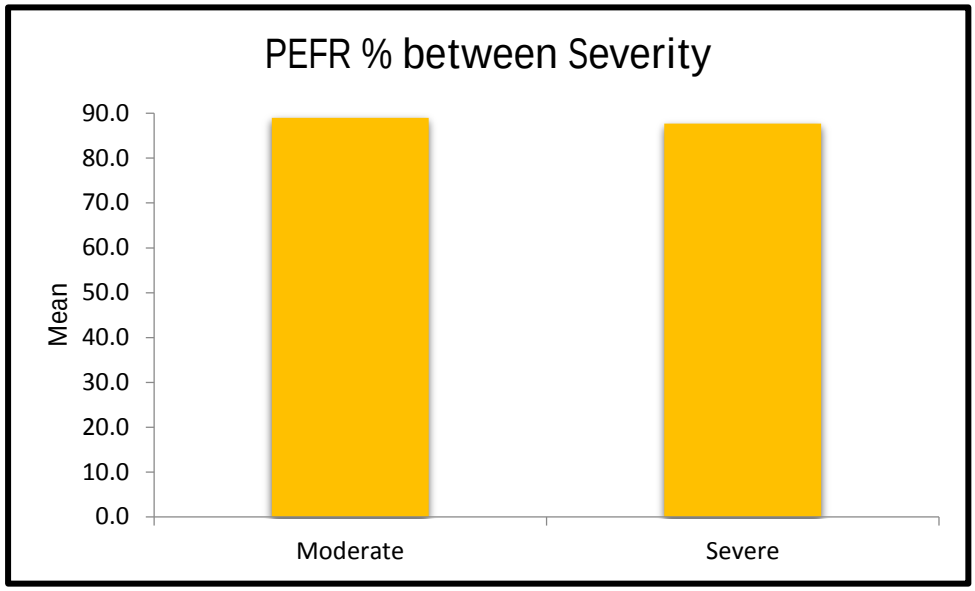


Figure 17

The above table shows comparison of PEFR % between Severity by Unpaired t-test were t-value=0.813, p-value=0.418>0.05 which shows no statistical significance difference at p > 0.05 level.

Table 18: Comparison of Binary logistic Regression Model for Severity

Variables in the Equation								
	B	S.E.	Wald	df	p-value	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Age	.292	.330	.784	1	0.376 #	1.340	.701	2.559
Gender	1.390	.672	4.283	1	0.038 *	4.017	1.076	14.988
Comorbidities	1.140	.685	2.776	1	0.096 #	3.128	.818	11.966

Smoking	.754	1.035	.530	1	0.466 #	2.125	.280	16.144
BMI	-.142	.275	.266	1	0.606 #	.868	.507	1.487
FEV1FVC	.060	.043	1.990	1	0.158 #	1.062	.977	1.154
FEV1	-.204	.064	10.246	1	0.001 **	.815	.719	.924
FVC	-.049	.050	.971	1	0.324 #	.952	.863	1.050
PEFR	.010	.054	.037	1	0.848 #	1.010	.909	1.124
Constant	9.468	6.098	2.411	1	0.121 #	12935.004		

The above table shows Binary logistic Regression Model for Severity of the disease which shows Gender and FEV1 were Statistically Significant predictor with p-value=0.038<0.05 and p-value = 0.001<0.001 respectively.

Summary

- The Age distribution were <20 years is 4.0%, 21-30 years is 18.0%, 31-40 years is 25.0%, 41-50 years is 24.0%, 51-60 years is 24.0%, >60 years is 5.0%.
- The Gender distribution were Female is 49.0%, Male is 51.0%.
- The Co morbidities distribution were Not known is 68.0%, Present is 32.0%.
- The Smoking habit distribution were Absent is 83.0%, Present is 17.0%.
- The BMI distribution were < 17.5 is 8.0%, 17.5 - 22.9 is 18.0%, 23 - 27.4 is 24.0%, 27.5 - 32.4 is 25.0%, 32.5 - 37.4 is 24.0%, > 37.5 is 1.0%.
- The Severity of the disease distribution were Moderate is 72.0%, Severe is 28.0%.
- The Abnormality distribution were Restrictive is 33.0%, Obstructive is 14.0%, Normal is 53.0%.
- The Age between Severity by Pearson's Chi-Square test were χ^2=13.244, p=0.021<0.05 which shows statistical significance between Age and Severity.
- The Gender between Severity by Pearson's Chi-Square test were χ^2=7.828, p=0.005<0.01 which shows highly statistical significance between Gender and Severity.
- The Co morbidities between Severity by Pearson's Chi-Square test were χ^2=8.316, p=0.004<0.01 which shows highly statistical significance between Co morbidities and Severity.
- The Smoking between Severity by Fisher's Exact test were χ^2=0.203, p=0.773>0.05 which shows no statistical significance between Smoking and Severity.

