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Striking Biochemical Markers in Laboratory Diagnosis for People in COVID-19 Pandemic

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ABSTRACT

During the Coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the importance of markers used to evaluate the severity of disease in humans may differ from others. In this review, the biochemical markers that attract much attention in COVID-19 outbreak were tried to be evaluated simply. Particular attention was paid to researches using some specific markers and meta-analyzes of hundreds of studies including laboratory findings obtained from different databases. Indicator informations obtained from comprehensive COVID-19 studies can contribute to clear and targeted examinations by taking into account tissue or organ functions not only during the COVID-19 outbreak process, but also during the development of diagnosis and monitoring technologies in all kinds of infections. The prevalence values of the most remarkable biochemical markers of organ function and infection analyzes were found to be approximately as C-Reactive Protein (CRP), Albumin (ALB), Lactate DeHydrogenase (LDH), D-dimer, Aspartate aminotransferase (AST), Procalcitonin (PCT), Creatin Kinase (CK), Alanine Aminotransferase (ALT), Bilirubin (Bil) and Creatinin (Cr) in decreasing order. As a result, biochemical or molecular markers and in order of importance are striking as significant auxiliary molecules in the analysis and grading of disease severity in COVID-19 patients.

KEYWORDS: Biochemical/molecular markers; COVID-19 pandemic; Laboratory findings

INTRODUCTION

Coronavirus disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and started in Wuhan City of China in December 2019. After COVID-19 was officially recognized and declared as a pandemic by the World Health Organization (WHO), while attempts to reduce the severity of infection and vaccination studies in countries quickly yielded results, the mutation of the virus and the exacerbation of the pandemic in the UK indicates that the pandemic process will take a long time. As scientists try to ensure that tests based on reverse transcriptase-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent testing (ELISA) techniques are sufficient and sensitive for diagnosis and prognosis to stop the COVID-19 outbreak, sensitive testing is needed to catch viral infections while they are still contagious. Sufficient production and routine use of antigen tests

and rapid lateral flow tests based on CRISPR gene editing technology are on the agenda. In this process, biochemical markers are frequently used to evaluate the severity of COVID-19 and the nature of response to treatment. In the last quarter of 2021, the world is struggling with new coronavirus variants. Although there is a significant decrease in the number of people who lost their lives thanks to vaccination, the severity of the epidemic still continues. During the COVID-19 pandemic which reached approximately over 230 million confirmed cases and 4.7 million deaths in 1.5 years in all world countries, especially in the USA, India, Brazil, UK, Russia, France and Turkey according to total confirmed cases and also USA, Brazil, India, Mexico, Peru, Russia and Indonesia according to total deaths [29, 30] while the publications on laboratory findings are shared rapidly with the public, we believe the idea that some biochemical or molecular parameters whose ratios dramatically variable need special attention. Updating the sensitive information obtained from laboratories conducting analyzes on COVID-19 infection in health institutions at any time will provide important and permanent clues to studies for the treatment of long-term or severe infectious diseases.

Many biochemical markers such as Lactate DeHydrogenase (LDH) [3, 9, 15, 19, 31], Alanine AminoTransferase (ALT) [21, 31], Aspartate AminoTransferase (AST) [12, 15, 21, 34], Alkaline Phosphatase (ALP), Gamma Glutamyl Transferase (GGT) [24, 31], Creatine Kinase (CK) [21, 34], Blood Urea Nitrogen (BUN), High-sensitivity cardiac troponin I (TNI) [20, 34], Albumin to Globulin Ratio (ALB/GLB) [8], Albumin (ALB) [12, 21, 31, 35], Total Bilirubin (TBil) [21, 31, 35], ferritin [3], Serum Amiloid A (SAA) [17, 22], Cystatin C (CysC) [14, 34], Procalcitonin (PCT) [3, 21, 34], Erythrocyte Sedimentation Rate (ESR) [16, 21, 34], C-Reactive Protein (CRP) [9, 16, 19, 35], D-dimer [3, 21], Creatinine (Cr) [14, 21], Interleukin-6 (IL-6) [22], Calcium (Ca) [34], Sodium (Na), Potassium (K) and bicarbonate ($HCO^{-}3$) [3] are used to assess the course and the severity of diseases.

