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REVIEW ARTICLE

Impact of COVID-19 on Biochemical Parameters: A Narrative Review

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Abstract

Coronaviruses have been a major threat to public health globally since last decades. Coronaviruses are enveloped and positive-stranded RNA genome. After SARS and MERS, SARS-CoV-2 is the third known coronavirus causing fatal respiratory diseases in humans. In the initial stage of SARS-CoV-2 infection, clinical features are quite nonspecific and not all suspected patients can be tested to exclude or confirm the diagnosis. The clinical course of the disease may cause changes in laboratory parameters. Early identification of causative agent SARS-CoV-2 and monitoring the blood biochemical parameters helps in assessment of disease severity and proper monitoring of the disease. In this review, the research studies on biochemical markers in COVID-19 till 31st August 2020 are retrieved and selected articles are reviewed. These data are extremely important in assessing the evolution of the disease, prognosis and directing therapeutic interventions. In the view of that the present study aimed to discuss the impact of biochemical markers in COVID-19.

Key Words: COVID-19, SARS-CoV-2, Biochemical markers

Introduction

Coronaviruses (CoVs) are the large (60-140nm diameter), enveloped positive sensed RNA viruses group belonging to the Coronaviridae family (1-3). The genome of CoVs is surrounded by a lipoprotein envelope containing several spicules of glycoprotein and helical capsid. Together it gives the virus a crown like appearance when observed under electron microscope and hence the word "corona" comes which in Latin means crown (4).

The disease caused by the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been named "coronavirus disease 2019" (COVID-19) by World Health Organization (WHO) and it has also been called once in a century pathogen. WHO declared COVID-19 as a pandemic on March 11, 2020 due to rapidly increasing number of cases across the globe (5).

According to Genome sequencing studies and phylogenetic analysis SARS-CoV-2 is a new type of zoonotic â-coronavirus with bats presumed to be original host (6). When it comes to infection of CoVs to humans, severity of the diseases varies. It can cause upper respiratory tract infections similar to a common cold, to liver, enteric, neurological diseases and lower respiratory tract infections such as pneumonia, bronchitis and severe acute respiratory syndrome (SARS) (1,3,7). Patients infected with SARS-CoV-2 are prone to death when they develop severe pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), or multiple organ failure (such as shock, acute heart injury, and acute kidney injury) (8). Intensive care with mechanical ventilation required in patients who have developed ARDS and extracorporeal membrane oxygenation (ECMO) has been

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used to save critically ill patients.

On September 8, 2020, 42,80,422 cases of COVID-19 have been diagnosed, and 72,775 deaths have been reported from the India to WHO. As per current scenario of increasing number of cases and deaths on each day and in this state of emergency only data from observational studies are readily available and accessible. Therefore, a descriptive review is needed to summarise the laboratory findings in each study which will help us to discriminate between severe and non-severe cases as well as to improve clinical situational awareness. It will also assist clinicians to take corresponding rescue measures in the early stage of the disease to reduce mortality.

Methods

Search Methods and Strategies for Identification of Studies

Literature search was performed in "PubMed"/ Medline, Embase "Web of Science", "Scopus", "ScienceDirect" and also in "JAMA", "BMJ", "Oxford" and "THE LANCET" journals from February 1 to 31st August 2020. The search strategy was based on following keywords: coronavirus, severe acute respiratory syndrome coronavirus 2, COVID-19, lab diagnosis, biochemical parameters. Moreover, we also searched lists of references of selected articles and relevant review articles and WHO reports identified by the above methods. Studies were excluded if used old data, had inappropriate topics and were not relevant to the focused purpose of the study.

Data Collection and Analysis

All review authors screened the titles and abstracts of all retrieved records in order to identify studies meeting the inclusion criteria. The studies were selected independently and the results were discussed to make the final selection. A final decision was made for each study only after reading the full text of all potentially eligible articles

Data Extraction and Management

Extraction of data was performed by the same all review authors who conducted the study selection independently, using a structured form that contained study characteristics including coronavirus genus, infectivity, pathogenesis and laboratory diagnosis. Any kind of disagreement was discussed during and after completion of data collection process and reviewers were consulted for each topic.

