"ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE"

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE ."** submitted by **Dr. AYYAPPAN P** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D Degree Branch-I (General Medicine) isa bonafide research work carried out by her under direct supervision and guidance.

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DECLARATION

I, **Dr. AYYAPPAN P** , solemnly declare that the dissertation titled **"ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE "** is a bonafide work done by me at Government Stanley Hospital, Chennai between April 2021 and March 2022 under the guidance and supervision of **Prof. Dr. Kalpana ramanathan. M.D.,** Professor of Medicine, Government Stanley hospital, Chennai. I also declare that this bonafide work or a part of this work was not submitted by me or any other forward degree or diploma to any other university, board either in India or abroad. This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree (Branch – I) in General Medicine.

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"What's broken can be mended, what's hurt can be healed. No matter how dark it gets, the sun's gonna rise again"- Meredith Gray

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ABBRREVIATIONS

ACE-2	Angiotensin converting enzyme 2
AKI	Acute kidney injury
APTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blockers
ARDS	Acute respiratory distress syndrome
CBC	Complete blood count
CVA	Cerebrovascular accident
DIC	Disseminated intravascular coagulation
ECMO	Extracorporeal membrane oxygenation
GGO	Ground glass opacity
HFNO	High flow nasal oxygen
HIV	Human immunodeficiency virus
JAK	Janus kinase

LDH	Lactate dehydrogenase
LFT	Liver function test
MAP	Mean arterial pressure
NLR	Neutrophil lymphocyte ratio
PEEP	Positive end expiratory pressure
PLR	Platelet to lymphocyte ratio
PT	Prothrombin time
RAAS	Renin angiotensin aldosterone system
RT-PCR	Reverse transcriptase polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome corona virus 2
SOFA	Sequential organ failure assessment
TNF	Tumour necrosis factor
T2DM	Type 2 diabetes mellitus
WHO	World health organization

"ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE"

ABSTRACT:

BACKGROUND: The COVID-19 disease is caused by the SARS-CoV-2 virus. This disease's clinical signs might range from a minor cold to serious respiratory distress. In this study we aimed to determine the effectiveness of hematological parameters analyzed on admission in predicting the severity of illness among the confirmed COVID-19 patients.

METHODS: 100 patients with COVID 19 who are admitted and have given consent will be included in the study and followed up for a period of 5 days. Data were obtained regarding patients clinical symptomatology, O2 saturation, Respiratory rate, blood pressure and pulse rate on admission and on day 3 and day 5. Hematological parameters (complete blood count), inflammatory markers were done on admission and data were collected. Disease severity is assessed by the respiratory rate, O2 saturation requirement for oxygen supplementation, noninvasive and invasive ventilation on day 5.

RESULTS: Comparison of lymphopenia with severity showed that the patients with more severe illness had increased association with lymphopenia. This is statistically significant ($p<0.005$). Comparison of thrombocytopenia with severity showed that higher severity had increased association with thrombocytopenia. This is statistically significant ($p<0.005$). Comparison of NLR with severity showed that higher severity

had increased association with NLR. This is statistically significant ($p<0.005$). Comparison of PLR with severity showed that higher severity had increased association with PLR. This is statistically significant ($p<0.005$). Comparison of D-Dimer with severity showed that higher severity had increased association with D-Dimer. This is statistically significant ($p<0.005$).

CONCLUSION: According to this study, haematological parameters like lymphopenia, thrombocytopenia, elevated NLR, PLR, and elevated d-Dimer values at the time of admission are the markers that can predict the severity in a patient, oxygen requirement and intensive care management. So these patients should be given extra care and intense monitoring at the earliest to prevent the complications and mortality. Therefore hematological parameters like lymphocyte count, platelet count, NLR, PLR and d-Dimer should be monitored from admission for predicting the prognosis of the covid-19 patients.

KEY WORDS: Lymphopenia, thrombocytopenia, Neutrophil to lymphocyte ratio,Platelet to lymphocyte ratio.

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INTRODUCTION

The global pandemic COVID-19 disease is caused by severe acute respiratory syndrome corona virus - 2 (SARS CoV-2). The infection caused by this virus has wide range of clinical syndromes. It ranges from mild disease like common cold to severe disease with respiratory distress and leading to many complications. The risk of severe disease is more common in patients in the elderly age group and those with various associated co-morbid illness like diabetes, systemic hypertension, obesity and COPD. These patients are at increased risk of severe inflammation and cytokine storm leading to severe lung damage and complications.

Hematological parameters like lymphocytes, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and red cell distribution width are the markers of systemic inflammation and are extensively studied in various diseases. Abnormalities detected in blood count results are considered to be the potential predictors of outcomes. In our study, we are aiming to identify the hematological parameters of the Covid-19 confirmed patients which are analyzed on admission to be used in predicting the progression of disease by studying their relationship with disease severity.

AIMS AND OBJECTIVES

AIM:

- To study the hematological parameters in confirmed COVID-19 disease patients.

OBJECTIVES:

- To correlate the haematological parameters like lymphopenia, thrombocytopenia, neutrophil lymphocyte ratio, platelet lymphocyte ratio, and elevated d- dimer levels with the severity of the illness in patients infected with SARS-CoV-2 and its complications.

REVIEW OF LIERATURE

EPIDEMIOLOGY:

SARS CoV 2 is the virus that causes the severe acute respiratory syndrome pandemic known as corona disease (covid 19). On December 12, 2019, Wuhan, Hubei Province, China, announced the first case of COVID 19. Since then, it has become an outbreak and has spread quickly throughout the world's nations. On January 31, 2020, WHO designated it a global health emergency. The World Health Organization subsequently labelled it a global pandemic on March 11, 2020.

As of December 5, 2021, there were approximately 264,815,815 confirmed cases of COVID 19 worldwide, according to the WHO. In the entire world, there have been around 5,249,793 deaths attributed to COVID 19. According to the WHO, there were approximately 34,633,255 confirmed cases in India as of December 5, 2021. Approximately 473,326 people have died in India overall as a result of the illness [1].

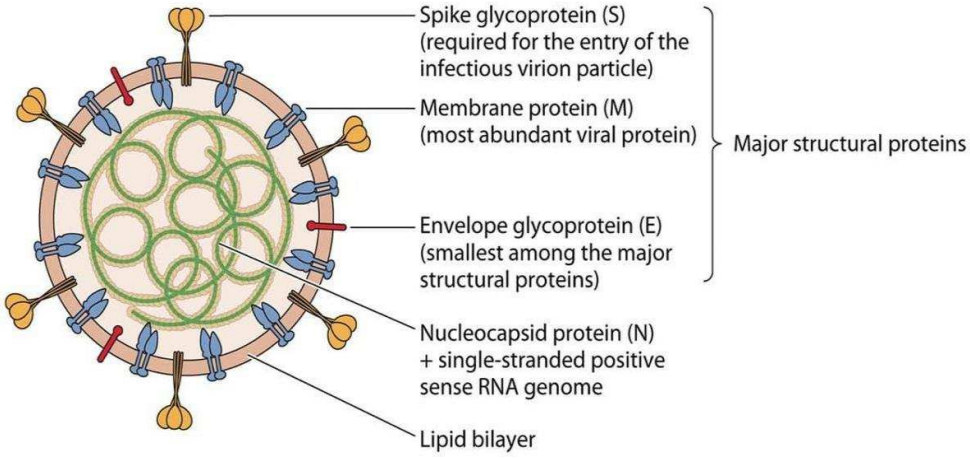
Table 1. Newly reported and cumulative COVID-19 confirmed cases and deaths, by WHO Region, as of 5 December 2021**

WHO Region	New cases in last 7 days (%)	Change in new cases in last 7 days *	Cumulative cases (%)	New deaths in last 7 days (%)	Change in new deaths in last 7 days *	Cumulative deaths (%)
Europe	2 687 257 (65%)	-3%	88 925 399 (34%)	28 990 (55%)	-2%	1 569 599 (30%)
Americas	935 062 (23%)	21%	97 679 255 (37%)	12 987 (25%)	38%	2 360 315 (45%)
Western Pacific	199 495 (5%)	-10%	10 370 429 (4%)	3 220 (6%)	2%	144 204 (3%)
South-East Asia	109 044 (3%)	-10%	44 638 985 (17%)	5 324 (10%)	49%	711 660 (14%)
Eastern Mediterranean	94 724 (2%)	0%	16 846 148 (6%)	1 622 (3%)	-8%	310 727 (6%)
Africa	79 491 (2%)	79%	6 354 835 (2%)	498 (1%)	-13%	153 275 (3%)
Global	**4 105 073 (100%)**	**2%**	**264 815 815 (100%)**	**52 641 (100%)**	**10%**	**5 249 793 (100%)**

**Percent change in the number of newly confirmed cases/deaths in the past seven days, compared to seven days prior*

SARS-CoV-2:

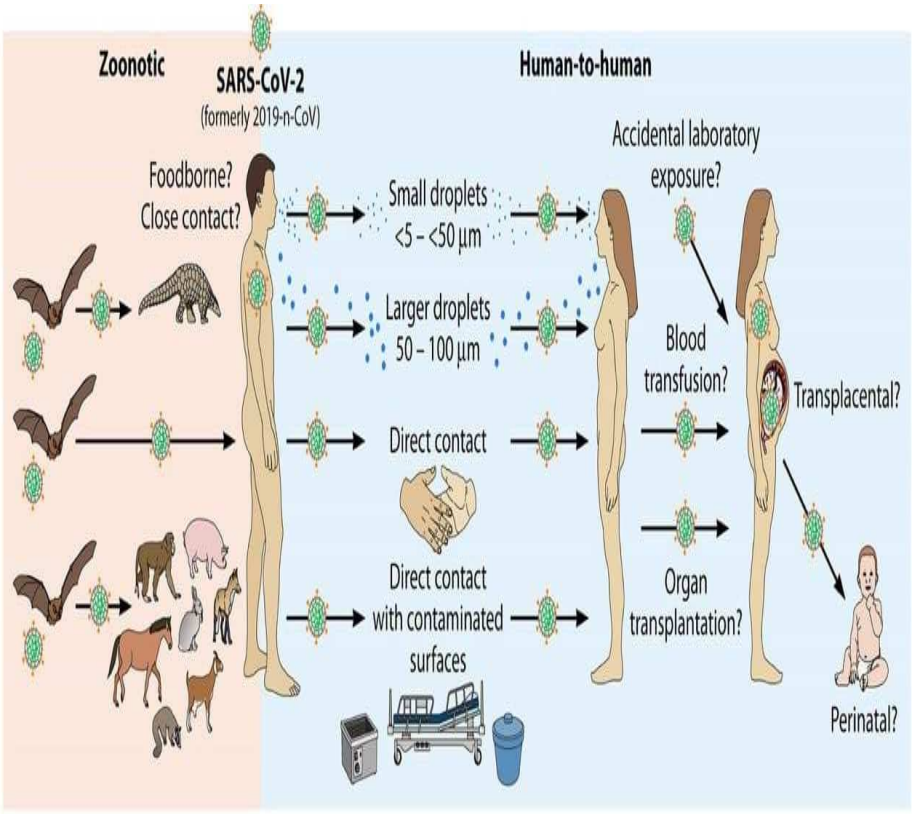
The COVID-19 disease is brought on by the SARS-CoV-2 virus. This disease's clinical signs might range from a minor cold to serious respiratory distress. The virus is a member of the family Coronaviridae, subfamily Orthocoronavirinae, and order Nidovirales, which is further classified into four genera. Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus are the four genrera. Gammacoronavirus and Deltacoronavirus emerged from avian and swine gene pools, while the genera Alphacoronavirus and Betacoronavirus arose from bats[2]. Coronavirus are single stranded, enveloped positive sense RNA viruses. The virus consists of four major structural proteins. It includes, spike protein(S), membrane protein(M), envelope protein(E), and nucleocapsid protein(N)[2].



SARS-CoV-2 structure[2]

ROUTE OF TRANSMISSION:

Infected respiratory droplets are the main means of SARS-CoV-2 transmission from one patient to another. Nasal, conjunctival, and oral mucosal surfaces become infected when they come into direct or indirect touch with these infectious droplets. Close contact with the animals or eating tainted food are the most likely causes of animal-related infections in humans. Direct contact with the contaminated surface, blood transfusion, organ transplantation, unintentional laboratory exposure, and transplacental transmission are additional possible transmission routes [2].

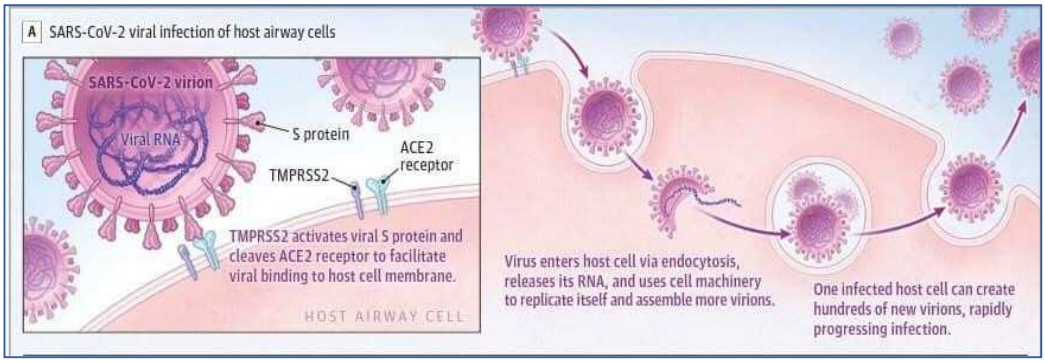


The risk of transmission is influenced by the type of contact, the environment,

the host's infectiousness, socioeconomic level etc. Close quarters contact (15 minutes face to face and within 2 metres) is the most prevalent method of virus transmission and is highly effective in spreading the illness. There are between 4% and 35% of secondary attacks per family. In a closed setting as opposed to an open one, the risk of transmission is higher[3].

PATHOPHYSIOLOGY:

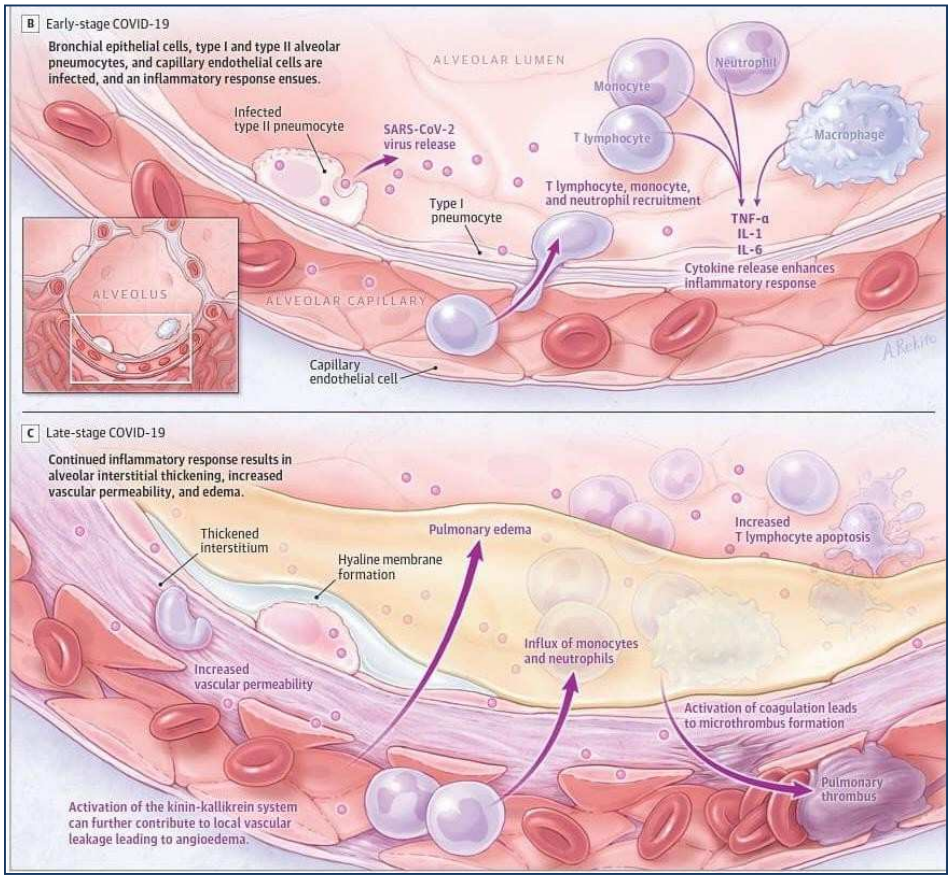
The spike protein (S) of the organism interacts with the ACE-2 receptor produced in the host cell membrane when the virus enters the host. By cleaving the ACE-2 receptor and activating the viral spike protein, the serine protease type 2 transmembrane serine protease (TMPRSS2), which is present in the host cell, enhances viral uptake. [4]



Bronchial epithelial cells, type 1 and type 2 alveloar pneumocytes, and capillary endothelial cells are all infected in the early stages of the illness. T lymphocytes, monocytes, and neutrophils are recruited to the inflammatory site as the inflammatory cascade starts. TNF alpha, IL-1, IL-6, and other cytokines are then released by the recruited cells, as well as by the infected cells and alveolar macrophages. These

cytokines intensify the inflammation even further.[4]

As the condition progresses, continuous inflammation causes the alveolar interstitium to thicken and vascular permeability to rise, both of which cause pulmonary edema. The kinin-kallikrein system is activated, which increases vascular leakage and permeability. Early acute respiratory distress syndrome (ARDS) is caused by pulmonary edema filling the alveolar gaps and by the production of hyaline membranes. The hallmarks of COVID disease include endothelial degradation, defective alveolar-capillary oxygen transport, and reduced oxygen diffusion capacity.[4]



Patients with advanced illness have microthrombi development when pulmonary endothelial cells and inflammatory lung tissue activate the coagulation cascade.

