REVIEW ARTICLE

Prognostic and Predictive Role of Selected Biochemical Markers in COVID-19

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ABSTRACT

Rapid emergence and spread of current pandemic of COVID-19 has evoked the medical science community to investigate quick, accurate and reliable diagnostic and prognostic approaches. Early identification of causative agent SARS-CoV-2 in host and monitoring the blood biochemical parameters for the assessment of disease severity leads to devise proper management and care to minimize mortality rate. The research studies on biochemical markers in COVID-19 published till May 15, 2020, are retrieved by using keywords "biochemical markers, biomarkers, COVID-19, and SARS-CoV-2" at web search engines (Google scholar & PubMed). Selected articles are reviewed for the selected biomarkers that can be useful prognosticators of mild and severe patient outcomes to provide assistance in clinical management of the outbreak for frontline medical personnel. Biochemical tests include panels of liver and renal functioning, lactate dehydrogenase, C-reactive protein, and interleukin-6 that have abnormal and deteriorated values as compared to normal controls and mild cases. Patients having baseline comorbidities such as hepatitis or chronic kidney disorder might develop multiorgan injuries during hospitalization but in other patients' biomarkers measure the status of inflammatory response and drug therapy outcomes.

KEYWORDS: SARS-CoV-2, COVID-19, Biochemical markers, Liver function tests, Renal function tests, C Reactive Protein, Interleukin-6.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). It was first recognized in December 2019 in Wuhan, China, and has since been spread globally, resulting in a continual pandemic.[1] As of 17th May 2020, more than 4.66 million cases have been recounted among 188 countries and territories, resulting in more than 312,000 demises. More than 1.7 million people have recuperated.[2] Extreme COVID-19 cases are identified with pneumonia and Acute Respiratory Syndrome as the primary cause of mortality. In addition to that septic shock and multiple organ dysfunction with identified or unidentified comorbidities have also been reported as secondary reasons of mortality.[3] In this regard understanding the abnormalities in biochemical markers might be the best indicators of overall health, disease severity, drug response and clinical outcome in SARS-CoV-2 infection which will improve prognostic and treatment capabilities and ultimate impact the mortality and morbidity.

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Biomarkers can be defined in various terms but the National Institute of Health (NIH) has defined the biomarkers or biochemical markers as: *"Biological characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathological processes or pharmacologic responses to a therapeutic intervention".*[4]

Biomarkers can be natural, or man-made. In clinical medicine, biomarkers used for diagnostic and prognostic measures are usually metabolites or derivatives of metabolites such as enzymes, proteins in the blood or specific tissue or specific DNA or RNA molecules in blood as blood analysis is widespread, cost effective and the least belligerent. Moreover, blood-based biomarkers are more efficient in a way that they can be measured at multiple stages for better judgement of the clinical picture and disease severity in a shorter timescale such as CRP measures after antibiotic therapy to determine antibody or immune response or disease severity in case of respiratory infections and pneumonia.[5]

Biomarkers' classification has various criteria with each classification done for the type of study involved. Most commonly these are classified on the basis of their characteristics as imaging biomarkers (PET, CT, NMR, MRI etc.) and molecular biomarkers. Molecular biomarkers have biophysical properties allowing them to be measured in samples such as blood plasma/serum, bronchial lavage, cerebrospinal fluid and tissue samples. Molecular biomarkers are of three types; volatile biomarkers (breath like), body fluid-based biomarkers, biopsy/autopsy biomarkers (tissue biomarkers). These most common of the molecular markers are the blood base biomarkers which comprise of nucleic acids, lipids, proteins, peptides and other small metabolites. Biomarkers are also categorized on the basis of their diagnostic application i.e. cardiac markers (Cardiac Troponin, Brain Natriuretic Peptide, CK-MB etc.), hematologic markers (CBC), inflammatory markers (CRP, IL-2, IL-6, IL-10, TNF etc.) and hepatic markers (AST, ALT, LDH, Bilirubin, Albumin).[6]

Here we review the important biochemical markers such as liver and renal function tests, IL-6, CRP that have potential prognostic effects in predicting the disease severity in mild and critical COVID-19 cases. Critical COVID-19 cases could develop multiple organ failure, CVD, renal dysfunction and hepatic stenosis and biomarkers could play important role in assessing the severity in beginning of disease.

