A CROSS SECTIONAL STUDY OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS AND ITS OUTCOME IN COVID 19 PATIENTS OF TERTIARY HEALTH CENTER.

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Department Of General Medicine

Govt.Stanley Medical College, Chennai

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Chennai

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled "**A CROSS SECTIONAL STUDY OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS AND ITS OUTCOME IN COVID 19 PATIENTS OF TERTIARY HEALTH CENTER**"presented here is the original work done by **DR.SANJEEV KUMAR** in the Department of General Medicine, Government Stanley Medical college and Hospital, Chennai -600001, in partial fulfillment of the University rules and regulation for the award of **M.D. DEGREE BRANCH-I GENERAL MEDICINE** - under my guidance and supervision during the academic period of 2020-2023

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DECLARATION

I, Dr.sanjeev kumar solemnly declare that dissertation titled " **A CROSS SECTIONAL STUDY OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS AND ITS OUTCOME IN COVID 19 PATIENTS OF TERTIARY HEALTH CENTER.** is a bonafide work done by me at Government Stanley medical college and Hospital Chennai, during April 2021- January 2022 under the guidance and supervision of **Prof. Dr. G. Ranjani, M.D.,** Professor of Medicine,Government Stanley Hospital, Chennai. I also declare that this bonafide work or a part of this work was not submitted by me or any other foreword, degree or diploma to any other university, board in India or abroad.

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University, toward the partial fulfillment of requirement for the award of M.D. Degree (Branch-I) in General Medicine.

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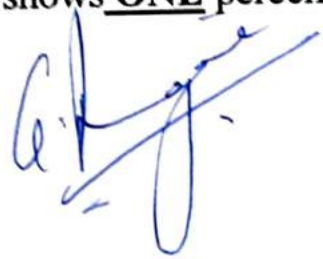

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ABSTRACT:

BACKGROUND:

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) that causes coronavirus disease-2019 (COVID-19) is a global pandemic, manifested by an infectious bronchopneumonia. Patients primarily present with fever, cough and breathing difficulty, some patients also develop gastrointestinal (GI) manifestations and hepatic enzyme Elevations. The most common GI symptoms reported are diarrhea, nausea,vomiting, and abdominal discomfort etc.

The digestive symptoms of COVID-19 likely occur because the virus enters the target cells through ACE 2 (angiotensin converting enzyme 2), a receptor found in both upper and lower gastrointestinal tract.Receptor is expressed at nearly 100-fold higher levels than in respiratory organs. SARS CoV-2 viral components found in the stool sample,which originated from infected intestinal cells particularly patient's ileum and colon.

The ACE 2 expression on intestinal enterocytes makes both the small and large intestines susceptible to SARS CoV-2 infection. In addition, viral nucleic acid is detected in feces in over half of the patients infected with COVID-19 and in nearly one-quarter of cases stool samples test positive when respiratory samples are negative.

Digestive symptoms indicate viral load and replication within the gastrointestinal tract.

Liver biochemistry abnormalities are Elevation of aspartate transferase, alanine transferase, and total bilirubin. Direct assault of SARS-CoV-2 on hepatocytes, leading to

abnormal liver enzyme level, SARS-COV-2 can invade the human body by binding to the human angiotensin converting enzyme 2 (ACE2) receptor, which causes liver tissue injury by the up regulation of ACE-2 expression in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells.

Preliminary study revealed a high level of ACE2 expression in cholangiocyte, also which suggesting an indirect cause of elevated liver enzymes as cholangiocyte dysfunction .

Another possibility in covid patients with extra pulmonary symptoms reported later for care because they did not initially have typical respiratory symptoms, and thus presented at a later and less curable stage of disease.

PRIMARY OBJECTIVES:

To determine the prevalence of gastrointestinal and hepatic manifestations in SARS-Cov-2 patients

To investigate the gastrointestinal and hepatic manifestations and its outcome in SARS-CoV-2 patients .

MATERIALS AND METHODS:

This is the **Descriptive Cross – Sectional Study**,which was conducted over a period of 1 year from april 2021 to january 2022.Patients selected for this study from COVID OP and COVID Ward in Government Stanley medical college and hospital,Chennai.Patients were selected based on inclusion and exclusion criteria.

Sampling was done **by SIMPLE RANDOM SAMPLING** technique. Relevant data were collected and analysed.

RESULTS: Primary symptoms distribution were 84.0% is Fever, 6.0% is Sore throat, 37.7% is Dry Cough, 41.9% is Expectoration, 25.7% is Chest Tightness, 14.1% is Shortness of Breath, 14.1% is Dizziness, 10.9% is Headache, 33.8% is Myalgia.

GI symptoms distribution were 18.0% is Diarrhea, 7.7% is Nausea, 6.0% is Vomiting, 9.9% is Abdominal Pain, 15.8% is Loss Appetite, 19.7% is Loss of Taste.

Hepatic enzyme Elevation distribution were 23.9% is SGPT, 23.9% is SGOT.

Complications distribution were 81.7% is Pneumonia, 1.8% is Acute Respiratory Distress Syndrome,

2.8% is Arrythmias, 2.8% is Shock, 1.8% is Acute Heart Failure.

Outcomes distribution were 19.7% is Outpatient Recovered, 53.5% is Discharge From Hospital, 19.7% is Staying in Hospital, 6.7% is Death.

CONCLUSION:

Patient affected with Gastrointestinal symptoms are mostly recovered completely, They are usually mild cases.

Mild covid affected patients showed mild hepatic enzyme Elevation.Although,Patients with more than 3 to 4 fold raise of hepatic enzyme Elevation had mild to moderate covid disease,but their outcome was good.

A CROSS SECTIONAL STUDY OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS AND ITS OUTCOME IN COVID 19 PATIENTS OF TERTIARY HEALTH CENTER

Introduction:

In 1960,Human corona viruses were discovered. At the end of 2019,a novel coronavirus was identified as the cause of cluster of pneumonia cases in Wuhan, a city in the Hubei Province of china.

Two genera,Seven strains of corona viruses causes diseases.

Alpha include Human corona virus 229E (HCoV-229E), human corona virus NL63(HCoV-NL63)

Beta include Human corona virusOC43(HCoV-OC43),human corona virus HKU1(HCoV-HKU1), cause mild disease[1].

It rapidly spreads,resulting in an epidemic throughout china,followed by increasing number of cases in other countries.In february 2020,WHO designated the disease COVID-19,which stands for coronavirus disease 2019[2].

SARS-COV-1,MERS-CoV,SARS-COV-2 may potentially cause severe disease.

SARS-COV-1 and SARS-COV-2 have similar genomic sequences and both viruses use angiotensin converting enzyme 2 (ACE2) as an entry receptor.It was abundantly expressed in lung cells but also on enterocytes of ileum and colon[3].

Viral RNA has been isolated from stool sample of COVID 19 patients.Severe acute respiratory syndrome corona virus 1 and middle east respiratory syndrome related corona virus infection may affect the gastrointestinal infections[4].

Corona viruses are important human and animal pathogens. It causes covid-19 is designated as severe acute respiratory syndrome corona virus 2(SARS-COV-2). Corona viruses are positive stranded-RNA enveloped viruses[5].

Direct Person to person respiratory transmission is main mode of SARS-CoV-2 transmission.It occur mainly through close range of contact with respiratory particles.(I.e.within approximately two meters or six feet)[6].

When an infected person coughs, sneezes,talks might infect another person if secretion is inhaled or direct contact with mucus membrane, and might also occur if a person hand contaminated with these secretions or by touching contaminated surfaces[7]. GI manifestations are reported in 11–61% of individuals with COVID-19, with different onset and variable severity. The majority of COVID-19-associated GI symptoms are mild to moderate and self-limiting and include anorexia, loose stools, nausea, vomiting and abdominal pain/discomfort. A minority of patients present with an acute abdomen with etiologies such as acute Pancreatitis, acute appendicitis, intestinal obstruction, bowel ischaemia, hemoperitoneum or abdominal compartment syndrome[8].

Severe acute respiratory syndrome cov-2 RNA has been found in biopsies from all parts of the alimentary canal.COVID-19 is affects mainly respiratory system.however,it can

cause significant impact on the gastrointestinal system. prevalence of GI symptom is approximately 17.8%(95% confidence interval, 12.3%-24.5%).

The virus is excreted in faeces during the acute disease even after the nasopharyngeal swab has become negative for viral Ribonucleic acid(RNA)[9].

Fecal viral excretion have clinical significance,possible feco-oral transmission of the infection.The digestive symptoms of COVID-19 likely occur because the virus enters the target cells through angiotensin-converting enzyme 2 , a receptor found in both the upper and lower gastrointestinal tract where it is expressed at nearly 100-fold higher levels than in respiratory organs[10].

The viral components found in the stool sample likely originated from infected enterocytes of the patient's ileum and colon. As previously mentioned, the expression of ACE2 on intestinal Enterocytes makes both the small and large intestines susceptible to SARSCoV-2 infection[11].

In addition, viral nucleic acid is detected in feces in over half of the patients infected with COVID-19 and in nearly one-quarter of cases' stool samples test positive when respiratory samples are negative[12].

10.5%-53% of patients with covid 19 particularly those with severe disease have been shown to have an Elevation of hepatic enzymes though biochemical and clinical jaundice are uncommon. Direct assault of SARS-CoV-2 on hepatocytes, leading to abnormal liver enzyme level, SARS-COV-2 can invade the human body by binding to the human angiotensin converting enzyme 2 (ACE2) receptor, which causes liver tissue injury by the

upregulation of ACE-2 expression in liver tissue caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells[13].

Preliminary study revealed a high level of ACE2 expression in cholangiocytes, also which suggesting an indirect cause of elevated liver enzymes as cholangiocyte dysfunction[14].

Abnormal levels of liver chemistries have consistently shown to be more prevalent in severe disease .when severity of the disease increases, digestive symptoms become more pronounced. digestive symptoms indicate viral load and replication within the gastrointestinal tract, which leads to more severe disease[15].

Watery loose stools is the most common GI symptom (20.3%) on covid 19 presentation.

(5.8%) presented with fever and loosestools in the absence of respiratory symptoms in covid 19 patients. The watery diarrhea without blood or mucus, Abdominal pain was mild in most cases. Of the remaining patients who did not report diarrhea on presentation, some patients developed symptoms of watery diarrhea during hospitalization.

There was no correlation between diarrhea on presentation with requirement of oxygen and mortality. However patients who had diarrhea during the course of illness had a higher percentage requiring ventilatory support (26.4% vs. 8.2%; $P = 0.004$) and higher admission rate to the ICU (49.0% vs. 11.8%; $P < 0.001$). There was no other identifiable pathogen, including *C. difficile* toxin, detectable in the stool of patients with diarrhea.[16]

AIMS AND OBJECTIVES

AIMS:

To determine the prevalence of gastrointestinal and hepatic manifestations in

SARS-Cov-2 patients

To assess the association of gastrointestinal manifestation with severity of illness.

OBJECTIVES:

To investigate the gastrointestinal and hepatic manifestations and its outcome in SARS-CoV-2 patients .

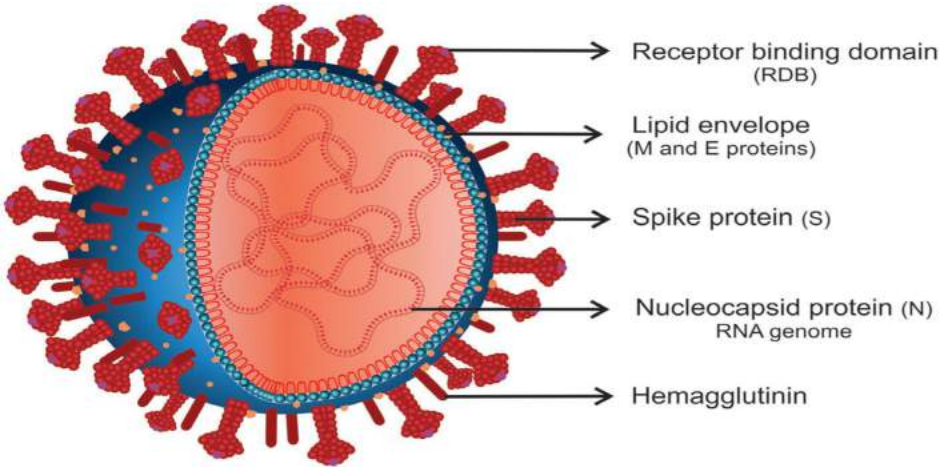
REVIEW OF LITERATURE:

VIROLOGY:

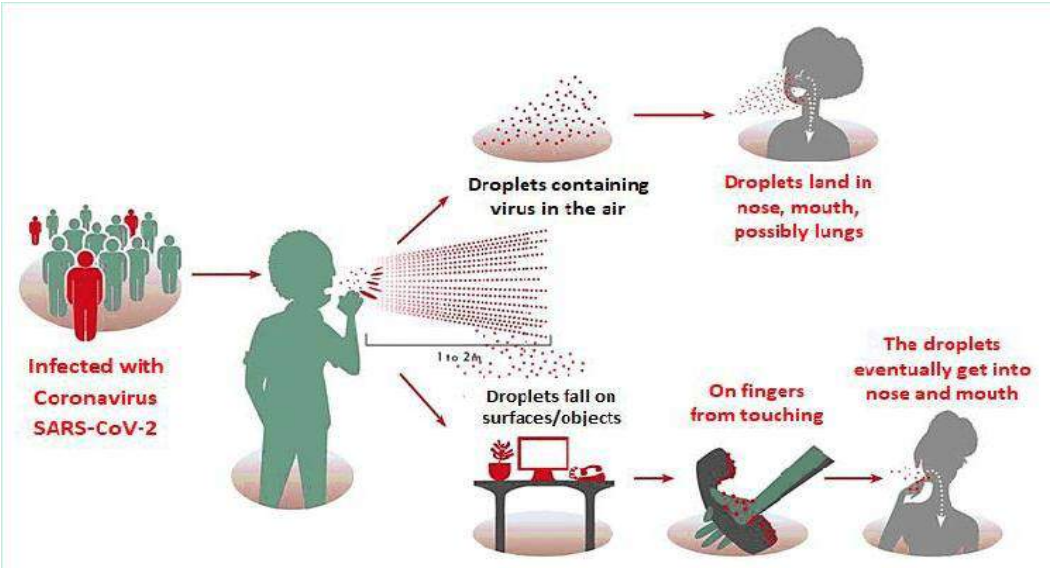
Corona viruses,so named because they looked like halos when viewed under the electron microscope, corona viruses are a large family of RNA viruses.The typical generic corona virus genome is a single strand of RNA,32 kilo bases long and is the largest known RNA virus genome[17].

The virus particle are organised with long RNA polymers in the center and surrounded by a protective capsid protein. These proteins are called nucleocapsid(N). The corona virus core particle is further surrounded by an outer membrane envelope made of lipids and derived from host cell but are modified to contain specific viral proteins,including the spike(S),membrane(M) and envelope (E) proteins.SARS-Cov-2 is sensitive to ultraviolet radiation and heat treatment at 56°C for 30 minutes,at a higher temperature of 65°C Virus inactivates in 7-10 minutes[18].

It remains sensitive to most disinfectants,including household bleach, 1% sodium hypochlorite, povidone iodine, chlorhexidine, benzalkonium chloride, ethanol 70%, chlorine and peracetic acid[19].



VIRAL TRANSMISSION:



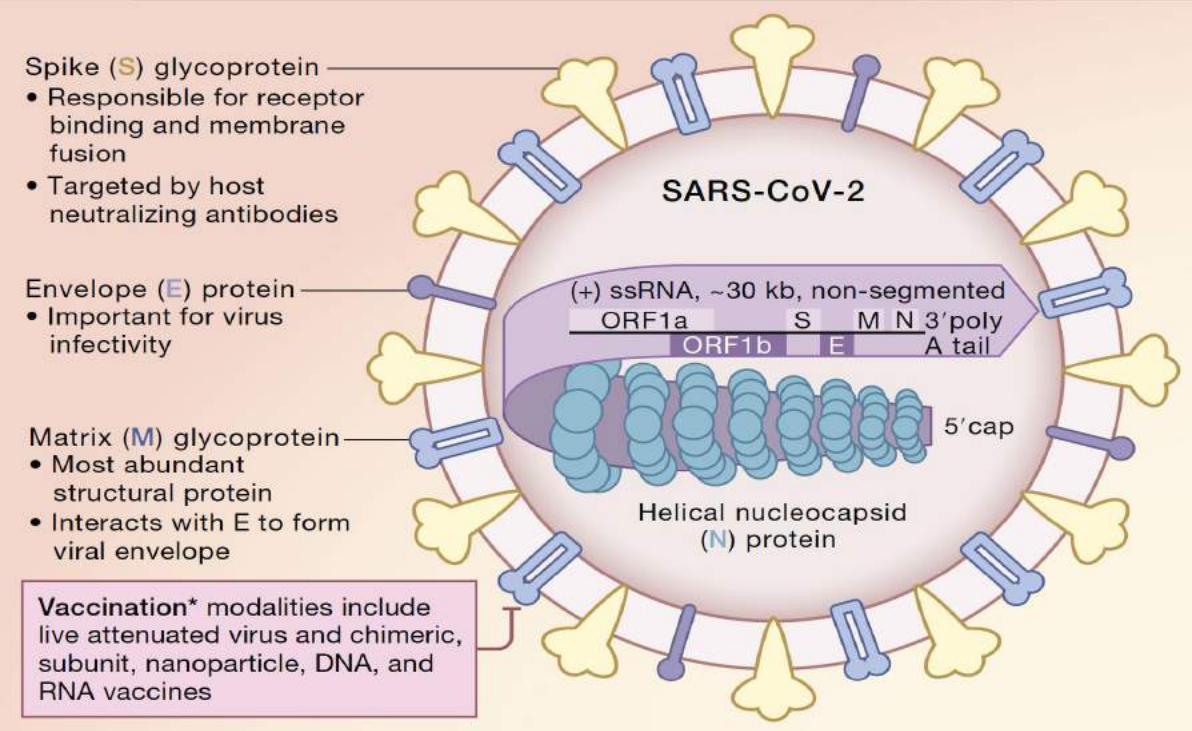
VIRAL TRANSMISSION:

Severe acute respiratory syndrome (SARS) coronavirus spread primarily by route of inhalation (via droplets, droplet nuclei, and aerosols). Droplets are respiratory particles of larger diameters, which settle rapidly within the vicinity of the source, i.e.,

approximately 1–2 meters. Aerosols are smaller (< 5 μm in diameter), stay suspended in air for longer duration and aerosols are carried over a longer distance. Coronavirus can be transmitted by this airborne route, when aerosol-generating procedures are performed. The debate about whether the virus is transmitted by droplets or aerosols should not be encouraged as the transmission is not binary but spread across a spectrum. A wide variation in the size of respiratory particles carrying the virus has been found during activities like breathing, speaking, coughing, sneezing, singing, and exercise. Transmission is also influenced by multiple factors like ventilation, humidity, and temperature.

Direct person to person transmission of respiratory secretions is the primary means of transmission of SARS-Cov-2. It occurs mainly through close range contact(I.e., within approximately six feet or two meters)via droplet particles when an infected person cough, sneezes or talks, and can infect another person if it is inhaled or makes direct contact with in the mucus membranes.

Air borne transmission of SARS-Cov-2 is not well established.It has been detected in non respiratory specimens,including stool,blood,eye specimen and semen, but the role of these sites in transmission is uncertain[20].



MUTANT STRAINS OF SARS-COV-2:

SARS-Cov-2 genome ranges between approximately 26,000 and 32,000 bases.

Multiple SARS-Cov-2 variants are circulating globally; a variant of SARS-Cov-2 with a D614G substitution in the gene encoding the spike protein emerged as early as late January 2020.Over a period of several months,the D614G mutated strain replaced the original SARS-Cov-2 Wuhan strain and by June 2020 became the dominant form of the virus circulating globally[21].

Variants include:

1. UK variant (B.1.1.7): This COVID-19 variant appeared in September 2020 in Leeds, UK and it spreads more easily and has an increased risk of death.It is neutralized by antibodies generated by existing COVID vaccines.

2. South african variant (B.1.351):this variant appears to spread more easily.it is not neutralized by antibodies generated by a previous COVID-19 infection or a COVID-19 vaccine.

3. US California variants B(1.427) and B(1.429):these appear to spread more easily.

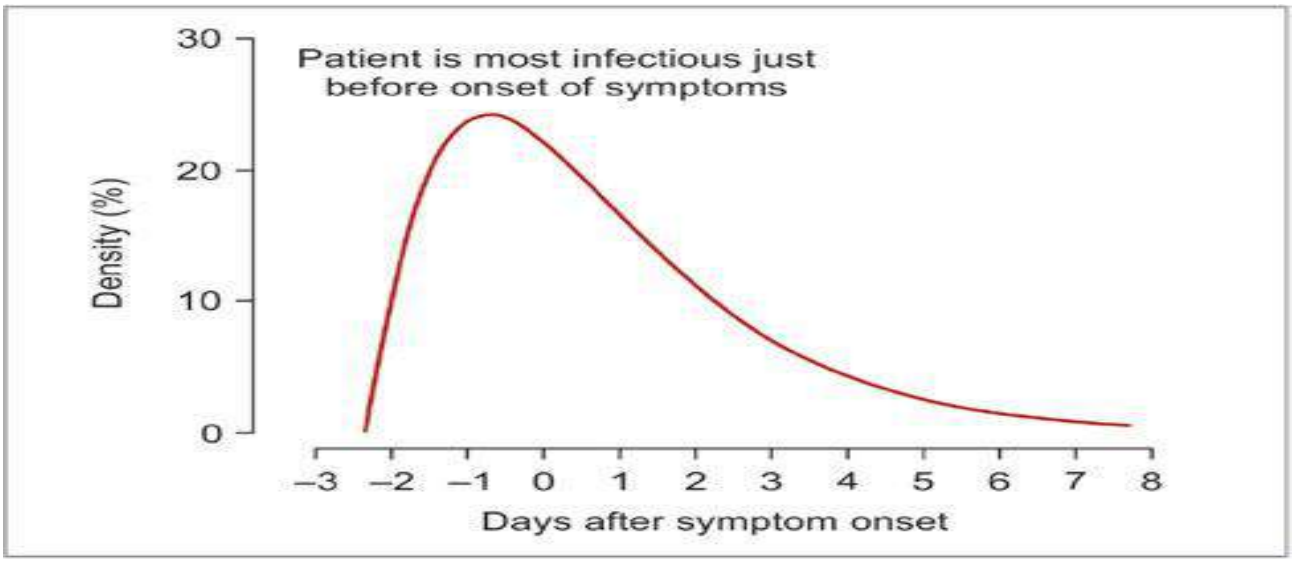
4. Indian double mutant variant B(1.617):the India SARS-Cov-2 consortium on Genomics (INSACOG) is a group of 10 national laboratories has been established by ministry of health and family welfare.INSACOG is carrying out genomic sequencing and analysis of circulating COVID-19 viruses and correlating epidemiological trends with genomic variants[22].