Pathophysiology

An important concern in COVID 19 is the capability of the pathogen to establish and induce infection with different clinical manifestations in human. Viral replication initially starts in the respiratory tract and then spread occurs to other organs and tissues. At the site of bone marrow, the virus causes apoptosis of cells which results in a reduction in haematopoiesis and so further a reduction in leukocytes and platelets (9,10). The circulating viral particles induces the activation of neutrophils, macrophages and mast cells and hence leading to the synthesis of pro-inflammatory substances, such as cytokines. It also acts on the progenitor cells in the bone marrow, and cause inactivation of the synthesis of platelets and other components, such as leukocytes (10).

Binding of circulating antibodies and immune complexes to platelet and tissue surfaces induced by circulating viral particles causes further tissue damage and thrombocytopenia. (9,10). At the level of pulmonary tissue, replication of virus induces hypoxia, cell death and lesions in the capillaries of this organ. Here, it triggers the inflammatory process, which leads to activation of platelets and formation of micro coagulation. When this process become widespread, it causes damage to other organs, such as the liver, heart and kidneys. (9,11,12). These inflammatory and pathological processes cause derangement in the functioning of several organs, thus assessing organ function related biomarkers could play important role in assessing the severity in beginning of disease as well as in the clinical follow-up of patients with COVID 19.

In this regard authors reviewed 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. 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 ultimately impact the mortality and morbidity.

Biomarkers Related to Liver Function

A panel of liver function tests constitutes Liver enzymes, proteins and bilirubin which includes biochemical parameters such as alanine aminotransferase (ALT),

aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), albumin, and total bilirubin. These liver biochemical markers reflect liver dysfunction and also been helpful as 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 (13,14). The reference values can vary according to the patient's age, sex and depending on the method and reagents used in the analysis.

Liver function tests have been analysed in several single and multicentred large scale studies which revealed rise in levels of liver enzymes (AST, ALT, ALP) in moderate to critically ill patients whereas rise in values in patients with mild infection was comparatively less (15-17). As previously mentioned, viral activity induces several inflammatory and haematological changes that lead to liver tissue damage, leading to increased levels of these enzymes (18,19).

A total of 150 hospitalized COVID-19 patients with clinically significant elevated aminotransferases (defined as >2 times upper limit of normal) were evaluated and compared with COVID-19 patients without an elevation in aminotransferases in a retrospective study from a single tertiary care academic medical centre in New York. The prevalence of elevation in AST/ALT was found to be 13.7% (20/145) in them and found that Elevated aminotransferases among hospitalized COVID-19 patients is associated with higher rates of mechanical ventilation (20). Wang *et al*. (18) in the study on 105 patients in China, found 89 patients with steatosis liver by abdominal ultrasound and it was observed that 16.2% had changes in liver enzymes, ALT or AST. 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 (21). 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 (22). 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 (23).

LDH is a major player in glucose metabolism which is present in tissues throughout the body which catalyses pyruvate to lactate conversion. It is released from cells when there is a damage of cytoplasmic membrane. Potential clinical and biological significance of elevated LDH are associated with pulmonary injury as well as widespread organ damage and severe course of the disease (24). Some studies reported, a significant increase and difference in LDH levels between two groups due to wild expression of ACE2 receptors in cardiac blood vessels and it is a marker of general ischaemic damage (23). Level of Albumin is reported significantly lower in serious COVID-19 patients. Underlying causes leading to hypoalbuminemia may include decreased biosynthesis due to insufficient protein intake and increased loss of albumin (25).

Biomarkers Related to Kidney Function

Several studies reported association of indicators of kidney disease such as elevated serum creatinine, blood urea nitrogen, proteinuria and hematuria with severity of COVID-19 (26-28). Along with type II alveolar cells of lungs, gastrointestinal and renal tubular epithelial cells also have abundant and wild expression of ACE-II protein receptors which is binding site of SARS-CoV-2. After invading respiratory system, it also targets other organs among which renal impairment is one of the common as reported by several studies (19,29). Further, circulating mediators could interact with kidney-resident cells which results in endothelial dysfunction, microcirculatory derangement and tubular injury. According to one of the Italian Report about 25–30% of COVID-19 patients develop acute kidney injury (AKI) which is associated with increased mortality risk (30). Some other studies reported deranged renal biomarkers and abnormal urinalysis on admission indicating association of AKI with severity of COVID-19 cases. (24). Cheng *et al*. (31) also reported association of elevated creatinine levels with poor clinical outcome and higher mortality.