Increased rates of arterial and venous thrombotic consequences, including pulmonary embolism, deep vein thrombosis (DVT), myocardial infarction, ischemic stroke, and limb ischemia are caused by this[4].

CLINICAL FEATURES:

Patients with COVID 19 disease exhibit a broad range of clinical symptoms. It might be anything from a minor cold to serious respiratory trouble. Patient may even show no symptoms.

Most common symptoms includes :[5]

- Fever (83-99%)
- Cough (59-82%)
- Fatigue (44-70%)
- Anorexia (40-84%)
- Shortness of breath (31-40%)
- Myalgia (11-35%)
- Other general symptoms include a sore throat, stuffy nose, headache, nausea, vomiting, diarrhoea, anorexia, and loss of taste (ageusia).
- There are also reports of neurological problems like dizziness, weakness, seizures, and signs of a stroke.
- Older adults and patients with immunocompromised states frequently have atypical symptoms such diminished alertness, disorientation, and decreased mobility.

- Symptoms like fever, cough are reported less in children than adults.

RISK FACTORS ASSOCIATED WITH SEVERE DISEASE: [5]

Several factors, including the following, are linked to the development of severe disease in COVID 19 disease patients:

- Age more than 60 years
- Diabetes mellitus
- Hypertension
- Obesity
- Cardiac disease
- Chronic kidney disease
- Chronic lung disease
- Cerebrovascular disease, dementia
- Immunosuppression and cancer
- HIV

Smoking, a higher SOFA score, and a D-dimer level of more than 1 microgram per litre upon admission are additional risk factors that are also linked to a greater death rate.

In pregnancy, increased maternal age, high body mass index, chronic illnesses, gestational diabetes, and pre-eclampsia are all risk factors.

COVID-19 DISEASE SEVERITY CLASSIFICATION:

As per WHO, COVID-19 disease is classified as follows:[5]

- Mild disease
- Moderate disease
- Severe disease
- Critical disease.

Mild disease		Patients that fulfill the COVID-19 case description but do not have viral pneumonia or hypoxia
Moderate disease	Pneumonia	Fever, cough, dyspnea, and fast breathing are all symptoms of pneumonia, but there are no signs of severe pneumonia, such as SpO2 levels more than or equal to 90% on room air. [6]
Severe disease	Severe pneumonia	Clinical signs of pneumonia (fever, cough,

		dyspnoea) plus one of the following:[6] • Respiratory rate >30 breaths/minute • SpO2 < 90% on room air • Severe respiratory distress
Critical disease	a) Acute respiratory distress syndrome (ARDS)[7]	• Onset : within 1 week of known clinical insult or new or worsening respiratory symptoms • Chest radiograph : Bilateral lung opacities unrelated to nodules, lobar or lung collapse, or volume overload. • Respiratory failure not fully explained by cardiac failure or fluid overload • Oxygenation impairment in adults includes : • Mild ARDS: 200 mmHg

		< PaO2/FiO2 ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O) • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O) • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O).
	b) sepsis[8]	Acute life threatening organ dysfunction due to dysregulated host response to the infection. Signs of organ dysfunction includes: • Altered mental status • Dyspnoea ,tachypnoea, tachycardia, low SpO2 • Cold extremities, weak pulse , low BP • Oliguria

		• Thrombocytopenia, coagulopathy • High lactate, acidosis, hyperbilirubinemia
	c) septic shock:[9]	persistent hypotension needing vasopressors to maintain MAP more than or equal to 65 and serum lactate levels greater than 2 mmol/L despite fluid resuscitation

DIAGNOSTIC TESTING:

A) POLYMERASE CHAIN REACTION:

The usual method of diagnosis uses reverse transcription polymerase chain reaction to detect SARS-Co2 RNA from respiratory samples. Compared to upper respiratory samples, lower respiratory tract samples have the highest positive rate. The timing of the test in relation to virus exposure also affects how sensitive the test is. According to one study, sensitivity was 33% 4 days after exposure, 62% on the first day of symptoms, and 80% 3 days afterwards[4].

Positivity rates of the various specimens in RT-PCR:[11]

- Bronchoalveolar lavage fluid(BAL) - 93% (highest)

- Sputum - 72%
- Nasal swabs - 63%
- Pharyngeal swabs - 32%

TABLE 2 Clinical specimens for detection of SARS CoV-2

Sample	Recommendation
Bronchoalveolar lavage fluid	+++
Sputum	+++
Nasal swabs	+++
Fibrobronchoscope brush biopsy	++
Pharyngeal swabs	++
Feces	+
Blood	+
Urine	+

[a]Recommendations are based on references 245 and 246. +++, strong; ++, moderate; +, weak.

B) SEROLOGY:[12]

Serological testing aids in the diagnosis and evaluation of vaccination response. Within five days of infection, IgM antibodies are found, peaking two to three weeks into the illness. Approximately 14 days after the onset of symptoms, the IgG response is seen. High levels of antibody titre are linked to severe illness.

C) LABORATORY FINDINGS:

The abnormal laboratory results in COVID-19 disease are crucial for both diagnosis and prognosis. Several valuable prognostic markers are provided to the clinicians by the basic haematological values, which play a significant role in the triage and care of the patients, according to research done in China. Complete blood count (CBC), coagulation profile (PT, aPTT, D-dimer), and inflammatory markers like ESR, CRP, ferritin and procalcitonin are among the standard studies done on patients with COVID-19. KFT and LFT are also performed since the virus has the potential in

infect several vital organs like the kidneys and the liver [13]

Some expected laboratory abnormalities in COVID 19 infection include lymphopenia, isolated neutrophilia, thrombocytopenia, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and D-Dimer. This literature review summarizes the hematological variations seen in COVID 19 and their clinical significance in aiding in a better understanding of the existing data about haematological alterations in COVID-19 infection, and debating particular prognostic markers which may be useful to stratify patients according to the severity of the disease.

1. COMPLETE BLOOD COUNT:

Lymphocytes:

The most common haematological defect in COVID-19 infected patients is lymphopenia, which can occur in up to 85% of severe cases and is correlated with prognosis. Most published series report the occurrence of lymphopenia, which is characterised by an absolute lymphocyte count of less than 1.0 x 10^9/L and is typically thought to be an inadequate immune response to viral infection(14). Since the SARS-CoV-2 was discovered, influenza has been used as a comparison for this new virus. The most thoroughly researched viral respiratory infection is influenza, which is frequently cited as the origin of epidemics. In comparison to the common COVID-19 and influenza groups, the severe COVID-19 group's lymphocyte count was observed to be considerably lower (P 0.001 and P = 0.012). Those who showed pneumonia on imaging were considered to be common cases of Covid-19 infection since they had a fever and respiratory symptoms.

Severe covid was defined as a case with:

a) shortness of breath with a respiration rate greater than 30 breaths per minute,

b) mean oxygen saturation of less than 93% while at rest,

c) partial pressure of arterial oxygen/oxygen concentration of less than 300 mmHg, was considered to be a severe case.

In severe cases, lesions that were discovered by lung imaging had progressed by more than 50% in just 24 to 48 hours. By analysing samples from nasal and pharyngeal swabs for RT-PCR, all influenza cases were verified. Influenza and severe COVID-19 groups had significantly lower lymphocyte percentage rates than the common COVID-19 group(P 0.001)[15]. However, distinct subpopulations of CD8+ T cells might be involved in COVID-19 and influenza. When analysing disease-specific transcriptional signatures in CD8+ T cells, the authors found that biological pathways for responses to interferon (IFN)-I and -II were associated more with the influenza-specific cellular cluster, whereas pathways for the response to tumour necrosis factor (TNF) or interleukin-1β (IL-1β) were more prominent in COVID-19-specific clusters..

It is well known that the number of total lymphocytes and the subsets change depending on the virus type, suggesting a possible connection between the changing of the lymphocyte subset and viral pathogenic mechanisms[16]. Lymphopenia may be brought on directly by immunological damage from inflammatory mediators or indirectly by virus attachment. Additionally, lymphopenia may result from the exudation of circulating lymphocytes into inflamed lung tissues. Twenty peer-reviewed studies that reported lymphocyte subset counts and the severity of COVID-

19 disease examined the relationship between the decline in lymphocyte subset count in COVID-19 patients. Those with severe/critical COVID-19 disease had a statistically significant decrease in their CD4+ T cell, CD8+ T cell, B cell, Natural killer (NK) cell, and total lymphocyte cell counts as compared to patients with mild/moderate disease[17]. Counts of total, CD4+, or CD8+ T cells lower than 800, 400, or 300/μL, respectively, were negatively correlated with the patient outcome; the counts of the total, CD4+, and CD8+ T cells, importantly, were significantly lower in ICU patients than non-ICU cases. Further, an age-dependent reduction of T cell numbers was observed with the lowest T cells numbers found in patients ≥ 60 years old, thus suggesting a potential cause for increased susceptibility in elderly patients[18].

While CD4+/CD8+ ratio was found to be positively connected with ESR and CRP, total lymphocytes, CD4+, and CD8+ T cells were found to inversely correlate with these inflammatory indicators. However, a typical automated cell counter is unable to detect the expression of cell surface and intracellular molecules; instead, flow cytometry must be used to do the analysis. Along with the severity of COVID-19 disease, a progressive T cell depletion has also been seen over the course of infection. This is caused by the production of certain immune-inhibitory molecules[19].

It is widely established that T cell fatigue caused by prolonged activation by the virus can reduce cytokine production and cause cellular malfunction. On the other hand, a rise in T cells and NK cells was a side effect of effective chloroquine therapy. Therefore, it is possible to speculate that SARS-CoV-2 correlates with functional exhaustion of cytotoxic cells at the early stage in COVID-19 patients with severe pulmonary inflammation, which could lead to illness[20]. A low T cells count, an

increase in naïve helper T cells, and a decrease in memory helper T cells were found in patients severely affected by COVID-19. Moreover, a lower level of regulatory T cells has been found in severe cases. Reconstitution of lymphocytes may be an important factor for recovery. Low lymphocyte count might be used by clinicians in risk stratification to predict severe and fatal COVID-19 in hospitalized patient.

Platelets:

The platelet count is an important determinant in many classification schemes that assess the severity of the disease, such as in case of multi organ dysfunction syndrome. The occurrence of thrombocytopenia in COVID-19 infection corresponds with the severity of the illness and denotes the presence of a consumption coagulopathy. It is present in roughly 60% of severe cases, which is consistent with published data on severe acute respiratory syndrome and Middle East respiratory syndrome infection[21]. Numerous studies link lower platelet counts to worse COVID-19 disease and death. Patients with either more severe illnesses or poor outcomes or even non-survivors had lower platelet counts than healthy patients. This aspect could be explained by the fact that COVID-19's late clinical stage is when thrombocytopenia tends to reach a significant level[22].

It is possible to hypothesise three processes of a cascade to account for thrombocytopenia in SARSCoV-2 infections:

1) Direct viral infection of bone marrow cells, which prevents platelet synthesis;

2) Immune system destruction of platelets;

3) platelet accumulation in the lungs, which results in the creation of microthrombi and additional platelet consumption. Megakaryocyte interactions with viruses can

result in decreased platelet production[23].

The original production of platelets and the ensuing thrombocytopenia are thought to be suppressed by the SARS-CoV-2 through particular receptors that limit bone marrow haematopoiesis. Pulmonary capillary damage is a result of viral infection and inflammation. Megakaryocyte rupture and higher platelet consumption may result from pulmonary endothelial cells and damaged lung tissues [24]. Additionally, SARS-CoV-2 can increase autoantibodies and immunological complexes, which causes the immune system to specifically destroy platelets. While platelets support the alveolar capillaries basal barrier integrity, they may potentially exacerbate lung damage in a number of pulmonary diseases and syndromes. Acute lung injury's aetiology may be influenced by platelet-leukocyte aggregates and platelet-endothelial interactions. Infection with Covid-19 can harm lung tissues and endothelial cells, which can lead to PLT aggregations, the development of microthrombi, and increased platelet consumption [25]. In fact, the majority of individuals with thrombocytopenia had high D-dimer concentrations and altered coagulation parameters, which supports the theory that these conditions can cause intravascular coagulation.

A 96% accurate prediction of the illness severity has been made using the platelet count in conjunction with the hypoxemia value. Contrarily, thrombocytosis affects a very tiny percentage of people [26]. The mean platelet volume (MPV) of COVID-19 patients was found to be considerably higher than that of critically ill non-COVID-19 patients who were matched for platelet count. Additionally, patients with COVID-19 showed a statistically significant tendency of increased immature platelet fraction (IPF). Additionally, COVID-19-positive patients had relative IPF 8% at platelet counts

up to 251 x109/L. COVID-19 positivity was highly predictive of an absolute IPF of 7.5 x109/L or greater. On comparison, only patients with platelet counts lower than 70 x109/L in the non-COVID-19 patients had a relative IPF of less than 8%[27]. These results imply that COVID-19 is linked to larger, immature platelet production because megakaryocytes react to higher platelet consumption.

Neutrophils:

Neutrophilia corresponds with a hyperinflammatory state and cytokine storm, which are key components of the pathogenic process of COVID-19, with the exception of patients with bacterial infections or superinfections. Numerous viral respiratory illnesses connected to ARDS involve neutrophils[28]. Leucocytosis, which is supported by neutrophilia, is only present in a small percentage of individuals; this finding seems to be associated with a more severe course. Neutrophilia has been found as a sign of severe respiratory disease and a poor outcome as COVID-19 progresses because the quantity of circulating neutrophils gradually rises [29].

Patients with severe COVID-19 infections had considerably more leukocytes and neutrophils than those with non-severe infections. There have been reports of morphological changes in circulating neutrophils in peripheral blood smear, including a decrease in nuclear lobularity and the presence of extensive cytoplasmic granulations. Prior to the emergence of the big reactive atypical cells that are indicative of viral infections, these morphological changes were brief and reversible [30]. SARS-CoV-2 infection encourages the generation of neutrophil extracellular traps, which, like other viral infections, can result in tissue damage. In COVID-19, abnormal neutrophil activation may make the host reaction worse.

Neutrophils were found in lung capillaries and extravasated into the alveolar space during lung autopsy. By enhancing degranulation and cytokine production, neutrophils play a critical role as drivers of the hyperinflammation associated with COVID-19 illness. In comparison to the moderate and mild groups, severe COVID-19 patients had a higher median neutrophil count on the day of hospital admission. The neutrophil count also rises from day 7 to day 9 after the onset of symptoms. It has been suggested that the shift in neutrophil numbers in peripheral blood or tissues may be strictly related to lung injury in COVID-19 patients given the link between neutrophilia and poor outcomes[30]. If these results are confirmed, it may be possible to target neutrophils and the mediators of their recruitment to lessen the severity of COVID-19.

Neutrophil-lymphocyte and platelet-lymphocyte ratio:

The neutrophil-lymphocyte ratio (NLR: absolute neutrophil count/absolute lymphocyte count) and platelet-lymphocyte ratio (PLR: absolute platelet count/absolute lymphocyte count) have been shown to be helpful in the diagnosis, follow-up, and survey of a variety of systemic inflammatory processes, including cholangiocarcinoma, ischemic heart disease, acute pancreatitis, and as a prognostic marker of malignant tumours. Patients with COVID-19 infection have higher neutrophil-lymphocyte ratios in their blood; NLR in combination with IgG may be a more accurate indicator of COVID-19 severity than neutrophil count alone [31]. Levels of NLR and PLR correlate with COVID-19 disease severity. Patients with severe disease had higher NLR and PLR values compared to non-severe diseases[32].

Although the mechanisms behind the independent roles of PLR and NLR in the progression of COVID-19 are unknown, the overall number of leukocytes in

peripheral blood is normal or declines in the early stages of COVID-19, while the lymphocyte count declines. In comparison to survivors, deceased patient's initial and peak NLR values were greater (P 0.001). The increasing rise in neutrophils and/or the fall in lymphocytes are both correlated with an increase in NLR. A weakened system is generally indicated by a rise in neutrophils, whereas a fall in lymphocytes indicates an underlying bacterial infection. These indicate that COVID-19 patients with elevated NLR require special attention.

Patients who presented with a peak in platelet count during the course of the disease had worse outcomes, and the PLR at the time of the platelet peak was found to be an independent predictive factor for prolonged hospitalisation. White blood cells, neutrophils, platelets, and the NLR steadily grew from the time of admission and peaked on day 14. The PLR peaked on day 9, and lymphocytes did not achieve their maximum value but instead merely showed an upward trend. Following the patient's recuperation on day 14, the NLR and the PLR gradually recovered to normal [33]. The levels of novel serological biomarkers, such as NLR and PLR, were higher in the severe illness group of COVID-19 patients than in the mild to moderate disease group. Increased ferritin and PLR were discovered to be separate predictors of disease severity in COVID-19 patients.

Hyperinflammation brought on by SARS-CoV-2 appears to elevate PLR, which favours a poor prognosis. According to studies, PLR was associated with inflammation and could predict patient's mortality. PLR and the NLR can simply be determined from a differentially profiled complete blood count. They function in relation to lymphopenia, thrombocytosis, and relative neutrophilia. NLR and PLR can be easily

estimated using the differential count and are cost-effective, especially for many third world nations, but several inflammatory markers like CRP, ESR, lactate dehydrogenase, ferritin, and PCT are often evaluated in COVID-19 patients. Clinicians may be able to identify and follow up on patients with a higher risk of progression by keeping track of the predictors of severity.