LABORATORY DIAGNOSIS OF COVID 19:

TRANSMISSION DYNAMICS AND SAMPLE COLLECTION:

Maximum viral shedding occurs 5–8 hours before onset of symptoms and culturable virus can be isolated for next 6–8 days and patient is infectious during this phase.

Replication competent virus has not been recovered after 10 days following symptom onset . As per national guidelines for routine COVID-19 screening, two reverse transcription polymerase chain reaction (RTPCR) swabs test should be done—nasopharyngeal (NP) and oropharyngeal (OP) swabs are collected and transferred in viral transport media (VTM). In order to properly obtain an NP swab specimen, the swab must be inserted deeply into the nasal cavity. Patients will likely flinch, during the sampling, that means the swab has hit the target[23].



Swabs should be kept in place for 10 seconds, while being twirled three times before taking it out. In case due to logistic reason only one swab can be collected; then always prefer NP over OP swab. However, for TrueNat testing as per manufacturer recommendation, only OP swab is collected in virus lysis media (VLM). Lower respiratory samples are better than upper respiratory samples and whenever possible, a lower respiratory tract specimen should be collected in intubated and mechanically ventilated patients.

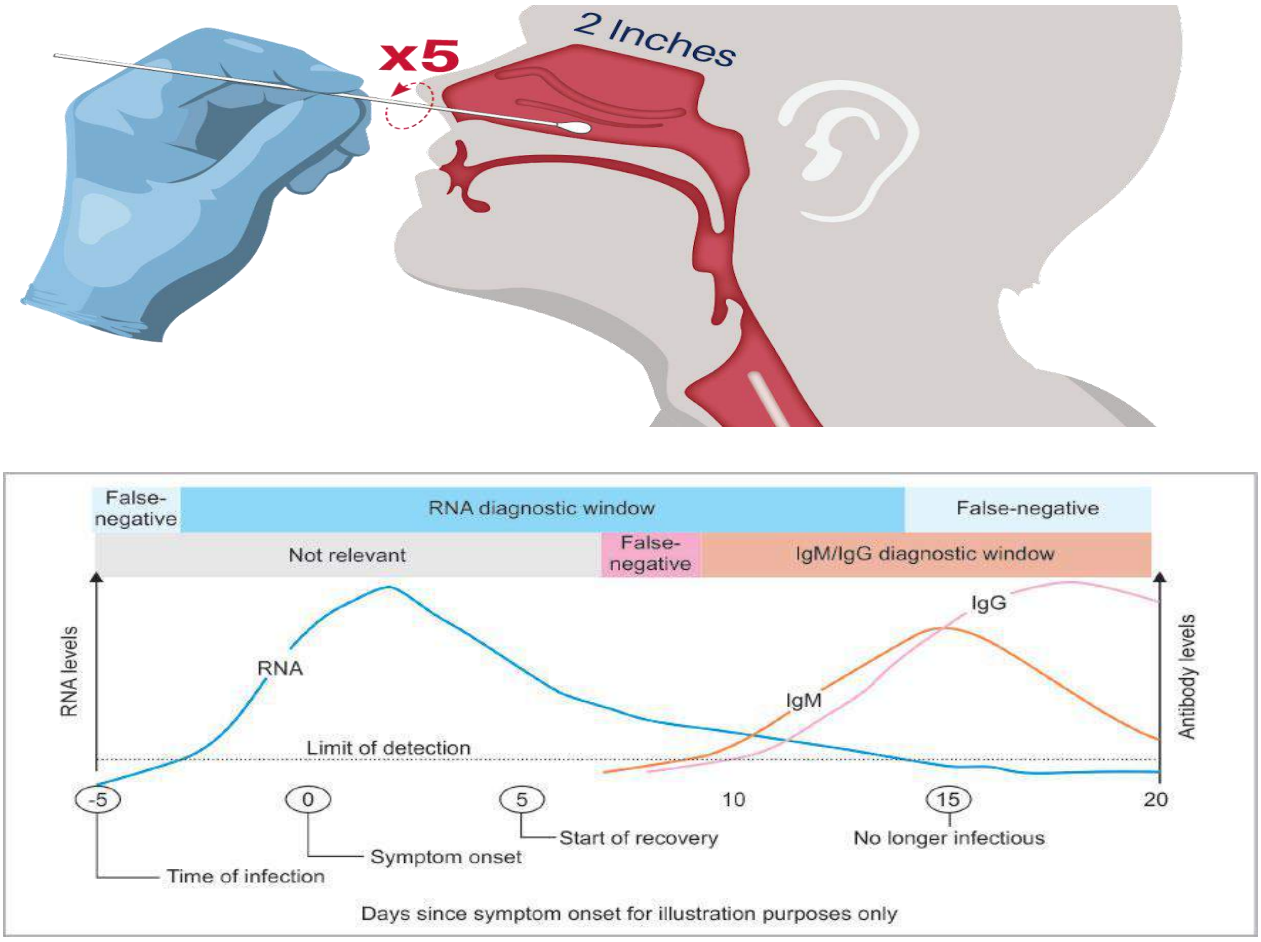
Bronchoalveolar lavage fluid specimens are considered as best sample for performing RTPCR. The collected sample is transported in cold chain at 2–8°C to microbiology laboratory.

Molecular Testing

The SARS-CoV-2 is an RNA virus and genome ranges between approximately 26 and 32 kilobases. These include genes encoding structural proteins such as glycoprotein spike

(S), envelope (E), nucleocapsid (N) and these genes are targeted in screening RTPCR testing.

In addition, there are species-specific accessory genes such as RNA-dependent RNA polymerase (RdRP), Open Reading Frame 1a (ORF1a) and Open Reading Frame 1b (ORF1b) which are highly conserved and used in confirmatory RTPCR testing .There are broadly three methods of testing: (1) direct, (2) indirect and (3) supplementary methods (**Table 1**).



Timeline of appearance of SARS-CoV-2 antigen, RTPCR and IgM/IgG antibodies.

Antigen Detection Test

Test to SARS-CoV-2 antigen is a point-of-care test and has to be conducted at patient bedside wearing complete personal protective equipment (PPE). Briefly a NP swab from patient is collected and added to a special buffer (company patented technology) and three drops of buffer are added to an ICT test strip, which gives positive bands similar to rapid HIV/HBV test. It is a useful test for individuals who are in the early stages of infection, when virus replication is highest and it remains positive for next 5–6 days.

Antigen detection is less sensitive then RTPCR and as per data provided by The Indian Council of Medical Research (ICMR), New Delhi the sensitivity of test is 50–60% with a high specificity of 95%. Thus, negative antigen test results in a symptomatic patient should be confirmed by RTPCR

Nucleic Acid Amplification Test

The diagnosis of COVID-19 is made primarily by direct detection SARS-CoV-2 RNA by nucleic acid amplification tests (NAATs) most commonly RT-PCR, followed by TrueNAT and CBNAT. Most NAATs target two or more genes, including screening genes such as the nucleocapsid (N), envelope (E), and spike (S) genes, and confirmatory genes regions in the first Open Reading Frame (ORF1a), including the RNA-dependent RNA polymerase (*RdRp*) gene[24].

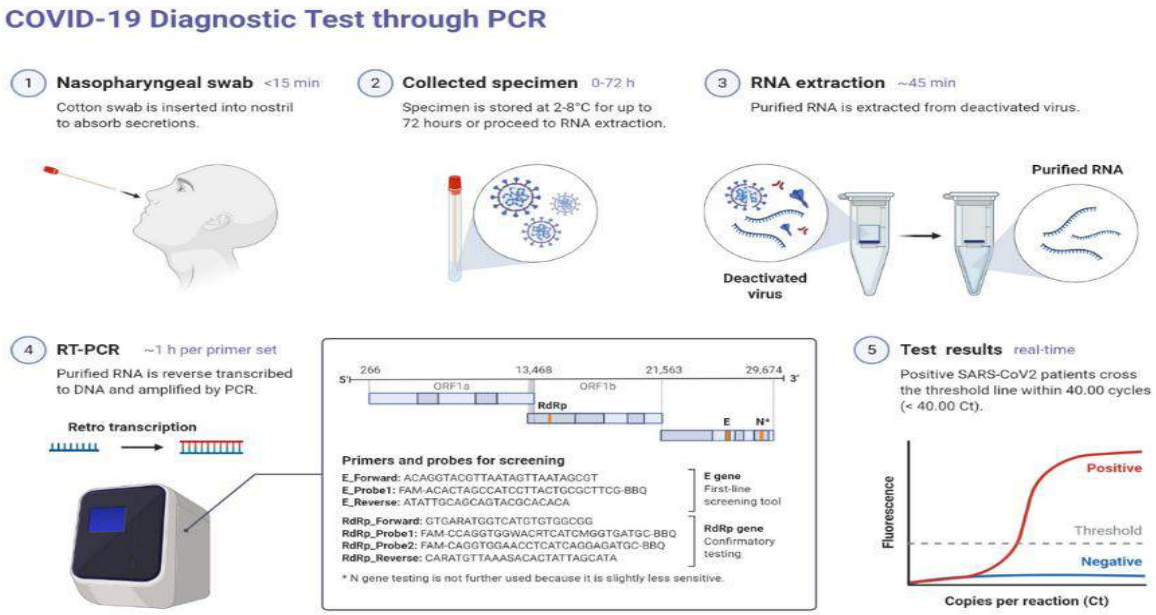


TABLE 1: Examples of various methods of laboratory diagnosis of COVID-19.

Type of test	Example	Uses
Direct	• Antigen detection • RTPCR (Reverse Transcriptase polymerase chain reaction) • Truenat • *Gene Xpert*: Cartridge-based nucleic acid testing (CBNAT)	Used for diagnosis of COVID -19
Indirect	Antibody detection	Not recommended for diagnosis. Useful for seroprevalence estimation
Supplementary	Chest X-ray, HRCT scan and other lab tests	Help in assessing the disease severity and prognosis

less common types of NAAT

isothermal amplification,

CRISPR-based assays, and

next-generation sequencing, etc.

The accuracy and predictive values of SARS-CoV-2 NAATs have not been systematically evaluated due to absence of another reference gold standard test. They are highly specific tests and NAATs have high analytic sensitivity in ideal settings (i.e., they are able to accurately detect low levels of viral RNA in test samples known to contain viral RNA), however clinical performance is more variable.

A positive RTPCR test generally confirms the diagnosis of COVID-19; no further diagnostic testing is necessary. A single negative RTPCR report is sufficient to exclude the diagnosis of COVID-19. However, false-negative RTPCR tests from upper respiratory specimens have been well documented in range of 20–30% cases. If initial testing is negative, but the clinical suspicion for COVID-19 remains high, a repeat the test . The optimal timing for repeat testing is 24–48 hours after the initial test.

If the laboratory reports indeterminate results, then the sample should be considered presumptive positive results and test should be repeated with properly collected sample. At present, there are no guidelines suggesting repeat RTPCR testing in recovered COVID-19 positive patients. Free of Symptoms is the most important aspect, repeat testing should not be done for those who had recovered and absence of symptoms.

TrueNat Testing for COVID-19:

It is a novel, simple and cost-effective point-of-care technique for COVID-19 diagnosis using the Truelab device (Molbio diagnostics pvt ltd, Goa, India).

TrueNat is a portable, light weight, real-time PCR based nucleic acid detection device, operated using a rechargeable battery power source. Briefly a single oropharyngeal swab is collected in Viral Lysis Medium(VLM) and shifted to laboratory at room temperature. RNA is extracted from sample using patented small RNA extractor fitted with machine, this step takes 20 minutes. The RNA is loaded on a disposable microchip, which comes with preloaded, room temperature stabilized PCR reagents enabling the user to just add the purified nucleic acid sample and start the test.

The software allows real-time monitoring of thermal cycling and PCR amplification. TrueNat chips targets screening E gene and confirmatory ORB1ab in a single chip and results are available (within 2 hours) faster turn around time[25].

Cycle Threshold in RTPCR:

RTPCR test based upon amplification of fluorescent signals,number of cycles that the fluorescent signal reach the threshold is called as cycle threshold.

As per (ICMR) guidelines,cycle threshold <35 considered as positive,more than 35 is considered as negative[26].

PATHOPHYSIOLOGY:

Coronaviruses are single-stranded RNA,enveloped viruses that infect a wide spectrum of hosts. The SARS-CoV-2 like the Middle East respiratory syndrome–related

coronavirus (MERS CoV) is a β Coronavirus. The virus has a diameter of 60–140 nm and has characteristic spikes on its surface, 9–12 nm in size. Person-to-person transmission of infection is through respiratory droplets and aerosols.

The SARS-CoV-2 has four vital structural proteins:

1. the spike (S),

2. membrane (M),

3. envelop (E) and

4. nucleocapsid (N).

Of these, the S protein (2 subunits—S1 and S2) is critical for attachment of the virus to host cells.

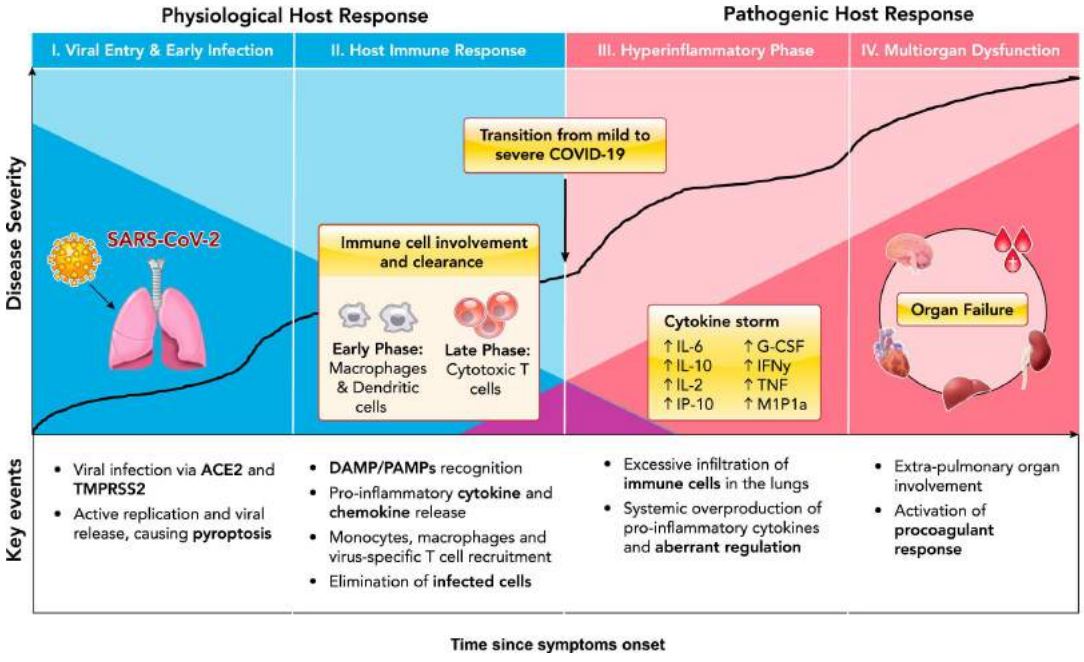
The virus gains entry into the host by binding to host receptors followed by cell entry through endocytosis. Angiotensin converting enzyme-2 (ACE2) has been identified as the principal host receptor for SARS-CoV-2. The S protein binds to the ACE2 receptor and facilitates viral entry into the host cell—the S1 unit helps in binding and the S2 subunit directs the endocytosis. Apart from the respiratory tract, ACE2 expression is also high in the heart, ileum, kidney, and urinary bladder. After gaining entry into the host cells, the virus uses the host cell machinery for translation of proteins and replication. The newly formed viral particles are released to invade new cells as well as serving to infect other susceptible hosts[27]

.Initial phase of infection, the nasal and bronchial epithelial cells and the pneumocytes are the target cells for the virus.

COVID 19 produce profound lymphopenia by three mechanism:

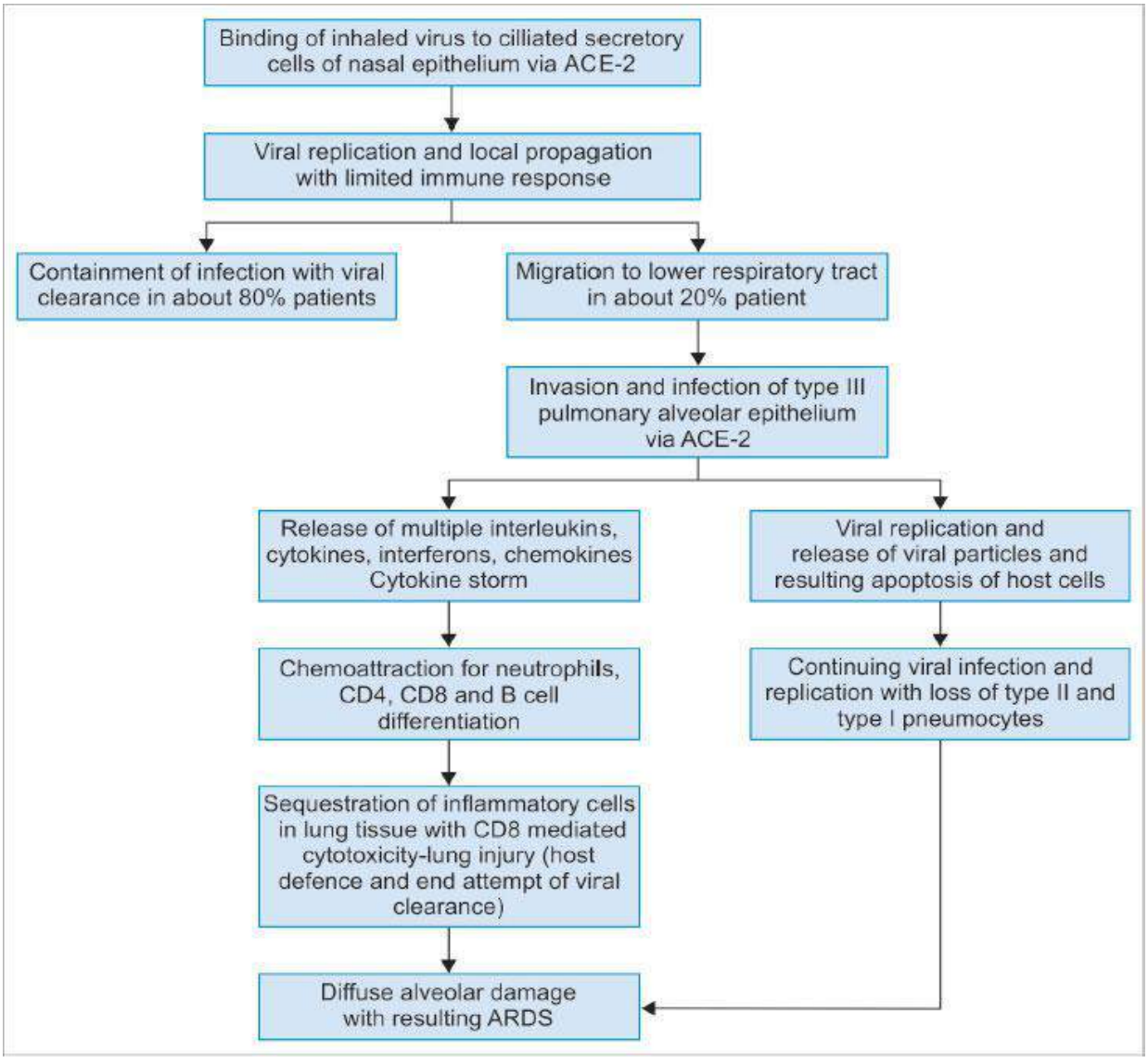
1. SARS-CoV-2 infects and kills the T-lymphocytes.
2. Suppressing lymphopoiesis by inflammatory response
3. Promoting lymphocyte apoptosis[38].

