Original Article

Comparative Analysis of Biochemical and Hematological Parameters in COVID-19 Patients

Noor K. Zaidan[1], Wisam M. Mohammed[2]*, Ihab M. Rashid[3]

[1]Department of Applied Chemistry, College of Applied Sciences, University of Fallujah, Iraq.
Email: noor_k.zidan@uofallujah.edu.iq
[2]Department of Applied chemistry, College of Applied Sciences, University of Fallujah, Iraq.
Email: wissamatea@uofallujah.edu.iq
[3]Ministry of Education, Iraq.
Email: eehab.malik@gmail.com

Abstract

Background: Coronavirus 2019 (COVID-19) or the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) have been linked to cases of mild to severe respiratory illnesses. Infections with COVID-19 constitute a worldwide pandemic, according to the World Health Organization ("WHO"). **Objective:** This study aimed to investigate at the relationship between a biochemical factors and COVID-19 infection in Anbar City, Iraq. All of the patients have already been given a COVID-19 diagnosis and show signs and symptoms of it. **Method:** A study at a Fallujah teaching hospital confirmed a diagnosis of COVID-19 in 45 patients and 50 healthy individuals . Laboratory evaluations included white blood cell count (W.B Cells), hemoglobin (Hb), Platlate count, Erythrocyte Sedimentation Rate (ESR), adenosine deaminase (ADA) activity, lactate dehydrogenase (LDH) activity, LDH/ADA ratio, aspartate transaminase (AST) activity, alanine transaminase (ALT) activity, D-dimer, vitamin D, and C-reactive protein (CRP). **Results**: COVID-19 patients exhibit increased white blood cell count, concentration, ESR, ADA levels, and serum LDH levels, while maintaining unaffected platelet count, ALT, AST, and d-Dimer levels.

Keywords: ADA., LDH, AST., ALT., CBC., ADA/LDH Ratio, Covid-19, D-dimer.

Introduction

The global pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is responsible for the spread of Coronavirus Disease 2019 (COVID-19).[1] While most individuals infected with SARS-CoV-2 exhibit mild symptoms and recover without medical intervention, the virus can lead to severe respiratory illness that poses a risk to life.[2] An investigation has been conducted to examine the correlation between several haematological factors and both the occurrence and severity of COVID-19 infection. These characteristics provide crucial insights on the patient's immune response and overall health condition during the course of the disease.[3] Several haematological parameters, such as neutrophil-lymphocyte ratio, platelet count, and total white blood cell count, were measured. [4] Based on the available research, findings from other published studies, and the published results, it can be inferred that there is a connection between these two viruses and their respective partners. Investigating the mechanisms that control the levels of purine nucleosides and adenosine could yield valuable insights into the progression of COVID-19 and potentially lead to novel therapeutic approaches for both the early and advanced stages of the disease.[5] The erythrocyte sedimentation rate (ESR) is a measurement of the speed at which red blood cells in a blood plasma sample settle over a defined period of time.This test assesses the physiological response of the organism to an inflammatory condition.[6]

Adenosine provides protection against a wide array of inflammatory processes. Adenosine deaminase, a vital enzyme produced by cells in response to viral or bacterial infections, is responsible for this.[7] ADA[8] catalyses the deamination of adenosine into inosine. The transporters responsible for nucleosides, specifically adenosine, interact intimately with both anabolic and catabolic purine enzymes to regulate adenosine levels.[9] ADA, an enzyme with high

Access this article online

Quick Response Code:

Website: www.jnsbm.org

DOI: https://doi.org/10.4103/jnsbm.JNSBM_15_1_3

Address for Correspondence: Department of Applied chemistry, College of Applied Sciences, University of Fallujah - Iraq.
Email: wissamatea@uofallujah.edu.iq

Submitted: 25th December, 2023 **Received:** 02nd January, 2024
Accepted: 10th January, 2024 **Published:** 08th February, 2024

How to cite this article: Zaidan N K, Mohammed W M, Rashid I M. Comparative Analysis of Biochemical and Hematological Parameters in COVID-19 Patients. J Nat Sc Biol Med 2024;15:28-35

capacity and low affinity, converts adenosine into inosine. ADA is crucial in situations where adenosine levels are elevated. Hence, reducing ADA levels to augment the defensive adenosine could potentially lead to improved clinical outcomes in individuals with COVID-19. It is important to note that adenosine-induced immunosuppression might hinder the elimination of the virus, but it can also impede its replication during the early stages of infection.[10] Lactate dehydrogenase (LDH) catalyses the conversion of pyruvate to lactate, which is the last step of aerobic glycolysis.[11] LDH has shown promise as a predictive biomarker in persons with COVID-19.[2] One relevant biomarker is LDH, as greater levels of LDH have previously been associated with more severe outcomes in patients with different viral infections.[12] Preliminary findings in COVID-19 participants indicate significant variations in LDH levels between individuals with severe illness and those without.[13]

