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TO CORRELATE THE ROLE OF SERUM FERRITIN AND D-DIMER AS A PROGNOSTIC BIOMARKER IN COVID-19 DISEASE

Dr Owais Siddiqui[*1], Dr Qurat Ul Ain Khan[2], Dr Adeel Sohail[3], Dr Ruhma Zainab[4], Dr Erum Amir[5]

[*1]*Mbbs Mphil (Clinical Pathology) Phd Scholar (Microbiology)*
[2]*Associate Professor Ccmhead of Department Critical CareZiauddin Hospital North*
[3]*Mbbs, Mcps Resident Critical CareZiauddin Hospital North*
[4]*MBBS MPHIL (Physiology)*
[5]*MBBS MPHIL PHD(Microbiology*

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Corresponding Author: *
Dr Owais Siddiqui

Abstract

Covid 19 pandemic is still a threat to public health. According to WHO, since the start of this pandemic, about 260 million cases with more than 5 million deaths reported globally. Including Pakistan, more than 200 countries have been affected so far. It is highly contagious disease, commonly spreads between people who are in close contact to each other. According to studies, hyper-inflammation followed by systemic inflammatory response, wide spreadendothelial damage and hypercoagulable state are the main cause of this disease. Therefore, evaluation of inflammatory state using biomarkers will be helpful in screening and early detection of severe disease.Objective To assess the severity of covid-19 by correlating serum ferritin and D-dimer levels with the clinical outcome of the disease.

Materials and method:It is a descriptive cross-sectional study, conducted in the department of clinical pathology, JPMC, with collaboration of ZiauddinMedical university hospital, during a period of six months with the approval of IRB. A total of 384 covid PCR positive patients were selected from covid wards and ICU and categorized into mild, moderate and severe disease group on the basis of WHO covid-19 disease severity classification. Serum ferritin and D-dimer levels was done at admission and repeated after 1 week of hospitalization, on automated clinical analyzer using principle of immuno-turbidimetry. All the patients were followed throughout the course of their disease. Results were analyzed and corelated with the clinical progression and outcomes of the disease.Results:Our study has shown, male dominance in mild, moderate and severe disease group i.e. we found 54.5% (n=12) males in mild disease group, 54.8% males in moderate disease group and 53.6% males in severe disease group. The mean age of patients with mild to moderate disease was less than 50 years whereas, patients with severe disease had a meanage of more than 50years. n mild disease group, mean serum ferritin level was 80.74 ng/ml and mean serum D-dimer level was 444.06 ng/ml, during first week of hospitalization with an average of 7 days of stay in hospital, no oxygen requirement and 100% survival rate, whereas in moderate disease group, we observe that mean

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serum ferritin level was 150.42 ng/ml and D-dimer level was 2676.5 ng/ml during first week of hospitalization. About 84.2% (n=166) patients with moderate disease gotsurvived and discharged, but unfortunately 15.7% (n=31) of patients, progresses to severe disease with complications and high oxygen requirement, their mean serum ferritin level was more than 220 ng/ml and D-dimer levels was more than 2000 ng/ml.In severe disease group, mean serum ferritin level was 333.6 ng/ml and mean D-dimer level was 6810.5 ng/ml during first week of hospitalization, with an average of 18 days of stay in hospital, with very high oxygen requirement, complications and only 6 % (n=8) survival rate.Conclusion:Our study showed the importance of serum ferritin and D-dimer levels as the primary biomarker which can help in early detection of severity of the disease, enabling the clinicians to make strategic planning and disease management. These steps would definitely decrease the mortality index and hospital stay.

INTRODUCTION:

The world has faced covid 19, as the biggest threat to public health and it is not over yet. According to WHO, since the start of this pandemic, about 260 million cases with more than 5 million deaths reported globally (Worldometer, 2021).

In this ongoing pandemic, currently Pakistan has the 29th highest number of cases in the world and 7th highest number of confirmed cases in Asia, with more than 1.5 million cases and thirty thousand deaths (WHO, 2022).

The corona virus disease 2019 (COVID-19) is caused by a newly discovered corona virus that was first identified in December 2019, from a bunch of pneumonia like cases in Wuhan City (China), later it was named as nCOV-2 or SARS-COV2 (CDC, 2019).

It is highly contagious disease, commonly spreads between people who are in close contact to each other, directly through respiratory droplets and aerosol whereas sharing of infected objects can be a source of infection (Harrison et al., 2020).