Later in the disease pathogenesis, the epithelial-endothelial barrier integrity of the lungs is compromised. The SARS-CoV-2 now infects the pulmonary capillary endothelium which augments the inflammatory response. This leads to infiltration of the air spaces by the infiltrating mononuclear cells and macrophages and alveolar and interstitial edema[28]



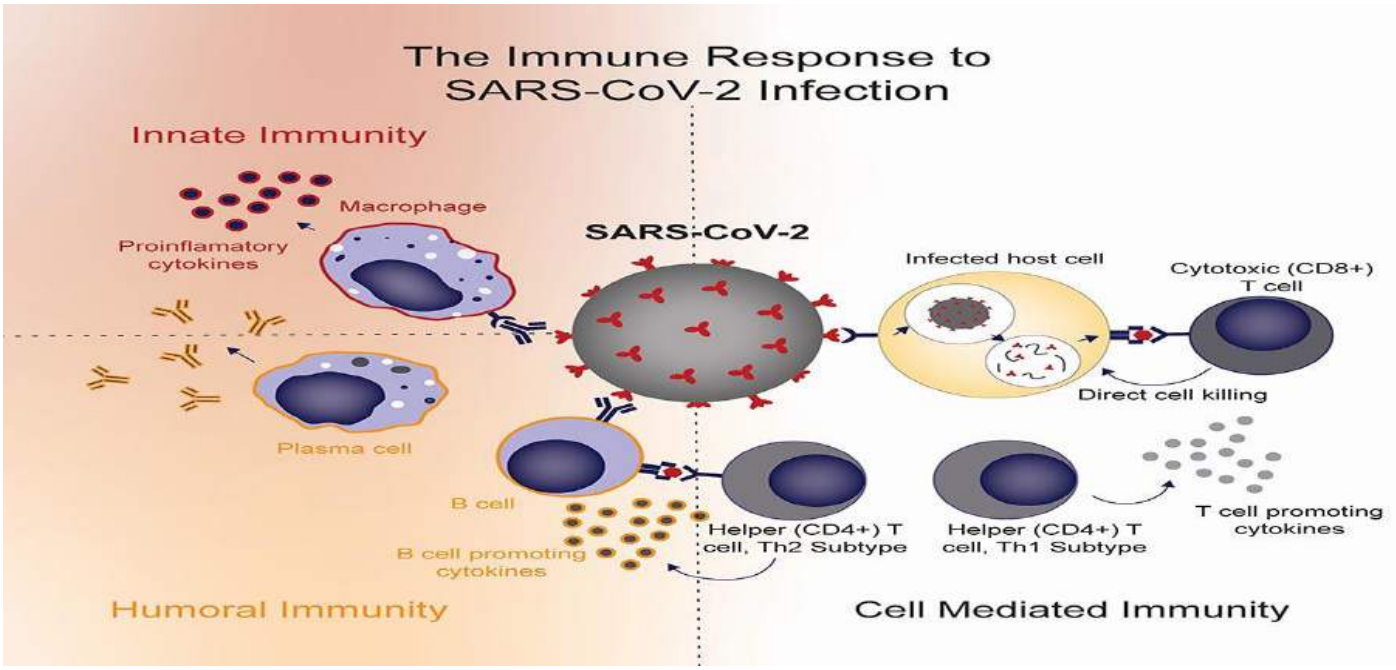
This is responsible for the characteristic ground glass opacities observed on radiology in these patients.

Further, these damaged type II pneumocytes trigger a cascade inflammatory response (local and systemic). Due to this exuberant release of cytokines, it is called as cytokine storm. There is extensive tissue damage due to a systemic inflammatory response syndrome. Additionally, there is also widespread activation of pro coagulant factors resulting in micro thrombi in various tissues ultimately leading to multiple organ dysfunction syndrome (MODS)[29].



IMMUNLOGY:

The immunology of COVID-19 is still being unraveled as we learn more about the pathogen and its intricate mechanisms. Similarities between the immune responses to SARS-CoV-2 and other corona viruses have helped us in understanding its immunological mechanisms.



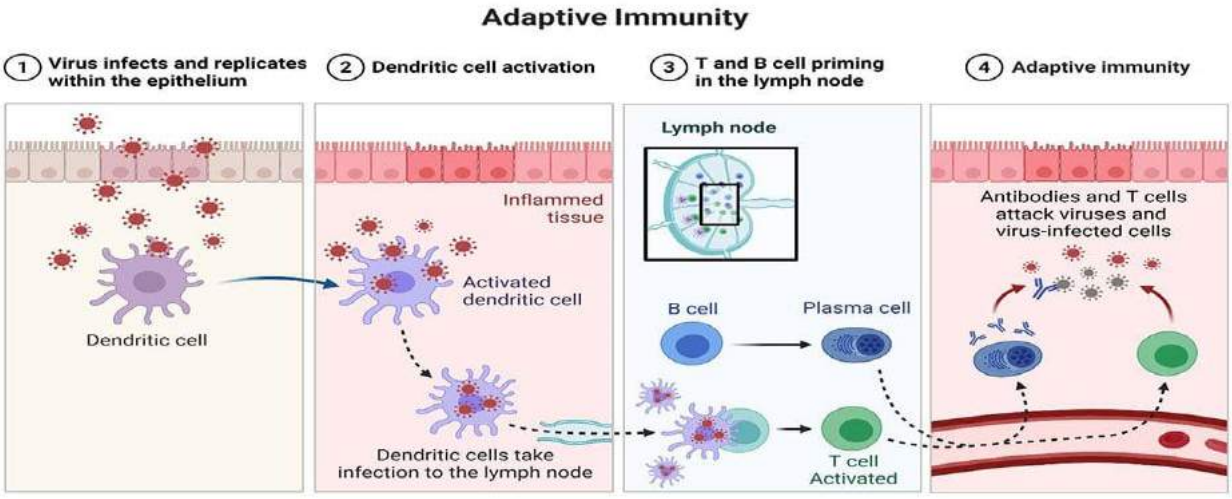
Innate Immunity and COVID-19

Innate immunity is the first line of defense against virus invasion. The dendritic cells, macrophages, and neutrophils are the first line of defense and initiate the initial immune reaction upon entry of SARS-CoV-2. The spike glyco proteins (S protein) on the viral

envelop binds to its receptor, ACE2, on the surface of human cells to gain entry. This virus entry activates the intra cellular pattern recognition receptors (PRRs) that sense the virus associated molecular patterns, such as double-stranded ribonucleic acid (RNA) or uncapped mRNA. This triggers the cascade of the cytolytic immune responses, mainly through the type I interferons (IFN) and natural killer cells. Interleukin 6 (IL-6), IL-18 are also released[30].

Adaptive Immunity

Adaptive immunity plays a major role in the clearance of SARS-CoV-2 from the body and consists of cell mediated immunity and humoral immunity.



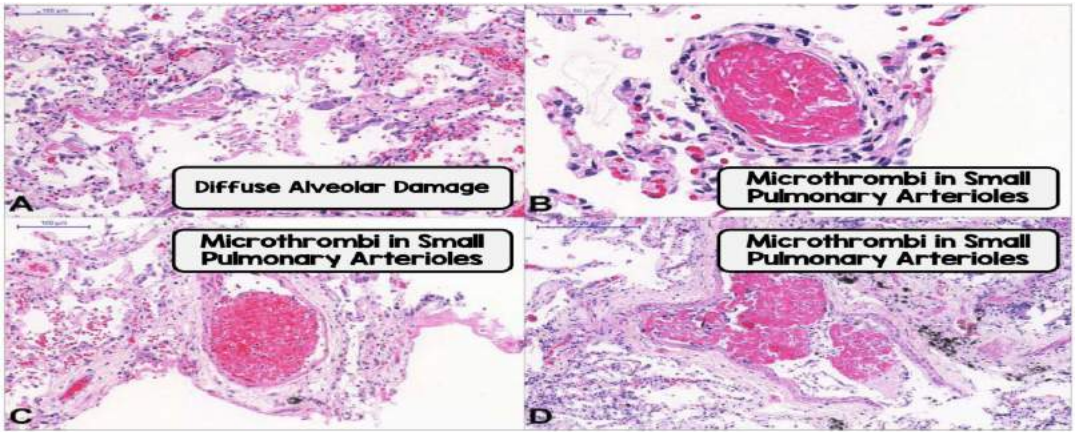
The activated cytotoxic T cells destroy the virus-infected cells and the antibody-producing B cells target the virus specific antigens. SARS-CoV-2, down regulates the major histocompatibility complex (MHC) class I and II molecules, which inhibits the T-cell mediated immune responses. Patients with COVID-19, have been reported to have lower total lymphocyte counts and higher plasma concentrations of a number of inflammatory cytokines such as IL-6 and tumor necrosis factor (TNF). CD4+ helper T

cells, CD8+ cytotoxic T cells, and natural killer cells are all significantly reduced in patients with severe COVID-19 infections. The proinflammatory T cell subsets and cytotoxic T cells are increased. This is thought to be responsible for the severe immune injury.

The antiviral immune response is crucial to eliminate the invading virus, but a robust and persistent antiviral immune response might also cause massive production of inflammatory cytokines and damage host tissues. The overproduction of cytokines caused by aberrant immune activation is known as a cytokine storm. In fact, in the late stages of COVID-19, cytokine storms are a major cause of disease progression and eventual death. Increased plasma concentrations of both Th1 (e g., IL-1β and IFNγ) and Th2 (e.g., IL-10) cytokines are observed.

The stimulation of the humoral and cellular immune response is exerted by virus-specific B and T lymphocytes, respectively. Antibody response against SARS-CoV viruses has a typical immunoglobulin pattern. Most of the patients develop antibodies after 7 days of disease onset.

By day 15 of the disease onset, IgM and IgG antibodies are detected in about 94.3% and 79.8% of the patients. The COVID-19 specific IgM antibodies may disappear at the end of the 3rd month. In contrast, the IgG antibody may persist longer, indicating that IgG antibodies are likely to be protective. SARS-specific IgG antibodies are predominantly against the S- and N-proteins. It has been shown that COVID-19 patients generate SARS-CoV-2 specific neutralizing antibodies. Neutralizing antibodies block the virus from entering the host cells and play a critical role in virus clearance[31].



Pathology in the Lungs

The lungs are the most important organs involved in COVID-19. There are autopsy-based studies that have helped in elucidation the histopathological changes in COVID. The microscopic features in the lungs depend on stage and severity of the disease. In the early stages the lungs show nonspecific changes including focal pneumocyte hyperplasia, focal chronic inflammatory infiltrate and multinucleated giant cells with absence of hyaline membrane formation. With increasing severity, diffuse alveolar damage, edema, and vascular changes including microvascular damage, thrombi, intra-alveolar fibrin deposits, features of acute fibrinous and organizing pneumonia are also seen. With more long standing and severe disease, fibrotic changes like interstitial fibrosis usually appear by 3 weeks after the onset of symptoms[32].

Pathology in Other Organs

Other than the lungs, SARS-CoV-2 has been detected in other organs, including the heart, liver, kidneys, gastrointestinal tract, spleen, lymph nodes, skin, and placenta. The pathological findings in these organs on autopsy studies are generally nonspecific.

Clinical Manifestations:

COVID-19 typically presents as an acute respiratory illness.

***Incubation period*:** The median incubation period of COVID-19., i.e., time from exposure to onset of symptoms is 4–5 days and the maximum period is believed to be 14 days. More than 97.5% of patients will have symptom onset by 11.5 days of exposure[33].

The common clinical manifestations of COVID-19 include:

- Fever with/without chills
- Cough
- Fatigue and generalized weakness
- Myalgias or body aches
- Headache
- Sore throat
- Coryza
- Nausea/Vomiting
- Diarrhea
- Shortness of breath or difficulty in breathing
- New loss of taste or smell

The symptoms of the disease vary in different patients and also vary with disease severity. For example, many patients with COVID-19 are completely asymptomatic, while shortness of breath or dyspnea is a sign of moderate- to-severe illness. Most infected people experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other nonspecific symptoms, such as sore throat, nasal congestion, headache, diarrhea, nausea and vomiting, have also been reported. Loss of smell (anosmia) or taste (ageusia) has been commonly reported, in nearly one-third of patients especially among women and younger or middle-aged patients. In some reports, anosmia and ageusia have been reported in nearly 60% of all patients[42]. In fact, many patients have been diagnosed to have COVID-19 after manifesting these two symptoms alone. It is important to note that the loss of smell and taste are not permanent and most people recover full function though recovery may be delayed to nearly 12 months in some patients. Dermatological or skin manifestations ranging from maculopapular to urticarial rash, and vesicular lesions have been reported though none is pathognomonic for the disease. Unusually, COVID toes, reddish-purple nodules on the distal parts of the digits have also been described. The neurological manifestations of COVID-19 are dizziness, agitation, weakness, seizures, or stroke. Atypical manifestations such as fatigue, reduced alertness diarrhea, and absence of fever are more likely in older people and patients with immunosuppression.

The clinical spectrum of COVID-19 infection varies from asymptomatic infection to mild, moderate to very severe disease[34].

Asymptomatic Infection

Asymptomatic COVID-19 infection is well documented and it is estimated that nearly one-third of infected patients remain entirely asymptomatic. This incidence is variable, from 43 to 77% asymptomatic infections are reported. Asymptomatic infections tend to occur more in younger people. Although these patients may not report any symptoms at all, objective signs like classic radiological findings on a chest X-ray or computed tomography (CT) scan are reported in them.

Clinical Course of Symptomatic COVID-19

The COVID-19 produces a spectrum of clinical manifestations that vary from mild to very critical and fatal disease. The clinical spectrum has been categorized into mild, moderate, and very severe on the basis of clinical criteria and oxygenation status. It is important to recognize that most patients will have mild disease and have a very good outcome.

Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) ≥94% on room air at sea level.

Severe illness: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

The Ministry of Health and Family Welfare, Government of India COVID guidelines on assessment of severity are summarized in **Table 2**.

The categorization of clinical severity not only assigns a prognosis to these patients, these categories also help in the stratification of these patients into the kind of clinical care that they need and deserve, such as home based care, hospitalization, intensive care, etc.

The Chinese Center for Disease Control and Prevention in a report on >44,000 patients observed that mild disease (no or mild pneumonia) was reported in 81% of patients. Critical disease (e.g., those with respiratory failure, shock, or MODS) was reported in 5%. The overall case fatality rate was 2.3%. The United States Centers for Disease Control and Prevention (CDC) also recorded that 14% patients were hospitalized, 2% needed ICU care and overall 5% died.

Not all COVID infected patient develop severe disease and certain risk factors that predispose to severe illness have been identified. Severe disease typically occurs with advancing age or older persons and those with certain comorbidities. Older age is the most important risk factor. Not only do the older persons infected with COVID develop more severe disease, they require more hospitalizations (1% in those between 20 and 29 years compared to 18% in those over 80 years). They also have higher mortality-case fatality rates in those above 70 years is 8–15%[35].

Table 2 Clinical severity and assessment parameters (MOHFW, GOI).

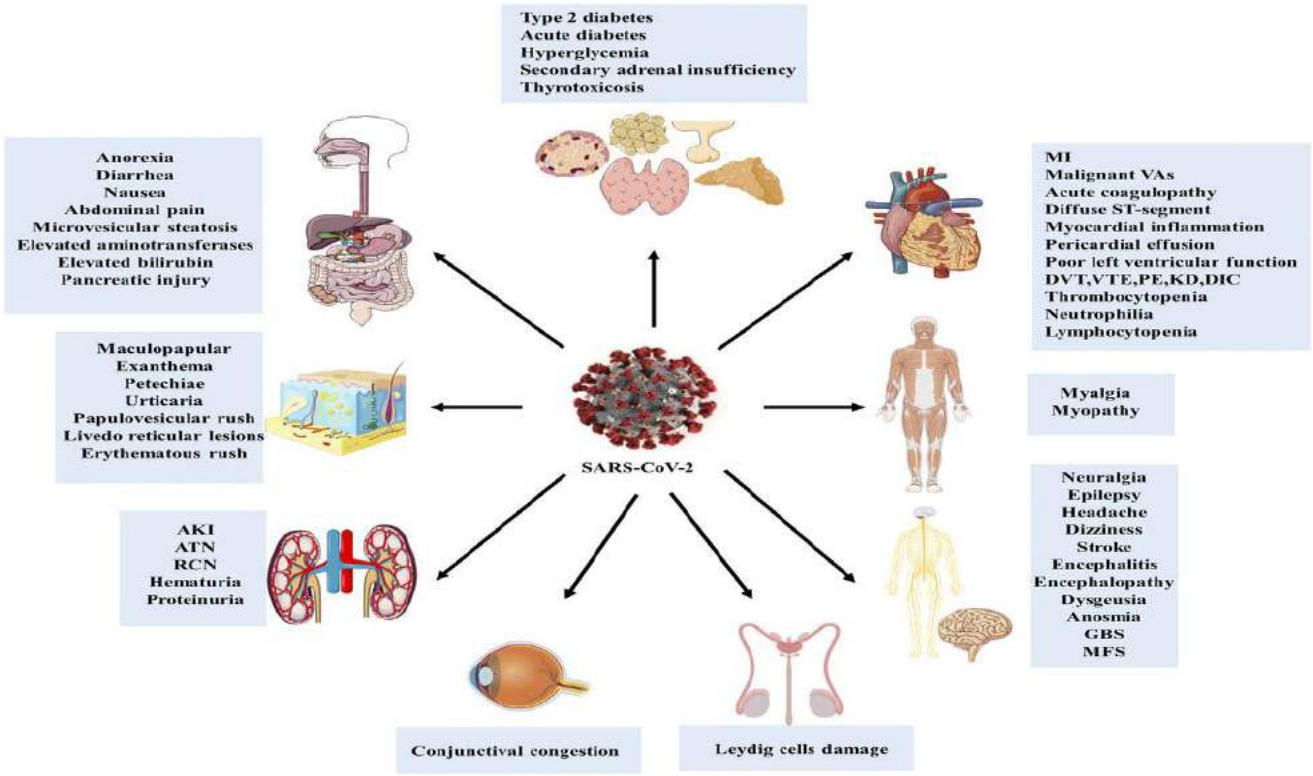
Clinical severity	Clinical presentation	Clinical parameters
Mild	Patients may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache	Without shortness of breath or hypoxia (normal saturation)
Moderate	Pneumonia with no signs of severe disease	Adults with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO_2 90 to ≤93% on room air, respiratory rate more or equal to 24/min
Severe	Severe pneumonia	Adults with clinical signs of pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% on room air
	Acute respiratory distress syndrome (ARDS)	*Onset*: • Origin of pulmonary infiltrates: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic cause of infiltrates/edema, if no risk factor present • Moderate ARDS: 100 mm Hg <PaO_2/FiO_2 ≤200 mm Hg with PEEP ≥5 cm H_2O • Severe ARDS: PaO_2/FiO_2 ≤100 mm Hg with PEEP ≥5 cm H_2O
	Sepsis	*Adults*: Acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: Altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia
	Septic shock	*Adults*: Persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mm Hg and serum lactate level >2 mmol/L

Pulmonary manifestations of acute covid:

The respiratory system is the most common system affected in COVID-19. Pulmonary manifestations vary from a nonspecific cough and dyspnea to hypoxemic respiratory failure and acute respiratory distress syndrome Thus, symptoms may range from “mild” without features of pneumonia, to “severe” (dyspnea, tachypnea, oxygen saturation <93% and PaO2: FiO2 ratio <300) and “critical” (respiratory failure, septic shock and multi-organ dysfunction) The timing of respiratory symptoms is also variable, and may appear or worsen 9–12 days after initial symptom onset. Risk factors for severe and critical disease include older age, male gender, diabetes, hypertension, chronic cardiac, renal and pulmonary conditions, obesity, smoking, malignancy and immunodeficiency states.

Although hypoxia is a common feature of COVID-19 pneumonia, but interestingly, it is often insidious and paradoxically may be well tolerated by the patients. This unusual clinical presentation, mostly seen relatively early in the disease course, is referred to as

"silent hypoxia" and is linked to the "atypical" features of the Acute Respiratory Distress Syndrome syndrome associated with COVID-19 pneumonia. COVID-19Acute Respiratory Distress Syndrome appears to have worse outcomes than Acute Respiratory Distress Syndrome from other causes, with mortality ranging between 26 and 61.5% in ICU setting, and between 65.7 and 94% in patients who receive mechanical ventilation[36].



	Ultra-Early Stage	Early Stage	Rapid progression Stage	Consolidation Stage	Dissipation Stage
Findings	• Prior to symptom onset. • Throat swab positive, laboratory negative • Usually within 1-2 weeks of exposure.	• Patients present with symptoms (within 1-3 days of symptoms like fever, dry cough). • On histopathology - There is congestion of alveolar capillaries resulting in alveolar and interlobular interstitial edema.	• This stage follows within 3-7 days of symptomatic presentation. • There is an escalation in the hyperinflammatory response. Fibrous extensions that connect the alveoli begin to develop.	• This phase coincides with 2nd week of clinical symptoms. • The vascular congestion diminishes and fibrosis predominates.	• It occurs about 2-3 weeks after initial symptomatic presentation. • There is more of a healing and repair response within the lungs .
Images					
	CT scan demonstrates Bilateral, subpleural, multiple scattered ground glass opacities.	CT scan shows multiple, bilateral ground glass opacities. Irregular, interlobular septa begin to develop.	CT findings include subpleural, posterior consolidations, dispersed air bronchograms along with superimposed irregular septa.	There is a decrease in size and density of consolidations.	CT scan shows patchy consolidation, reticular opacities (strip-like opacities), bronchial and interlobular septal thickening.

Radiological findings are useful for supporting the diagnosis of COVID-19. Chest X-ray is abnormal in up to 75% of symptomatic patients with typical findings of bilateral patchy and peripheral ground-glass opacities or consolidation. Linear atelectasis is also common. Chest computed tomography (CT) has high sensitivity (70–80%) and specificity (90%) in diagnosis of COVID-19 and commonly shows bilateral ground-glass opacification at the bases and/or peripheries. Several CT-based scoring systems or grades have been proposed for a reliable diagnosis of covid-19, such as the CORADS . Pulmonary thromboembolism (PTE) is another common occurrence that is seen in up to 21% of COVID-19 patients. PTE should be suspected in the presence of tachycardia, pleuritic chest pain or new right heart strain pattern on ECG, with/without raised D-dimer

levels, and should warrant early CT pulmonary angiography (CTPA) or empiric anticoagulation if imaging is not immediately available[37].

The most common symptoms are fatigue and dyspnea followed by joint pain and chest pain. In addition to that specific organ related dysfunctions are also noted.

***Cardiovascular*:**

- Myocardial injury as defined by raised troponin level
- Thromboembolic diseases
- Myocardial inflammation—myocarditis
- Sudden onset arrhythmia
- Increased incidence of heart failure

***Pulmonary*:**

- Interstitial thickening and pulmonary fibrosis
- Decreased diffusion capacity for CO
- Diminished respiratory muscle strength
- Pulmonary artery hypertension

***Neurologic*:**

- Most common is headache, vertigo, chemosensory dysfunction
- Cerebrovascular stroke
- Encephalitis
- Seizure
- Major mood swing

***Neuropsychiatric*:**

- Depression
- Anxiety
- Post-traumatic stress disorder
- Substance abuse
- Chronic fatigue syndrome

***Endocrine and metabolic*:**

- Increased risk of dyslipidemia
- Increased risk of hyperglycemia
- Hypocortisolism
- Primary and central hypothyroidism

***Neuromuscular*:**

- Persistent musculoskeletal pain and aches
- Reactive arthritis
- Femoral head necrosis[38].

