Asian Journal of Biochemistry, Genetics and Molecular Biology

10(4): 48-56, 2022; Article no.AJBGMB.84613
ISSN: 2582-3698

An Overview on Biochemical Parameters and Organ Injury in COVID-19 Patients

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJBGMB/2022/v10i430252

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/84613

Review Article

Received 24 February 2022
Accepted 04 April 2022
Published 11 April 2022

ABSTRACT

The Coronavirus disease (COVID-19) is considered as a respiratory disease which can cause a multi-organ injury like acute cardiac injury, kidney injury, and liver dysfunction. COVID-19 patients had The different of blood biochemical abnormalities where found in covid -19 patients which might indicate multiple organ dysfunction.

Hence the aim of the present study is provision of overview on organ injury and changes in biochemical parameters in Covid-19 patients.

The common laboratory abnormalities in COVID-19 patients included elevated inflammatory markers like CRP, ferritin, procalcitonin, cytokines and IL-6, IL-2, IL-7 and elevated prothrombin time and D-dimer. The cardiac injury is shown by increased concentration of CK-MB, LDH, and cTn and brain natriuretic peptide (BNP).

In liver and kidney dysfunction mild or moderate elevation of AST, ALT, total bilirubin, ALP, GGT, hypoalbuminemia, blood urea, creatinine and electrolyte disturbances were seen.

Hence reviewing currently available data, the present study can suggest that monitoring of the biochemical parameters may help in prediction of organ damage which further can prevent disease progression early interventions.

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Keywords: 2019 novel coronavirus; COVID-19; biochemical parameters; interleukins.

1. INTRODUCTION

"A contagious disease known as Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019 the first case was identified in Wuhan, China and since its spread over world, leading to pandemic.

The WHO recommended it's in January 2020 as severe acute respiratory disease" [1] and the official names COVID-19 and SARS-CoV-2 were given on 11 February 2020 [2].

"The corona virus is a β-coronavirus, which is non-segmented positive-sense RNA virus (subgenus *sarbecovirus*, *Orthocoronavirinae* subf amily) [1]. Coronaviruses (CoV) are divided into four genera, including α−/β−/γ−/δ-CoV. The γ- and δ-CoV tend to infect birds while α- and β-CoV are able to infect mammals" [3].

"The corona viruses can infect animals or humans, with some strains being zoonotic. The SARS-CoV outbreak in 2002 originated from bats in China [4] and theMERS-CoV outbreak in 2012 from dromedary camels, though also likely transmitted from bats, in the Middle East" [5]. It has been hypothesized that SARS-CoV-2 might be transmitted by bats [6], snakes [7], or pangolins [8]. It is a virus highly transmissible from human to human through respiratory droplets and aerosols.

A number of studies have reported the epidemiological and clinical characteristics of covid 19 patients but very few studies are available on biochemical investigations.

Hence the perspective of present study is to provide an overview on organ biochemical parameters in Covid-19 patients.

2. MATERIALS AND METHODS

The authors had searched data from published article inPubMed, Embase, Scopus, WHO, Google scholar and Cochrane, Elsevier, Wikipedia, Web of science etc,

2.1 General Aspects of Pathogenesis of Coronavirus Disease

"The virion entry into the host cell is by interactions between the S protein and its receptor. The cellular enzyme furin break the spike (S) protein of SARS-CoV2 at the S1/S2 site which is essential for viral entry to the lung cells. The activated S protein is primed by the *TMPRSS2* and attaches ACE 2 receptors to enter the host cells" (Fig. 1) [9,10].

"The cell receptor ACE2 found in the lower respiratory tract of humans [11]. Which regulates both the cross-species and human-to-human transmission" [12]. "The viral genome RNA is released into the cytoplasm, and this uncoated RNA translates two polyproteins, pp1a and pp1ab" [13], which further encode non-structural proteins, and form replication-transcription complex (RTC) [14]. This RTC continuously replicate and synthesize a nested set of sub genomic RNAs [15], and encoding accessory and structural proteins. Finally all these components assemble and form viral particle buds. Lastly, the virion-containing vesicles fuse with the plasma membrane to release the virus [16].

"In human being coronavirus can cause diseases of varying severity, from upper respiratory tract infections like a common cold, to neurological enteric, liver diseases and lower respiratory tract infections like bronchitis, pneumonia and severe acute respiratory syndrome (SARS)" [17,18,19].

2.2 Laboratory Diagnosis of COVID 19 Patients

"For diagnosis of COVID-19 patient RT-PCR is the gold standard. The other used tests are serologic tests like Anti-SARS-CoV-2 IgA, IgM and/or IgG. Also the SARS-CoV-2 antigen test for upper respiratory tract specimens" [20,21,22,23].