Patients with increasing age, having known co-morbid like hypertension, diabetes, cardiovascular, renal and respiratory disease are at higher risk of having this disease (CDC, 2019).

Most people will develop mild disease and recover with or without medication at home, but some people with moderate to severe disease need to be hospitalized. Patients with Pregnancy or any preexisting immune mediated or metastatic disease are associated with severe disease and high mortality (Oran & Topol, 2020).

Patients with mild disease came with complains of Fever, cough, nasal congestion, throat pain, headache and myalgia, but some patients also experience loss of smell (anosmia) and loss of taste (ageusia), with decrease in appetite. Other non-specific GI symptoms include vomiting and diarrhea. Patient with severe disease complains of difficulty in breathing, respiratory distress and altered level of consciousness (Agyeman et al., 2020).

According to studies, the inhaled virus binds to the angiotensin-converting enzyme 2 (ACE2) receptors of the host cell through its spike glycoprotein, membrane fusion between virus and the host cell is activated and the viral RNA is subsequently released into the cytoplasm, establishing infection (Verdecchia et al., 2020).

ACE2 receptor are present on the cellular surface of almost all organs of our body in different levels, but mainly expressed in lungs on type II alveolar epithelial cells, suggesting that the lungs will be affected more than any other organ. Viral replication and cellular destruction activate macrophages and monocytes which causes the release of cytokines and chemokines (Letko et al., 2020)

In severe disease, due to increase secretion of cytokines and chemokines, systemic inflammatory

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immune response (SIRS) occurs called as cytokine release syndrome, leading to hypercoagulable state and multiorgan failure. (Marik et al., 2021)

Accumulated evidence shows macro and micro vascular thrombosis associated with increasing risk of developing pulmonary embolism, myocardial infarction, stroke and other associated disease with poor prognosis (CEBM, 2019).

Therefore, evaluation of hyper inflammation and coagulable state in covid-19, using biomarkers like CRP (C reactive protein), PCT (Procalcitonin), D-dimers, Ferritin and LDH (lactate dehydrogenase) will be helpful in early assessment and management of this disease.

PCT, CRP, ferritin and D-dimer are four important acute phase reactants, there concentration increases in inflammatory state, due to release of cytokines. (Jain et al., 2011)

PCT (Procalcitonin) is a peptide precursor of calcitonin hormone, produce by Parafollicular cells of thyroid and neuroendocrine cells of Lung and intestine. PCT is more specific for bacterial infection and it remains normal or get slightly elevated in case of viral infection. (Covington et al., 2018)

whereas CRP is a plasma protein of hepatic origin, its physiological role is to bind with receptors on dead or dying cell, activating complimentary system for their removal by macrophages (Pepys & Hirschfield, 2003), it also act as a inflammatory marker (nonspecific), and their concentration increases in any bacterial, fungal or viral infection (Hytest, et al).

Ferritin is a protein that contains iron in blood, it usually indicates iron stores in our body, but as an acute phase protein, its synthesis increases nonspecifically in wide range of inflammatory conditions, independent of iron stores (Wang et al., 2010).

D-dimer is a fibrin degraded product; it is a protein fragment, which is produce as result of fibrinolysis in coagulable state (Asakura et al., 2020). It is used as a biomarker for coagulation disorders. Elevated D-dimer levels are commonly due to a Venous Thromboembolism or DIC but it may also be elevated due to a recent surgery, trauma, infection, cancers, liver or kidney disease, d-dimer levels are also found to be elevate in Covid-19 infection. A four-fold increase in the protein is an indicator of poor prognosis (Ponti et al., 2020).

In a recent study, conducted in a private hospital of Karachi, serum ferritin appears to be a strong predictor of mortality in covid 19 (AKU, 2021). While in another study conducted in public sector hospital, elevated serum ferritin and D-dimer levels are associated with poor outcome of this disease (Baqi et al., 2021)

Similarly, studies conducted in other countries also showed that, among the inflammatory markers, serum ferritin and D-dimer levels are strongly associated with the severity of covid 19, so with this study we try to Correlate serum ferritin and D-dimer levels with the clinical outcome of the disease.

Coronaviridae family contains two genera, i.e. Coronavirus and Torovirus, they are different from each other due to the symmetry of their nucleocapsid, coronavirus have nucleocapsid of helical symmetry, whereas torovirus have it of tubular symmetry (Mei-Yue Wang et al, 2020).