Liver dysfunction is a commonly observed clinical sign in people infected with SARS-CoV, although it is often mild in nature. Liver injury serves as a prognostic indicator for patient progression in COVID-19 and holds important importance. The elements that lead to liver damage include the direct attack of SARS-CoV-2, drug toxicity from COVID-19 treatment, acute inflammatory changes, and hypoxia.[14]

Studies have shown that plasma D-dimer levels can serve as a prognostic indication for outcomes in COVID-19 patients. Increased levels of D-dimer, a marker for the development and breakdown of blood clots, may indicate a greater likelihood of thrombotic events in COVID-19 patients.[15]

1, 25-dihydroxyvitamin D, a bioactive derivative of vitamin D, enhances the activity of innate antiviral defence mechanisms and regulates inflammation during infection.[16] Furthermore, there is a possibility of acquiring vitamin D insufficiency, which might subsequently elevate the risk of contracting a severe COVID-19 infection.[17]

C-reactive protein (CRP), an acute-phase protein and potent regulator of the host innate immune system, is highly predictive of the need for ventilator support and may be advantageous in guiding the intensification of treatment for uncontrolled inflammation associated with COVID-19.[18]

Materials and Methods

Study Design and Participants

A comparison study was conducted at al-Fallujah Teaching Hospital, throughout the period of October 2020 to December 2020, in which blood samples were taken from two participant groups. Group A consists of 45 patients. These individuals are experiencing moderate symptoms of COVID-19. They have been confirmed to have COVID-19 using RT-PCR testing (Reverse Transcription Polymerase Chain Reaction). Group B (consisting of 50 people) has been confirmed negative for COVID-19 using RT-PCR testing. According to the interim recommendations of the World Health Organisation (WHO), patients with COVID-19 were diagnosed.[19] This guidance encompasses diagnostic criteria for COVID-19, which include both clinical and laboratory investigations. Laboratory confirmation was achieved by employing RT-PCR testing on specimens collected from the nasopharynx or throat using swabs. This method is commonly used to detect the existence of the SARS-CoV-2 virus, which is responsible for generating COVID-19. All patients who tested positive for the presence of the virus in their nasopharyngeal/throat swab samples using RTPCR, and whose results were validated by a physician or laboratory, were included in the study. However, suspected cases with similar clinical symptoms were not included. The study excluded people who had prior experience using vitamin D supplements, hypercalcemia, renal or hepatic disease, hypoparathyroidism, were pregnant, or had musculoskeletal disorders.

Clinical and Biochemical Parameters

The laboratory tests employed in this study encompassed a diverse range of assessments to evaluate the immune response, blood parameters, inflammation, and organ function, among other aspects of health and the impact of COVID-19 on the patients. Researchers can utilise them to enhance comprehension of the impacts of COVID-19 on the body and potential connections between the disease and these variables. Measurement of white blood cells, platelet count, erythrocyte sedimentation rate (ESR), haemoglobin concentration (Hb%), D-dimer levels, vitamin D levels, C-reactive protein levels, adenosine deaminase (ADA) levels, aspartate aminotransferase (AST) levels, alanine aminotransferase (ALT) levels, lactate dehydrogenase (LDH) activity, and the LDH/ADA ratio in individuals with COVID-19. The Beckman-Coulter method for size measurement and counting use discernible alterations in electrical resistance caused by nonconductive particles suspended in an electrolyte. A concurrent flow of an electric current and a suspension of blood cells occurs through a minuscule aperture simultaneously. The user's text is simply "A". The region where suspended particles are detected is a narrow aperture located between electrodes. Successful. Every particle in the detecting zone displaces an equivalent volume of electrolyte. Beckman Coulter, Inc. The displaced volume is determined by measuring a voltage pulse, where the magnitude of each pulse is directly proportional to the volume of the particle. The quantity of suspension drawn through the opening is precise and consistent. Beckman Coulter use high-speed technology to enumerate and measure individual particles at a rapid rate of thousands of times per second. This approach is universally applicable, irrespective of particle morphology, hue, or dimensions.[20] ESR: The Erythrocyte Sedimentation Rate (ESR) using the Wintrobe Method is a quantitative assessment of the speed at which red blood cells (RBCs) drop to the bottom of a vertical test tube during a specified duration.[21] The serum ADA activity of all study participants was evaluated using the well-established classic colorimetric approach developed by Giusti and Galanti.[22] LDH catalyses the conversion of pyruvate to lactate and NADH to NAD. The rate of NADH oxidation can be quantified by observing the absorbance at 340nm, which is directly related to the activity of LDH in the serum. The compound α-Ketoglutarate undergoes a chemical reaction

