RESCUE THERAPY FOR SEVERE COVID-19-ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA)- RETROSPECTIVE OBSERVATIONAL STUDY

BY
REGISTRATION NO: BR0120003

Dissertation

Submitted to
KAHER, Belagavi, Karnataka.
In partial fulfillment
of the requirements for the degree of

M.D in
RESPIRATORY MEDICINE

DEPARTMENT OF RESPIRATORY MEDICINE
J. N. MEDICAL COLLEGE
BELAGAVI- 590010. KARNATAKA

JUNE/JULY - 2023

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To,

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"RESCUE THERAPY FOR SEVERE COVID-19 – ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME WITH RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR (rtPA) – RETROSPECTIVE OBSERVATIONAL STUDY",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Smita Sonoli)
Member Secretary
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on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
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LIST OF ABBREVIATIONS

ARDS	-	Acute Respiratory Distress Syndrome
CTSS	-	Computed tomography severity scoring
GGOs	-	Ground glass opacities
HFNC	-	High Flow Nasal Cannula
NIV	-	Non Invasive Ventilator
PAI-1	-	plasminogen activator inhibitor 1
PRR	-	Pathogen recognition receptors
NETS	-	neutrophil extracellular traps
ACE2	-	Angiotensin-converting enzyme
FVII	-	Factor VIII
TF	-	Tissue factor
TNF	-	Tumour necrosis factor
vWF	-	von Willebrand factor
IDSA	-	Infectious Diseases Society of America
LMWH	-	low molecular weight heparin
UFH	-	unfractionated heparin
TMPRSS2	-	type 2 transmembrane serine protease

ABSTRACT

Background and Objective: Prothrombotic coagulopathy is a characteristic feature of severe COVID-19 leading to multiorgan failure and death. Extensive pulmonary vascular microthrombi with relatively preserved lung compliance has been described to be a critical factor for refractory hypoxemia in severe COVID-19**.** This study is done to assess the effect of recombinant tissue plasminogen activator in severe COVID-19 patients associated with hypoxemia refractory to standard line of treatment.

Method: Patients with severe COVID-19 infections confirmed by standard tests (RTPCR or HRCT thorax) who were admitted to ICU between August 1 2020 to October 31 2020 and who received rtPA were retrospectively analyzed using medical records.

Results: A total of 40 patients were selected based on the inclusion and exclusion criteria out of which 77.5% were males and 22.5% were females with a mean age was 61.30+/- 11.72 years, 100% of patients with a CORADS score of 5, 55% of them having CT severity score (CTSS) of >15. There was no statistically significant improvement in the biomarkers hs-CRP, ferritin, IL-6, or LDH. However, there was a statistically significant increase in D-dimer after rtPA administration**.** There was a statistically significant improvement in PaO2 ($p<0.03$) and PaO2/FiO2 ratio ($p<0.001$) 24-48 hrs after rtPA administration. 32.5% of the patients had adverse events post rtPA administration, the most common being haematuria (10%) and nasal bleeding (10%). 70% of the patients who received rtPA expired.

Conclusion: rtPA administration did not have any mortality benefits in addition to standard of care treatment although there was improvement in the PaO2 and PaO2 /FiO2 ratio 24-48 hours post-administration in severe COVID-19 patients with severe refractory hypoxemia. Mortality was seen in 70% of the patients.

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INTRODUCTION

A novel coronavirus known as SARS-COV2 caused the COVID-19 respiratory illness outbreak in the year 2019(December). In Wuhan, Hubei, China, a wholesale wet market for seafood was where the first outbreak was discovered. The outbreak of this mysterious illness manifested as pneumonia characterized by fever, dry cough, easy fatiguability, cold, sore throat, and occasional gastrointestinal symptoms.[1]

Most patients with COVID-19 demonstrate mild symptoms with a good prognosis while some patients progress rapidly and develop ARDS, acute respiratory failure, and other complications that eventually result in significant morbidity and mortality in intensive care units. Regardless of the cause, ARDS is linked to fibrin deposition in air spaces and fibrin-platelet microthrombi in the pulmonary vasculature, both of which are frequently seen in the lung microvasculature of COVID-19 patients. With increased clot formation and propagation as well as fibrinolysis suppression, this pathologic fibrin deposition is a sign of a dysfunctional clotting system.[2]

This prothrombotic state created as a result of COVID- 19 infection, leads to disseminated microvascular thrombi in the lungs. These microvascular thrombi further worsen the severity of ARDS.[3] This is supported by pathological evaluations of patients who died of respiratory failure due to COVID-19 infection which revealed extensive pulmonary microvascular thrombi after autopsy. Furthermore, the assessment of whole blood coagulation in critically ill COVID-19 patients using viscoelastic testing consistently showed a hypercoagulable state with increased clot strength and fibrinolysis resistance. [4]

These factors suggest that the patients with refractory hypoxemia secondary to severe COVID-19 had relatively preserved lung compliance but have been associated with severe perfusion defects.

Hypoxemia secondary to COVID-19-induced ARDS was refractory to traditional supportive therapies.

Clinical outcomes and survival to discharge were improved in patients who were not yet in need of invasive mechanical ventilation by therapeutic anticoagulation when compared to the prophylactic anticoagulation arm in a Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia trial.[4] On the other hand, no benefit was observed when anticoagulants were given in therapeutic doses after the onset of severe respiratory failure, indicating this treatment is only effective when initiated before a significant clot burden has built up in the lung vasculature.[4]

For the benefit of patients with ARDS with associated pulmonary clot formation, targeting the coagulation and fibrinolytic systems appears appropriate. Hardaway and colleagues described a small, uncontrolled human trial in severe ARDS in 2001, demonstrating that uro/streptokinase led to a significant improvement in oxygen requirements without bleeding events.[2]

Among the fibrinolytics tPA is considered to be having higher therapeutic efficacy and safety. Therefore, it is hypothesized that tPA has a potential role as a fibrinolytic in restoring the patency of pulmonary microvasculature, improving oxygenation, and decreasing dead space ventilation in such group of patients with COVID-19 induced severe respiratory failure with increased risk of mortality.

Patients with prothrombotic presentations, relatively preserved lung compliance on the ventilator, and high alveolar-arterial oxygen gradients may potentially be considered for fibrinolytic therapy.[4]

Many successful treatments of ARDS due to COVID-19 disease with fibrinolytic therapy has been reported in various case reports.

Barrett et al., [4] in a large vanguard multicentre randomized control study consisting of 2 groups, tPA bolus (50-mg) group vs control group and tPA infusion (2 mg/h) group vs control group, proved that at 6 hours through 168 hours after randomization, the PaO2 to FiO2 ratios in the group who received tPA bolus were significantly (P.017) higher than baseline. There was no significant improvement in the control group. Patients who received tPA bolus did not differ statistically significantly from control participants in the percentage change of PaO2 to FiO2 ratio at 48 hours (16.9% control vs. 29.8% tPA bolus), ventilator-free days (0 vs. 12), and mortality (41.2% vs. 21.1%). Patients who recieved tPA infusion had no clinical benefits.

Hence the present study is undertaken to evaluate the role of rtPA as salvage therapy in patients who had refractory hypoxemia due to COVID-19 infection or in those patients requiring higher oxygen supplementation including NIV support and HFNC supplementation.

OBJECTIVES

1. To assess the mortality benefits of Recombinant Tissue Plasminogen Activator (rtPA) in severe and critical patients of COVID-19 accompanied by refractory hypoxemia.
2. Comparison of COVID inflammatory markers in patients following treatment with rtPA.

REVIEW OF LITERATURE

DEFINITION:

WHO defines coronavirus disease as an acute respiratory infection caused by the severe acute respiratory syndrome (SARS) Coronavirus-2

EPIDEMIOLOGY:

In December 2019, a series of atypical respiratory infections wrecked the Wuhan city of Hubei province of China. [5] After being declared a public health emergency on 30th January 2020, COVID-19 disease was declared a pandemic on 11th march 2020 by WHO.[5] Initially, the outbreak of severe pneumonia was limited to China. Eventually spread throughout the world. Within each country and community, the incidence of COVID-19 depended on population density, degree of testing, and timing of mitigation strategies such as social distancing.

As of February 6th, 2020, a total of 28,276 confirmed cases with 565 deaths globally involving at least 25 countries.111.5 million cases worldwide with approximately 5,36,893 deaths as of July 6th, 2020.On October 11th, 2020, 37 million confirmed cases with 1 million deaths as per data received by WHO by national authorities.[6]On January 30, India reported its first COVID-19 case. On March 4, 2020, 22 new cases were identified, mostly in a group of Italian tourists.[7]

Globally, the largest cumulative cases were seen in the United States, India, and Brazil.[6]

SARS COV-2 VIRUS – EVOLUTION

Unknown pneumonia was discovered in Wuhan city, Hubei province, China, in November 2019. The symptom onset of the first laboratory-confirmed case was on December 1, 2019, in Wuhan.[6]Initially, an outbreak involving at least 41 people was reported at a local market, the Huanan Seafood Market. A total of 59 suspected cases of fever and dry cough were directed to a specific hospital (the Jin Yin-tan Hospital). Next-generation sequencing or RT-PCR confirmed 41 of 59 suspected cases. In the days that followed, a wave of cases spread from Wuhan to the rest of Hubei province.

As a result, this virus infected many cities and provinces. One of the reasons could be the huge transportation load during the Chinese Lunar New Year period (January 25). On January 13, 2020, the first exported case arrived in Thailand. The disease, on the other hand, spread quickly and globally. Officially WHO named the disease outbreak “Coronavirus Disease-2019 (COVID-19)” on February 11, 2020, and the virus SARS-CoV-2 was named by the International Committee on Taxonomy of Viruses (ICTV). After SARS-CoV and MERS-CoV, SARS-CoV-2 is the century's third zoonotic human coronavirus.[6]

VIROLOGY

TAXONOMY[8]

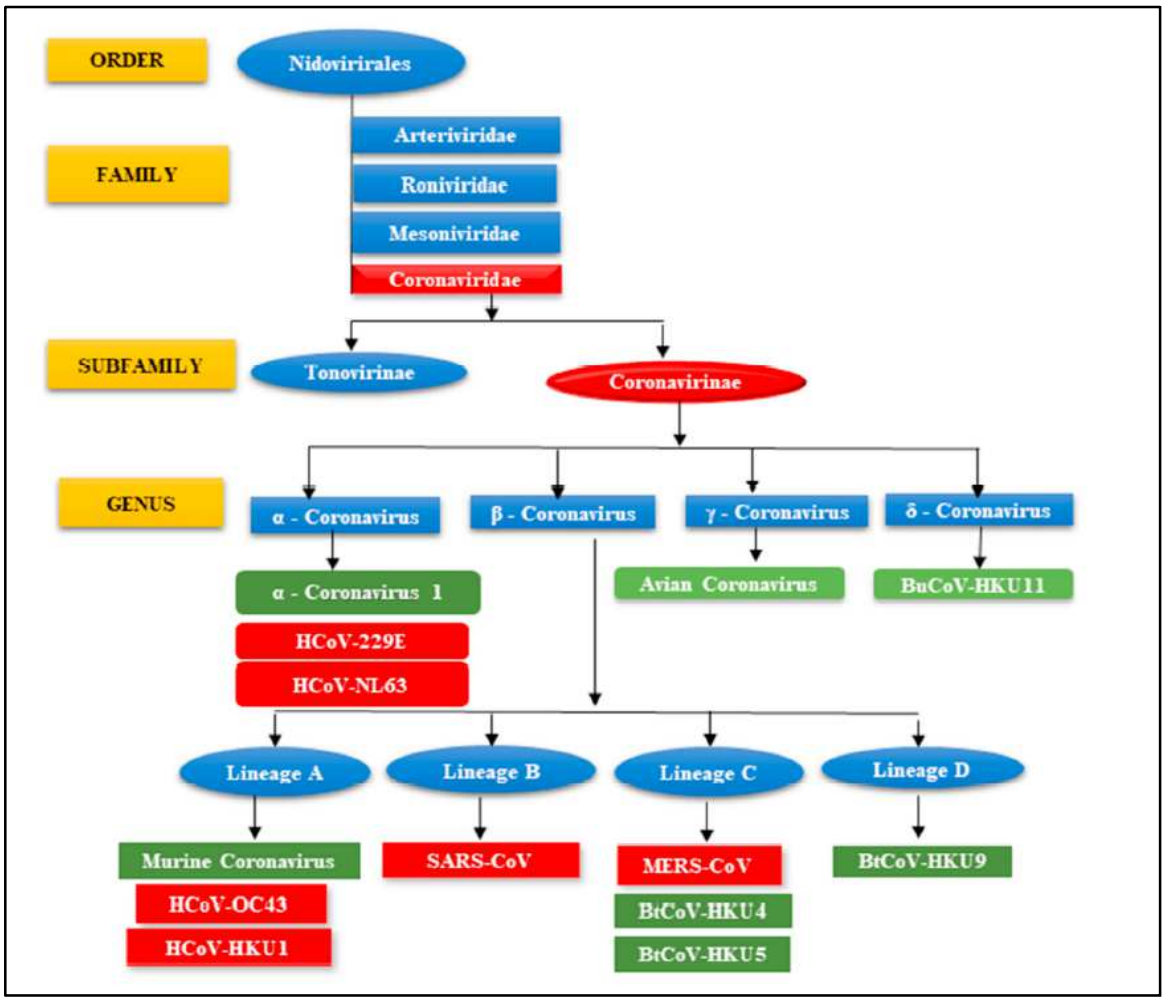


Figure 1: Taxonomy of SARS-CoV-2

Because of the presence of crown-like morphology-based electron microscopic studies, the term "Coronavirus" was coined in 1968. In 1975, the International Committee on Virus Taxonomy classified it as belonging to the family "Coronaviridae" of the order "Nidovirales."[8]

Coronaviruses (CoV) are categorised into four genera, including α/β/γ/δ-CoV.

MORPHOLOGY [8]

SARS CoV-2 virus is an enveloped virus. The diameter of the virions ranges from 60 nm to 140 nm. It has club-shaped spikes on the surface, the size of which ranges from 9 nm to 12 nm giving the appearance of a solar corona to the virus and a large positive sense RNA genome (26-32 kilobases). The enzyme functions that combat the “high error frequency of viral RNA polymerase” help the RNA genome's unique replication strategy.

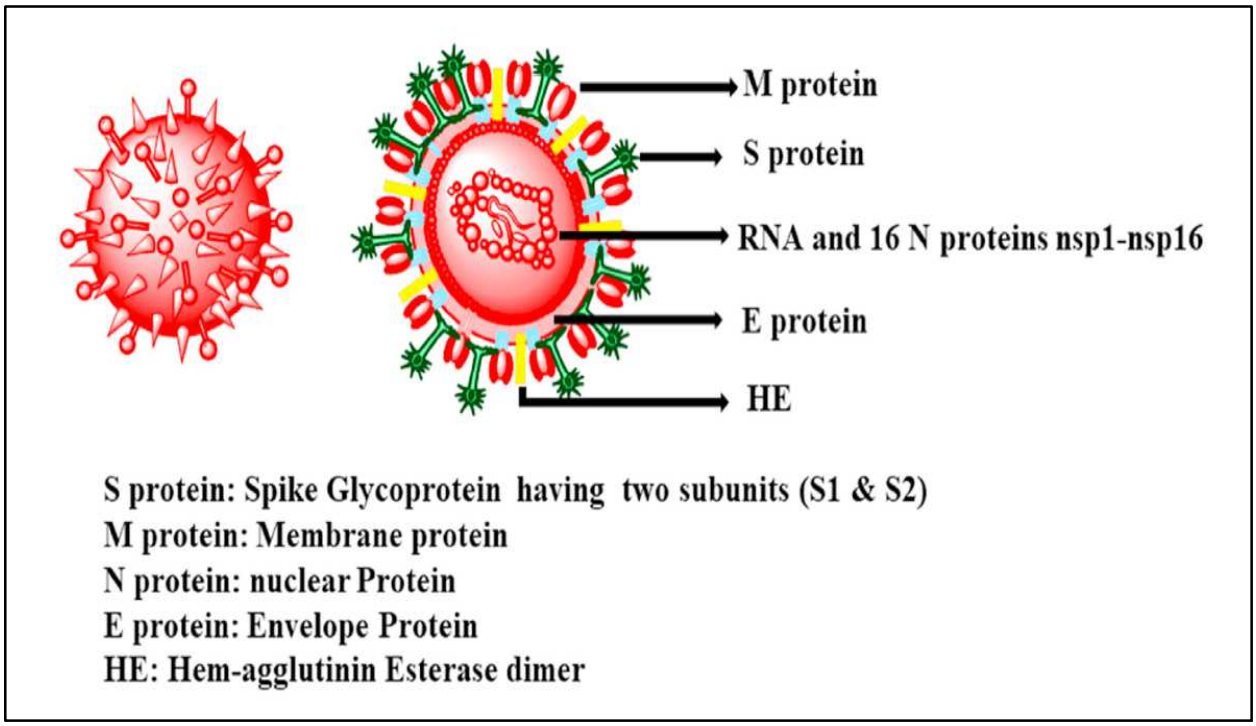


Figure 2: Structure of SARS-CoV-2

The structural elements of virus are:

1 Spike protein (S),

2 Membrane protein (M)

3 16s Nucleo-capsid protein (N) and

4 Envelope protein (E)

5 Viral genome

SPIKE PROTEIN:

These are club-shaped projections protruding from the virion's surface. These spikes are unique to the virion and resemble a solar corona, hence the name Coronavirus. These are made of peplomers of 80–160 nM in size with 27–32 kb positive polarity.

The S protein has two subunits

“S1 subunit” - made of “N-terminal domain (NTD)” and receptor binding domain (RBD). Binding to the receptor on the host cell is the primary function S1 subunit.

“S2 subunit” - Creates the stalk that gives the spike its shape thus facilitating the fusion of viral membrane and host cell membrane.

Between the S1 and S2 subunits is the S1-S2 protease cleavage site. Host proteases cleave spike glycoprotein at the S2' cleavage site for all coronaviruses, activating the proteins that are required to fuse the membranes of viruses and host cells via irreversible conformational changes.

RBD present on SARS-CoV-2 spike protein specifically recognizes the ACE2 receptor. RBD contains a receptor binding motif (RMF) that contains the majority of ACE-2 binding sites. RBD undergoes conformational transitions like a hinge, resulting in exposure of the spike protein's determinants to engage a host cell receptor.[6]

RBD is an important target for antiviral agents and antibodies

M PROTEIN [9]

The CoV membrane protein (M) is the most abundant glycoprotein in the CoV particle and is a type III transmembrane glycoprotein. Despite variations in the primary M protein sequence, M protein predicted secondary structures are maintained. The M protein is about 230 amino acids long and is made up of three parts: a short N-terminal domain outside the virion membrane, three transmembrane domains, and a carboxy-terminal domain inside the particle. M protein, which is found in the virus envelope along with small amounts of E, is the primary driver of the virus budding process.

M interacts with itself, the nucleocapsid protein N, E, and the S protein during the assembly of the authentic virion. M protein exists as a dimer in the virion, and high-resolution imaging has revealed that it exists in two conformations, long and compact (MLONG and MCOMPACT), which together induce membrane curvature and nucleocapsid binding.

NUCLEOCAPSID PROTEIN [10]

It is a highly conserved structural protein throughout the Coronavirus genus. The N protein of SARS-CoV-2 is 419 amino acids long and is encoded by the virus's ninth ORF.

Functions:

- packaging the viral genome RNA into a long helical ribo- nucleocapsid (RNP) complex

- viral assembly by interacting with the viral genome and membrane protein M.

The N protein and genomic RNA combine to form a helical nucleocapsid which is surrounded by viral membrane (M) proteins with icosahedral structures.

ENVELOP PROTEIN [11]

The CoV E protein is a short, integral membrane protein containing 76-109 amino acids and weighing 8.4 to 12 kDa.

E is abundantly expressed inside the infected cell during the replication cycle, but only a small portion of it is incorporated into the virion envelope. The majority of the protein is found in intracellular trafficking sites such as the ER, Golgi, and ERGIC, where it participates in CoV assembly and budding. Recombinant CoVs lacking E have significantly lower viral titers, and are unable to mature, or produce propagation incompetent progeny, demonstrating the importance of E in virus production and maturation.

The CoV E protein serves three functions.

1. The interaction of the cytoplasmic tails of the M and E proteins drives the production of VLP (virus-like particles), implying that E is involved in viral assembly.
2. The hydrophobic trans membrane domain of E is also important for viral release.
3. Finally, SARS-CoV E is linked to the virus's pathogenesis.

VIRAL GENOME [12]

Coronaviruses have the largest known non-segmented RNA viral genome, which is linear positive-sense, infectious, single-stranded RNA that is ~30 kb and is 5′ capped and 3′ polyadenylated.

A leader sequence and an untranslated region (UTR) containing multiple stem-loop structures required for RNA replication and transcription are found at the 5′ end of the genome. Furthermore, at the start of each structural or accessory gene are transcriptional regulatory sequences (TRSs) that are required for each of these genes to be expressed. The 3′ UTR also contains RNA structures required for viral RNA replication and synthesis.

The coronavirus genome is organized as follows: 5′-leader-UTR-replicase (ORF1ab)-spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)-3′UTR-poly (A) tail.[12]

5' -terminal two-thirds of the genome

Which is about 20kb and contains two open reading frames (ORFs), 1a and 1b, which encode for replicase polyprotein which cleaves itself to form 16 non-structural proteins(nsps) required for replication transcription complex (RTC) formation.[13]

The enzymatic activities and functional domains of CoV's non-structural proteins(nsps) are expected to be conserved across CoV genera, implying their importance in viral replication.[13]

3' – terminal proximal third of the genome

It is about 10kb. The four major structural proteins are encoded in these reading frames: spike, envelope, membrane, and nucleocapsid. Reading frames for

the accessory proteins are interspersed between these reading frames. The number of accessory proteins and their functions varies according to the coronavirus.

THE RNA-DEPENDENT RNA POLYMERASE (RdRp)

In coronavirus replication/transcription, RdRp is an important component that catalyzes viral RNA synthesis. It is a significant antiviral drug target.[6] SARS-CoV-2 replication is dominated by a replication/ transcription complex composed of several subunits. The complex is made up of viral non-structural protein, with the RdRp in nsp12 serving as its core.[6]

THE MAIN PROTEASE [6]

The main protease (Mpro) of SARS-CoV-2 is critical in mediating viral gene replication and transcription. Mpro hydrolyzes the polyprotein(pp) at least eleven conserved sites, beginning with cleaving Mpro's pp1a and pp1b.

Host cell infiltration by SARS-CoV-2 requires spike protein. RdRp and main protease are required for SARS-CoV-2 replication. As a result, the spike protein, main protease, and RdRp are important anti-SARSCoV-2 drug targets, providing ideas for antibody, drug, and vaccine development.

VIRAL LIFE CYCLE [14]

The life cycle of SARS CoV-2 inside the host cell is divided into several stages. The viral protein S binds to the ACE2 cell receptor present in the bronchial epithelial cells and alveolar pneumocytes in the host. The resulting conformational changes in the spike protein cause fusion of viral envelop with the host cell membrane

by endosomal pathways and viral replication. Membrane fusion allows the virus entry into the cell. Once inside the host cell, the virus releases its RNA into the cell which is translated into functional RNA polymerase protein with the help of host ribosomal machinery. The polymerase helps to make a series of mRNAs by interrupted transcription, and ultimately these mRNAs are translated into appropriate viral proteins, N, M, S, and E proteins. The N protein is translated in the cytoplasm, whereas the M, E, and S proteins are translated on the rough endoplasmic reticulum (RER) due to post-translational modifications. The structural proteins M, E and S, and N proteins are then assembled.

In the Golgi vesicle, the assembled viral components mature further to form the mature virion with the lipid envelope. By the process of exocytosis, matured virions are released outside the host cell, ready to bind to other host cells. This occurs repeatedly.

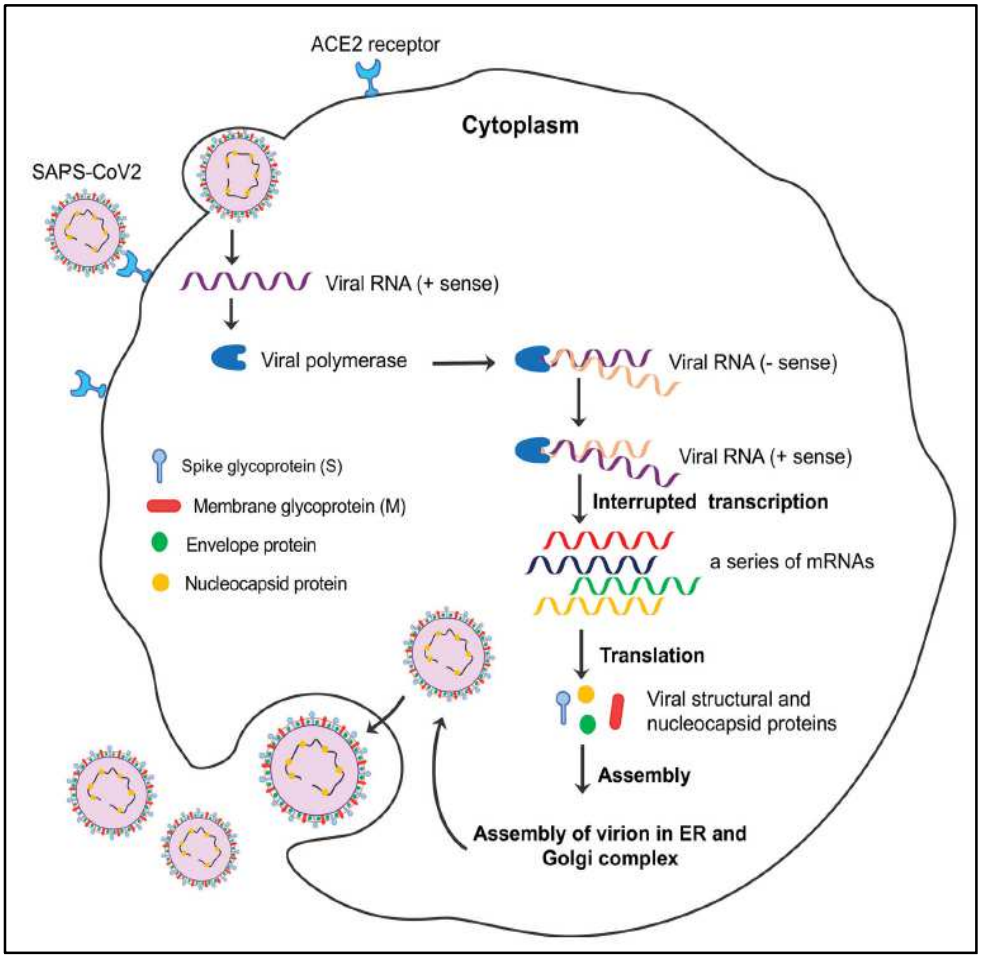


Figure 3: Life cycle of SARS-CoV-2

TRANSMISSION: [15]

Person-to-person transmission via respiratory droplets is thought to be the most common mode of transmission. Such transmission is thought to occur in close proximity (less than 6 feet, or 2 m) via respiratory droplets larger than 5 m in diameter.

Respiratory secretions of the patients infected can come into direct contact with the mucosa of healthy individuals who are not infected while sneezing, coughing, or talking. As a result, wearing masks in public is considered a cornerstone of SARS-CoV-2 prevention, with indirect evidence indicating efficacy.

The role of aerosolized virus (particles smaller than 5 m in diameter that may remain suspended in the air) as a mode of transmission over distances greater than 2 m is debatable but may have a role in some cases.

Following are examples of evidence that support aerosol transmission:

(1) SARS-CoV- 2 grown in tissue culture remained viable in aerosol for up to 3 hours

(2) The viral RNA was found in the ventilators used for infected patients

(3) respiratory droplets generated by speaking were shown to dehydrate into aerosols that remained airborne for extended periods.

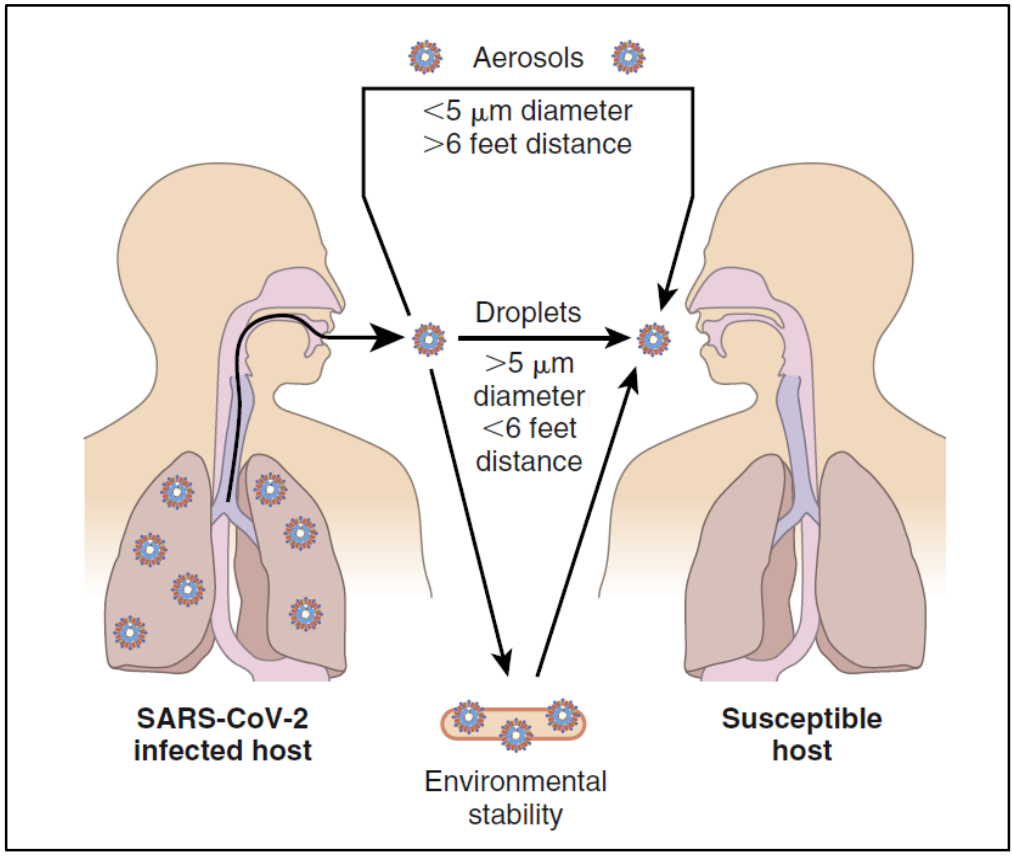


Figure 4: Transmission of SARS-CoV-2[15]

Type and exposure duration also have an impact on transmission, with prolonged close contact in confined, crowded, or poorly ventilated environments posing the greatest risk.

The precise duration of a person's infectivity with the SARS-CoV-2 virus is unknown, but current evidence suggests that infected individuals may be infectious 2 to 3 days before symptoms appear, and that asymptomatic or presymptomatic infection plays a significant role in disease transmission. The amount of viral RNA shed varies and may be affected by the severity of the illness; however, it is unclear whether RNA shedding correlates with the presence of an infectious virus.

PATHOGENESIS

Through the process of genetic recombination and variation, coronaviruses can adapt to new hosts and cause infection.

Early in infection, SARS-CoV-2 targets cells such as nasal and bronchial epithelial cells, as well as pneumocytes, via the viral structural spike(S) protein, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Transmembrane serine protease 2 (TMPRSS2) present on type 2 alveolar cells cleaves ACE2 and activates the S-protein of the virus which promotes viral entry into the host cell.[16]

Following endocytosis, the membrane fuses between the mature endosome and virion with the help of TMPRSS2, resulting in the release of SARS-CoV- 2 RNA into the intracellular space. The replicase and structural proteins are produced by translating the RNA by host machinery. The replicase is cleaved into non-structural

proteins by host and SARS-CoV-2 proteases, including the RNA-dependent RNA polymerase (RdRp). [16]

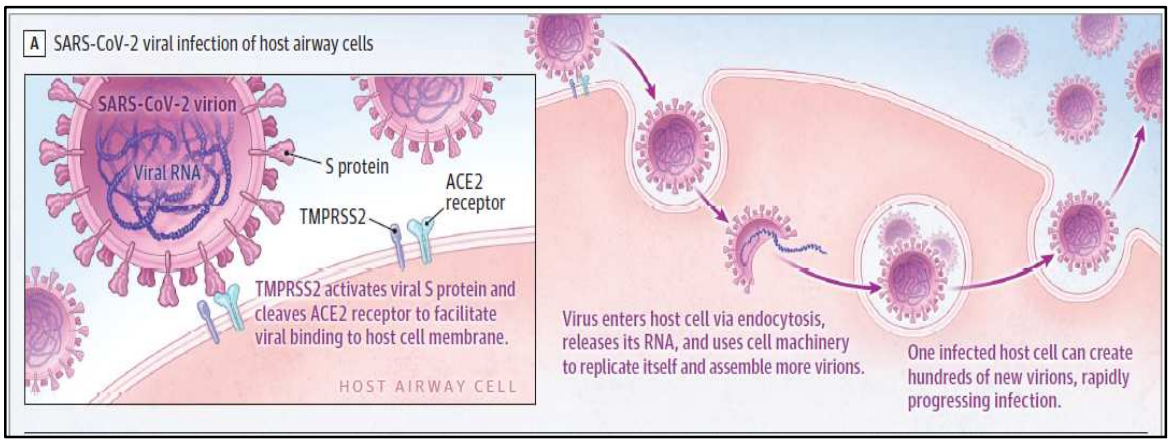
RdRp is involved in RNA replication and amplification. SARS-CoV-2 transmembrane proteins (spike [S], envelope [E], and membrane [M]) are transported to the forming viral capsids via the endoplasmic reticulum and Golgi apparatus. Through association with the transmembrane viral proteins, the virus is assembled by adding viral RNA and nucleocapsid (N) protein. The newly synthesized viral particles are released as a result of exocytosis.[16]

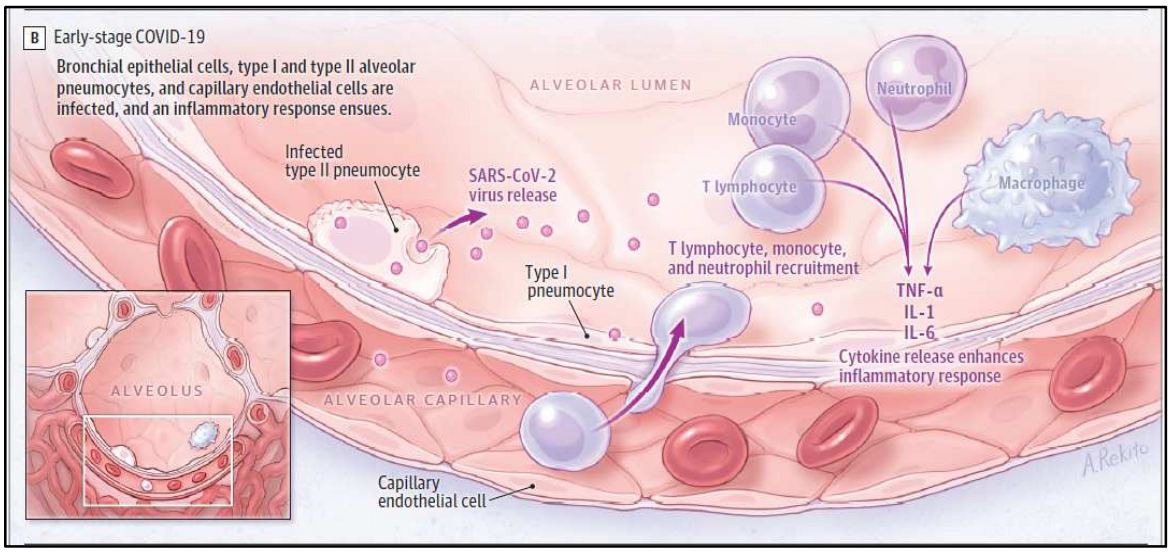
The viral immune responses which include both the innate and adaptive immune responses reduce the synthesis of lymphocytes and increase lymphocyte apoptosis.

