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A Review Article on the Evaluation of Prognosis and Outcome in COVID-19 Patients Using Several Biomarkers

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ABSTRACT

COVID-19 virus which was imported to India via the travelers from abroad became the biggest nightmare of the decade. It not just involved a single continent but the entire globe. Therefore, it became necessary to discover each and every detail about the virus so as to manage the cases suffering and to avoid further spread of the infection. The entire pathophysiology and the modes of spread of the virus were studied in great detail. The use of hand sanitizers and face masks became popular and widespread. The importance of proper hand hygiene came into play. All social gatherings were suspended or converted to online events. Even schools, colleges and work places were shut for a very long period of time. During this time there were a number of researches going on regarding the treatment and prevention of the virus. Data was recorded and compared and conclusions drawn from them. There were several biochemical and inflammatory markers whose values were compared and conclusions drawn from the same. The value of these biomarkers was later found to be useful in the predicting the outcome of the disease in majority of the individuals. Innumerable studies have been conducted to study the role of these biomarkers but still a lot of research needs to be done for knowing more about these markers. Measurement of these markers at initial stages of the disease might prove to be very helpful in changing the end result of the disease.

Key words: COVID-19, Biochemical, Inflammatory markers, Biomarkers, Outcome

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INTRODUCTION

COVID-19 virus which was first thought to be an epidemic originating in Wuhan, China became a pandemic in no time. It is an RNA virus. This virus caused a huge amount of morbidity and mortality across the globe. It also caused huge economic crisis throughout the world. Therefore, it became a necessity to study each and every aspect of the disease and virus so as to overcome the losses caused by the virus and to avoid any further damage from the same [1].

Transmission of COVID-19 virus

COVID-19 virus interacts with receptor which is used by severe acute respiratory syndrome CoV-2 that is, Angiotensin Converting Enzyme 2 (ACE-2). The spread is mainly through respiratory tract. The main source is aerosols which are spread by human to human contact. This can occur by contact with infected surfaces, through droplets or with hands. The spread of infection can also occur by direct contact with the mucous membranes of the infected person [2].

LITERATURE REVIEW

Mechanism of invasion of COVID-19 virus

The virus's life cycle inside the host cell comprise of below mentioned steps: Adherence, infiltration, neo synthesis, development and liberation. After attaching to host cell receptors that are penetration, COVID-19 virus is internalized by the host cell by formation of processes which surround the virus which bud off to form a vesicle within the cell. Once the virus' particles have been released into the cells of the host, the RNA of the virus starts multiplying inside the nucleus of the host cells. Viral messenger RNA is employed in the production of viral proteins (neo synthesis). After maturation, new virus particles are produced and released. The main structural proteins of the COVID-19 virus are four in number: The Envelop protein (E), the Nucleocapsid protein (N), the Spike protein (S) and the Membrane protein (M) [3].

S protein comprise of two subunits which are active functionally: The S_1 subunit adheres with the cell membrane receptors. Membranes of host cell merge with

protein of virus with the help of S_2 subunit. COVID-19 virus interacts with receptor which is used by severe acute respiratory syndrome CoV-2 that is, Angiotensin Converting Enzyme 2 (ACE-2) [4].

Diagnosis of COVID-19 virus

Diagnosis of COVID-19 disease can be done using RT-PCR that is, reverse transcriptase polymerase chain reaction. The sample can be in the form of tracheal aspirate, nasal swab or Bronchoalveolar swab (BAL). Collection of oropharyngeal and nasal swab is the main method of choice for acquiring sample *via* the upper respiratory tract for diagnosis of the disease. Collection of sample *via* bronchoscopy that is, Broncho Alveolar Lavage (BAL) may lead to higher risk of exposure for the health worker as well as the patient. BAL is preferred only in case of intubated patients where nasopharyngeal and oropharyngeal swab have been found negative [5].

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) has a very high specificity. In case of asymptomatic patients there may be a number of false positive results due to swab contamination. Sensitivity of the test is approximately calculated to be around 66% to 80%. [6].