Coronavirus are enveloped viruses, containing single strand of positive-sense RNA (ribonucleic acid) in their genome and a nucleocapsid of helical symmetry. They contain characteristic of club shaped spikes that project from their surface, which in electron micrograph, gives a crown like appearance (BPS Blog,2022).

The SARS-CoV-2 is about 80 to 200 nm in diameters, with a molecular mass of about 40,000 kDa. The viral envelope is made up of lipid bilayer with four different types of proteins, including the spike (S) protein, membrane (M) protein, envelop (E) protein and nucleocapsids (N) (NIH,2020).

The membrane (M) and envelope (E) proteins are the main structural proteins that provide viral shape. Membrane proteins, form a thick layer with amino acid, whereas E proteins are embedded in lipid layer. The spike or "S" protein are present on the viral surface, subdivided into two types i.e., S_1 (responsible for attachment to the host cell) and S_2 (responsible for fusion of

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membrane between virus and the host cell) (APS,2020).

The nucleocapsid (N) protein of SARS-CoV-2 is located inside the cytoplasm, it binds with positive sense RNA genome to form ribonucleoproteins and plays an important role in viral replication and pathogenesis.

Covid-19 virus spreads from infected person via respiratory droplets and aerosols. The inhaled virus, enters in the respiratory tract of humans and binds itself to the receptors on host cell through it spike glycoprotein (NIH.,2021).

Angiotensin converting enzyme-2 (ACE-2) is a transmembrane receptor for SARS-CoV-2 on host cells. These receptors are present on the cellular surface of almost all organs of our body in different levels, but mainly expressed on pulmonary epithelium, type II alveolar cells in greater quantity (Letko et al., 2020), suggesting high risk of respiratory failure and multiorgan involvement in severe cases of covid-19.

As the disease progresses, the viral antigen travels from upper respiratory tract to lower respiratory tract and attaches itself to the pneumocytes with the help of it spike glycoprotein through ACE 2 receptors on the host cell. Viral antigen and host cell complex are now formed which is then followed by fusion of membranes between them by proteolysis, subsequently releasing the viral RNA inside the host cell by endocytosis. viral replication takes place inside the host cell, releasing new viral particles to infect another adjacent cell through apoptosis (Verdecchia et al., 2020).

Typically, there are two types of basic immune response to covid-19 i.e., the innate immune response and the adaptive immune response. As a first line of defense, innate immune response helps to identify the foreign invader like virus, to activate white blood cells , complement system and cytokines. Whereas the adaptive immune response as a second line of defense, take few days to develop and it causes the development of antibodies by activation of T-cells and B-cells, to neutralize the invading antigen (Chowdhury A, et al, 2020).

Viral antigen-host cell complex and viral replication both activate innate immune response in our body, it activates pro-inflammatory cascade and release of neutrophils, complement system, different cytokines such as interleukins (IL-1, IL-6, IL-8, IL-120 and IL-12), tumor necrosis factor-αlpha (TNF-α), IFN-λ and IFN-β, CXCL-10 and monocyte chemoattractant protein (MCP-1).

Release of cytokines by activated immune cells, act as chemoattractant for neutrophils, CD4 helper T cells and CD8 cytotoxic T cells, causing inflammation and cellular damage in different organs of body. Similarly, in Lungs, with greater number of ACE-2 receptors, severe inflammatory process damages respiratory epithelial cells (pneumocytes), leading to alveolar damage and acute respiratory distress syndrome.

Immune response in covid-19 varies from patient to patient, many ongoing studies are trying to find different factors which are responsible for different levels of immune response in this disease. In severe disease, due to increase secretion of these cytokines (cytokine storm), systemic inflammatory immune response (SIRS) occurs called as cytokine release syndrome (CRS), leading to hypercoagulable state and multiorgan failure. (Marik et al., 2021)

Hypercoagulable state in covid-19, characterized by intravascular thrombosis with greater chance of thromboembolic events, occur due to exaggerated systemic inflammation and wide spread endothelial damage. Deep venous thrombosis (DVT), pulmonary embolism (P.E), Myocardial infarction and stroke are among most common complications in covid-19 related hypercoagulable state (Mouhamed Y et al, 2020).

Other clinical manifestation of covid-19 also include acute gastroenteritis and acute renal failure but few patient was also seen with deranged liver enzymes, viral myocarditis and meningoencephalitis.