Lactate Dehydrogenase (LDH) enzyme is an important molecule in glucose metabolism, which catalyzes pyruvate into lactate during rapid energy recovery in tissues in the body and releases into the extracellular space due to damage to cell membranes [11]. LDH is a marker of cellular damage that indicates the extent of tissue damage and recommended as a strong predictor of patient mortality [3, 32]. Liver dysfunction is indicative of poor outcome in aggravated diseases and is traditionally characterized by elevated ALT, AST, ALP and Bil levels in these patients [4]. GGT is a cell membrane-bound peptide transfer enzyme in many parenchymatous organs and compared with ALP levels to differentiate skeletal and liver disease [24]. GGT, ALP, ALT, AST, TBil and ALB levels were used as markers of liver function in the COVID-19 period [31]. BUN as a strong marker is important for hemodynamic differences and renal perfusion conditions [2]. BUN/Cr ratio draw attention as a potential indicator of increased metabolic breakdown elements that are often found with protein energy malnutrition and inflammation [25]. Serum Cr levels are used in the analysis of kidney function in humans, but it is noted that serum CysC can be evaluated as an alternative to serum Cr levels [14]. The troponin isoforms TNI and TNT, which are a component of the contraction apparatus in skeletal and cardiac myocytes are known as Cardiac Troponins (cTn) because they are highly sensitive and specific to cardiac myocytes [20]. Increases of CK and myoglobin levels are considered as biomarkers of muscle damage [6]. Analysis of D-dimer as a specific cross-linked fibrin degradation product is used in the diagnosis of severe diseases and venous thromboembolic disorders in all organs [1, 3]. ESR and CRP are frequently used indirect diagnostic methods in the diagnosis of infectious diseases. It has been noted that the combination of ESR and CRP provides higher diagnostic accuracy [16]. CRP is an acute phase reactant synthesized by hepatic tissue in response to both infectious and inflammatory diseases. There are three isoforms of the SAA protein, a pentraxine such as CRP, but only two of them are acute phase proteins and the other is a structural serum amyloid A protein and the main production site is the liver [26]. IL-1, TNF-α and IL-6 are considered to be the main cytokines involved in acute SAA induction [22]. Ferritin, whose serum concentrations are increased during inflammation and liver injury, is an iron storage and acute phase protein that is posttranscriptionally regulated by cellular iron concentrations via iron-sensitive elements in the messenger RNA [7]. PCT, a peptide precursor of calcitonin hormone that plays a role in calcium homeostasis is widely recommended as the most useful marker of severe systemic inflammation in the prognosis and diagnosis of sepsis [23]. Also, the parameters such as Lymphocyte (L), Platelet (PLT) and White Blood Cells (WBC) are used as indicators of inflammation [17].

MOLECULES USED AS BIOCHEMICAL MARKERS IN COVID-19 OUTBREAK

Using databases for incidence, risk factors, and prognosis in COVID-19 patients, a systematic review and meta-analysis was performed by Wu et al. (2020), and abnormal liver biochemical test findings were collected in a pool. In the 45 studies used in the meta-analysis, the number of COVID-19 patients ranged from 18 to 1099. ALT, AST, TBil, ALP, ALB and GGT were taken into consideration for liver biochemical findings. Accordingly, ALB level was found as the most common indicator of abnormal liver detected during admission to hospitals with an incidence of 39.8%. GGT is in second place with an incidence of 35.8%. As the abnormal liver biochemical parameters detected in hospitalization period, abnormalities in ALT and AST levels were 38.4% and 28.1%, respectively. It has been reported that an abnormality in TBIL levels in hospitalized patients has an incidence of 23.2% [31]. Henry et al. (2020) included a total of 21 studies, including 3377 patients and 33 laboratory parameters, in a study in which they evaluated hematological, biochemical and immunological biomarkers

in patients with and without severe or fatal forms of COVID-19. Accordingly, in organ function analyzes in both severe and fatal COVID-19 patients, it was stated that liver AST, LDH and creatinine levels increased significantly, and ALB levels decreased when statistically evaluated [20]. It has been stated that ALB/GLB ratio and CRP/GLB ratio will be very useful in evaluating the course or severity of the disease by including it in first evaluation of patients with PCR positive in terms of SARS-CoV-2 [34].

Pourbagheri-Sigaroodi et al. (2020) conducted laboratory examinations of 2988 COVID-19 patients, 16.1% of whom were severe COVID-19 patients registered in 19 scientific studies in PubMed, Web of Science and Scopus medical databases to better understand the importance of abnormal laboratory findings in the diagnosis and prognosis of COVID-19. According to the findings recorded in the laboratory tests, they were reported that COVID-19 patients had high ESR, CRP, LDH, D-dimer, AST, ALT, CK, PCT, Cr and Bil levels and low ALB levels. The percentage changes of these levels are summarized in the figure (Figure 1) [21]. Considering the prevalence of laboratory findings in a meta-analysis study in 3600 COVID-19 patients, high CRP (68.6% [58.2-78.2]) and LDH (51.6% [31.4-71.6]) findings are remarkable in terms of biochemical markers (Figure 2) [9]. One of the most common laboratory findings (95% CI) was rates of decreased ALB (62.9%) with increased CRP (73.6%) and LDH (46.2%) in a meta-analysis study of 4,663 patients, 46.7% of whom were women and with average 48.4 years old of all taking 1106 articles from PubMed, CNKI (China) and Web of Science and other sources. In the evaluation of laboratory findings, it was reported that heterogeneity was found with statistical significance (P= .000) by referring to I2 varying between 70.5% and 98.1% and ill people with high CRP and LDH levels in severe group had a higher risk compared to nonsevere group [23].