Several biomarkers have been demonstrated to have a significant influence in the prognosis and end result of COVID-19 illness. Assessment of WBC (White Blood Cell), NLR (Neutrophil to Lymphocyte Ratio), SGOT (Serum Glutamic Oxaloacetic Transaminase), sodium and potassium in early stages of the disease have proven to affect the outcome [7]. It was also observed that there is an association between the value of platelets, C-Reactive Protein (CRP), Procalcitonin (PCT), Lactate Dehydrogenase (LDH) and D-dimer and the outcome of COVID-19 disease. It also helps in identification of high risk patient thereby leading to better management of cases as well as the resources available [8].

The COVID-19 disease mainly involves the respiratory tract. WHO states the most common signs and symptoms of the disease to be pyrexia, cough, fatigue, dysgeusia and anosmia? The less frequent were pain in throat, headache, aches and pains, diarrhea, red or irritated eyes, skin rash or change in color of toes or fingers. Severe features are chest pain, breathlessness, aphonic or mobility or confusion. All the features take almost a week to manifest post infection from the virus but may take up to 2 weeks for the same [9].

The diagnosis of the disease can be made by chest Computerised Tomography (CT) even when RT-PCR (Reverse Transcriptase–Polymerase Chain Reaction) comes out to be negative. On chest CT bilateral pulmonary parenchymal ground glass and consolidative pulmonary opacities, occasionally with a rounded shape and peripheral lung distribution, are common observations [10]. CT alterations are usually noticed on the tenth day of illness [11].

There have been various studies which have proven the importance of biomarkers in the likely course and outcome of COVID-19 disease. These biomarkers included in the study are C-Reactive Protein (CRP), D-dimer, Lactate Dehydrogenase (LDH), Interleukin-6 (IL-6), platelet counts, cardiac markers and renal markers [12,13].

Materials and methods

After a thorough study of articles from the WHO (World Health Organisation), PubMed, SCOPUS, Google scholar the biomarkers have been studied in great detail and the strategy used to reach the conclusions drawn from the same have been stated below.

This study includes biomarkers: C-Reactive Protein (CRP), D-dimer, Lactate Dehydrogenase (LDH), Interleukin-6 (IL-6), platelet counts, cardiac markers and renal markers.

Methods to assess biomarkers

D-dimer assay: D-dimer helps in measuring fibrinolysis and fibrin turnover. It also helps in detecting abnormalities of fibrinolysis. Its values are also increased in case of intravascular thrombosis. When a thrombus degrades by fibrinolytic mechanism it leads to formation of fibrin degradation products. One such product is D-dimer. Therefore, D-dimer assay can be used to assess the coagulation and fibrinolysis [14].

The values of D-dimer on admission were reported to be impactful in forecasting the fate of COVID-19 illness. The value of D-dimer was calculated to be four times the normal value that is, it was greater than 2.0 µg/ml and was found to be an impactful marker for predicting the fatality of the patients suffering from the disease in hospital.

Therefore D-dimer assay can be very efficacious in determining the prognosis and thereby help in improvement of management of the infected persons [15].

C-reactive protein: The levels of C-reactive protein increase in presence of inflammation. CRP is unaltered by various factors such as gender, age group or physical parameters [16].

High C-reactive protein concentration leads to activation of complement system and enhancement of the process of phagocytosis thus killing all the harmful pathogens that enter the body. The diagnosis of pneumonia can be made very early using C-reactive protein [17].

CRP concentrations were strongly linked with lung abnormalities in the initial phases of COVID-19 and might represent illness activity [18].

Lactate Dehydrogenase (LDH): Lactate dehydrogenase is an enzyme observed within the cell in virtually every organ. It catalysis the conversion of pyruvic acid to lactic acid, also leads to the simultaneous conversion of NADH (Nicotinamide Adenine Dinucleotide Hydrogen) to NAD^+ (Nicotinamide Adenine Dinucleotide) [19].