Monocytes:

Monocytes make up around 5-9% of all peripheral leukocytes, and they stay in the bloodstream for one to two days before they can develop into tissue-resident macrophages. Through the angiotensin-converting enzyme (ACE2), SARS-CoV2 infects CD14+ monocytes, however viral replication in these cells is typically negligible or undetectable. Anyway, the COVID-19-associated cytokine storm is supported by the SARS-CoV-2-infected monocytes high production of inflammatory mediators. In particular, COVID-19 patients had lower levels of circulating classical monocytes (CD14++CD16), but higher levels of intermediate (CD14++CD16+) and non-classical (CD14+CD16++) monocytes.

Additionally, COVID-19 patients have larger-than-normal monocytes that are clearly recognised by regular flow cytometry. These FSC-high monocytes have the inflammatory markers CD11b+, CD14+, CD16+, CD68+, CD80+, CD163+, and CD206+ and release IL-6, IL-10, and TNF-alpha. Patients with a high percentage of normal monocytes, however, have a better prognosis and are more likely to recover quickly and leave the hospital sooner. We have not observed a similar pattern in patients with other viral diseases, such as H1N1 influenza and human immunodeficiency virus (HIV), and these findings appear to be rather specific for

COVID-19 [34]. Additionally, it was shown that monocytes from COVID-19 patients were capable of secreting GM-CSF, or granulocyte-macrophage colony-stimulating factor. It has been proposed that the rise in GM-CSF+ monocytes and IL-6+ monocytes in the peripheral blood is the cause of the inflammatory cytokine storms that occur during COVID-19 infection because the monocyte is the pathogenic GM-CSF responsive cell that requires GM-CSF to promote tissue damage in both mice and humans. The antiviral adaptive immune responses are negatively impacted when monocytes, which serve as antigen-presenting cells, are infected with SARS-CoV-2. Therefore, preventing the infection of monocytes and the subsequent stimulation of cytokine production and signalling pathways mediated by cytokines can also reduce systemic inflammation.

Eosinophils:

Eosinophils are not known to play a part in coronavirus-19 illness. Tissue-resident eosinophils play regulatory roles in organ growth and metabolism, protective immunity, and the gastrointestinal tract and the lung, respectively, according to physiological distribution. In a group of 140 SARS-CoV-2 patients in Wuhan, 53% of the patients developed eosinopenia at admission[35]. The percentage of eosinophils was 0.3%, while the absolute eosinophil count was 0.01 x 10^9/L. On admission, individuals with COVID-19 had lower levels of eosinophils, which, according to Spearman's correlation coefficient ($r_s = -0.462$; $P = 0.003$), were inversely connected to the severity of the disease. Additionally, before being discharged, the patient's peripheral blood eosinophils reverted to normal levels, suggesting a potential function for eosinophils in forecasting the patient's prognosis[36]. Uncertainty surrounds the

pathophysiology of eosinopenia in COVID-19, but it is likely multifactorial and connected to eosinophil migration to the inflammatory site, inhibition of eosinophil mobilisation from the bone marrow, blockade of eosinophilopoiesis, reduced expression of chemokine receptors/adhesion molecules, and/or direct eosinophil apoptosis induced by IFN-I released during the acute phase of inflammation [37].

Basophils

In-vivo, during allergic inflammation and infection, basophils leave the circulation and go to inflammatory areas, where they bind antigens to strengthen immune memory responses. Activated basophils promote IgM secretion by B cells as well as class switching to IgG or IgA. Basophil depletion was shown by Rodriguez et al. to occur during acute and severe COVID-19, indicating that the degree of basophil depletion may affect the effectiveness of IgG responses to SARS-CoV-2. In comparison to healthy controls, COVID-19 and influenza groups had lower basophil counts. Li et al. discovered that basophil numbers were lower in COVID-19 patients than in controls in the early stages of the disease. Both basophils and eosinophils have been shown to be capable of producing IL-4, a crucial cytokine for promoting the division of activated B and T cells. Therefore, the drop in lymphocyte count in COVID-19 patients may also be explained by the drop in basophil and eosinophil counts. It's interesting to note that viral infections in immunosuppressed patients were linked to reduced basophil numbers. Contrarily, it has been shown that a number of HIV proteins can interact with various surface receptors on human basophils; in addition, HIV-positive basophils have been discovered in the peripheral blood of AIDS patients. These factors could lead one to hypothesise that a viral encapsulation

mechanism in basophils is one reason why patients with COVID-19 infection have low basophil counts.

Red blood cells and haemoglobin:

It has been shown that SARS-CoV2-infection has a considerable effect on the protein and lipid balance of red blood cell (RBC) structural membranes. RBCs from COVID-19 patients had higher levels of glycolytic intermediates, along with membrane protein oxidation and fragmentation. As a result, COVID-19 affects two vital processes that regulate the fine tuning of red cell membranes and haemoglobin oxygen affinity. When moving from the lungs to the bloodstream, RBCs from COVID-19 patients may not be able to adapt to environmental changes in haemoglobin oxygen saturation, which could impair their ability to transport and distribute oxygen. Nitric oxide (NO) levels in RBC are higher in COVID-19 patients than in non-COVID-19 hypoxemic patients, however the mechanism(s) underlying this accumulation of intracellular NO in COVID-19 patient's RBC is yet unknown.

Recently, patients with COVID-19 were shown to have autoimmune hemolytic anaemia (AIHA). RBCs can modify platelet function through chemical signalling or direct RBC-platelet interactions, and autoimmune hemolytic anaemia promotes platelet cell death. Therefore, the microvascular coagulation observed in COVID-19 patients may be explained by signs of hemolysis. A positive direct antiglobulin test(DAT) was found in roughly half of the individuals with COVID-19 tested at Berzuini et al blood's centre. Eluates, on the other hand, reacted with red blood cells from COVID-19 patients whose DAT results were negative but not with any test cells. This implies that COVID-19 might alter the red cell membrane and produce fresh

antigenic epitopes (38). Patients with COVID-19 have lower haemoglobin levels and pathologically higher ferritin concentrations. Low haemoglobin levels (below 110 g/L) were linked to illness progression. Serum ferritin mean differences were greater in severe COVID-19 patients compared to moderate instances. While there was a non-linear relationship between patient variables and ferritin concentration in survivors and non-survivors, there was a linear relationship between age and ferritin concentrations in severe and mild COVID-19 cases. Throughout the clinical course, non-survivors' serum ferritin concentrations were higher than those of survivors (562 ng/mL vs. 492 ng/mL), and they also rose as the disease progressed (39). Severe COVID-19 cases had decreased haemoglobin and RBC and increased ferritin and red cell distribution width (RDW) when compared to mild cases.

Anemia may occur from a pattern of anemia similar to sideroblastic anemia caused by changes in iron metabolism. Functional iron insufficiency was not linked to an increased risk of in-hospital death, ICU admission, or the requirement for mechanical ventilation, but it was strongly linked to significantly worse clinical conditions and a longer hospital stay. The death rate and increased ferritin concentrations did not significantly correlate. The new SARS-CoV2 attack on bone marrow erythroblasts has been found to interfere with haemoglobin at both the erythrocyte and bone marrow levels. Additionally, studies show elevated RDW in COVID-19 patients, indicating the presence of underlying erythroid myelodysplasia since RDW is higher when immature cells are generated [(40)]. It has been discovered that SARS-CoV-2 interacts with erythrocytes and/or blood cell precursors via ACE2, CD147, CD26, and other receptors, leading to viral endocytosis. As a result, the virus would attack the heme on

the 1-beta chain of haemoglobin, causing hemolysis and a complex to form with the released heme that would result in the production of a quantity of haemoglobin that was defective.

2. INFLAMMATORY MARKERS IN COVID

The pathogenesis of COVID-19 is a diffuse systemic process involving a complex interplay of the immune, inflammatory, and coagulative pathways rather than a localised respiratory infection.

A biomarker is defined as a “characteristic that can be objectively measured and evaluated as an indicator of normal biological and pathological processes, or pharmacological responses to a therapeutic intervention”.

The immunological, inflammatory, and coagulative cascades are closely interlinked. Infection with SARS-CoV-2 causes an innate and adaptive immune response. Tissue damage results from the former's excessively pro-inflammatory response and the latter's dysregulated host response. The accompanying tremendous production of cytokines and chemokines, known as the "cytokine storm," results in widespread uncontrolled immunological dysregulation.

The release of interleukin-6 (IL-6) and TNF-alpha is the result of a number of mechanisms, including NF-B, JAK/STAT, and the macrophage activation pathway, which are the hallmarks of SARS CoV2 infection. A crucial component of the cytokine storm, IL-6 activates various cell types and creates a positive feedback loop. Acute-phase reactants like C-reactive protein(CRP) are produced at higher rates because of the large-scale, uncontrolled synthesis of interleukins, especially IL-6 .

The Coagulative Cascade and Escalating Inflammation:

Endothelial cells, platelets, neutrophils, monocytes, and macrophages are all a part of the coagulation cascade. Both a healthy vascular endothelium and an anti-inflammatory response are present. In COVID-19, this barrier of protection is broken, which causes inflammation and thrombosis that are predominantly fueled by thrombin.

The first step in primary hemostasis is platelet activation. Once active, platelets draw in other platelets and form fibrinogen crosslinks with them. Vascular endothelial growth factor (VEGF) and other proangiogenic substances are secreted by platelets, which also encourage leukocyte activation and extravasation. Thrombocytopenia can be caused by an increased inflammatory state, thrombi development, and platelet consumption, while thrombocytosis is brought on by a cytokine storm.

The coordinated extrusion of mature neutrophil chromatin results in neutrophil extracellular traps (NET), which are formed when neutrophils are attracted to developing thrombi. NETs are prothrombotic and antibacterial.

Plasmin is produced by macrophages that have been drawn into fibrin thrombi and used to break down fibrin into D-dimers. Thus macrophages possibly contribute to the extremely severe elevation of D-dimers seen in COVID-19. Inflammatory cytokines and chemokines are produced by activated monocytes and damage-associated molecular patterns from damaged tissues, which prompt neutrophils, lymphocytes, platelets, vascular endothelial cells, and monocytes to express tissue factor and phosphatidylserine and start coagulation.

Autopsy studies have revealed increased lung megakaryocyte production of immature, more thrombogenic platelets as well as fibrin-rich thrombi with neutrophils

in the alveolar capillaries . Due to the lung's high fibrinolytic capability, there is active fibrinolysis that produces D-dimers that leak into the blood.

Coagulative Parameters:

When compared to typical disseminated intravascular coagulation, COVID-19's coagulopathy has a higher level of fibrinogen, a normal or mildly increased prothrombin time and activated partial thromboplastin time, a platelet count >100 × 10^3/ml, but no significant bleeding .

Patients with COVID-19 commonly experience elevated D-dimer values. D-dimer levels are associated with illness severity and in-hospital mortality, and several meta-analyses have demonstrated their predictive significance. A level of >2.0μg/ml on admission may indicate mortality [55, 56]. D-dimer is a potential early marker to help treat patients with Covid-19.

D-Dimer:

A complex protein molecule known as a D-dimer is produced when cross-linked fibrin is broken down by plasmin. The D-dimer circulates in the plasma as a soluble compound until it is excreted by the renal and reticuloendothelial pathways . It is interesting that D-dimer has an 8-hour plasma half-life and that it only becomes detectable in blood 2 hours after the formation of a thrombus. Only during the production and breakdown of the cross-linked fibrin molecules, which take place during coagulation and fibrinolytic processes, do D-dimers arise. D-dimer molecules are thus used to both directly and indirectly track these events and the presence of thrombotic activity.

COVID-19 and Thrombosis:

A higher sequential organ failure assessment (SOFA) score, male gender, and a number of concomitant conditions, such as diabetes, hypertension, and coronary heart disease, have all been linked to an increased risk of COVID-19. A D-dimer level of more than 1 μg/mL has also been linked to a higher risk of COVID-19, according to numerous studies. When COVID-19 patients were hospitalised, the development of thrombi has been observed in both the venules and the arterioles. In COVID-19 patients, the development of such thrombi and the subsequent angiogenesis frequently result in compromised microcirculation. Previous research on COVID-19 patients has demonstrated that endothelial damage and cell membrane breakdown are frequently brought on by the new coronavirus. As a result, endothelial cells produce less fibrinolysis, which encourages the development of thrombi.

Association between Levels of D-Dimer and COVID-19

As already mentioned, the amounts of D-dimer are directly correlated with the rate of plasmin synthesis and degradation. Therefore, any clinical condition that accelerates plasmin production and breakdown would likewise raise D-dimer levels. Thus, diseases like rheumatoid arthritis, asthma, and cancer that encourage chronic inflammation also cause an increase in D-dimer levels. It follows that exposure to a novel coronavirus, which causes individuals' inflammatory responses to be increased, would also result in higher levels of D-dimer. This is supported by the results of a number of earlier investigations, which found that D-dimer levels were much higher in COVID-19 patients, particularly in those who were either very ill or had passed away.

Some researchers have hypothesised that patients with severe new coronavirus infection may have elevated D-dimer levels that are related to their severe sickness, greater rates of thrombotic activity, and higher fatality rates.

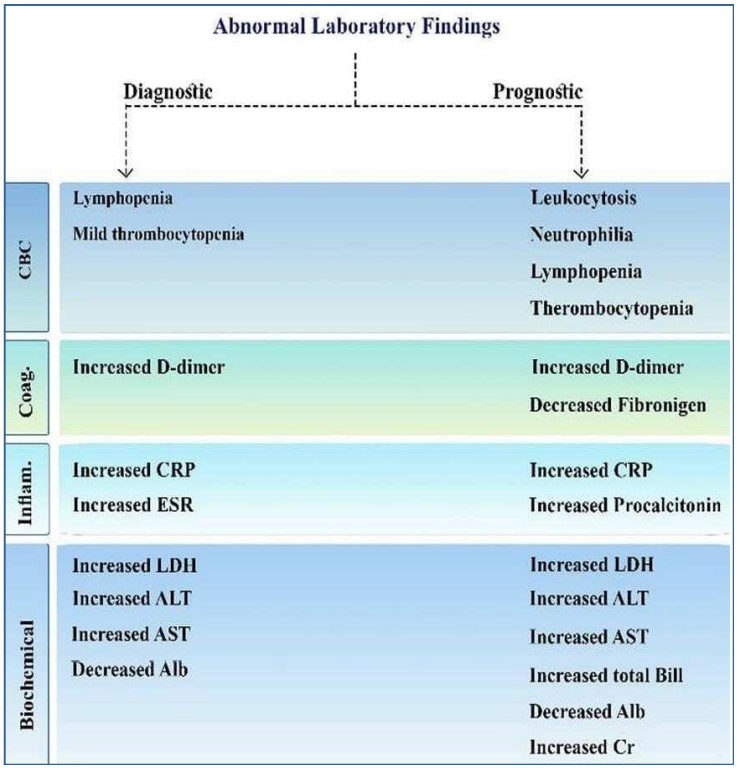
In 2020, Guan et al. released the findings of a sizable retrospective analysis that for the first time showed a relationship between aberrant D-dimer levels and the severity of the disease in COVID-19 patients. They discovered that a higher percentage of new coronavirus-infected people with severe disease showed abnormally high levels of D-dimer than those with only mild or moderate sickness, setting a cut-off point of a D-dimer level of more than 0.5 mg/L. Furthermore, COVID-19 individuals with a severe level of illness had levels of D-dimer that were almost 3.5 times greater than those who simply had mild or moderate levels of disease, according to Tang et al. Their findings were supported by Wang et al., who found that COVID-19 patients with a severe level of illness had D-dimer levels that were 2.5 and 5 times greater, respectively, than those who simply had mild or moderate levels of disease. In agreement with these results, Wang et al. discovered that the D-dimer levels in COVID-19 patients with severe sickness were more than two times lower than the levels of D-dimer in COVID-19 patients who had passed away. Tang et al findings that COVID-19 patients with severe sickness had D-dimer levels that were roughly four and nine times lower than those of COVID-19 patients who had passed away corroborated their findings.

The novel coronavirus infection leads to upregulation of the inflammatory pathways. The abnormal increment in the levels of D-dimer under inflammatory conditions indicates that the upregulation of inflammatory reactions and

proinflammatory agents might be associated with the induction of the coagulatory pathways . Hence, it follows that the coagulatory events in the COVID-19 patients might be triggered by the upregulated inflammatory reactions. The levels of D-dimer of more than 0.5 mg/L indicated abnormally high blood coagulability of COVID-19 patients and were significantly correlated with poor outcomes of such patients.

3. BIOCHEMICAL PARAMETERS: [13]

- Elevated lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels, as well as decreased serum albumin levels, are the most common abnormalities in biochemical parameters.
- Creatinine levels also elevated in few patients.
- When compared to people without severe disease, all of these are likewise significantly higher in individuals with severe disease. All of this therefore indicates a poor prognosis.
- The elimination of viral mRNA during therapy is directly correlated with a decrease in LDH and CK levels. Therefore, they probably forecast how a treatment would work.

