Review Research

ALTERATIONS IN BIOCHEMICAL MARKERS OF COVID–19 AND USING IT AS DIAGNOSTIC AND PROGNOSTIC TOOLS

Athraa Sami

Department of Clinical Laboratory Science, Faculty of Pharmacy, University of Kufa, Alnajaf Al-Ashraf, Iraq

**Corresponding author: athraas.alshebani@uokufa.edu.iq*

ABSTRACT

Biochemical markers (BM) play an important role in the early identification of COVID-19 and monitoring of infected people in order to evaluate the severity of infection and providing the proper care and optimum management to decrease mortality rate and disease progression. Prognostic tools are consider the essential approaches for making a decision in patient management and treatment for patients with COVID-19 infection. In this review, we determine the most important biomarkers of immunity, coagulation, cardiac and renal dysfunction as a highly valuable laboratory tools for diagnostic, monitoring, predicting the progressive complications of coronavirus infectious disease in order to give the effective treatment and for more efficiently control the pandemic.

Keywords: Biochemical markers, COVID-19, disease progression, renal dysfunction.

Introduction

The rapid spread of the COVID-19 pandemic worldwide has prompted the health science community to investigate the appropriate, fast and accurate diagnostic and prognostic tools (Bano et al., 2020). These tools will assist risk classification, guide interventional reports to target infected patients at increased risk of development severe infection and identify allocation of limited technical and human resources in the current outbreak (Henry et al., 2020).

Moreover, laboratory biomarker is one of the most critical factor in prediction of progression and detection of complications of COVID-19 (Gallo Marin et al., 2020). Signs and symptoms are also used in the early diagnosis of COVID-19 infection and involve:1) fever more than 37.8°C, 2) headache, 3) dry cough.4) breathless on light effort ,5) diarrhea ,6) loss of sense of taste and smell. While symptoms of severe condition during infection include:1) high respiratory rate (more than 20 breaths/minute), 2)breathing difficulty, 3) high heart rate (more than 100 beats /minute), 4) loss of appetite,5) chest tightness, 6) confusion, 7) temperature more than 38°C,8), hypoxia (Emperador & Dittrich, 2020).

BM have been referred to a measurement variable that is based on the results of the progression of the disease (Ballman, 2015). A measurable alterations can be assessed as a sign of normal, abnormal biological processes or pharmacological reactions to treatment intervention leading to an understanding the causes of disease, methods to diagnose it, regression, progression, and the outcome of management of disease (Kinja & Gupta, 2011). Immunoassays and Real-Time PCR (RT-PCR) are the main methods that used in the diagnosis of COVID-19, which can be performed through a variety of clinical samples, including nasal and pharyngeal swabs, sputum, feces or blood (Whetton et al., 2020). Although the role of BM in screening patients that are infected with COVID-19 has not been accurately established as compared to RT-PCR, but the alteration in its values can be used to detect the result of coronavirus test and prediction of COVID-19 patients especially when it linked to clinical feature (Mardani et al., 2020). In addition, a high costs and the limited medical resources of RT-PCR resulted in restriction to their application, therefore the appropriate and the effective approaches are urgently required in the diagnostic process as well as to evaluate the severity of disease(Peng et al., 2020). BM are divided into two main types: 1) biomarkers of disease that are utilized in diagnosis and monitoring the progression of diseases, 2) biomarkers of exposure that are utilized in risk prediction (Mayeux, 2004) .

The study reviewed a correlation between the alterations in BM and the severity of COVID-19 in addition to their diagnostic role. BM that measured and used clinically in evaluation of COVID-19 were WBC count, lymphocytes, eosinophils, neutrophils, D-dimer, fibrin degradation product, interleukin-6 (IL-6), antithrombin, platelets, creatine phosphokinase, cardiac troponin and renal biomarkers (Kermali et al., 2020).