When viral replication accelerates in the later stages of infection, the integrity of the epithelial-endothelial barrier is compromised. Pulmonary capillary endothelial cells are also infected by the virus thus enhancing the inflammatory response and causing the migration of monocytes and neutrophils to the site of infection.[16]

In addition to endothelialitis, the alveolar wall thickens due to the infiltration of mononuclear cells. Alveoli are filled with fluid followed by hyaline membrane formation corresponding to the early phase of ARDS. Lung angioedema induced by bradykinin may contribute to the disease.

COVID -19 induced ARDS is characterized by endothelial barrier disruption, impaired oxygen diffusion capacity, and dysfunctional alveolar-capillary oxygen transmission. The interstitial mononuclear inflammatory infiltrates and edema appear as ground-glass opacities on CT thorax.[16]


A SARS-CoV-2 viral infection of host airway cells
SARS-CoV-2 virion
Viral RNA
S protein
ACE2 receptor
TMPRSS2
TMPRSS2 activates viral S protein and cleaves ACE2 receptor to facilitate viral binding to host cell membrane.
HOST AIRWAY CELL
Virus enters host cell via endocytosis, releases its RNA, and uses cell machinery to replicate itself and assemble more virions.
One infected host cell can create hundreds of new virions, rapidly progressing infection.


B Early-stage COVID-19
Bronchial epithelial cells, type I and type II alveolar pneumocytes, and capillary endothelial cells are infected, and an inflammatory response ensues.
ALVEOLAR LUMEN
Neutrophil
Monocyte
T lymphocyte
Macrophage
Infected type II pneumocyte
SARS-CoV-2 virus release
T lymphocyte, monocyte, and neutrophil recruitment
Type I pneumocyte
TNF-α
IL-1
IL-6
Cytokine release enhances inflammatory response
ALVEOLUS
ALVEOLAR CAPILLARY
Capillary endothelial cell
A.Rekito

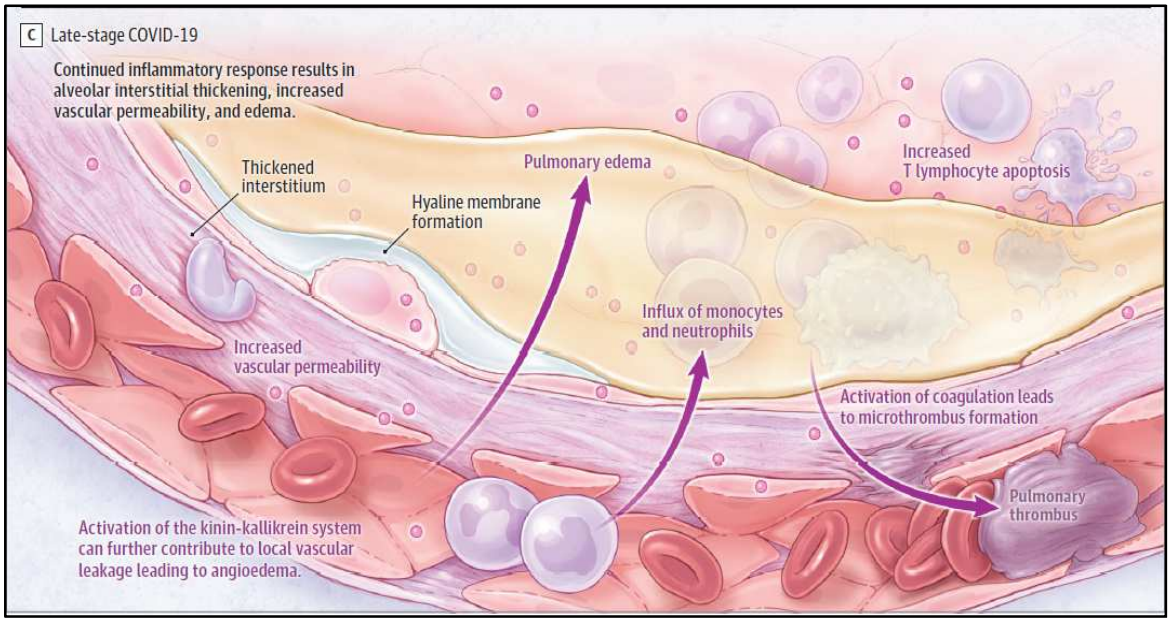


Figure 5: Pathophysiology of COVID-19 disease[16]

Coagulopathy and Thrombosis in COVID-19

COVID-19 induces a hypercoagulable state through distinct mechanisms centered on thrombosis and inflammation. The initiation of the inflammatory and thrombotic cycle occurs when the SARS-CoV-2 gains entry into the alveolar epithelium through ACE-2 receptors. This results in a heightened inflammatory response which sets an environment suitable for thrombosis via the mechanisms like complement activation, cytokine storm, endothelium, etc.[17]

Several studies show that high levels of LDH, CRP, IL-6, ferritin, D-dimer, and fibrinogen suggest that COVID-19 causes a severe proinflammatory state strongly supporting the concept of thrombo-inflammation [17]

1) Localized intravascular coagulopathy

The initial viral damage to the alveolar epithelium and pulmonary vascular endothelium after the viral entry into the cells induces an inflammatory response and formation of pulmonary microvascular thrombi. This process may progress into the systemic circulation leading to more generalized endothelial dysfunction and micro-thrombotic complications in various other organs like kidneys, brain, etc resulting in multiple organ failure.[17]

2) Inflammatory cytokines

Cytokines are the signaling molecules that control and regulate immune responses, inflammatory responses, hematopoiesis, and cell migration. [18] Dysregulated immune response resulting in cytokine storm is an important driver of pathology in critically ill COVID-19 patients.

Following are the mechanisms through which cytokines are involved in the pathology of covid 19:

- Increased expression of IL-6 in the airway epithelium of the infected patients is caused by the binding of NF-κB regulatory elements of the IL-6 promoter N protein of the virus. SARS-CoV-2-specific PRR activation is thought to be the mechanism through which high IL-6 levels are maintained. [19] The vascular permeability is increased due to the actions of IL-6, IL-1, and TNF-α leading to the destruction of alveolar-capillary barrier and edema in the alveoli. Fibrosis in addition to lung inflammation is caused by TNF-α. [20]
- In addition to these pro-inflammatory cytokines are known to cause the downregulation of important physiological anticoagulant pathways, as well as abnormal clot formation and platelet hyperactivation.

- Excess release of cytokines causes thrombosis via a variety of other mechanisms such as the **activation of monocytes, neutrophils, and endothelial cells**, all of which result in a prothrombotic state.[17]

3) <u>Endothelial activation & dysfunction</u>

COVID-19 is thought to cause endothelial activation or dysfunction via the following mechanisms:

a) inflammatory cytokines : as described previously

b) activation of complement in the blood

The complement system is an innate immune response mediator that promotes inflammation, defends against bacterial infections, and frequently neutralizes infectious viruses.

Generally, complement cascade is activated through three pathways:

1. Classical pathway: stimulated by antibody-antigen complexes
2. Alternative pathway: stimulated by specific surface antigens
3. Lectin pathway: stimulated by binding mannose residues on the pathogen surface.

All the 3 paths converge to a common pathway that begins with the activation of C3 and C5 components. C3 convertase cleaves C3 into C3a and C3b. C3b cleaves C5 into C5a and C5b. C6-9 combines with C5b to form a membrane attack complex.

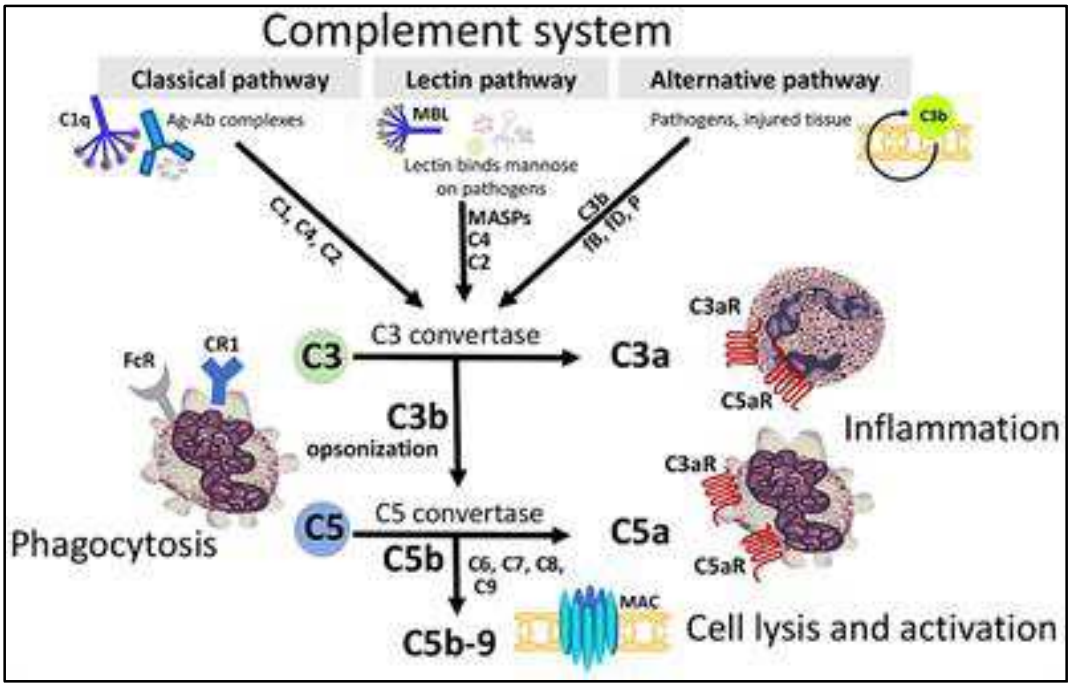


Figure 6: Complement pathway

Functions of complement components:

- C3a and C5a: induce local inflammation
- C3b: opsonization of pathogen
- Membrane attack complex: lysis of pathogen leading to cell death

The activation of the coagulation cascade by the virus in turn causes complement hyperactivation. The proteins in the coagulation pathway namely thrombin and plasmin can cleave C3 into C3a and C5 into C5a the levels of which are significantly raised in severe COVID-19 patients.

Dysregulated activation of the complement system also contributes to cytokine storm, through the pro-inflammatory effects of C3a and C5a anaphylatoxins. This

vicious cycle repeats leading to pulmonary microvascular thrombi, DIC, and multiorgan failure. These effects are likely to be more severe in patients who have a genetic predisposition for decreased complement regulation.

c) Sars-COV-2 infection of endothelial cells via the ACE-2 receptor

RAS dysfunction has an important role in ARDS in general and COVID-19 infection in particular due to various reasons. SARS CoV-2 has a high affinity to the enzyme ACE-2. Therefore, the spike protein fuses with the ACE-2 present on the host membrane to invade the host cell.

Angiotensin I (ANGI) is cleaved by the enzyme ACE-2 to produce ANGII which causes vasoconstriction when it binds to the Angiotensin Type I Receptor (AT1R). Binding of the virus to ACE-2 results in the depletion of ACE-2 due to virus internalization and ACE-2 shedding. As a result of a decrease in ACE-2 levels, degradation of ANGII decreases resulting in exaggerated injury to the lung. ANGII via negative feedback inhibits ACE-2 which is primarily expressed on the cell surfaces of lung vascular endothelial cells, but also found in extrapulmonary tissue, the heart, the nervous system, the intestine, kidneys, blood vessels, and muscles, which may explain the multi-organ dysfunction seen in COVID-19 patients. The binding of ANGII to AT1R may stimulate IL-6 release, further contributing to cytokine storm.

Recent studies showed lung injury and viral load were directly proportional to ANGII levels in the plasma. Furthermore, in patients with comorbidities like HTN, DM, and cardiac diseases which are associated with low ACE-2 expression at the baseline (implying imbalance in ACE/ACE-2), COVID-19 appears to be associated

with poor outcomes. Therefore, the RAS pathway derangements contribute to a hypercoagulable state and subsequent morbidity and mortality.

4) Mononuclear phagocytes (MNPs)

Macrophages, which are derived from circulating monocytes, are antigen-presenting cells involved in phagocytosis. Release of vasodilators like cytotoxic nitric oxide, proinflammatory cytokines production, and phagocytosis of pathogens are carried out by M1 macrophages whereas production of IL-10 and other anti-inflammatory molecules and tissue repair is carried out by M2 macrophages.[21] In the early stages of infection macrophages limit the viral replication by inciting type I IFN response, inducing CD4+ T-cell differentiation, and recruiting other immune cells.[22]

The virions, on the other hand, can infect macrophages directly and alter them to avoid detection. These macrophages release IL-6 in large quantities which in turn triggers the release of CRP, which is usually not seen in viral infections.

Slow recovery of the tissues and complications which persists for a long time eventually results in death because of the rise in M1 phenotypic macrophages.[23]

5) Neutrophil extracellular traps

Infections caused by bacteria and fungi are marked by neutrophils which are the "first responders". The burst release of IL-6 and chemokines such as CXCL8 and CXCL2 causes neutrophils to migrate from the bone marrow and be rapidly recruited to the lung parenchyma.[20]

The functions of the neutrophils are: [24]

- Pathogen phagocytosis and antimicrobial protein degranulation thereby preventing the infection.
- Inhibit replication of virus by producing cytokines
- Suppress viral activity by producing a large number of reactive oxygen radicles.
- Neutrophils activated by SARS-CoV-2 can also induce apoptosis of infected cells
- Creates NETs containing bacteria-killing proteins such as cathepsin G, neutrophil elastase, and lysozyme that stop the virus from spreading by trapping and inactivating the virus.[24,25]

Exaggerated NETosis causes damage to the endothelium of pulmonary vasculature leading to the release of von Willebrand factor. This factor will stimulate neutrophils and platelets to form clots. An elevated neutrophil count is a poor prognostic indicator, and NETosis is associated with organ damage and death in patients with severe COVID-19 infection.

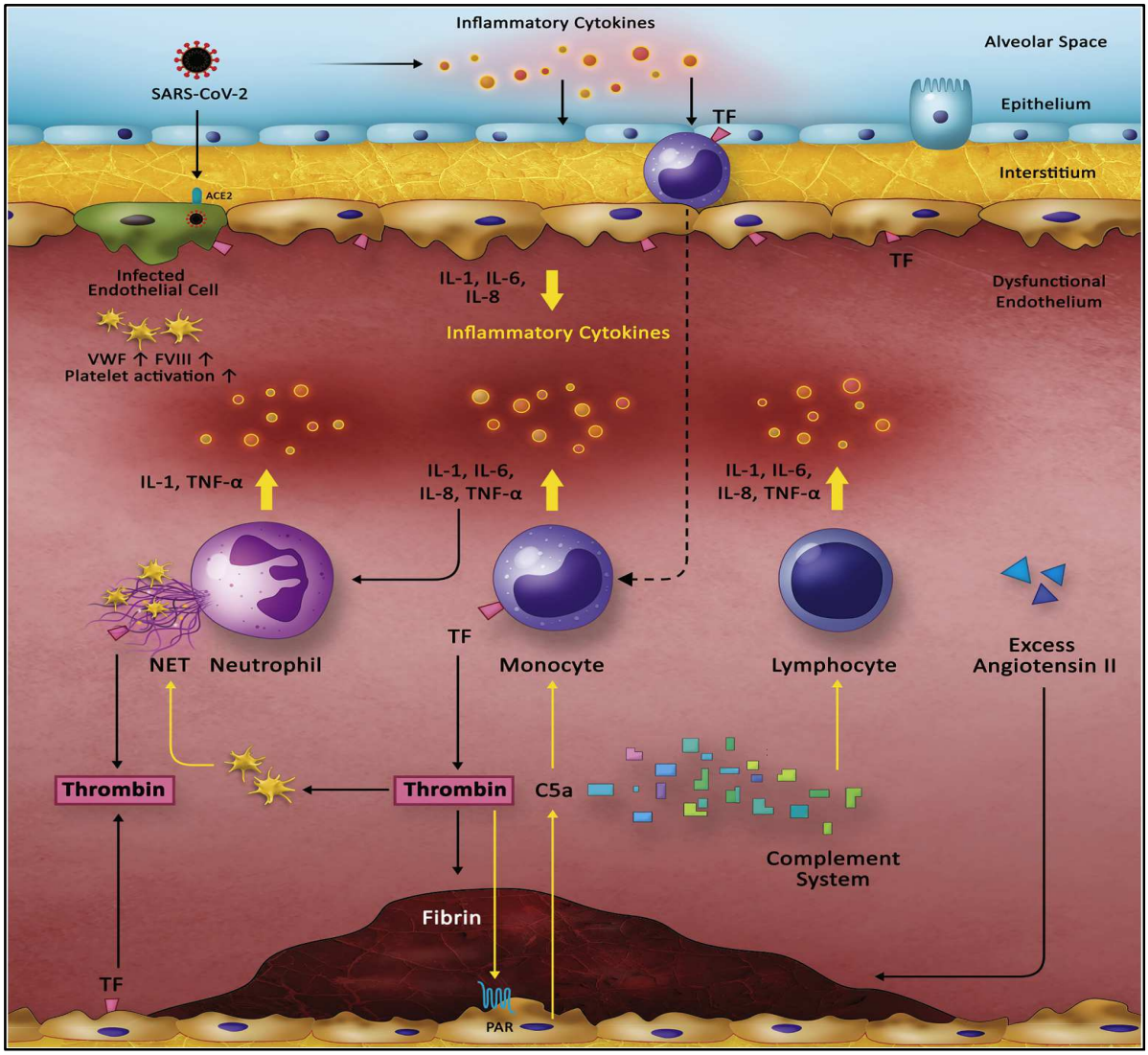


Figure 7: Pathophysiology of coagulopathy in COVID-19.

COVID-19-induced coagulopathy has a bidirectional interaction of inflammation and thrombosis. Following the entry of the virus severe inflammatory response is initiated in the alveoli. As a result, inflammatory cytokines released activate epithelial cells, monocytes, and macrophages. Direct binding of the virus to the ACE2 receptor causes endothelial damage, expression of TF, activation of platelets, and rise in levels of VWF and FVIII. This leads to thrombin production and fibrin clot formation. Thrombin promotes NET formation in neutrophils via its effect on platelets which aggravates inflammation. It also activates endothelial cells via the PAR receptor leading to C5a release, which further contributes to hypercoagulability. [17]

CLINICAL FEATURES

Incubation period: 14 days post-exposure, but in most of the patients it is 4–5 days post-exposure.

Clinical presentation varies widely from asymptomatic to respiratory failure and death.

Phases of COVID-19 infection:

Early phase (Phase I): [26]

The first stage occurs during disease inoculation and early establishment. SARS-CoV-2 multiplies and settles in the host, concentrating on the respiratory system. During this time, SARS-CoV-2 binds to its target via the angiotensin-converting enzyme 2 receptors on human cells. These receptors are abundant in the epithelium of the human lung and small intestine, as well as the vascular endothelium. The infection usually presents with mild respiratory and systemic symptoms due to the airborne mode of transmission and affinity for pulmonary ACE- 2 receptors.

Most people experience an incubation period characterized by mild and often non-specific symptoms such as malaise, fever, and a dry cough. Patients may also present with less frequently occurring symptoms like a sore throat, arthralgia, chills, rhinorrhea, nausea, vomiting, or loss of taste or smell

Prognosis and recovery are excellent in patients who can keep the virus limited to this stage of COVID-19.

While some patients remain in this stage, others move on to stage II or stage III, which are more severe.

Pulmonary phase (phase II):[26]

Phase II of the virus infection involves the virus infecting the lungs and invoking the innate immune response. There is viral multiplication and localized inflammation in the lung. Patients develop viral pneumonia at this stage, with cough, fever, and possibly hypoxia (defined as PaO2/FiO2 300 mm Hg). Patients experience symptoms like a worsening cough, fever, dyspnea, and low oxygen levels. Most patients need to be hospitalized during this phase. Antiviral therapy is used to prevent viral entry and invasion while also limiting viral replication during this phase of treatment.

Hyperinflammatory phase (phase III):[26]

A subset of COVID-19 patients will progress to the third and most severe stage of the illness, known as extra-pulmonary systemic hyperinflammation syndrome. Systemic inflammatory markers appear to be elevated at this stage. COVID-19 infection reduces the number of helper, suppressor, and regulatory T cells. Inflammatory cytokines and biomarkers such as IL-2, IL-6, IL-7, granulocyte colony-stimulating factor, macrophage inflammatory protein 1-a, tumor necrosis factor-a, C-reactive protein, ferritin, and D-dimer are significantly higher in patients with a more severe disease which is known as the cytokine storm. Cytokine storm is defined as a life-threatening overactivation of immune cells and dysregulated inflammatory cytokine/chemical production [2] Troponin and N-terminal pro-B-type natriuretic peptide levels can also rise the number of T cells decreased. Patients may experience a variety of complications as a result, including multiorgan failure, ARDS, and sepsis. Shock, vasoplegia, respiratory failure, and even cardiopulmonary collapse can be seen at this stage. During this stage, systemic organ involvement, including myocarditis, would manifest.

Overall, the prognosis and likelihood of recovery from this critical stage of the illness are poor.

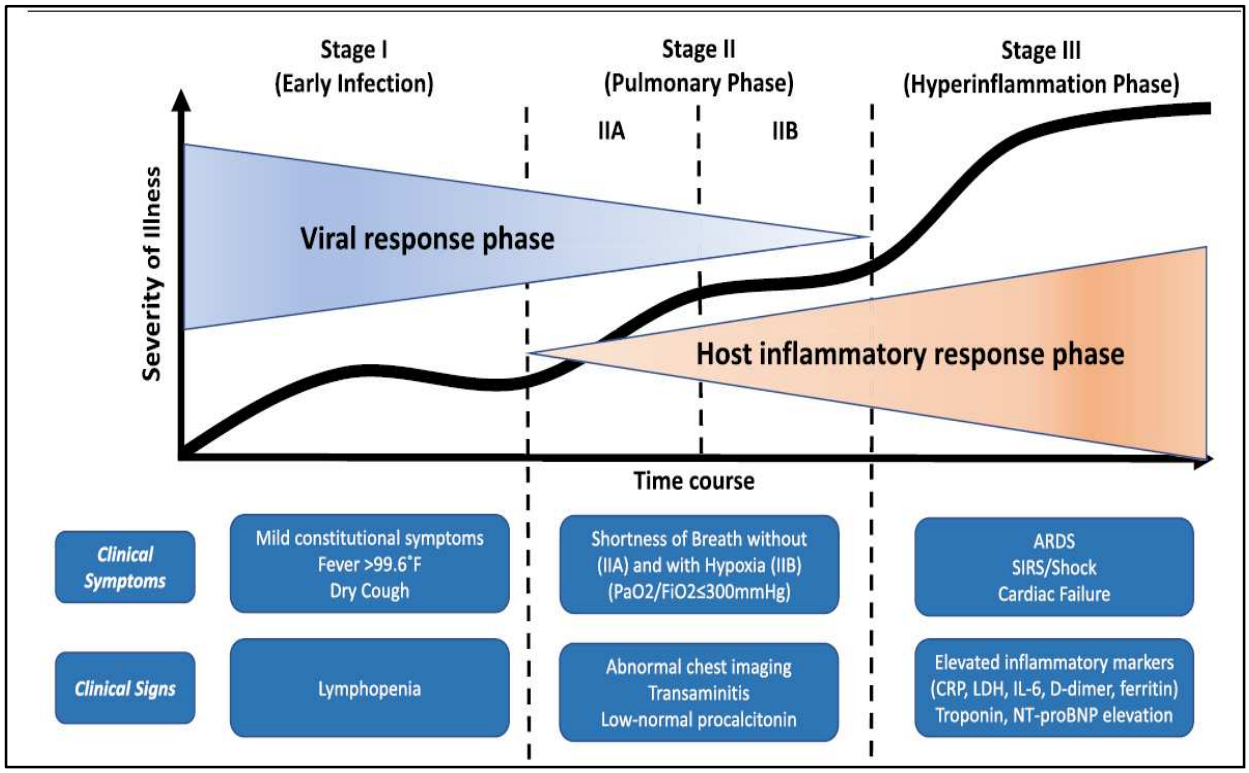


Figure 8: Phases of COVID-19 disease

ASYMPTOMATIC INFECTION:

Asymptomatic infections have been extensively studied.[28–34] 33% of people infected with SARS-CoV-2 never develop symptoms according to a study which was conducted before the introduction of vaccines for COVID 19.[35]

Asymptomatic patients may have objective clinical abnormalities such as typical ground-glass opacities or patchy shadowing, as well as atypical imaging abnormalities on the CT thorax.

Some people who are asymptomatic at the time of diagnosis develop symptoms later on (i.e., they were actually pre-symptomatic).

<u>The spectrum of severity and fatality rates</u>

The severity of symptomatic infection ranges from mild to severe; the majority of infections are not severe. According to a report from the Chinese CDC which included 44,500 confirmed cases showed the following. [36]

- 81% of mild cases (no pneumonia or mild pneumonia)
- 14% had severe disease (e.g., dyspnoea, hypoxia, or >50% lung involvement on imaging within 24 to 48 hours)
- 5% had a critical disease (e.g., respiratory failure, shock, or multiorgan dysfunction)
- The overall case fatality rate was 2.3 percent, with no deaths among noncritical cases reported.

Acute course and complications

Some patients with mild symptoms may progress over a week. [37] In a study done on 138 hospitalized patients in Wuhan, it was observed that dyspnea appeared an average of 5 days after the onset of symptoms, and hospital admission took place after an average of 7 days of symptoms. The average time to develop dyspnea in a different study was eight days. [38]

Respiratory failure:

Immediately after the onset of dyspnea, ARDS can occur, which is a major complication in critically ill patients. The most important risk factor for developing

ARDS seems to be age. Other factors include male sex, socioeconomic background, high fever (39°C), blood type, and specific laboratory and viral features. Comorbidities (such as obesity, hypertension, and metabolic syndrome) are also the important risk factors.

Specifically, among the critically ill:

- The predominant finding is a profound acute hypoxemic respiratory failure from ARDS.[39–41]
- Hypercapnia is uncommon (unless associated with, for example, COPD exacerbation or narcotic overdose).
- During ICU admission, fevers frequently wax and wane, especially in the first few days to a week.
- Between 20 and 100 percent of critically ill patients who are admitted to the ICU require mechanical ventilation.[41–44]

Thromboembolic manifestations:

The spectrum of thromboembolic manifestations is wide and seems to vary greatly between different people. Even when prophylactic anticoagulation was used, venous thromboembolism (VTE), including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), was very common in critically ill COVID-19 patients early in the pandemic, occurring in up to one-third of patients in the intensive care unit (ICU).[45–47]

In ICU patients: The prevalence of VTE was high in case series of intensive care unit (ICU) patients during the early stages of the pandemic (range, 20 to 43 percent), with

the majority of cases being pulmonary embolisms (PE), despite prophylactic-dose anticoagulation, and decreasing rates of VTE over time.

Inpatients (non-ICU): The rate of VTE is higher in non-ICU inpatients, but to a lesser extent than in ICU patients.

Outpatients: Although thrombotic events have been observed in COVID-19 patients who were not hospitalized, VTE appears to be uncommon in outpatients.

Sepsis, septic shock

In the 2016 update of the SSC guideline, sepsis is now defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [27] The risk of progression from severe COVID-19 infection to ARDS, multiple organ failure, and death is seen in patients who are older and have comorbidities such as T2D, HTN, COPD, BA, heart disease, and weakened immune systems.

Sepsis has two distinct phases, the first of which is a hyper-inflammatory phase followed by an immunosuppressive phase.[48]

In hyper inflammatory phase numerous markers such as procalcitonin, tumor necrosis factors (TNF), CRP, IL-1, and IL-6 are produced. As an initial response to infection, certain pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 are released. IL-6 stimulates the liver to produce CRP in response to infection. The most useful marker of severe systemic inflammation is procalcitonin. Many of these markers are considered to be the biomarkers of sepsis which aid in the diagnosis and management of the patient.[49] Similarly, levels of these biomarkers have been shown to be elevated in severe COVID-19 infections.[39,50,51]

The cytokine storm that is suggestive of sepsis is seen in the severe form of COVID-19 disease as well. [52,53] The multiorgan failure is attributed to hypoxia and circulatory disorders due to microvascular dysfunction such as disseminated intravascular coagulation and microembolism by interrupting blood flow to the lungs.

According to Lin HY, all of the hallmarks of sepsis including the presence of a specific pathogen seen in severe COVID-19 should thus be considered viral infection-induced sepsis.

Multi-system involvement	**Varying/exaggerated/ dysregulated immune response**	**Hyperinflammation**
Cytokine storm	**Hypercoagulopathy**	**Vascular involvement**
Acute respiratory distress syndrome	**Multi-organ failure**	**Death**

Figure 9: Clinical spectrum of sepsis in COVID-19

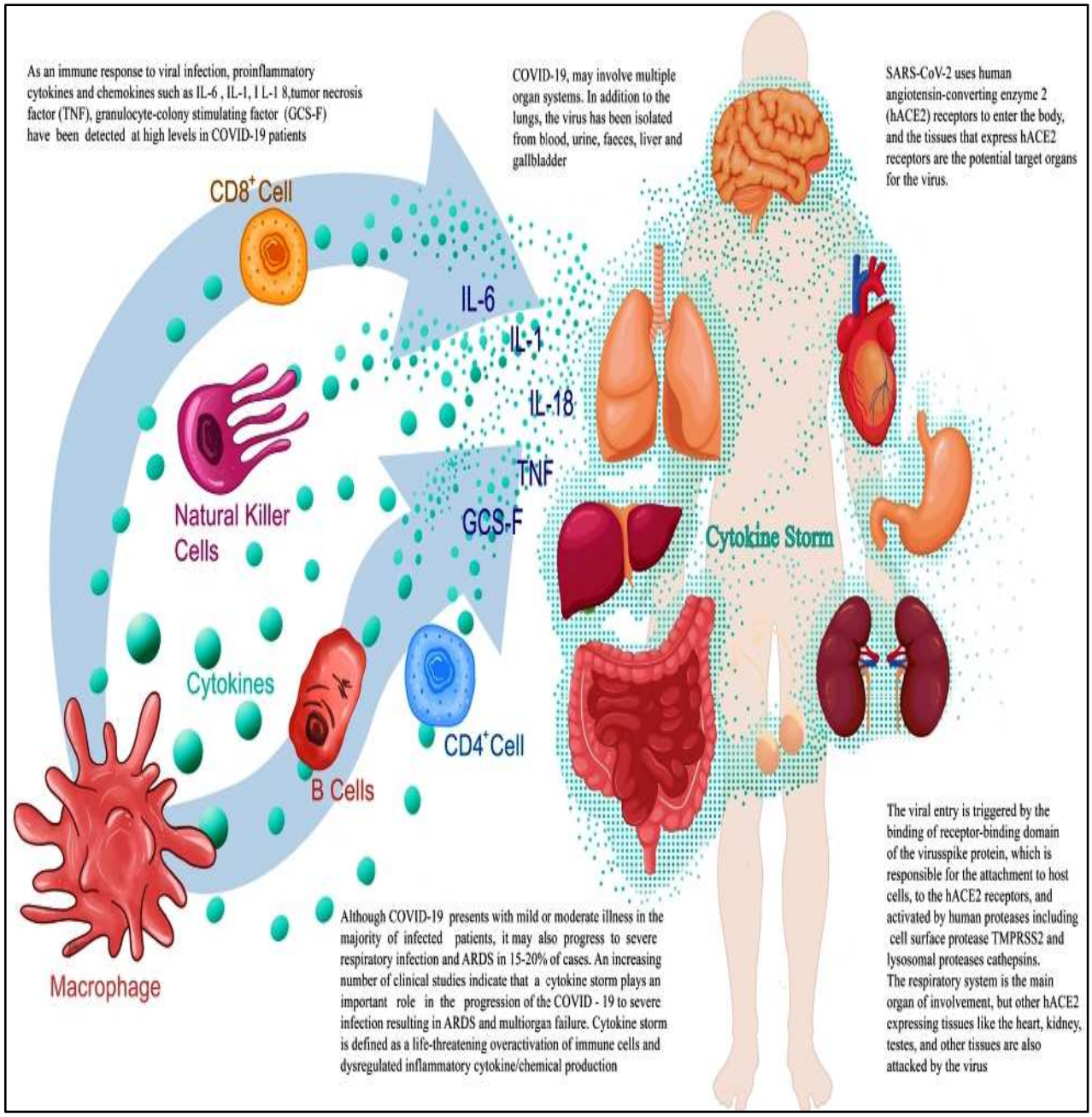


Figure 10: Cytokine storm and organs affected in COVID-19 sepsis [27]

INVESTIGATIONS

A) LABORATORY FINDINGS AND RECOMMENDATIONS

1. Hemogram: decrease in lymphocyte count and platelet counts are seen. Significantly decreased platelet count could be an indicator of poor prognosis

2. Renal function test: is helpful in the early identification of compromised renal function and associated dyselectrolytemia.