2.3 Acute Respiratory Distress Syndrome in COVID 19 Patients

"The corona patients develops acute respiratory distress syndrome (ARDS) characterized by a rapid onset of bilateral inflammation in the lungs which involves an acute increase in several pro-inflammatory cytokines, termed as "cytokine storm." The risk of multi organ damage enhanced due to leakiness of the blood vessels and an induction of a procoagulant state.

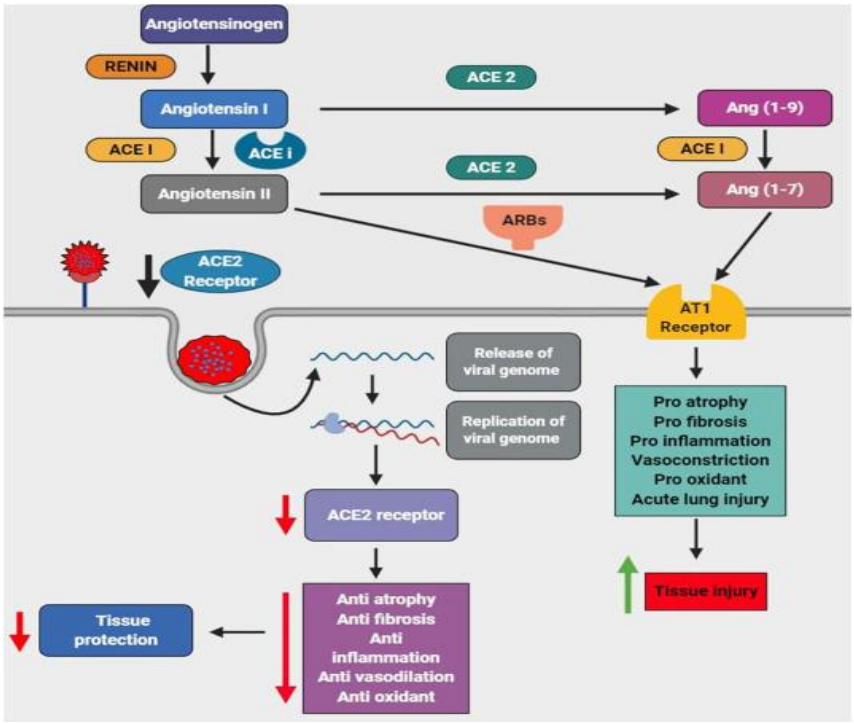

Fig.1. pathogenesis of Coronavirus Disease

Predominant elevation of IL-1b and interleukin-6 (IL-6) and cytokines, predicts a higher likelihood of an unfavorable outcome, including death" [24,25]. The various studies has reported that in Covid 19 patients number of inflammatory biomarkers are increased such as cytokines, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α,IL-6, IL-2, IL-7, TNF-α, interferon (IFN)-γ, granulocyte colony stimulating factor (G-CSF), and procalcitonin (PCT), erythrocyte sedimentationrate (ESR) and ferritin.

"C-reactive protein (CRP) is a non specific acute phase reactant produced by the liver and induced by various inflammatory mediators which is used as a biomarker for inflammatory conditions. CRP shows positive correlation as its levels has increased significantly at the early stage of the disease" [26,27,28,29]. Tan et al. [30] showed that CRP act as a strong indicator to show the presence and severity of COVID-19 infection.

The contributing factor for cytokine storm is immune dysregulation mediatoris Ferritin, especially under extreme hyperferritinemia, direct immune-suppression and pro-inflammatory effects.

Chen et al. analyzed "the clinical characteristics of 99 patients, in which 63 of them had abnormal serum ferritin level" [31]. The autopsies of 12 patients showed elevated ferritin levels whose cause of death was Covid 19 [32] hence this study concluded that serum ferritin levels were closely related to the severity of COVID-19 [33].

2.4 Abnormal Coagulation Function in COVID 19

The Fibrinogen is a plasma protein also known as an acute phase protein which is necessary for blood coagulation. This cascade reaction is induced by interleukin 6 and associated with inflammatory responses [32]. In infection hepatic synthesis of fibrinogen increases 2 to 10 times [33]. Severe COVID-19 patients present hypercoagulability than consumptive coagulopathy [34, 35].

"The deficiency of anticoagulant, coagulation factor, and fibrinolysis causes prolonged prothrombin time (PT) which have been used as laboratory tools to predict bleeding" [36, 37].

"D-dimers are fragments produced by cleavage of plasmin. The D-dimer elevations were seen in COVID-19 patients" [38,39]. "The value of D-dimer greater than 1 µg/ml is considered as one of the risk factors for mortality in adult in patients with COVID-19" [40].