- The BMI between Severity by Pearson's Chi-Square test were □2=11.453, p=0.043<0.05 which shows statistical significance between BMI and Severity.
- The Abnormality between Severity by Pearson's Chi-Square test were □2=19.646, p=0.0005<0.01 which shows highly statistical significance between Abnormality and Severity.
- The FEV1/FVC % between Severity by Unpaired t-test were t-value=1.121, p-value=0.265>0.05 which shows no statistical significance difference at p > 0.05 level.
- The FEV1 % between Severity by Unpaired t-test were t-value=7.184, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.
- The FVC % between Severity by Unpaired t-test were t-value=6.644, p-value=0.0005<0.01 which shows highly statistical significance difference at p < 0.01 level.
- The PEFR % between Severity by Unpaired t-test were t-value=0.813, p-value=0.418>0.05 which shows no statistical significance difference at p > 0.05 level.

- The Binary logistic Regression Model for Severity of the disease which shows Gender and FEV1 were Statistically Significance predictor were in Gender p-value=0.038<0.05 and whereas in FEV1 p-value=0.001<0.001 respectively.

DISCUSSION

Covid 19 is a emerging infectious disease carrying a high risk of severe course and intensive care unit admission, it is particularly important to explore COVID-19 clinical characteristics, which may help to manage properly its sequelae in the post-acute phase. COVID-19 patients may present with a spectrum of symptoms ranging from asymptomatic, mild upper respiratory tract symptoms, to severe pneumonia and multiorgan failure.

The lung is the most common organ affected in SARS-CoV-2 infection. The predominant pattern of lung abnormalities during illness is ground-glass opacity. Furthermore, many patients have residual opacity on the chest CT scans, in which the main pattern is ground-glass opacity at the time of discharge . The pathology of the lung in COVID-19 patients includes diffused alveolar damage bronchiolitis, alveolitis and interstitial fibrosis . Thus, patients who are infected with SAR-CoV2 may have a restrictive or obstructive defect on a spirometry during recovery. Previous studies in Severe Acute Respiratory Syndrome (SARS) showed that patients had an abnormal pulmonary function test up to 20% after recovery from SARS. Few studies, mainly in China have reported abnormal lung function and six-minute-walk test (6MWT) in patients who were infected with SARS-CoV-2 after recovery. Most of these previous studies were conducted only in patients with pneumonia and those with mild symptoms were not included.

Results of the present case series suggest that COVID-19 pneumonia may result in clinically relevant alterations in pulmonary function tests, with a restrictive pattern in 10

out of 13 patients at the time of hospital discharge. After 6 weeks, pulmonary function improved, but some degree of restrictive alteration still persisted.

Alessia Fumagalli et al study revealed COVID-19 pneumonia may result in significant alterations in lung function, with a mainly restrictive pattern, partly persisting at 6 weeks after recovery. Further studies are needed to confirm this observation on wider populations and with a more detailed diagnostic work-up(24).

Yiying Huang et al concluded as Impaired diffusing-capacity, lower respiratory muscle strength, and lung imaging abnormalities were detected in more than half of the COVID-19 patients in early convalescence phase. Compared with non-severe cases, severe patients had a higher incidence of DLCO impairment and encountered more TLC decrease and 6MWD decline(25)

Xiaoneng mo et al study reveals that, in discharged survivors with COVID-19, impairment of diffusion capacity is the most common abnormality of lung function, followed by restrictive ventilatory defects, which are both associated with the severity of the disease. Pulmonary function tests (not only spirometry but also diffusion capacity) should be considered in routine clinical follow-up for certain recovered survivors, especially in severe cases. Subsequent pulmonary rehabilitation might be considered as an optional strategy.(26)

.

Previous data suggest that pulmonary function needs to be carefully investigated in COVID-19 patients, as it was already done for other atypical pneumonia. Indeed, pulmonary function tests were found to improve significantly in the first 3 months but with

no further significant improvement from 3 to 6 months after discharge among survivors to severe influenza A (H1N1) pneumonia and other studies showed a complete normalization of pulmonary function 6 months after H1N1-related ARDS.