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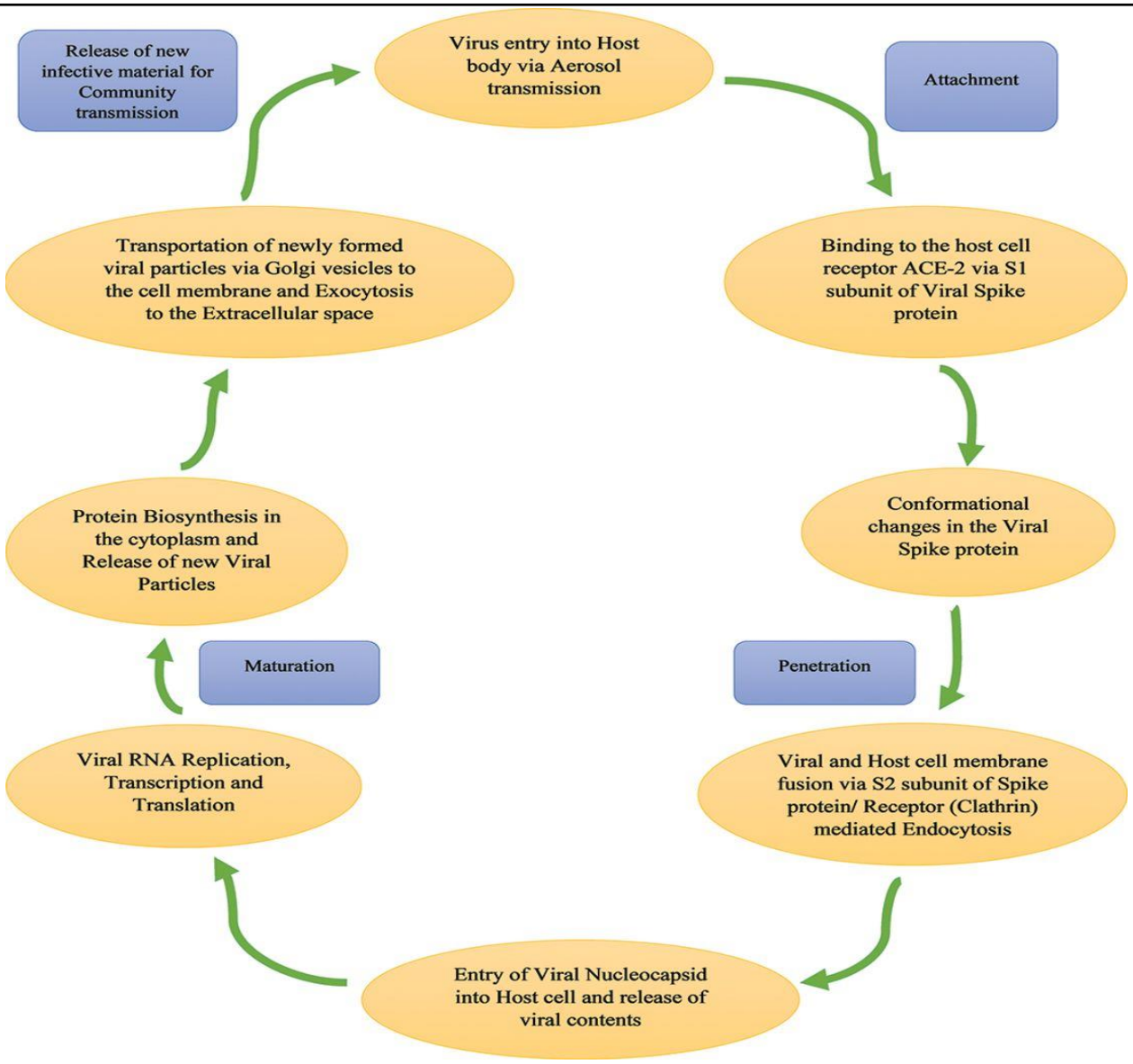

Figure 3: Steps of covid-19 infection

Retrieved from: https://pmj.bmj.com/content/postgradmedj/97/1147/312/F1.large.jpg