Corona virus attacks various systems in the body, firstly through inhalation of virus-filled particles which entered into the nasopharynx and exert its effect on the pulmonary arteries by targeting ACE2 receptors and initiating a series of micro-thrombi formation leading to consequent hypoxemic damage to many systems especially the immune system, blood vessels and gastrointestinal system because of the availability of ACE2 receptors. The immune response to a viral infection lead to formation of cells such as T helper cells and the natural killer (NK) cells that contribute in the destruction of lymph nodes, spleen, thymus and liver (Garg et al., 2020).

BM of immunity dysfunction

The potential mechanisms of immune defect in patients infected with covid-19 is induce the depletion and promote the exhaustion of lymphocytes especially t cells, however decreasing the level of t cell which is inversely related with il-6, il-10 and TNFA levels (proinflammatory cytokines) is associated with an elevating in inflammatory cytokine levels (Yang et al., 2020). Lymphopenia in covid-19 patients may be occur as a result of the inhibition of cell proliferation by acidosis, recruitment of monocytes and lymphocytes from circulation into the site of infection, prevention of t cell recirculation under the influence of tnf-α 2 which stimulate the connection of these cells to the of lymphatic organs, also lymphocytopenia may be present due to activation prompted cell death of t cell by the influence of cytokine il-6 (Fouladseresht et al., 2020). il-6 gene expression is typically increased in response to a variety of infections especially viral infection and also observed in the state of hypoxia, therefore the circulating levels of il-6 (pro-inflammatory cytokine) are noticed to be higher in patients with covid-19 (McElvaney et al., 2020).

Furthermore, measuring the IL-6 levels is consider a good biomarker in the prediction and evaluation the progression of COVID19 patients (Changsong Wang et al., 2020). Several studies used in analysing the immune response in COVID-19 patients and showed an enhancing in inflammatory cytokine (Luo et al., 2020; Liu Fang, et al., 2020) and decline in lymphocyte count (Wagner et al., 2020; Zhang et al., 2020; Guan et al., 2020). Eosinophils less than 100 cells/mm3 is called as an eosinopenia which represent a valuable diagnostic method that help to identify patients with COVID-19 infection especially if the imaging resources has been lacking. Moreover, many studies (Djangang et al., 2020; Sun et al., 2020; Tan et al., 2020; Gong et al., 2020; Qin et al., 2020) found that eosinopenia may be occur as a result of the inflammatory state and the migration of eosinophils from the bone marrow into the peripheral tissues or decreased their production. Neutrophilia is a part of abnormal immune responses and act as a biomarkers for predicting COVID-19 disease. This is consistent with prior findings showing that patients with COVID-19 exhibiting a higher neutrophil count through the period of disease (Wang et al., 2020; Kong et al., 2020; Extracellular & Drive, 2020; Zhao et al., 2020). Like neutrophils, WBC count are also parameter that used as an indicator of inflammatory state. Several studies found that leukocytosis are associated with cytokine storm due to virus invasion in the human body (Yuan et al., 2020; Zhao et al., 2020; He et al., 2020) (Table 1 & 2)

Table 1: Research articles that commonly use biochemical markers as diagnostic tool

Authors	Study period	Sample size	Biomarker	Type of alteration	Comments
(Changzheng Wang et al., 2020)	January 23-February 13, 2020	45	WBC count	Increased	Leukocytosis may reflect a state of severe inflammation in lung and other organs that occur due to aggravation of the Covid-19 disease by be a cytokine storm
(Yuan et al., 2020)	February 15- March 30, 2020	117			
(Zhao et al., 2020)	February 3-March 3, 2020	619			
(He et al., 2020)	Jan 15-Mar 10, 2020	288			
(Wagner et al., 2020)	January 3-January 5, 2020	57	Lymphocytes	Decreased	Lymphocyte count has a laboratory value aiding physicians in managing Covid-19 infection and used as diagnostic tool
(Liu et al., 2020)	December 30, 2019-January 15, 2020	78			
(jin Zhang et al., 2020)	January 16-3-Feb-20	242			
(Guan et al., 2020)	December 11, 2019-January 29, 2020	1099			