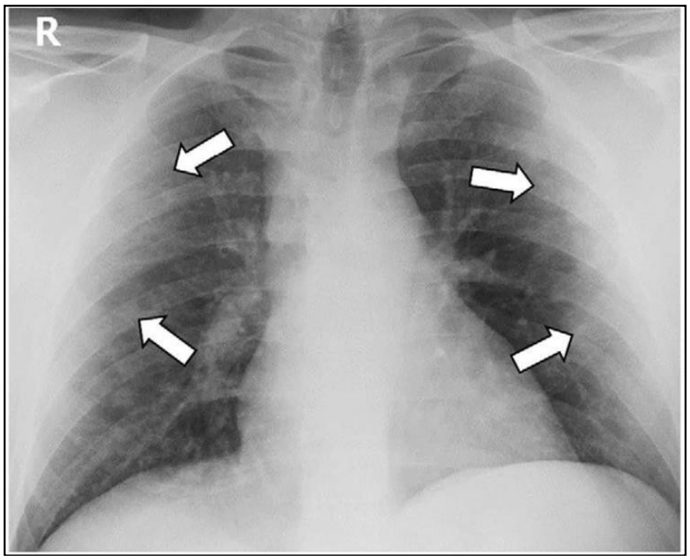


IMAGING:

One of the initial diagnostic tests for patients with suspected COVID is a chest radiograph. However, it is not typically advised for people with asymptomatic COVID. Patients with hypoxemia and functional impairment should have a CT chest. Additionally, the severity of the condition is evaluated using it. In the early stages of the disease, a chest CT scan and chest radiograph may both be normal. [41]

A) CHEST RADIOGRAPH:[14]

A chest radiograph of a COVID-19 patient may reveal everything from normal lung function to unilateral or bilateral lung opacities, perhaps with a characteristic peripheral distribution. Compared to the CT chest, it is less sensitive in the diagnosis. Additionally, it can be used to assess how serious the condition is [41].



Chest xray PA view showing mild, ill-defined pulmonary opacities in periphery of bilateral lung fields (arrows).

REPORTING SYSTEM FOR CHEST RADIOGRAPHY:

British Society of Thoracic Imaging :[42]

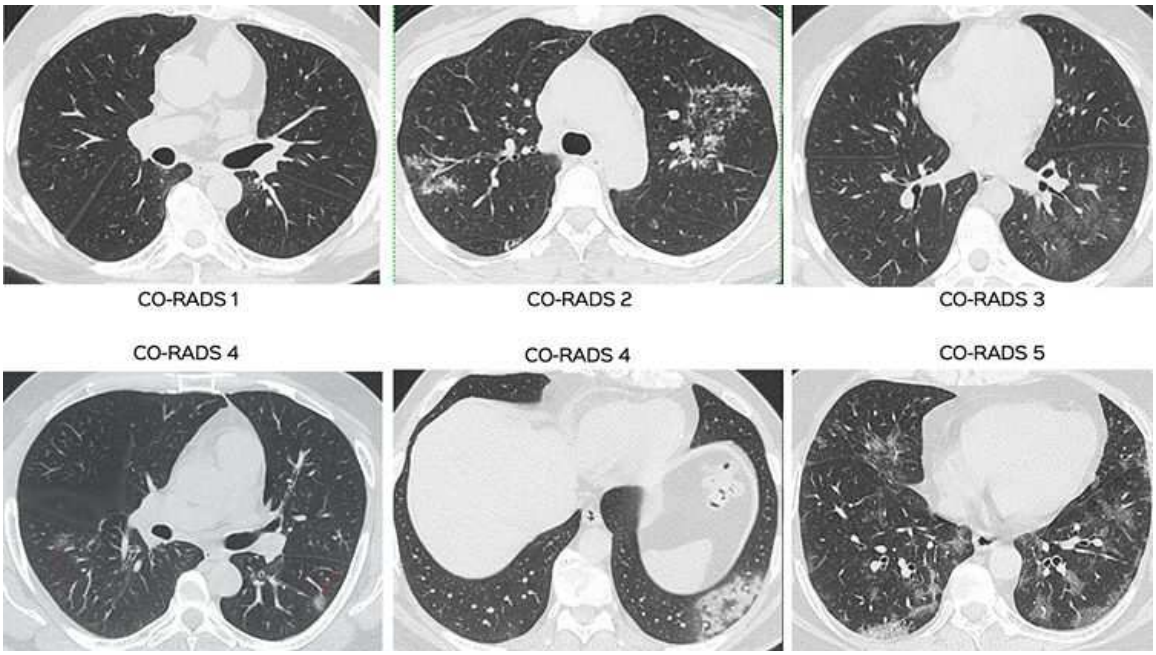
Classic or probable COVID-19	Multiple bilateral Lower lobe and peripheral predominant opacities
Indeterminate for COVID-19	Does not fit classic or non–COVID-19 features
Non–COVID-19	• Lobar pneumonia • Pneumothorax • Pulmonary edema • Pleural effusion • Other
Normal	

B. **CT-CHEST:**[15]

Chest CT is more reliable than chest radiography for the diagnosis of COVID-19. It is useful for both diagnosis and prognosis. Similar to CXR, it may be normal in the early stages of the illness. The intensity of symptoms, clinical manifestations, and inflammation markers all correspond with CT severity rating determined with the amount of lung involvement. The CT severity ranking system also forecasts the risk of fatality. A CT severity score of >18/25 in one study indicates a higher probability of mortality.[43]

SUMMARY OF CORADS:[17]

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



TREATMENT :

Clinical characteristics of COVID-19 are influenced by both infection and host immune response. Early on in the disease's progression, infection is primarily to blame for the symptoms. Clinical signs later in the disease's course are mostly caused by the host's dysregulated immunological and inflammatory response to SARS-CoV-2. On the basis of this, different medications are researched and utilised to treat COVID-19. The severity of COVID-19 and the patient's need for oxygen will determine the course of treatment. [45]

NON HOSPITALIZED PATIENTS WITH ACUTE INFECTION:

A) GENERAL MANAGEMENT:[45]

- All outpatients entering the healthcare system should be asked to schedule follow-up appointments through telehealth or in person..

- The patient needs to be kept in isolation and counselled with warning signs like dyspnea, which call for hospitalisation and additional care.
- Depending on the patient's tolerance, adequate rest is advised during the acute phase of the disease.
- The Patient should be instructed to take adequate fluids to maintain hydration and educate patients about breathing exercises.

B) THERAPEUTIC MANAGEMENT :[45] [46] [47] [48]

PATIENT CONDITION	RECOMMENDATION
Not requiring supplemental oxygen or hospitalisation	In patients with mild or moderate disease who are at high risk of developing severe disease, anti-SARS-CoV-2 monoclonal antibodies are advised. • Bamlanivimab + etesevimab • Casirivimab + imdevimab • Sotrovimab Using dexamethasone or other systemic glucocorticoids are not indicated.
Discharged from the hospital after stabilising and no longer required supplemental oxygen	Use of dexamethasone, remedesivir, baricitinab are not recommended after hospital discharge.
Having been discharged from a hospital's	There is not enough data to support either

inpatient setting and needing supplemental oxygen	continuing to use dexamethasone, remdesivir, or barcitinib.
Discharged from the emergency room (ED) despite a new or increasing demand for supplemental oxygen because inpatient admission was not possible due to restricted hospital resources	The use of dexamethasone 6 mg PO once day for as long as supplemental oxygen is needed (but not for more than 10 days). There is insufficient data to advise remdesivir use either for or against.

OTHER AGENTS IN OUTPATIENT SETTING:

- It's not advised to use chloroquine or hydroxychloroquine.
- It is not advised to use lopinavir/ritonavir or any other HIV protease inhibitors.
- It is not advised to use antibiotics like azithromycin and doxycycline without another indication.
- Ivermectin use is not indicated.
- In the outpatient context, anticoagulant and antiplatelet therapy should not be started for DVT prophylaxis.

C) TREATMENT OF COEXISTING ILLNESS:

- Regular medications of patients should be continued.
- Statins, ACE inhibitors, oral/inhahed/intranasal corticosteroids, NSAIDS indicated for coexisting illness should be continued.
- It is not advisable to use nebulized medication around other people.

- Antiretroviral treatment should not be changed or discontinued.
- Before continuing their medicine, immunomodulator users should consult with their doctor.
- Patients with obstructive sleep apnea can continue using CPAP or BiPAP.

HOSPITALIZED PATIENTS WITH COVID-19:

DISEASE SEVERITY	**RECOMMENDATION**
Hospitalized patients but not requiring supplemental oxygen	Use of dexamethasone or other glucocorticoids are not advised There is insufficient data to suggest remdesivir use either for or against. can be taken into account in patients with a high risk of disease progression.
Hospitalized patients and requiring supplemental oxygen	Remdesivir is prescribed to people who require minimal oxygen support. Dexamethasone + remdesivir – for the patients who requiring increased oxygen supplementation. Dexamethasone alone – when remdesivir is contraindicated not available There is insufficient data to support the use of tocilizumab or baricitinib.. Prednisone, methylprednisolone, and hydrocortisone are alternative steroids that

	can be used if dexamethasone is not readily available.
Hospitalized and in need of noninvasive ventilation or high flow oxygen supplementation	Dexamethasone Dexamethasone plus remdesivir Add either IV tocilizumab or baricitinib to one of the above options If baricitinib or IV sarilumab are not available or convenient to use, tofacitinib and tocilizumab can be replaced. The risk of opportunistic infection or reactivation rises as a result of the immunosuppressive medications used above of latent infection.
Hospitalized patients and requiring invasive mechanical ventilation or ECMO	Dexamethasone Patients within 24 hours of ICU admission should receive IV tocilizumab and dexamethasone If tocilizumab is neither feasible or available, IV sarilumab may be used instead. The risk of opportunistic infection or the reactivation of latent infection is increased by the immunosuppressive medications mentioned above.

	Patients started on remedesivir can be continued. There is insufficient data to support the use of further tocilizumab doses.

DRUG DOSING AND COMMENTS :[45]

Drug	Regimen	Comments
Remdesivir	Remdesivir 200 mg IV once a day, followed by remdesivir 100 mg IV once a day for 4 days or until discharge	If there is not a significant clinical improvement by Day 5, the course of treatment may be continued for up to 10 days. Complete the remdesivir course if the patient develops a more serious illness. Remdesivir is not recommended if eGFR is less than 30 mL/min/1.73 square metres.
Dexamethasone	Dexamethasone 6 mg IV or PO once a day for up to 10	If dexamethasone is unavailable, prednisone,

	days or until discharge from hospital.	methylprednisolone, and hydrocortisone can be used in an equivalent dose.
Baricitinib	Dose of Baricitinib is depends on eGFR. Duration of therapy is up to 14 days or until discharge from hospital.	eGFR ≥60 mL/min/1.73 m2 - Baricitinib 4 mg PO once a day dose. eGFR 30 to <60 mL/min/1.73 m2 - Baricitinib 2 mg PO once a day dose. eGFR 15 to <30 mL/min/1.73 m2 - Baricitinib 1 mg PO once a day dose. eGFR <15 mL/min/1.73 m2 - Baricitinib is not recommended.
Tofacitinib	10 mg PO twice daily Tofacitinib for up to 14 days or until discharge from hospital.	If baricitinib is not available or not feasible to use, alternatives can be used. eGFR <60 mL/min/1.73

		m2 - Tofacitinib 5 mg PO twice a day.
Tocilizumab	a single IV dose of tocilizumab 8 mg/kg of body weight (up to 800mg)	There is insufficient data to support the use of increased tocilizumab doses.
Sarilumab	For SQ injection, use the single-dose, pre-filled syringe rather than the pre-filled pen. Sarilumab 400 mg should be reconstituted in 100 cc of 0.9% NaCl and given as an hour-long IV infusion.	If tocilizumab is not available or not feasible to use,alternatives can be used. SQ injection is the only method of sarilumab administration that is currently authorised in the United States.

ANTITHROMBOTIC THERAPY IN PATIENTS WITH COVID-19:

- Patients can continue taking anticoagulants or antiplatelets if they were previously taking them for a comorbid condition.
- All hospitalised non-pregnant persons with COVID-19 can take an anticoagulant prophylactic dosage for the prevention of venous thromboembolism. It is not advised for non-hospitalized individuals and should not be used to prevent arterial thrombosis.
- The use of thrombolytics and larger doses of anticoagulants in hospitalised

patients is not recommended because there is not enough data to support either side of the debate.

- The probability of thromboembolic illness should be assessed in hospitalised patients who have rapidly declining pulmonary, cardiac, or neurological function, and the patient should begin receiving therapeutic doses of anticoagulant medication. Patients in whom a diagnosis is not feasible but thromboembolism is strongly suspected may also begin therapeutic dosages.
- Following hospital discharge, venous thromboembolism prophylaxis is not advised for COVID-19 patients. Patients with a low risk of bleeding but a high risk of venous thromboembolism can take it into consideration.

OTHER AGENTS:

- Convalescent plasma - Use of COVID-19 convalescent plasma is not advised for the treatment of COVID-19 patients.
- Anti-SARS-CoV-2 specific immunoglobulin - There is inadequate data to support either a recommendation for or a recommendation against using immunoglobulin in the management of COVID-19

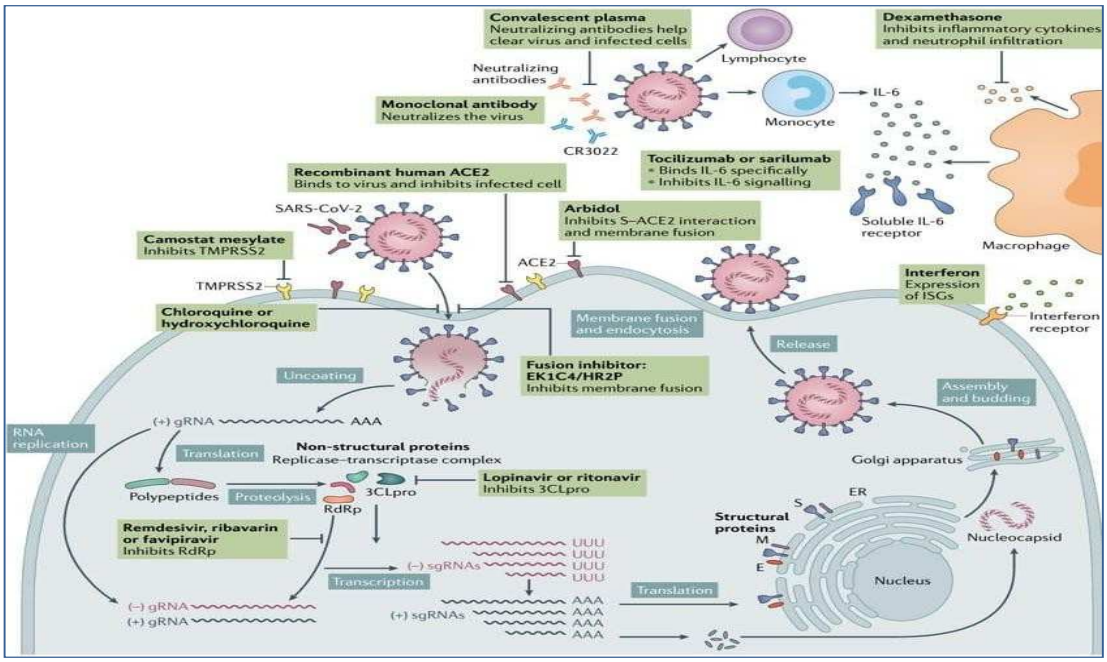
IMMUNOMODULATORS:[45]

RECOMMENDED	INSUFFICIENT EVIDENCE	NOT RECOMMENDED
1)Corticosteroids **2)IL-6(Interleukin) inhibitors – Tocilizumab**	1)Anakinra 2)Fluvoxamine	1)Baricitinib + tocilizumab 2)Canakinumab

(or sarilumab) **3)JAK (Janus kinase) inhibitors** **- Baricitinib (or tofacitinib)**	3)Colchicine for nonhospitalized patients 4)Inhaled budesonide 5)Interferon beta for treatment of mild to moderate COVID-19 patients 6)Granulocyte-macrophage colony stimulating factor (G-csf) inhibitors for hospitalized patients	3)Interferons (alfa or beta) for the treatment of severe or critically ill COVID-19 patients. 4)Colchicine for hospitalized patients 5)(Non-SARS-CoV-2 specific) intravenous immunoglobulin (IVIG) for the treatment of patients with acute COVID-19 This advice shouldn't prohibit the use of IVIG for MIS-C or in other circumstances where it's necessary. 6)JAK inhibitors other than baricitinib and tofacitinib (e.g., ruxolitinib) Siltuximab 7)Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib,

		zanubrutinib)
Sarilumab	For SQ injection, use the single-dose, pre-filled syringe rather than the pre-filled pen. Sarilumab 400 mg should be reconstituted in 100 cc of 0.9% NaCl and given as an hour-long IV infusion.	If tocilizumab is not available or not feasible to use,alternatives can be used. SQ injection is the only method of sarilumab administration that is currently authorised in the United States.

MECHANISM OF ACTION OF VARIOUS DRUGS:



TREATMENT OF CRICALLY ILL COVID-19 PATIENTS:

HEMODYNAMIC MANAGEMENT:

Use of buffered or balanced crystalloids is advised for acutely resuscitated COVID-19 patients who have shock. Dynamic factors, skin temperature, capillary refilling time, and serum lactate levels are used to evaluate fluid responsiveness. It is not advised to use albumin or hydroxyethyl starches.