3. Hepatic parameters: Mild elevation of enzymes like SGOT and SGPT

4. Markers of inflammation:

a) hs-C Reactive Protein[54]

- It is an indirect biomarker of generalized inflammation and positive acute phase protein produced by the liver.
- It is crucial for immunity, the removal of damaged tissue, and the prevention of autoimmune disease.
- In response to inflammatory conditions such as bacterial infections or intracellular antigens like in viral infections, the blood of hs-CRP rises.
- In COVID-19 disease, severity and unfavorable outcomes are directly related to serum levels of hs-CRP.
- To predict mortality in COVID-19, Shabrawy et al. suggested that serum levels of HsCRP >33.9 ng/L as cut-off has 76.5% sensitivity and 88.9% specificity.

b) IL-6 [54]

- IL-6 not only has pro-inflammatory but also anti-inflammatory properties which is an important mediator of humoral immunity and
- Exaggerated production of IL-6 as a result of the dysregulated immune response has been known to cause respiratory distress, shock, MOF, and death.
- Shabrawy et al. proposed that IL-6 levels >32.3 pg/mL in the serum have 82.4% sensitivity and 94.4% specificity in predicting mortality in COVID-19.

c) Serum Procalcitonin(PCT)

- PCT, the 116-amino acid precursor of the hormone calcitonin, is normally produced and released by thyroid parafollicular C cells.[55]
- It can, however, be synthesized in many extra thyroid tissues during bacterial infection, which is mediated by increased levels of tumor necrosis factor-alpha (TNF) and interleukin 6[56]
- Several studies have recently reported that elevated PCT level is closely related to the COVID-19 severity.[39,57–59] Also in a meta-analysis it was found that increased PCT levels are associated with a 5-fold increased risk of severe SARS-CoV-2 infection [56]
- Serial PCT measurements may aid better in the prediction of the prognosis.[55]

d) Ferritin[54]

- Liver cells produce ferritin in response to inflammation which is an acute phase protein. It participates in iron metabolism by binding to it in the cell.
- Raised ferritin levels in the blood cause immune dysregulation due to its immune suppressive and pro-inflammatory actions. Excessive ferritin is also responsible for cytokine storm by stimulating the macrophages to release cytokines. Hence, it very well may be presumed that hyperferritinemia is related to unfortunate results in Coronavirus
- Cut off value of 1873 ng/ml for serum ferritin has 68.4% sensitivity and 79.3% specificity in predicting mortality in COVID-19 patients as per the study done by Lino et al.

e) LDH-[54]

- LDH is an intracellular enzyme found in nearly all organ systems that catalyzes the interconversion of pyruvate and lactate, as well as the simultaneous interconversion of NADH and NAD+.
- The enzyme is made up of two major subunits (A and B) and is found in humans in five different isozymes. Pneumocytes contain isoenzyme 3.
- Although LDH has been used as a marker of cardiac damage since the 1960s, abnormal values can result from multiple organ injuries and decreased oxygenation due to glycolytic pathway upregulation.
- The acidic extracellular pH caused by increased lactate caused by infection and tissue injury activates metalloproteases and promotes macrophage-mediated angiogenesis.
- Patients with serious Coronavirus disease with an extreme type of interstitial pneumonia frequently progress to ARDS. As LDH (isozyme 3)

is found in lung tissue, it is expected that these patients will have higher blood levels of LDH.

- In a pooled analysis of nine studies, Brandon et al. discovered that elevated LDH was associated with a >16-fold increase in mortality risk.

Coagulation profile:

i. prothrombin time, INR

ii. activated partial thromboplastin time

iii. D-dimer [54]

- It is a fibrin degradation product, the levels of which are raised in coagulation and thrombotic disorders.
- In severe COVID-19 patients, the coagulation cascades activated by the cytokine storm lead to thrombotic complications and coagulopathies such as DIC where higher levels of D-dimer are evident as a result.
- Poudel et al. discovered that non-survivors had higher mean plasma D-dimer levels (3.2 2.6 g/mL) than survivors (1.067 1.7 g/mL).
- A cut-off of 2 g/ml has 92.3% sensitivity and 83.3% specificity in predicting mortality as suggested by Zhang et al.

MOLECULAR TESTING

1. NAAT (nucleic acid amplification test):

NAAT recognizes SARS-CoV-2 RNA. The most common type of NAAT used is RT-PCR by which current infection can be diagnosed.[60,61]

Performance features:[60,61]

Given the ideal circumstance, it has high analytic sensitivity and specificity. The specimen's clinical efficacy will be determined by the duration of the disease at the time of testing, in addition to its type and quality.

Depending on the test, the reported false-negative rate ranges from 5 to 40%. In most cases, a single positive test confirms the diagnosis. If the first test is negative and clinical suspicion remains, a second test can improve diagnostic yield.

Turnaround time: 15 minutes to 8 hours.[60,61]

Low complexity rapid tests can be performed at the point of care and provide results in less than an hour. Most moderate- to high-complexity laboratory-based tests take several hours to complete. The time it takes for a clinician or patient to receive a result, on the other hand, is determined by how frequently the test is run and other processing factors.

The test used and the laboratory workflow both influence turnaround time.

Specimens used: The CDC advises collecting one of the following specimens:

- Nasopharyngeal swab specimen
- Nasal swab specimen: both anterior nares using a spun polyester swab, mid-turbinate swab using a flocked taper swab collected on-site or at home
- aspirate or wash from the nose/nasopharynx

- swab taken from the oropharynx
- saliva specimen around 1-5ml which the patient collects

Interpretation of NAAT:

i) **Positive result**: A positive SARS-CoV-2 nucleic acid amplification test (NAAT; e.g., RT-PCR) normally confirms the COVID-19 diagnosis. There is no need for additional diagnostic testing. Additional testing, however, might be required for management in hospitalized patients. Patients with COVID-19 can still detect SARS-CoV-2 RNA in upper respiratory tract specimens weeks after the onset of symptoms. However, continuous detection of viral RNA does not always mean continued infection.[62]

ii) **Negative results:** The absence of COVID-19 can be ruled out by a negative NAAT result. False-negative results from tests on specimens from the upper respiratory tract are possible. The test can be repeated 24 to 48 hours after the initial test if symptoms are highly suspicious for COVID-19 (symptoms with no apparent alternative cause) and confirmation of infection is required for infection management or control. The test should not be repeated within 24 hours.

iii) **Inconclusive or indeterminate nucleic acid amplification test (NAAT) results —** The interpretation of an inconclusive or indeterminate result depends on the specific NAAT carried out; the clinician should speak with the performing laboratory about additional testing.

An unresolved or undecided result may mean that only one of the two or more genes that the NAAT targets was found in some instances. Considering the high specificity of NAAT assays, these results can be regarded as presumptive positive

results. If the patient is still in the early stages of the disease, repeat testing can be helpful.

Accuracy: precision and predictive values of NAAT in the detection of SARS CoV-2 have not been assessed.

Specificity: is high.[63,64]

Sensitivity: The clinical performance of NAAT is less consistent even though it is accurate in detecting low viral loads in the samples which contain RNA in ideal conditions. False-positive results are rare. False-negative rates are estimated to range between 5 and 40%.[65]

The sensitivity of the results is influenced by the severity of the disease at the time of the test, the type and quality of the sample used, and the particular test.

Test results by type of specimen: Specimen type may affect test sensitivity.

Nasopharyngeal, nasal, and saliva samples from the upper respiratory tract have high sensitivity, whereas oropharyngeal swab samples have lower sensitivity.[66–69]

The combined sensitivity for nasopharyngeal swabs was 86%, saliva 85%, and throat swabs 68% compared with nasopharyngeal swab PCR results in a meta-analysis that included 23 studies and 8,000 participants.[68] 97 percent of samples came from the throat and nasal passages combined.

High viral load is seen in lower respiratory tract specimens and is more likely to give a positive test when compared to those of the upper respiratory tract.[66,68]

Test results by length of illness: [70,71]In an analysis of seven studies that assessed RT-PCR performance rate of false-negative results were as follows:

Day	Rate of false positivity
Day of exposure	100%
Day 5	38%
Day 8	20%
Day 21	66%

Test results by assay type: The major commercial NAAT assays differ in their limits of detection, and repeating tests on various platforms may produce inconsistent results. [63,64] In an orderly survey by IDSA, the responsiveness of the RT-PCR examination was like that of lab NAAT when compared to the reference standard. The rapid isothermal Abbott ID NOW test has a sensitivity of 81%, while the laboratory NAAT has a sensitivity of 99%. The specificity of each method was 97%.

2. ANTIGEN TESTS:

These tests detect current infection[72–74]

Turnaround Time:[72–74] Since they can be completed quickly and at the point of care, tests that detect SARS-CoV-2 antigen are more accessible and have quicker turnaround times than most NAAT. One hour is needed to complete the test.

Antigen test interpretation:

Antigen tests may be more useful than NAAT for diagnosing symptomatic patients. Antigen tests work best when done within the first 5-7 days of the onset of symptoms.

Positive result: An individual with symptoms who has a positive antigen test has a SARS-CoV-2 infection. Rate of false positives is low

Negative result: An additional test should be conducted after a negative antigen test in a symptomatic person because it could be a false negative and does not rule out SARS-CoV-2 infection. According to the advice from the US Food and Drug Administration (FDA), people conducting at-home tests should repeat an antigen test after 48 hours.

Sensitivity: high in the first week of illness, when viral replication is at its peak; however, it is less sensitive than NAAT. [74,75] Antigen testing in series seems to increase sensitivity.

Specificity: Antigen tests are extremely specific. In a systematic review that included 152 studies, 49 commercially available antigen tests were analyzed on specimens that were already subjected to NAAT and it was found that the overall specificity exceeded 98%.[75]

Screening: To identify carriers early and test people repeatedly in high-risk and outbreak-affected areas, antigen testing may be the fastest and easiest method of testing.

OTHER DIAGNOSTIC TESTS

Serology (antibody detection)-

This is done for identification of a previous infection (or an infection that has lasted at least 3 to 4 weeks). The development of IgG antibodies takes 14 days after the onset of symptoms, but they are only detectable after several days to weeks. [61,76] There have been reports of cross-reactivity with other coronaviruses.

Even the serologic tests which are highly specific will have low positive predictive value in environments with low seroprevalence. Therefore, individual results should be interpreted cautiously.

Turnaround time: 15 minutes to 2 hours. Laboratory workflow and tests used by laboratories influence the turnaround time.

Sensitivity: The time taken to detect antibodies varies from test to test. A systematic review of 38 studies found that IgM was found in 23% of COVID-19 patients after one week, 58% after two weeks, and 75% after three weeks, while IgG was found in 30, 66, and 88 percent of patients, respectively. [77] According to other studies, IgG positivity reaches 100% within 16 to 20 days.[78]

Specificity: Specificity is also influenced by the type of serologic assay. When compared to IgG antibody and total antibody tests, IgM and IgA antibodies and IgM/IgG differentiation tests typically have specificities below 99 percent. A potential worry is the cross-reactivity of some coronaviruses and other viral pathogens.[79]

VIRAL CULTURES: Clinical laboratories should not receive samples from patients with suspected or confirmed COVID-19 for viral culture due to safety concerns. The primary use of viral culture is limited to research.

B) IMAGING

The air from the alveolar spaces is displaced by the inflammation and edema caused by an immune response to viral entry and replication. This helps the detection of the disease through imaging of the thorax.[80] However, the early phases of COVID-19 do not always involve lung parenchyma. Therefore, in early phases imaging is not useful for evaluation. In such instances, RT-PCR, not thoracic imaging, is regarded as the gold standard for COVID-19 diagnosis. [80] In conditions where RT-PCR isn't accessible or results are anticipated, imaging can be depended upon within the sight of normal side effects of Coronavirus. Despite its limitations, thoracic imaging contributes significantly to patient diagnosis, monitoring, and follow-up. Imaging aids clinical decision-making in determining whether or not a patient needs to be admitted to a hospital, in addition to clinical and laboratory evaluation.

CHEST RADIOGRAPH:

Characteristic COVID-19 patterns are:[80]

- 47%- consolidation
- 33%- Ground glass opacities
- 41%- Peripheral distribution
- 50% - lower-zone distribution (most common locations) with typical bilateral involvement (50%)
- 3%- Pleural effusion

Nevertheless, chest radiography findings of most of the patients at baseline are normal or have only mild pathology.

According to a Cochrane review, chest radiography can diagnose COVID-19 with a pooled sensitivity of 80.6 percent and specificity of 71.5 percent. [81]

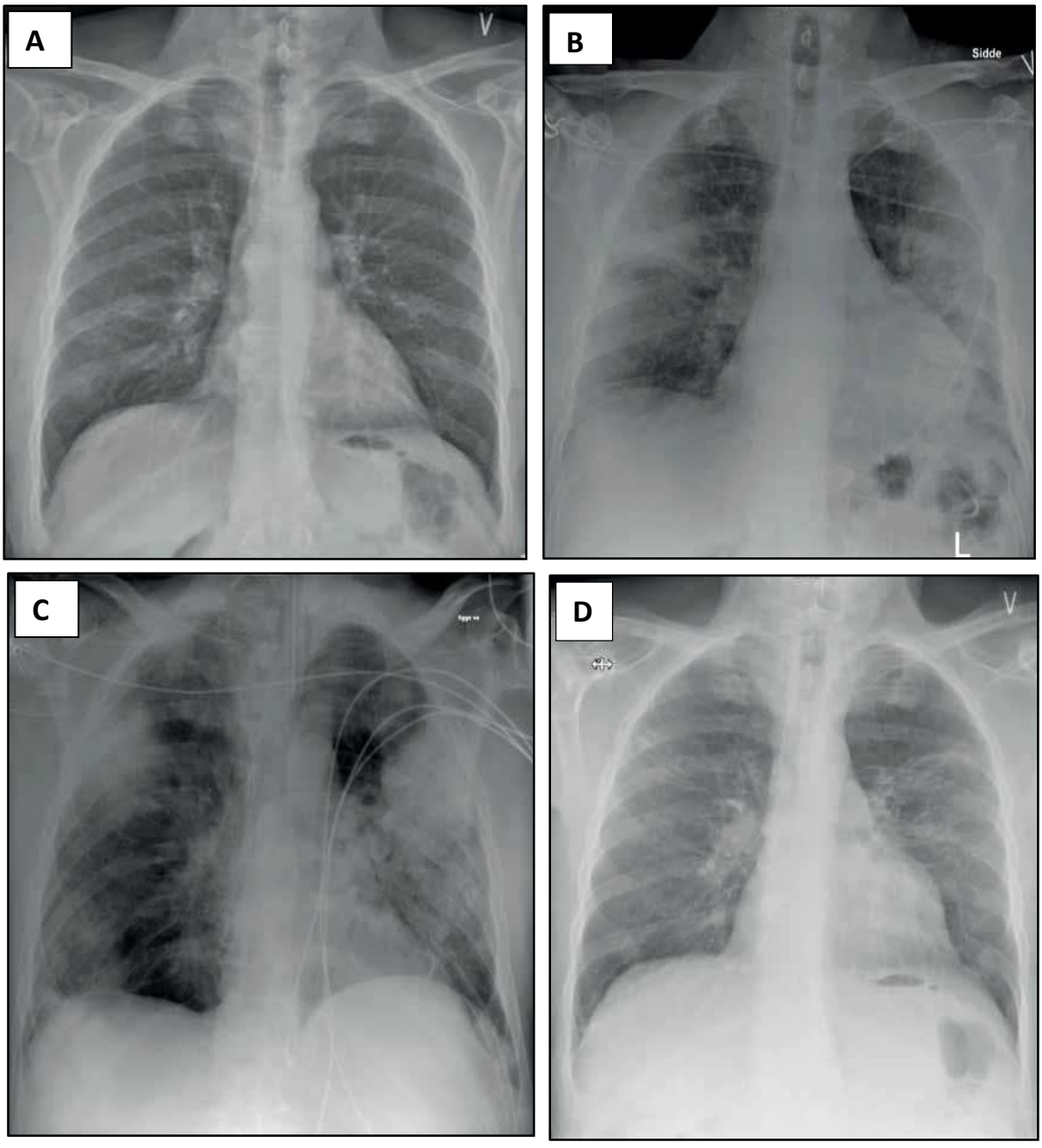


Figure 11: Chest x-rays of COVID-19 patient A) 11 months prior to the admission to hospital. B) On the day of admission. C) 4 days post admission. D) Approximately 2 months post admission. Reticular-pattern persists but the b/l opacities have diminished.[80]

COMPUTED TOMOGRAPHY

In the first few days of the disease, CT scans show no abnormal findings or only minimal GGOs. However, after 5-8 days of symptom onset, CT scans show a crazy paving pattern in addition to extensive GGOs. [82,83] The most common finding, which clinically corresponds to the onset of acute lung injury, is typically a combination of consolidation and GGOs 9–13 days after the disease's peak.

The absorption stage comes after the peak stage, when consolidations and GGOs start to decline, which can take several weeks in some patients. Over the due course of time, maybe weeks to months the GGOs and the consolidations are converted to reticular opacities in some patients which may be attributed to fibrosis. Other findings like traction bronchiectasis may also be seen.[84]

According to reports, GGOs, reticular abnormalities, and parenchymal bands are the most frequently seen residual parenchymal abnormalities.[85]

Table 1: CT findings in COVID-19 disease

COVID-19 pneumonia imaging classification	Rationale	CT findings	Suggested reporting language
Typical appearance	Commonly reported imaging features of greater specificity for COVID-19 pneumonia.	▪ Peripheral, bilateral, GGO with or without consolidation or visible intralobular lines ("crazy-paving") ▪ Multifocal GGO of rounded morphology with or without consolidation or visible intralobular lines ("crazy-paving") ▪ Reverse halo sign or other findings of organizing pneumonia (seen later in the disease)	"Commonly reported imaging features of (COVID-19) pneumonia are present. Other processes such as influenza pneumonia and organizing pneumonia, as can be seen with drug toxicity and connective tissue disease, can cause a similar imaging pattern."
Indeterminate appearance	Nonspecific imaging features of COVID-19 pneumonia.	▪ **Absence of typical features AND** ▪ **Presence of:** • Multifocal, diffuse, perihilar, or unilateral GGO with or without consolidation lacking a specific distribution and are non-rounded or non-peripheral. • Few very small GGO with a non-rounded and non-peripheral distribution.	"Imaging features can be seen with (COVID-19) pneumonia, though are nonspecific and can occur with a variety of infectious and noninfectious processes."
Atypical appearance	Uncommonly or not reported features of COVID-19 pneumonia.	▪ **Absence of typical or indeterminate features AND** ▪ **Presence of:** • Isolated lobar or segmental consolidation without GGO • Discrete small nodules (centrilobular, "tree-in-bud") • Lung cavitation • Smooth interlobular septal thickening with pleural effusion	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered."

Sensitivity and specificity: Although common in COVID-19, these findings are not specific to the virus and are frequently observed in other viral pneumonias. [86]

Table 2: Sensitivity and Specificity of CXR and chest CT[80]

Imaging modality	Sensitivity (95% CI)#	Specificity (95% CI)#	Strengths	Weaknesses
CXR	80.6% (69.1–88.6%)	71.5% (59.8–80.8%)	Acceptable sensitivity Can be performed at bedside (supine) Standard for image storage and comparison	Low specificity Patient needs to be moved (erect, two views) More staff exposed Time use Radiation exposure
Chest CT	87.9% (84.6–90.6%)	80.0% (74.9–84.3%)	High sensitivity and specificity Can provide information on relevant differential diagnosis Can be supplemented with assessment for pulmonary embolism Standard for image storage and comparison	Patient needs to be moved More staff exposed Time use Costs Radiation exposure

Ai et al.'s study found that included 1014 patients underwent both CT chest and RT-PCR. It was shown that a "positive" chest CT for COVID-19 (as determined by a consensus of two radiologists) had a **sensitivity of 97%**, using the PCR tests as a reference, but **specificity was only 25%**. [87]

Table 3: CORADS scoring [88]

CO-RADS score	Level of suspicion	Findings
CO-RADS 0	Not interpretable	Scan technically insufficient for assigning a score
CO-RADS 1	Very low	Normal or non-infectious
CO-RADS 2	Low	Typical for other infections but not COVID-19
CO-RADS 3	Equivocal/unsure	Features compatible with COVID-19, but also other diseases
CO-RADS 4	High	Suspicious for COVID-19
CO-RADS 5	Ver high	Typical for COVID-19
CO-RADS 6	Proven case	RT-PCR positive for SARS-CoV-2

Table 4: CT Severity Scoring [88]

% Involvement (single lobe)	Score
0-5 % lung involvement	1
5-25 % lung involvement	2
25-50 % lung involvement	3
50-75 % lung involvement	4
75-100 % lung involvement	5

Table 5: CT Severity Score Calculation Criterion[88]

CT severity	SCORE
Mild	< 8
Moderate	9 - 15
Severe	> 15
Total score	~ 25

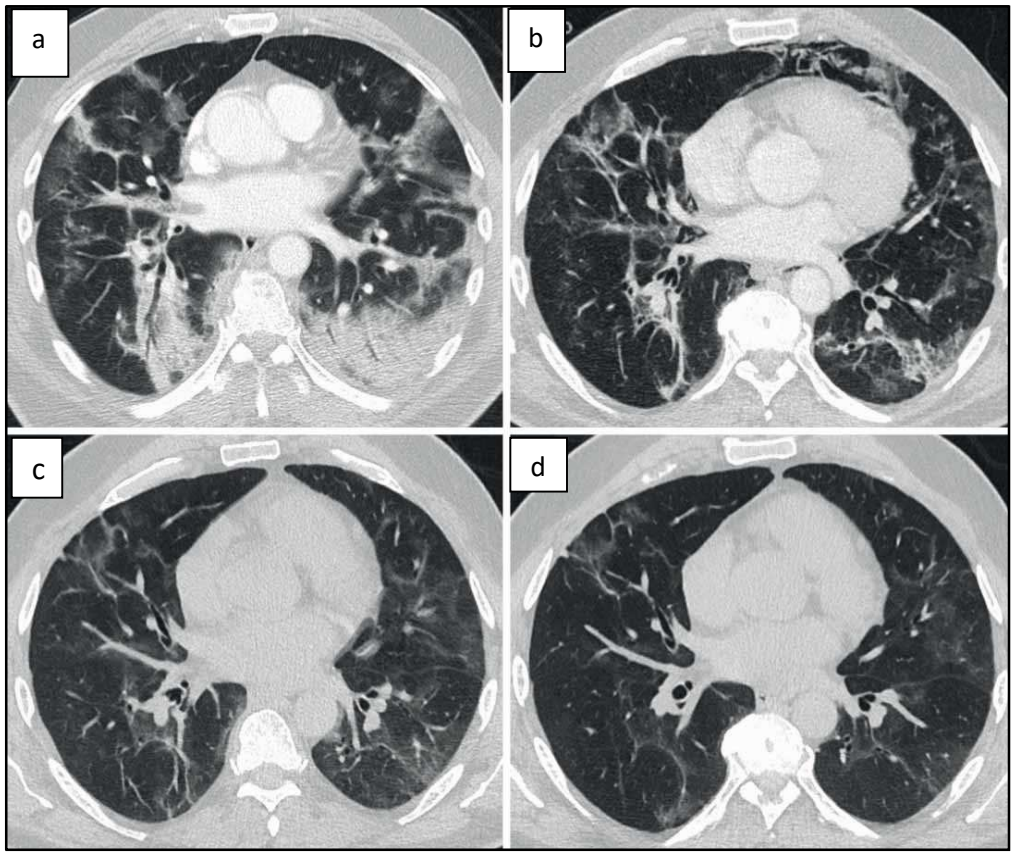


Figure 12: CT thorax of COVID-19 patient– Evidence of a gradual decrease in the CT findings at a) 2 weeks, b) 3 weeks, c) 14 weeks and d) 24 weeks after disease onset [80]

TREATMENT

WHO definitions of disease severity for COVID-19 [89]

- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe COVID-19-**Defined by any of the following: oxygen saturation < 90% on room air; signs of pneumonia; signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis, or presence of any other general danger signs including the inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).
- **Non-severe COVID-19** – Defined as the absence of any criteria for severe or critical COVID-19.

Following are the updated recommendations for the treatment of COVID-19 disease.[89]

COLCHICINE

Due to the lack of human trials to demonstrate colchicine's safety and efficacy, the guidelines for its use were developed using data gathered from experiments on animal models of SARS-CoV-2 infection.

There are many hypotheses on it its mechanism of action that was presumed to alleviate the inflammatory process in COVID 19 which includes decreasing the

production of chemokines, decreasing neutrophil chemotaxis, and inhibiting inflammasome signaling.

In non-severe COVID-19, colchicine has little or no beneficial effect on the requirement of mechanical ventilation, hospitalizations, and mortality. It might also lead to drug discontinuation due to its adverse effects.[89]

Strong recommendation against the use of colchicine in non-severe COVID-19

IVERMECTIN

As the fourth version of the WHO living guideline, the recommendation for ivermectin was released on March 31, 2021. Increased international interest in ivermectin as a potential treatment option led to this.[89]

Currently, no direct evidence exists on its antiviral effects against COVID-19 at present. It has no beneficial effects on hospitalizations, duration of hospital stay, mechanical ventilation, and mortality.

Ivermectin is not recommended in any case of COVID-19 except for research purposes.

ANTIVIRALS[89]

There are two broad categories of antiviral therapies.

Direct-acting antivirals (DAAVs): If the viral target lacks a cellular homologue, DAAVs can target viral enzymatic activities and be less toxic.

Host-directed therapy (HDT): HDT targets host cells, which are necessary for the virus's replication or persistence.

HOST DIRECTED THERAPY

1. HYDROXYCHLOROQUINE

Some small-scale clinical trials conducted early in the pandemic in the year 2020 showed that HCQs may have benefits in COVID-19. Some small-scale clinical trials conducted early in the pandemic in the year 2020 showed that HCQs may have benefits in COVID-19 treatment.[89]

However, RCTs of a larger scale showed that HCQ was not effective in treating COVID-19. According to the WHO SOLIDARITY trial, which evaluated COVID-19 treatments in RCTs involving 11330 patients from 30 nations, HCQ failed to treat COVID-19.

DIRECT-ACTING ANTIVIRALS

1. REMDESIVIR

Remdesivir is an antiviral nucleotide analog which acts against all the variants of SARS-CoV-2 namely α, β, γ, δ and Omicron. [89]

Based on data from four RCTs with 7333 participants hospitalized for COVID-19, an initial conditional recommendation was issued on November 20, 2020, suggesting that remdesivir not be used for patients with COVID-19, regardless of illness severity.

Mechanism of action

Viral polymerase incorporates the drug into endogenous adenosine nucleoside at the time of RNA replication , a process known as chain termination which differs

from lethal mutagenesis. After the addition of 3 or more nucleotides RNA synthesis stops instead of stopping at the point where remdesivir gets incorporated thereby causing delayed chain termination, unlike many other chain-terminating drugs.[90]

Indications [89]

Patients with confirmed non-severe COVID-19, >12 years of age and >40 kg

- At high risk of hospitalization
- With symptoms lasting less than 7 days
- When alternative treatment options are unavailable or clinically inappropriate

Contraindications [89]

Hypersensitivity to any of the constituents of the drug

Recommendations for not starting or continuing Remdesivir [89]

- Age < 12 years
- Weight < 40 kgs
- eGFR < 30 mL/min in the presence of renal impairment
- ALT more than 5 times the upper limit of normal
- symptoms or signs of liver inflammation along with elevation in ALT/AST

Dosage and route

1.Route:[89]

- IV after reconstitution and dilution.
- Separate IV line to be dedicated for remdesivir administration

2. Dosage [89]

The total duration of treatment is 3 days. 200 mg as loading dose given by IV infusion on day 1 followed by 100 mg of remdesivir given once daily on days 2 and 3. It is more effective if administered within 7 days of the onset of symptoms.

3. Dose adjustment

- In Renal impairment: [89]

There is no dose adjustment with an eGFR > 30 mL/min. If eGFR < 30 mL/min, it should not be used. Betadex sulfobutyl ether sodium is one of the excipients which is excreted through the kidneys. Therefore, it accumulates in patients with decreased renal function.

- In Hepatic impairment: [89]

Remdesivir has not been studied in patients with hepatic impairment. It should not be used in patients with a rise in liver enzymes more than 5 times the upper limit of normal

Remdesivir is a conditional recommendation for use in non-severe COVID-19 patients who are at risk of hospitalization and for severe COVID-19 infections and conditional recommendation against the use in critical COVID-19 patients

2. FAVIPRAVIR

It is an effective broad-spectrum antiviral against influenza, norovirus, and flavivirus among others. The concept of its beneficial effects early in the course of the disease in other viruses paved the way for its experiments in COVID-19 infection as well. Numerous previous in vitro studies and reports, oral dosing, and safety profile also indicated its use in the disease. [91]

Mechanism of action: [91]inhibits viral replication by 2 mechanisms

1. Inhibits the activity of the RdRp enzyme of the virus
2. Competes with purine nucleosides for its insertion into the nascent viral RNA

Dose: 3600mg in divided doses on day 1 followed by 1600mg in divided doses from day 2 to day 7.

According to data from a small, non-randomized study, favipiravir may have fewer side effects than lopinavir-ritonavir while also causing the virus to clear up more quickly and clearing up radiological findings. [92]

3. LOPINAVIR /RITONAVIR

The combination of DAAV and protease inhibitors is currently used against HIV. This combination of drugs along with HCQ did not have any effect in reducing viral load but lowered the overall clinical score.[80]

The combination of these drugs did not prove any beneficial effect in reducing mortality, progression to mechanical ventilation, or the length of hospital stay. A small study showed that the number of days spent in ICU was reduced by 5 days, but in the RECOVERY trial, it was found that there was no benefit for COVID-19 patients receiving IMV with the use of this combination [80]

4. **MOLNUPIRAVIR**

As the ninth version of the WHO living guideline, the recommendations for the use of molnupiravir in patients with non-severe COVID-19 were released on March 3, 2022.

Molnupiravir is an orally available antiviral which was repurposed for its use in the early phase of covid 19 infection.[93,94]. It is a nucleoside drug which is a prodrug of ß-D-N4-hydroxycytidine

Mechanism of action: SARS-CoV-2 RdRp enzyme during replication of RNA incorporates the NHC instead of nucleosides C or U into the genomic or sub-genomic RNA. This process known as lethal mutagenesis produces NHC containing RNAs that are used as a template to produce more RNAs which are unlikely to produce functional viruses. [95,96]

The route, dose, and dosage:

Dose and dosage: 800mg BD for 5 days. Maximum plasma concentration is achieved at 3600ng/ml in healthy volunteers [97]

Route: oral

t1/2 life: 3 hours [97]

Contraindications:

- Pediatric patient
- Breastfeeding women
- Pregnancy

Conditional recommendation for the use in patients with non-severe COVID-19 at risk of hospitalization except in those contraindicated

JANUS KINASE INHIBITORS

Mechanism of action:

JAK1, JAK2, JAK3, and tyrosine kinase 2 are members of the small family of kinases known as the Janus kinases (JAKs). The cytokine receptors, both type I and type II, are where several interleukins, interferons, and hormones act.

Through multifactorial effects on cytokine signaling, JAK inhibitors inhibit intracellular signaling. Numerous cellular responses like antiviral responses, ACE2 expression, T cell function, differentiation, and macrophage activation are disrupted.[98]

Baricitinib, ruxolitinib, and tofacitinib are three important JAK inhibitors useful in COVID-19. All these are non-specific JAK inhibitors, but there are differences in specificity and potency for different JAKs. Baricitinib is a JAK1/JAK2 inhibitor, Ruxolitinib is a JAK1/JAK2 > TYK2 inhibitor, and Tofacitinib is a JAK3/JAK1 > JAK2/TYK2 inhibitor. [98–100]

BARICITINIB

Route, dosage, and duration:[89]

Adults with an eGFR of 60 mL/min/1.73 m^2 should take 4 mg daily orally.

It is given for 14 days or until hospital discharge, whichever comes first. The optimal duration of treatment is unknown.

Dose adjustment:[89]

To be done in patients with leukopenia, renal impedance, or hepatic hindrance. Dose reductions should be made in patients taking strong organic anion transporter 3 (OAT3) inhibitors (like probenecid) due to the drug interactions**.**

Timing:[89]

Specific time to start baricitinib is unknown but should be started at the same time as systemic corticosteroids.