Table 3 Classification of COVID-19 severity.

Disease severity	Clinical manifestation	Diagnostic criteria
Mild disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of or hypoxia
Moderate disease	Pneumonia	• *Adolescent or adult* with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air • *Child* with clinical signs of nonsevere pneumonia (cough or difficulty breathing + fast breathing and/chest indrawing) and no signs of severe pneumonia
Severe disease	Severe pneumonia	• *Adolescent or adult* with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room • *Child* with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: ◦ Central cyanosis or SpO_2 <90%; severe respiratory distress (e.g., fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions
Critical disease	Acute respiratory distress syndrome (ARDS)	• *Onset*: Within 1 week of a known clinical insult (i.e., pneumonia) or new or worsening respiratory symptoms • *Chest imaging* (radiograph, CT scan, or lung ultrasound): Bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules • *Origin of pulmonary infiltrates:* Respiratory failure not fully explained by cardiac failure or fluid overload • *Oxygenation impairment in adults*: ◦ Mild ARDS: 200 mm Hg < PaO_2/FiO_2a ≤300 mm Hg (with PEEP or CPAP ≥5 cm H_2O) ◦ Moderate ARDS: 100 mm Hg <PaO_2/FiO_2 ≤200 mm Hg (with PEEP ≥5 cm H_2O) ◦ Severe ARDS: PaO_2/FiO_2 ≤100 mm Hg (with PEEP ≥5 cm H_2O)

Table 4, CORADS categories for radiological suspicion of COVID-19.

CORADS Category	Level of suspicion for pulmonary involvement of COVID-19	Summary
0	Not interpretable	Scan technically insufficient for assigning a score
1	Very low	Normal or noninfectious
2	Low	Typical for other infection but not COVID-19
3	Equivocal / Unsure	Features compatible with COVID-19 but also other diseases
4	High	Suspicious for COVID-19
5	Very high	Typical for COVID-19
6	Proven	RT-PCR positive for SARS-CoV-2

(CORADS: COVID-19 Reporting and Data System)

Table 5, Clinical spectrum of covid 19:

Asymptomatic	• No clinical symptoms • Positive NST swab • Normal chest X-ray
Mild illness	• Fever, sore throat, dry cough, malaise, body aches or • Nausea, vomiting, abdominal pain, loose stool
Moderate illness	• Symptoms of pneumonia without hypoxemia • Significant lesions on HRCT chest
Severe illness	Pneumonia with hypoxemia (SpO_2<92%)
Critical illness	ARDS along with shock, coagulation defects, encephalopathy, heart failure, AKI

(AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; HRCT: high-resolution computed tomography; NST: nasopharyngeal swab test)

Chronic pulmonary manifestations of covid 19:

Although majority of patients with COVID-19 recover completely from the acute episode, a small proportion continue with persistent symptoms. A recent systematic review reported the incidence of at least one symptom at 2 weeks to be around 80%. A UK-based survey demonstrated the persistence of symptoms in 1 out of 5 patients for at least 5 weeks and in 1 out of 10 patients for beyond 12 weeks. The most common symptoms reported were fatigue, cough and headache. fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%) and shortness of breath (24%) were the most common persistent symptoms in patients who recovered from acute COVID-19. Persistent impairment of lung function, especially reduced diffusion capacity for carbon monoxide (DLCO) has also been reported.

In a substantial proportion of patients, pulmonary symptoms may persist for several weeks or even months. These pulmonary disorders in the post-COVID period have been assigned various terminologies, including post-COVID interstitial lung disease (ILD), post-COVID fibrosis, post-COVID lung syndrome, post-COVID lung sequelae and post-COVID pulmonary sequelae. The terms post-COVID fibrosis or post-COVID ILD should be limited to individuals with persistent (and/or progressive) pulmonary fibrosis on radiological examination. The most suitable term, in our opinion, is post-COVID pulmonary sequelae that encompass various clinicoradiological manifestations ranging from a mild cough to hypoxemia and few ground glass opacities (GGO) to extensive fibrosis on computed tomography[39].

POST COVID PULMONARY SEQUALE:

Persistent cough and shortness of breath are the most common respiratory symptoms following initial recovery from acute COVID-19. The symptoms are usually non-progressive and improve with time. Acute onset localized chest pain and hemoptysis should prompt a search for pulmonary thromboembolism. Patients developing secondary infections may complain of persistent fever, sputum production, and hemoptysis.

Patients who were hypoxic in the active disease stage are at maximum risk of developing post-COVID pulmonary sequale. The other risk factors include: Old age, history of smoking, severe disease at baseline, and need for ICU admission and invasive mechanical ventilation. The common post-COVID pulmonary sequelae include: impaired gas exchange and pulmonary fibrosis, pulmonary embolism, pulmonary hypertension, secondary infections including tuberculosis and fungal pneumonia, respiratory muscle weakness and impaired exercise capacity. It is essential to periodically assess oxygen saturation using pulse oximeters as persistence of hypoxia is not uncommon and may warrant initiation of domiciliary oxygen therapy[40].

IMPORTANT COMPLICATIONS:

- *Respiratory failure*: Acute respiratory distress syndrome (ARDS) is the major complication in these patients and usually manifests in a median of 8 days after symptom onset.
- *Cardiovascular complications*: These include arrhythmias, myocardial injury, heart failure, and shock.

- *Thromboembolic complications*: COVID-19 predisposes to a hypercoagulable state. Venous thromboembolism including extensive deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in severely ill patients with COVID-19. Arterial thrombosis manifesting as acute stroke and peripheral arterial occlusions are also reported.
- *Neurologic complications*: Encephalopathy, cerebrovascular accidents, movement disorders, ataxia, and seizures are described.
- *Inflammatory complications*: Some patients with severe COVID-19 have a severe inflammatory response with persistent fever, elevated inflammatory laboratory markers (e.g., D-dimer, ferritin), and elevated proinflammatory cytokines. This clinical event has been called a cytokine storm or cytokine release syndrome.
- A multisystem inflammatory syndrome (MIS-C) similar to those of Kawasaki disease has been described in children with COVID-19.
- *Secondary infections*: Secondary infections do not appear to be common complications of COVID-19 overall. In the recent second wave of COVID-19 in India, an excess of cases of Rhinocerebral Mucormycosis has been noted. Whether it was due to the widespread and unregulated use of corticosteroids or due to underlying comorbidities like diabetes mellitus in critically ill COVID patients is unclear. But it has definitely added to the overall morbidity and mortality in these patients.
- *Recovery and long-term sequelae*: The time to recovery from COVID-19 is highly variable and depends on age and preexisting comorbidities in addition to illness severity.

A long COVID syndrome has been described in patients with long-term persistent symptoms following COVID 19[41].

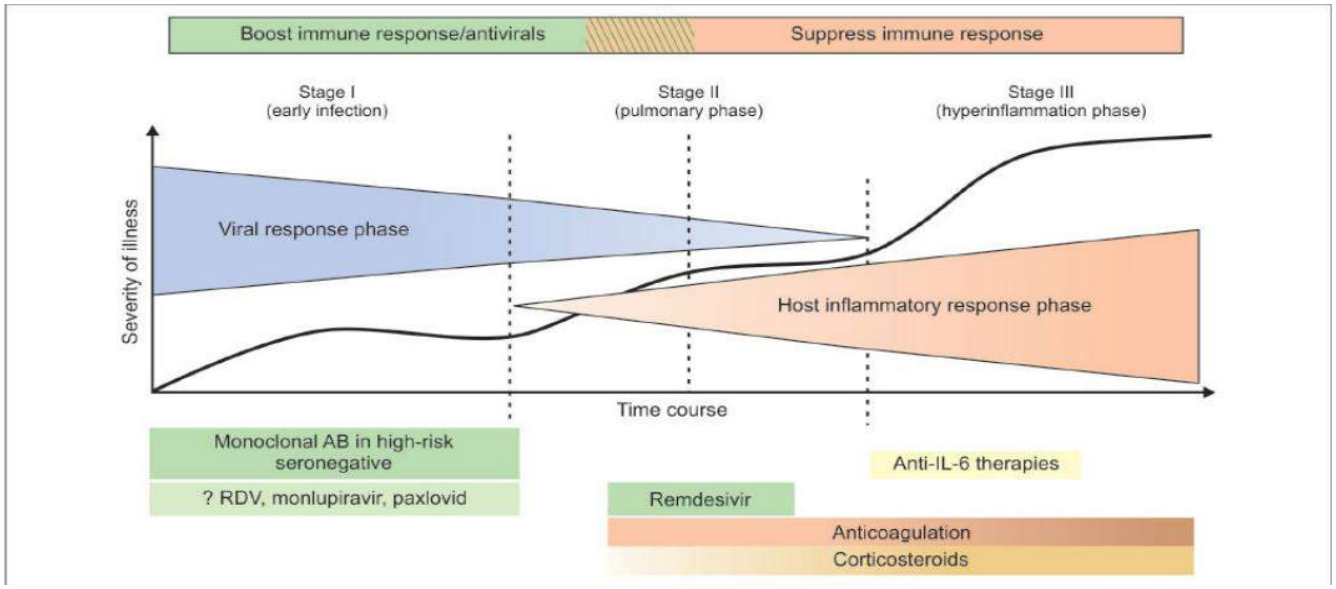
Management of covid pneumonia:

The treatment of COVID pneumonia depends on the severity and degree of hypoxia and respiratory compromise. Oxygen and steroids form the cornerstone of COVID pneumonia with hypoxia, i.e., room air oxygen saturation below 94%. Several oxygen delivery devices have been used, such as nasal prongs, face mask, non-rebreathing mask, high-flow nasal cannula, and noninvasive ventilation. Patients with Acute Respiratory Distress Syndrome need invasive mechanical ventilation; in selected cases, extracorporeal membrane oxygenation (ECMO) has also been tried as a bridge to lung transplantation[42].

Steroid therapy is recommended for all patients with moderate-to-severe COVID-19 and hypoxia. Either dexamethasone (0.1–0.2 mg/kg/day) or methylprednisolone (0.5–1.0 mg/kg/day) have been extensively used with similar efficacy. Usually, a short course of 7–10 days is sufficient, however, a small proportion of patients may need longer duration of therapy. In severe cases, or in the hyper inflammatory phase with markedly elevated inflammatory markers, intravenous high-dose pulse steroids upto 125–250 mg of methyl prednisolone have also been administered, followed by tapering over the subsequent days to weeks depending on clinical and biochemical response.

Administration of low molecular weight heparin is recommended for all moderate and severe disease. Prone positioning is a simple procedure which has significant benefits on improving oxygenation and is now routinely recommended.

COVID-19 infection, which is predominantly a respiratory illness, has now been recognized to have multisystem presentations. It can have a wide array of acute clinical presentations or long-term sequelae. The clinical presentation may range from asymptomatic to severe acute respiratory distress syndrome (ARDS). In patients with severe COVID-19, the pathogenesis has been described into two phases—(1) the viremic phase and (2) the hyperinflammatory phase. The immune dysregulation and the cytokine release syndrome associated with the (inflammasome pathway and interferonopathy) disease are primarily responsible for the worse outcomes and mortality. The cornerstone of management includes oxygen therapy, suppression of hyperinflammatory drive, anti coagulation[43].



Therapeutic modalities for COVID-19	
Drugs with antiviral properties	• Viral transcription inhibitor: Remdesivir, favipiravir, molnupiravir • Viral entry inhibitor: Umifenovir • Viral replication inhibitor: Ivermectin • Protease inhibitor: Lopinavir/ritonavir, ritonavir-boosted nirmatrelvir (paxlovid) • Interferes with endosomal acidification: HCQ
Anti-inflammatory drugs	• Anti-inflammatory action: Corticosteroids • Anti-IL-6 agents: Tocilizumab, sarilumab • Anti-CD6 IgG monoclonal antibody: Itolizumab • JAK inhibitor: Baricitinib, Ruxolitinib
Anticoagulants	• Low-molecular-weight heparin • Unfractionated heparin
Others	• Convalescent plasma therapy • Combination monoclonal antibody: Casirivimab and Imdevimab (together called REGN-COV2), sotrovimab • Possible immune booster: Zinc, vitamin C

(HCQ: hydroxychloroquine)

BOX 1 **Comorbidities the CDC classifies as risk factors for severe COVID-19.**

- *Established and probable risk factors*:
  - Cancer
  - Cerebrovascular disease
  - Pregnancy
  - Smoking (current and former)
  - Sickle cell disease
  - Solid organ or blood stem cell transplantation
  - Substance use disorders
  - Use of corticosteroids or other immunosuppressive medications
- *Possible risk factors*:
  - Cystic fibrosis
  - Thalassemia
- *Possible risk factors but evidence is mixed*:
  - Asthma
  - Hypertension
  - Immune deficiencies
  - Liver disease

BOX 1 **High-risk factors for severe disease or mortality in COVID-19.**

- Advanced age > 60 years
- Cardiovascular disease including hypertension and coronary artery disease
- Diabetes mellitus and other immunocompromised states
- Chronic lung/kidney/liver disease
- Cerebrovascular disease
- Obesity

BOX 2 **Management guidelines for mild COVID-19.**

- Home isolation with contact and droplet precautions; strict hand hygiene
- Symptomatic management (antipyretic, antitussives)
- Stay in contact with treating physician
- Peripheral oxygen saturation (by applying a SpO_2 probe to fingers) should be monitored at home
- Inhalational budesonide (given via MDI/DPI at a dose of 800 µg BD for 5–7 days) to be considered in patients with risk factors for disease progression, if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset
- No role of systemic steroids and home based RDV

(MDI: metered dose inhaler; DPI: dry powder inhaler)

BOX 3 **Management guidelines for moderate COVID-19.**

- Oxygen support is the key to management
- Awake proning should be encouraged in all patients who are requiring supplemental oxygen therapy (sequential position changes every 1–2 hours)
- Anti-inflammatory or immunomodulatory therapy: Injection Methylprednisolone 0.5–1 mg/kg (or equivalent dose of dexamethasone 0.1–0.2 mg/kg) IV in two divided doses for 5–10 days
- Patients may be initiated or switched to oral route if stable and/or improving
- Anticoagulation: Low-dose prophylactic UFH or LMWH (weight based, e.g., enoxaparin 0.5 mg/kg per day SC). There should be no contraindication or high risk of bleeding.

(LMWH: low-molecular-weight heparin; UFH: unfractionated heparin)

BOX 4 **Management guidelines for severe COVID-19.**

Respiratory support

- Consider use of NIV (helmet or face mask interface depending on availability)/HFNC in patients with increasing oxygen requirement, if work of breathing is LOW
- Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated
- Use conventional ARDSnet protocol for ventilatory management

Anti-inflammatory or immunomodulatory therapy

- Injection methylprednisolone 1 to 2 mg/kg in 2 divided doses for 5 to 10 days (or equivalent dose of dexamethasone)

Anticoagulation

- Conventional dose prophylactic UFH or LMWH (e.g., enoxaparin 0.5 mg/kg/dose SC OD)

Supportive measures

- Maintain euvolemia
- If sepsis/septic shock: Manage as per existing protocol and local antibiogram
- Physiotherapy, nutrition, and rehabilitation

Clinical monitoring is vital. It is important to watch out for work of breathing, hemodynamic instability, change in oxygen requirement

Serial CXR; CT chest to be done ONLY if deteriorating or suspecting secondary pathology

Lab monitoring: CRP 48-72 hourly; D-dimer at baseline and repeat as required; CBC, KFT, LFT 24-48 hourly

The basic principles of infection control are

Reduction in Inoculum of the Virus

Personal Protective Equipment:

Personal protective equipment (PPE) consists of masks, gowns, gloves and eye protection (face shields or goggles).

Masks can be of three types: (1) cotton fabric masks, (2) medical masks and (3) filtering face piece respirators (FFRs) . N95 is the name given to the Niosh certified, non-oil resistant FFR masks which filter out 95% of particles of size 0.3 μm and above.

Masks with exhalation valves or vents are avoided as they do not provide source control[44].

HCWs should not keep the masks used in patient care areas hanging around their necks, to avoid the contaminated outer surface coming in contact with the chest.

Gloves and gowns are worn to minimize indirect transmission by fomites. Same gloves should not be used for multiple patients as they can transmit other organisms such as multidrug resistant bacteria and lead to outbreaks in the COVID-19 facilities. In the scenario where double gloving is practiced, the outer pair of gloves should be discarded after each patient contact and hand hygiene performed immediately. Gowns should be water resistant and certified by the textile ministry of the Government of India[45].

Eye protection is required when the risk of aerosolization arises. Face shield is preferred as it provides full face cover and reduces contamination of the mask. This allows for the extended use of the N95 masks up to 8 hours. Eye shield is not needed if a powered air-purifying respirator (PAPR) is used. Fogging of eyeglasses inside the PPE can be avoided by using a snugly fitting mask. Alternatively, allowing soap solution to dry on the eyeglasses leaves a layer of surfactant which inhibits accumulation of mist on the glasses. Anti-fogging sprays are also available commercially.

Types of masks and recommendations for their use.

Type of mask	Specifications	Comments
Cotton masks	They should be multilayered	• Used by the general public • Not recommended for HCWs • Daily cleaning with soap and water is necessary
Medical (surgical) masks	These are triple layered. The outermost layer is water resistant, while the innermost layer is absorbent. The darker colored layer is the outer layer	• Recommended for the general public, especially for symptomatic or high-risk individuals • Provided to all the patients with COVID-19 • Recommended for routine use in healthcare settings • These are disposable masks, and should be changed when damp, soiled or used for more than 6 hours
Filtering facepiece respirators (N95, KN95, etc.)	It consists of a fine mesh of synthetic polymer (polypropylene) fibers	• Recommended for aerosol-generating procedures • Fit-testing is necessary to avoid leakage of air. • Facial hair in the form of a beard or moustache crossing the edge of the mask leads to ill-fitting and air leakage

Maintaining Social Distance

A distance of 6 feet or 2 meters is found to be appropriate for reducing the risk of transmission. If this is not possible, at least 1 meter distance should be maintained in all the areas. Care should be taken by HCWs, especially during lunch hours, in duty rooms, seminar rooms and during clinical rounds, so as not to gather in a crowd.

Sequence of donning and doffing:

Donning of PPE	Doffing of PPE
• Don the PPE before entering the COVID-designated area • Perform hand hygiene • Put on gown/coveralls • Wear a face mask or respirator (secure the straps on the crown of the head for the top strap and base of the neck for the bottom strap, do not crisscross the straps) • Wear a face shield or goggles • Put on gloves and extend them to cover the cuffs of the gown (use best-fitting gloves)	• Remove gloves (avoid touching the outer surface of gloves with bare hands. Remove only the outer pair of gloves in case of double gloving) • Perform hand hygiene • Remove the gown (by rolling it inside out, do not reuse gowns) • Perform hand hygiene • Exit the patient care area • Remove the face shield/goggles • Perform hand hygiene • Remove the respirator or face mask (untie or remove the lower strap first to avoid the mask from falling on your chest) • Perform hand hygiene Remove the inner pair of gloves (in case of double gloving) Perform hand hygiene

Recommendations for the use of PPE in the healthcare settings.

Risk level	Area/ Procedure	PPE recommendation
Low risk	• Reception • Billing area • Administrative offices • Non-COVID wards	Medical mask
Moderate risk	• Triage • Pulmonology, ENT, ophthalmology and dental OPDs • Mortuary • Sanitation • CSSD/Laundry	N95 respirator *plus* Gloves (Face shield when aerosol exposure is anticipated)
High risk	• Designated COVID areas (ICUs and wards) • ER • Endoscopy suite • COVID testing laboratory • All areas where AGPs* are performed	N95 or higher respirator *plus* Gloves *plus* Gown *plus* Eye protection

Note: Transmission from procedures which do not directly involve the respiratory tract is unclear.

*AGPs: aerosol-generating procedures [bronchoscopy, endoscopy, colonoscopy, cardiopulmonary resuscitation, noninvasive ventilatory (NIV) support, open suctioning of endotracheal tubes, intubation, extubation, tracheostomy. High flow oxygen delivery and nebulizer treatment have an uncertain role in transmission].

MATERIALS AND METHODS

STUDY DESIGN: Descriptive Cross – Sectional Study

STUDY POPULATION:Patients chosen from covid op and covid ward in Government Stanley medical college and hospital,Chennai.

STUDY DURATION: Period of 1 year from April 2021 to January 2022. by SIMPLE RANDOM SAMPLING method.

INCLUSION CRITERIA:

Patients in the age more than 18 years to 80 years

All Adult SARS-Cov-2 patients confirmed by RT-PCR of nasopharyngeal specimen and oropharyngeal specimen.

EXCLUSION CRITERIA:

1.All adult SARS-Cov-2 patients with preexisting chronic liver disease.

2.All adult SARS-Cov-2 patients with inflammatory bowel disease/irritable bowel syndrome/gastroesophageal reflux disease

3.All adult patients with chronic ethanol ingestion.

4.All adult patients with drugs which causing liver injury.

5.Patients with altered bowel habits

SAMPLE SIZE:

FORMULA:
$n=z^2 \times p(1-p) \div d^2$
where
z=confidence level at 95%(standard value of 1.96)
p= 20% estimated prevalence
d= 5% absolute error or relative precision

on substituting in the formula
n = (1.96x1.96)x20(100-20) ÷(5x5)
n=284
Therefore sample size n=284

PATIENT PARTICIPATION TIME DURING STUDY:

From initial presentation to 14-21 days

PROCEDURE AND DATA COLLECTION:

After obtaining written consent from covid 19 patients.

History will be obtained from patient regarding general symptoms and gastrointestinal symptoms of covid 19 such as diarrhea,nausea, vomiting,abdominal pain, loss of appetite,loss of taste.

Patient examined for respiratory rate,oxygen saturation,blood pressure,pulse rate,respiratory system,cardiovascular system,per abdominal,central nervous system.

Patient blood samples are obtained for liver biochemistries,complete blood count,renal function test.