Biomarkers of Liver Chemistries

Liver enzymes, proteins and bilirubin constitute a panel of liver function tests which includes biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin, and total bilirubin. These biochemical markers are not only a measure of liver dysfunction but are also a screening tool for several medical conditions. The normal reference ranges for ALT, AST, ALP, LDH, albumin and bilirubin in adult's blood serum are 5-40 U/L, 13-40 U/L, 30-120 U/L, 100-190 U/L, 3.5-5.0 g/dL, 0.1-1.2 mg/dL respectively.[7, 8]

The levels of liver enzymes i.e. ALT, AST, ALP, LDH and liver products such as albumin and total bilirubin have been analyzed in single or multi centered large scale studies. Research data shared by scientific community in last few months have revealed the slight rise in levels of ALT, AST, ALP and bilirubin without the signs and symptoms of jaundice, hemolysis or bone disease in critically ill patients but the rise in values in patients with mild infection was even less.[9-15] In a study including 417 COVID-19 confirmed cases, abnormal liver tests were reported in 318 cases and 90 subjects of them developed liver injury during treatment at hospital that led to the disease severity.[16] In another study regarding patient care during hospitalization, 34 COVID-19 confirmed cases admitted to hospital with baseline liver impairment and abnormal liver tests had prolonged hospital stay.[17] COVID-19 patients with higher levels of ALT, AST, ALP and bilirubin without baseline liver impairment were at higher risk of admitting to ICU/CCU suggesting that elevated enzymes are due to systemic inflammation and predict disease progression.[18]

Moreover, a significant increase and difference in LDH levels between two groups has been reported owing to wild expression of ACE2 receptors in cardiac blood vessels[18-21] and it is a marker of general ischaemic damage.[22] Albumin

level is reported significantly lower in serious COVID-19 patients. Underlying causes of hypoalbuminemia include decreased biosynthesis due to insufficient protein intake and increased loss of albumin.[23]

Due to weak ACE2 receptor expression in hepatocytes, liver impairment is not reported as a feature of previous severe acute respiratory syndromes but in SARS-CoV-2 infection liver enzyme anomalies have been associated with disease progression and mortality with unclear status of liver damage.[25] Systemic inflammatory response due to cholangiocyte dysfunction and pathology report showing mild to moderate microvesicular steatosis might associate the SARS-CoV-2 infection with liver injury.[25,26]This indicates that abnormal liver function tests can determine the nature of the ailment in addition to the hepatic health of individual.[27]

Post admission gradual monitoring of liver enzymes and protein products has revealed that the liver enzyme indices are associated with clinical outcome of hospitalized patients specially LDH and albumin can be confidently used as prognostic biomarkers in monitoring COVID-19 progression, severity and ultimate clinical outcome.

Biomarkers of Renal Function

Indicators of kidney disease such as elevated serum creatinine, blood urea nitrogen, proteinuria and hematuria[28] have been associated with COVID-19 disease severity in several studies.[28-32] Normal range of creatinine and BUN in adult blood serum is 0.6 to 1.2 mg/dL and 5 – 20 mg/dL respectively.[33]

Abnormalities in coagulation pathway lead to the disease severity has been interpreted by elevated serum creatinine levels in a study of 701 ICU admitted patients and is also associated with in-hospital mortality.[34] In a retrospective study including 333 patients, 251 had renal abnormalities with proteinuria, and hematuria at the time of admission and half of the critically ill cases developed Acute Kidney Injury (AKI) during hospitalization.[35] Few other studies reported abnormal urinalysis and serum renal biomarkers on admission revealing that kidney impairment and AKI might be associated with severe COVID-19 cases.[28,31,33,36] Cheng et al.[34] also reported raised creatinine levels associated with poor clinical outcome and patients with elevated baseline creatinine have higher death incidence rate. On the contrary, a study published in American Journal of Nephrology demonstrates that despite of the mild increase in kidney related biochemical parameters, SARS-CoV-2 infection does not result in AKI and considered that abnormal renal function was due to hypoxemia.[36] Other studies supporting uncommon AKI in COVID-19 admit the association of high levels of urea and creatinine with high mortality.[28-30,37]

Spike protein of SARS-CoV-2 binds with the ACE2 protein receptors which have abundant and wild expression not only in type II alveolar cells of lungs, but also in gastrointestinal and renal tubular epithelial cells. Thus SARS-CoV-2 may invade respiratory system and also target other organs resulting in comorbidities in COVID-19 among which renal impairment is common as reported in multiple studies.[38,39] On the basis of such reports, urea and creatinine levels might be declared as reliable prognostic markers in assessment, progression, severity, and clinical management of COVID-19.

Interleukin-6 (IL-6)

Interleukin 6 (IL-6) is also known as interferon beta-2 and B cell stimulatory factor 2 (BSF-2). It performs different biological functions such as the final differentiation of B cells into immunoglobulin secreting cells is once such task.[41] It also induces nerve cell differentiation and myeloma/ plasmacytoma growth. While in hepatocytes, it induces acute phase reactants.[42] Cytokines of the IL6/MGF/GCSF family are glycoproteins in nature which contain about 170 to 180 residues. It contains four highly conserved cysteine amino acid residues which make disulphide bonds. These disulfide bonds are involved in stabilizing compactness and globularity of these protein folds (relevant to other interleukins). A stable structure of its alpha helix is crucial for the proper functioning of this molecule.[43]