with L-alanine to produce L-glutamate and pyruvate. This reaction is utilised in a method to measure the rate at which reduced nicotinamide adenine dinucleotide (NADH) is consumed. The International Federation of Clinical Chemistry advocates for the implementation of standardised protocols for ALT measurement, which involve optimising substrate concentration, utilising tris buffer, and initiating substrate reaction.[23] The International Federation of Clinical Chemistry advocates the adoption of standardised protocols for ALT measurement, which involve optimising substrate concentration, employing Tris buffer, preincubating the sample, initiating the substrate reaction, and ensuring optimal activation of pyridoxal phosphate. Transaminases facilitate the conversion of amino acids and α-keto acids.[24] These techniques exhibit high sensitivity and specificity, leading to a minimal occurrence of reagent blanks. The colorimetric analytical approach developed by Lippi and Guidi can identify combinations within approximately 5 minutes at a temperature of 37°C.[25] D-dimer: Monoclonal antibodies are employed for the identification and measurement of D-dimer in blood, plasma, or serum. The mini-vidas D-dimer test is extensively utilised and is not affected by any interfering factors. Specialised D-dimer tests are commonly employed in clinical studies to exclude the presence of venous thromboembolism.[26] The precision of the 25-OH vitamin D total assay was evaluated by testing assay controls and serum samples. The precision was established by using samples with 25(OH)D levels ranging from 10 to 130 ng/mL.[27] The ELFA test for antigen detection employs a two-stage enzyme immunoassay sandwich method, which is supplemented with a subsequent fluorescence detection phase. The equipment automatically performs each step by using pre-dispensed reagents. The conjugate attaches to the antigen during the initial phase after the sample is collected and undergoes repeated cycling in and out of the Solid Phase Receptacle (SPR).[28]

Statistical Analysis

The statistical analysis was performed using the SPSS (version 20) program. The results were presented as mean± SD. A T-independent test was used in the statistical analysis to determine whether there were any differences between the two groups. Multiple range tests at $p \leq 0.05$ were recognized as significant, therefore even though very significant results were discovered at $p \leq 0.001$, and the range tests at $p \leq 0.05$ were considered to be non-significant.

Results and Discussion

Hematological Parameter

In this experiment, 95 samples—45 COVID-19 patients and 50 healthy control subjects—were used. The levels of hematological parameter (mean ± SD) for the groups that were examined is shown in table (1).

Table 1: Levels of Hematological Parameter (mean ± SD) for All Studied Groups.

Hematological Parameter	Patient Group (No.=45)	Control Group (No.=50)	p- Value
White blood celles count, (×200/µL)	9500 ±1200	6400 ± 705	0.000
Hemoglobin (g/dl)	11.3 ± 0.6	12.1± 0.74	0.033
Platelet count (count/µL)	478000 ± 24000	380000 ± 41000	0.685
Lymphocytes, %	13 ± 2	23 ±3	<0.001
Erythrocyte sedimentation rate(ESR), (mm/60 min)	62 ± 5	40 ± 6	0.001

Table (1) displays a comparison of the total white blood cell count, haemoglobin concentration, platelet count, lymphocyte count, and erythrocyte sedimentation rate (ESR) indices between patients with COVID-19 and the control group without COVID-19. The results of our study indicate a significant rise in the concentration of total white blood cell count and erythrocyte sedimentation rate (ESR) in COVID-19 patients compared to the control group. The average ± standard deviation (SD) values of the haemoglobin (Hb) concentration and lymphocyte count demonstrate a statistically significant decline in individuals with COVID-19 when compared to the control group. Nevertheless, there was no notable disparity in platelet count levels seen between the two groups.