Authors	Study period	Sample size	Biomarker	Type of alteration	Comments
(Ndieugnou Djangang et al., 2020)	March 10-31 March, 2020	174	Eosinophils	Decreased	sensitivity of eosinophils for the detection of COVID-19 are more than lymphocytes in the term of disease diagnosis, it was markedly decreased in majority of peoples infected with COVID-19 at their disease onset
(Sun et al., 2020)	January 19-February 20, 2020	116			
(Tan et al., 2020)	January 30-February 30, 2020	40			
(Gong et al., 2020)	Jan 28-Mar 26, 2020				
(Qin et al., 2020)	10 January-12 February 2020	452			
(Wang et al., 2020)	January 23-March 15, 2020.	55	Neutrophils	Increased	Excessive neutrophils act as a biomarkers for predicting COVID-19 disease
(Kong et al., 2020)	27 January-9 March 2020	210			
(Extracellular & Drive, 2020)					
(Zhao et al., 2020)	January 13-March 4, 2020	539			

BM of Coagulation abnormalities

COVID-19 infection stimulates the immune-hemostatic response, therefore triggering an excessive inflammation, thrombotic complications and tissue damage and leading to many complications such as respiratory dysfunction, acute lung injury, many organ failure and the highest mortality rate**.** A wide range of laboratory tests including the coagulation parameter was reported in peoples with COVID-19 and appeared abnormalities, including D-dimer, fibrinogen degradation products, antithrombin, platelet count and prothrombin time (Fei et al., 2020). All these biochemical parameters are prognostic markers for the severity of the pathological condition for patients who have admitted to COVID-19 infection (Yao et al., 2020).

D-dimer could be an effective and helpful biomarker to improve management and treatment of Covid-19 patients (Zhang et al., 2020). In addition increasing D-dimer level was related to a hazard ratio for death due to the underlying thromboembolic burden and increased mortality among those patients (Naymagon et al., 2020). Moreover, D-dimer is a reflective of high thrombotic activity and may not only be a biomarker of prothrombotic state and a hypercoagulability but may contribute in pathogenesis of acute pulmonary dysfunction (Berger et al., 2020). Elevated fibrin degradation products has been reported in several studies leading to serious condition caused by disseminated intravascular coagulation, which requires continuous attention and prompt intervention (Terpos et al., 2020; Zheng et al., 2020). While the reduction in antithrombin levels in patients with COVID-19 are also appear to have an important role in patient prognosis through both arterial and venous thrombotic complications (Liao et al., 2020; Christensen et al., 2020). Like antithrombin, a low platelet count is accompanying by fivefold increased risk of disease and mortality in COVID-19 patients and therefore should used as prognostic indicator of worsening disease during hospitalization (Lippi et al., 2020). Many studies revealed a thrombocytopenia in groups of patients with severe COVID-19 and associated with increasing the mortality many times higher than in patients without thrombocytopenia (Liu et al., 2020; Zhao et al., 2020).

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BM of Cardiac complications

COVID-19 usually presents as viral pneumonia that may resulting in acute respiratory distress syndrome and it has a signifcant effect on the cardiovascular system through severe systemic inflammatory response, hypoxia, direct myocardial damage, lung injury and the major cardiac complications are myocardial infarction, acute myocarditis, arrhythmia and abnormal clotting (Bandyopadhyay et al., 2020). Creatine phosphokinase and cardiac troponin are a prognostic tool that utilized as a circulating cardiac injury marker, and a patients with higher levels of these biomarkers are associated with increased severity of COVID-19 death (Qin et al., 2020; Masetti et al., 2020; Izquierdo et al., 2020; Salvatici et al., 2020; Shah et al., 2020). (Table 2)

Table 2: Study details of research articles that commonly used biochemical markers as prognostic tools

Authors	Study period	Sample size	Biomarker	Type of alteration	Comment
(Zhang et al., 2020)	January 12- March 15, 2020	343	D-dimer	Increased	The apoptotic processes of virus triggered coagulopathy by targeting the vascular endothelial cells, so that a greater level of D-dimer on admission was correlated to a worse prognosis of disease.
(Naymagon et al., 2020)	March 1- April 1, 2020	2032			
(Berger et al., 2020)	March 1- April 08, 2020	2377			
(Terpos et al., 2020)			Fibrin Degradation Product	Increased	Elevated fibrin degradation products leading to serious condition caused by disseminated intravascular coagulation
(Zheng et al., 2020)	February 15th, 2020	55			
(Liao et al., 2020)	Jan 23 - Feb 23, 2020	466	antithrombin	Decreased	Reduction antithrombin activity is associated with the increasing the severity of COVID-19 and mortality
(Christensen et al., 2020)		N/A			