Baricitinib has beneficial effect not only in reducing the mortality but also the duration of mechanical ventilation and hospital length of stay in severe or critically ill patients. It is likely to result in a small or no increase in serious adverse events.

In severe and critically ill COVID-19 patients Baricitinib is strongly recommended

TOFACITINIB

Route and Dose: [89]

10 mg twice daily orally for up to 14 days or until hospital discharge

Time: [89]

There is no specific time for starting the drug during hospitalization or illness. It can be started along with systemic corticosteroids.

The beneficial effects on hospital length of stay, need for mechanical ventilation and mortality are still unknown. Drug discontinuation can occur in case of a severe adverse event. [89]

Conditional recommendation against its use in severe and critical COVID-19 patients

SYSTEMIC CORTICOSTEROIDS

The WHO living guidelines for corticosteroids were released on September 2, 2020, followed by the BMJ Rapid Recommendations on September 5, 2020.[89]

Route:

Systemic corticosteroids can be given orally or intravenously. Dexamethasone has a very high bioavailability. They may be administered intravenously rather than orally if intestinal dysfunction is suspected.[89]

Dose and dosage: dexamethasone 6mg once daily

Duration: The total duration of the regimen ranged from 5 to 14 days which was evaluated in 7 trials. Most of the patients were given up to 10 days. It was stopped during discharge from the hospital.[89]

Timing: Steroid administration after 7 days or more of symptom onset has a beneficial effect (RECOVERY TRIAL)[89]

In severe or critical COVID-19 systemic steroids are strongly recommended for its use

IL-6 INHIBITORS -TOCILIZUMAB

After the RECOVERY and REMAP-CAP trials, their data of 1020 patients who were on tocilizumab or sarilumab was published in February 2021 and made available to the WHO on June 1, 2021. Therefore, WHO published the recommendations for IL-6 receptor blockers in its 5th version on July 6 2021[89]

Mechanism of action: Immune response to infections is stimulated and regulated by the cytokine IL-6. The IL-6 receptor (IL-6R/IL-6R) both in its membrane-bound and soluble form is inhibited by this monoclonal antibody thereby suppressing the immune response.

Dose, Duration, and Route: [89]

Tocilizumab is administered at a dose of 8 mg/kg body weight. Can be given up to a maximum of 800 as a single IV infusion for 1 hour. A second dose may be administered 12 to 48 hours after the first dose.

IL-6 receptor blocker therapy should be used along with systemic corticosteroids which can be given orally or intravenously.

Monitoring:

- Baseline routine blood workup such as neutrophil count, platelets, transaminases, and total bilirubin should be checked.
- Signs and symptoms of infection like tuberculosis, invasive fungal infections, and opportunistic pathogens (risk of infection increase due to immunosuppression in addition to systemic corticosteroids).

Tocilizumab should be used cautiously in patients with severe active infection other than COVID-19 or patients with a history of chronic infections. The risks and benefits should be weighed before considering the therapy. [89] Based on strong evidence, IL-6 receptor blockers reduce mortality and the need for mechanical ventilation.

Strong recommendation for the use in severe COVID-19 patients

SOTROVIMAB

On September 15, 2022, an updated recommendation for patients with non-severe COVID-19 was made for sotrovimab.

Mechanism of action: Sotrovimab (VIR-7831; GSK4182136) is a single human monoclonal antibody that binds to a conserved epitope of the SARS-CoV-2 spike protein, blocking virus entry into cells. [89]

Conditional recommendation against the use of Sotrovimab in non-severe COVID- 19 patients

Previously, it was recommended in patients with non-severe COVID-19 who were at high risk of hospitalization. However, there is strong evidence to suggest that sotrovimab should not be used because it lacks in vitro neutralization activity against the circulating SARS-CoV-2 variants and subvariants (such as Omicron), which are currently dominating worldwide.

CASIRIVIMAB-IMDEVIMAB

On September 15, 2022, an updated recommendation for this combination of neutralizing antibodies for COVID-19 patients was included in the 12th edition of the WHO guideline. In non-severe COVID-19 patients who are at high risk of hospitalization, and severe and critical patients who were seronegative a conditional recommendation for its use was proposed.

Mechanism of action

Casirivimab and Imdevimab are two fully human antibodies (REGN10933 and REGN10987) that exhibit their inhibitory effects on the virus by binding to the

SARS-CoV-2 spike protein. [101] It was postulated to have more beneficial effects in patients who did not have antibodies to spike protein i.e seronegative patients.

Dose: 1200mg (600mg of each antibody)

Route: IV infusion

t1/2 life: 25 to 37 days for both antibodies

ANTICOAGULATION

The majority of patients have relatively normal lung compliance, with markedly elevated dead space ventilation which is the hallmark of vascular occlusive respiratory failure.[4]

In >80% of severe cases of COVID-19, there is a gross elevation of d-dimer levels in the blood which is a marker of not only the fibrin clot formation and degradation but also the severity of the disease. [80]

Barrett et al. in a multicentre randomized control study showed that therapeutic anticoagulation, when given even before the formation of significant clots in the lung vasculature, had more beneficial effects than when it is started after the onset of severe respiratory failure.[4]

Even after anticoagulants are given as prophylaxis, there is an increased risk of disseminated coagulation in COVID-19 patients which results in complications like DVT, pulmonary embolism, MI, and stroke which endangers the patient's life. Therefore, in such a cohort of patients, it was hypothesized that tissue plasminogen activator (tPA) if given for lysis of the already formed clot where anticoagulants have no role helps in restoration of patency of pulmonary microvasculature, reducing dead space ventilation and also in improving the oxygenation.[4]

NIH GUIDELINES ON ANTITHROMBOTIC THERAPY IN COVID -19 (UPDATED- DECEMBER 1 2022)[102]

SCREENING:

- There is insufficient evidence for the Panel to recommend either for or against routine screening for venous thromboembolism (VTE) in COVID-19 patients who do not have signs or symptoms of VTE, regardless of their coagulation markers' status.
- The Panel recommends that hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion be evaluated for thromboembolic disease (AIII)

Treatment of thrombosis with anticoagulants

- When diagnostic imaging is not feasible the panel advises starting therapeutic anticoagulation in treating patients with COVID-19 who have a high risk of developing the thromboembolic disease (AIII).
- Antithrombotic therapy should be administered to COVID-19 patients who require ECMO, continuous renal replacement therapy, or who have catheter-related thrombosis in accordance with the institutional protocols for non-COVID-19 patients (AIII), as recommended by the Panel.

Antithrombotic Therapy for Hospitalized, Nonpregnant Adults Without Evidence of Venous Thromboembolism

- For Coronavirus patients who have no proof of thrombosis, the board exhorts against utilizing anticoagulant or antiplatelet treatment not withstanding the

norm of care to forestall arterial thrombosis (AIII). Low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over oral anticoagulants in hospitalized patients (AIII). These heparin subtypes' shorter half-lives allow for a quick reversal of their effects.

- They have fewer drug-drug interactions than oral anticoagulants and can also be administered intravenously or subcutaneously.
- LMWH is chosen over UFH.

For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care:

- Therapeutic dose of heparin is advised by the panel in patients who require low-flow oxygen but D-dimer levels are above the upper limit of normal (CIIa).
- Therapeutic anticoagulation is contraindicated in COVID-19 patients with low platelet count (<50 x 10^9/L), low HB (8 g/dL), those who require dual antiplatelet therapy, those with a history of bleeding within the previous 30 days that necessitated an ER visit or hospitalization, a history of a bleeding disorder or an inherited or active acquired bleeding disorder.
- A prophylactic dose of heparin is advised by the panel in patients who do not meet the criteria for therapeutic heparin or in those who are not receiving therapeutic heparin for any other reasons unless it is contraindicated (AIIb).
- The Panel advises against the use of an oral anticoagulant in therapeutic doses for prophylaxis of VTE or to stop the progression of COVID-19, except in a clinical trial (AIIa).

- The Panel lacks sufficient data to advise either in favor of or against using thrombolytic agents to treat COVID-19.
- In patients who are not critically ill, the use of antiplatelet therapy to prevent the progression or death in such patient the Panel advises against its use (BIIa).

For adults who require ICU-level care, including those receiving high-flow oxygen:

- Prophylactic dose of heparin is advised by the panel for prevention of VTE unless there is a contraindication (AI).
- For patients in whom the therapeutic dose of heparin was started in a non-ICU setting and then moved to ICU, switching the therapeutic dose to a prophylactic dose of heparin is advised by the panel unless VTE is confirmed (BIII).
- An intermediate dose (such as enoxaparin 1 mg/kg once daily) or a therapeutic dose of anticoagulation for the prevention of VTE is not advised by the panel except in clinical trials (BI).
- The Panel is in debt of sufficient data to advise regarding the use of antiplatelet therapy in COVID-19 patients who are critically ill.

RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

It is derived from human tissue culture and produced using recombinant DNA technology.

Mechanism of action:[103]

rtPA has moderate specificity for fibrin-bound plasminogen, because of which the amount of circulating fibrinogen is only reduced by about 50%.

Fibrin deposition in the hemostatic plug of platelets leads to the formation of a thrombus. Once the repair is done, the fibrinolytic system gets activated and degrades the fibrin with the help of plasmin (serine protease).

rtPA activates plasminogen to plasmin which helps in the digestion of fibrin.

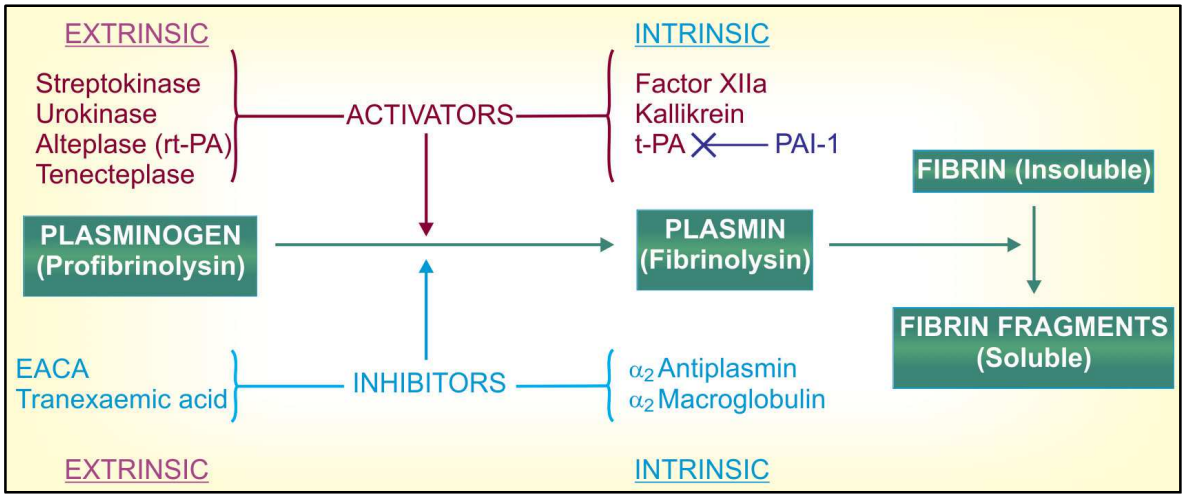


Figure 13: Mechanism of action of tissue plasminogen activator (alteplase)

Metabolism: The liver quickly eliminates it, and plasminogen activator inhibitor-1 renders it inactive (PAI-1).

t1/2 life: 4–8 minutes. Due to the short t12, it must be administered via slow intravenous infusion, and heparin is frequently co-administered.

Side effects: Despite being non-antigenic, it can still cause nausea, mild hypotension, and fever.

Christie et al. [3] identified COVID-19-positive patients with severe hypoxia who either required non-invasive ventilator or mechanical ventilator in a case series of five patients. All of the patients were eligible for thrombolytic therapy because their D-dimer values were elevated (greater than 1.5 g/mL). The following protocol was followed when giving tPA: a two-hour intravenous bolus of 25 mg, followed by a 22-hour continuous infusion of 25 mg of tPA. Each patient began receiving a weight-based continuous heparin infusion following thrombolytic therapy. All patients experienced an initial rise in PaO2 following the first administration of tPA. However, the PaO2 levels of all patients consistently decreased for the next 24 hours following this rise. Additionally, it was noted that after the initial improvement, the downward PaO2 trend did not return to the patient's pre-treatment baseline levels but rather settled in a more tolerable PaO2 range. The patients in this series were ultimately able to tolerate supplemental oxygen de-escalation while maintaining a stable PaO2, whereas oxygen requirements were rising before treatment. Therefore, following fibrinolytic therapy, there was an overall improvement in oxygenation and in the effort to liberate patients from the need for mechanical ventilation, early application of tPA in the respiratory deteriorating COVID-19 patient may be beneficial.

In a case series of five patients with severe COVID-19 respiratory failure who were treated with off-label intravenous administration of tPA (alteplase) in the context of an apparent thrombotic coagulopathy, Barrett et al. [104] reported that all five patients appeared to have an improved respiratory status following tPA administration one patient had an initial marked improvement that partially regressed after several hours, one patient had transient improvements that were not sustained, and three patients had sustained clinical improvements following tPA administration.

The use of tPA in 3 cases were reported by Janice Wang et al. [105]. The P/F ratio of all three patients treated with tPA showed an initial improvement, ranging from 38% to a rise of more than 100%. One patient's observed improvement lasted for a long time, but two patients' improvements faded over time after their tPA infusion was finished.

In another case series of five patients by Andre et al. [106] with suspected pulmonary embolism on echocardiograph (based on a combination of findings like obstructive shock, acute cor pulmonale, and sudden cardiac arrest) received tPA at a dose of 100mg intravenously, as rescue systemic fibrinolysis. Following fibrinolysis, it was found that the condition of 2 patients with obstructive shock improved with a lower norepinephrine dose. However, despite veno-arterial extracorporeal membrane oxygenation (V-A ECMO) support, a second rescue therapy for the second hit failed, resulting in multi-organ failure. Fibrinolysis in another patient failed to alleviate shock, necessitating V-A ECMO.

In case series done by Goyal et al.[107] which included 3 patients, a low dose of tPA (30–50 mg) was given to three COVID-19 critically ill patients who were in worsening respiratory failure despite being on therapeutic anticoagulation. All patients had respiratory rate > 40; FiO2> 0.7(on NIV); PiO2/FiO2 ratio < 100 and D-dimer>1000 ng/ml. After thrombolysis, dramatic changes in oxygenation were noted. All patients became off oxygen within 3–7 days and were discharged within 2 weeks.

All had significant early improvement compared to other patients earlier admitted with COVID-19 in ICU with similar severe conditions.

Barett et al. [4] in a large vanguard multicentre randomized control study consisting of 2 groups tPA bolus (50-mg tPA IV bolus followed by 7 days of heparin) vs control group and tPA drip (50-mg tPA IV bolus, followed by tPA drip 2 mg/h plus heparin 500 units/h over 24 h, then heparin to maintain aPTT of 60-80 s for 7 days) group vs control group, proved that at 6 through 168 hours after randomization, the tPA bolus group had significantly (P.017) high PaO2/FiO2 ratio than baseline. There was no significant improvement seen in the control group. There was no statistically significant difference in the change of PaO2 to FiO2 ratio at 48 hours (16.9% control vs. 29.8% tPA bolus), VFD (0.0 vs. 12.0), and in-hospital mortality (41.2% vs. 21.1%) between the control group and tPA bolus group. No benefits were observed in the tPA drip group.

Christopher et al.'s [108] multicentre retrospective observational study included 79 COVID-19-confirmed patients with severe respiratory failure who received 50mg of tPA. The primary outcome was an increase in the ratio of PaO2/FiO2 from baseline to 48 hours after receiving tPA. After 48 hours of tPA administration, significant improvement in PaO2/FiO2 was seen which was sustained up to 72 hours. They concluded that in severe COVID-19 patients, fibrinolytic therapy with tPA is associated with significant improvement in oxygenation and respiratory function and was most effective in patients who had declining respiratory function rather than in patients with a plateau or improving phase of respiratory function.

Data from a multicentre cohort study of critically ill COVID-19 patients called STOP-COVID, which included 68 hospitals across the United States, was collected in a study by Douin et al. [109] to evaluate the safety and efficacy of tPA. After exclusion total of 59 patients were selected who had confirmed pulmonary embolism

or suspected pulmonary microthrombi within 14 days of ICU admission. Infusions of 50 milligrams of tPA were given to patients over two hours, and they were followed up until hospital discharge or death. This study found that tPA administration did not alter oxygenation or the parameters of ventilation. PaO2:FIO2 ratio increased by >50% in only 19% of the patients. Major bleeding occurred in 10.2% of patients within 7 days, and 6.8% of patients within 2 days of tPA administration, all of whom died. The in-hospital mortality rate was 79%.

15 patients with confirmed COVID were included in a retrospective study conducted in the United States by Orfanos et al. [110] These patients received tPA at a mean dose of 42 mg over a mean time of 136 minutes, followed by therapeutic heparin infusion. It was found that there was an insignificant increase in PaO2/FiO2 by 68.9%(p=0.14) after 24 hours and by 54.49%(p=0.23) after 48 hours of tPA administration. Only 2 out of 15 patients developed bleeding (intramuscular and intracranial). Therefore, it was determined that even though there was a trend toward improved oxygenation following thrombolytic therapy, there was no significant improvement in the PaO2/FIO2 ratio. Treatment of microthrombi without affecting the alveolar epithelial damage seen in COVID-19 may account for greater improvement in ventilation as opposed to oxygenation.

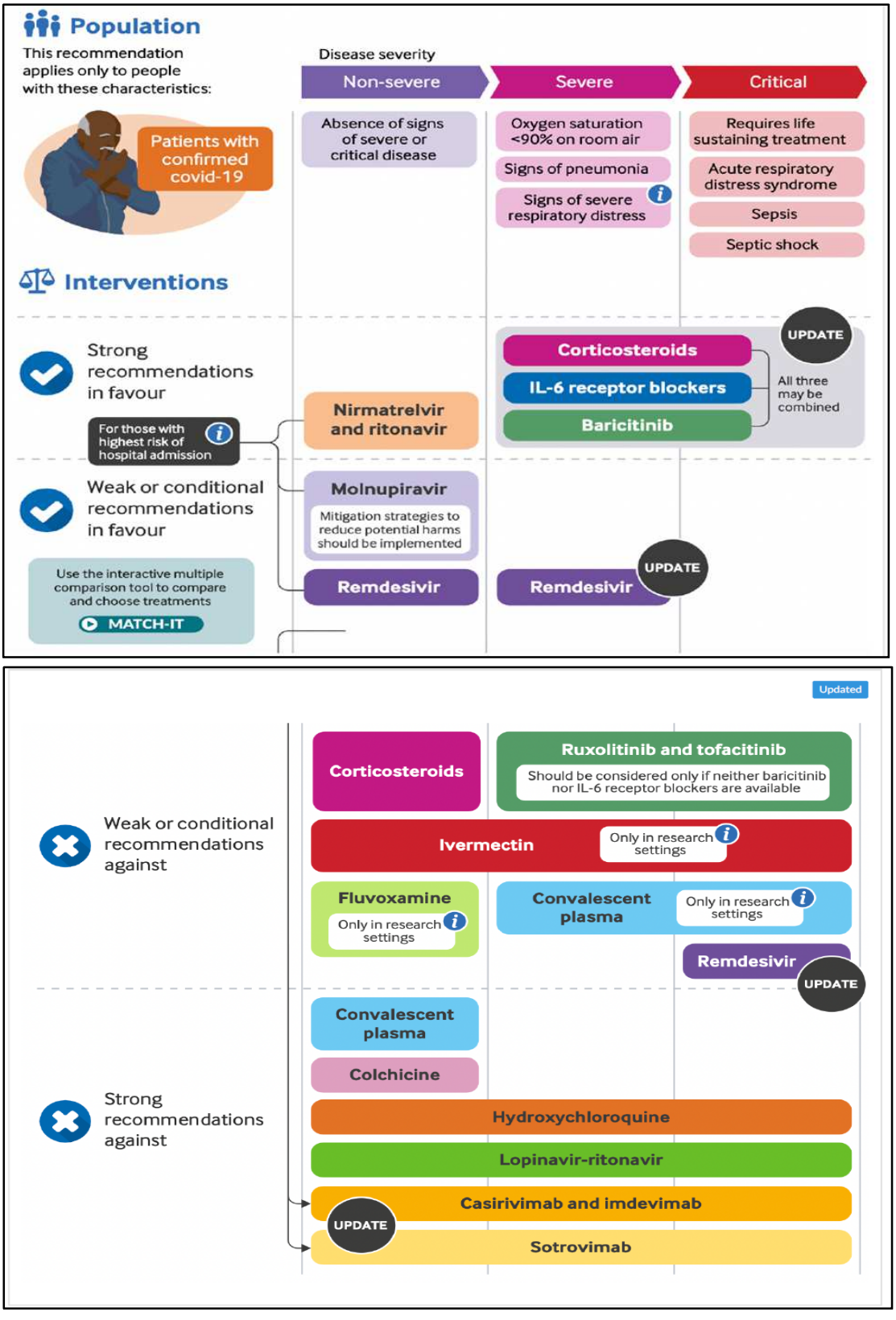


Figure 14: WHO Recommendations for treatment of COVID-19 based on the severity (updated: 2022)[89]

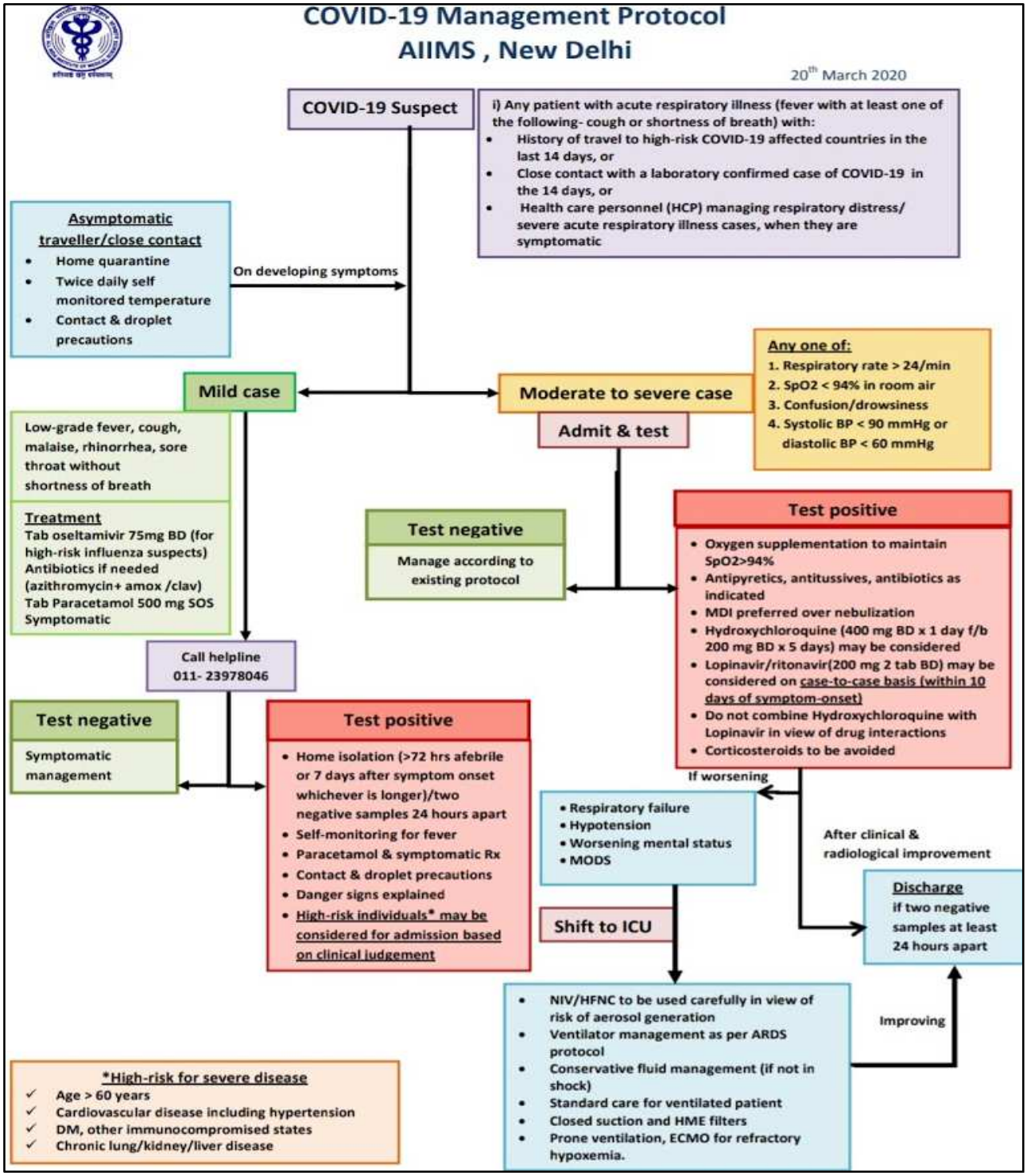


Figure 15: COVID-19 Management, AIIMS Protocol 2020

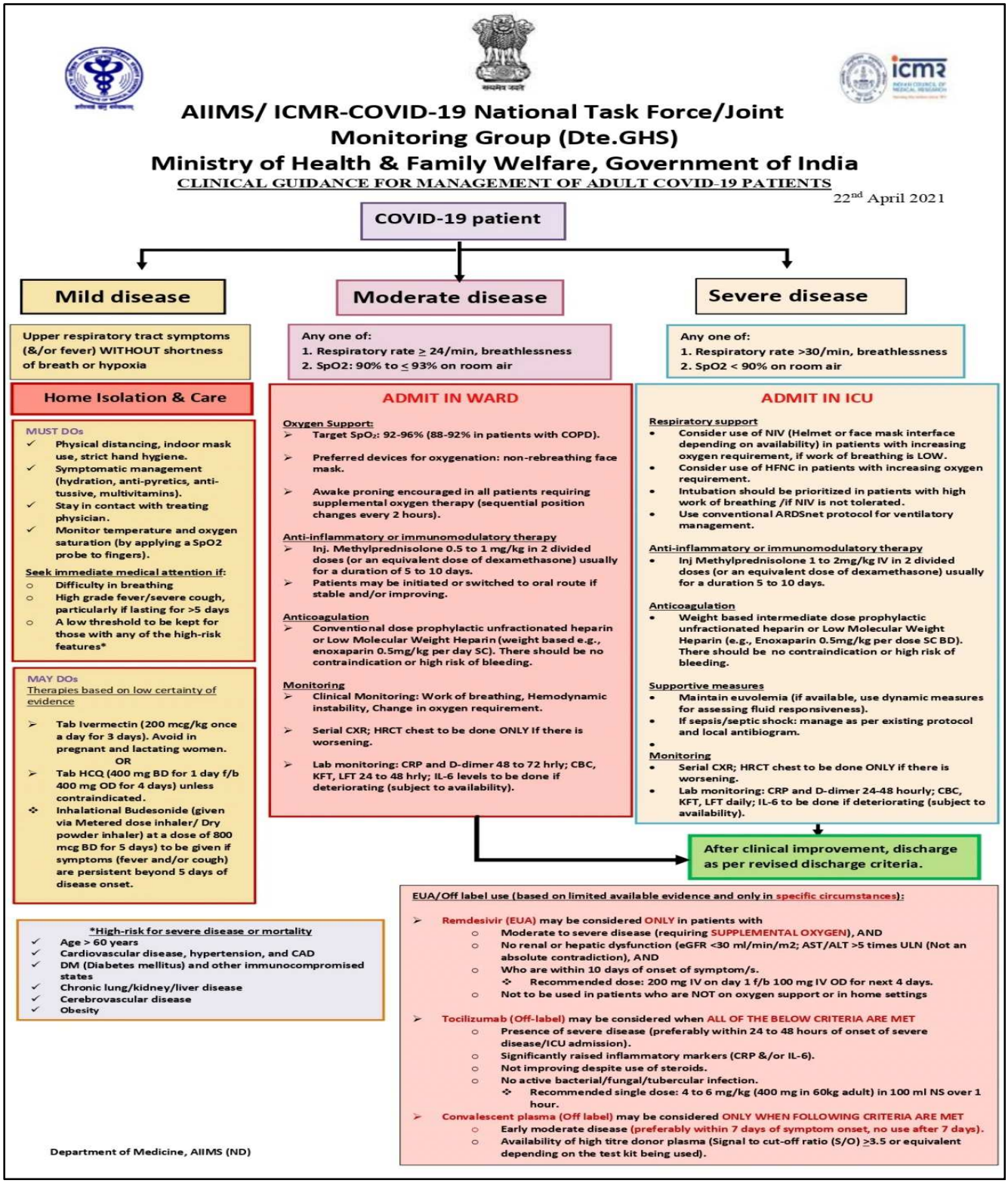


Figure 16: Clinical guidance for management of adult COVID-19 patients - AIIMS/ICMR National task force- 2021

MATERIALS AND METHODS

Source of Data: Patients with confirmed COVID-19 disease with RTPCR were included in the study. Study subjects consisted of patients admitted in Intensive Care Unit (ICU) and who were given rtPA under continuous monitoring.

Study design: RETROSPECTIVE OBSERVATIONAL STUDY

Study period: JANUARY 2021 TO DECEMBER 2021

Sample size: Was estimated based on the outcome of days of oxygen withdrawal (5 ± 2 days) among COVID-19 patients treated with rtPA from the study by Goyal et al. Considering SD of 2, at 1% alpha error and 95% Confidence level sample size of 32 was obtained and will be included in the study.

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2 SD^2}{d^2}$$

$Z_{1-\alpha/2}$ = Is standard normal variate as mentioned in previous section.
SD = Standard deviation of variable. Value of standard deviation can be taken from previously done study or through pilot study.
d = Absolute error or precision as mentioned in previous section

Z = at 1% alpha error = 2.58

SD = 2

d= 15% error (Absolute error)

N = 32 patients with COVID-19 on rtPA can be included in the study

Method of Collection of data

Inclusion Criteria:

1. Patients who were newly admitted, if there was severe hypoxemia despite conventional therapy for more than 72 hours with
   i. PaO2/FiO2 ratio <100
   ii. Patients who required FiO2 of 1.0 for more than 3 days on non-invasive ventilation (NIV).
2. COVID-19 patients who were hospitalized in ICU for at least 7 days,
   i. Patients in whom there was difficulty in reducing FiO2 to less than 0. 70 from NIV or High Flow Nasal Cannula (HFNC)
   ii. D-Dimer more than 1000 ng/ml

Exclusion Criteria:

1. Patients with recent myocardial infarction who were thrombolysed.
2. Bleeding and coagulation disorders
3. Platelet count less than 50,000/cubic ml
4. Focal neurological deficits
5. Hemodynamic instability (Hypotension / persistent uncontrolled HTN)

METHODOLOGY

Patients meeting the above inclusion and exclusion criteria were given recombinant tissue plasminogen activator (rtPA) at a dose of 40-50 mg (40mg for patients less than 70 kgs and 50 mg for patients weighing more than 70 kg) as an intravenous infusion over 4 hours followed by low molecular weight heparin twice daily in therapeutic dose in addition to the standard line of treatment.

All the COVID-19-infected patients received the standard line of treatment which included

1. Broad spectrum IV Antibiotic
2. Inj Remdesivir 200mg in 100ml NS IV stat followed by 100mg in 100ml NS from day 2 to day 7
3. Inj Methylprednisolone 40mg or 60mg bd
4. Inj Tocilizumab 400mg in 100ml NS IV over 4 hrs stat, if indicated
5. Inj Enoxaparin 40 or 60mg S/C od /bd, depending on the severity of the infection
6. Tab Favipiravir 3600mg/day in divided doses on day 1 followed by 1600mg /day in divided doses from day 2 to day 7
7. supportive treatment

Patients were monitored with serial ABG 24 to 48 hours post-rtPA administration to assess the need for oxygen reduction. Inflammatory biomarkers were repeated after 72 hours post-rtPA administration to look for improvement. Patients were followed up until hospital discharge or death for any drug-related adverse events.

The records of these patients were searched and data were collected from the medical records section after obtaining consent to access.

OUTCOME VARIABLES

Primary outcome variables:

I. Number of days required for reduction of oxygen at FiO2 <0.40

Secondary outcome variables:

i. Mortality due to COVID-19
ii. Length of ICU stay
iii. Number of days free of ICU stay post rtPA administration

The data was collected from the medical records after obtaining permission from the medical records department.

The following data were collected

1. Patients' demography
2. Date of COVID-19 testing
3. Symptoms and duration of symptoms
4. Co-morbidities
5. CXR and HRCT thorax findings
6. Treatment modalities before rtPA (mode of oxygen delivery, drugs, and dosages)
7. O2 requirement before rtPA administration.
8. Platelets

9. Date and dose of rtPA administration
10. Inflammatory biomarkers (hs-CRP, D-dimer, Ferritin, IL-6, LDH) pre and post-rtPA administration
11. Arterial blood gas analysis pre and post (24-48hrs) rtPA administration
12. Oxygen requirement after rtPA administration
13. Number of days in ICU
14. Number of days free of ICU after rtPA administration
15. Number of days on NIV and HFNC
16. Outcome – oxygen reduced to 40% /recovered/ /expired.

STATISTICAL ANALYSIS: [111–113]

Data were entered into a Microsoft Excel data sheet and were analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. The **chi-square test** was used as a test of significance for qualitative data.

The normality of the continuous data was tested by Kolmogorov–Smirnov test and the Shapiro–Wilk test.

Continuous data were represented as mean and standard deviation.

Paired t-test was the test of significance for paired data such as before and after TPA for quantitative data.

Wilcoxon Signed rank test is the test of significance for paired data such as before and after tPA for quantitative data with skewed distribution.

Graphical representation of data: MS Excel and MS word were used to obtain various types of graphs such as bar diagrams, Pie diagrams.

p-value (Probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests.