Inflammatory Biomarkers

Most severe form of COVID-19 is characterised by uncontrolled systemic inflammatory response due to the release of large amounts of pro-inflammatory cytokines which is called as "cytokine storm" and it leads to ARDS and MOF (multiorgan failure) (32). Increased levels of several inflammatory biomarkers have been reported in COVID-19 patients among them IL-6, CRP, LDH are found to be progressively raised according to severity of the disease.

Interleukin 6 (IL-6) performs different biological functions. It plays important role in final differentiation

of B cells into immunoglobulin secreting cells while it induces acute phase reactants in hepatocytes (33). Various studies reported high order of fatality among COVID-19 patients with elevated levels of IL-6 and it has also been found to have link between disease progression and levels of IL-6 (34,35). Faster viral replication results in an increased reaction of IL-6-induced severe respiratory disease. Hence measuring levels of IL-6 in blood play crucial role in assessing progression of the disease.

CRP is an important biomarker for infectious diseases and serum levels of CRP correlate directly with the rate of progression of various infections as with COVID-19 infections. CRP levels in peripheral blood are independent of the factors such as age, physical conditions and gender which makes it a useful biomarker for the disease progression (36). Some studies reported a positive correlation between increased CRP levels and disease severity and its level was found to be raised significantly at an early stage of the disease (37-39).

D-dimers are fibrin degradation products and is one of the markers for thrombosis. However, elevated D-dimer levels in COVID-19 patients is related to inflammation. Yu *et al*. (40) reported that D-dimer levels were higher in COVID-19 patients and were related with markers of inflammation as well as with poor prognosis. Levels of D-dimer decreased synchronous with hsCRP levels in patients with good clinical prognosis. Infection-induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases. Hence, a higher D-dimer level on admission was related to a worse prognosis of COVID-19 (41,42). According to Li *et al*. (43) dynamic changes of D-dimer level are positively correlated with the prognosis of COVID-19 and anticoagulant treatment may benefit severe COVID-19 patients, especially those without cardiovascular disease.

Biomarkers for Muscle and Cardiac Injury

As muscle tissue also expresses ACE2 receptor, SARS-CoV-2 also targets cells of the muscle tissue. Hence biomarkers of muscle injury, namely creatine-kinase (CK) and myoglobin are found to be raised in COVID-19 (24).

SARS-CoV2 infection on cardiomyocytes causes cardiac injury which is common characteristic feature of COVID-19. It may result in acute myocardial infarction (IMA), heart failure, impaired renal function (leading to troponin accumulation), myocarditis, arrhythmias, cardiac arrest, sepsis, septic shock, and pulmonary embolism and it might be due to systemic inflammatory response (44). Hence evaluation of cardiac biomarkers forms important tool for early detection of cardiac injury and helps in taking decision on further interventions. Few studies reported association of elevated levels of cardiac troponin (cTn) and brain natriuretic peptide (BNP)/NT-proBNP with worse prognosis (38,44-46).

Conclusion

As per the literature available on SARS-CoV-2 infection till now, there is scientific evidence of major laboratory changes which reflects systemic inflammation and impairment of multiple organs to a lesser or greater extent as virus can infect cells through the interaction with the ACE2 receptor, which is highly expressed in many organs and tissues. Since December 2019 this pandemic is spreading rapidly and discovery of an effective antiviral drug therapy and a vaccine is still under process. The SARS-CoV-2 infection results in a respiratory disease and causes several biochemical alterations. These biomarkers are useful in categorizing the COVID-19 patients in mild and severely ill and serves important tool for predicting progression of the disease. Though, behaviour of the biomarkers in the COVID-19 disease course is yet to be very clear, these markers can still help clinicians to improve the prognosis of the disease and predicting critically ill patients beforehand. The present literature review may be pertinent, not only to disseminate what is already known, but it may also serve as a valuable base for future investigations.

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Conflicts of Interest

There are no conflicts of interest.

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