Electrocardiography,echocardiography were done in stable outpatients and in hospital patients.

Treatment given in hospital patient and prescription given to outpatients.

Advised home quarantine

Collect his/her own phone number and alternate phone number,contact details.

All details entered by proforma on day1,

Outpatient will be followed by telephonic contact on day14 and day 21 ,

Inpatient will be reviewed on day 7 and day 14 with relevant investigations and assessed for severity of disease.

Analysis :

After collecting the data will be complied and entered in Microsoft excel sheet.

Aalysis will be done by IBM SPSS statistics for windows version 23.3.

All continuous variables expressed in Mean and Standard deviation,

All categorical variables expressed as percentages and proportion.

Ethical consideration:

Institutional ethical committee permission obtained

RESULTS AND OBSERVATIONS:

The collected data were analyzed with IBM SPSS Statistics for Windows, Version 23.0.(Armonk, NY: IBM Corp).To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significance in qualitative categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In both the above statistical tools the probability value .05 is considered as significant level.

Table: 1 Age distribution in the study population

Age		
	Frequency	Percent
21 - 30 yrs	24	8.5
31 - 40 yrs	71	25.0
41 - 50 yrs	69	24.3
51 - 60 yrs	78	27.5
61 - 70 yrs	34	12.0
Above 70 yrs	8	2.8
Total	284	100.0

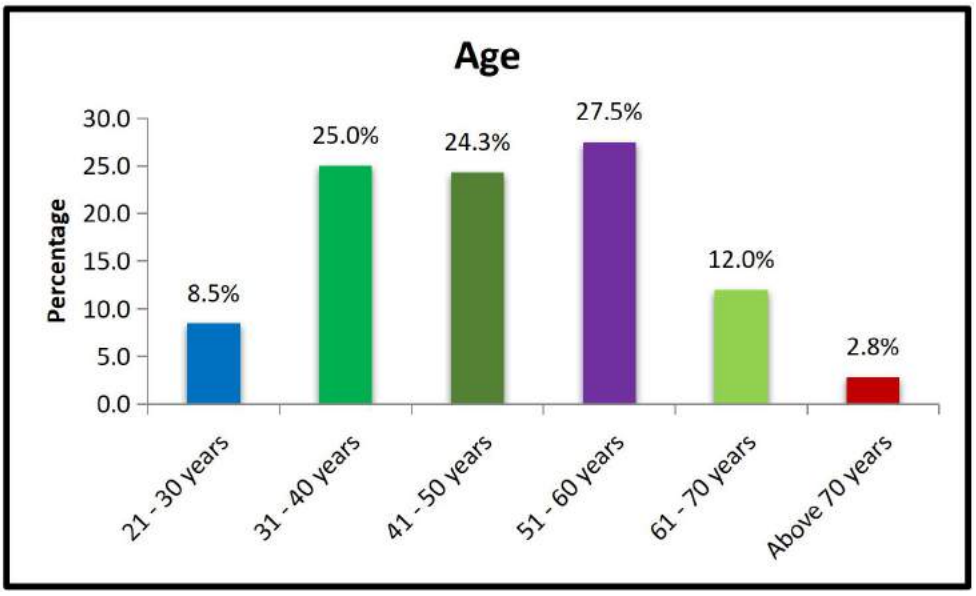


Figure: 1

The above table shows Age distribution among the study population of the present study shows that 8.5% of them belongs to 21-30 yrs, 25.0% were belongs to 31-40 years, 24.3% were belongs to 41-50 years, 27.5% were belongs to 51-60 years, 12.0% were belongs to 61-70 years and 2.8% were belongs to Above 70 years of age groups.

Table: 2 Gender distribution in the study population

Gender distribution		
	Frequency	Percent
Female	140	49.3
Male	144	50.7
Total	284	100.0

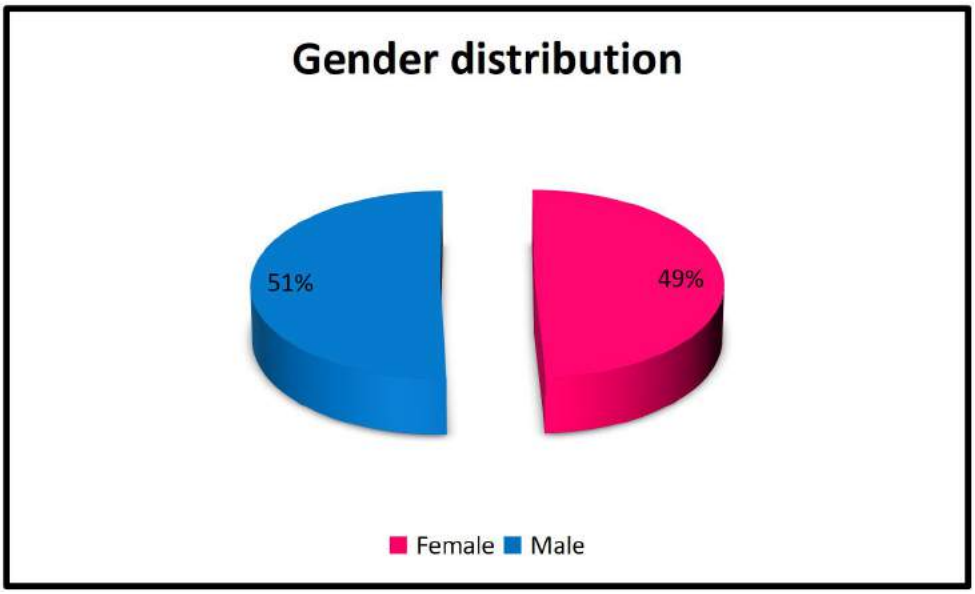


Figure: 2

From the above table and graph it shows the Gender distribution among in the study population of the present study 49.3% of them were Female and 50.7% of them were Male.

Table: 3 GI Symptoms distribution in the study population

GI Symptoms in the study population		
	Frequency	Percent
Yes	135	47.5
No	149	52.5
Total	284	100.0

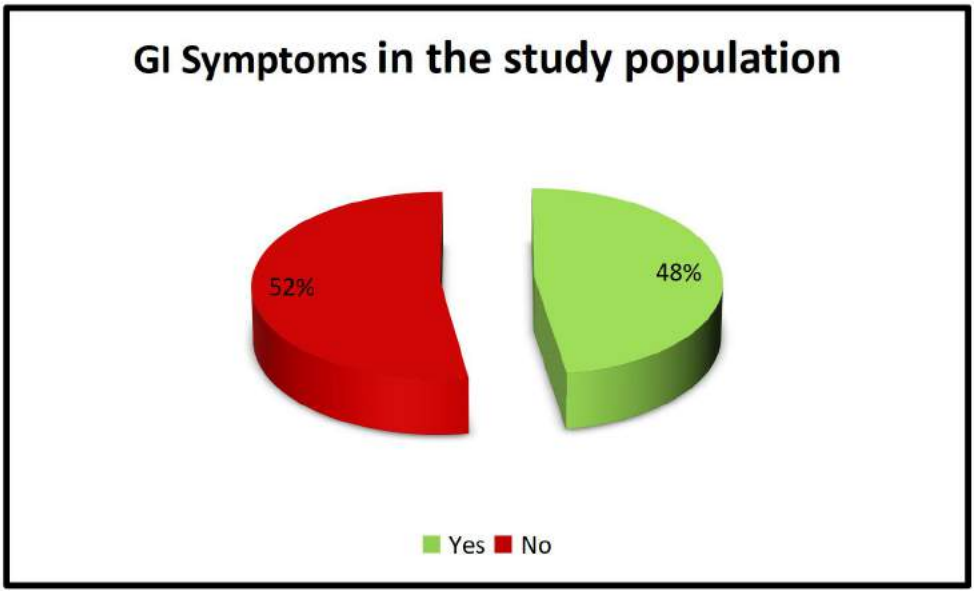


Figure: 3

From the above table and graph it shows GI Symptoms distribution in the study population of the present study 47.5% were with presence of GI symptoms and 52.5% were with absence of GI symptoms.

Table: 4 Hepatic enzyme Elevation(HEE) distribution

HEE		
	Frequency	Percent
Yes	68	23.9
No	216	76.1
Total	284	100.0

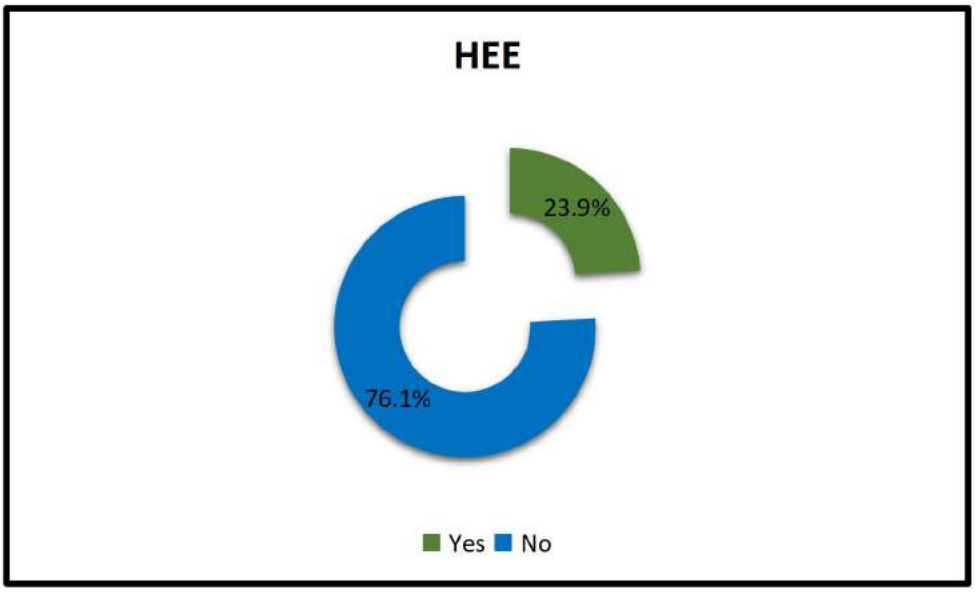


Figure: 4

The above table showsHepatic enzyme Elevation(HEE) distribution were 23.9% is Yes, 76.1% is No.

Table: 5 Primary symptoms distribution

Primary symptoms		
	Frequency	Percent
Fever	238	84.0
Sore throat	17	6.0
Dry Cough	107	37.7
Expectoration	119	41.9
Chest Tightness	73	25.7
Shortness Of Breath	40	14.1
Dizziness	40	14.1
Headache	31	10.9
Myalgia	96	33.8

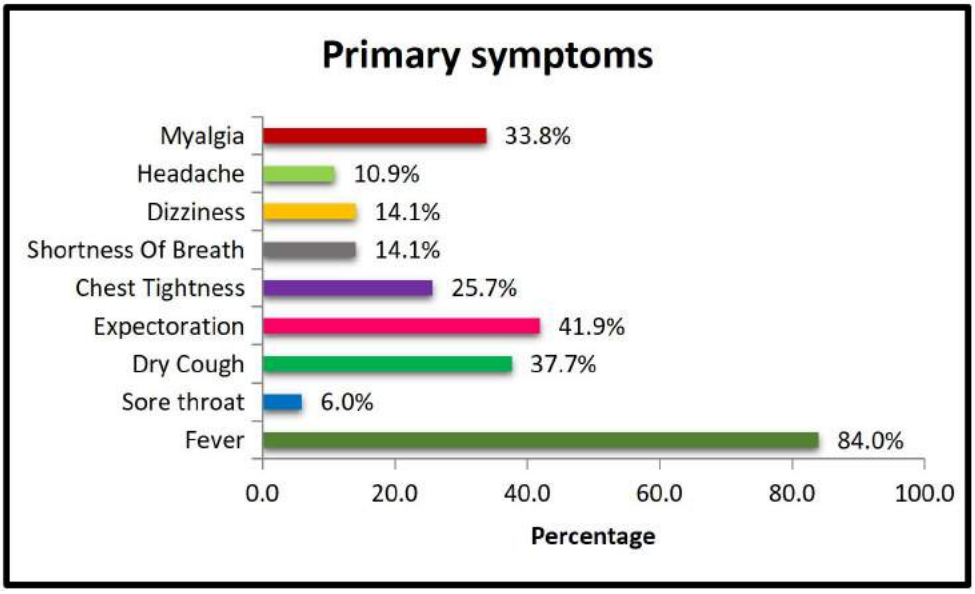


Figure: 5 The above table shows Primary symptoms distribution were 84.0% is Fever, 6.0% is Sore throat, 37.7% is Dry Cough, 41.9% is Expectoration, 25.7% is Chest Tightness, 14.1% is Shortness of Breath, 14.1% is Dizziness, 10.9% is Headache, 33.8% is Myalgia.

Table: 6 GI Symptoms distribution

GI Symptoms		
	Frequency	Percent
Diarrhea	51	18.0
Nausea	22	7.7
Vomiting	17	6.0
Abdominal Pain	28	9.9
Loss Of Appetite	45	15.8
Loss Of Taste	56	19.7

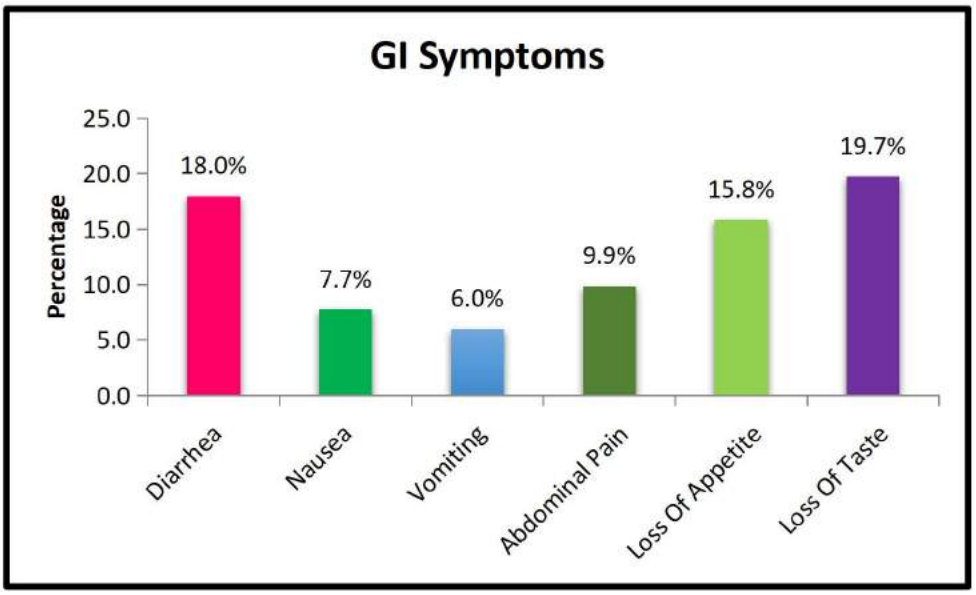


Figure: 6

The above table shows GI symptoms distribution were 18.0% is Diarrhea, 7.7% is Nausea, 6.0% is Vomiting, 9.9% is Abdominal Pain, 15.8% is Loss Appetite, 19.7% is Loss of Taste.

Table: 7 Hepatic enzyme Elevation distribution

Hepatic enzyme Elevation		
	Frequency	Percent
SGPT/ SGOT Elevation	68	23.9
NO Elevation	216	76.1

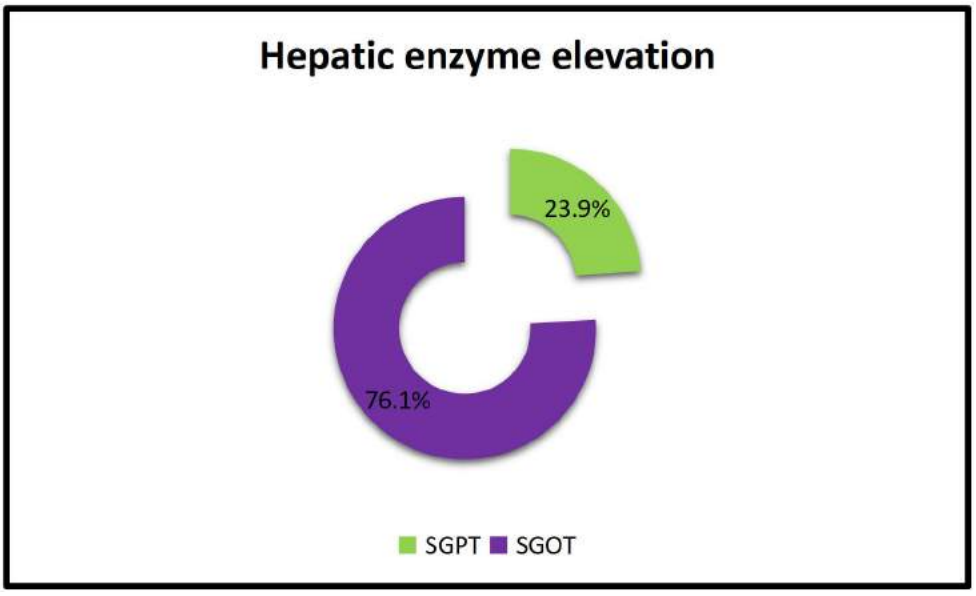


Figure: 7

The above table shows Hepatic enzyme Elevation distribution were 23.9% is SGPT, 23.9% is SGOT and no Elevation were 76.1%.

Table: 8 Complications distribution

Complications		
	Frequency	Percent
Pneumonia	232	81.7
Acute Respiratory Distress Syndrome	5	1.8
Arrythmias	8	2.8
Shock	8	2.8
Acute Heart Failure	5	1.8

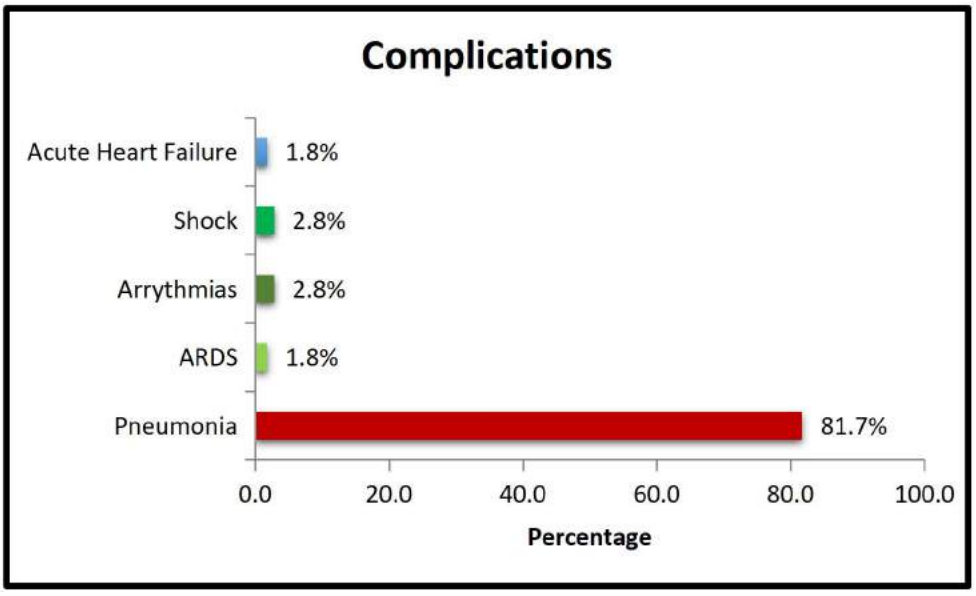


Figure: 8

The above table shows Complications distribution were 81.7% is Pneumonia, 1.8% is Acute Respiratory Distress Syndrome, 2.8% is Arrythmias, 2.8% is Shock, 1.8% is Acute Heart Failure.

Table: 9 Outcomes distribution

Outcomes		
	Frequency	Percent
Outpatient Recovered	56	19.7
Discharge From Hospital	152	53.5
Staying In Hospital	56	19.7
Death	19	6.7

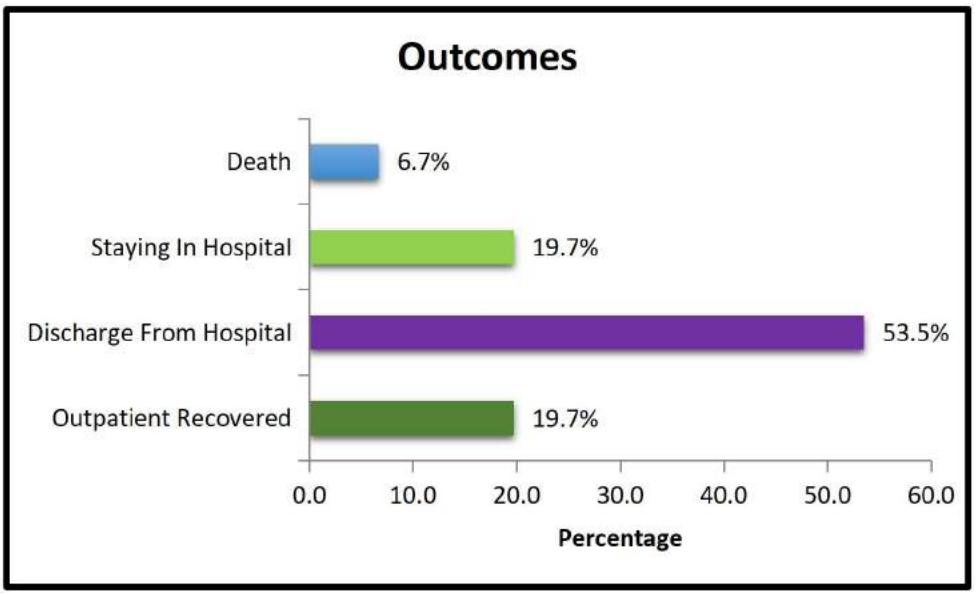


Figure: 9

The above table shows Outcomes distribution were 19.7% is Outpatient Recovered, 53.5% is Discharge From Hospital, 19.7% is Staying in Hospital, 6.7% is Death.