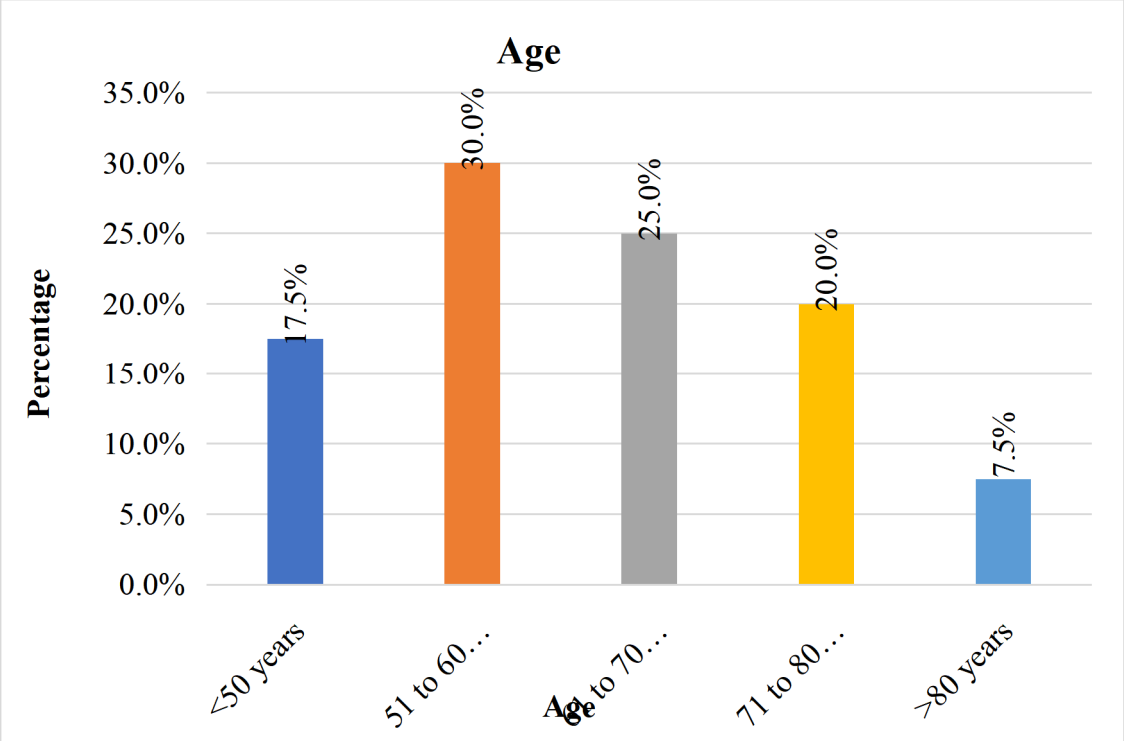
Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS:

Table 6: Age distribution of patients

		NO.	%
Age	<50 years	7	17.5%
	51 to 60 years	12	30.0%
	61 to 70 years	10	25.0%
	71 to 80 years	8	20.0%
	>80 years	3	7.5%
	Total	40	100.0%

The mean age of patients was 61.30 ± 11.726 years. The majority of patients were in the age group 51 to 60 years (30%).

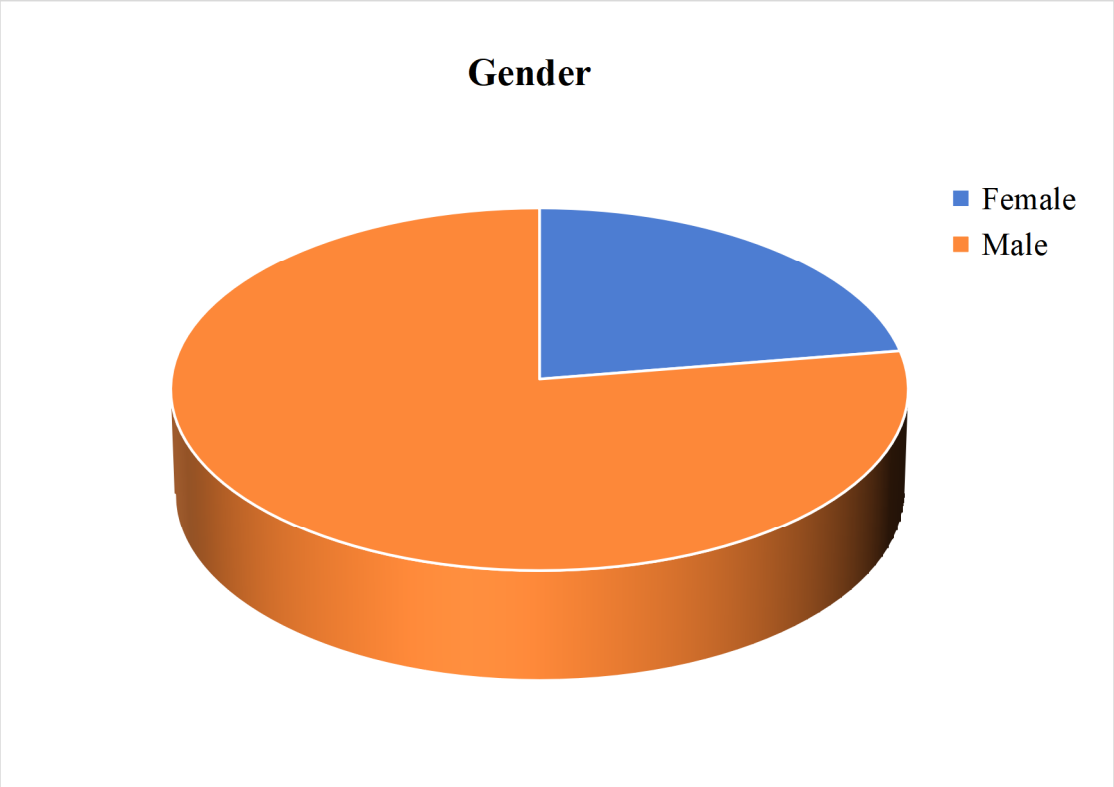


Graph 1: Bar diagram showing the age distribution of patients

Table 7: Gender distribution of patients

		NO.	%
Gender	Female	9	22.5%
	Male	31	77.5%
	Total	40	100.0%

In the study 77.5% were males and 22.5% were females.

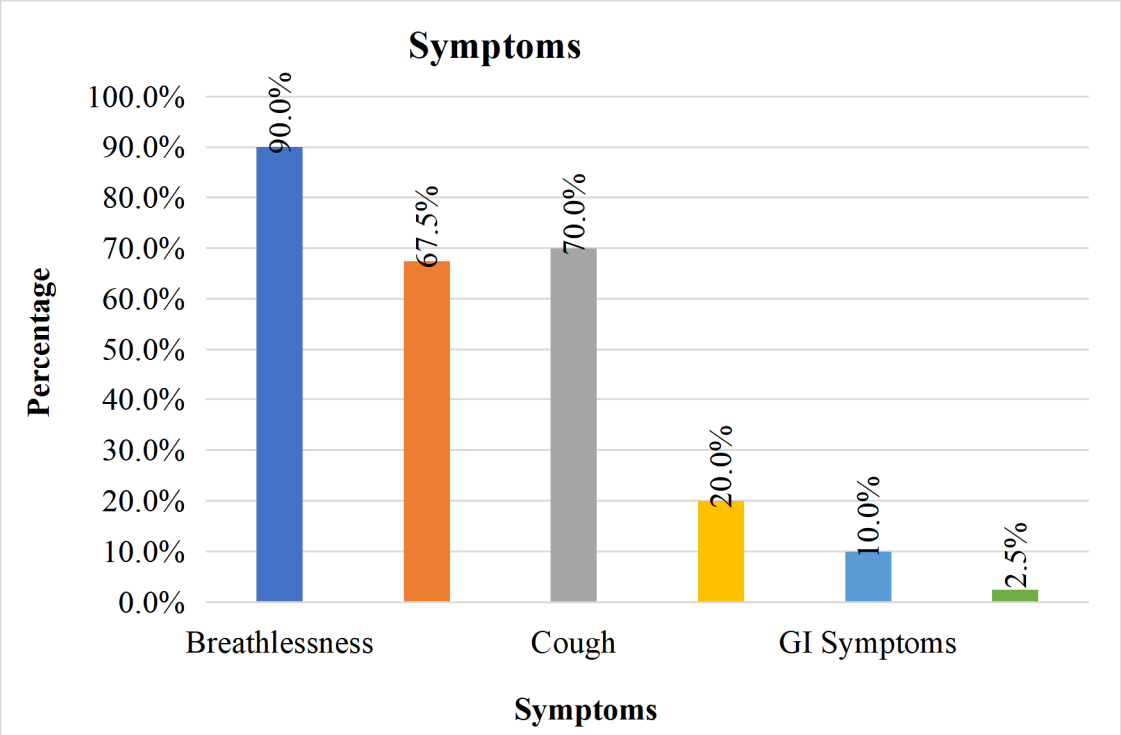


Graph 2: Pie diagram showing Gender distribution of the patients

Table 8: Symptoms distribution of the patients

	NO.	%
Breathlessness	36	90.0%
Fever	27	67.5%
Cough	28	70.0%
Weakness	8	20.0%
GI Symptoms	4	10.0%
Anuria	1	2.5%

In the study 90% of patients had breathlessness, 67.5% had a fever, 70% had a cough, 20% had weakness, 10% had GI symptoms and 2.5% had anuria.

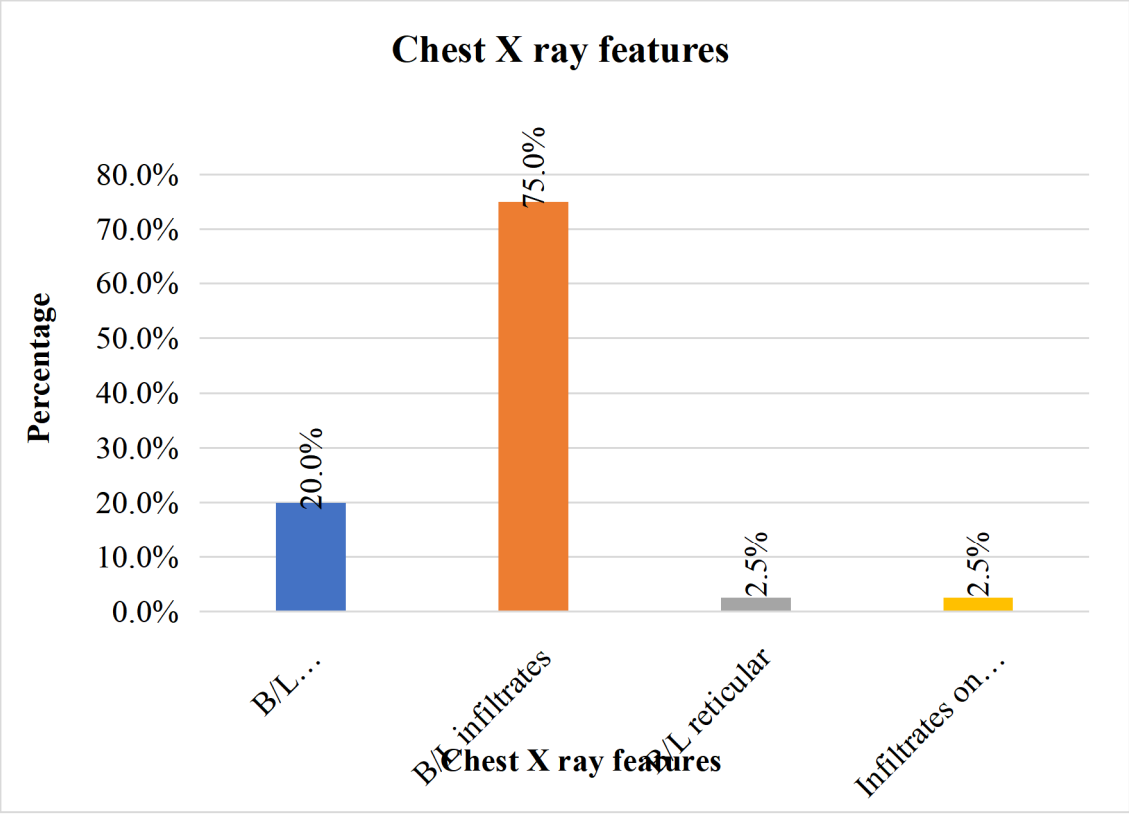


Graph 3: Bar diagram showing Symptoms distribution of the patients

Table 9: Chest X-ray features

		NO.	%
Chest X-ray features	B/L consolidation	8	20.0%
	B/L infiltrates	30	75.0%
	B/L reticular pattern	1	2.5%
	Infiltrates on the right side	1	2.5%
	Total	40	100.0%

In the study, on chest X-rays, 75% had B/L infiltrates, 20% had B/L consolidation, and 2.5% had B/L reticular pattern and 2.5% had infiltrates on the right side.

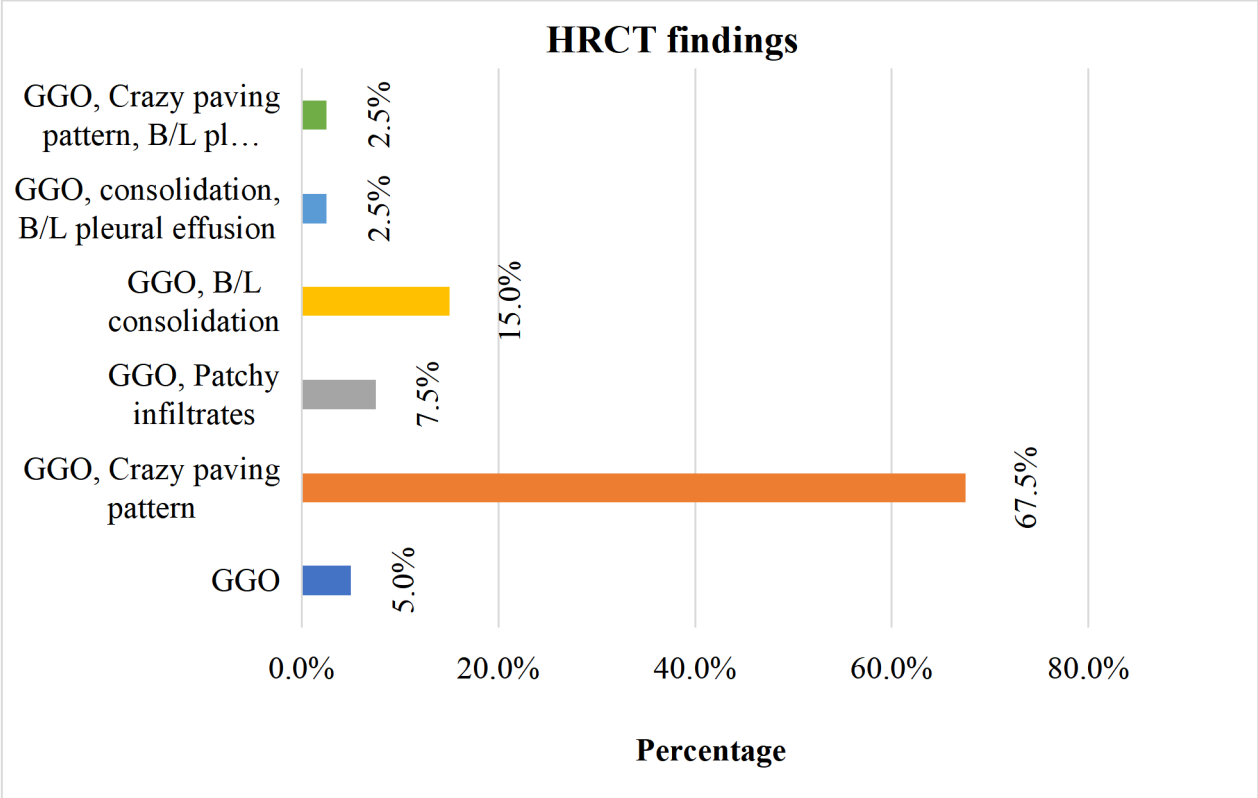


Graph 4: Bar diagram showing Chest X-ray features

Table 10: HRCT findings

		NO.	%
HRCT features	GGO	2	5.0%
	GGO, Crazy paving pattern	27	67.5%
	GGO, Patchy infiltrates	3	7.5%
	GGO, B/L consolidation	6	15%
	GGO, consolidation, B/L pleural effusion	1	2.5%
	GGO, Crazy paving pattern, B/L pleural effusion	1	2.5%
	Total	40	100.0%

In the study, the most common findings observed were GGOs and crazy paving pattern (67.5%). (Table 10)



Graph 5: Bar diagram showing HRCT findings

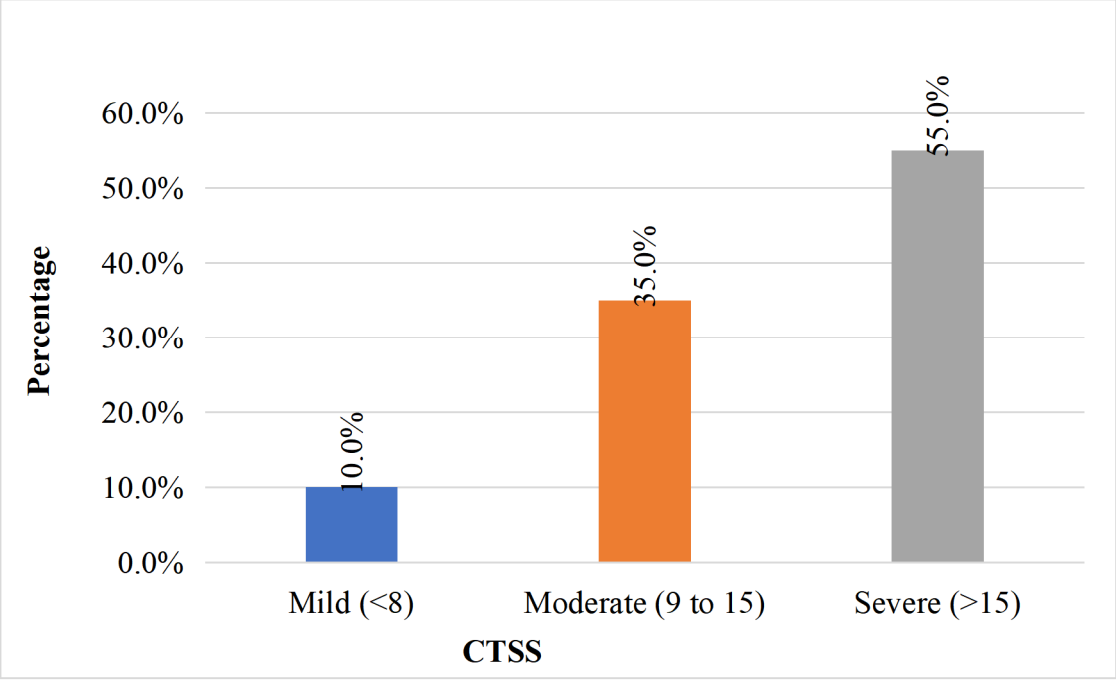
Table 11: CORADS SCORE distribution

		NO.	%
CORADS Score	5	40	100.0%

Table 12: CTSS distribution

		NO.	%
CTSS Grade	Mild (<8)	4	10.0%
	Moderate (9 to 15)	14	35.0%
	Severe (>15)	22	55.0%
	Total	40	100.0%

In the study 10% of them had a mild grade, 35% had a moderate grade and 55% had a severe grade depending upon the CT Severity Index (table 12)

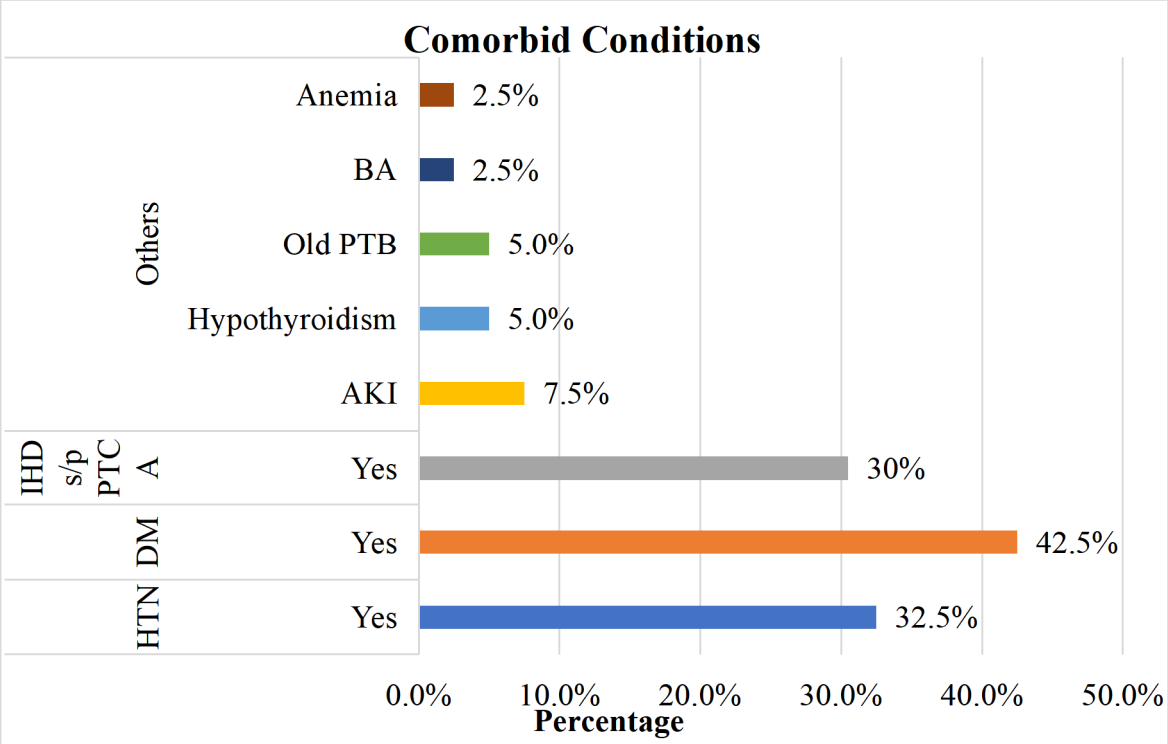


Graph 6: Bar diagram showing CTSS distribution

Table 13: Comorbid Conditions

		Count	%
HTN	Yes	13	32.5%
DM	Yes	17	42.5%
IHD, S/P PTCA	Yes	7	30%
Others	AKI	3	7.5%
	Hypothyroidism	2	5.0%
	Old PTB	2	5%
	BA	1	2.5%
	Anemia	1	2.5%

In the study 32.5% had HTN, 42.5% had DM, 30% had IHD s/p PTCA, and others as shown in the above table.



Graph 7: Bar diagram showing Comorbid Conditions

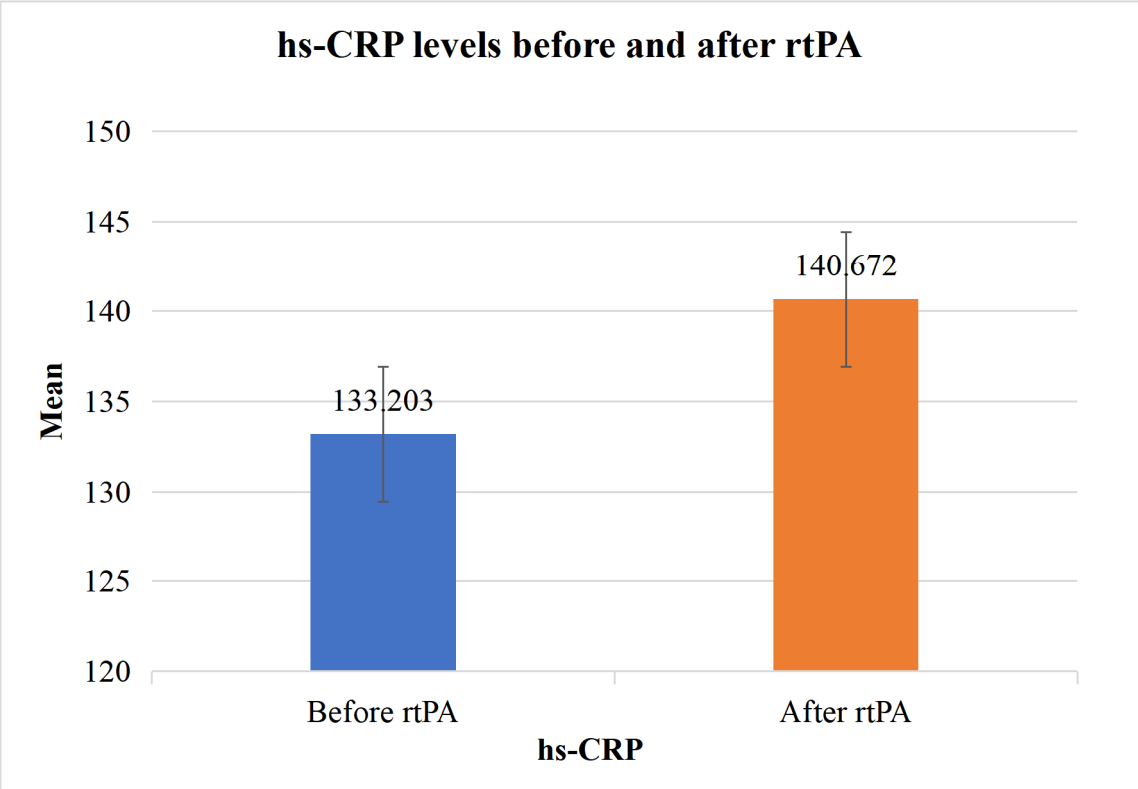
Table 14: hs-CRP levels before and after rtPA

hs-CRP	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	133.203	104.3831	10.5	526.0	55.975	109.700	176.500	0.097
After rtPA	40	140.672	204.5749	6.8	1206.0	51.200	99.900	130.000	

Wilcoxon Signed Ranks Test

Mean hs-CRP before rtPA was 133.203 ± 104.38 and after rtPA was 140.67 ± 204.57.

There was no significant difference in mean hs-CRP after the rtPA administration.



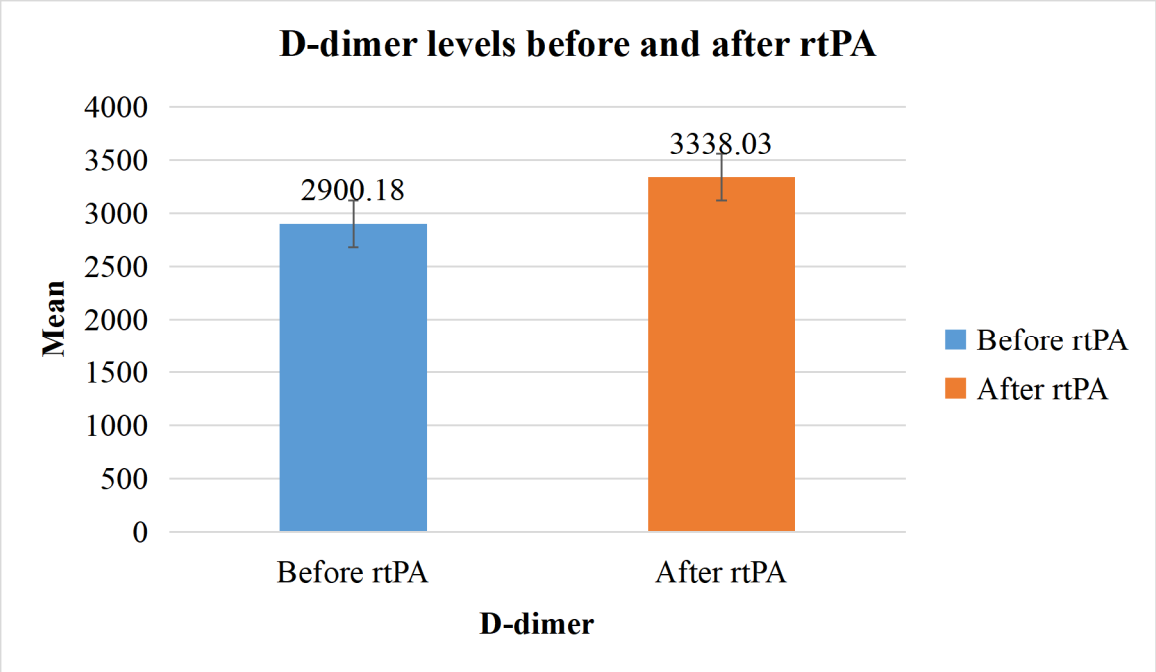
Graph 8: Bar diagram showing hs-CRP levels before and after rtPA

Table 15: D-dimer levels before and after rtPA

D-Dimer	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	2900.18	2006.423	481	6911	1086.00	2000.00	5000.00	**0.041***
After rtPA	40	3338.03	1980.113	1050	7122	1372.50	3469.50	5000.00	

Wilcoxon Signed Ranks Test

Mean D-dimer before rtPA was 2900.18 ± 2006.423 and after rtPA was 3338.03 ± 1980.113. There was a significant increase in mean D-dimer after rtPA administration.



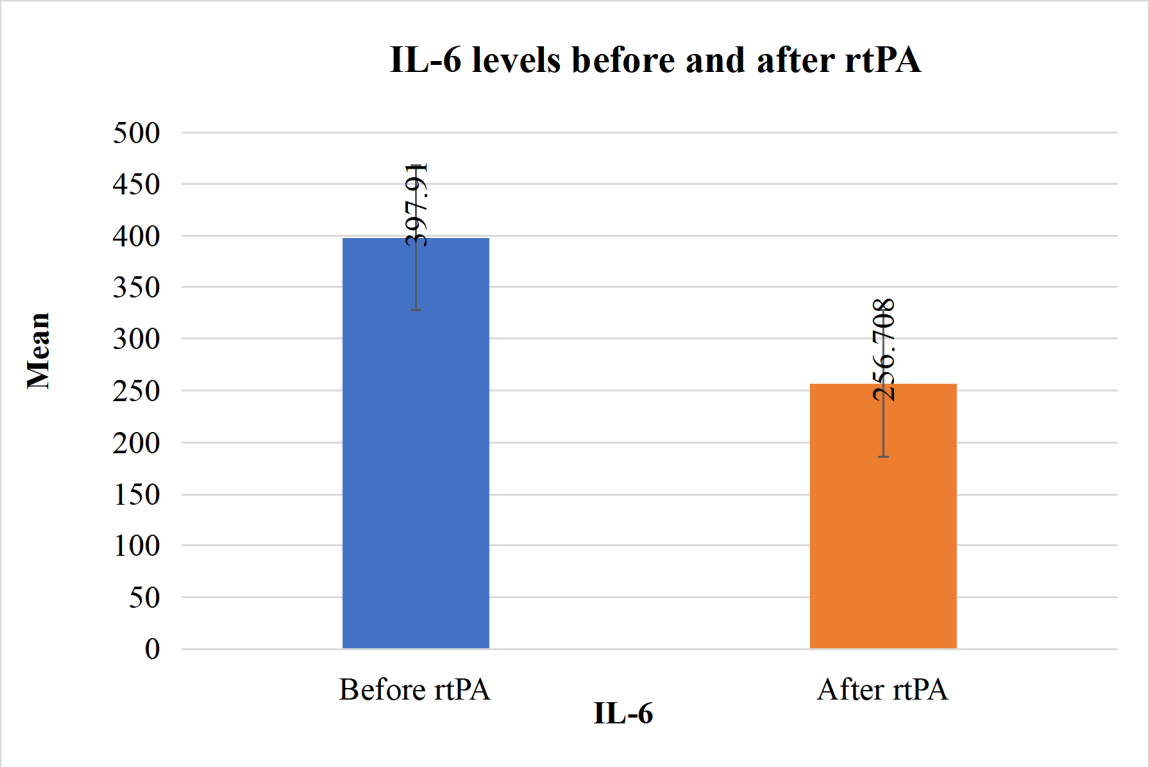
Graph 9: Bar diagram showing D-dimer before and after rtPA

Table 16: IL-6 levels before and after rtPA

IL-6	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	397.910	997.2789	1.5	4616.0	45.825	100.900	352.250	0.775
After rtPA	40	256.708	419.6120	1.5	2452.0	34.000	107.000	308.500	

Wilcoxon Signed Ranks Test

Mean IL-6 before rtPA was 397.910 ± 997.2789 and after rtPA was 256.708 ± 419.6120. There was no significant difference in mean IL-6 after rtPA administration.