This enzyme is made up of two primary subunits (A and B). In humans five different isozymes are found: LDH-1 in

cardiac cells, LDH-2 in the cells of reticulo endothelial system, LDH-3 in the cells of the lung, LDH-4 in renal cells and pancreatic cells and LDH-5 in hepatic cells and skeletal muscle cells. Although LDH is also a diagnostic indicator of myocardial injury since many years, aberrant readings can occur from various organ injury and reduced oxygenation due to glycolytic pathway activation. The activation of metalloproteases occurs due to the acidic pH as a result of increased lactate levels due to tissue damage and infection. This aids in angiogenesis mediated by macrophages [20].

The increments in the levels of lactate dehydrogenase are found to be related with six time's escalated severity of COVID-19 disease. More crucially, increase in the levels of LDH was linked to a >16 times increase mortality risk. As a result, LDH levels in patients should be continuously watched for any symptoms of illness advancement or decompensation. Because the LDH concentrations used in the analysis were acquired at the initial visit or the first point while hospitalization, initial LDH levels might be included in long term risk assessment strategies for COVID-19 intensity and fatality [21].

Interleukin-6 (IL-6): Interleukin-6 is an inflammatory cytokine which is found to be raised in infected persons with increased severity of disease. Its presence might denote inflammatory condition of the lung, damage to the lungs and may also lead to multiple organ failure [22].

Interleukin-6 (IL-6) is a significant cytokine whose production is related to a variety of inflammatory disorders. Subjects infected with SARS-CoV-2 showed significant values of IL-6, which were linked to patient symptoms such as pulmonary inflammation and significant lung injury [23]. Furthermore, individuals infected with SARS-CoV-2 had reduced concentrations of suppressor of cytokine signaling-3, a protein that regulates and regulates the IL-6 inhibitory feedback loop [24].

Platelet count: Thrombocytopenia or low platelet count is common in critically ill patients and usually indicates serious organ dysfunction. There might not always be a primary hematologic cause. It might lead to the development of intravascular coagulopathy, which may lead to Disseminated Intravascular Coagulation (DIC) [25].

The mechanism for thrombocytopenia in COVID-19 individuals is quite complex. It has been postulated that the conjunction of viral illness and mechanical ventilation induces endothelial damage in SARS, leading in platelet activation, clumping and thrombosis in the lung, culminating in enormous platelet consumption [26].

Decreased platelet number may enhance the incidence of serious fatality and morbidity in COVID-19 patients and should thus be used as a clinical predictor of deteriorating sickness during treatment [27].

Cardiac troponins: The concentration of troponin-I are higher in COVID-19 patients, this might be one of the cause for the increased mortality in COVID-19 disease. When the levels of troponin-I are normal during the first day of admission. It has a strong negative predictive value among all death in the institution. This has a good prognosis for survival after treatment [28].

Renal markers: A research devoted for analysis of data regarding biochemical parameters to distinguish severe COVID-19 patients and moderately infected patients showed that individuals with serious symptoms have considerably greater concentration of serum urea, creatinine and cystatin C than those with less severe conditions. These indicators may be associated to the glomerular filtration function, which may be utilized to differentiate between moderate and severe COVID-19 cases [29].

In case of severe COVID-19 disease, there is impaired renal function. Also factors such as male gender, increased blood pressure and elderly have a poorer prognosis than the others [30].

DISCUSSION

After rigorous efforts by various researchers the studies have concluded that the level of the biomarkers has played a pivotal function in identification of virus, management and prevention of COVID-19 disease [13] (Table 1).

Table 1: The data revealed changes in the values of biomarkers as follows.

Biomarkers which increased	Biomarkers which decreased
CRP	Platelet count
IL-6	
LDH	
D-dimer	
Cardiac troponin	
Urea and creatinine	

The values of these biomarkers have been found to be useful to determine the outcome of the patients and in better use of the resources available for the masses.

Markers and their specificity in prognosis of the disease

CRP: C-Reactive Protein (CRP) is an acute marker which is elevated in circulation in presence of infections. It is produced in the cells of liver. Its production is regulated by Interleukin (IL)-6 [31].