Table: 10 Comparison between Pneumonia with GI Symptoms by Pearson's Chi-Square test

Pneumonia		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	121	111	232	10.844	0.001 **
	%	89.6%	74.5%	81.7%		
Absent	Count	14	38	52		
	%	10.4%	25.5%	18.3%		
Total	Count	135	149	284		
** Highly Statistical Significance at p < 0.01 level						

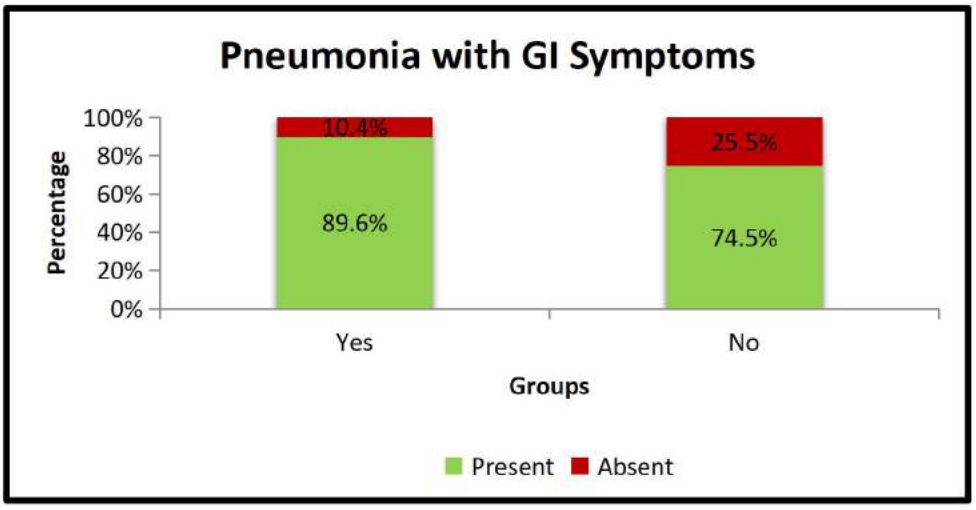


Figure 10

The above table shows comparison between Pneumonia with GI Symptoms by Pearson's Chi-Square test were x2=10.844, p=0.001<0.01 which shows highly statistical significance association between Pneumonia and GI Symptoms.

Table: 11 Comparison between Acute Respiratory Distress Syndrome with GI Symptoms by Pearson's Chi-Square test

Acute Respiratory Distress Syndrome		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	4	1	5	2.151	0.194 #
	%	3.0%	.7%	1.8%		
Absent	Count	131	148	279		
	%	97.0%	99.3%	98.2%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

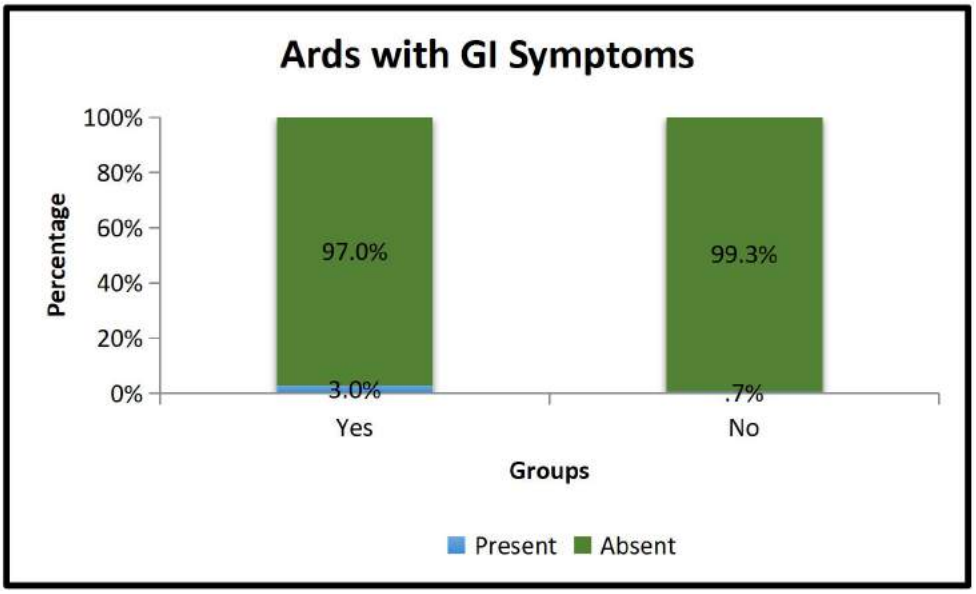


Figure 11

The above table shows comparison between Acute Respiratory Distress Syndrome with GI Symptoms by Pearson's Chi-Square test were x2=2.151, p=0.194>0.05 which shows no statistical significance association between Acute Respiratory Distress Syndrome and GI Symptoms.

Table: 12 Comparison between Arrythmias with GI Symptoms by Pearson's Chi-Square test

Arrythmias		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	4	4	8	0.020	1.000 #
	%	3.0%	2.7%	2.8%		
Absent	Count	131	145	276		
	%	97.0%	97.3%	97.2%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

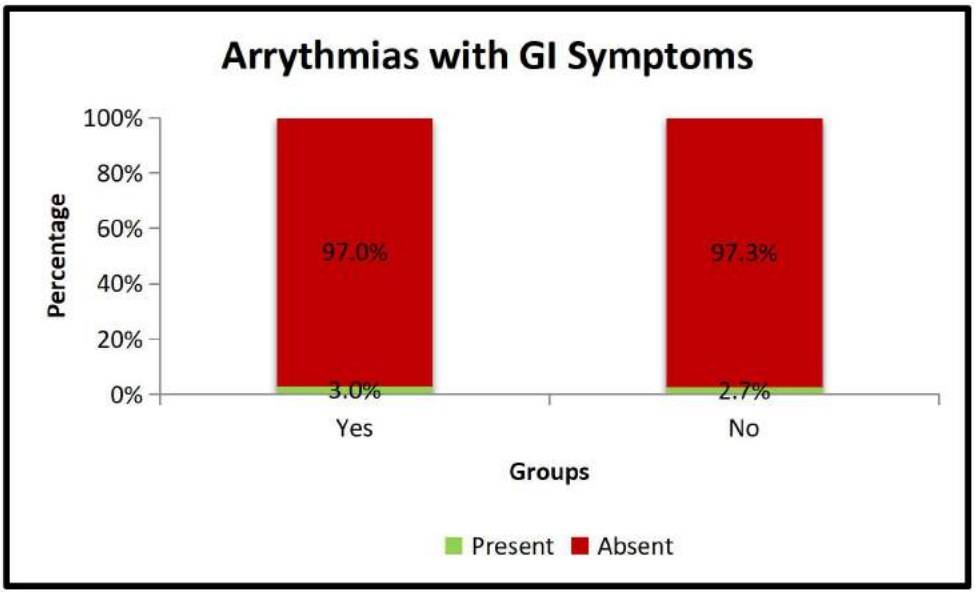


Figure 12

The above table shows comparison between Arrythmias with GI Symptoms by Pearson's Chi-Square test were x2=0.020, p=1.000>0.05 which shows no statistical significance association between Arrythmias and GI Symptoms.

Table: 13 Comparison between Shock with GI Symptoms by Pearson's Chi-Square test

Shock		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	1	7	8	4.052	0.069 #
	%	.7%	4.7%	2.8%		
Absent	Count	134	142	276		
	%	99.3%	95.3%	97.2%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

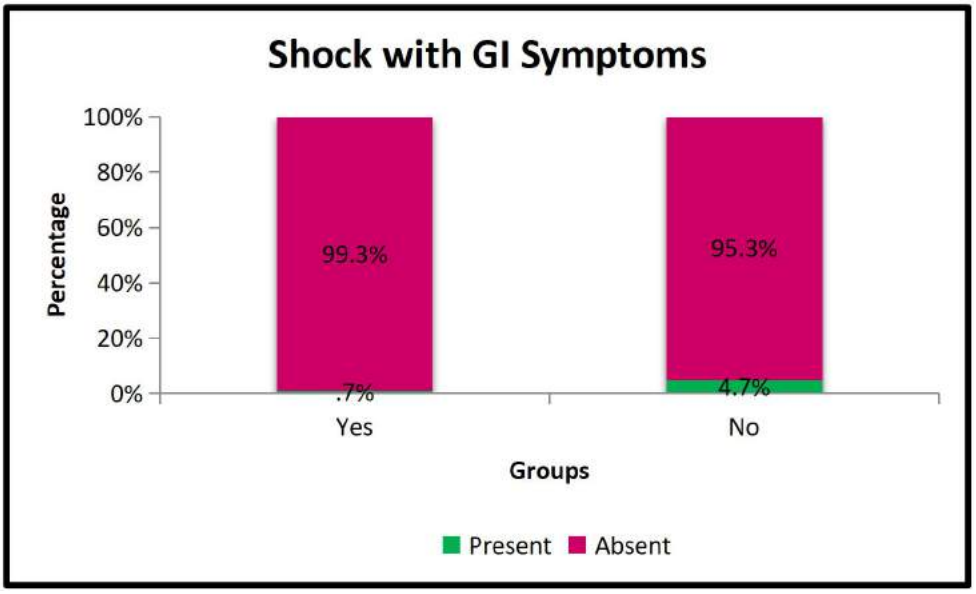


Figure 13

The above table shows comparison between Shock with GI Symptoms by Pearson's Chi-Square test were x2=4.052, p=0.069>0.05 which shows no statistical significance association between Shock and GI Symptoms.

Table: 14 Comparison between Acute Heart Failure with GI Symptoms by Pearson's Chi-Square test

Acute Heart Failure		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	2	3	5	0.116	1.000 #
	%	1.5%	2.0%	1.8%		
Absent	Count	133	146	279		
	%	98.5%	98.0%	98.2%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

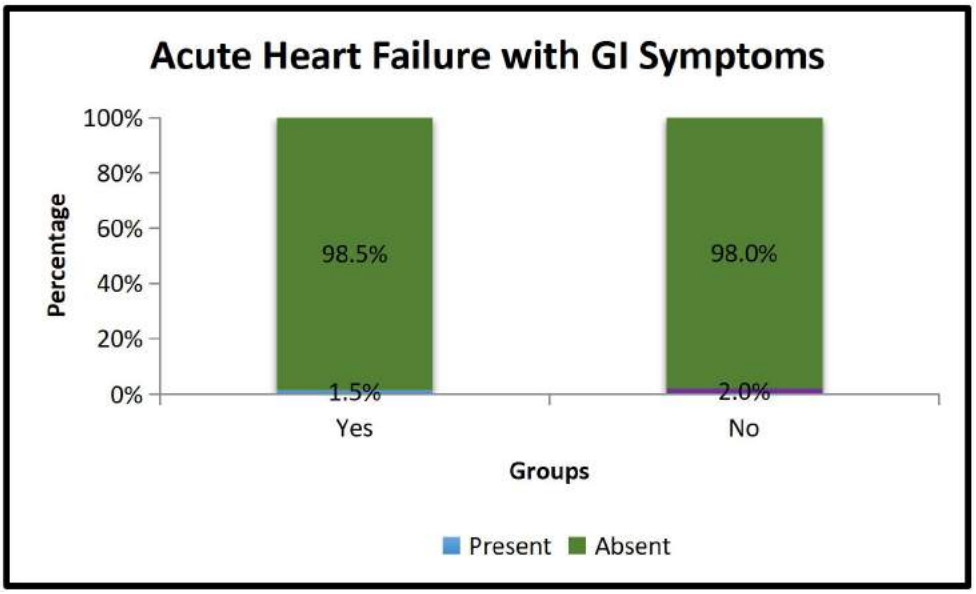


Figure 14

The above table shows comparison between Acute Heart Failure with GI Symptoms by Pearson's Chi-Square test were x2=0.116, p=1.000>0.05 which shows no statistical significance association between Acute Heart Failure and GI Symptoms.

Table: 15 Comparison between Outpatient Recovered with GI Symptoms by Pearson's Chi-Square test

Outpatient Recovered		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	9	47	56	27.689	0.0005 **
	%	6.7%	31.5%	19.7%		
Absent	Count	126	102	228		
	%	93.3%	68.5%	80.3%		
Total	Count	135	149	284		
** Highly Statistical Significance at p < 0.01 level						

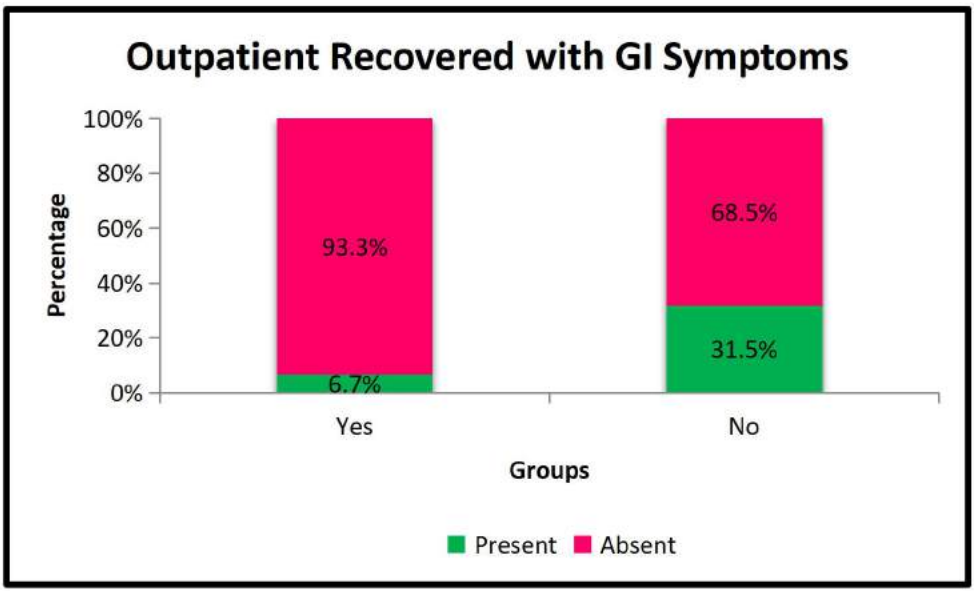


Figure 15

The above table shows comparison between Outpatient Recovered with GI Symptoms by Pearson's Chi-Square test were x2=27.689, p=0.0005<0.01 which shows highly statistical significance association between Outpatient Recovered and GI Symptoms.

Table: 16 Comparison between Discharge From Hospital with GI Symptoms by Pearson's Chi-Square test

Discharge From Hospital		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	87	65	152	12.342	0.0004 **
	%	64.4%	43.6%	53.5%		
Absent	Count	48	84	132		
	%	35.6%	56.4%	46.5%		
Total	Count	135	149	284		
** Highly Statistical Significance at p < 0.01 level						

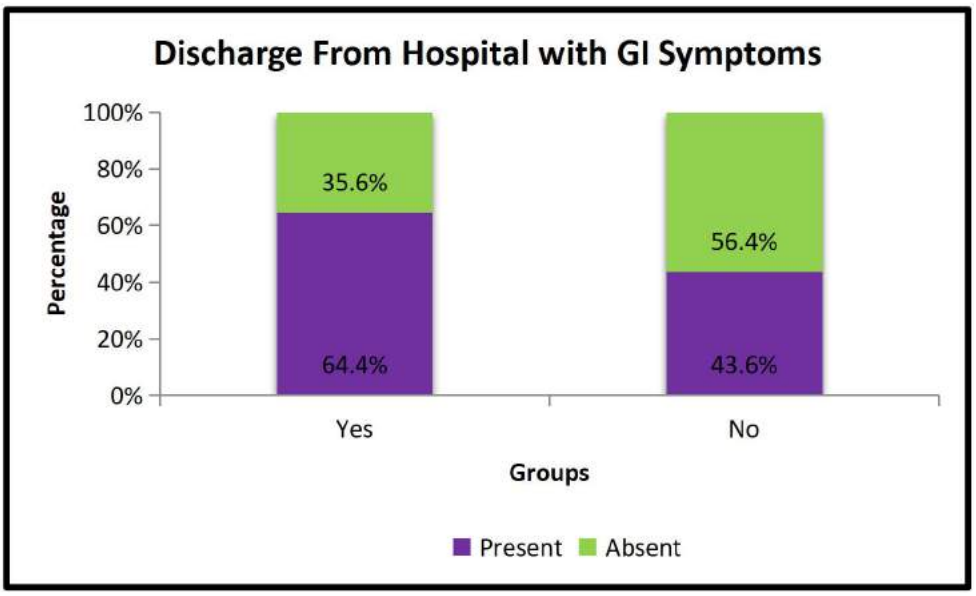


Figure 16

The above table shows comparison between Discharge From Hospital with GI Symptoms by Pearson's Chi-Square test were x2=12.342, p=0.0004<0.01 which shows highly statistical significance association between Discharge From Hospital and GI Symptoms.

Table: 17 Comparison between Staying in Hospital with GI Symptoms by Pearson's Chi-Square test

Staying In Hospital		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	32	24	56	2.582	0.108 #
	%	23.7%	16.1%	19.7%		
Absent	Count	103	125	228		
	%	76.3%	83.9%	80.3%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

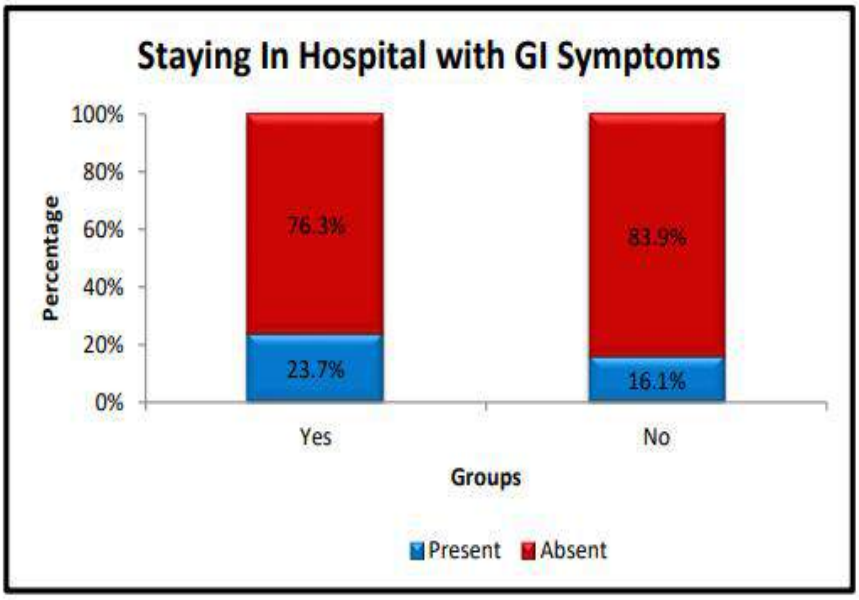


Figure 17

From the above table and graph it shows the comparison between Staying in Hospital with GI Symptoms by Pearson's Chi-Square test were Chi-Square value =2.582, p=0.108>0.05 level of significance which shows no statistical significance association between Staying in Hospital and GI Symptoms in the present study.

Table: 18 Comparison between Death with GI Symptoms by Pearson's Chi-Square test

Death		GI Symptoms		Total	x 2 - value	p-value
		Yes	No			
Present	Count	7	12	19	0.934	0.334 #
	%	5.2%	8.1%	6.7%		
Absent	Count	128	137	265		
	%	94.8%	91.9%	93.3%		
Total	Count	135	149	284		
# No Statistical Significance at p > 0.05 level						

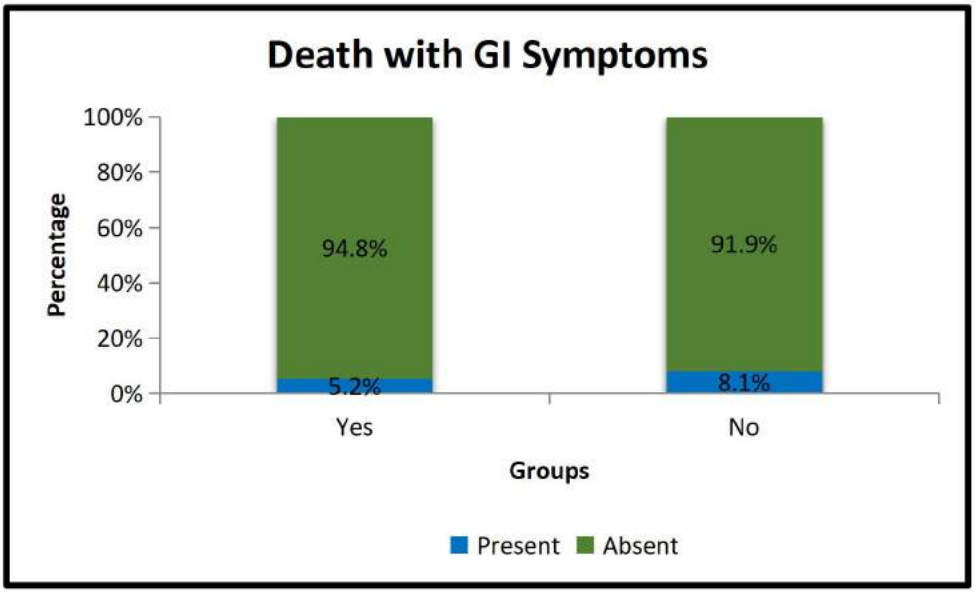


Figure 18

The above table shows comparison between Death with GI Symptoms by Pearson's Chi-Square test were x2=0.934, p=0.334>0.05 which shows no statistical significance association between Death and GI Symptoms.