Graph 10: Bar diagram showing IL-6 levels before and after rtPA

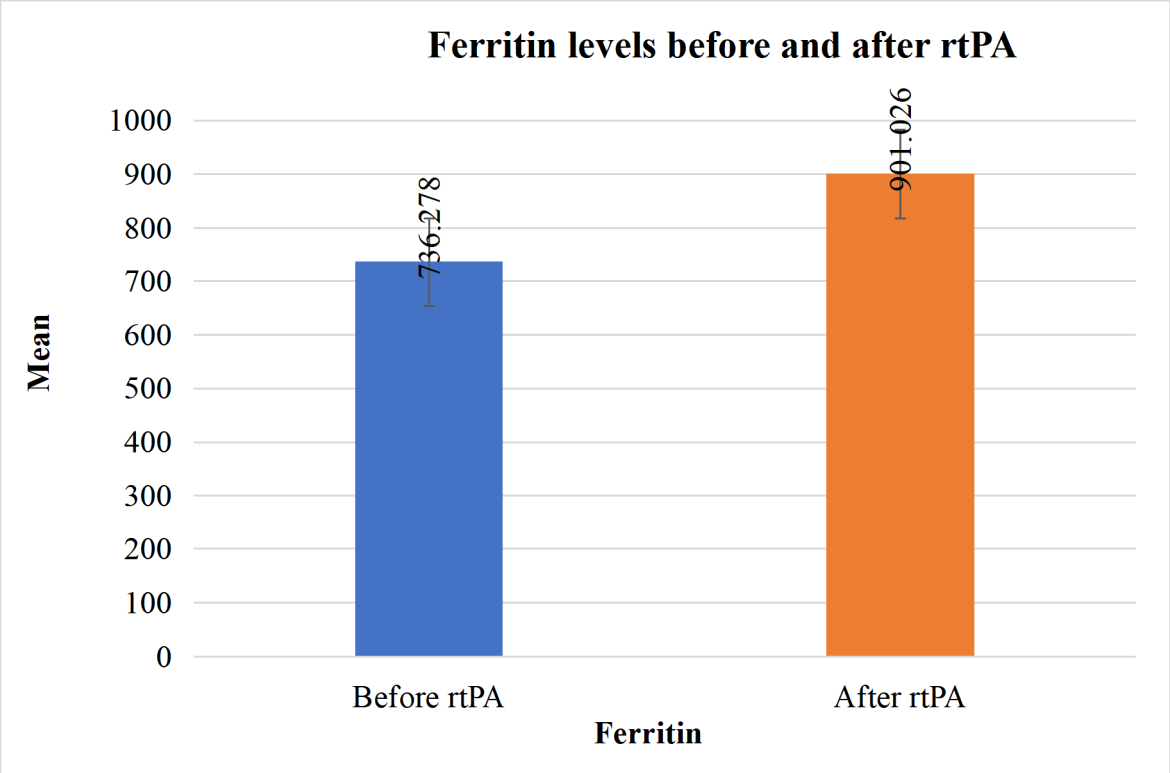
Table 17: Ferritin levels before and after rtPA

Ferritin	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	736.278	612.4663	39.0	2763.0	274.925	530.500	1090.000	0.075
After rtPA	40	901.026	633.1162	121.0	3036.0	407.000	764.000	1295.000	

Wilcoxon Signed Ranks Test

Mean ferritin before rtPA was 736.27 ± 612.46 and after rtPA was 901.026 ± 633.11.

There was no significant difference in mean ferritin after rtPA administration.



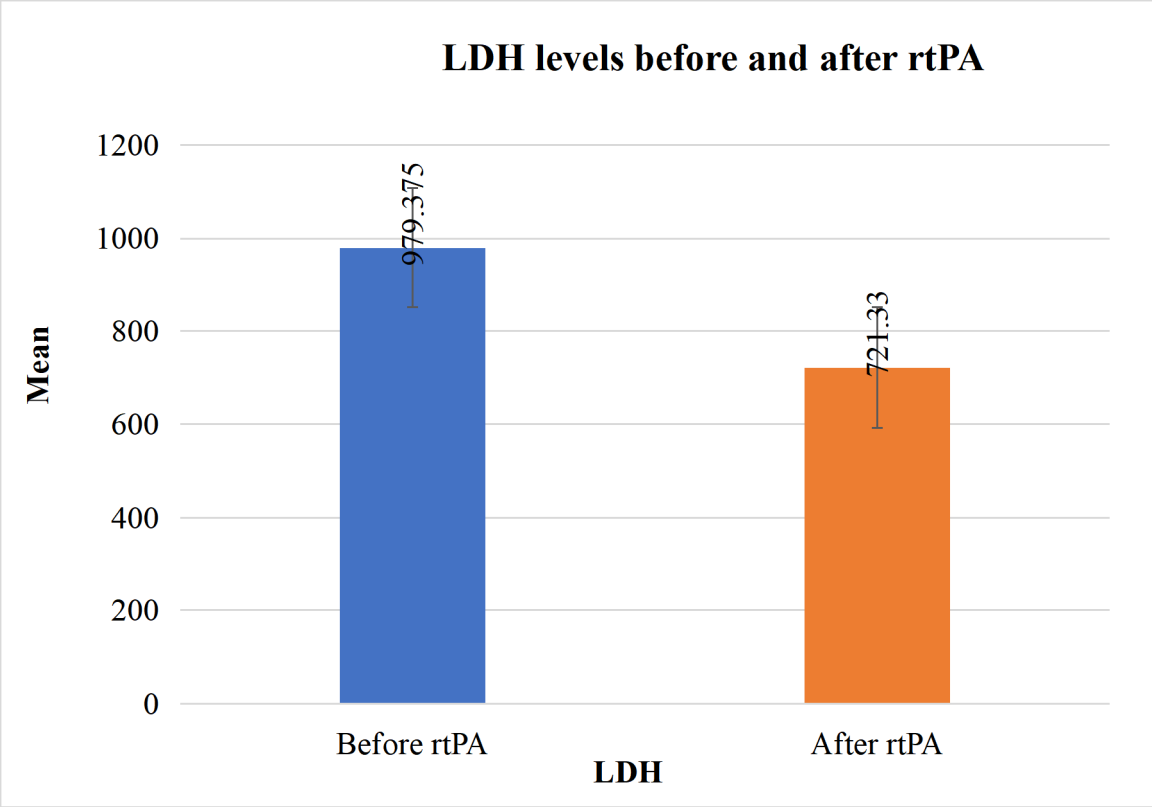
Graph 11: Bar diagram showing Ferritin levels before and after rtPA

Table 18: LDH levels before and after rtPA

LDH	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	979.375	1377.9918	333.0	9245.0	558.000	709.500	886.500	0.429
After rtPA	40	721.33	401.443	66	1821	500.00	678.00	876.00	

Wilcoxon Signed Ranks Test

Mean LDH before rtPA was 979.375 ± 1377.99 and after rtPA was 721.3 ± 401.44. There was no significant difference in mean LDH after rtPA administration.



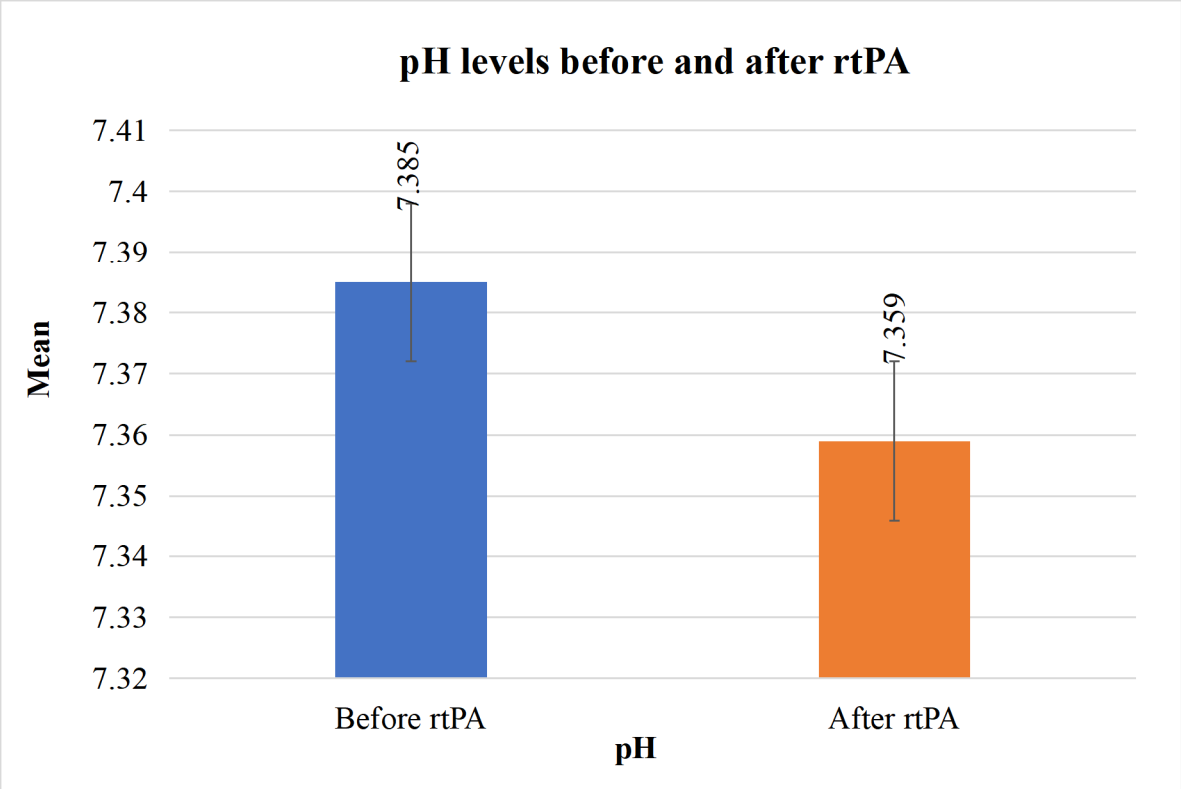
Graph 12: Bar diagram showing LDH levels before and after rtPA

Table 19: pH levels before and after rtPA

pH	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	7.385	.0630	7.3	7.5	7.300	7.400	7.400	0.048*
After rtPA	40	7.359	.0686	7.2	7.5	7.300	7.400	7.400	

Paired t-test

The mean pH before rtPA was 7.385 ± 0.063 and after rtPA was 7.359 ± 0.068. There was a significant decrease in mean pH after rtPA administration.



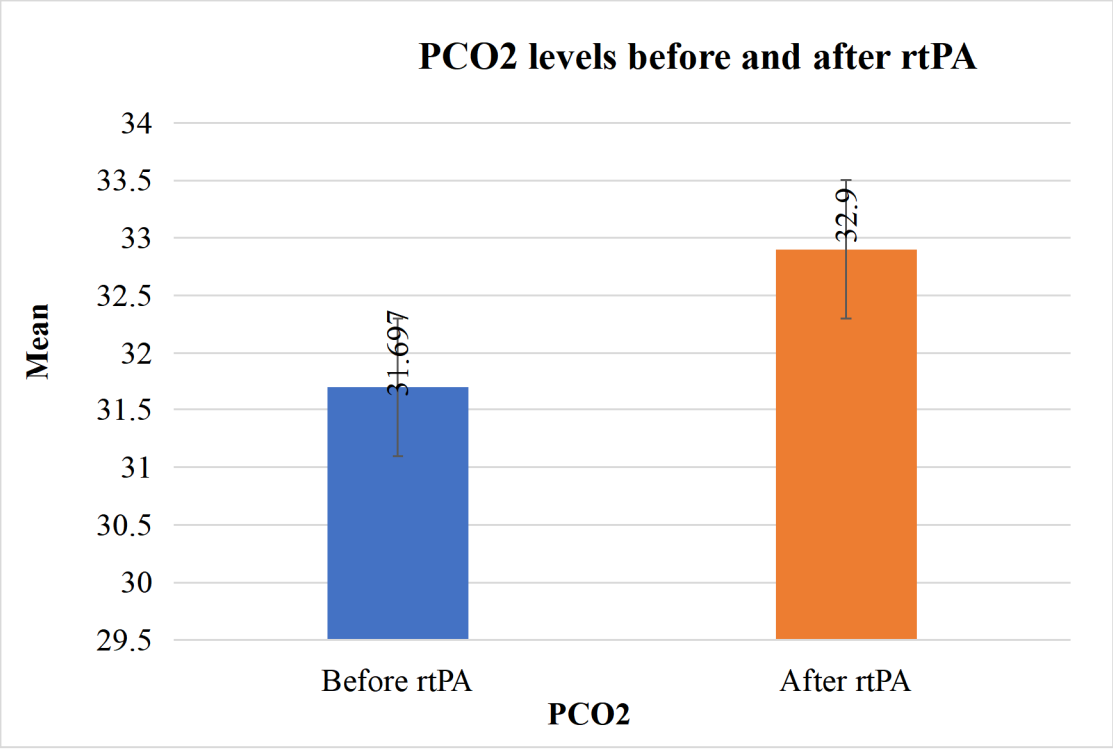
Graph 13: Bar diagram showing pH levels before and after rtPA

Table 20: PCO2 levels before and after rtPA

PCO2	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	31.69	6.327	12.3	45.5	29.000	32.000	35.500	0.330
After rtPA	40	32.90	5.714	25.0	50.5	29.000	32.900	35.000	

Paired t-test

Mean PCO2 before rtPA was 31.697 ± 6.32 and after rtPA was 32.90 ± 5.714. There was no significant change in mean PCO2 after rtPA administration.



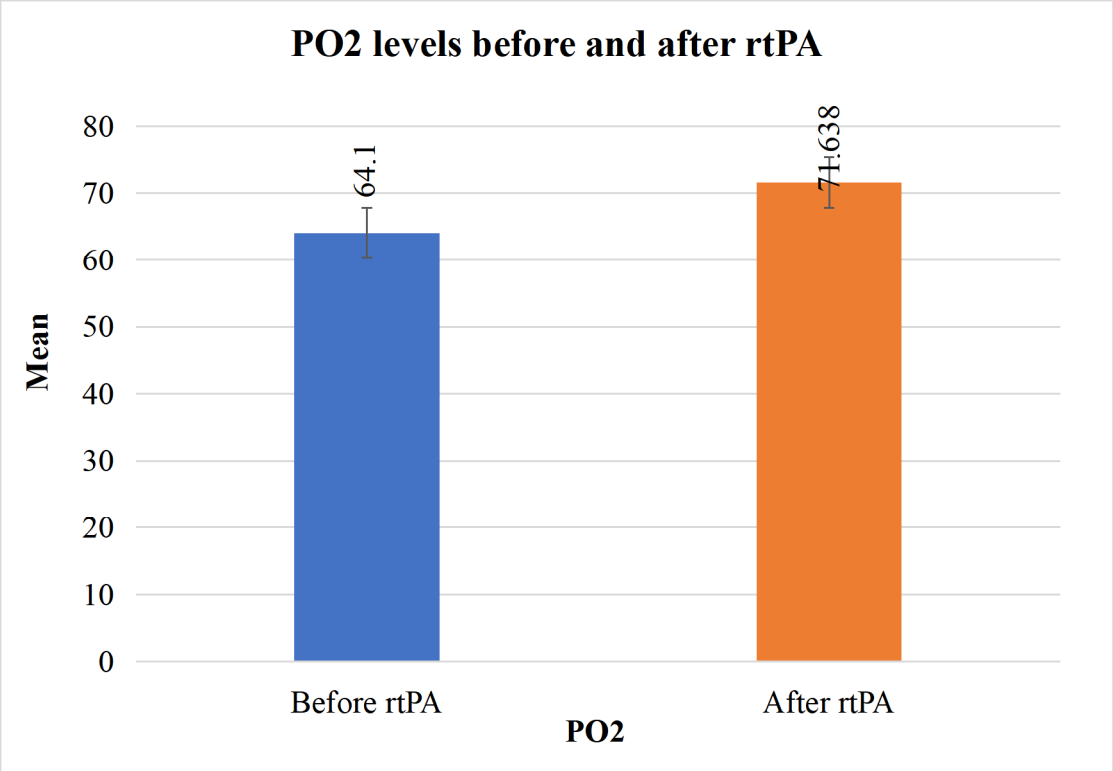
Graph 14: Bar diagram showing PCO2 levels before and after rtPA

Table 21: PO2 levels before and after rtPA

PO2	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	64.100	12.4330	37.0	93.5	57.000	61.600	76.000	**0.03***
After rtPA	40	71.638	19.4521	34.9	125.0	60.000	70.400	84.500	

Paired t test

Mean PO2 before rtPA was 64.1 ± 12.43 and after rtPA was 71.63 ± 19.45. There was a significant increase in mean PO2 after the rtPA administration.



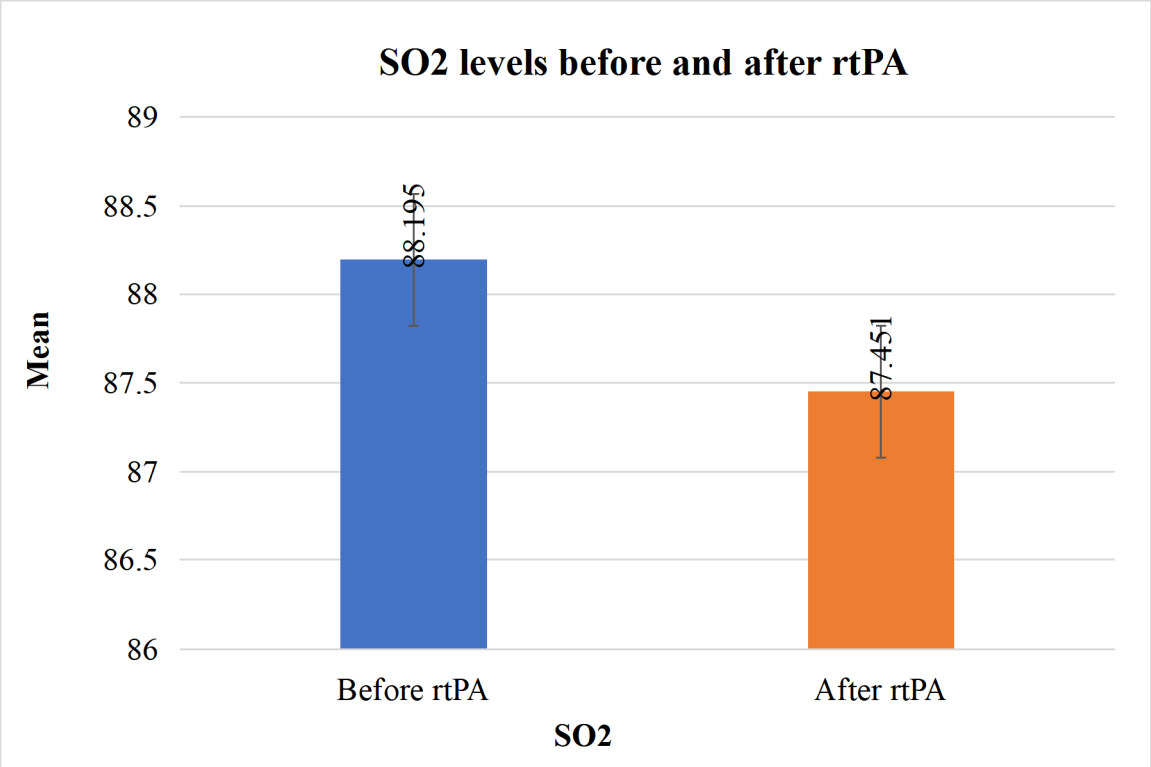
Graph 15: Bar diagram showing PO2 levels before and after rtPA

Table 22: SO2 levels before and after rtPA

SO2	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	88.195	13.4943	16.2	99.4	87.000	91.000	95.000	0.580
After rtPA	40	88.195	14.4736	20.0	98.0	85.300	90.000	95.900	

Paired t-test

Mean SO2 before rtPA was 88.195 ± 13.49 and after rtPA was 87.45 ± 14.47. There was no significant improvement in mean SO2 after rtPA administration.



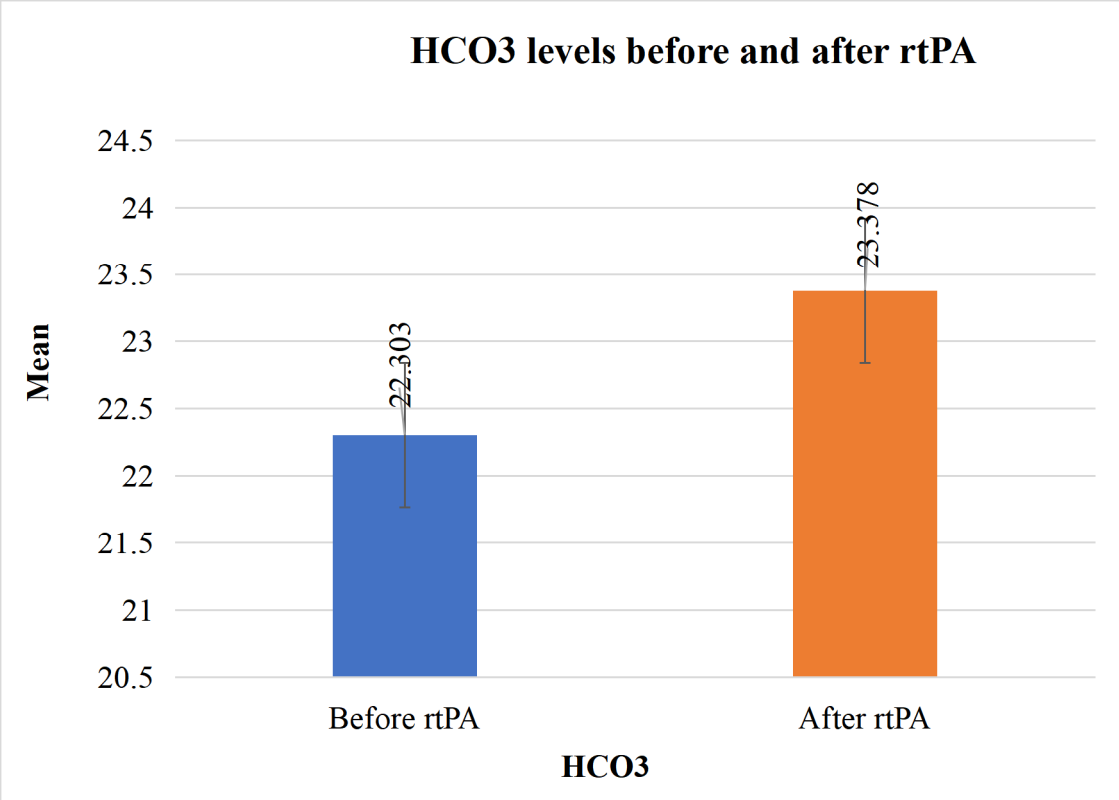
Graph 16: Bar diagram showing SO2 levels before and after rtPA

Table 23: HCO3 levels before and after rtPA

HCO3	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	22.303	11.8845	8.2	90.0	18.300	21.000	22.500	0.286
After rtPA	40	23.378	11.4349	14.0	88.0	20.000	21.200	25.000	

Paired t-test

Mean HCO3 before rtPA was 22.303 ± 11.88 and after rtPA was 23.37 ± 11.43. There was no significant change in mean HCO3 after the rtPA administration.



Graph 17: Bar diagram showing HCO3 levels before and after rtPA

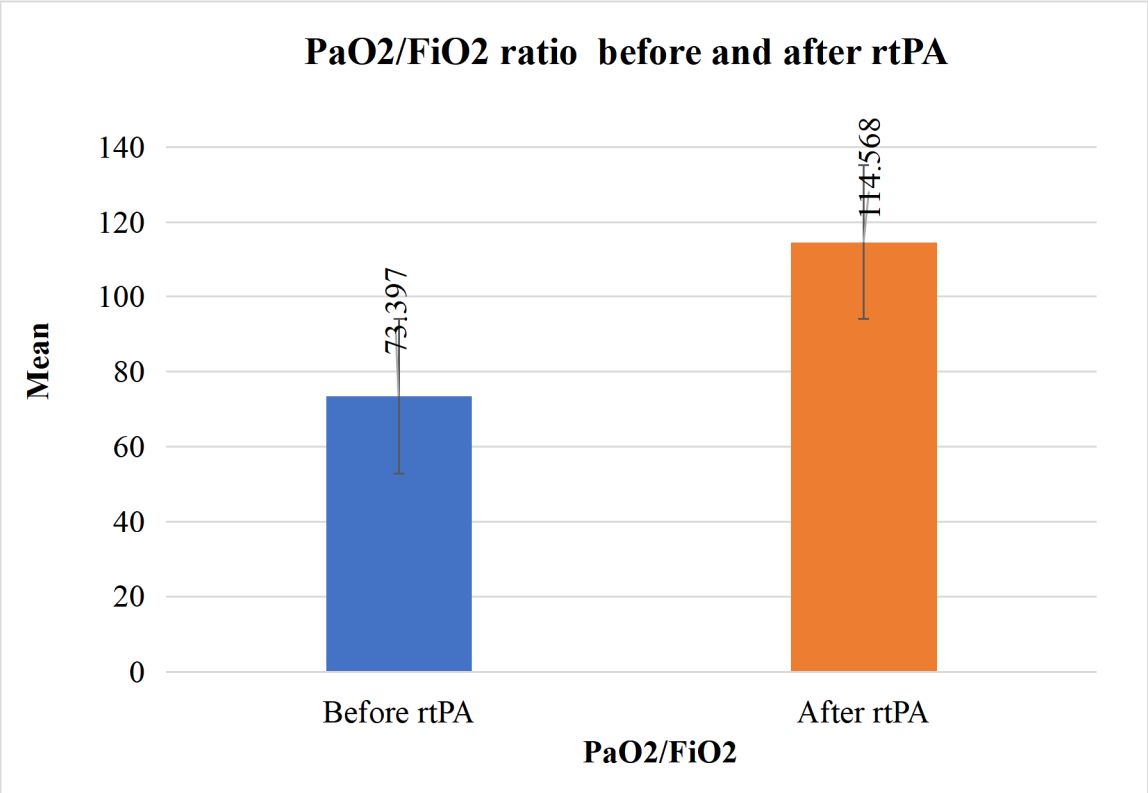
Table 24: PaO2/FiO2 ratio before and after rtPA

PaO2/FiO2	N	Mean	SD	Minimum	Maximum	Percentiles			P value
						25th	50th (Median)	75th	
Before rtPA	40	73.397	15.9996	46.0	100.0	61.400	73.300	88.000	**0.001***
After rtPA	40	114.568	72.4768	40.0	314.0	61.100	81.000	167.500	

Paired t-test

Mean PaO2/FiO2 before rtPA was 73.39 ± 15.99 and after rtPA was 114.56 ± 72.47.

There was a significant increase in mean PaO2/FiO2 after rtPA administration.

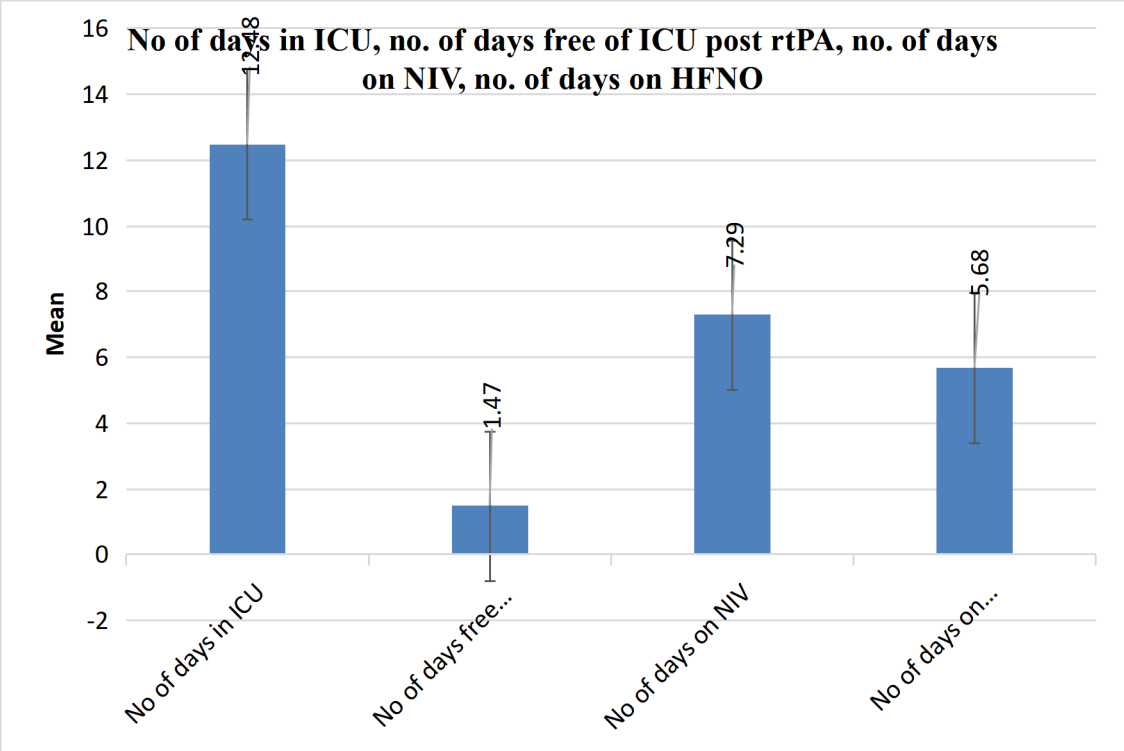


Graph 18: Bar diagram showing PaO2/FiO2 ratio before and after rtPA

Table 25: No of days in ICU, no. of days free of ICU post-rtPA, no. of days on NIV and HFNO

	No days in ICU	No days free of ICU post-rtPA	No of days on NIV	No of days on HFNO
N	40	40	39	19
Mean	12.48	1.47	7.92	5.68
SD	7.404	2.563	5.503	2.162
Minimum	1	0	1	2
Median	11.00	0	7.00	6.00
Maximum	32	10	22	9

In the study mean no. of days in ICU was 12.48 ± 7.404 days. The mean no of days free of ICU post-rtPA was 1.47± 2.563 days, the mean no. of days on NIV was 7.92 ± 5.503 days, and the mean no. of days on HFNO was 5.68 ± 2.162 days.

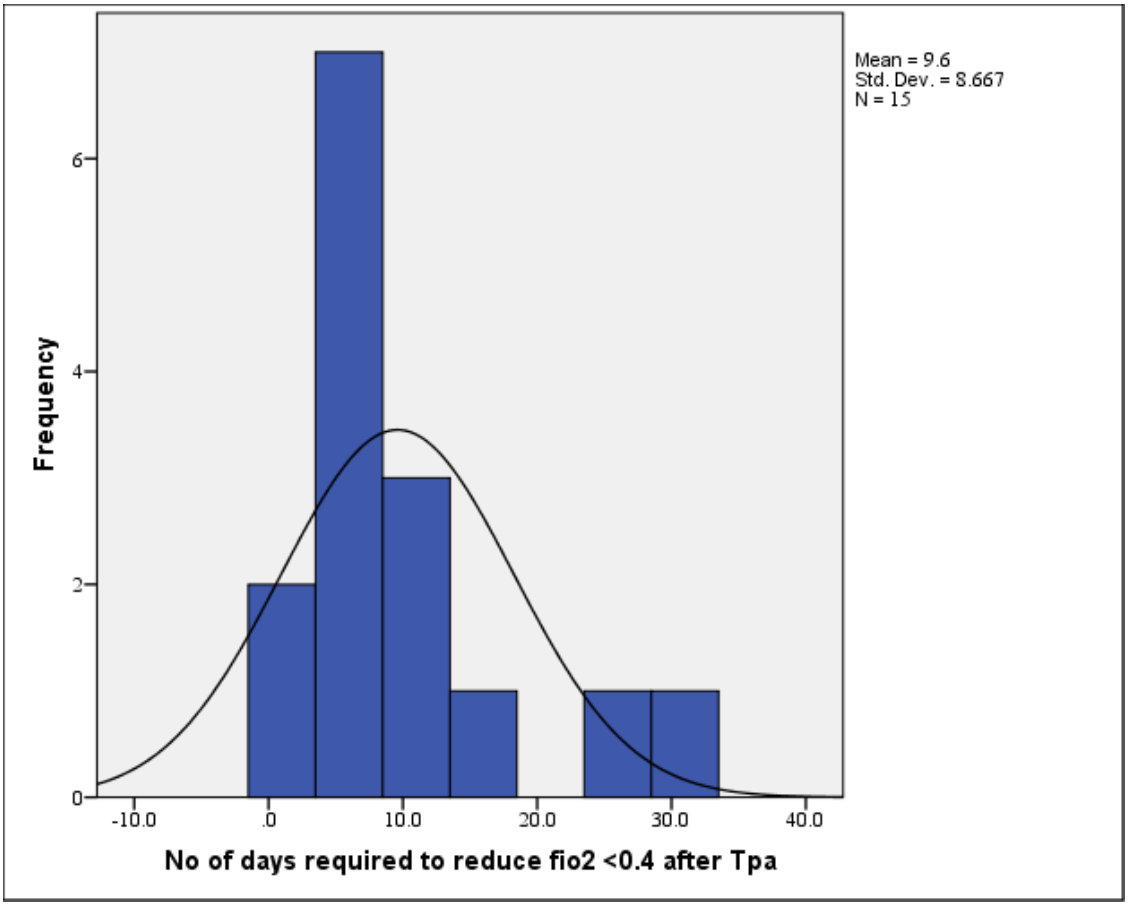


Graph 19: Bar diagram showing No of days in ICU, no. of days free of ICU post-rtPA, no. of days on NIV and HFNO

Table 26: Mean No of days required to reduce FiO2 <0.4 after rtPA infusion

	No of days required to reduce FiO2 <0.4 after rtPA
N	15
Mean	9.600
SD	8.6668
Minimum	1.0
Median	5.000
Maximum	30.0

In the study mean days required to reduce FiO2 <0.4 after rtPA was 9.60 ± 8.66 days.