Ionotropes should be begun to maintain MAP 60-65 mm Hg when BP does not improve with fluid resuscitation. The first vasopressor of choice is norepinephrine. To reach the goal MAP, norepinephrine should be combined with vasopressin or epinephrine, which is the second choice of vasopressors. Dopamine at low doses is not recommended for protecting the kidneys. If the patient develops cardiac dysfunction and hypotension after receiving adequate fluid support and vasopressor assistance, dobutamine may be given. Low dose corticosteroid therapy is advised for patients who have refractory shock after completing their course of steroid treatment for COVID.[9]

OXYGENATION AND VENTILATION:

Non-invasive positive pressure ventilation is preferred over high flow nasal cannula oxygen (HFNO) for individuals who have acute hypoxemic respiratory failure despite traditional oxygen administration (NIPPV). In the absence of HFNO, NIPPV may be employed. If the patient is consistently hypoxemic and endotracheal intubation is not necessary, awake proning may be tried to increase oxygenation.

Endotracheal intubation should be performed when needed, and the ARDS protocol for ventilation should be followed. For patients on mechanical ventilation,

recommendations include: [52]

- Low tidal volume(Tv) (4 – 8 mL/kg body weight)
- Target plateau pressure < 30cm of H2O
- Higher positive end expiratory pressure (PEEP) strategy
- Conservative fluid management
- For patients who persist with refractory hypoxemia despite these interventions, prone ventilation for 12–16 hours per day is advised.
- For protective lung ventilation, the use of intermittent boluses or continuous infusion of neuromuscular blocking agents is recommended.
- Routine use of inhaled nitric oxide is not advised.

ACUTE KIDNEY INJURY:

According to KDIGO, AKI is defined as an:

- Increase in serum creatinine by ≥0.3 mg/dL within 48 hrs OR,
- Increase in serum creatinine to ≥1.5 times baseline (i.e. 50% above baseline), which is known or presumed to have occurred within the prior 7 days OR,
- Urine volume <0.5 mL/kg/hr over a period of 6 hours

Continuous renal replacement treatment (CRRT) is advised for critically sick patients who have indications for renal replacement therapy. Hemodialysis is recommended as a backup if extended intermittent RRT is not available.

ANTIMICROBIAL THERAPY:

There is inadequate data to support either a recommendation for or against the empirical use of broad spectrum antibiotics in critically ill COVID-19 patients.

VACCINES IN COVID-19

The most promising method for controlling the COVID-19 pandemic is vaccination against SARS-CoV-2 infection. A particular organism's (antigen) weak or inactive portions are found in vaccines, which cause the body to produce an immune response. Instead of the antigen itself, more recent vaccinations contain a recipe for making antigens. Whether the vaccination contains the antigen itself or a blueprint for the antigen that the body will generate, this weaker form won't actually cause disease in the recipient; instead, it will stimulate the immune system to react much as it would have during its initial response to the pathogen. Some immunizations need to be administered in numerous doses, weeks or months apart. This is often required to enable the creation of memory cells and long-lasting antibodies. By creating a memory of the pathogen in this way, the body is prepared to fight a specific disease-causing organism when exposed to it in the future.

COVID VACCINES IN INDIA

As of October 2022, There are totally 12 vaccines are approved in India for use,

COVISHIELD

It is recombinant vaccine manufactured by serum institute of india approved on Jan 202. Vaccination course consists of 2 separate doses of 0.5 ml intramuscularly each 4-12 weeks apart.

COVAXIN

It is india's first indigenous COVID-19 vaccine.It is developed using whole-Virion Inactivated vero cell approved on Jan 2022. It is a 2 dose vaccination regimen given 28 days apart.

There are some other vaccines that are approved for restricted use in emergency situation in the country are moderna vaccine (mRNA vaccine), Sputnik-v, ZyCoV-D vaccine, Janssen vaccine (recombinant), Sputnik light, Corbevax, Covovax.

MATERIAL AND METHODS

ETHICAL COMMITTEE APPROVAL:

Obtained

STUDY DESIGN:

Cross sectional Study

STUDY AREA:

COVID ward, Government tertiary care hospital, Chennai

STUDY POPULATION:

COVID-19 RT-PCR positive patients admitted in COVID-19 wards in Government tertiary hospital chennai.

PERIOD OF STUDY: April 2021 - March2022

INCLUSION CRITERIA:

- ✓ RT- PCR for COVID 19 positive patients who gives informed written consent
- ✓ Subjects aged more than 18 years

EXCLUSION CRITERIA:

- ✓ Patients with Haematological malignancies
- ✓ Coagulation disorders
- ✓ Postoperative patients

STUDY TOOLS :

- ✓ Detailed history
- ✓ Clinical examination
- ✓ Complete blood count
- ✓ D-Dimer

SAMPLE SIZE:

Based on the reference study done by Yang et al, China

Formula:

$n = Z^2pq / d^2$

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

p =85 % (Proportion of critically ill COVID 19 patients with lymphopenia from previous study.)

q = 15% (100-p)

d = 10 % relative precision (ie 10% of 85 =8.5)

On substituting, in the formula

n = 3.84 x 85 x 15 / 72.26

n = 68

Adding 10% non response rate (i.e 10% of 68=7)

n = 75 (minimum sample size)

Therefore Sample size n = 100 (1 group).

DATA COLLECTION :

All patients with COVID 19 who are admitted and have given consent will be included in the study and followed up for a period of 5 days. Data were obtained regarding patients clinical symptomatology, O2 saturation, Respiratory rate, blood pressure and pulse rate on admission and on day 3 and day 5. Hematological parameters (complete blood count), inflammatory markers were done on admission and data were collected. Disease severity is assessed by the respiratory rate, O2 saturation requirement for oxygen supplementation, noninvasive and invasive ventilation on day 5 and patients are classified as mild , moderate and severe as per WHO definitions:

- Mild disease - Patients that fulfill the COVID-19 case description but do not have viral pneumonia or hypoxia
- Moderate disease - Fever, cough, dyspnea, and fast breathing are all symptoms of pneumonia, but there are no signs of severe pneumonia, such as SpO2 levels more than or equal to 90% on room air.
- Severe disease - Clinical signs of pneumonia (fever, cough, dyspnoea) plus one of the following:
    - Respiratory rate >30 breaths/minute
    - SpO2 < 90% on room air
    - Severe respiratory distress

Then complications like ARDS, acute kidney injury, thromboembolic manifestations and sepsis/shock were noted .

STATISTICAL ANALYSIS:

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

OBSERVATION AND RESULTS

1. Age distribution table

The mean age of the participants is 53.7 years (S.D. =18.1) ranging between 21 and 93.

N		100
	Missing	0
Mean		53.780
Median		52.000
Std. Deviation		18.1105
Minimum		21.0
Maximum		93.0

Table 1: Age distribution table

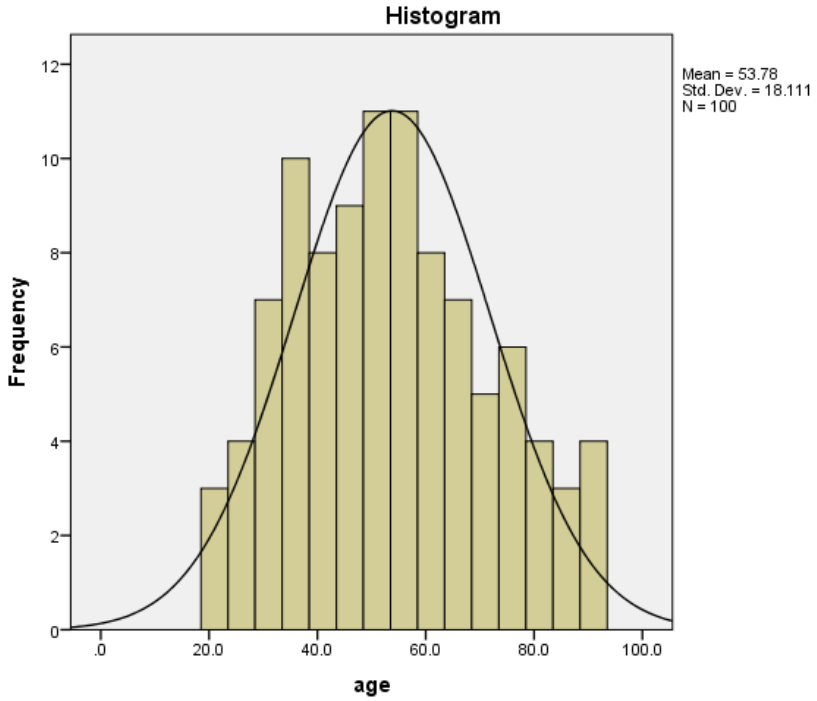


Figure 1: Age distribution table

2. Gender distribution

Around 56% of them were males and the rest were females.

Gender Distribution		Frequency	Percent
	Male	56	56.0
	Female	44	44.0
	Total	100	100.0

Table 2: Gender distribution

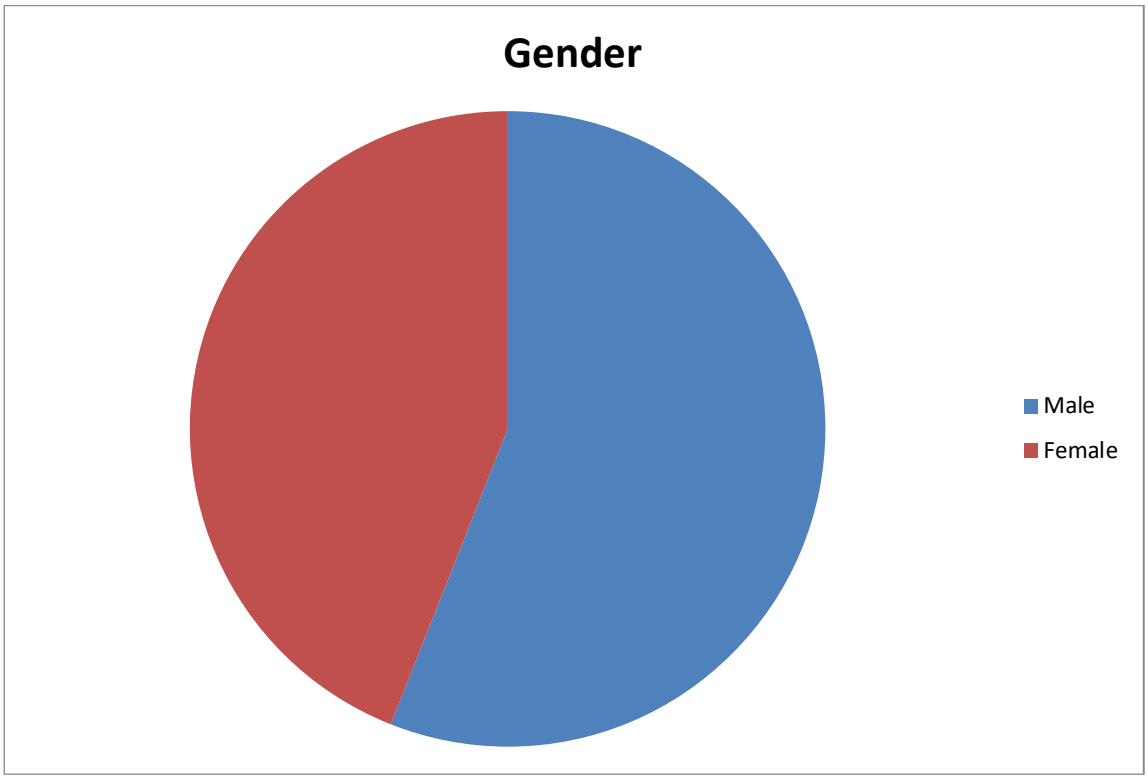


Figure 2: Gender distribution

3. Comparison of spo2 with severity (spo2 in room air on day 5)

Day 5 oxygen saturation levels were lesser as severity increased. This was statistically significant ($p<0.005$).

SEVERITY AS PER RR AND SPO2 ON DAY5		DAY 5_SPO2
Mild	Mean	97.135
	Std. Deviation	1.6807
	N	52
Moderate	Mean	91.185
	Std. Deviation	1.0391
	N	27
Severe	Mean	83.952
	Std. Deviation	3.9303
	N	21
Total	Mean	92.760
	Std. Deviation	5.6606
	N	100

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
	Between Groups	(Combined)	2691.156	2	1345.578	271.306	.000
	Within Groups		481.084	97	4.960		
	Total		3172.240	99			

Table 3: Comparison of spo2 with severity (spo2 in Room air on day 5)

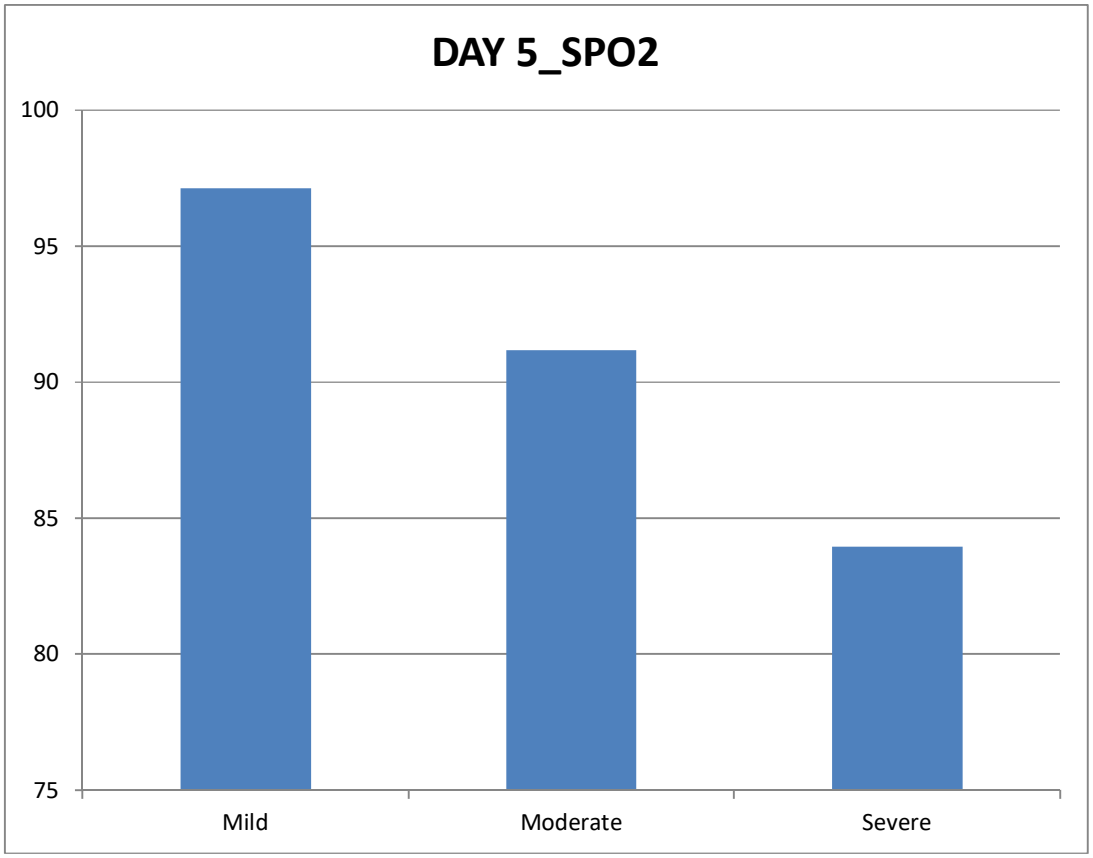


Figure 3: Comparison of spo2 with severity (spo2 in Room air on day 5)

4. Comparison of severity with respiratory rate on day 5

Day 5 respiratory rates were higher as severity increased. This was statistically significant ($p<0.005$).