The measurement of total white blood cell count is an often recorded abnormality in patients infected with COVID-19. [4] The study found that individuals with COVID-19 exhibited significantly elevated levels of total white blood cells compared to the control group. An increased total white blood cell count is commonly observed in many viral infections, including COVID-19. The immune response elicited by COVID-19 is accountable for the elevated leukocyte count reported in these individuals. In response to viral infections such as this one, the body usually generates and releases a greater quantity of white blood cells.[29] In our investigation, we made an important observation: the concentration of haemoglobin (Hb) was lower in people with COVID-19 compared to the control group. The decreased levels of haemoglobin in individuals with COVID-19 can be attributed to various factors. For instance, the intense inflammatory response of the body can potentially affect the production of red blood cells, leading to a decrease in haemoglobin levels.[30] A recent study demonstrated that individuals diagnosed with COVID-19 saw a swift decline in haemoglobin (Hb) and red blood cell (RBC) levels. This decline can be attributed to the disruption of the normal process of red blood cell production in the bone marrow, which is caused by the release of cytokines, especially in severe cases of COVID-19.[31] COVID-19 can also interfere with iron metabolism, a vital process for the formation of haemoglobin.[4]

No significant disparity in platelet counts was seen between the COVID-19 individuals and the control group in the ongoing trial. Some viral infections can cause either an increase (thrombocytosis) or a decrease (thrombocytopenia) in platelet counts. COVID-19 can impact the blood and immune system in various ways, but it does not always cause a consistent change in platelet counts for every person.[32] The results of our study align with previous research that has shown a correlation between thrombocytopenia in COVID-19 infection and the severity of the disease. This indicates the presence of a consumption coagulopathy.[31] A prominent characteristic observed in numerous cases of COVID-19 is a statistically significant reduction in lymphocyte levels among infected patients, as compared to a control group. Our analysis confirms this finding. The immunological response to COVID-19 is often associated with a reduction in lymphocyte levels in patients. Nevertheless, various investigations have consistently reported that lymphocytopenia is the most commonly observed abnormality in patients of COVID-19. Furthermore, subsequent studies observed neutrophilia. There is a strong correlation between the severity of the disease and a decrease in the number of lymphocytes. This may offer a rationale for the disparity in results between the present study and the referenced papers.[32]

The erythrocyte sedimentation rate (ESR) has a restricted function in evaluating the severity and prognosis of coronavirus disease 2019 (COVID-19).[33]

Based on our research, A notable finding is that individuals with COVID-19 exhibited a significantly elevated Erythrocyte Sedimentation Rate (ESR) in comparison to a control group. Within the context of COVID-19, an increased erythrocyte sedimentation rate (ESR) signifies heightened inflammation within the body. This aligns with the understanding that inflammation plays a significant role in the development of COVID-19, which is acknowledged as an inflammatory condition. There may be a connection between the increased erythrocyte sedimentation rate (ESR) and the immune system's reaction to the infection, as well as the resulting inflammation in many organs and tissues.[34] Elevated erythrocyte sedimentation rate (ESR) is not specific to any one disease; it can be detected in COVID-19 as well as other inflammatory conditions. Typically, it is employed to assist in the identification and tracking of medical disorders, in combination with further clinical and laboratory findings.[35]

Enzyme Markers

Table 2: Levels of Enzymes Marker(mean ± SD) for All Studied Groups.

Enzymes	Patient Group (No.=45)	Control Group (No.=50)	p- Value
ADA (U/L)	36.19±1.09	13.96 ±2.73	0.000
LDH (U/L)	137± 9	118 ± 6	0.000
meanLDH/meanADA	3.80	8.45	0.000
AST (U/L)	27.6 ± 8.2	8.0 ± 3.1	0.022
ALT (U/L)	21.0 ± 5.6	5.2 ± 7.0	0.050

The enzymological analysis revealed a considerable rise in ADA levels in COVID-19 patients compared to the control group, as seen in table (2). The serum LDH level had the most pronounced significance in patients when compared to healthy individuals. The average serum LDH/ADA ratio in COVID-19 patients exhibited a statistically significant difference when compared to the control group in this experiment. The study found that there was no significant rise in the mean blood ALT and AST values in COVID-19 patients compared to the healthy volunteers. The average serum levels of ALT, AST, and d-Dimer in COVID-19 patients showed no significant increase compared to the healthy volunteers in this study. The investigation's findings indicate that COVID-19 patients exhibited a notable deficiency in vitamin D levels when compared to individuals without the virus. Additionally, the levels of CRP were significantly elevated in patients as opposed to healthy volunteers.