Table: 19 Comparison between Pneumonia with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Pneumonia		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	64	168	232	9.232	0.002 **
	%	94.1%	77.8%	81.7%		
Absent	Count	4	48	52		
	%	5.9%	22.2%	18.3%		
Total	Count	68	216	284		
** Highly Statistical Significance at p < 0.01 level						

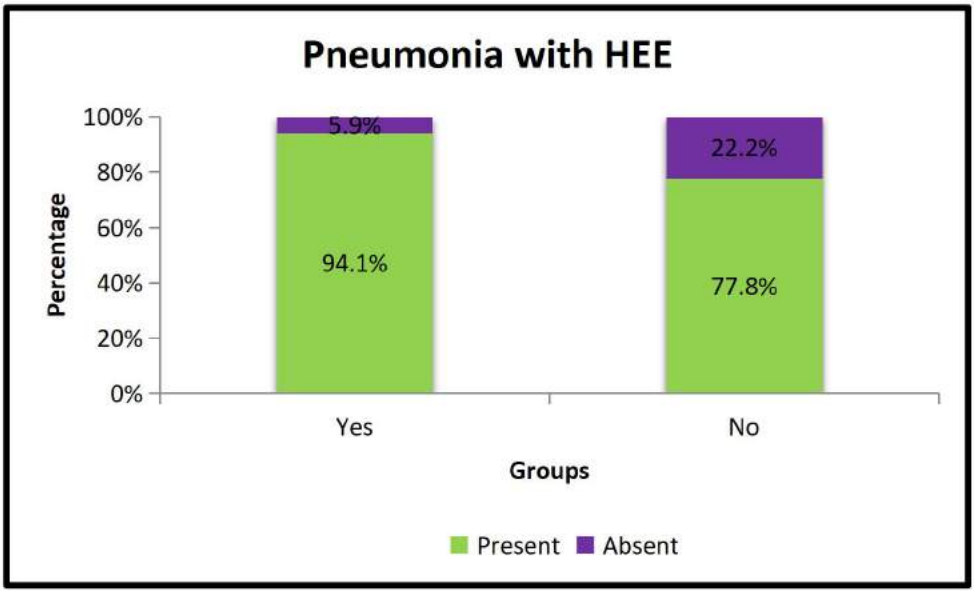


Figure 19

The above table shows comparison between Pneumonia with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=9.232, p=0.002<0.01 which shows highly statistical significance association between Pneumonia and Hepatic enzyme Elevation(HEE).

Table: 20 Comparison between Acute Respiratory Distress Syndrome with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Acute Respiratory Distress Syndrome		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	3	2	5	3.633	0.091 #
	%	4.4%	.9%	1.8%		
Absent	Count	65	214	279		
	%	95.6%	99.1%	98.2%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

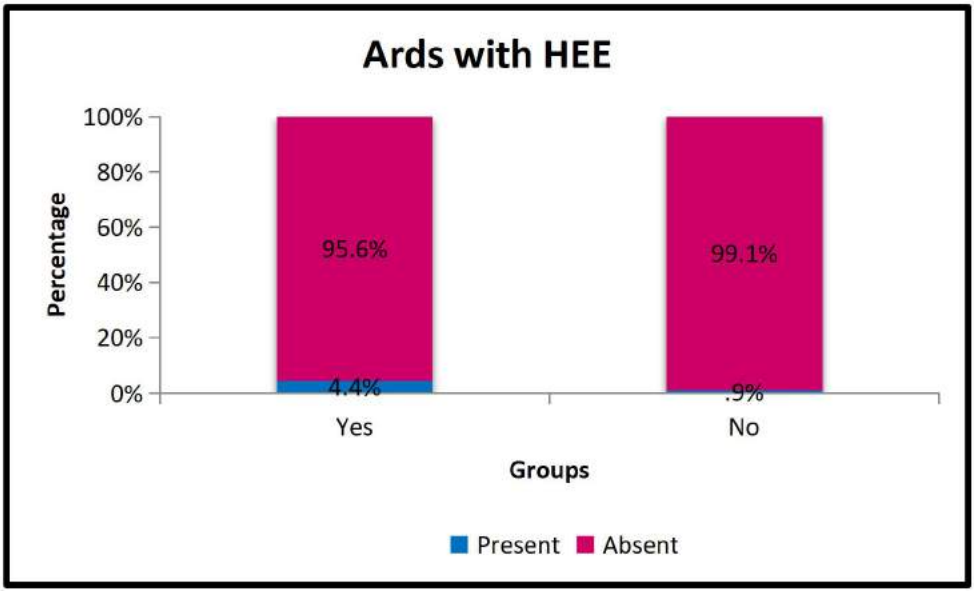


Figure 20

The above table shows comparison between Acute Respiratory Distress Syndrome with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=3.633, p=0.091>0.05 which shows no statistical significance association between Acute Respiratory Distress Syndrome and Hepatic enzyme Elevation(HEE).

Table: 21 Comparison between Arrythmias with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Arrythmias		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	2	6	8	0.005	1.000 #
	%	2.9%	2.8%	2.8%		
Absent	Count	66	210	276		
	%	97.1%	97.2%	97.2%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

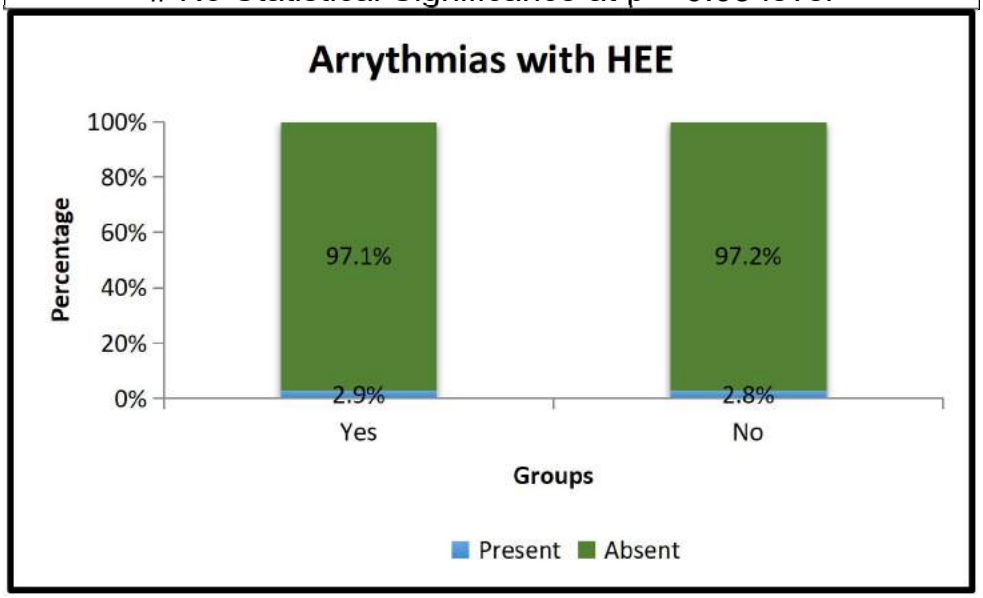


Figure 21

The above table shows comparison between Arrythmias with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=0.005, p=1.000>0.05 which shows no statistical significance association between Arrythmias and Hepatic enzyme Elevation(HEE).

Table: 22 Comparison between Shock with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Shock		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	3	5	8	0.831	0.402 #
	%	4.4%	2.3%	2.8%		
Absent	Count	65	211	276		
	%	95.6%	97.7%	97.2%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

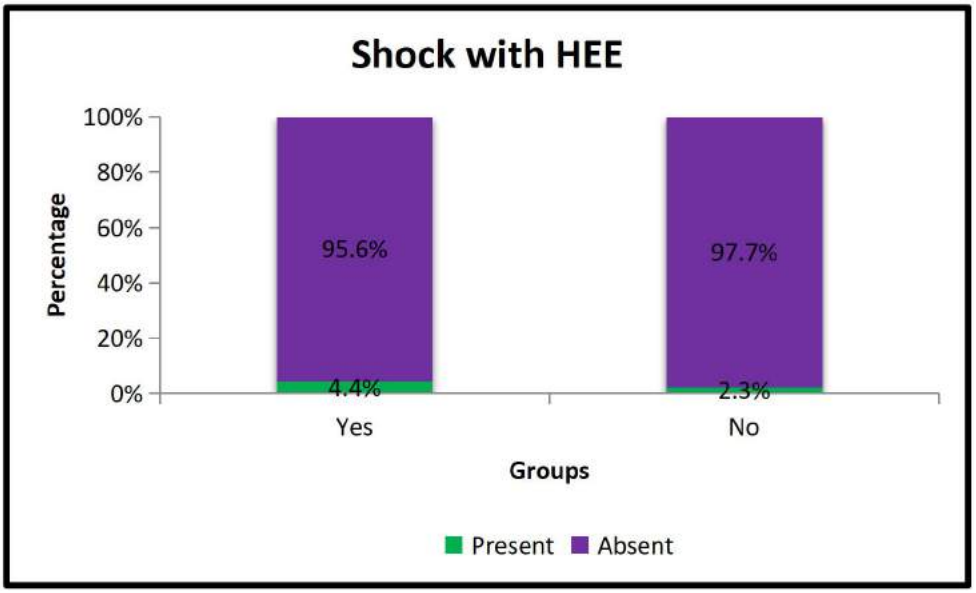


Figure 22

The above table shows comparison between Shock with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=0.831, p=0.402>0.05 which shows no statistical significance association between Shock and Hepatic enzyme Elevation(HEE).

Table: 23 Comparison between Acute Heart Failure with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Acute Heart Failure		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	1	4	5	0.043	1.000 #
	%	1.5%	1.9%	1.8%		
Absent	Count	67	212	279		
	%	98.5%	98.1%	98.2%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

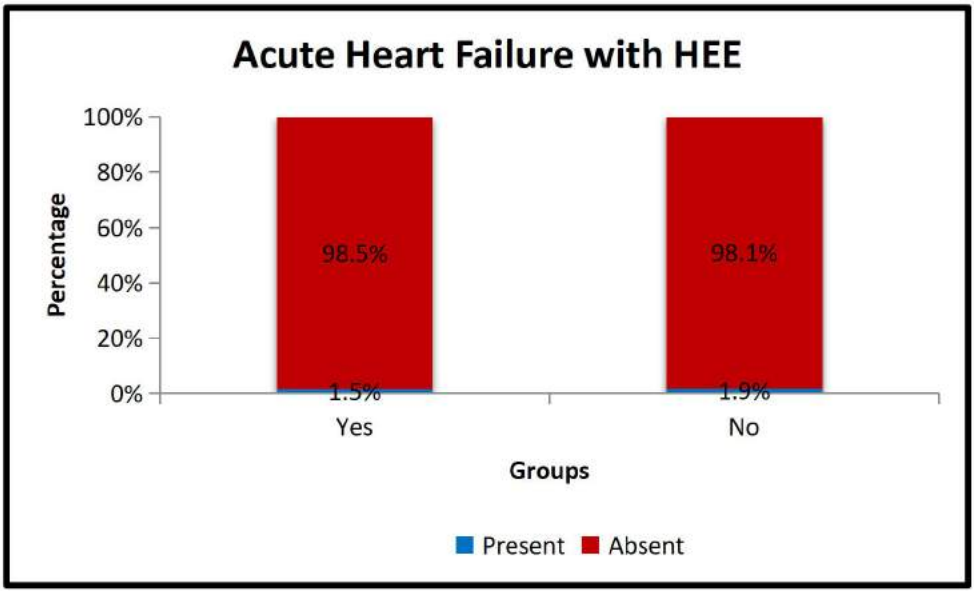


Figure 23

The above table shows comparison between Acute Heart Failure with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=0.043, p=1.000>0.05 which shows no statistical significance association between Acute Heart Failure and Hepatic enzyme Elevation(HEE).

Table: 24 Comparison between Outpatient Recovered with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Outpatient Recovered		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	1	55	56	18.806	0.0005 **
	%	1.5%	25.5%	19.7%		
Absent	Count	67	161	228		
	%	98.5%	74.5%	80.3%		
Total	Count	68	216	284		
** Highly Statistical Significance at p < 0.01 level						

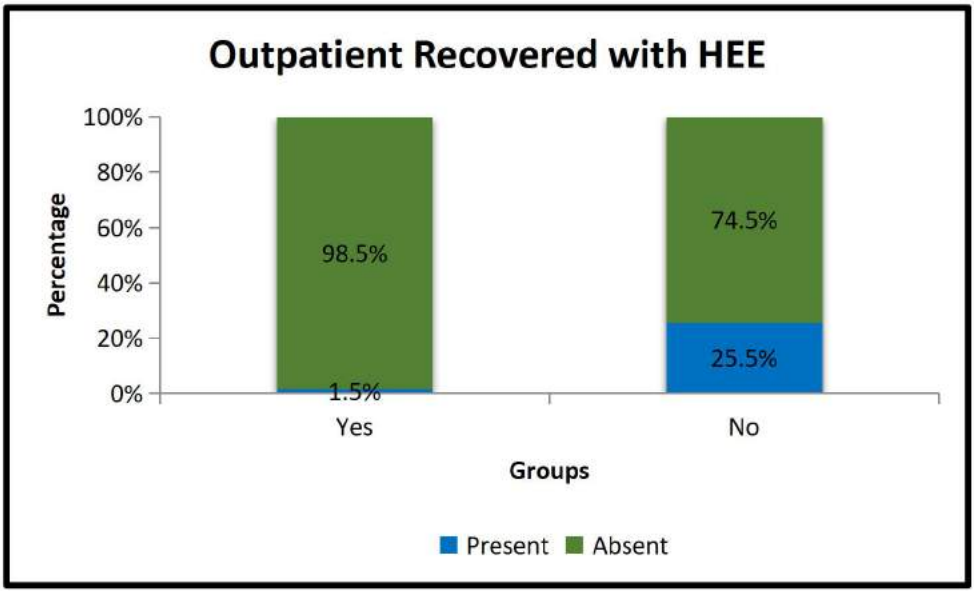


Figure 24

The above table shows comparison between Outpatient Recovered with hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=18.806, p=0.0005<0.01 which shows highly statistical significance association between Outpatient Recovered and Hepatic enzyme Elevation(HEE).

Table: 25 Comparison between Discharge From Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Discharge From Hospital		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	41	111	152	1.649	0.199 #
	%	60.3%	51.4%	53.5%		
Absent	Count	27	105	132		
	%	39.7%	48.6%	46.5%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

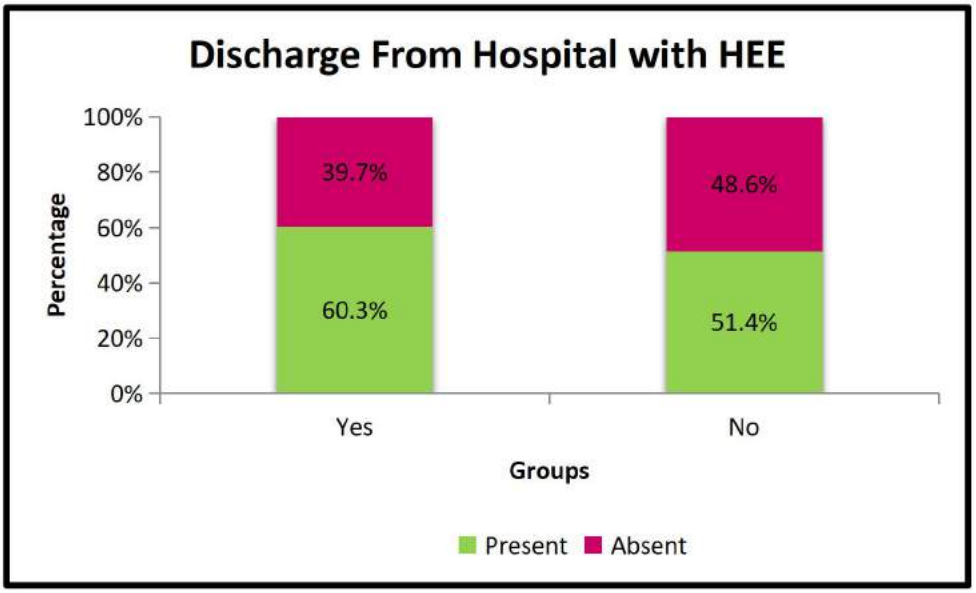


Figure 25

The above table shows comparison between Discharge From Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were x2=1.649, p=0.199>0.05 which shows no statistical significance association between Discharge From Hospital and Hepatic enzyme Elevation(HEE).

Table: 26 Comparison between Staying In Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Staying In Hospital		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	20	36	56	5.307	0.021 *
	%	29.4%	16.7%	19.7%		
Absent	Count	48	180	228		
	%	70.6%	83.3%	80.3%		
Total	Count	68	216	284		
* Statistical Significance at p < 0.05 level						

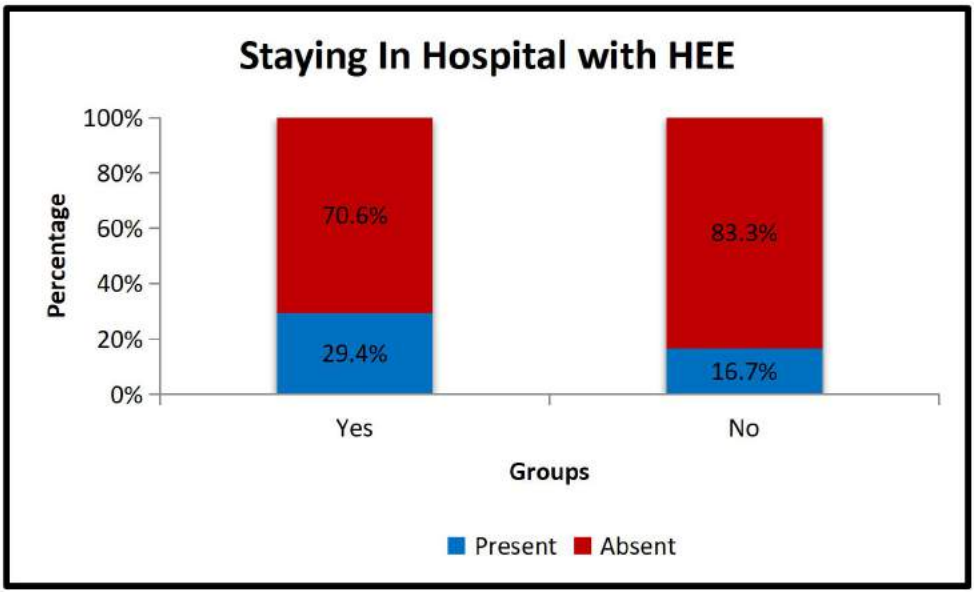


Figure 26

The above table shows comparison between Staying In Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=5.307$, $p=0.021<0.05$ which shows statistical significance association between Staying In Hospital and Hepatic enzyme Elevation(HEE).

Table: 27 Comparison between Death with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test

Death		HEE		Total	x 2 - value	p-value
		Yes	No			
Present	Count	6	13	19	0.652	0.419 #
	%	8.8%	6.0%	6.7%		
Absent	Count	62	203	265		
	%	91.2%	94.0%	93.3%		
Total	Count	68	216	284		
# No Statistical Significance at p > 0.05 level						

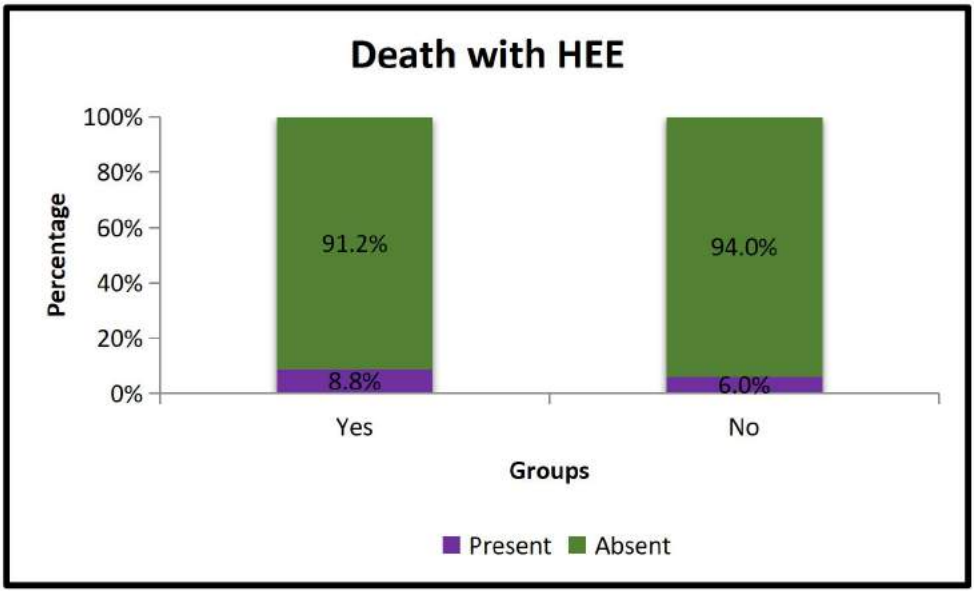


Figure 27

The above table shows comparison between Death with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=0.652$, $p=0.419>0.05$ which shows no statistical significance association between Death and Hepatic enzyme Elevation(HEE).

ANALYSIS AND RESULTS:

- Age distribution were 8.5% is 21-30 years, 25.0% is 31-40 years, 24.3% is 41-50 years, 27.5% is 51-60 years, 12.0% is 61-70 years, 2.8% is Above 70 years.
- Gender distribution were 49.3% are Female, 50.7% are Male.
- GI Symptoms distribution were 47.5% is Yes, 52.5% is No.
- HEE distribution were 23.9% is Yes, 73.1% is No.
- Primary symptoms distribution were 84.0% is Fever, 6.0% is Sore throat, 37.7% is Dry Cough, 41.9% is Expectoration, 25.7% is Chest Tightness, 14.1% is Shortness of Breath, 14.1% is Dizziness, 10.9% is Headache, 33.8% is Myalgia.
- GI symptoms distribution were 18.0% is Diarrhea, 7.7% is Nausea, 6.0% is Vomiting, 9.9% is Abdominal Pain, 15.8% is Loss Appetite, 19.7% is Loss of Taste.
- Hepatic enzyme Elevation distribution were 23.9% is SGPT, 23.9% is SGOT.
- Complications distribution were 81.7% is Pneumonia, 1.8% is Acute Respiratory Distress Syndrome, 2.8% is Arrythmias, 2.8% is Shock, 1.8% is Acute Heart Failure.
- Outcomes distribution were 19.7% is Outpatient Recovered, 53.5% is Discharge From Hospital, 19.7% is Staying in Hospital, 6.7% is Death.
- Pneumonia with GI Symptoms by Pearson's Chi-Square test were $x2=10.844$, $p=0.001<0.01$ which shows highly statistical significance association between Pneumonia and GI Symptoms.