So we have included the post covid recovered patients from moderate and severe covid at the time of admission who came fo follow up after 3 months from recovery

This study evaluated a total of 100 patients There were 51 men and 49 women with all age groups . 17% patients had a history of smoking.with 32% patients had pre existing comorbidities. No patient was reported having chronic respiratory diseases Among all subjects, 28 were severe cases (28%), 72 moderate cases (72%). There were mainly female patients(71.4%)in the severe group compared with moderate group with mainly male patients (59.7%). 33 patients (33%) had impairment of FVC, with majority from severe covid recovered patients(60.7%) There was no difference FEV1/FVC between the two groups. The majority of the impairment in FEV1 and FVC suggests a restrictive abnormality..

If our data will be confirmed by a more comprehensive diagnostic assessment, it will likely be necessary to rethink the pneumology services with an increase in the availability of respiratory rehabilitation units in the areas

LIMITATION

- small sample size in stratified analysis, only provides a short follow-up.
- pulmonary function tests before COVID-19 infection are not available for our patients for comparision
- The association between CT images and the lung function parameters was not analysed in our study.
- DLCO & Other lung volumes are not calculated because of the limited resource
- Other methods of pulmonary function assessment like 6 minute walk test Radiological investigations were not included

CONCLUSION

Patients surviving to COVID-19 pneumonia may present with a restrictive pulmonary pattern and some obstructive pattern with residual lung lesions, which is known to be associated with increased risk of life-threatening comorbidities While the need of further data with DLCO and plethysmography deserves to be recognized, our results suggest that survivors to COVID-19 pneumonia should be carefully screened for pulmonary function and rehabilitation needs at the end of acute phase, and eventually referred to specific care pathways to monitor and manage clinically relevant sequelae during follow-up

BIBLIOGRAPHY

1. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge | European Respiratory Society [Internet]. [cited 2022 Jan 8]. Available from: https://erj.ersjournals.com/content/55/6/2001217.short

2. Task Force of Pulmonary Function Testing and Clinical Respiratory Physiology, Chinese Association of Chest Physicians, Pulmonary Function Testing Group, Respiratory Therapeutics Group, Chinese Thoracic Society. [Expert consensus on pulmonary function testing during the epidemic of coronavirus disease 2019]. Zhonghua Jie He He Hu Xi Za Zhi Zhonghua Jiehe He Huxi Zazhi Chin J Tuberc Respir Dis. 2020 Apr 12;43(4):302–7.

3. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. :365.

4. CDC. COVID-19 and Your Health [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2022 Jan 9]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/how-covid-spreads.html

5. Lotfi M, Hamblin MR, Rezaei N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. Clin Chim Acta. 2020 Sep 1;508:254–66.

6. Walker K, O'Donoghue K, Grace N, Dorling J, Comeau J, Li W, et al. Maternal transmission of SARS-COV-2 to the neonate, and possible routes for such transmission: a systematic review and critical analysis. BJOG Int J Obstet Gynaecol. 2020 Oct;127(11):1324–36.

7. ClinicalManagementProtocolforCOVID19.pdf [Internet]. [cited 2022 Jan 9]. Available from: https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf

8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020 Mar 28;395(10229):1054–62.

9. Kidney impairment is associated with in-hospital death of COVID-19 patients | medRxiv [Internet]. [cited 2022 Jan 9]. Available from: https://www.medrxiv.org/content/10.1101/2020.02.18.20023242v1

10. Wong SH, Lui RN, Sung JJ. Covid-19 and the digestive system. J Gastroenterol Hepatol. 2020;35(5):744–8.

11. Liver injury in COVID-19: management and challenges - The Lancet Gastroenterology & Hepatology [Internet]. [cited 2022 Jan 9]. Available from: https://www.thelancet.com/journals/langas/article/PIIS2468-1253(20)30057-1/fulltext

12. COVID-19: consider cytokine storm syndromes and immunosuppression - The Lancet [Internet]. [cited 2022 Jan 9]. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext

13. Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: a retrospective case series study | medRxiv [Internet]. [cited 2022 Jan 9]. Available from: https://www.medrxiv.org/content/10.1101/2020.02.22.20026500v1

14. Jin Y-H, Cai L, Cheng Z-S, Cheng H, Deng T, Fan Y-P, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Mil Med Res. 2020 Feb 6;7(1):4.

15. Living guidance for clinical management of COVID-19 [Internet]. [cited 2022 Jan 9]. Available from: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-2

16. Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE [Internet]. NICE; [cited 2022 Jan 9]. Available from: https://www.nice.org.uk/guidance/ng191

17. Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020 Mar;25(3):278–80.