The prevalence of change (increase) in biochemical parameter levels (95% CI) in study that included 43 investigations using Web of Science, EMBASE, PubMed, and CNKI (Chinese Database) databases to support to efforts to treat, characterize and control the COVID-19 outbreak was reported high for LDH, D-dimer, AST, CRP, PCT, CK and Cr in critically and noncritical ill patients with COVID-19 (Figure 3) [9].

In a study that suggested potential biomarkers and angiotensin receptor blocker (ARB) drug related to increased angiotensin II (ACE2) level in blood plasma to cure of COVID-19 was reported that all of 12 patients had pneumonia, 7 of them were over 60 years of age and in 6 of them developed acute respiratory distress syndrome (ARDS), and the CRP and LDH levels of ill people were significantly high [19]. It was reported the increased prevalence of LDH (≥ 250 U/L), CRP (≥ 10 mg/L), AST (> 40 U/L) and D-dimer (≥ 500) as infectious markers in studies grouping COVID-19 on the order of all, non-severe and severe patients (Figure 4) [7, 27, 28, 33].

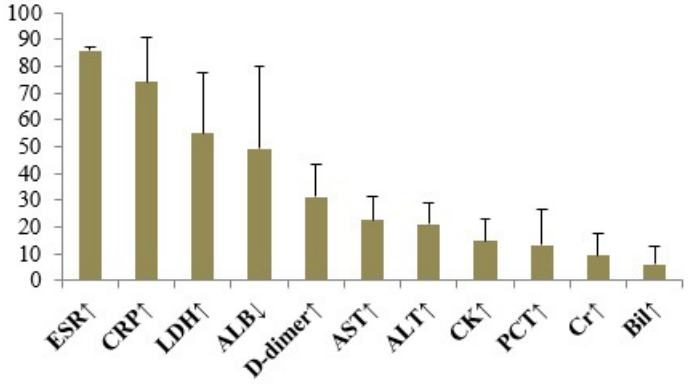

Figure 1: % changes of the parameters in selected examinations for COVID-19 (mean ± SD)

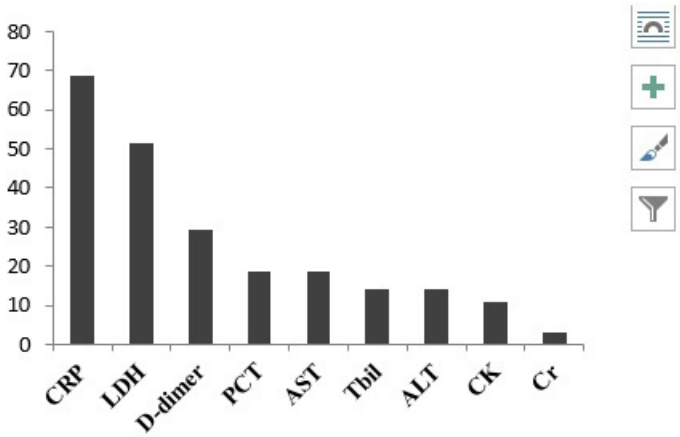

Figure 2: % changes of some biochemical findings in individuals with COVID-19

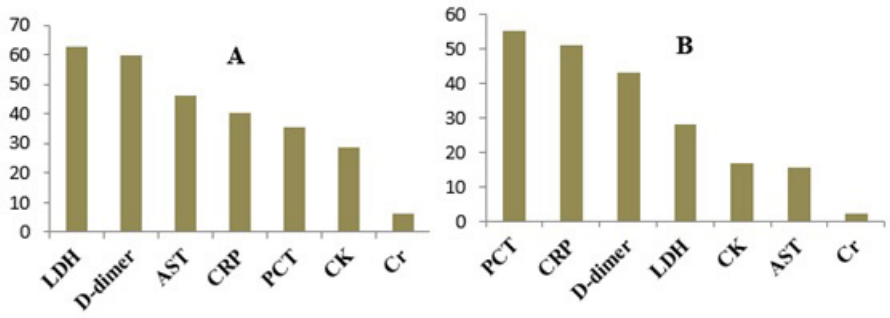

Figure 3: % changes of the laboratory findings in the critical (A) and non-critical (B) illness of COVID-19.