SEVERITY AS PER RR AND SPO2 ON DAY5		DAY 5_Respiratory Rate
Mild	Mean	17.423
	Std. Deviation	2.8100
	N	52
Moderate	Mean	26.481
	Std. Deviation	1.7180
	N	27
Severe	Mean	31.571
	Std. Deviation	2.2265
	N	21
Total	Mean	22.840
	Std. Deviation	6.4066
	N	100

ANOVA Table							
			Sum of Squares	df	Mean Square	F	Sig.
	Between Groups	(Combined)	3484.864	2	1742.432	292.124	.000
	Within Groups		578.576	97	5.965		
	Total		4063.440	99			

Table 4: Comparison of severity with respiratory rate on day 5

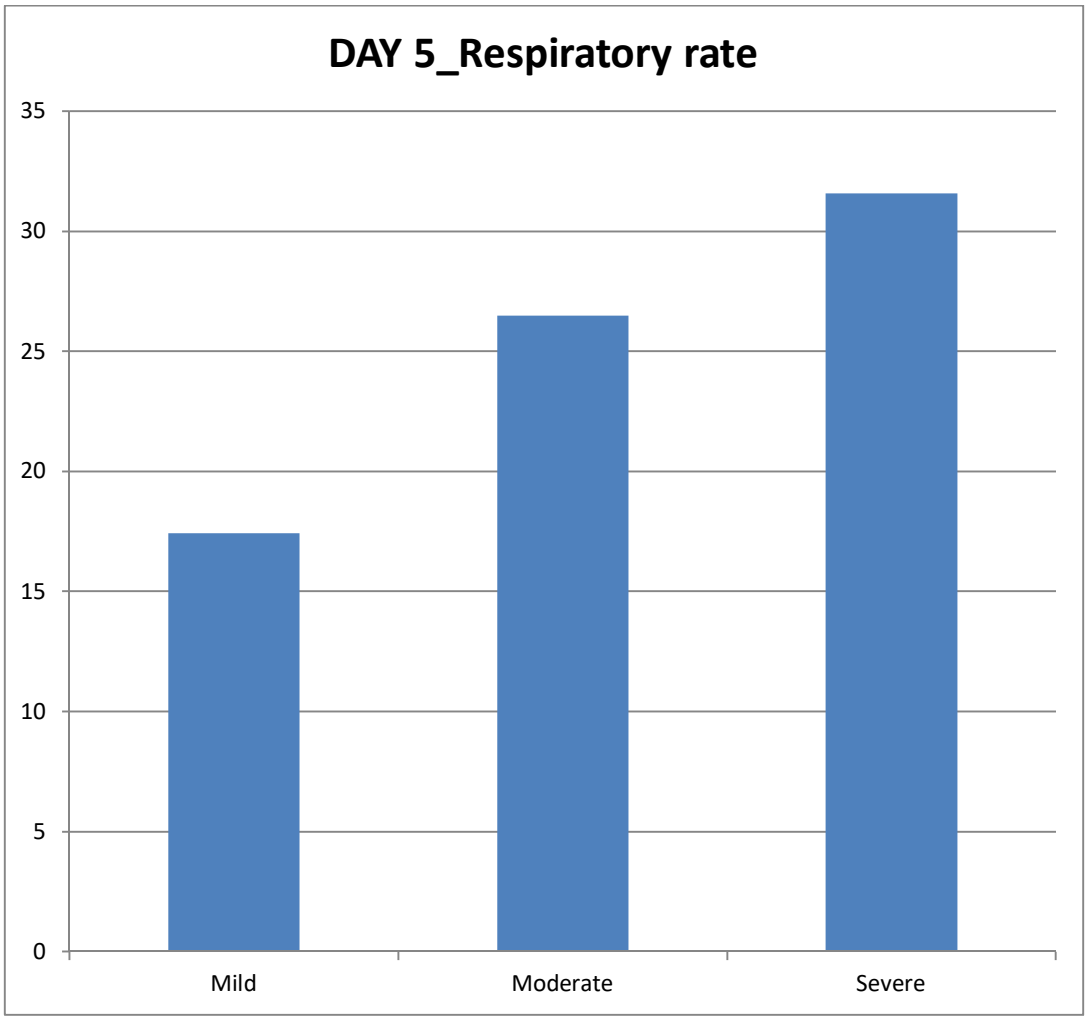


Figure 4: Comparison of severity with respiratory rate on day 5

5. Prevalence of comorbidities

Diabetes mellitus was present in 25% of the subjects, hypertension in 19%, CAD in 10%, CKD in 8% and COPD in 9% of the subjects.

		Frequency	Percent
DM	Absent	75	75.0
	Present	25	25.0
	Total	100	100.0
SHTN	Absent	81	81.0
	Present	19	19.0
	Total	100	100.0
DM+SHTN	Absent	86	86.0
	Present	14	14.0
	Total	100	100.0
CAD	Absent	90	90.0
	Present	10	10.0
	Total	100	100.0
CKD	Absent	92	92.0
	Present	8	8.0
	Total	100	100.0
COPD	Absent	91	91.0
	Present	9	9.0
	Total	100	100.0

Table 5: Prevalence of comorbidities

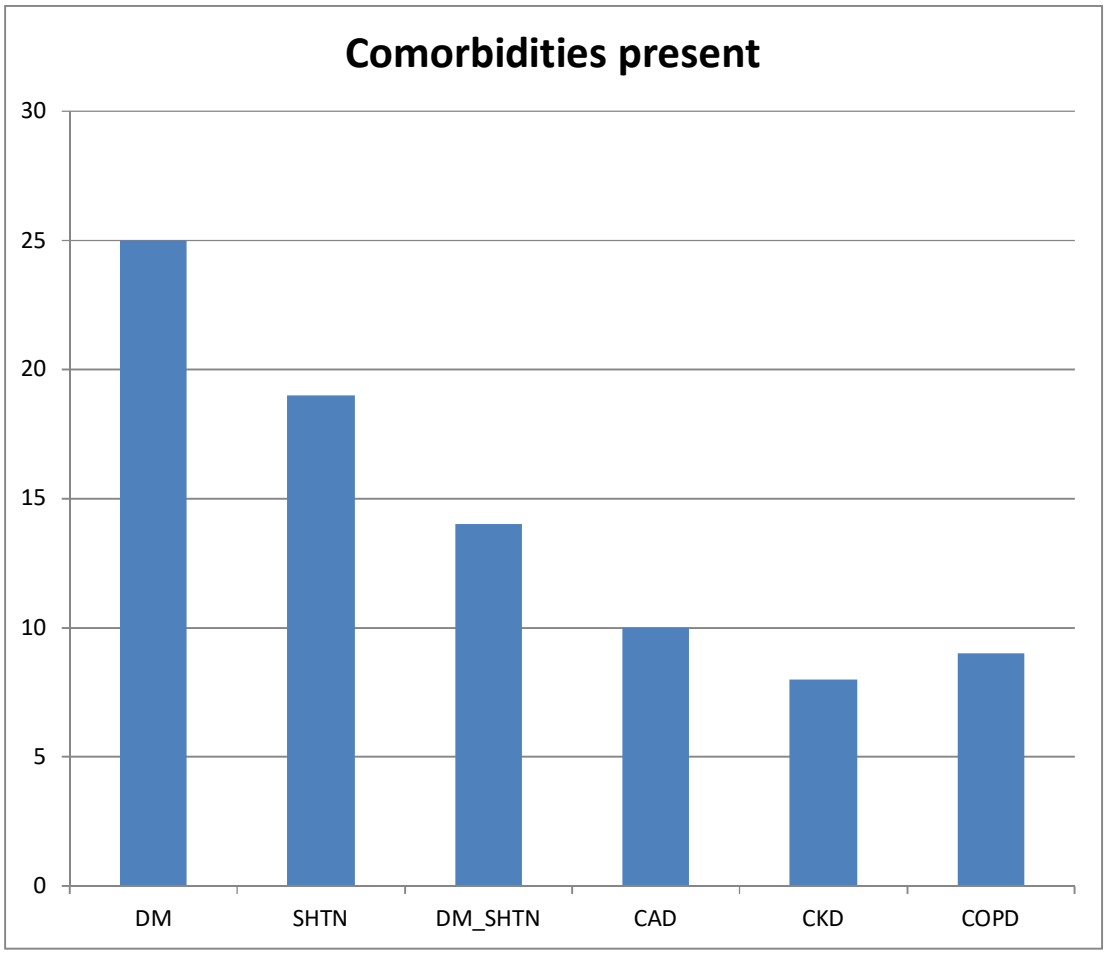


Figure 5: Prevalence of comorbidities

6. Comparison of lymphopenia with severity

Comparison of lymphopenia with severity showed that patients with more severe illness had increased association with lymphopenia. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
LYMPHOPENIA	Absent	51	17	2	70
	Present	1	10	19	30
Total		52	27	21	100

Chi-Square Tests			
	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	56.731[a]	2	.000
Likelihood Ratio	63.487	2	.000
Linear-by-Linear Association	55.427	1	.000
N of Cases	100		

Table 6: Comparison of lymphopenia with severity

7. Comparison of thrombocytopenia with severity

Comparison of thrombocytopenia with severity showed that that patients with more severe illness had increased association with thrombocytopenia. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
THROMBOCYTOPENIA	Absent	44	20	2	66
	Present	8	7	19	34
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	38.663[a]	2	.000
Likelihood Ratio	39.446	2	.000
Linear-by-Linear Association	32.291	1	.000
N of Cases	100		

Table 7: Comparison of thrombocytopenia with severity

8. Comparison of NLR with severity

Comparison of NLR with severity showed that that patients with more severe illness had increased association with NLR. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
NLR	Not elevated	49	3	1	53
	Elevated	3	24	20	47
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	74.123[a]	2	.000
Likelihood Ratio	88.452	2	.000
Linear-by-Linear Association	62.487	1	.000
N of Cases	100		

Table 8: Comparison of NLR with severity

9. Comparison of PLR with severity

Comparison of PLR with severity showed that that patients with more severe illness had increased association with PLR. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
PLR	Not elevated	50	22	10	82
	Elevated	2	5	11	18
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	23.880[a]	2	.000
Likelihood Ratio	22.385	2	.000
Linear-by-Linear Association	22.493	1	.000
N of Cases	100		

Table 9: Comparison of PLR with severity

10. Comparison of D-Dimer with severity

Comparison of D-Dimer with severity showed that that patients with more severe illness had increased association with D-Dimer. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
D-DIMER	Not elevated	46	7	3	56
	Elevated	6	20	18	44
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	46.979[a]	2	.000
Likelihood Ratio	51.865	2	.000
Linear-by-Linear Association	41.669	1	.000
N of Cases	100		

Table 10: Comparison of D-Dimer with severity

11. Level of NLR

The mean levels of NLR is 3.61 (S.D. =1.9) ranging between 1.03 and 8.5.

Statistics	NLR
Mean	3.6150
Median	3.1850
Std. Deviation	1.93351
Minimum	1.03
Maximum	8.50

Table 11: Level of NLR

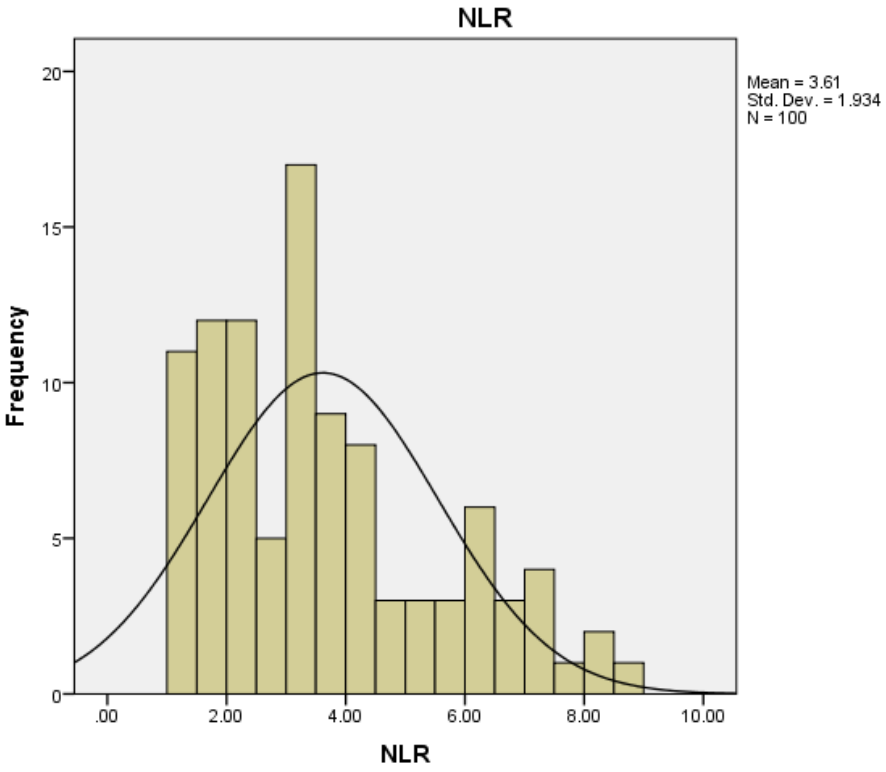


Figure 6: Level of NLR

12. **Level of biomarkers**

D-Dimer was elevated in 44% of the subjects, IL-6 in 31%, Ferritin in 30% and CRP in 40% of the subjects.

		Frequency	Percent
D-DIMER	Not elevated	56	56.0
	Elevated	44	44.0
	Total	100	100.0
IL6	Not elevated	69	69.0
	Elevated	31	31.0
	Total	100	100.0
FERRITIN	Not elevated	70	70.0
	Elevated	30	30.0
	Total	100	100.0
CRP	Not elevated	60	60.0
	Elevated	40	40.0
	Total	100	100.0

Table 12: Level of biomarkers

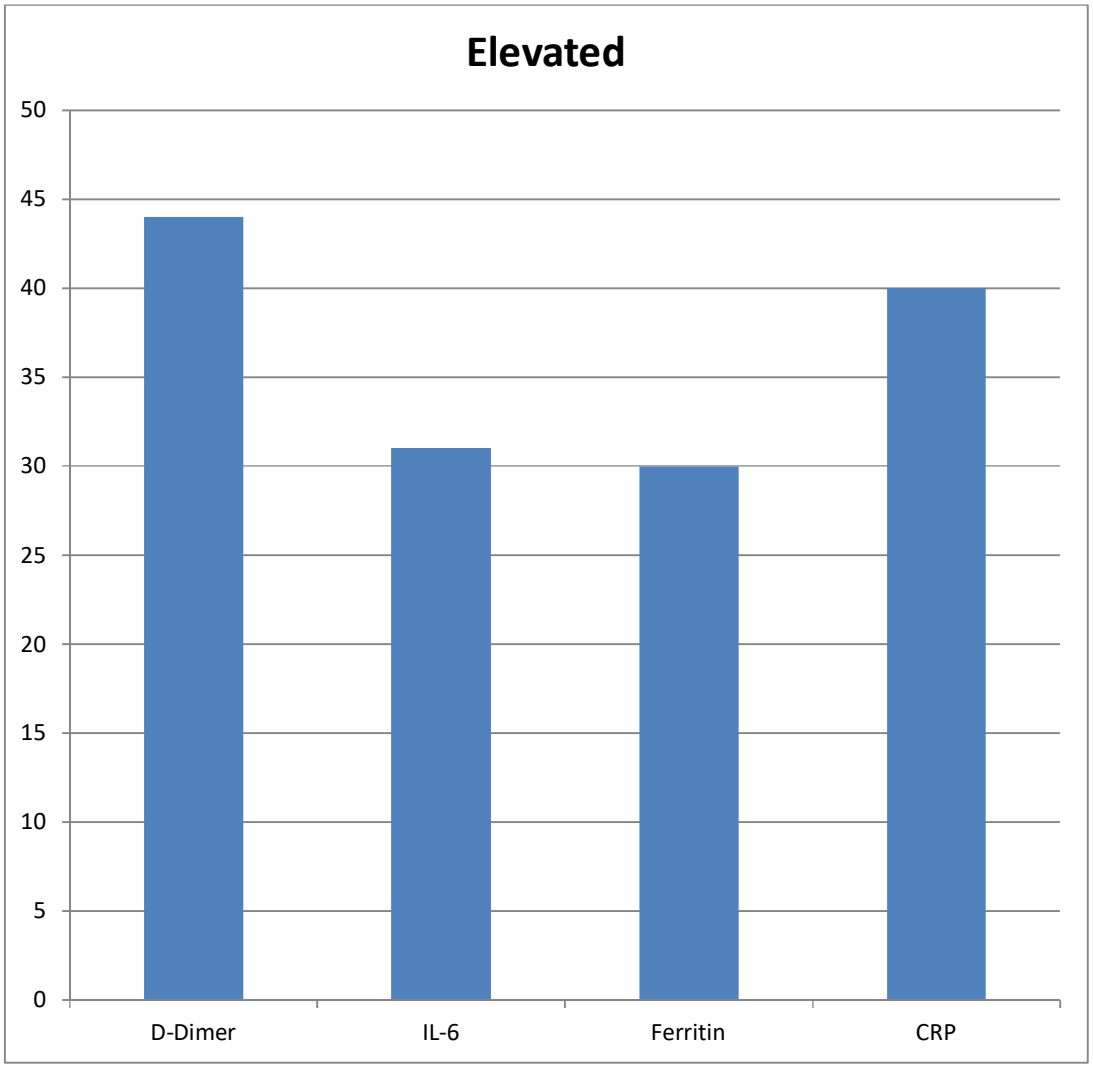


Figure 7: Level of biomarkers

13. Distribution of type of complication

Complications were present in 21% of the subjects. Around 10% had ARDS, 11% had AKI and 7% had sepsis/shock.

Complications			Frequency	Percent
	Absent		79	79.0
	Present		21	21.0
	Type of complication	ARDS	10	10.0
		AKI	11	11.0
		Stroke/ACS	2	2.0
		VTE	1	1.0
		Sepsis/shock	7	7.0

Table 13: Distribution of type of complication

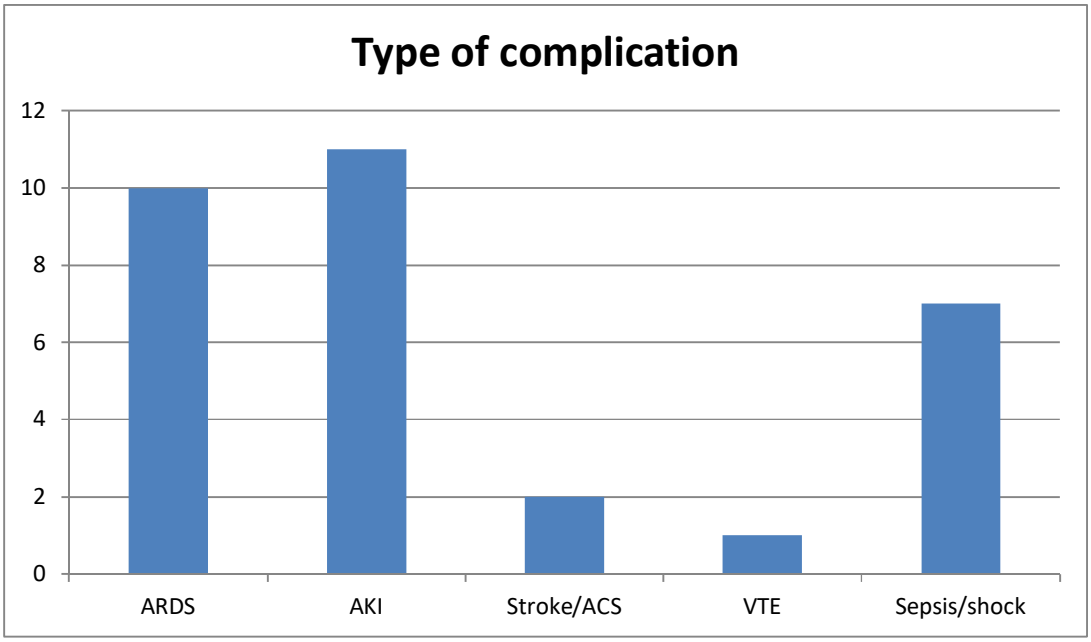


Figure 8: Distribution of type of complication

14. Type of complication with severity

Increased severity was associated with increased complications. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
Complications	Absent	49	23	7	79
	Present	3	4	14	21
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	34.292[a]	2	.000
Likelihood Ratio	30.466	2	.000
Linear-by-Linear Association	28.863	1	.000
N of Cases	100		

Table 14: Type of complication with severity

15. Type of oxygen requirement with severity

Increased oxygen requirement was associated with increased complications. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
O2 REQUIREMENT	No	43	0	0	43
	Yes	9	27	21	57
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	69.636[a]	2	.000
Likelihood Ratio	88.747	2	.000
Linear-by-Linear Association	56.093	1	.000
N of Cases	100		

Table 15: Type of oxygen requirement with severity

Mild cases of severity were managed with face mask.