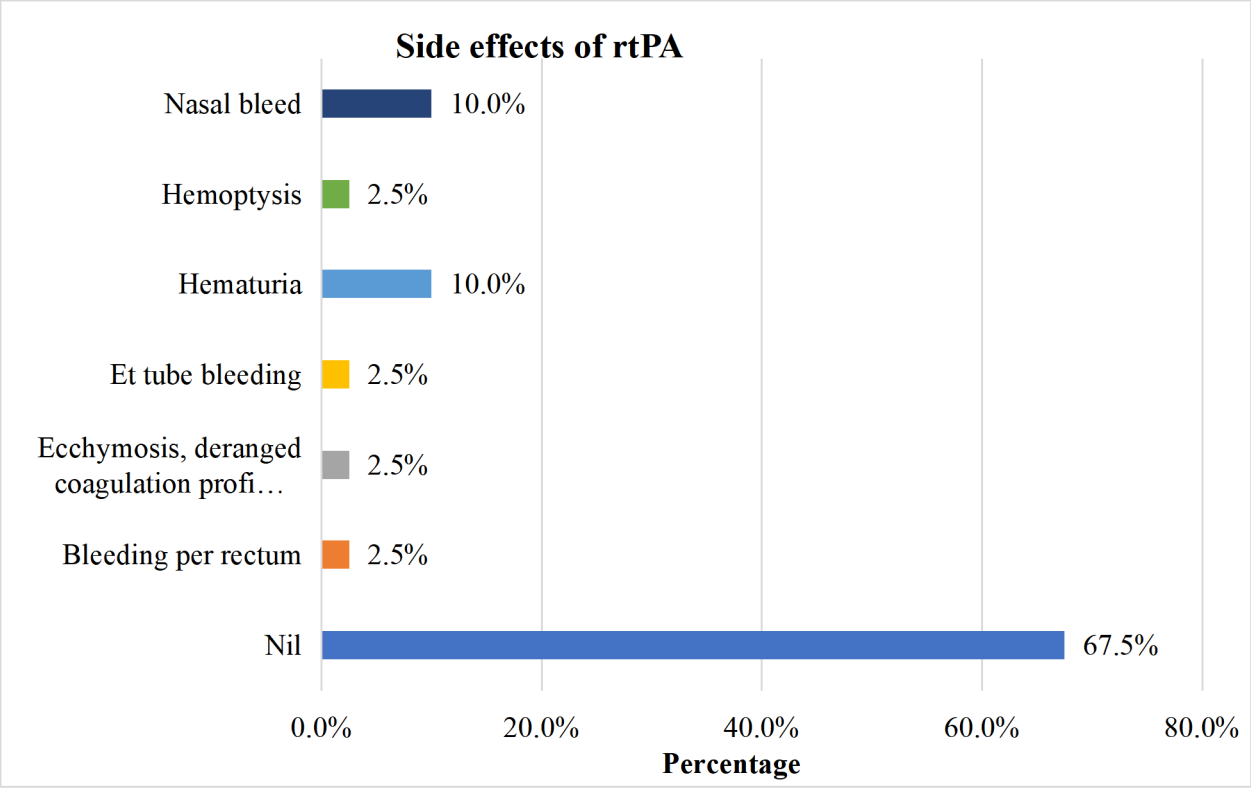


Graph 20: Histogram showing the mean no. of days required to reduce FiO2 <0.4 after rtPA infusion

Table 27: Side effects of rtPA

		Count	%
Side effects of rtPA	Nil	27	67.5%
	Bleeding per rectum	1	2.5%
	Ecchymosis, deranged coagulation profile, thrombocytopenia	1	2.5%
	ET tube bleeding	1	2.5%
	Haematuria	4	10.0%
	Haemoptysis	1	2.5%
	Nasal bleed	4	10.0%
	Purpura in the right upper limb	1	2.5%
	Total	40	100.0%

In the study, 67.5% had no side effects. However 32.5% of patients had minor side effects of which haematuria and nasal bleeding were most common.

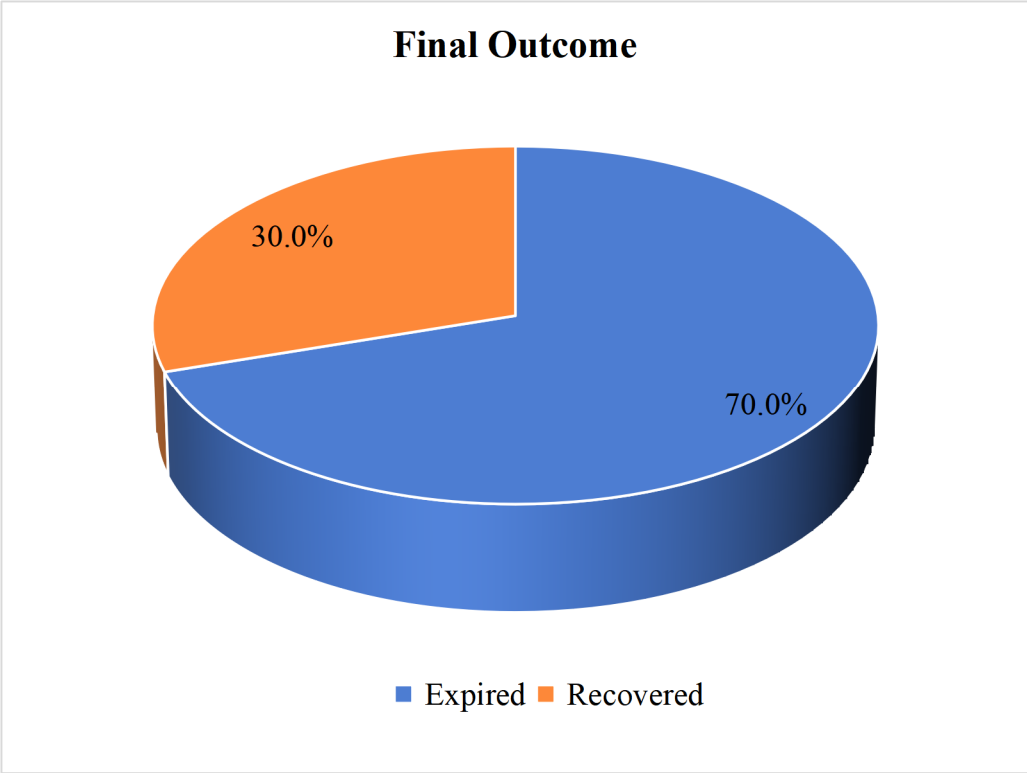


Graph 21: Bar diagram showing Side effects of rtPA

Table 28: Final Outcome - Mortality benefits

		Count	%
Final Outcome	Expired	28	70.0%
	Recovered	12	30.0%
	Total	40	

In the study, 70% expired, and 30% recovered.



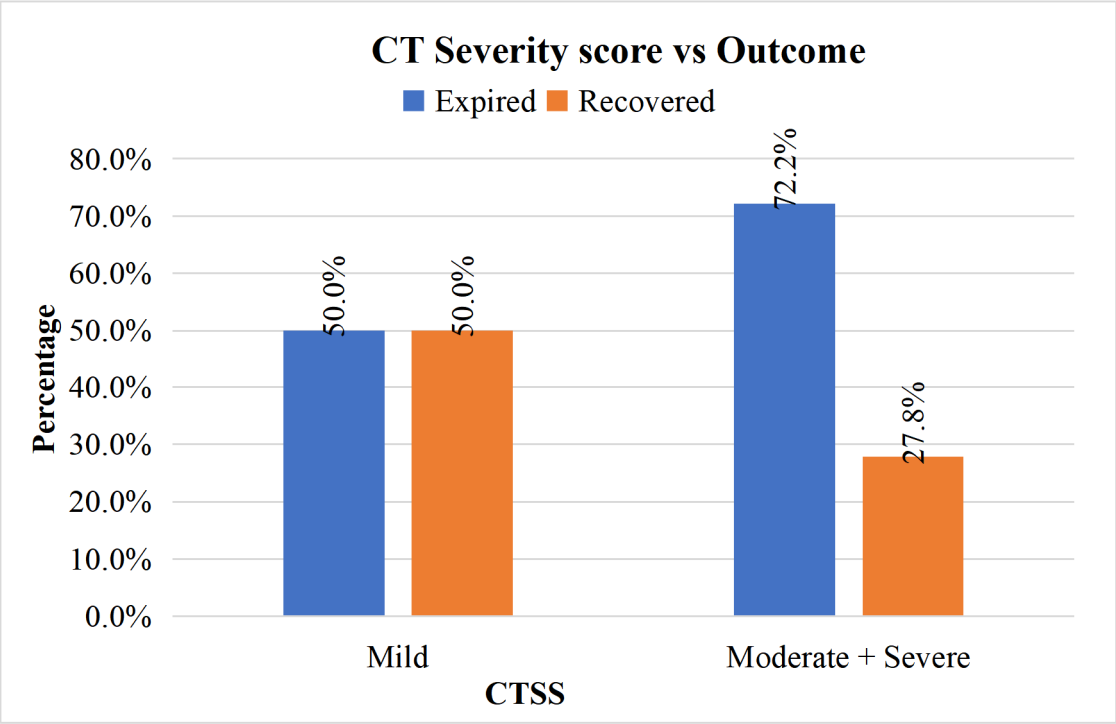
Graph 22: Pie diagram showing the Final Outcome- Mortality benefits

Table 29: Association between CT Severity score and Outcome

		Outcome				
		Expired		Recovered		Total
		Count	Row N %	Count	Row N %	Count
CTSS Grade	Mild	2	50.0%	2	50.0%	4
	Moderate + Severe	26	72.2%	10	27.8%	36
	Total	28	70.0%	12	30.0%	40

χ 2 = 0.8466, df =1, p = 0.357 **[Chi-square test]**

In the study among patients with mild CTSS grade, 50% had mortality, among patients with moderate and severe CTSS grade, 72.2% had mortality. There was no significant association between CTSS grade and Outcome.



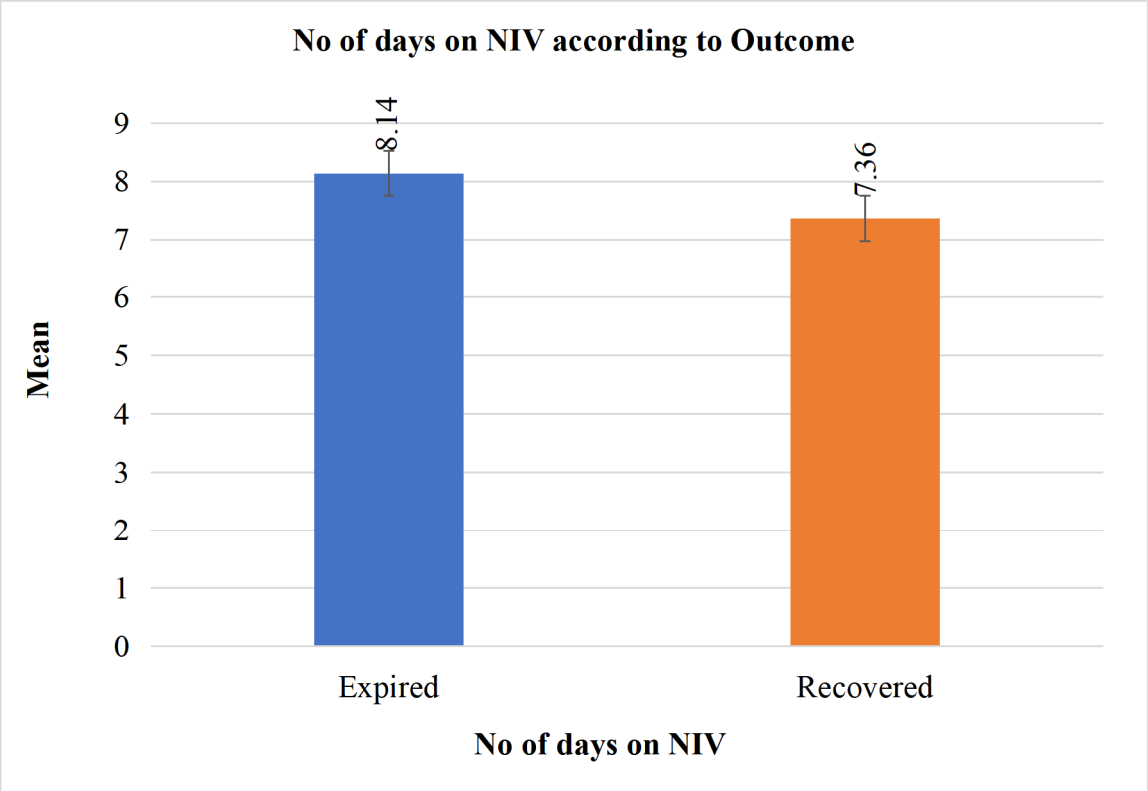
Graph 23: Bar diagram showing Association between CT Severity Score and Outcome

Table 30: No of days on NIV according to Outcome

		N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum	P value
					Lower Bound	Upper Bound			
No of days on NIV	Expired	28	8.14	5.576	5.98	10.30	1	22	0.696
	Recovered	11	7.36	5.537	3.64	11.08	2	21	
	Total	39	7.92	5.503	6.14	9.71	1	22	

Independent t-test

The mean no of days on NIV among patients who died was 8.14 ± 5.576 days and among patients who recovered was 7.36 ± 5.537. There was no significant difference in the no. of days on NIV according to outcome.



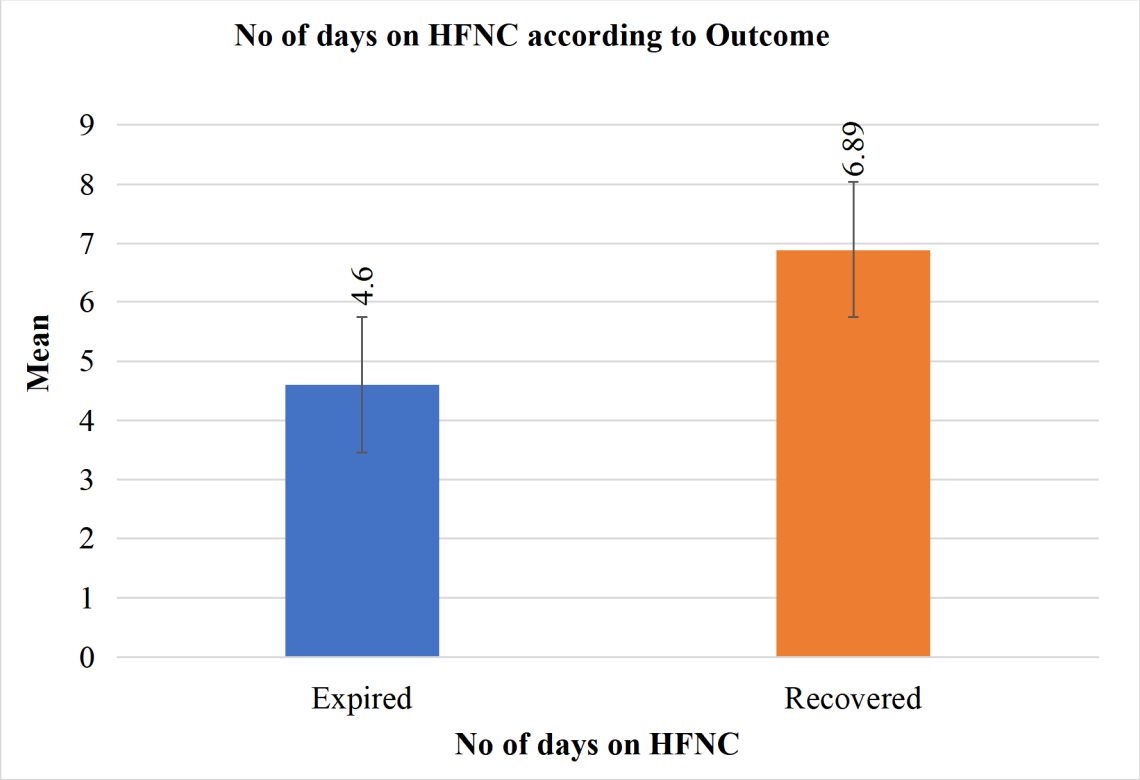
Graph 24: Bar diagram showing No of days on NIV according to Outcome

Table 31: No of days on HFNC according to Outcome

		N	Mean	SD	95% Confidence Interval for Mean		Minimum	Maximum	**P value**
					Lower Bound	Upper Bound			
No of days on HFNC	Expired	10	4.60	1.713	3.37	5.83	2	7	0.016*
	Recovered	9	6.89	2.028	5.33	8.45	3	9	
	Total	19	5.68	2.162	4.64	6.73	2	9	

Independent t-test

The mean no of days on HFNC among patients who died was 4.60 ± 1.71 days and among patients who recovered was 6.89 ± 2.028. There was a significant difference in the days on HFNC according to outcome.

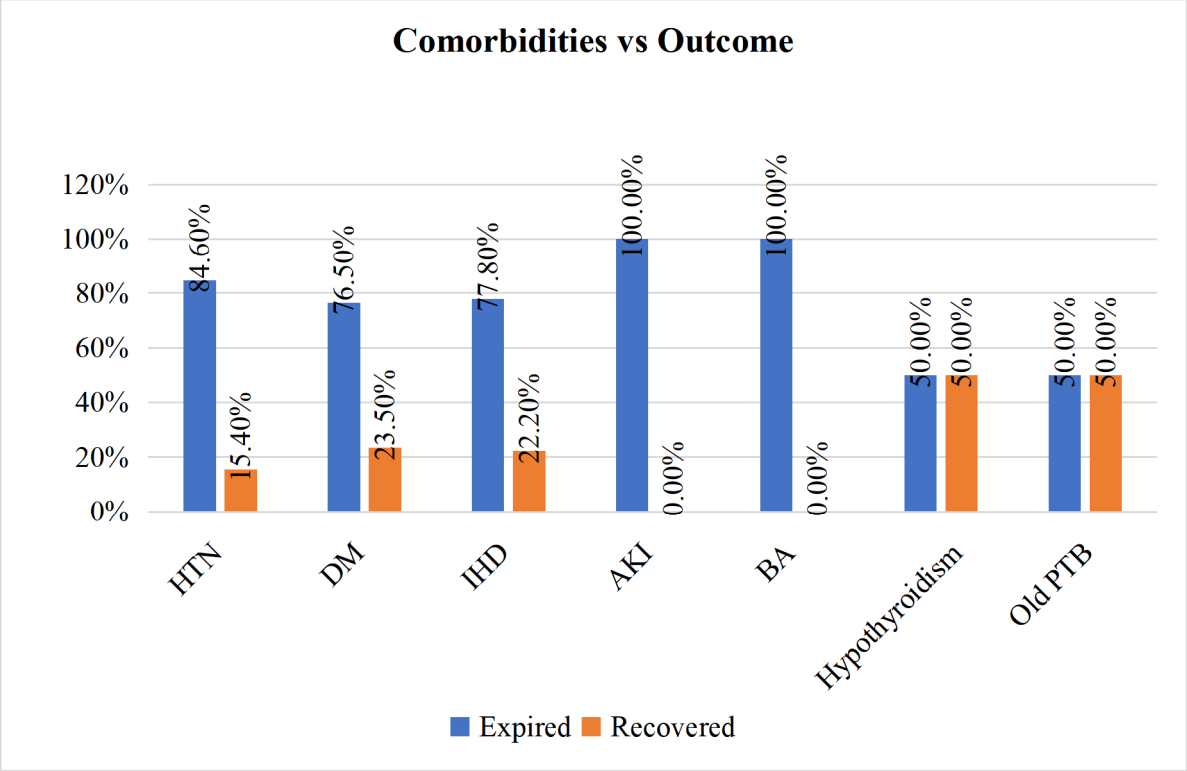


Graph 25: Bar diagram showing No of days on HFNC according to Outcome

Table 32: Association between Comorbidities and Outcome

		Outcome				P value
		Expired		Recovered		
		Count	Row N %	Count	Row N %	
HTN	Yes	11	84.6%	2	15.4%	0.162
	No	17	63.0%	10	37.0%	
DM	Yes	13	76.5%	4	23.5%	0.443
	No	15	65.2%	8	34.8%	
IHD	Yes	7	77.8%	2	22.2%	0.563
	No	21	67.7%	10	32.3%	
Others	AKI	3	100.0%	0	0.0%	0.610
	BA	1	100.0%	0	0.0%	
	Hypothyroidism	1	50.0%	1	50.0%	
	Old PTB	1	50.0%	1	50.0%	

In the study among patients with HTN, 84.6% had mortality and among patients without HTN, 63% had mortality. Among patients with DM, 76.5% had mortality and among patients without DM, 65.2% had mortality. Among patients with IHD, 77.8% had mortality and among patients without IHD, 69.7% had mortality. Among patients with AKI, 100% had mortality and among patients with Bronchial Asthma, 100% had mortality, among patients with Hypothyroidism, 50% had mortality, among patients with old PTB, 50% had morality. There was no significant association between comorbidities and outcome.



Graph 26: Bar diagram showing Association between Comorbidities and Outcome

DISCUSSION

The patients who died of respiratory failure due to COVID-19, when evaluated pathologically after an autopsy showed a common pattern of disseminated pulmonary microvascular thrombosis.[114,115] Several decades ago, therapy was proposed for use in organ failure.[116] The safety and potential feasibility of fibrinolytic therapy in patients with ARDS was proven in two small phases 1 clinical trials.[117] Moore et al was the first to propose the use of fibrinolytic therapy in COVID-19 respiratory failure.[118] Subsequently several case series and a small retrospective observational study was published proving the beneficial role of rtPA.[119,120] Hence a retrospective observational study was conducted among 40 severe COVID-19 patients admitted to the ICU under the Department of Respiratory Medicine, Jawaharlal Nehru Medical College, Belagavi for 1 year. Ethics committee approval was obtained before the start of the study.

General Profile:

The mean age of patients was 61.30 ± 11.726 years. The majority of patients were in the age group 51 to 60 years (30%). 77.5% were males and 22.5% were females

Table 33: Comparison of the General profile of COVID positive patients

	Number of subjects	Age	Gender (M: F)
Present study	40	61.30 ± 11.726 years	77.5% and 22.5%
Han et al[121]	114	54 ± 12 years	70% and 30%
Gu et al [122]	155	42.97 ± 14.85	56.2% and 43.8%
Liang et al[123]	88	42.7 years (Range, 4– 82 years)	58.0% and 42%
Pan et al[124]	63	44.9 ± 15.2 years	52.3% and 47.7%
Wang et al[125]	484	47 years (Median)	-
Barrett CD et al [Vanguard multicenter study][4]		59.0 (47.0-65.0)	78.9% and 21.1%

In our study, the mean age of the patients was high in severe COVID-19 patients. Male preponderance was seen among COVID-19. Hence similar male preponderance was observed in the present study as well.

This predominant male composition could be attributed to the increased occurrence of the disease and hospitalization of male patients as compared to their female counterparts. In these studies, also the higher severity of the disease was observed with increased advancing age of the patients which was also observed in our study denoting that increased age could be a risk factor for developing severe COVID-19.

Clinical Profile of COVID-19 patients

90% of patients had breathlessness, 67.5% had a fever, 70% had a cough, 20% had weakness, 10% had GI symptoms and 2.5% had anuria.

Table 34: Comparing the clinical profile of COVID-19 patients

	Present study	**Islam et al.**[126]	**Gu et al.**[122]	**Liang et al.**[123]	**Paudel et al.**[127]
Breathlessness	90%	55%	16.13%	13.6%	17%
Cough	70%	77.4%	56.13%	56.8%	68%
Fever	67.5%	76%	78.06%	84.1%	88.8%

In the present study since severe COVID-19 cases were included breathlessness was the most common symptom observed, similar to the study by **Islam et al.**[126] Other studies showed fever as the most common symptom.

Clinical features depend on the stage of presentation. As the disease progresses symptoms worsen especially breathlessness which can be attributed to the development of ARDS or pulmonary embolism leading to respiratory failure.

HRCT findings:

In the present study on HRCT, the most common findings were GGO, Crazy paving pattern (67.5%).

In a study by **Xiong et al.,**[128] the initial chest CT showed single or multiple GGO, consolidation in 55%, interstitial thickening or reticulation in 41%, air bronchograms in 33%, and pleural effusion in 12%. **Pan et al.,**[124] in their study observed that in initial HRCT 22.2% of patients had GGO, 85.7% had

patchy/punctate ground glass opacities, 19.0% of patients had patchy consolidation, 17.5% of patients had fibrous bands and 12.7% had irregular solid nodules.

Our findings were similar to the study by **Han et al**.,[121]Most common findings were GGO, followed by consolidation. A crazy-paving pattern is defined as the presence of GGOs with superimposed interlobular septal thickening giving the appearance of irregular paving stones. It has been reported in 5–36% of COVID-19 patients.

CT Severity Score:

The COVID-19 infection was confirmed largely by RTPCR assays. But the limitations of RT-PCR tests like low sensitivity, insufficient stability, and relatively long processing time to obtain results forced them to rely on comprehensive assessment using CT thorax and clinical manifestation. Some studies reported that the positive rate of RT-PCR assays for throat swab samples was 30–60%.[87,129]Many factors such as sampling operations, specimen sources (upper or lower respiratory tract), sampling timing, and the detection kit's performance can affect the RT-PCR results.[129]

In the study by **Tabatabaei et al.,**[130] 43.3% were mild, 50% were moderate and 6.7% were severe as per HRCT score. In the study by **Saeed et al.,**[131] Mild diseases were seen in 329/209 (36.5%), moderate in 309/902 (34.3%), and severe in 61/209 (6.8%) patients.

The appearance of the lesions could be attributed to the time at the presentation from the disease onset leading to multiple spectra of presentation ranging from the subtle appearance of GGOs progressing to consolidation and crazy paving

pattern which also increase the CT severity score. The association of pleural effusion has been a rare occurrence to be reported. HRCT lesions may also alter due to the presence of secondary bacterial and other infections

Comorbidities among Covid Cases:

In the present study, 32.5% had HTN, 42.5% had DM, 17.5% had IHD s/p PTCA, 7.5% had AKI, 5% had Hypothyroidism,5% had h/o old PTB,2.5 % had bronchial asthma, 2.5% had anemia.

In the study by **Islam et al.,** [126] major co-morbid conditions were diabetes mellitus, hypertension, bronchial asthma, and chronic kidney disease (CKD). Out of 100 patients, 75.5% patient had co-morbidity whereas 24.5% of patients did not have any co-existing disease. In the meta-analysis by **Paudel** [127] **,** it was observed that among COVID patients, 15.8% had HTN, 11.7% had cardiovascular diseases, 9.4% had DM, 1.4% had respiratory comorbidities and 0.8% had renal disorders. The current study has similar findings where HTN was the predominant co-morbidity in the patients.

Barrett CD et al., [4] **in a vanguard multicentre study** observed that 31.6% had DM, 94.7% had Cardiac disease, 21.1% had HTN, 78.9% had COPD, 26.3% had hyperlipidemia and 3.8% had other comorbidities. In this study majority of the patients had cardiovascular disease, unlike the present study where patients with cardiovascular disease were only 17.5% and had undergone PTCA.

Inflammatory markers:

Mean hs-CRP before rtPA was 133.203 ± 104.38 and after rtPA was 140.67 ± 204.57. There was no significant difference in mean hs-CRP after the rtPA administration. **Mean D-dimer before rtPA was 2900.18 ± 2006.423 and after rtPA was 3338.03 ± 1980.113. There was a significant increase in mean D-dimer after rtPA administration.** Mean IL-6 before rtPA was 397.910 ± 997.2789 and after rtPA was 256.708 ± 419.6120. There was no significant difference in mean IL-6 after rtPA administration. Mean Ferritin before rtPA was 736.27 ± 612.46 and after rtPA was 901.026 ± 633.11. There was no significant difference in mean Ferritin after rtPA administration. The mean LDH before rtPA was 979.375 ± 1377.99 and after rtPA was 721.3 ± 401.44. There was no significant difference in mean LDH after rtPA administration.

Price et al. [132] in their study observed that immediately after thrombolysis, D-dimer increased (from 3832 (1062–18829) to 16,011 (10,920–42,146) ng/ml, p¼0.10), and at 11 (10–14) hours after thrombolysis, fibrinogen fell from 6.75 (5.95–8.83) g/L to 4.40 (3.88–6.60) g/L (p ¼0.04). Other parameters showed no statistically significant improvement over the same time period (C-reactive protein 280mg/L (185–318) to 263mg/L (158–373), p¼0.85; white blood cells 17.9109 (12.9–22.2) to 16.3109 (13.2–19.6), p¼0.73).

The present study showed statistically no significant change in inflammatory markers, except D-dimer which is the expected outcome after the administration of fibrinolytic. However clinically any improvement cannot be abandoned. These findings of the current study were consistent with the findings of a study done by

Barrett et al. [133] which demonstrated a correlation between the lysis of the formed clot and a significantly elevated D-dimer immediately following tPA.

Arterial Blood Gas Analysis

In the present study mean pH before rtPA was 7.385 ± 0.063 and after rtPA was 7.359 ± 0.068. There was a significant decrease in mean pH after the rtPA administration. Mean PCO2 before rtPA was 31.697 ± 6.32 and after rtPA was 32.90 ± 5.714. There was no significant change in mean PCO2 after rtPA administration. **Mean PO2 before rtPA was 64.1 ± 12.43 and after rtPA was 71.63 ± 19.45. There was a significant increase in mean PO2 after the rtPA administration**. Mean SO2 before rtPA was 88.195 ± 13.49 and after rtPA was 87.45 ± 14.47. There was no significant improvement in mean SO2 after the rtPA administration. Mean HCO3 before rtPA was 22.303 ± 11.88 and after rtPA was 23.37 ± 11.43. There was no significant change in mean HCO3 after the rtPA administration.

Mean PaO2/FiO2 before rtPA was 73.39 ± 15.99 and after rtPA was 114.56 ± 72.47. There was a significant increase/improvement in mean PaO2/FiO2 after the rtPA administration.

Barrett et al. [133] in their study observed that tPA was associated with significant PaO_2/FiO_2 improvement at 48 h (estimated paired difference = 23.1 ± 6.7), which was sustained at 72 h (interaction term $p < 0.00$). Improvement in PaO_2/FiO_2 ratios in patients who had deteriorating respiratory status before rtPA administration was more significant than in patients who had poor but stable respiratory status. The results of this trial show that the use of tPA (alteplase) as a bolus with immediate therapeutic anticoagulation after its administration for severe

COVID-19 respiratory failure is safe and seems to improve oxygenation over baseline in a sustained fashion (from 6 through 168 h after randomization)

Price et al [132] in their study found that Alteplase improved PaO2/FiO2 ratio (from 97.0 (86.3–118.6) to 135.6 (100.7–171.4), p¼0.03) and ventilatory ratio (from 2.76 (2.09–3.49) to 2.36 (1.82–3.05), p¼0.011) at 24 h. The findings were similar to the present study where improvement in PaO2/FiO2 ratio was observed 24 hours post tPA administration.

Barrett et al.,[4] **in their vanguard multicentre study** showed that the percent change of PaO2 to FiO2 ratio at 48 hours was 29.8% in tPA bolus group[IQR, 4.5%-88.7%]. They observed that patients who received a tPA drip did not experience benefit. The findings of our study were similar in the improvement of the PaO2 to FiO2 ratio and percentage change

Table 35: Comparison of PaO2/FiO2 of present study with other studies

tPA Bolus Group	**Barrett CD et al Phase 1**	**Barrett CD et al Phase 2**	**Present study**
	Vanguard multicenter study		
PaO2 to FiO2 ratio			
Baseline	113.3 (89.0-135.0)	109.7 (77.0-132.9)	73.39 ± 15.99
At 24 h	144.0 (122.9-217.1)	94.5 (71.0-114.5)	114.56 ± 72.47
% Improvement over baseline at 24 h	44.4 (–3.4 to 78.0)	–16.7 (–37.4 to 36.5)	-
At 48 h	157.1 (130.0-188.0)	103.5(78.8-105.0)	-

% Improvement over baseline at 48 h	29.8 (4.5-88.7)	–19.6 (–21.7 to 2.3)	-
Composite outcome: PaO2 to FiO2 ratio % Improvement at 48 h of > 50% or PaO2 to FiO2 ratio of > 200	9 (47.4)	1 (16.7)	-

Since serial monitoring of ABG was not feasible in the present study due to the overwhelming burden of COVID-19, it is not possible to comment on the persistence of the improvement in the PaO2/FiO2 ratio beyond 48 hours.

No of days in ICU, no of days free of ICU post-rtPA administration, no. of days on NIV, no. of days on HFNC.

In the present study mean no of days in ICU was 12.48 ± 7.404 days, the mean no of days free of ICU post-rtPA was 1.47± 2.563 days, the mean days required to reduce fio2 <0.4 after tPA was 9.60 ± 8.66 days, mean no. of days on NIV was 7.92 ± 5.503 days and mean no. of days on HFNC was 5.68 ± 2.162 days. In this study, a total of 70% of the patients expired, and 30% recovered.

Table 36: Comparison of Length of ICU stay and No of days on NIV of the present study with other studies

tPA Bolus Group	Barrett CD et al Phase I	Barrett CD et al Phase II	Present study
	Vanguard multicenter study		
Length of ICU stay	16.0 (11.0-28.0)	19.0 (17.0-25.0)	12.48 ± 7.404 days
Ventillation days	13.0 (8.0-25.0)	17.5 (16.0-25.0)	7.92 ± 5.503 days

In the **Vanguard multicentre** study by **Barrett CD et al.,**[4] the mean duration of ICU stay was 16.0 (11.0-28.0) days, and the mean days on ventilation was 13.0 (8.0-25.0) days.

Duration of ICU stay and no. of days on NIV was lower in the present study compared to the study done by Barrett et al. The reason could be due to the beneficial effect of rtPA in fibrinolysis, restoring the ventilation and reducing the oxygen requirement thereby reducing the need for NIV although this improvement was not sustained for a long time as reflected by the mortality in the present study.

Final Outcome - Mortality Benefits

While COVID-19 overall mortality likely ranges from 1% to 5%, this is much higher in patients with COVID-19–induced acute respiratory distress syndrome (ARDS) (22%-64%).[42,134,135]

In the present study, 70% expired, and 30% recovered. Our study included patients admitted to ICU or MICU hence the mortality rates were higher in the present study

In the vanguard multicentre study done by **Barrett et al.**, [4] there was no significant difference in in-hospital mortality between tPA bolus and control group (41.2% vs 21.1%; P = 0.19). The tPA drip group did not show any benefits when compared to controls.

In a retrospective observational study done by **Ashwathappa et al.,** [136] included 34 patients out of which 13 patients with severe ARDS were thrombolysed. It demonstrated lower ICU mortality in thrombolysed patients than in non-thrombolysed patients (23.1% vs. 71.4%, *P* = 0.006).

CT Severity score and Outcome:

In the present study, the mean number of days in ICU was 12.48 ± 7.404 days, the mean days required to reduce Fio2 <0.4 after rtPA was 9.60 ± 8.66 days, the mean no. of days on NIV was 7.92 ± 5.503 days and mean no. of days on HFNO was 5.68 ± 2.162 days. In the study, 70% expired, and 30% recovered.