2.5 Organ Injury and Alteration Biochemical Investigations in COVID 19 Patients

The data shows in addition to respiratory failure of COVID-19 patients have acute cardiac, kidney injury, and also liver dysfunction [41,42].

Some patients with COVID-19 had different degrees of blood biochemical abnormalities, which might indicate multiple organ dysfunction (Fig. 2).

2.6 Cardiac Injury and Biochemical Parameters

"The Covid 19 patients infection may experience a variety of cardiac manifestations, such as arrhythmia, myocardial injury, and cardiac arrest may lead to sudden deterioration in cardiac function. The corona virus damages myocardial cells and induces changes of laboratory cardiac markers. The increase of cardiac troponin (cTn) and brain natriuretic peptide (BNP) has been associated with worse prognosis" [43].

Han et al. reported that "higher concentrations of some biomarkers, such as myohemoglobin (MYO), creatine kinase-MB (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP)), and cTnI were linked to the severity and rate of fatal cases in patients with COVID-19 infection" [44].

The meta-analysis showed abnormalities in CK. The overall proportion of CK abnormalitiesin patients with COVID-19 was 0.13 (95% CI) [45].

"The pyruvate is converted to lactate by lactate dehydrogenase enzyme its secretion is triggered by necrosis of the cell membrane, reflecting viral infection or lung damage, like pneumonia induced by SARS-CoV-2. The value of LDH was significantly higher in severe patients than in non-severe patients" [45]. Huang et al. reported that LDH levels were increased ICU patients.

2.7 Liver Dysfunctionand Biochemical Parameters

Individuals with severe COVID-19 have a higher incidence of mild, severe and transient liver impairment [46]. The evidences showed that liver enzymes are predominantly increased in severe and critical cases of COVID-19.

Xiaoling Deng et al [47] reported "meta analysis ALT abnormalities. The overall proportion of ALT abnormalitiesin patients with COVID-19 was 0.16 (95% CI)also showed AST abnormalities. The overall proportion of AST abnormalities among patients was 0.20 (95% CI)".

The study of Xiaoling Deng et al [48] meta analysis evaluated "albumin abnormalities in COVID-19patients albuminis decreased in151 patients".

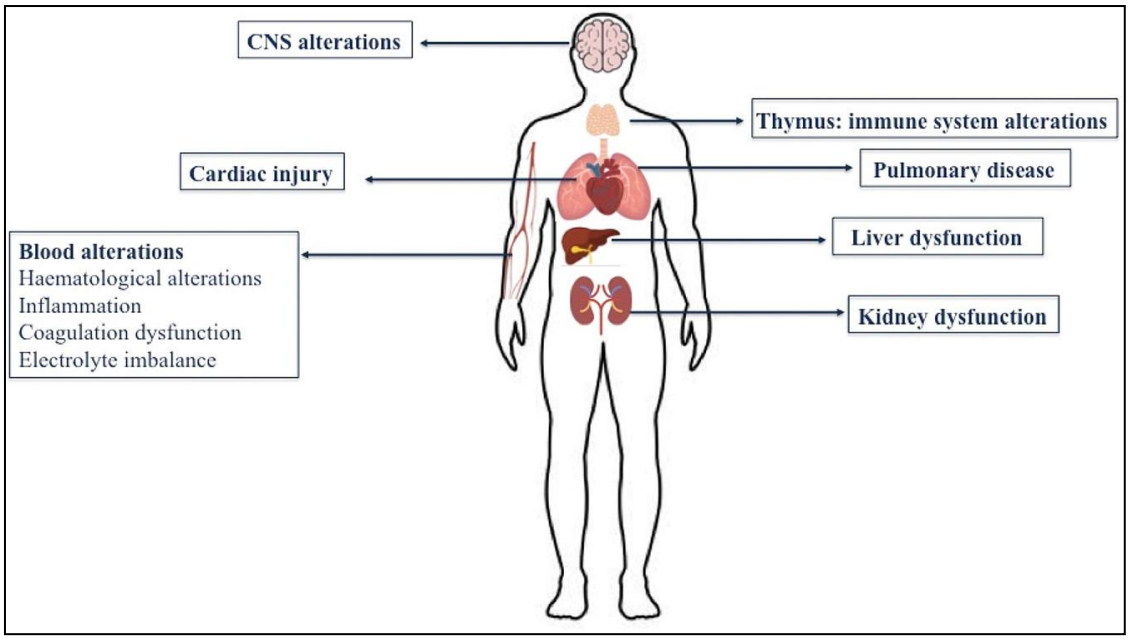

Fig. 2. Main biochemical alterations associated with COVID-19

Xiaoling Deng et al [48] also reported “abnormal quantitative synthesis of total bilirubin.It showedan increase in total bilirubin and overall proportion of total bilirubin abnormalities was 0.06 (95%)”.