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
FACEMASK	No	47	27	21	95
	Yes	5	0	0	5
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.858[a]	2	.088
Likelihood Ratio	6.782	2	.034
Linear-by-Linear Association	3.913	1	.048
N of Cases	100		

Table 16: Type of oxygen requirement with severity

Mild and moderate cases of severity were managed with NRM. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
NRM	No	48	7	21	76
	Yes	4	20	0	24
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	51.330[a]	2	.000
Likelihood Ratio	51.109	2	.000
Linear-by-Linear Association	1.013	1	.314
N of Cases	100		

Table 17: Type of oxygen requirement with severity

Moderate cases of severity were managed with HFNC. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
HFNC	No	52	22	21	95
	Yes	0	5	0	5
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	14.230[a]	2	.001
Likelihood Ratio	13.828	2	.001
Linear-by-Linear Association	.790	1	.374
N of Cases	100		

Table 18: Type of oxygen requirement with severity

Moderate and severe cases were managed with CPAP. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
CPAP	No	52	25	4	81
	Yes	0	2	17	19
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	66.927[a]	2	.000
Likelihood Ratio	62.535	2	.000
Linear-by-Linear Association	53.170	1	.000
N of Cases	100		

Table 19: Type of oxygen requirement with severity

All severe cases were managed with mechanical ventilation. This is statistically significant ($p<0.005$).

		SEVERITY AS PER RR AND SPO2 ON DAY5			Total
		Mild	Moderate	Severe	
MV	No	52	27	17	96
	Yes	0	0	4	4
Total		52	27	21	100

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	15.675[a]	2	.000
Likelihood Ratio	13.138	2	.001
Linear-by-Linear Association	11.167	1	.001
N of Cases	100		

Table 20: Type of oxygen requirement with severity

RESULTS

The mean age of the participants is 53.7 years (S.D. =18.1) ranging between 21 and 93. Around 56% of them were males and the rest were females. Day 5 oxygen saturation levels were lesser as severity of the disease increased. This was statistically significant ($p<0.005$). Day 5 respiratory rates were higher as severity increased. This was statistically significant ($p<0.005$). Diabetes mellitus was present in 25% of the subjects, hypertension in 19%, CAD in 10%, CKD in 8% and COPD in 9% of the subjects.

Comparison of lymphopenia with severity showed that that patients with more severe illness had increased association with lymphopenia. This is statistically significant ($p<0.005$). Comparison of thrombocytopenia with severity showed that higher severity had increased association with thrombocytopenia. This is statistically significant ($p<0.005$). Comparison of NLR with severity showed that higher severity had increased association with NLR. This is statistically significant ($p<0.005$). Comparison of PLR with severity showed that higher severity had increased association with PLR. This is statistically significant ($p<0.005$).

Comparison of D-Dimer with severity showed that higher severity had increased association with D-Dimer. This is statistically significant ($p<0.005$). The mean levels of NLR is 3.61 (S.D. =1.9) ranging between 1.03 and 8.5. D-Dimer was elevated in 44% of the subjects, IL-6 in 31%, Ferritin in 30% and CRP in 40% of the subjects. Complications were present in 21% of the subjects. Increased severity was

associated with increased complications. This is statistically significant with a p value of <0.005.

Increased oxygen requirement was associated with increased complications. This is statistically significant ($p<0.005$). Mild cases of severity were managed with face mask. Mild and moderate cases of severity were managed with NRM. This is statistically significant ($p<0.005$). Moderate cases of severity were managed with HFNC. This is statistically significant ($p<0.005$). Moderate and severe cases were managed with CPAP. This is statistically significant ($p<0.005$). All severe cases were managed with mechanical ventilation. This is statistically significant ($p<0.005$).

DISCUSSION

The immunological response to a viral infection is mainly based on lymphocytes. It has been hypothesised that a considerable decrease in lymphocyte count in COVID-19 patients may be brought about by increased lymphocyte consumption, the breakdown of lymphatic tissues, and cytokine-induced T-cell apoptosis. Lymphopenia is a symptom of advanced illness that is not unique to COVID-19. It has also been observed in other viral pneumonia-causing organisms, like influenza. Notably, we observed that COVID-19 patients who suffer from severe disease had lower lymphocyte count and higher NLR and PLR. In consistency with our study, Yang et al. suggested NLR ≥3.3 as an indicator with clinical symptoms to change disease status from mild to severe disease . According to reports, NLR can be used as an early indicator for a severe disease, which is consistent with earlier research on a different patient population. In the current study, patients with severe COVID had a greater median PLR than those with less severe instances. When deciding whether to transfer a patient to the intensive care unit, the PLR, which measures both aggregation and inflammation control, performs better than platelet or lymphocyte count alone. Platelet activity and count changes are closely related to different disorders. Several studies have shown a clear correlation between low platelet counts and the severity of the illness in COVID-19 patients. In addition to aiding in hemostasis, platelets also take part in inflammation and host defence. Patients with COVID-19 are thought to experience thrombocytopenia as a result of decreased platelet generation and higher consumption brought on by diffuse alveolar destruction. In line with earlier research, it

was discovered that COVID patients who required transfer to the ICU had lower haemoglobin levels than COVID patients with less severe symptoms.

Yang et al. studied 52 critically ill patients and found that about 85% had lymphopenia (Yang et al., 2020).A similar blood picture was seen in the ICU patients studied in Singapore ($p<0.0001$) (Fan et al., 2020). Lymphopenia was more severe in patients who ultimately succumbed to the disease (Wang et al., 2020). Based on a meta analysis involving nine studies, thrombocytopenia is directly associated with the severity of SARS- CoV2 infection (Lippi et al., 2020). Cytokine storm causes platelet activation, which in turn results in a high platelet to lymphocyte ratio now considered a prognostic marker (Qu et al., 2020). Elevated D-dimer levels were found in around 36% of the total number of cases assessed in a study in China (Chen et al., 2020b). Those with High prothrombin time and D dimer levels on admission were more likely to require ICU support during their hospital stay (Huang et al., 2020). Wang et al.(2020) demonstrated the same in his analysis.

Therefore disseminated intravascular coagulation and D-dimer elevation are seen with severe SARS-CoV2 infection (Lippi and Favaloro, 2020). Endothelial dysfunction and immune deregulation play a part in the pathophysiology of the disease (Lillicrap, 2020). Early diagnosis and treatment are important in patients who develop PE to prevent morbidity and mortality. D- dimer, USG venous Doppler, bedside echo etc. can be used in patients with PE/DVT. CT pulmonary angiography confirmed cases of PE had higher D-dimer levels as compared to those without PE (Chen et al., 2020a). Unfractionated heparin or low molecular weight heparin are preferred over direct oral anticoagulants due to drug-drug interaction with concomitant antiviral and

antibacterial treatment (Thachil et al., 2020Tang et al. demonstrated the efficacy of LMWH in patients with markedly elevated D-dimer levels or those meeting the criteria for DIC (Tang et al., 2020a).

Similar to the above reference study the results of my study also confirmed that Lymphopenia, thrombocytopenia and raised NLR, PLR and D-Dimer were seen in patient with severe SARS COVID 19 disease and had been statistically significant. Thus these lab parameters which are easily available even in resource limited setting had been proved to be a prognostic marker of severity of the disease. Hence presence of these parameters need intense monitoring of those and timely management of the complications for the better outcome in severely ill covid19 disease patients.

CONCLUSION

Our lives are being changed by the COVID-19 pandemic in unanticipated ways. The capacity of health-care systems around the world has been severely tested (and in some countries completely exhausted), and the effect of this pandemic on health-care delivery, social connections, and global economy is still growing. Researchers from all over the world must work together to investigate and integrate biochemical and clinical data linked to COVID-19 in order to address the urgent need for efficient treatments and preventative measures. COVID-19 has prominent manifestations from the hematopoietic system. Common haematological abnormalities have been identified in COVID-19 patients.

According to this study, hematological parameters like lymphopenia, thrombocytopenia, elevated NLR, PLR, and elevated d-Dimer values at the time of admission are the markers that can predict that a patient can end up in a severe disease and the need of oxygen requirement and intensive care management. So these patients should need extra care and intense monitoring at the earliest to prevent the complications and mortality. Therefore initial hematological parameters like lymphocyte count, platelet count, NLR, PLR and d-Dimer should be monitored for predicting the prognosis of the covid-19 patients.

LIMITATIONS

There were few limitations in the study which are as follows:

- The sample size of this study was relatively small
- Mortality of the disease was not studied
- Not all age groups are equally studied
- It was a single centre study, multicenter clinical studies might be required to support this data
- Effect of vaccination was not evaluated in this study

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

TITLE OF THE WORK	:	"ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HAEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE"
PRINCIPAL INVESTIGATOR	:	DR. P. AYYAPPAN,
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.

25/3/21.
MEMBER SECRETARY,
IEC, SMC, CHENNAI.

PROFORMA

Name: Age/sex:

I.P. NO.:

Date of admission:

Date of RT-PCR positive:

Presenting complaints:

Symptoms	Yes	No
Fever		
Cough		
Breathlessness		
Myalgia		
Anosmia and ageusia		
Diarrhoea		
Sore throat		
Others		

Past history :

DM/SHT/CAD/CVA/CKD/CLD/COPD

Clinical examination:

Vitals:

	Day 1	Day 3	Day 5
Pulse rate(/min)			
Respiratory rate(/min)			
Spo2 %			
Blood Pressure (mm/hg)			

Laboratory findings:

Total count (/μL)	
Differential count(%)	
Hemoglobin(g/dl)	
Platelets($\times 10^5$/μL)	
NLR	
Blood urea (mg/dl)	
S. creatinine(mg/dl)	
Sodium (meq/dl)	
Potassium (meq/dl)	
PLR	
D-Dimer	
IL-6	
CRP	
Serum ferritin	
Urea	
S.Creatinine	

Imaging :

- **Chest X-ray :**
- **CT severity scoring :**

O2 requirement	Day 1	Day 3	Day 5
	YES/NO	YES/NO	YES/NO
Nasal oxygen			
NRM			
HFNO			
NIV			
Invasive ventilation			

INOTROPES: YES / NO

Complications:	Yes	No
ARDS/Respiratory Failure		
Acute kidney injury		
Acute coronary syndrome/Stroke		
Sepsis/Shock		
Venous thromboembolism		
Others		

INFORMED CONSENT

TITLE : "ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE."

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 suppose to do by taking part in this study and I assure that I would extend my full cooperation for this study

SIGNATURE OF PARTICIPANT SIGNATURE OF INVESTIGATOR

PLACE:

DATE:

ஆராய்ச்சி ஒப்புதல் படிவம்

Title: "ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE."

பெயர்:

வயது:

பாலினம்: ஆண் / பெண்

பங்கு பெறுபவர் அடையாள எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கமும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

இந்த சோதனையில் நான் கலந்து கொண்டு ரத்த பரிசோதனைக்கக சம்மதிக்கிறேன்.

எனக்கு விளக்கப்பட்ட விஷயங்களை புரிந்து கொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

நான் என்னுடைய சுய நினைவுடன் மற்றும் முழு சம்மதத்துடன் இந்த ஆராய்ச்சிக்கு என்னை பரிசோதிக்க சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :

நாள் :

ஆராய்ச்சி தகவல் தாள்

Title: "ANALYTICAL CROSS SECTIONAL STUDY TO DETERMINE THE EFFECTIVENESS OF HEMATOLOGICAL PARAMETERS IN ASSESSING THE SEVERITY OF ILLNESS AMONG COVID 19 PATIENTS IN A TERTIARY CARE CENTRE."

இதனால் தங்களது ஆய்வறிக்கையோ, அன்றாட செயல்பாடுகளோ பாதிக்கப்படாது என்று தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ தங்கள் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்து கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது அதன் முடிவில் அறிவிக்கப்படும் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது .மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

பங்கேற்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

இடம் :

நாள் :

KEYS			
Sex	Male-1	Female-2	
Severity as per spo2 and resp.rate on day5	Mild-1	Moderate-2	Severe-3
Respiratory rate	Mild:<24/min	Moderate:24-30/min	Severe:>30/min
Spo2	Mild:>94%	Moderate:90-94%	Severe:90%
Comorbidities	YES-1	NO-0	
O2 requirement	YES-1	NO-0	
LYMPHOPENIA	YES-1	NO-0	
THROMBOCYTOPENIA	YES-1	NO-0	
NLR SEVERITY	ELEVATED-1	NOT ELEVATED-0	
PLR SEVERITY	ELEVATED-1	NOT ELEVATED-0	
INFLAMMATORY MARKERS(D-dimer,IL-6,Ferritin,C	ELEVATED-1	NOT ELEVATED-0	
COMPLICATIONS	YES-1	NO-0	