In the study among patients with mild CTSS grade, 50% had mortality, among patients with moderate CTSS grade. In the study among patients with mild CTSS grade, 50% had mortality, among patients with moderate + Severe CTSS grade, 72.2% had mortality. There was no significant association between CTSS grade and outcome. This can be attributed to the progression of the disease and the increase in CTSS with disease progression which led to poor outcomes.

Saeed et al., [131] observed that the death rate in their study was significantly increased among patients with severe CT findings. Similar findings were observed in the study **by Li et al.,** [137]

In a retrospective study done by **Francone et al**.[138] 130 symptomatic COVID-19 patients were enrolled and CT thorax findings were retrospectively evaluated. It was found that in severe and critical COVID-19 patients the CT score was significantly higher compared to those with mild COVID infection ($p < 0.0001$), and among those patients in the late phase as compared to those in the early phase ($p < 0.0001$). A CT score of more than 18 was viewed as prescient of death and to be related to an increased mortality risk.

A retrospective study done by **Xiao et al.** [139] which included a total of 243 patients, assessed the correlation of CTSS with disease progression and found that the highest CT score was associated with disease progression.

However, in our study, there was no statistically significant association between CTSS and outcome. This can be due to the use of rescue rtPA.

Number of days on NIV and HFNC according to Outcome

In the present study mean no of days on NIV among subjects who died was 8.14 ± 5.576 days and among patients who recovered was 7.36 ± 5.537. There was no significant difference in the days on NIV according to the outcome.

The mean no of days on HFNO among patients who died was 4.60 ± 1.71 days and among patients who recovered was 6.89 ± 2.028. **There was a significant difference in the no. of days on HFNC according to the outcome.**

This indicates that patients who were shifted from NIV to HFNC and who recovered had a greater benefit from rtPA administration**.**

Comorbidities with Outcome

In the study among patients with HTN, 84.6% had mortality and among patients without HTN, 63% had mortality. Among patients with DM, 76.5% had mortality and among patients without DM, 65.2% had mortality. Among patients with IHD, 77.8% had mortality and among patients without IHD, 69.7% had mortality. Among patients with AKI, 100% had mortality and among patients with Bronchial asthma, 100% had mortality. Among patients with Hypothyroidism, 50% had mortality, among patients with Old PTB, 50% had morality. There was no significant association between comorbidities and outcome.

In the present study, the lack of association of co-morbidities with mortality in patients who were administered rtPA could be because of the inclusion of severe cases whose prognosis was poor irrespective of the comorbidity, progression of disease in patients with mild infection who did not have any co-morbidities.

Side effects of rtPA:

In the present study, 67.5% of patients had no side effects. However 32.5% of the patients had minor side effects of which haematuria and nasal bleeding were present in 10% of patients each.

Barrett CD et al.[4] in their **vanguard multicentre** study incidence of adverse events following rtPA administration was 68.4%. Bleeding events were 15.8%. The incidence was higher compared to the present study.

In a multicentre retrospective observational study done by **Christopher et al.**[133] consisting of 79 patients, bleeding complications were reported in 13 (16.5%) of the patients, with nine of these episodes occurring within 72 hours of tPA (50mg) administration. There was one intracranial hemorrhage that caused death.

Goyal et al. [107] also did not encounter any bleeding episodes in their case series of 3 patients. In the clinical trial, they observed that thrombolysis is a relatively safe and effective option in carefully selected critically ill patients of COVID-19. However, the usefulness of fibrinolytic agents in management will be clearer, once the results of a randomized trial of tPA will be available.

The findings of this study were of high clinical significance during a global pandemic of a disease with high morbidity and mortality. Of particular importance was safety: no major bleeding events occurred, including intracranial hemorrhage, that was associated with tPA answering an important question for future investigations and clinical use.

LIMITATIONS:

1. A major limitation of this study was no comparison group. Hence its real beneficial effect among severe COVID-19 patients must be evaluated by conducting a double or triple-blinded randomized controlled trial.
2. Confounding factors affecting mortality were not analyzed.
3. The sample size was small hence larger sample size is to be included.
4. Different doses and routes of rtPA administration were not evaluated.
5. Combination therapy with heparin was not evaluated.

RECOMMENDATIONS:

From the study findings, it was recommended that Recombinant Tissue Plasminogen activator (rtPA) due to its ability to manipulate the fibrinolytic system can be a promising treatment option in reducing mortality and morbidity in carefully selected severe COVID-19 patients.

The exact role of rtPA as a treatment option for severe COVID-19-infected patients with refractory hypoxemia or those at high risk of developing cytokine storm requires future studies.

CONCLUSION:

From the study findings, it was concluded that the use of Recombinant Tissue Plasminogen Activator (rtPA) in severe COVID-19 induced ARDS resulted in a significant increase in PaO2/FiO2 ratio and PO2 after 24-48 hours of rtPA administration. It also increased D-dimer levels showing its efficacy in the lysis of the clot. However, there was no significant improvement in the other inflammatory parameters post-rtPA administration. The duration of ICU and no of days on NIV was lesser when compared to other similar studies.

In a resource-constrained crisis, such as the COVID-19 pandemic, where ventilators and ECMO circuits may be short in supply, fibrinolytic therapy along with therapeutic enoxaparin in carefully selected cases where laboratory markers and respiratory parameters point to thrombotic coagulopathy with vascular occlusive pulmonary physiology appears to be promising in improving oxygenation with acceptable safety profile.

SUMMARY:

A retrospective observational study was conducted among 40 Severe COVID subjects admitted to ICU under the Department of Respiratory Medicine,Dr. Prabhakar Kore Hospital and MRC, Belagavi for 1 year.

1. The majority of subjects were in the age group 51 to 60 years (30%) and majority of them were males. The most common comorbidity was HTN in 32.5% of the patients
2. The most common symptom was breathlessness and on chest X-ray 75% had B/L infiltrates.
3. CORADS Score – 100% had a score of 5, CTSS score was mild in 10%, moderate in 35%, and severe grade in 55% of the patients. On HRCT, the common finding was GGO and crazy paving pattern (67.5%).
4. In the study, there was no significant difference in hs-CRP, IL-6, Ferritin, and LDH after rtPA administration. However, there was a statistically significant increase in d-dimer after rtPA administration indicating effective fibrinolysis.
5. Mean PO2 before rtPA was 64.1 ± 12.43 and after rtPA was 71.63 ± 19.45. Mean PaO2/FiO2 before rtPA was 73.39 ± 15.99 and after rtPA was 114.56 ± 72.47. There was a significant increase in mean PO2 and mean PaO2/FiO2 after rtPA administration. There was no significant increase in mean PCO2, SpO2, and HCO3 after rtPA administration.
6. The mean no of days in the ICU was 12.48 ± 7.404 days
7. The mean no of days free of ICU post-rtPA was 1.47± 2.563 days
8. The mean no. days required to reduce FiO2 <0.4 after rtPA was 9.60 ± 8.66 days.

9. Among patients with mild CTSS grade, 50% had mortality, among patients with moderate and severe CTSS grade, 72.2% had mortality. There was no significant association between CTSS grade and Outcome.
10. The mean no of days on NIV among patients who died was 8.14 ± 5.576 days and among patients who recovered was 7.36 ± 5.537. There was no significant difference in no. of days on NIV according to the outcome.
11. The mean no of days in HFNC among patients who died was 4.60 ± 1.71 days and among patients who recovered was 6.89 ± 2.028. There was a significant difference in the no. of days on HFNC according to the outcome.
12. There was no significant association between comorbidities and outcome.
13. In the study, 67.5% of the patients had no side effects. However 32.5% had minor side effects of which haematuria and nasal bleeding were common.
14. Mortality was seen in 70% of the patients who received rtPA.

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ANNEXURE – I - PROFORMA

Patient initials :

Age :

Sex :

Date of COVID testing:

Symptoms and duration:

X-ray features : consolidation/infiltrations/reticular

Unilateral/bilateral

HRCT features : 1.Unilateral/Bilateral

2.GGO/Reticular/crazy paving

3.consolidation/multiple/patchy

4.cavitation/effusion

5.CORADS Score: ____

6.CTSS: _____

Comorbid Conditions: IHD/HTN/DM/Malignancies/Post PTCA/ Others

Treatment modalities tried before rtPA:

- oxygen, face mask, RBM, HFNO, NIV
- days

- Enoxaparin
- Methyl prednisolone – normal dose/high dose
- Remdesvir
- Tocilizumab/Alzumab
- Oxygen requirement before rtPA

Dose of rtPA administered: 30mg 40mg 50mg

Laboratory parameters

	Before tPA administration	After tPA administration
hs-CRP		
D-dimer		
Ferritin		
IL-6		
LDH		

Platelets:

ABG:

	ABG before rtPA	ABG 24-48 hrs after rtPA
pH		
PCO2		
PO2		
SO2		
HCO3		
PaO2/FiO2		

No of days required to reduce FiO2 <0.4 after rtPA

No of days in ICU:

No. of days on NIV:

No. of days on HFNC:

No. of days free of ICU post rtPA:

Oxygen requirement after rtPA:

Complication of rtPA if any:

Repeat HRCT, If any:

Final outcome: Oxygen reduced to 40%

Recovered

Died

ANNEXURE - II – PHOTOGRAPHS

PHOTOGRAPH 1: VENTILLATOR

PHOTOGRAPH 2: HIGH FLOW NASAL CANNULA

ANNEXURE - III - KEY TO MASTERCHART

CTSS	-	CT severity score
MP	-	Methyl Prednisolone
rtPA	-	Recombinant Tissue Plasminogen Activator
ABG	-	Arterial blood gas analysis
NIV	-	Non-Invasive ventilation
HFNC	-	High Flow Nasal Cannula

ANNEXURE - IV –

MASTERCHART

IP N0	patient initials	age	sex	symtoms and duration	date of COVID testing	cxr features	HRCT features	CORADS SCORE	CTSS	Comorbidities	treatment modalities before rtPA					o2 requirement before rtPA	dose of rtPA adm	platelets	lab parameters before tPA administration					lab parameters after TPA adm					ABG before tPA					Pao2/FiO2 before rtPA	ABG after rtPA					O2 requirement after rtPA (48 hrs after rtPA)	Pao2/FiO2 after rtPA	no of days in ICU rtPA	no of days free of icu post rtPA	no of days required to reduce fio2 <0.4 after rtPA	no of days on niv	No of days on hfno	side effects of rtPA	final outcome
												ENOXAPARIN	MP						HsCRP	D-DIMER	IL-6	FERRITIN	LDH	HSCRP	D-DIMER	IL-6	FERRITIN	LDH	PH	PCO2	PO2	SO2	HCO3		ph	pco2	po2	so2	hco3									
1025521	R	56	F	breathlessness , cough , expectoration x 6 days	16-10-2020	b/l consolidation	GGP,crazy paving pattern	5	23/25	-	face mask	60 mg	40mg	alzumab	remdesvir	cpap -60/6/12 - spo2 94%	50 mg	1,29,000	58.9	>5000	85.11	464.6	1230	99.9	1460	22.3	764	986	7.4	32	60	91	21.2	100	7.4	30.9	107.8	98	22.7	NRBM - 10L O2/min fio2-95%, spo2-94%	112	20	0	0	12	2	-	EXPIRED
1023503	N	55	F	fever with chills , cough , expectoration x 3 days	21-09-2021	b/l consolidation	GGO	5	22/26	-	NRBM,HFNO	40 mg	500mg	alzumab	given	hfno -fio2-60 ,50l/min , spo2-90%	50mg	5,10,000	90	1290	27.08	231	550	60	900	20.08	468	600	7.4	31	57	90.5	21	95	7.43	32.9	68.7	93.9	21.2	HFNO-50L/min ,fio2-40%, spo2-95%	170	7	6	5	-	5	-	RECOVERED , O2 REDUCED TO 40%
1023036	M	68	M	breathlessness,cough , fever x 7 days	16-09-2021	b/l infiltrates	GGO , Crazy paving pattern	5	13/25	HTN	NIV	60(BID) mg	500mg	tocilizumab	given	cpap-100/12/16 , spo2-90%	50mg	3,02,000	89	>5000	384	1324	744	100	6391	2452	1989	1248	7.4	34	73.5	95	23.7	73.5	7.47	28	61.9	91.4	17.8	CPAP-100/16/20 , spo2-92%	61	7	0	0	7	-	-	EXPIRED
1024541	BP	80	M	breathlessness ,disorientation x 2 days	01-10-2021	B/L infiltrates	GGO , Crazy paving pattern	5	20/25	T2DM ,AKI	NRBM,NIV	60 mg	500mg stat dose	-	given	NRBM-15L/MIN fio2-60, SPO2-85%	50mg	78,000	100	>5000	1.52	1000	733	90	4356	320	1223	456	7.3	37	37	98	18.1	46.25	7.3	30	66	78	20	NRBM-10L/min, Spo2-94%	82.5	1	0	1	1	-	-	EXPIRED
1023620	DS	58	M	breathlessness , cough,expectorationx 4days	18-09-2020	b/l infiltrates	GGO , patchy	5	17/25	post PTCA	NRBM/HFNO	60mg	500MG	-	given	HFNO-60L/MIN ,FIO2-80%, SPO2-90%	50MG	1,04,000	350	1059	686	992	416	370	2050	540	690	399	7.4	31	59	91	20.5	73.75	7.4	33	46.7	84	22.7	CPAP-100/12/16 , SPO2-90%	46.7	6	0	0	1	4	-	EXPIRED
1021857	MP	64	M	breathlessness , fever ,cough x 4 days	27-08-2021	b/l infiltrates	GGO , Crazy paving pattern	5	14/25	IHD,HTN,T2DM ,post PTCA	HFNO, NIV	60mg	40mg		given	CPAP-100/6/10, spo2-96%	40mg	1,58,000	260	>5000	500	703	800	100	>5000	12.95	1065	796	7.3	45	60	88	18	60	7.3	50.5	34.9	65.1	28.5	nrbm-10l/min , spo2-95%	43.6	20	7	5	5	8	Bleeding per rectum	RECOVERED , O2 REDUCED TO 40%
1025672	RB	72	M	breathlessness x 4-5 days ,cough,expectoration x 3 days ,pain abdomen x 1 day, vomiting x 1 day	11-10-2020	b/l infiltrates	GGO , crazy paving pattern	5	15/25	T2DM	face mask,HFNO,NIV	40mg	40MG	alzumab	given	CPAP-60/6/10 , SPO2-89%	50MG	2,63,000	51.6	4439	57	773	699	90	6100	140	1898	348	7.3	22	55	80	11.8	91	7.3	35	70	84	25	CPAP-100/8/12 , SPO2-75%	70	3	0	0	3	-	-	EXPIRED
1021950	IK	58	M	fever 5 days back , breathlessness x 2 days ,cough x 2 days	30-08-2020	b/l reticular	GGO , Crazy paving pattern	5	18/25	HTN, T2DM	NIV	40mg	500mg(5 days)-40mg 1	tocilizumab	given	CPAP-90/8/12, SPO2-92%	40MG	2,87,000	55	1320	160	529	683	88	4000	70	989	678	7.4	24.2	82	96.4	16.4	91	7.3	28	85	90	20	CPAP -90/8/12, SPO2-92%	94.4	8	0	0	8	-	-	EXPIRED
1021494	SP	81	M	fever , breathlessness , generalised weakness x 3 days	22-10-2020	b/l infiltrates	GGO , patchy	5	12/25	T2DM	face mask,NIV	40mg	500mg (5 days)-40mg (3days)	alzumab	given	CPAP- 90/10/14 ,sp02 -92%	40MG	1,31,000	312	7122	475	186.3	667	200	5000	275	212	867	7.4	24.4	57	16.2	90	63	7.3	28	50	20	88	CPAP-80/10/14, SPO2-94%	62.5	9	0	0	7	-	hemoptysis	EXPIRED
1020880	PL	65	M	breathlessness , generalised weakness x 1 day	10-08-2021	b/l consolidation	GGO , Crazy paving pattern ,consolidation	5	18/25	IHD	NRBM,HFNO,NIV	40mg	40mg tid		given	CPAP-80/6/10 , spo2-98%	40MG	1,95,000	10.5	1417	391.3	92.05	753	48.4	1266	308.5	300	651	7.4	39.4	60	73.4	25.5	49.25	7.3	35	50	80	26.2	CPAP-50/6/10,SPO2-92%	100	22	0	0	19	3	hematuria	EXPIRED
1024235	S	72	M	breathlessness (sudden onset) , fever (continuos , high grade x 7 days	29-09-2020	b/l infiltrates	GGO,Crazy paving pattern, b/l pleural effusion	5	20/25	HTN,T2DM	NRBM	60mg	40mg		given	HFNO -60L, fio2-100 %, SPO2-95%	50MG	4,78,000	49	1398	16.5	2763	725	6.8	1030	1.5	1443	295	7.4	30.4	66.1	93	19.4	66	7.4	35	78	80	20.4	HFNO-60L , fio2-100%, SPO2-95%	78	18	0	4	5	7	hematuria	EXPIRED
1023707	R	65	M	fever x 10 days , cough with expectoration x 4 days ,breathlessness x 4 days	22-09-2020	b/l consolidation	GGO, consolidation , b/l pleural reffusion	5	24/25	HYPOTHYROIDISM	NRBM,HFNO,NIV	40mg	40mg		given	CPAP -90/12/16,SPO2-94%	50MG	3,62,000	152	>5000	72.8	1478	688	100	3522	50.1	900	800	7.46	38	58	91	26	64	7.3	45	60	92	25	CPAP-100/12/16 , SPO2-95%	60	16	0	0	9	5	hematuria	EXPIRED
1021332	FD	53	M	cough , breathlessness , fever x 3 days	20-08-2020	B/L infiltrates	GGO,Crazy paving pattern,consolidation	5	9/25	-	NIV	40mg	40mg	tocilizumab, alzumab	given	CPAP -90/10/14, SPO2-92%	50MG	5,15,000	526	>5000	405	732	1582	600	2000	500	1400	986	7.4	31	49	85	20.9	54	7.3	31	60	90	25	CPAP-100/16/20 ,SPO2-88%	60	7	0	0	7	-	-	EXPIRED
1023024	JK	62	M	fever , cough ,expectoration, generalised weakness x 10 days (home quarantine with home treatment)	09-09-2020	b/l infiltrates	GGO, crazy paving pattern	5	14/25	-	NRBM ,NIV	40MG	1 GM IV infusion 1-0-0	tocilizumab	given	CPAP -80/8/12 , spo2-95 %	50mg	4,22,000	143	>5000	81	1874	864	150	1086	54	728	500	7.4	36	77	95	22	96	7.3	35	89	96	20	CPAP -40/6/12 , SPO2-99%	222	13	4	9	9	-	-	RECOVERED , O2 REDUCED TO 40%
1023301	P	65	F	fever , breathlessness , cough x 8 days	16-09-2020	b/l infiltrates	GGO,crazy paving	5	8 on 25	IHD ,BA	NIV	40MG	500MG IV infusion 1-0-0	tocilizumab	given	cpap -90/12/16 ,spo2-96%	40MG , 50MG	1,78,000	180	2346	29	178	529	130	1295	261	456	549	7.4	36	60	90	22	66	7.3	41	125	98	23	CPAP- 70/10/14 ,spo2-92	178	20	0	0	20	-	-	EXPIRED
1022425	S	63	M	cough, cold , generalised weakness, breathlessness x 3 days	05-09-2020	b/l rinfiltrates	GGO, crazy paving pattern	5	19/25	-	RBM,HFNO,NIV	60MG	40MG	-	given	CPAP-90/10/14 , SPO2-96%	50MG	2,54,000	119	1517	36.3	517	894	56	494	1.76	407	533	7.4	34	76	92	24	84	7.4	30	80	95	20	HFNO -60L ,fio2-40%, SPO2 -90%	200	12	5	5	3	8	-	RECOVERED , O2 REDUCED TO 40%
1025335	A	72	M	cough, breathlessness, feverx 7 days ,sorethroat,loosestools 5 days back	14-10-2020	b/l infiltrates	GGO , Crazy paving pattern	5	5/25	IHD POST CABG ,HTN,T2DM ,AKI	NIV	40MG	500MG IV INFUSION 1-0-0	tocilizumab	given	HFNO -60L fio2-90%, SPO2-98%	50MG	1,11,000	46.3	>5000	202.2	1515	1683	174.2	3277	65.3	3036	1746	7.4	34	80	97	23	88	7.3	31	90	93	21	HFNO - O2 -20L ,fio2-40%, SPO2 -96%	225	11	0	7	6	5	-	EXPIRED
1023428	B	48	M	breathlessness , cough x 1 day	18-09-2020	b/l consolidation	GGO,crazy paving pattern consolidation	5	21/25	-	NIV	40MG	500MG IV infusion	tocilizumab	given	CPAP -90/8/12 , spo2-96%	50mg	60,000	72	1463	182	1548	1623	50	986	70	1148	832	7.4	20.9	66	93	13	73.3	7.3	35	80	90	15	CPAP-100/14/16 ,SPO2-90%	80	13	0	0	5	3	nasal bleed	EXPIRED
1024543	SM	41	M	fever ,vomiting x 5 days ,breathlessness x 9 days	03-10-2020	b/l infiltrartes	GGO , crazy paving pattern	5	5/25	T2DM	NIV	60MG	40MG	-	given	cpap -90/12/12 , spo2 -90%	50mg	3,69,000	99.7	1218	5	2080	1130	77	1310	4.8	1411	367	7.4	30	78	96	20	86	7.4	25	90	96	25	nasal prongs -3l/min ,fio2-32,spo2-95%	281	11	6	5	7	3	-	RECOVERED O2 REDUCED TO 40%
1024119	M	61	M	breathlessness , anuria , constipation,decreased appetite x 1 day	28-09-2020	B/L infiltrates	GGO , Crazy paving pattern	5	23/25	HTN , T2DM	NIV	60MG	500MG IV infusion 1-0-0	tocilizumab	given	CPAP 100/14/20 , spo2-96%	40mg	1,58,000	148.7	1510	118	532	645	10	>5000	262.5	365	999	7.3	34	61.4	89	18.3	61.4	7.3	33	60	90	20	CPAP-90/14/18 , SPO2-94%	66	10	0	0	6	4	nasal bleed	EXPIRED
1022690	SS	53	M	cough x 3 days , breathlessness x 1 day	09-09-2020	b/l infiltrates	GGO , carzy paving	5	23/25	-	NIV	40mg	1gm iv infiusion 1-0-0	tocilizumab	given	CPAP 100/18/22 , SPO2-90%	50MG	2,39,000	17.1	>5000	4616	1160	924	30	>5000	224	1560	800	7.4	12.3	77	95	8.2	77	7.4	38	84	96.6	25	CPAP - 60/12/18 , SPO2-95%	140	14	0	0	14	-	-	EXPIRED
1022988	SG	60	M	feevr , bretahlessness x 5 days , generalised weaknessand decreased appetite x 3 days	10-09-2020	b/l infiltrates	GGO , crazy paving pattern	5	17/25	T2DM	HFNO , NIV	40MG	1 GM IV infusion 1-0-0	-	given	CPAP 90/12/20 , SPO2-98 %	50MG	2,20,000	128	1193	110	615	613	100	700	120	500	545	7.3	35.5	41.4	73	19.4	46	7.3	33	40	56	20	CPAP -100/14/18 , SPO2 -78%	40	3	0	0	3	-	-	EXPIRED
1022906	GM	78	M	coughx 5 days ,breathlessness x 1 day	11-09-2020	b/l infiltrates	GGO , crazy paving pattern	5	24/25	T2DM	HFNO, NIV	40mg	500mg iv infusion 1-0-1	-	given	HFNO FIO2-70%, 02-50l	50MG	1,87,000	84	6883	257	510	509	69.3	6702	8.96	1925	876	7.3	29	50	78	22	71.4	7.4	33	95	98	23	02 mask -5l/min, spo2-94%	237	21	3	10	2	9	nasal bleed	RECOVERED , O2 REDUCED TO 40%
1022966	SB	71	F	breathlessness x 2 days ,loose stools x 4-5 days	12-09-2020	b/l infiltrates	GGO , crazy paving pattern	5	15/25	T2DM	NIV	40MG	40MG	tocilizumab	given	CPAP 100/8/12 , spo2-97%	50MG	2,09,000	133	1182	76.8	50.9	333	96	1000	417	121	561	7.3	33	93.5	96	18.4	93.5	7.4	25	86	90	15	CPAP-100/12/16 SPO2-94%	86	11	0	0	11	-	-	EXPIRED
1024843	ST	60	M	cough, feevr , breathlessness x 3 days	07-10-2020	b/l infiltrates	GGO, crazy paving pattern	5	15/25	IHD,HTN,T2DM	HFNO, NIV	60MG	40MG BD	-	given	HFNO 60L, fio2-100 ,SPO2 -94%	50MG	3,53,000	41	>5000	26.6	434	726	41.3	>5000	400	473	862	7.5	29	54	78	22	54	7.4	30	80	90	25	CPAP - 40/10/14 , SPO2-93%	200	10	5	5	3	6	-	RECOVERED , O2 REDUCED TO 40%
1023569	SH	43	M	breathlessness , cough, fever x 3 days	10-09-2020	b/l infiltrates	GGO, crazy paving pattern	5	10/25	-	o2 mask, HFNO	40mg	500mg iv in 100ml NS	tocilizumab	given	CPAP -80/10/14 , SPO2-92 %	50MG	2,56,000	126	4941	499	619	485	100	3450	500	1124	1000	7.4	20.8	72	94	20	90	7.4	31.7	81.9	95.8	19.3	CPAP -100/14/20 SPO2-84%	81	4	0	0	4	-	-	EXPIRED
1021620	S	54	F	fever , cough, generalised weakness x 3 days	25-08-2020	b/l infiltrates	GGO, crazy paving pattern	5	20/25	-	O2 mask , RBM,HFNO, NIV	40MG	40MG TID	alzumab	given	CPAP -60/8/12 , SPO2-97%	40MG	3,09,000	217	>5000	67.9	639	720	102.1	1217	6.65	207	505	7.3	45.5	52.5	90.1	25.2	87.5	7.4	40	88	96	22	nasal prongs - 2L/MIN , SPO2-96%	314	13	3	3	4	-	-	RECOVERED , O2 REDUCED TO 40%
1023272	SD	52	F	cough, fever , breathlessness x 1 day	18-09-2020	b/l infiltrates	GGO, crazy paving pattern	5	15/25	HTN	RBM , NIV	40MG	50MG	tocilizumab +alzumab	given	CPAP- 100/18/24 SPO2-72%	50MG	1,50,000	218.6	>5000	685	516	819	200	6911	720	1295	1669	7.4	29	78	95	18	78	7.4	25	80	90	20	CPAP-100/18/24 SPO2-77%	80	8	0	0	8	-	-	EXPIRED
1021183	SB	82	M	breathlessness , cough x 2-3 days	18-08-2020	B/L infiltrates	GGO, crazy paving pattern	5	20/25	HTN , T2DM ,IHD POST CABG	NIV	60MG	500MG IN 100ML NS 1-0-0	tocilizumab	given	CPAP-100/10/14 SPO2-92%	40MG	2,56,000	218	1562	223	383	1156	198	1680	26.5	188	1821	7.3	37	72	93	22	72	7.2	40	60	88	14	CPAP-100/14/18 SPO2-80%	60	8	0	0	8	-	-	EXPIRED
1023170	AT	47	M	cough , cold , fever x 3 days	15-09-2020	B/L infiltrates	GGO, crazy paving pattern	5	9/25	old PTB	HFNO	40MG	1GM IV infusion (Fb) 40mg BD	tocilizumab	given	HFNO - 60L,fio2-80% SPO2-98%	50MG	1,84,000	107.4	1141	45.5	284	582	58	1514	259	1120	100	7.5	32	62	92	22	77.5	7.3	25	63	90.8	14.7	HFNO 40L,fio2-60%, SPO2-94%	105	10	0	0	2	7	-	EXPIRED
1022407	JK	67	M	fever with chills x 5 days , breathlessness x 2 days	5/9/202	b/l infiltrates	GGO, crazy paving pattern	5	19/25	HTN, T2DM	HFNO,NIV	40MG BD	500MG IN 100ML NS 1-0-0	tocilizumab	given	cpap 100/10/14 ,spo2-87%	50mg	2,00,000	82	1320	46.8	269.4	514	100	2000	86	580	890	7.5	28.9	53.8	90.5	21.8	53.8	7.4	30	48	80	25	mechanical ventillation - volume control - 100/8/12/420 , spo2-80 %	48	5	0	0	4	-	hematuria	EXPIRED
1021997	J	71	M	fever , cough, breathlessness	28-08-2020	b/l consolidation	GGO, B/L consolidation	5	18/25	IHD , POST CABG 4 months back	NIV	40MG BD	500MG IN 100ML NS 1-0-0	tocilizumab	given	cpap-100/10/14spo2-90%	40mg	2,73,000	14.2	1063	91.78	271.9	677						7.4	31	58.5	92.1	22.5	58.5						mechanical ventillation - volume control - 100/10/14/400 , spo2-50%	-	4	0	0	4	-	Et tube bleeding	EXPIRED
1022999	SG	48	M	fever , cough , breathlessness x 5 days	26-09-2020	B/L infiltrates	GGO , crazy paving pattern	5	21/25	-	NIV	60MG BD	40MG BD	tocilizumab , convalescent plasma	given	cpap 70/16/22 SPO2-92 %	40mg	2,80,000	42.3	1650	36.75	226.3	374	20	481	935	309	569	7.3	33	66	85	16	94.2	7.3	25	80	95	20	cpap -100/12/18 spo2-88% , 98% with 3l o2	80, 250	32	3	30	21	8	-	recovered , o2 reduced to 40%
1022690	SS	53	M	fever , cough , breathlessness x 3 days	08-09-2020	B/L infiltrates	GGO , crazy paving pattern	5	20/25	cellulitis	NIV	40MG BD	1GM in 100ml NS od	tocilizumab	given	cpap 90/12/18 spo2 -90%	50mg	2,39,000	17.1	>5000	4616	1120	9245	51.2	>5000	224	1560	66-0	7.4	38.8	84	96.6	24.8	93.3	7.46	35	49.1	86.6	24.2	CPAP- 80/10/14 spo2 -85	61.25	14	0	0	14	-	-	expired
1022761	HK	61	F	sorethroat , fever x 3 days , breathlessness x 1 day	08-09-2020	infiltrates on the right side	GGO , Patchy infiltrates on rigth side	5	12 on 25	hypothyroidism , AKI , anemia	face mask , NIV	40mg bd	40mg bd	plasma	given on alternate days	cpap -90/8/14 spo2 -95-96%	40mg	1,69,000	285.6	1050	138.3	1280	465	1206	2890	107	890	340	7.4	31.7	80	99.4	20.3	88	7.4	31.7	82.5	96.5	21.1	cpap 60/8/10 spo2-93%	165	15	3	15	12	-	pupura in right upper limb	recoovered , o2 reduced to 40 %
1022359	TU	38	M	fever , breathlessness x 5 days	03-09-2020	b/l infiltrations	GGO, crazy paving pattern	5	8 ON 25	-	face mask,NRBM,HFNO,NIV	40MG BD	500MG IN 100ML NS 1-0-0	---	given	hfno - fio2 90 % spo2-985	40mg	3,20,000	166	1364	54.65	335.3	930	112	1069	34	342	526	7.4	32.2	61.6	91	20.3	68.4	7.4	35.6	44.1	97	24	cpap- 100/12/14 spo2-98%	44.1	30	10	28	10	9	-	recovered , o2 reduced to 405
1023361	S	44	M	fever , cough,breathlessness X 5 days	17-09-2020	b/l infilttrates	GGO	5	20/25	-	NRBM, HFNO,NIV	40MG BD	40MG	tocilizumab	given	CPAP -90/8/12 , spo2-96%	50MG	2,29,000	189	6032	208	39	692	221	4654	96.6	554	692	7.4	34.2	61.6	91.4	21.8	68.4	7.5	28	70.4	95	25	hfno - 60l , fio2 50% spo2 -91%	140	`13	4	12	5	6	ecchymosis , derranged coagulation profile	recovered
1021918	S	72	F	cold,x 2 days , fever and breathlessness x 1 day	28-08-2020	b/l consolidation	GGO,b/l consolidation	5	11 on 25	HTN , T2DM	NIV	40mg bd	1gm iv in 100ml NS x 5 days	-	given	CPAP-100/10/14 SPO2-96%	40MG	1,59,000	112	1220	87.6	800	591	19	4900	88	542	678	7.3	31	63.6	82	17.3	63.6	7.3	30	50	60	17	CPAP - 100/6/10 SPO2-88 %	50	6	0	0	6	-	nasal bleed	expired
1024729	SK	84	F	fever , cough , breathlessness , giddiness x 4 days	05-10-2020	b/l infiltrates	GGO, crazy paving pattern	5	13 on 25	HTN , T2DM	NRBM,HFNO,NIV	40MG	500MG X 3 DOSES -->40MG	plasma	given	CPAP- 100/10/12 SPO2-90%	40MG	2,02,000	93.1	1420	110	347	795	112	1567	222	765	876	7.5	28	46.4	87	33	46	7.35	39	65.6	90	21.2	CPAP-100/10/12 SPO2-75%	65	15	0	0	12	-	-	EXPIRED
1022737	SP	55	M	cough, breathlessness x 2 days	08-09-2020	b/l consolidation	GGO, B/L consolidation	5	20/25	HTN	NIV	60MG	1GM IN 200ML NS	tocilizumab	given	CPAP - 90/8/12 spo2-90%	40mg	1.89,000	124	>5000	4.9	39.4	387	50	849	105	193	120	7.3	28	55	60	32	61						cpap-90/12/14 spo2-100%		29	0	0	22	6	-	EXPIRED