Authors	Study period	Sample size	Biomarker	Type of alteration	Comment
(Liu et al., 2020)	January 2 March 1, 2020.	383	Platelets	Decreased	Platelet count is readily available biomarker,could distinguish COVID-19 patients with severe disease.
(Zhao et al., 2020)	January 7-February 28, 2020	1066			
(Qin et al., 2020)	December 31, 2019-March 4, 2020	3219	creatine phosphokinase	Increased	creatine phosphokinase is a prognostic tool using as a circulating cardiac injury marker
(Masetti et al., 2020)	28 February-10 April 2020	229			
(Izquierdo et al., 2020)	February 27 -April 7, 2020	872			
(Salvatici et al., 2020)	1 March-14 April 2020	523	cardiac troponin	Increased	Cardiac troponin is a useful biomarker of myocardial injury and the elevation in its concentration associated with increased mortality rate in patients with worse clinical outcomes in COVID-19 infection.
(Shah et al., 2020)	March 2-June 7, 2020	309			
(Cheng et al., 2020)	8 February-11 March 2020	305	Blood urea nitrogen	Increased	Blood urea nitrogen is consider an important marker for predicting, estimation of renal function and represent a valuable prognostic factor of COVID-19 severity
(Gao et al., 2020)	January 23-February 29, 2020	210			

(Cheng et al., 2020)	January 28- February 11 2020,	701	Creatinine	Increased	Creatinine measurements is a very useful prognostic tool in the early detection of kidney injury
(Pei et al., 2020)	January 28 - February 9, 2020	333			
(Nimkar et al., 2020)	March 10- May 13, 2020	370			
(Liu et al., 2020)	January 21 - February 16, 2020	69	Interleukin-6	Increased	High level of IL6 mayreflect a state of acute inflammatory cytokine storm indicating disease progression
(Liu Tao et al., 2020)	January 21 - February 16, 2020	80			
(Liu Fang, et al., 2020)	January 18- March 12, 2020	140			
(Luo et al., 2020)	January 27- 5 March 2020	15			

BM of Renal failure

Recent studies show that renal injury is commonly occur in coronavirus patients because of a highly presented ACE2 receptors in the renal cells which making them targeted and infected by the coronavirus (Valizadeh et al., 2020). However, The possible mechanisms for the kidney manifestations of COVID-19 are:1) renal dysfunction due to viral replication, 2) systemic inflammatory response for the cytokine storm, 3) disturbance in renin angiotensin aldosterone system homeostasis (Kunutsor & Laukkanen, 2020). Increased level of blood urea nitrogen is a risk factors for poor prognosis of coronavirus especially when it infected the elderly patients with comorbidities (Cheng et al., 2020; Gao et al., 2020). The occurrence of acute renal injury as a one complication of COVID-19 infection is a partly detected through measuring creatinine levels, because of the diagnosis of renal injury is generally depend on the acute changes in the levels of creatinine in the serum which has a substantial effect on detection rate (Cheng et al., 2020; Pei et al., 2020; Nimkar et al., 2020).

Conclusion

In conclusion, we found that there are many biochemical markers that play an important roles in predicting of COVID-19 infection with a clear evidence of how their levels may alter according to the severity of COVID-19. This may be ultimately helped the clinicians in their clinical practice to guide management and to determine the necessity for admission to ICU in order to decrease the mortality rates.

Recommendation

To illustrate that a biomarkers are predictive of management and treatment benefit, the study requires biomarkers status on all patients preferably in the context of a randomized study and to determine whether a biomarkers are purely prognostic, it requires to be demonstrated that there is a significant correlation between the biomarkers and outcome.

Conflicts of Interest:

The authors declare no conflicts of interest.

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