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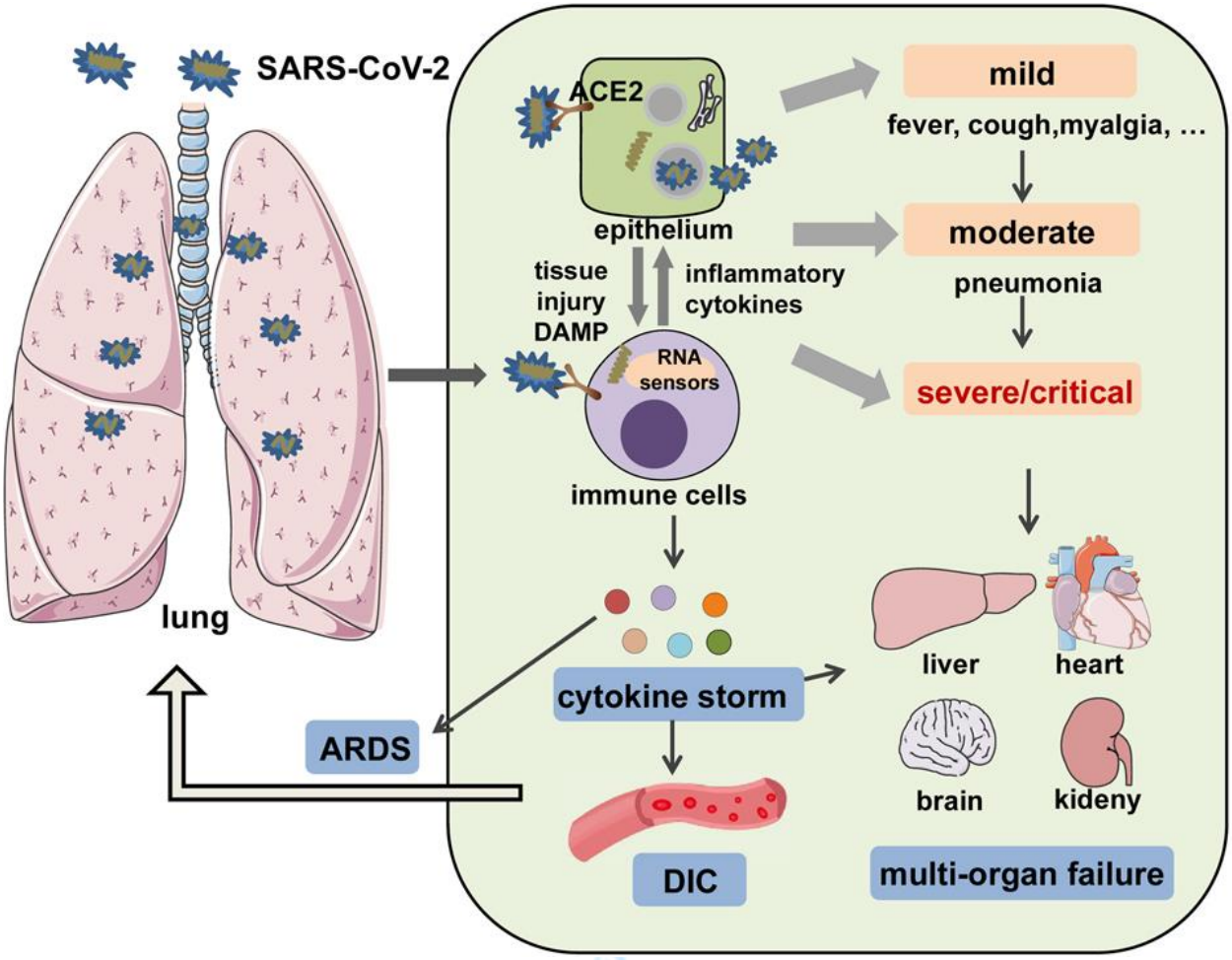

Figure no 4: Cytokine storm and multiorgan involvement

Source: Signal transduction and targeted therapy (July 2021), The signal pathways and treatment of cytokine storm in COVID-19 Retrieved from: https://www.nature.com/articles/s41392-021-00679-0

Methodology:

It is a Descriptive, cross-sectional study, conducted in the department of clinical pathology, JPMC with collaboration of Ziauddin Medical university hospital, over a duration of six months with the approval of institutional board.

We included all Covid PCR positive patients that was admitted in covid wards and ICU, radiologically suggestive of pneumonia with no prior history of respiratory disease, whereas all Covid PCR negative patient are excluded.

A sample size of 384 patients is calculated for infinite population by using openepi software, keeping 95% of confidence level, 5% of margin of error and 50% of prevalence rate.