- Acute Respiratory Distress Syndrome with GI Symptoms by Pearson's Chi-Square test were $x2=2.151$, $p=0.194>0.05$ which shows no statistical significance association between Acute Respiratory Distress Syndrome and GI Symptoms.
- Arrythmias with GI Symptoms by Pearson's Chi-Square test were $x2=0.020$, $p=1.000>0.05$ which shows no statistical significance association between Arrythmias and GI Symptoms.
- Shock with GI Symptoms by Pearson's Chi-Square test were $x2=4.052$, $p=0.069>0.05$ which shows no statistical significance association between Shock and GI Symptoms.
- Acute Heart Failure with GI Symptoms by Pearson's Chi-Square test were $x2=0.116$, $p=1.000>0.05$ which shows no statistical significance association between Acute Heart Failure and GI Symptoms.
- Outpatient Recovered with GI Symptoms by Pearson's Chi-Square test were $x2=27.689$, $p=0.0005<0.01$ which shows highly statistical significance association between Outpatient Recovered and GI Symptoms.
- Discharge From Hospital with GI Symptoms by Pearson's Chi-Square test were $x2=12.342$, $p=0.0004<0.01$ which shows highly statistical significance association between Discharge From Hospital and GI Symptoms.
- Staying in Hospital with GI Symptoms by Pearson's Chi-Square test were $x2=2.582$, $p=0.108>0.05$ which shows no statistical significance association between Staying in Hospital and GI Symptoms.

- Death with GI Symptoms by Pearson's Chi-Square test were $x2=0.934$, $p=0.334>0.05$ which shows no statistical significance association between Death and GI Symptoms.
- Pneumonia with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=9.232$, $p=0.002<0.01$ which shows highly statistical significance association between Pneumonia and Hepatic enzyme Elevation(HEE).
- Acute Respiratory Distress Syndrome with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=3.633$, $p=0.091>0.05$ which shows no statistical significance association between Acute Respiratory Distress Syndrome and Hepatic enzyme Elevation(HEE).
- Arrythmias with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=0.005$, $p=1.000>0.05$ which shows no statistical significance association between Arrythmias and Hepatic enzyme Elevation(HEE).
- Shock with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=0.831$, $p=0.402>0.05$ which shows no statistical significance association between Shock and Hepatic enzyme Elevation(HEE).
- Acute Heart Failure with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=0.043$, $p=1.000>0.05$ which shows no statistical significance association between Acute Heart Failure and Hepatic enzyme Elevation(HEE).
- Outpatient Recovered with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=18.806$, $p=0.0005<0.01$ which shows highly statistical significance association between Outpatient Recovered and Hepatic enzyme Elevation(HEE).

- Discharge From Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=1.649$, $p=0.199>0.05$ which shows no statistical significance association between Discharge from Hospital and Hepatic enzyme Elevation(HEE).
- Staying In Hospital with Hepatic enzyme Elevation(HEE) by Pearson's Chi-Square test were $x2=5.307$, $p=0.021<0.05$ which shows statistical significance association between Staying In Hospital and Hepatic enzyme Elevation(HEE).
- Death with Hepatic enzyme Elevation by Pearson's Chi-Square test were $x2=0.652$, $p=0.419>0.05$ which shows no statistical significance association between Death and Hepatic enzyme Elevation.

DISCUSSION:

The correlation between GI symptoms , hepatic enzyme Elevation with complications and outcomes of SARS CoV-2 Which was to improve the diagnosis and treatment plan of coronavirus–infected pneumonia .

In multiple studies mentioned below showed significant correlation and prevalence of GI symptoms.

Jayani c kariyawasam et al : GI manifestations are reported in 11.4-61% of individuals with COVID 19,with variable onset and severity

Luo et al. -high levels of nausea and vomiting following COVID-19

Lin et al - 61.1% of COVID-19 patients with GI symptoms

Fang et al.- 79.1% of patients are experienced gastrointestinal symptoms.

Shao- rui hao et al : 28.2% of patients with COVID-19 presented with elevated liver enzyme levels on admission, which could partially be related to SARS-CoV-2 infection

In this study showed prevalence of GI symptoms and Hepatic enzyme Elevation(HEE) are 18.0% is Diarrhea, 7.7% is Nausea, 6.0% is Vomiting, 9.9% is Abdominal Pain, 15.8% is Loss Appetite, 19.7% is Loss of Taste.

Hepatic enzyme Elevation were 23.9% is SGPT, 76.1% is SGOT in covid 19 patients

CONCLUSION:

Covid Patient affected with Gastrointestinal symptoms mostly have recovered completely, They are usually mild cases.

Mild covid affected patients showed mild hepatic enzyme Elevation.Although,Patients with more than 3 to 4 fold raise of hepatic enzyme elevation had mild to moderate covid disease,but their outcome was good.

LIMITATIONS:

In this study,other analysis like Stool RTPCR,stool culture were not done,because of not availability and also which was not feasible.Different strain variants has different phenotype presentation,variable communication rate and outcome,we were unable to find out strain variant of every patients.Covid immunization was not taken part in this study as vaccination was provide only to health care worker during later part of this study.

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Study Proforma :

NAME:

AGE:

SEX:

CONTACT ADDRESS AND PHONE NO:

CONTACT HISTORY:

TRAVEL HISTORY:

WHEN RETURNED TO HOME:

COVID POSITIVE ON

CLINICAL FEATURES:		DURATION
FEVER	YES/NO	
SORE THROAT	YES/NO	
DRY COUGH	YES/NO	
EXPECTORATION	YES/NO	
CHEST TIGHTNESS	YES/NO	
SHORTNESS OF BREATH	YES/NO	
DIZZINESS	YES/NO	
HEADACHE	YES/NO	
MYALGIA	YES/NO	
LOOSE STOOLS	YES/NO	
NAUSEA/VOMITING	YES/NO	
ABDOMINAL PAIN	YES/NO	
LOSS OF APPETITE	YES/NO	
LOSS OF TASTE	YES/NO	

COMORBITIES:
DIABETES /SHTN/CAD/CVA/SEIZURE DISORDER/THYROID DISORDER/DRUG INTAKE/ CHRONIC HEPATITIS INFECTION/CHRONIC LIVER DISEASE/INFLAMMATORY BOWEL DISEASE/CHRONIC SMOKER/CHRONIC ALCHOLIC

ON EXAMINATION:
VITALS PR: BP: RR: SPO2

SYSTEMIC EXAMINATIONS

CVS: RS:

P/A: CNS:

INVESTIGATIONS

CHEST X RAY:

CT CHEST:

COMPLETE BLOOD COUNT:

RENAL FUNCTION TEST:UREA CREATININE

SGOT/SGPT (10-40):

ECG AND ECHOCARDIGRAPHY:

TREATMENT ADVICE:

LOW MOLECULAR WEIGHT HEPARIN ,STEROIDS,TAB.IVERMECTIN

INJ.REMDESIVIR

COMPLICATIONS:PNEUMONIA,Acute Respiratory Distress Syndrome,ARRYTHMIAS,SHOCK, ACUTE HEART FAILURE

OUTCOME:Outpatient/recovered,Discharge from hospital,Staying in hospital,Death

INFORMED CONSENT

A Cross sectional study of Gastrointestinal and hepatic manifestations and its outcome in Covid 19 patients
Place of study: Govt. Stanley Hospital, Chennai- 600001

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

I have completely understood the details of the study.

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

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

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

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

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

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

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

Investigator Signature and date

A Cross sectional study of Gastrointestinal and hepatic manifestations and its outcome in Covid 19 patients

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

நான் .....,இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்துகொண்டேன்.ஆய்வில் பங்குஎடுத்துபோது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களைபற்றி நான்அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்பமுடியும், அதன்பின்னர்,நான் வழக்கம் போல் மருத்துவசிகிச்சை பெற முடியும் என்றுபுரிந்துகொள்கிறேன்

நான் ஆய்வில்பங்கு எடுத்து பணம் எதையும் பெறமுடியாது என்றுஅறிந்துள்ளேன்.

இந்தஆய்வின்முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை,

என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்ககூடாது.

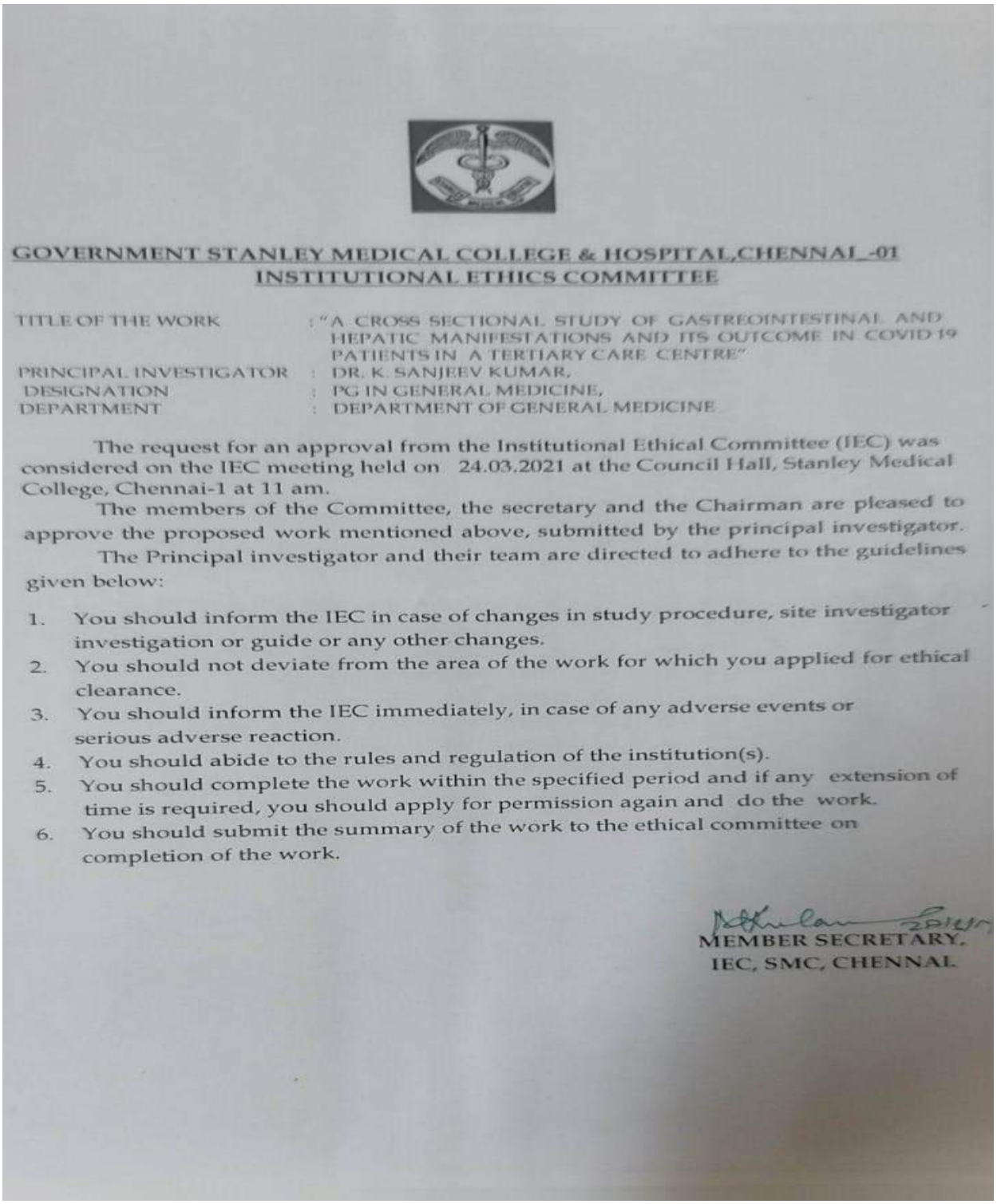
நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்யபோகிறேன் என்று தெரியும்

நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்
பெயர் மற்றும் முகவரி
கையொப்பம் / விரல்ரேகை

சாட்சி

INSTITUTIONAL ETHICAL COMMITTEE CERTIFICATE:



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

TITLE OF THE WORK	:	"A CROSS SECTIONAL STUDY OF GASTROINTESTINAL AND HEPATIC MANIFESTATIONS AND ITS OUTCOME IN COVID 19 PATIENTS IN A TERTIARY CARE CENTRE"
PRINCIPAL INVESTIGATOR	:	DR. K. SANJEEV KUMAR,
DESIGNATION	:	PG IN GENERAL MEDICINE,
DEPARTMENT	:	DEPARTMENT OF GENERAL MEDICINE

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 24.03.2021 at the Council Hall, Stanley Medical College, Chennai-1 at 11 am.

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

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

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

MEMBER SECRETARY,
IEC, SMC, CHENNAI.

ABBREVIATIONS:

SARS CoV-2: SEVERE ACUTE RESPIRATORY SYNDROME CORONA VIRUS 2

SGOT: Serum glutamic oxaloacetic acid transaminase

SGPT:Serum glutamic pyruvate transaminase

HEE: Hepatic enzyme Elevation

ARDS: Acute respiratory distress syndrome

MIS: multisystem inflammatory syndrome

PTE: Pulmonary thromboembolism

DVT: Deep venous thrombosis

GGO: Ground glass opacities

CORADS: Covid 19 reporting and data system

ACE-2 : Angiotensin converting enzyme-2

ILD: Interstitial lung disease

CO:carbon monooxide

HCQ:Hydroxychloroquine

CTPA:Computed Tomography Pulmonary Angiography

MOHFW:Ministry of Health and Family Welfare

GOI: Government of India

MHC:Major Histocombatability complex

TNF:Tumor necrosis factor

RTPCR: Reverse Transcription polymerase chain reaction

RdRP:RNA-dependent RNA polymerase

ORF1a: Open Reading Frame 1a

ORF1b: Open Reading Frame 1b

VLM:Viral Lysis Medium

NAAT: Nucleic acid amplification test

s.no	age	sex	fever	sore throat	DRY COUGH	EXPECTORATION	CHEST TIGHTNESS	shortness of breath	DIZZINESS	HEADACHE	MYALGIA	DIARRHEA	NAUSEA	VOMITING	ABDOMINAL PAIN	loss of appetite	loss of taste	ALT	AST	PNEUMONIA	ARDS	ARRYTHMIAS	SHOCK	ACUTE HEART FAILURE	OUTPATIENT RECOVERED	DISCHARGE FROM HOSPITAL	STAYING IN HOSPITAL	DEATH
1	45	MALE	1	0	1	0	1	1	1	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
2	56	MALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1
3	54	MALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
4	53	MALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
5	45	MALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
6	54	MALE	1	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
7	47	MALE	1	0	1	0	1	0	0	1	1	0	1	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0
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9	56	MALE	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
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80	65	MALE	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
81	76	MALE	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
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85	34	MALE	1	0	0	1	0	1	1	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
86	23	MALE	1	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
87	33	MALE	1	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
88	56	MALE	1	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	1
89	36	MALE	1	0	0	1	0	1	1	0	0	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
90	35	MALE	1	0	0	1	0	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
91	32	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
92	40	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
93	50	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	1	0
94	30	MALE	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
95	29	MALE	1	0	1	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	1	0	0
96	45	MALE	1	0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	1	0
97	38	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
98	35	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
99	32	MALE	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
100	22	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
101	44	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
102	33	MALE	1	0	1	0	0	0	0	0	0	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
103	54	MALE	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
104	45	MALE	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
105	56	MALE	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
106	54	MALE	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
107	53	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
108	45	MALE	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
109	54	MALE	1	0	1	0	0	0	0	0	0	0	0	1	0	1	1	1	1	1	0	0	0	0	0	0	1	0
110	47	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
111	52	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0
112	56	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
113	58	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
114	48	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
115	49	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
116	50	MALE	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
117	51	MALE	0	1	0	1	0	0	0	0	0	0	0	0	1	0	0	1	1	1	0	0	0	0	0	0	1	0
118	52	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
119	40	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
120	43	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
121	44	MALE	1	0	0	1	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
122	47	MALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
123	45	MALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
124	42	MALE	1	0	0	1	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0
125	52	MALE	1	0	1	0	0	0	0	0	0	1	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
126	54	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
127	59	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	0

128	60	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
129	45	MALE	1	0	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0
130	34	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
131	36	MALE	1	0	1	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
132	47	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
133	56	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
134	37	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
135	38	MALE	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0
136	65	MALE	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
137	61	MALE	0	1	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
138	65	MALE	1	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
139	56	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
140	54	MALE	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
141	43	MALE	1	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
142	34	MALE	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
143	36	MALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0
144	39	MALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
145	54	FEMALE	1	0	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
146	74	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
147	45	FEMALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1	0
148	56	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0
149	67	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
150	65	FEMALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
151	43	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
152	43	FEMALE	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
153	44	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
154	55	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
155	66	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
156	55	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
157	33	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
158	22	FEMALE	0	0	0	1	0	0	0	1	1	1	0	0	1	0	1	1	1	1	0	0	0	0	0	1	0	0
159	33	FEMALE	0	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
160	34	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	1	0	0	0
161	34	FEMALE	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	1
162	67	FEMALE	1	0	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0
163	65	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
164	54	FEMALE	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	1
165	43	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	0
166	46	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
167	23	FEMALE	1	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	1
168	56	FEMALE	1	0	0	1	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
169	44	FEMALE	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
170	43	FEMALE	1	0	1	0	0	0	0	0	1	1	0	0	0	0	0	1	1	1	0	0	0	0	0	1	0	0
171	65	FEMALE	1	0	1	0	1	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
172	67	FEMALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	1
173	68	FEMALE	1	0	1	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1
174	63	FEMALE	1	0	1	0	1	0	0	0	1	0	1	0	0	0	0	1	1	1	0	0	0	0	0	1	0	0
175	39	FEMALE	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
176	52	FEMALE	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
177	53	FEMALE	0	0	0	0	1	1	0	0	1	1	0	1	0	1	1	1	1	1	0	0	0	0	0	1	0	0
178	56	FEMALE	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
179	57	FEMALE	1	0	0	0	1	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
180	54	FEMALE	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
181	44	FEMALE	1	0	0	0	1	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
182	55	FEMALE	1	0	1	0	1	0	0	1	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
183	65	FEMALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
184	76	FEMALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
185	76	FEMALE	0	0	1	0	1	0	0	0	1	1	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0
186	54	FEMALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
187	43	FEMALE	1	0	1	0	1	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	1	0	0	0	0	1
188	34	FEMALE	1	0	1	0	1	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
189	23	FEMALE	1	0	1	0	1	0	0	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
190	33	FEMALE	1	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
191	56	FEMALE	1	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
192	36	FEMALE	0	1	1	0	1	1	1	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0

193	35	FEMALE	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
194	32	FEMALE	0	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
195	40	FEMALE	1	0	1	0	1	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
196	50	FEMALE	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
197	30	FEMALE	1	0	1	0	1	0	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
198	29	FEMALE	1	0	1	0	1	0	1	1	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
199	45	FEMALE	1	0	0	0	1	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
200	38	FEMALE	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
201	35	FEMALE	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
202	32	FEMALE	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
203	22	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
204	44	FEMALE	1	0	0	0	0	0	0	0	0	1	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
205	33	FEMALE	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
206	54	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
207	43	FEMALE	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	1	1	0	0	0	0	1	0	0
208	44	FEMALE	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1
209	55	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0
210	66	FEMALE	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
211	55	FEMALE	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
212	33	FEMALE	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
213	22	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
214	33	FEMALE	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
215	34	FEMALE	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0
216	34	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
217	67	FEMALE	1	0	0	0	0	0	0	0	1	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
218	65	FEMALE	1	0	0	0	0	0	0	1	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
219	54	FEMALE	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
220	43	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
221	46	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
222	23	FEMALE	1	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
223	56	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
224	44	FEMALE	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
225	43	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
226	65	FEMALE	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	1	0	0
227	67	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
228	68	FEMALE	0	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
229	63	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
230	39	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
231	52	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
232	53	FEMALE	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1	0	0
233	56	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
234	57	FEMALE	1	0	0	0	0	0	0	0	1	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
235	54	FEMALE	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	1	0
236	44	FEMALE	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
237	55	FEMALE	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
238	65	FEMALE	1	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
239	76	FEMALE	1	0	1	0	0	0	1	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0
240	76	FEMALE	1	0	1	0	0	0	0	0	1	0	0	0	0	0	1	1	1	1	0	1	0	0	0	0	0	1
241	54	FEMALE	1	0	1	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
242	43	FEMALE	0	0	1	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
243	34	FEMALE	1	0	1	0	0	0	1	0	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
244	23	FEMALE	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
245	33	FEMALE	1	0	1	0	0	0	1	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
246	56	FEMALE	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
247	36	FEMALE	1	0	1	0	0	1	1	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
248	35	FEMALE	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
249	32	FEMALE	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
250	40	FEMALE	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0	0
251	50	FEMALE	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
252	30	FEMALE	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	1	0	0
253	29	FEMALE	1	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
254	45	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
255	38	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
256	35	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
257	32	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0

258	22	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
259	44	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0
260	33	FEMALE	1	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1	0
261	54	FEMALE	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	1	0
262	30	FEMALE	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	0	1
263	29	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	1	0
264	45	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
265	38	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
266	35	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
267	32	FEMALE	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
268	22	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	0	0	0	0	0	1	0	0
269	44	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
270	33	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	0	0	0	1
271	54	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0
272	54	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
273	43	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
274	34	FEMALE	1	0	0	1	0	0	0	0	0	0	1	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
275	23	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
276	33	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
277	56	FEMALE	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	0
278	36	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0
279	35	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
280	32	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	1	1	1	1	1	1	0	0	0	0	1	0	0
281	40	FEMALE	1	0	1	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0
282	50	FEMALE	1	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	1	0	0	0	1
283	30	FEMALE	1	0	1	1	0	0	0	0	1	1	0	0	1	1	1	1	1	1	0	0	0	0	0	1	0	0
284	29	FEMALE	0	0	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0
	144																													
	140																													
	284		238	17	107	119	73	40	40	31	96	51	22	17	28	45	56	68	68	232	5	8	8	5	56	152	56	19