The utilisation of adenosine deaminase activity as a diagnostic method has been employed to recommend a therapy for COVID-19.[36] The study's findings indicate that COVID-19 patients will exhibit elevated levels of ADA compared to uninfected control participants. Elevated ADA levels during COVID-19 indicate a heightened immune response in patients. This aligns with the understanding that COVID-19 is associated with an inflammatory response when the body combats the virus.[37] The increased levels of ADA observed in COVID-19 patients are associated with the release of the enzyme from deceased lung cells, which is in turn connected to the activation of immunological markers such as cytokines.[38] The results align with other studies that discovered ADA was accumulated in tissues at the site of inflammation and functioned as a ligand for receptors produced by lymphocytes, triggering signalling pathways during lung inflammation caused by bacterial or viral infections.[39]

LDH serves as an indicator for several inflammatory disorders, such as infections, malignancies, ischemia, sepsis, and cardio-pulmonary failure.[40] An often noted discovery in the present study is an elevation in lactate dehydrogenase (LDH) activity among COVID-19 patients in comparison to healthy participants. Increased levels of LDH in the bloodstream can serve as a sign of harm to tissues or cells. Elevated LDH activity in individuals with COVID-19 is often associated with the disease's impact on various bodily tissues and organs, indicating potential tissue and lung injury in these patients.[41] The severity of the disease may be associated with increased

LDH levels, indicating tissue destruction. Monitoring LDH levels can simplify the assessment of tissue damage and overall health in COVID-19 patients. This is because COVID-19 can lead to insufficient tissue perfusion and malfunction of different organs, perhaps caused by several factors such as thrombosis.[42]

The primary results The current study concludes that the measurement of ADA level and LDH in COVID-19 samples lacks precision and therefore does not provide significant diagnostic benefits for COVID-19. The LDH/ADA ratio is a potential biomarker for diagnosing COVID-19. The LDH/ADA ratio demonstrates sufficient accuracy in diagnosing COVID-19, suggesting its potential as a beneficial diagnostic tool for identifying instances of COVID-19. The LDH/ADA ratio is sometimes included in a panel of laboratory tests for diagnosing COVID-19. The table above demonstrates a notable disparity between the sick and healthy cohorts. The precision of this ratio may vary depending on several factors, including the size of the population being studied, the stage of the disease, and the specific testing methods employed.[43] The most significant data were provided by the test that specifically aids in diagnosing COVID-19, which involves evaluating the LDH/ADA ratio.

The average serum ALT and AST levels in COVID-19 patients showed a statistically negligible increase. Elevated levels of the liver enzymes ALT and AST in the blood are often associated with liver injury or inflammation. The impact of specific viral infections, such as COVID-19, on liver enzymes can exhibit variability. COVID-19 patients may encounter liver issues, and although the exact reason for the impaired liver function remains uncertain, several highly plausible theories have been suggested. An immediate consequence of the illness could be modified liver functionality.[44] In addition, Feng *et al*.[45] postulated that the elevated viral load of SARS-CoV-2 could potentially lead to hepatic impairment. SARS-CoV-2 gains entry into hepatocytes and cholangiocytes via binding to ACE2 receptors located on their surface.[45]

Other Parameter

Table 3: Levels of Other Parameter (mean ± SD) for All Studied Groups.

Other Parameter	Patient Group (No.=45)	Control Group (No.=50)	p- Value
Age, (yr)	38 ± 9	33 ± 7	0.230
d- Dimer (mg/L)	12.1 ± 2.6	3.33 ± 1.7	0.000
Vitamin D_3 (nmol/L)	19.54 ±	57.8± 8.67	0.000
CRP (mg/L)	13.43±5.66	2.1±0.3	0.000

The average serum levels of d-Dimer and CRP in COVID-19 patients showed a statistically negligible rise compared to the healthy volunteers in this study. The investigation's findings indicate a notable disparity in vitamin D levels between COVID-19 patients and individuals in good health, as evidenced by the data presented in table (3).

An established observation among individuals with COVID-19, as compared to those who are healthy, is an increase in D-dimer levels. This increase is commonly seen in severe cases of the disease. COVID-19 can induce a hypercoagulable condition, increasing the likelihood of blood clot development. Elevated D-dimer values indicate the dissolution of these clots. The assays are widely performed as a stage in a diagnostic process to rule out the existence of thrombosis. However, any medical or non-medical procedure that enhances the production or breakdown of fibrin also increases the levels of plasma D-dimer.[46] Our findings align with several studies that have identified the virus's ability to harm the endothelium, the inner lining of blood vessels. This damage can trigger a series of clotting reactions, leading to elevated D-dimer levels and an increased likelihood of death in individuals with COVID-19.[47]