All the patients included in the study are characterized on the basis of symptoms into mild moderate and severe disease on the basis of WHO covid 19 disease classification. Serum ferritin and Ddimer levels was done at admission and repeated after 1 week of hospitalization on automated clinical analyzer using principle of immuno-turbidimetry. All the patients were followed throughout the course of the disease, results were analysed and co related with the clinical progression and outcome of disease. Computer

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software SPSS version 24 was used to record data and for its statistical analysis.

Basic laboratory principle immuno-turbidimetry:

Latex bound antibodies react with the antigen in the sample to form a complex. Turbidity formed due to antigen/antibody complex are measured which is directly proportional to the concentration of analyte present.

Selected biomarkers with normal values:

Selected markers	Normal values
D-dimer	220-500 ng/ml
Ferritin	20-250 ng/ml (for adult male), 10-150ng/ml (for adult female)

Results:

In this study, according to sample size, A total of 384 covid positive patients were included, but later 29 patients got discharge on request and did not continue their treatment in hospital, so the sample size was then subsequently reduced to 355. We categorized these patients into mild, moderate and severe groups (WHO, 2020). It was observed that, out of these patients, 22 patients were with mild disease, 197 patients were with moderate disease and 136 patients were with severe disease.

All the patients were followed throughout their course of the disease, Serum ferritin and D-dimer levels were done at admission, designated as F1 and D1, whereas repeated serum ferritin and D-dimer levels after 1 week, designated as F2 and D2 respectively.

In mild disease group, out of 22 patients, 54 % (n=12) patients were male and 45% (n=10) patients were females, with a mean age of 35 years and no known co-morbid. In these patients, mean serum ferritin level at admission (f1) was 68.45 ng/ml and repeated serum ferritin level (f2) was 93.04 ng/ml , whereas mean serum D-dimer levels at admission (D1) was 418.72 ng/ml and repeated serum D-dimer level (D2) was 469.40 ng/ml, there average stay in hospital is about 7 days, with no oxygen requirement, no complications and 100% survival rate.

In moderate disease, 197 patients were identified, 55 % (n=108) patients were male and 45% (n=89) patients were females, with a mean age of 37 years and different known co-morbid. In these patients, mean serum ferritin level (f1) was 149.08 ng/ml and (f2) was 151.76 ng/ml, whereas mean serum D-dimer levels (D1) was 1832 ng/ml and mean D2 was 3521.19 ng/ml, their average stay in hospital is about 18 days.

About 84.2% (n=166) patients with moderate disease got survived and discharged, but unfortunately remaining 15.7% (n=31) of patients, progresses to severe disease with high oxygen requirement and different complications, their mean serum ferritin level was more than 220 ng/ml (F2) whereas their D-dimer levels was more than 2000 ng/ml (D2), during first week of hospitalization.

In severe disease, out of 136 patients, 53% (n=73) patients are male and 47% (n=63) patients are females, with an average 51 years of age, and different known co-morbid and, In these patients with severe disease, mean F1 levels was 283.65 ng/ml and mean F2 levels was 383.67 ng/ml , whereas mean D1 levels was 6122.74 ng/ml and mean D2 levels was 7498.31 ng/ml, with an average 18 days of stay in hospital, with very high oxygen requirement, different complications and only 6 % (n=8) survival rate.

Discussion:

The impact of covid-19 crises, is that it causes loss of human lives and burden on healthcare providers, along with its unexpected impacts on our social, economic and financial systems across

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the globe. Due to necessary shutdown measures taken by the government, billions of people were in lockdown, unemployed, struggling during isolation. People were unable to visit one another, separated from their loved ones, leading to severe mental health issues and family life disturbances.

The covid-19 pandemic demonstrates us about our health care and value of freedom. Risk of having spread of disease will always be there. It is very important for everyone to adapt safety measures and maintain good hygiene for the development of healthy environment, in this way we will be able to decrease the rate of infection and spread of disease.

Up till now there is no definite treatment for covid 19, this disease can progress rapidly to severe form within few days of hospitalization and it is very important to identify the patients who are at risk of having severe disease at early stage. Clinicians and researchers are working together to develop comprehensive risk management plan and treatment strategies.

Our study has shown male dominance in all three groups of disease severity i.e. mild, moderate and severe disease. we found 54.5% males with mild disease, 62.9% males with moderate and 59.5% males with severe disease. Our study was in concordance with studies conducted by Saluja et al. showing 60.9% of patients of covid were males and 39.1% were females.