18. Harrison's Principles of Internal Medicine, 20e | AccessMedicine | McGraw Hill Medical [Internet]. [cited 2021 Dec 20]. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookId=2129&sectionId=159213747

19. Papandrinopoulou D, Tzouda V, Tsoukalas G. Lung Compliance and Chronic Obstructive Pulmonary Disease. Pulm Med. 2012;2012:542769.

20. Ingbar DH. Fishman's pulmonary diseases and disorders, 5th edition. Ann Am Thorac Soc. 2015 Aug 1;12(8):1255–6.

21. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the Normal Maximal Expiratory Flow-Volume Curve with Growth and Aging. Am Rev Respir Dis. 1983 Jun 1;127(6):725–34.

22. wms-GOLD-2017-Pocket-Guide.pdf [Internet]. [cited 2022 Jan 9]. Available from: https://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf

23. Media_678202_smxx.pdf [Internet]. [cited 2022 Jan 9]. Available from: https://www.gla.ac.uk/media/Media_678202_smxx.pdf

24. Fumagalli A, Misuraca C, Bianchi A, Borsa N, Limonta S, Maggiolini S, et al. Pulmonary function in patients surviving to COVID-19 pneumonia. Infection. 2020 Jul 28;1–5.

25. Huang Y, Tan C, Wu J, Chen M, Wang Z, Luo L, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. Respir Res. 2020 Jun 29;21(1):163.

26. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J [Internet]. 2020 Jun 1 [cited 2022 Jan 9];55(6). Available from: https://erj.ersjournals.com/content/55/6/2001217

STUDY PROFORMA

DEMOGRAPHIC DETAILS:

Name:
Age:

Gender:

Address:

Occupation:

Contact number:

Travel History:

History of contact with COVID19 positive patient:

Place of contact with COVID19 positive patient:

CO-MORBIDITIES:

Hypertension:

Diabetes:

Coronary Artery Disease:

Chronic Obstructive lung disease:

Chronic Kidney Disease:

Malignancy:

Immunosuppression:

HABITS:

Smoking:

Alcohol consumption:

PATIENT CATSGORY

Parameters assessed:

FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; PEFR peak expiratory flow rate

FEV1/FVC			
FEV1			
FVC			
PEFR			

INFORMED CONSENT

Assessment of Pulmonary Function in Post covid patients in a Tertiary care Institutions A Prospective observational study

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

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

I have completely understood the details of the study.

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

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

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

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

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

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

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

Investigator Signature and date

INFORMED CONSENT

Assessment of Pulmonary Function in Post covid patients in a Tertiary care Institutions A Prospective observational study

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

நான் ……,இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

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

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

நான் ஆய்வில் பங்குஎடுத்து பணம் எதையும் பெறமுடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை,

என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்ககூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்யபோகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல்ரேகை:	கையொப்பம் /விரல்ரேகை:
தேதி	தேதி

ஆராய்ச்சியாளராக கையொப்பம் மற்றும் தேதி

Age	Sex	Co morbidities	Smoking	BMI	PATIENT CATEGORY	FEV1/FVC %	FEV1 %	FVC %	PEFR %
3	1	1	1	1	1	78	82	77	88
4	2	2	1	4	1	96	98	97	90
2	2	1	1	3	1	105	108	104	98
5	1	2	1	5	1	68	84	75	78
1	1	1	1	5	1	87	95	96	94
6	1	2	1	4	2	89	97	76	97
2	1	1	1	3	1	94	99	92	88
1	2	1	1	2	1	94	91	94	87
3	2	1	1	3	2	69	76	88	76
5	2	2	1	4	2	76	78	77	98
4	2	1	2	2	2	91	93	72	90
6	1	2	1	5	2	95	75	77	98
2	1	1	1	4	1	83	88	86	99
4	2	1	1	5	1	88	98	75	91
3	2	1	1	3	1	87	106	75	83
5	1	2	1	5	1	83	105	103	93
2	1	1	1	3	1	94	103	100	90
3	1	1	2	2	1	85	97	99	83
4	2	2	1	4	2	95	96	76	103
5	2	1	1	5	1	85	84	74	93
3	2	1	1	3	1	93	88	90	73
4	1	1	1	5	1	86	97	95	90
5	1	2	1	4	1	95	97	78	98
2	2	1	1	2	1	83	93	92	89
6	1	2	2	3	2	94	76	79	88
3	1	2	1	4	2	84	83	73	90
5	2	1	1	2	1	92	87	88	96
4	2	1	1	5	1	86	84	85	98
3	1	1	2	4	1	68	78	83	75
4	1	2	1	5	1	89	104	105	98
2	2	1	1	3	1	98	106	108	90
5	2	1	1	5	1	94	105	103	89
3	1	2	1	2	1	97	88	79	87