S no	age	sex	DM	SHTN	CAD	CKD	COPD	RATORY RATE		SPO2 IN ROOM AIR		EVERITY AS PER RR AN		EQUIREM	ACEMAS	NRM	HFNC	CPAP	MV	HOCYTE	MPHOPEN	LATELET	MBOCYTO	NLR	R SEVERI	PLR	R SEVERI	D-DIMER	IL6	FERRITIN	LDH	CRP	PLICATI	ARDS	AKI	CS/STRO	VTE	SEPSIS/SHOCK
								DAY 1	DAY 3	DAY 5	DAY 1	DAY 3	DAY 5																				0					
1	48	2	1	1	1	0	1	22	28	32	94	89	78	3	1	0	0	0	1	0	729	1	120000	1	7.1	1	164	0	1	1	1	1	1	0	0	0	0	0
3	75	1	1	1	0	1	0	23	29	33	92	90	84	3	1	0	0	0	1	0	972	1	120000	1	3.12	0	123	0	0	0	1	1	1	1	1	1	0	1
4	75	2	1	1	1	0	1	28	33	37	89	82	76	3	1	0	0	0	0	1	427	1	63100	1	8.17	1	147	0	1	1	1	1	1	1	1	0	0	1
5	65	2	1	0	0	0	1	18	23	30	92	90	87	3	1	0	0	0	1	0	1382	0	150000	1	6.10	1.00	221	1	1	1	1	1	1	1	0	0	1	0	0
7	50	2	1	0	0	1	0	22	29	33	95	91	88	3	1	0	0	0	1	0	483	1	120000	1	6.98	1	248	1	1	1	1	1	1	1	0	0	1	0	0
18	86	2	1	1	1	0	0	20	27	33	94	89	79	3	1	0	0	0	1	0	475	1	92000	1	7.50	1.00	193	1	1	1	1	1	1	1	1	0	0	1
36	34	1	0	0	0	0	0	24	30	34	89	85	79	3	1	0	0	0	0	1	608	1	76000	1	7.25	1	125	0	1	1	1	1	1	0	0	0	0	0	0
37	79	1	0	1	0	0	0	14	18	30	95	89	85	3	1	0	0	0	1	0	648	1	120000	1	6.14	1	185	1	1	1	1	1	1	1	0	1	0	0	1
48	57	1	1	1	0	0	0	24	30	32	95	90	84	3	1	0	0	0	1	0	543	1	217000	0	5.67	1	386	1	1	1	1	0	0	1	0	0	0	0	0
49	58	1	1	0	0	1	0	21	27	32	95	91	87	3	1	0	0	0	1	0	574	1	140000	1	6.19	1	243	1	1	1	1	1	1	1	1	0	0	0	0
50	54	2	1	1	0	0	0	18	25	31	89	84	80	3	1	0	0	0	1	0	850	1	140000	1	6.01	1	164	0	0	0	1	0	1	1	1	0	0	0	0
55	77	1	0	1	0	0	0	19	24	30	96	92	85	3	1	0	0	0	0	1	479	1	150000	1	6.71	1	313	1	1	1	1	1	1	0	0	0	0	0	0
58	51	2	1	1	0	0	0	25	29	34	90	84	80	3	1	0	0	0	0	1	492	1	71900	1	8.50	1.00	146	0	1	1	1	1	1	1	1	0	0	0	0
59	34	1	0	0	0	0	1	17	22	29	94	90	88	3	1	0	0	0	1	0	496	1	210000	0	6.60	1.00	423	1	0	1	1	1	1	1	0	1	0	0	1
66	56	2	1	0	0	0	0	16	22	30	95	91	85	3	1	0	0	0	1	0	723	1	140000	1	5.91	1	193	1	1	0	1	0	1	1	1	0	0	0	0
67	70	1	0	1	0	0	0	24	27	32	94	90	84	3	1	0	0	0	1	0	1010	0	140000	1	6.21	1	138	0	1	1	1	1	1	0	0	0	0	0	0
75	39	1	1	0	0	0	0	23	30	34	94	92	86	3	1	0	0	0	1	0	628	1	150000	1	4.17	1	238	1	1	1	1	1	1	1	1	0	0	0	0
76	65	1	1	1	0	1	0	19	24	27	90	85	82	3	1	0	0	0	1	0	542	1	120000	1	4.21	1	221	1	1	1	1	1	1	1	1	0	0	0	0
83	85	1	0	0	1	0	0	20	24	30	95	92	89	3	1	0	0	0	1	0	680	1	110000	1	3.82	1	161	0	1	0	0	0	1	1	0	0	0	1	0
87	60	2	0	0	0	1	0	17	26	30	97	93	89	3	1	0	0	0	1	0	650	1	58000	1	7.38	1	89	0	1	1	1	1	1	0	0	0	0	0	0
98	83	1	1	1	1	0	0	20	24	30	94	90	88	3	1	0	0	0	1	0	842	1	140000	1	7.19	1	166	0	1	1	1	1	1	0	0	0	0	0	0
2	65	2	1	1	0	0	1	18	23	27	96	94	90	2	1	0	0	1	0	0	944	1	140000	1	5.12	1	148	0	1	0	1	0	1	0	0	0	0	0	0
8	52	1	0	1	0	0	0	21	24	29	97	92	92	2	1	0	1	0	0	0	1890	0	312000	0	3.41	1	165	0	0	1	0	1	1	0	0	0	0	0	0
9	62	1	1	1	0	0	0	20	24	29	96	93	90	2	1	0	1	0	0	0	994	1	92000	1	3.72	1	92	0	1	1	1	1	1	0	0	0	0	0	0
10	62	2	0	0	0	0	0	18	22	26	97	94	92	2	1	0	0	1	0	0	990	1	179000	0	4.24	1	180	1	1	0	0	0	1	0	0	0	0	0	0
13	42	1	0	0	0	0	0	24	24	26	96	95	92	2	1	0	1	0	0	0	1522	0	212000	0	3.35	1	139	0	0	0	1	1	0	0	0	0	0	0	0
15	22	1	0	0	0	0	0	20	20	25	96	95	92	2	1	0	1	0	0	0	849	1	150000	1	4.14	1	176	0	1	1	0	0	1	0	0	0	0	0	0
22	41	1	0	0	1	0	0	20	22	28	95	94	92	2	1	0	1	0	0	0	1680	0	240000	0	3.79	1	142	0	0	1	1	1	0	0	0	0	0	0	0
25	57	1	0	0	0	0	0	16	20	24	97	95	90	2	1	0	1	0	0	0	2400	0	292000	0	3.35	1	121	0	0	0	0	0	0	0	0	0	0	0	0
27	61	1	0	0	0	0	0	24	27	29	95	92	90	2	1	0	0	0	1	0	936	1	140000	1	5.16	1	149	0	1	1	1	1	1	0	0	0	0	0	0
28	68	2	0	0	1	0	0	20	24	28	95	94	92	2	1	0	1	0	0	0	853	1	170000	0	4.63	1	199	1	1	1	0	0	1	1	1	0	0	0	0
30	55	1	0	0	0	0	1	16	20	26	94	94	90	2	1	0	1	0	0	0	1766	0	273000	0	3.52	1	154	0	1	0	0	0	0	0	0	0	0	0	0
38	49	2	0	0	0	0	0	18	20	26	96	92	90	2	1	0	1	0	0	0	2150	0	270000	0	3.18	0	125	0	1	1	0	0	0	0	0	0	0	0	0
44	44	2	0	0	0	0	0	18	21	25	97	93	91	2	1	0	1	0	0	0	1300	0	203000	0	3.41	1	156	0	1	0	0	1	0	0	0	0	0	0	0
45	40	1	0	0	0	0	0	18	22	26	95	91	90	2	1	0	1	0	0	0	745	1	190000	0	4.12	1	255	1	1	1	0	0	1	0	0	0	0	0	0
54	32	2	0	0	0	0	0	16	24	28	96	93	91	2	1	0	0	1	0	0	1320	0	200000.0	0.0	4.13	1	151	0	0	0	0	0	0	0	0	0	0	0	0
64	37	2	0	1	0	0	0	17	19	25	98	94	91	2	1	0	1	0	0	0	1549	0	210000	0	3.65	1	135	0	1	0	1	1	1	0	0	0	0	0	0
65	81	1	1	1	1	0	0	22	22	26	94	92	90	2	1	0	0	0	1	0	721	1	132000	1	5.71	1	183	1	1	1	0	0	1	1	0	1	0	0	0
68	78	2	0	0	0	0	0	21	22	24	96	96	93	2	1	0	0	1	0	0	872	1	150000	1	3.17	0	172	0	0	0	1	0	0	0	0	0	0	0	0
69	29	1	0	0	0	0	0	17	19	24	97	94	93	2	1	0	1	0	0	0	972	1	150000	1	4.72	1	154	0	1	0	0	1	1	0	0	0	0	0	0
74	72	1	0	0	1	0	0	19	23	27	95	95	92	2	1	0	1	0	0	0	1490	0	201000	0	4.12	1	134	0	0	0	0	0	1	0	0	0	0	0	0
77	30	1	0	0	0	0	1	22	25	29	95	93	90	2	1	0	0	1	0	0	2200	0	278000	0	4.67	1	126	0	1	1	1	1	1	0	0	0	0	0	0
78	91	1	1	0	0	1	0	18	22	25	97	94	91	2	1	0	1	0	0	0	1235	0	180000	0	3.92	1	145	0	1	0	0	0	1	1	0	1	0	0	0
81	68	2	0	0	0	0	0	20	24	24	97	93	91	2	1	0	1	0	0	0	1120	0	215000	0	3.15	0	191	1	1	0	0	0	0	1	0	1	0	0	0
92	48	1	0	0	0	0	0	20	22	28	96	96	93	2	1	0	1	0	0	0	1700	0	230000	0	4.16	1	135	0	1	0	0	0	1	0	0	0	0	0	0
93	58	1	0	0	0	0	0	24	26	26	95	92	92	2	1	0	1	0	0	0	1460	0	190000	0	5.41	1	130	0	1	0	1	0	0	0	0	0	0	0	0
95	39	2	0	0	0	0	0	18	22	26	95	93	91	2	1	0	1	0	0	0	1680	0	200000.0	0.0	3.79	1	119	0	1	0	1	1	0	0	0	0	0	0	0
97	89	1	1	0	0	1	0	21	26	29	95	94	91	2	1	0	1	0	0	0	1021	0	161000	0	3.78	1	157	0	1	1	0	0	1	0	0	0	0	0	0
6	21	1	0	0	0	0	0	16	15	14	97	97	98	1	0	0	0	0	0	0	1834	0	134000	1	2.41	0	73	0	0	0	0	0	0	0	0	0	0	0	0
11	55	1	0	0	0	0	0	16	18	17	99	98	98	1	0	0	0	0	0	0	3128	0	265000	0	1.08	0	84	0	0	0	0	0	0	0	0	0	0	0	0
12	47	2	0	0	0	0	0	16	20	20	98	96	94	1	1	0	1	0	0	0	1578	0	235000	0	3.10	0.00	148	0	0	0	0	0	0	0	0	0	0	0	0
14	33	2	0	0	0	0	0	18	17	16	99	98	98	1	0	0	0	0	0	0	2300	0	192000	0	1.72	0	83	0	0	0	0	0	0	0	0	0	0	0	0
16	27	2	0	0	0	0	0	20	20	23	96	95	94	1	1	0	1	0	0	0	2798	0	312000	0	2.35	0	111	0	1	1	0	0	0	0	0	0	0	0	0
17	61	1	0	0	0	0	0	16	16	15	98	98	99	1	0	0	0	0	0	0	1200	0	158000	0	2.98	0	131	0	0	0	0	0	0	0	0	0	0	0	0

19	71	1	0	0	0	0	0	19	18	18	95	96	97	1	0	0	0	0	0	0	1723	0	234000	0	8.42	1	135	0	0	0	0	0	0	0	0	0	0	0	0
20	77	2	0	0	0	0	0	16	15	16	98	98	97	1	0	0	0	0	0	0	2534	0	178000	0	3.15	0	70	0	0	0	0	0	0	1	0	1	0	0	1
21	29	2	0	0	0	0	0	17	18	16	95	97	96	1	0	0	0	0	0	0	2432	0	179000	0	3.17	0	73	0	0	0	0	0	0	0	0	0	0	0	0
23	66	2	0	0	0	0	0	16	16	16	97	98	98	1	0	0	0	0	0	0	1200	0	97000	1	1.05	0	80	0	0	0	0	0	0	0	0	0	0	0	0
24	35	2	0	0	0	0	0	17	17	16	95	97	98	1	0	0	0	0	0	0	1357	0	138000	1	1.76	0	101	0	0	0	0	0	0	0	0	0	0	0	0
26	89	1	1	0	0	0	0	16	19	24	96	95	94	1	1	1	0	0	0	0	3176	0	275000	0	1.52	0	86	0	1	0	0	0	1	0	0	0	0		0
29	51	2	1	1	0	0	0	18	18	18	97	98	98	1	0	0	0	0	0	0	1321	0	89000	1	6.17	1	67	0	0	0	0	0	0	0	0	0	0	0	0
31	52	2	0	0	0	0	0	17	17	17	98	99	98	1	0	0	0	0	0	0	1520	0	190000.00	0.00	1.05	0	125	0	0	0	0	0	0	0	0	0	0	0	0
32	51	1	0	0	0	0	0	16	18	17	96	99	98	1	0	0	0	0	0	0	991	1	257000	0	2.05	0	259	1	0	0	0	0	0	0	0	0	0	0	0
33	38	2	0	0	0	0	0	17	16	14	97	98	97	1	0	0	0	0	0	0	2314	0	237000	0	1.61	0	102	0	0	0	0	0	0	0	0	0	0	0	0
34	35	1	0	0	0	0	0	18	19	22	95	95	94	1	1	0	1	0	0	0	2700	0	356000	0	2.10	0.00	131	0	1	0	0	1	1	0	0	0	0	0	0
35	62	2	0	0	0	0	0	20	22	24	95	95	94	1	1	1	0	0	0	0	3100	0	210000.00	0.00	1.75	0	67	0	0	0	0	0	0	0	0	0	0	0	0
39	39	1	0	0	0	0	0	17	17	18	98	97	97	1	0	0	0	0	0	0	1500	0	198000	0	1.45	0	132	0	0	0	0	0	0	0	0	0	0	0	0
40	51	2	0	0	0	0	0	16	15	16	96	97	99	1	0	0	0	0	0	0	1624	0	163000	0	3.05	0	100	0	0	0	0	0	0	0	0	0	0	0	0
41	37	1	0	0	0	0	0	16	15	17	99	99	98	1	0	0	0	0	0	0	1231	0	123000	1	1.90	0.00	99	0	0	0	0	0	0	0	0	0	0	0	0
42	54	2	1	0	0	0	1	16	17	18	97	99	96	1	0	0	0	0	0	0	1863	0	201000	0	2.94	0	107	0	0	0	0	0	0	0	0	0	0	0	0
43	38	1	0	0	0	0	0	17	18	17	97	98	98	1	0	0	0	0	0	0	1990	0	276000	0	2.17	0	138	0	0	0	0	0	0	0	0	0	0	0	0
46	46	1	0	0	0	0	0	16	14	15	99	99	99	1	0	0	0	0	0	0	1974	0	254000	0	2.98	0	128	0	0	0	0	0	0	0	0	0	0	0	0
47	27	1	0	0	0	0	0	15	14	14	98	99	98	1	0	0	0	0	0	0	1598	0	190000.00	0.00	1.17	0	118	0	0	0	0	0	0	0	0	0	0	0	0
51	25	1	0	0	0	0	0	14	14	15	97	99	99	1	0	0	0	0	0	0	1280	0	160000.00	0.00	1.33	0	125	0	0	0	0	0	0	0	0	0	0	0	0
52	27	1	0	0	0	0	0	16	15	17	99	98	99	1	0	0	0	0	0	0	1823	0	109000	1	2.68	0	60	0	0	0	0	0	0	0	0	0	0	0	0
53	85	1	1	0	0	0	0	18	18	22	97	96	94	1	1	0	1	0	0	0	1821	0	198000	0	2.14	0	108	0	1	0	0	0	1	1	0	1	0	0	0
56	75	2	0	0	0	0	0	16	16	16	98	98	97	1	0	0	0	0	0	0	1920	0	145000	1	3.61	1	75	0	0	0	0	0	0	0	0	0	0	0	0
57	62	2	0	0	0	0	0	18	16	16	95	97	98	1	0	0	0	0	0	0	3183	0	154000	0	3.21	0	48	0	0	0	0	0	0	0	0	0	0	0	0
60	56	1	0	0	0	0	0	18	20	24	95	95	94	1	1	1	0	0	0	0	2194	0	301000	0	2.16	0	136	0	1	1	0	0	0	0	0	0	0	0	0
61	73	2	0	0	0	0	0	16	18	23	98	97	94	1	1	1	0	0	0	0	2170	0	198000	0	1.68	0	91	0	1	1	1	0	0	0	0	0	0	0	0
62	50	2	0	0	0	0	0	17	16	16	98	98	98	1	0	0	0	0	0	0	1539	0	204000	0	2.41	0	132	0	0	0	0	0	0	0	0	0	0	0	0
63	33	2	0	0	0	0	0	14	16	15	99	98	98	1	0	0	0	0	0	0	2317	0	192000	0	1.13	0	82	0	0	0	0	0	0	0	0	0	0	0	0
70	44	1	0	0	0	0	0	16	16	15	98	98	99	1	0	0	0	0	0	0	1938	0	357000	0	3.17	0	184	1	0	0	0	0	0	0	0	0	0	0	0
71	43	2	0	0	0	0	0	15	16	16	99	98	98	1	0	0	0	0	0	0	1527	0	179000	0	2.06	0	117	0	0	0	0	0	0	0	0	0	0	0	0
72	23	1	0	0	0	0	0	14	15	14	98	98	99	1	0	0	0	0	0	0	1988	0	310000.00	0.00	1.50	0.00	155	0	0	0	0	0	0	0	0	0	0	0	0
73	48	1	0	0	0	0	1	15	16	18	98	95	97	1	0	0	0	0	0	0	2530	0	198000	0	1.57	0	78	0	0	0	0	0	0	0	0	0	0	0	0
79	34	1	0	0	0	0	0	15	16	16	97	98	99	1	0	0	0	0	0	0	1720	0	243000	0	1.39	0	141	0	0	0	0	0	0	0	0	0	0	0	0
80	38	1	0	0	0	0	0	15	17	17	98	99	97	1	0	0	0	0	0	0	2914	0	185000	0	1.03	0	63	0	0	0	0	0	0	0	0	0	0	0	0
82	44	2	0	0	0	0	0	20	18	17	96	98	97	1	0	0	0	0	0	0	1987	0	276000	0	2.13	0	138	0	0	0	0	0	0	0	0	0	0	0	0
84	93	2	0	0	1	0	0	21	23	24	96	95	94	1	1	1	0	0	0	0	2120	0	197000	0	2.45	0	92	0	0	0	0	0	0	0	0	0	0	0	0
85	50	1	0	0	0	0	0	15	16	16	97	95	97	1	0	0	0	0	0	0	2013	0	162000	0	1.05	0	80	0	0	0	0	0	0	0	0	0	0	0	0
86	52	1	1	1	0	0	0	16	17	16	97	98	97	1	0	0	0	0	0	0	2034	0	219000	0	1.89	0	107	0	0	0	0	0	0	0	0	0	0	0	0
88	32	1	0	0	0	0	0	14	16	18	99	99	99	1	0	0	0	0	0	0	2200	0	200000.00	0.00	1.07	0	90	0	0	0	0	0	0	0	0	0	0	0	0
89	42	1	0	0	0	0	0	18	17	16	98	97	98	1	0	0	0	0	0	0	1524	0	193000	0	1.56	0	126	0	0	0	0	0	0	0	0	0	0	0	0
90	68	1	1	0	0	1	0	15	16	16	98	97	98	1	0	0	0	0	0	0	1672	0	103000	1	3.19	0	61	0	0	0	0	0	0	0	0	0	0	0	0
91	60	2	0	0	0	0	0	17	16	16	98	97	97	1	0	0	0	0	0	0	1958	0	275000	0	3.05	0	140	0	0	0	0	0	0	0	0	0	0	0	0
94	48	2	0	0	0	0	0	17	18	15	97	96	99	1	0	0	0	0	0	0	1729	0	158000	0	2.84	0	91	0	0	0	0	0	0	0	0	0	0	0	0
96	72	2	0	0	0	0	0	18	16	18	96	95	95	1	0	0	0	0	0	0	1648	0	199000	0	1.98	0	120	0	0	0	0	0	0	1	0	1	0	0	1
99	55	2	0	0	0	0	0	16	16	18	97	97	98	1	0	0	0	0	0	0	2987	0	163000	0	3.21	0	54	0	0	0	0	0	0	0	0	0	0	0	0
100	81	1	0	0	0	0	0	18	18	18	95	96	97	1	0	0	0	0	0	0	1720	0	238000	0	2.46	0	138	0	0	0	0	0	0	0	0	0	0	0	0