There are several mechanisms that regulate severe disease progression and one of them is a cytokine storm that has been discovered recently.[44] It is also discovered that the increase level of IL-6

causes high order fatality among COVID-19 infected patients.[45] Meta-analysis on the IL-6 data has suggested a link between IL-6 level in blood serum and disease progression in such patients. Moreover, it seems likely that the increased pathogenicity of SARS-CoV-2 is linked with faster viral replica formation and the propensity to affect the lower respiratory area which results in an increased reaction of IL-6-induced severe respiratory disease. That is why, it is crucial to identify and measure the amount of circulating IL-6 in blood to recognize disease progression in patients. An increased 1level of IL-6 was proven to show the severity of Hepatitis B virus (HBV) infection making it a good biomarker for its identification.[46] Therefore, based on such reports, it is rational that the COVID-19 patients should be immediately tested and estimated for IL-6 level on hospital admission. Because it has potential benefits to measure disease progression in COVID-19 patients and deteriorating clinical features.

In the present situation with astounded intensive care units and congested emergency rooms, correct diagnosis of such patients in need of intensive care is important. IL-6 is an effective biomarker that can be helpful to indicate upcoming respiratory failure with better accuracy and assist doctors correctly assign patients at an early stage.

C-Reactive Protein (CRP)

CRP is an important biomarker for infectious diseases and same is the case observed in COVID-19 infections. Serum levels of CRP correlate directly with the rate of progression of various infections. Likewise, in case of COVID-9 infections, CRP levels are observed to rise with the severity the symptoms. Studies suggest that CRP levels in peripheral blood are independent of the factors such as age, physical conditions and gender, making it a useful biomarker for the disease progression.[47]

CRP levels rise during infections as a defense mechanism as it activates the immune complement system, increasing phagocytosis to get rid of the pathogens.[48] As CRP is used as a biomarker for pneumonia and other pulmonary infections, it is also used for the diagnosis of disease progression.[49] The levels of CRP in blood are directly correlated to the disease severity in case of pneumonia and other respiratory tract infections.[50]

In various studies conducted to analyze COVID-19 disease, it was revealed that the magnitude of lung lesion increased in parallel to the peripheral CRP levels in patients proving that CRP is a very sensitive and good indicator of disease severity as CRP levels in the COVID-19 critically ill patients were reported to have risen from an early stage even when no computed tomography severity score was observed. The levels of CRP were observed to be higher in critically ill patients even at early stages as well as progression stages of the infection than the patients with mild severity. Thus, CRP can be very useful in predicting the patient's condition and clinical symptoms and severity. CRP levels are positively correlated with the CT score but negatively correlated to lymphocyte count. CRP and erythrocyte sedimentation rate were found to be elevated significantly in the early disease stages of fatally ill patients than the mildly ill patients. This suggest that ESR and CRP should be used for the early identification and prediction of the critical patients before any CT score.[51-54] This is more helpful for the developing countries where CT opportunities are not available to all patients. CRP could access and predict critical patients beforehand in such condition and it would also provide great economic benefits.[56]

CONCLUSION

A mild COVID disease having fever aches, pains, myalgias and mild cough might show negative RT-PCR due to low viral load and improve but there are two problems associated with it. First is patient/carrier might pass it to so many others who will remain asymptomatic and will unknowingly transmit to others and one of them may progress to severe disease ending up ICU in critical condition. Second, mild disease can progress to moderate disease without any warning signs and symptoms (it's a very deceptive disease as patient does not know his disease is progressing) and moderate disease can progress to severe disease. Simple tests for observing biomarkers such as LFTs, RFTs, CRP, LDH, IL-6 can safely predict the risk of disease progression from mild to moderate or to severe COVID-19.

Hence, it is concluded that biomarkers are helpful for diagnosis and prognosis of many diseases. They could also be applied in the clinical diagnosis and disease severity determination in case of COVID-19 which is a respiratory infection with different underlying diseases including multiple organ dysfunction either due to cytokine inflammatory response of the body or administration of antiviral drugs resulting in unexpected clinical outcomes. Though, behavior of the biomarkers in the COVID-19 disease course is still not very clear, these markers can still help clinicians to improve the disease prognosis and prediction of critically ill patients beforehand. Biomarkers are useful important predictors of disease categorizing the COVID-19 patients in mild and severely ill groups to manage the pandemic more efficiently.

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LIMITATIONS OF STUDY

The review focuses on biomarkers related to acute liver or renal injury and two basic markers of acute phase reactions. Markers of acute lung injury needs to be addressed in association with clinical findings.

CONFLICT OF INTEREST

None to declare.

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Author's Contribution

FB: Conception of idea, critical review with intellectual input, final approval of the manuscript.

AT: Conception of idea, acquisition of data, drafting of manuscript, final approval of the manuscript.

MG: Conception of idea, final approval of the manuscript.