4	1	1	1	3	2	84	74	79	88
5	2	1	1	4	2	96	84	85	89
2	1	1	2	5	1	83	90	89	90
3	2	2	2	2	2	67	78	81	79
4	2	1	1	3	1	97	95	75	92
5	1	1	1	4	2	68	75	70	72
2	2	1	1	1	1	86	100	99	86
6	1	2	1	4	1	95	88	73	89
4	1	1	1	2	2	84	86	88	85
3	2	2	1	5	2	97	83	89	80
5	2	1	1	1	2	86	88	75	85
5	1	1	2	1	1	88	110	107	85
4	2	2	1	2	1	63	76	73	75
3	1	1	2	1	1	90	99	98	90
2	1	1	1	3	1	98	92	90	94
3	2	1	1	5	1	89	86	88	89
4	2	1	1	4	2	97	73	72	86
2	1	1	1	1	1	87	88	87	87
5	1	2	1	2	1	85	95	74	90
4	2	1	1	4	2	64	79	85	78
5	2	1	1	3	1	96	88	73	90
3	2	2	1	5	2	94	75	73	97
5	1	1	2	2	1	67	79	89	77
3	1	1	1	3	1	85	98	97	85
2	1	1	1	4	1	80	95	98	87
4	2	2	1	5	1	80	84	78	94
5	2	2	2	3	2	88	83	74	91
3	1	1	1	2	1	86	78	80	93
5	1	2	1	1	1	66	82	90	74
4	2	1	1	4	2	63	78	84	76
2	1	1	1	4	1	96	99	97	89
3	2	1	1	3	2	89	88	90	84
4	1	2	2	2	1	90	107	105	83
2	2	1	1	5	1	80	104	103	88

5	2	1	1	4	2	84	74	71	85
4	1	1	2	5	1	96	110	108	96
5	2	1	1	3	1	93	92	77	94
3	1	2	1	2	1	84	91	89	95
5	2	2	1	4	2	98	89	88	98
2	1	1	1	3	1	94	106	105	95
3	1	2	1	5	1	89	95	93	92
4	2	2	1	4	1	68	82	79	73
5	2	1	1	5	1	94	87	76	86
2	1	1	2	3	1	94	106	103	88
3	1	1	1	1	1	96	93	95	94
4	2	1	1	3	1	89	97	98	96
1	2	1	1	4	1	74	95	98	80
3	1	1	2	3	1	90	89	92	93
2	1	1	1	4	1	97	86	88	96
1	1	1	1	5	1	86	83	82	93
4	2	2	1	2	2	85	81	70	87
4	2	1	1	6	1	80	99	78	98
3	1	2	2	3	1	82	90	76	94
2	1	1	1	5	1	83	107	104	90
5	2	2	1	4	2	87	76	73	95
4	2	1	1	3	1	64	76	80	79
5	1	2	1	4	2	89	78	76	89
3	1	2	1	2	1	95	110	112	88
2	2	1	1	5	1	86	101	105	83
4	2	2	1	3	2	80	84	76	95
3	1	1	2	4	1	94	98	97	96
5	1	1	1	5	1	86	93	78	90
4	2	1	1	2	1	66	72	83	70
5	2	1	1	3	1	95	89	91	99
3	1	1	1	4	1	93	82	85	88
6	1	1	2	5	1	84	106	104	94
3	2	1	1	2	2	68	77	79	75

Age group	
<20yrs	1
21-30 yrs	2
31-40 yrs	3
41-50 yrs	4
51-60 yrs	5
>60yrs	6

BMI	
<17.5	1
17.5-22.9	2
23-27.4	3
27.5-32.4	4
32.5-37.4	5
>37.5	6

Sex	
Male	1
Female	2

Co morbidities	
No known	1
DM/HTN/CKD/CAD/MALIGNANCY/ IMMUNOSUPPRESSION	2

Smoking	
No	1
YES	2

Patient category	
MODERATE	1
SEVERE	2

FEV1/FVC	Numbers
FEV1	numbers
FVC	numbers
PEFR	Numbers