Avinash et al, also showed male to female ratio as 1:0.6, similarly Firdevs et al. and Sharma G et al. showed 69.9% and 70% of male dominance respectively.

Our study showed, that patients with more than 50 years of age are at higher risk of having severe disease with poor prognosis. About 87.6% of patients with severe disease have an age of more than 50 years, with only 13.3% of survival rate. In concurrence with these findings, other study conducted by Zhang et al, showed that more than 50% of the expired patients were in between 50-60 years of age.

Serum ferritin and D-dimer, are two primary biomarkers of covid-19. Ferritin is a protein that stores iron but according to studies, it is also an acute phase protein and a well-known inflammatory marker, its concentration increases in inflammatory state, stress and cancer. In covid-19, its concentration increases due to hyperinflammation and systemic inflammatory response (SIRS).

D-dimer is a fibrin degraded product, it is produced after fibrinolysis of blood clot in hypercoagulable state. It is commonly found raised in conditions like infection, pregnancy, trauma, heart disease and recent surgery. In covid-19, due to widespread inflammation and endothelial damage, its concentration increases many folds.

Our study observed, higher levels of serum ferritin and D-dimer in covid positive patients, it also showed that, patients with mild to moderate disease, have a mean serum ferritin level of about 115.58 ng/ml, whereas, in patients with severe disease , it is about 333.66 ng/ml, during first week of hospitalization, with only 6 % survival rate. Similarly, a retrospective observational study conducted in Pakistan by Sibtain et al. 2021, also showed higher serum ferritin levels i.e. 1096.4 ng/ml (median) in non-survivor group.

Study done by Deng F et al. reported that serum ferritin levels were about 2 to 5 times more elevated (median 1722.25 ng/ml), in patients with critical disease, as compared to patients with moderate disease (median 501.9 ng/ml). Similarly, a meta-analysis of 18 studies, conducted by Linlin Cheng et al, also observed that serum ferritin levels was significantly increased in severe disease group and non-survivor groups.

The mean D-dimer level of patients in our study having mild to moderate disease was about 1560.32 ng/ml. and in patient with severe disease it was about 6123 ng/ml. this finding was in concordance to a retrospective study, done by Hai-han et al, in China, demonstrating association of higher serum D-dimer levels (above 1000 ng/ml) with disease progression, greater risk of thromboembolic complications and 28 days mortality.

Due to progression of disease, about 16% of patients from moderate disease were shifted to intensive care unit, their mean serum ferritin level was more than 220 ng/ml whereas their D-dimer

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levels was more than 2000 ng/ml, during first week of hospitalization.

A study conducted by Humera F et al, noted that D-dimer levels in survivor group was less than 2000ng/ml, whereas in non-survivor group, it was more than 2000 ng/ml, hence suggesting that D-dimer levels of more than 2000 ng/ml are strongly associated with high mortality rate in covid patients.

Incidental finding noted in this study, was association of length of stay in hospital, with increase oxygen requirement and ventilator support. It was noted that, patients with severe disease had a mean stay of 18 days in hospital.

About 94% of our patients with more than 18 days of stay, needed ventilator support for increase oxygen requirement and only 6% of patients with less than 18 days of stay in hospital did not require ventilator support and got discharged on non-invasive ventilation. We also noted that all the patients from moderate disease, that was shifted to intensive care, also had length of stay of more than 18 days with more than 40 L of oxygen on non-invasive ventilation.

Although vaccination programs were started globally, Pakistan also started mass vaccination, but due to lack of awareness and circulating rumors, majority of the population were reluctant in taking the vaccination.

Our small analysis of 355 patients showed that only 4.5% (n=14) of patients were completely vaccinated (two doses) and 15% of patients were partially vaccinated (single dose), reflecting the rate of vaccination and hence hampering the goal of herd immunity.

Conclusion:

Our study showed the importance of serum ferritin and D-dimer levels as the primary biomarker which can help in early detection of severity of the disease, enabling the clinicians to make strategic planning and disease management. These steps would definitely decrease the mortality index and hospital stay.

Limitation:

- Covid-19 is highly contagious disease with high mortality rate so we collected the data in strict isolation on preformed Performa.
- We did not compare our results with the vaccination status as most of the patients were not vaccinated at all.
- We did not compare our results with the treatment plans of the selected patients

Recommendations:

According to our study data, serum ferritin and D-dimer levels are identified as two important inflammatory biomarkers for evaluation of disease severity in covid-19, these markers should also be correlated with the different treatment strategies

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