“The liver regeneration and immune response require bile cells so liver injury in individuals with COVID-19 may damage to bile duct cells, but not liver cell hence ACE2 expression in bile duct cells is much higher compared with liver cells” [47].The high levels of aspartate amino transferase (AST) and alanine aminotransferase (ALT) indicating abnormal liver function. A multi-centre study on 1099 individuals documented increased levels of AST and ALT in 22.2% and 21.3% ofCOVID-19 patients, respectively.

Wang et al. [49], reported that “patients who had increased transaminaselevels presented higher concentrations of γ-glutamyl transferase the drug-induced liver injury and preexisting chronic infections are possible contributing factors for the observed abnormalities in liver blood tests” [43,27].

Zhang et al. conducted “a case-control type study of 240 patients [50] and showed mild ALP elevation as compared to 15.79% in the community acquired pneumonia (CAP) patients”.

2.8 Renal Dysfunction and Biochemical Parameters

“Renal failure on admission in patients with SARS-CoV-2 infection is frequent and is associated with a greater number of complications and in-hospital mortality.

Some studies reported, the association of acute kidney injury (AKI) and COVID-19 has a high mortality” [51]. However, the incidence of reported AKI associated with COVID-19 varies widely [51,52]. “It would be expected that kidney involvement is frequent since the virus enters the cell through the angiotensin-converting enzyme 2 (ACE2), which is expressed, in addition to pulmonary type 2 alveolar cells, on renal proximal tubular cells, glomerular visceral and parietal epithelium, and the cytoplasm of the distal tubules and collecting ducts” [53,54].

Xiang Jet al [55] studies have demonstrated significantly higher levels of renal biomarkers such as serum urea, creatinine and markers of glomerular filtration rate in severe cases [55].

Cheng Yet al [56] study revealed “701 patients had elevated serum creatinine levels on admission which is correlated with severity due to significant abnormalities in the coagulation pathway”.

The cohort study of “701 Covid 19 patients reported that increased baseline level of blood urea nitrogen, serum creatinine, proteinuria and haematuria could be independent risk factors for in-hospital death after adjusting for age, sex, disease severity, co-morbidity and leucocyte count” [56].

“Some authors described alterations of electrolyte levels of sodium, potassium, chloride, and calcium, in COVID-19 patients” [57,43]. Specifically, hyponatremia, hypokalemia, and hypocalcemia have been associated with severe disease [58].

“The host immune response is the critical factor in driving COVID-19 and analysis of this response may provide a clearer picture and also it is crucial SARS-CoV-2 for vaccine development.Thepatient experiencing cytokine storm syndrome (CSS) are belived to have a worse prognosis and increased fatality rate. In this condition the regulation of immune cells is often defective, resulting in the increased production of inflammatory proteins that can lead to organ failure and death. Among these inflammatory mediators released by immune effector cells are the cytokines IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, and transforming growth factor (TGF)β and chemokines” [59]. “Early clinicalfeatures and laboratory (blood hyperferritinemia, lymphopenia, prolonged prothrombin time, elevated lactate dehydrogenase, elevated IL-6, elevated C-reactive protein etc) results from critically ill COVID-19 patients suggest the presence of a CSS causing ARDS and multi-organ failure [60] as seen with SARS-CoV and MERS-CoV infection” [60].

The study of Omer Faruk Kocak, examined “serum Zn, Se concentrations, and biochemical parameters in patients with different severity of COVID-19, compared them with healthy individuals which showed that serum Zn and Se values were significantly lower in COVID-19 patients compared to the control group”. The study concluded that Zn LDH, PLT, and ferritin values were evaluated depending on the severity of COVID-19 disease [61].

3. CONCLUSION

The blood biochemical abnormalities in COVID-19 patients, indicates multiple organ dysfunction.

The laboratory abnormalities in COVID-19 patients included elevated inflammatory markers like cytokines and IL-6, IL-2, IL-7, CRP, ferritin, procalcitonin, and coagulation dysfunction. The elevation of prothrombin time and D-dimer also observed. The cardiac injury is reflected by elevation of LDH, CK-MB and cTn levels and brain natriuretic peptide (BNP).

The liver and kidney dysfunction are reflected by mild or moderate elevation of ALT, AST, total bilirubin, ALP, GGT, hypoalbuminemia, BUN, creatinine and electrolyte disturbance.

Hence reviewing currently available data, the present study can suggest that monitoring of the biochemical parameters may help in organ damage prediction and prevention of disease progression by early interventions.

Also the host immune response will provide molecular insights into mechanisms which may help protection and long-term immune memory and to design of prophylactic and therapeutic measures to overcome future outbreaks of similar coronaviruses.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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