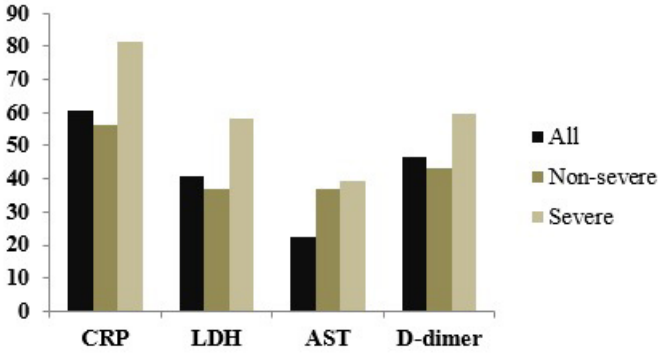

Figure 4: % changes of levels of the LDH, CRP, AST and D-dimer in the all, nonsevere and severe individuals with COVID-19

Asghar et al. [3] evaluated the effect of some parameters on COVID-19 prognosis and order of activity among the biochemical indicators in their study to understand the probability of death in COVID-19 patients. The mean age of a total of 364 patients included to study was 52.6 ± 15.8 years, with an average age of 48.4 ± 16.4 for women and 54.6 ± 15.2 for men, and the gender-related age difference was found to be significant (P< 0.001). It has been stated that increased levels of LDH, D-dimer and PCT according to laboratory findings are superior to increased levels of CRP and ferritin in serum as effective biomarkers in evaluation the severity of COVID-19 in terms of mortality. Increased levels of urea, Cr and Na in those who lost their lives have also been accepted as important parameters for the COVID-19 severity and mortality during outbreak. In addition, the increase in Na ion levels and decrease in $HCO^{-}3$ levels detected in survivors and non-survivors were remarkable [3]. Li et al. (2020) found increased SAA and CRP levels of patients in which they examined the dynamic changes in the blood of 132 patients around 62 years old with COVID-19. It has been stated that SAA levels are a sensitive indicator for assessing the severity and prognosis of COVID-19. As the disease progressed from mild to critical status, it was also reported that lymphocyte count (L) decreased while the levels of SAA and CRP gradually increased (P< 0.05). Therefore, it has been noted that the changes in levels of CRP, SAA and L are very effective in categorizing the disease and WBC, PCT and PLT levels are little importance [17]. In a research that included 172 patients with COVID-19 and 60 of them turned into severe cases was notified that the levels of TNI, LDH, AST, CK-MB, CK, CRP, PCT, CysC and ESR were statistically higher among the biochemical findings of moderate COVID-19 cases during acceptance in the severe infected group compared to mild infected group. Also, it was reported that the levels of the TNI, CRP, PCT and calcium between the most predictive characteristics used in the diagnosis model for COVID-19 infection were important [34]. In a study involving 77 patients diagnosed with COVID-19 infection, it was reported that among the parameters considered, there was a direct correlation between CRP levels and chest computed tomography scan scores, and the strongest correlation was between serum ALB levels and computed tomography screening scores. In addition, it was noted that the decrease in ALB levels and high serum BIL levels and computed tomography scan scores were consistent [35].

The severity of COVID-19 was investigated by Liu et al. (2020) through biochemical parameters of 119 patient urine samples including urine occult blood (BLOOD), bilirubin, protein (PRO), hydrogen potential (pH), urobilinogen, urine glucose (GLU), nitrite, specific gravity (SG), leukocytes (LEU) and ketone (KET). It was found that more than 90% of ill individuals with severe COVID-19 had increased levels of urine GLU, and this rate was 60% in critic patients. Urine PRO levels were determined to be more than 40% in severe patients and 50% in critic patients. According to these statistically important findings, it has been suggested that increases in urine GLU and PRO levels may be caused by cytokine storm which can be prevented with certain drugs and

as response to infection [18]. It reported to be a more significant risk of death in patient individuals with COVID-19 and the sick renal tissue related to high basal serum Cr, BUN, hematuria, proteinuria, and acute kidney injury [5, 13].

CONCLUSION

When the databases are examined, it is seen that prevalence studies are intense by referring to biochemical parameters in a short time and the findings related to these prevalence studies are taken into consideration in order to stop COVID-19 outbreak. According to the comprehensive literature reviews, it has been revealed that the prevalence values of the most remarkable biochemical or molecular markers of organ function and infectios analysis are approximately in the form of CRP, LDH, ALB, D-dimer, AST, PCT, CK, ALT, TBil and Cr in descending order has been released. In order of importance, these markers can be considered to be important auxiliary molecules in the analysis and grading of disease severity in individuals with COVID-19.

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