CRP can help in removing the microorganisms by the process of phagocytosis with the help of CRP receptors macrophages. A huge increase in the levels of cytokines was found in COVID-19 pneumonia which led to increased fatality [32].

Majority of deaths that occurred in the ICUs were due to septic complications caused by the virus, which could be detected by the increased levels of CRP [33].

LDH: Lactate dehydrogenase enzyme is present in cells in all organs in the body. It helps in conversion of pyruvate to lactate and also aids in conversion of NADH to NAD^+ [34].

LDH is released in case of severe infections [35]. LDH is found in lungs in the form of isozyme 3. In case of interstitial pneumonia LDH levels are massively increased in the circulation and may lead to acute respiratory distress syndrome. The rise in the levels of LDH may also cause thrombotic microangiopathy and may lead to kidney failure and myocardial injury [36-38].

D-dimer and platelet counts: It is found that in severe COVID-19 disease the concentration of D-dimer escalates many times and there is reduction in the level of platelets (thrombocytopenia), suggestive of a hypercoagulable state. This may increase the risk of poor outcome and may even lead to death in these patients [39,40].

The COVID-19 disease caused a huge havoc not only nationwide but across the globe. The virus which was thought to be a variant of respiratory infection proved to be fatal and caused innumerable deaths across the globe. Therefore, it became necessary to limit the disease and to get hold of the infection by stopping further spread. It became vital to know the cause for such a varied response by individuals for the same virus. The effect of the viral infection was found to be very diverse in different individuals. In some it caused mild flu like symptoms whereas, it led to the death of many others [41-45].

From the studies we can conclude that the coagulation profile and the liver enzymes of the patient are very crucial in the diagnosis of the disease. Also, markers like C-Reactive Protein (CRP), platelets, Interleukin-6 (IL-6), D-dimer, Lactate Dehydrogenase (LDH), Cardiac troponins and renal markers help in determining the prognosis and management of the disease. These markers not only help in determining the prognosis but also warn about the complications which could be caused in future, thereby avoiding mortality due to the same [46,47].

CONCLUSION

The higher the level of D-dimer on admission, the worse the prognosis. It is observed that a D-dimer level more than 2 micrograms per milliliter was found to be a poor prognostic marker. It also leads to higher number of in hospital deaths. Therefore, early detection of D-dimer is helpful in better management and avoidance of complications. The levels of C-reactive protein help in detecting the occurrence of pneumonia in a patient with COVID-19 disease. The quantities of C-reactive protein have a positive connection with the lesions found in the lung. Therefore, C-reactive protein is a very useful indicator in determining the patient's prognosis. The levels of Lactate Dehydrogenase (LDH) do not correspond to a particular organ system. Therefore, rise in the level of LDH cannot be taken as a marker for a specific system. Increase in the levels of LDH is thought to have caused increased severity in COVID-19 disease by 6 times. Elevation in the levels of LDH also increases the risk of mortality in COVID-19 disease by 16 times. The elevation of inflammatory cytokines like Interleukin-6 (IL-6) causes extensive damage to the lungs. This leads to pulmonary complications in case of COVID-19 disease. Thrombocytopenia or reduced platelet counts in presence of severe acute respiratory illness may prove to be fatal. Also, low platelet count with hypoxemia can cause severe COVID-19 disease. Fall in the number of platelets may also lead to thrombotic phenomenon and may cause intravascular coagulation which may further lead to Disseminated Intravascular Coagulation (DIC). In case of severe COVID-19 disease, there is impaired renal function because of acute kidney injury caused due to the disease. Also factors such as male gender, increased blood pressure and elderly have a poorer prognosis than the others. Increased level of cardiac troponin I can cause heart damage in patients with COVID-19 disease. It is also found that there is high mortality in patients who have higher levels of troponin I in the initial 24 hours of hospitalization. Therefore, cardiac troponin I is an important marker in forecasting the course and outcome of the COVID-19 disease.

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