A noteworthy finding reveals that COVID-19 patients exhibited significantly reduced levels of vitamin D in contrast to healthy persons. There is a suggestion that there could be a correlation between COVID-19 and a lack of vitamin D. To determine the potential correlation between vitamin D status and COVID-19 incidence, severity, or outcomes, researchers can compare COVID-19 patients who have insufficient levels of vitamin D with healthy volunteers. [48] Scientists have conducted extensive research on the influence of vitamin D on immune system functionality and respiratory infections. The immunomodulatory properties of vitamin D are widely recognised, and insufficiencies in this vitamin have been associated with a higher susceptibility to respiratory infections, including those affecting the lungs. The impact of vitamin D on SARS remains uncertain, despite evidence indicating its potential to reduce the occurrence and severity of many respiratory illnesses, including the flu and the common cold. COVID-19 is a disease caused by the SARS-CoV-2 virus. The correlation between vitamin D and COVID-19 is currently under investigation. An association has been established between a vitamin D deficiency and a heightened susceptibility to severe COVID-19, as indicated by specific research findings.[48]

Furthermore, studies have shown that the CRP (C-reactive protein) can be used as a reliable indicator to predict the progression of COVID-19 in patients. During the COVID-19 pandemic, individuals with elevated CRP levels compared to healthy individuals are likely experiencing an inflammatory reaction caused by the viral infection. Individuals diagnosed with COVID-19 often exhibit elevated levels of C-reactive protein (CRP), which serves as an indicator of the extent of inflammation associated with the disease. Healthcare personnel may find C-reactive protein (CRP) to be an indispensable tool for assessing a patient's condition and monitoring the

advancement of an illness. Elevated levels of C-reactive protein (CRP) have been associated with heightened severity of COVID-19 symptoms and outcomes, since they may indicate a more intense or forceful inflammatory reaction.[29] The present study's results align with earlier research indicating that the liver's significant synthesis of acute-phase proteins (APPs), including CRP, leads to an elevation in CRP levels. CRP is a sensitive biomarker used to detect tissue injury in response to infectious illnesses. Acute inflammation unequivocally leads to elevated levels of C-reactive protein (CRP) in the bloodstream.[49]

Conclusion

The findings suggest that lymphocyte percentages, CRP, and ESR can serve as indicators for COVID-19, providing information on the link between haematological alterations and the advancement and result of the illness. This review emphasises the significance of utilising the LDH/ADA ratio instead of assessing the levels of ADA and LDH in the serum of COVID-19 patients. This approach would yield a more precise diagnosis.

References

1. Farhan SS, Tahmasebi P, Al-Dahmoshi HOM, Gatea HS. Gene Expression of TNF-α among Iraqi COVID-19 Patients with a Different Severity Status. Med J Babylon. 2023; 20(1): 90-94. doi: https://doi.org/10.4103/MJBL.MJBL_270_22.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223): 497-506. doi: https://doi.org/10.1016/s0140-6736(20)30183-5.
3. Dey G, Majumdar A, Sinha A. Altered Hematological Profile: The Forerunner of Fatalities Caused by COVID-19. Med J Babylon. 2022; 19(3): 379-82. doi: https://doi.org/10.4103/MJBL.MJBL_44_22.
4. Palladino M. Complete blood count alterations in COVID-19 patients: A narrative review. Biochem Med (Zagreb). 2021; 31(3): 030501. doi: https://doi.org/10.11613/bm.2021.030501.
5. Abouelkhair MA. Targeting adenosinergic pathway and adenosine A(2A) receptor signaling for the treatment of COVID-19: A hypothesis. Med Hypotheses. 2020; 144: 110012. doi: https://doi.org/10.1016/j.mehy.2020.110012.
6. Esteves Pairazaman AT, Parreño Tipian JM, Arbieto Mamani O, et al. Erythrocyte sedimentation rate in COVID-19 patients treated at the CLAS health center, Nuevo Lurín, 2021 [version 1; peer review: awaiting peer review]. F1000Res. 2022; 11: 1278. doi: https://doi.org/10.12688/f1000research.125002.1.
7. Morote-Garcia JC, Rosenberger P, Nivillac NM, Coe IR, Eltzschig HK. Hypoxia-inducible factor-dependent repression of equilibrative nucleoside transporter 2 attenuates mucosal inflammation during intestinal hypoxia. Gastroenterology. 2009; 136(2): 607-18. doi: https://doi.org/10.1053/j.gastro.2008.10.037.
8. Köhler D, Streienberger A, Morote-García JC, et al. Inhibition of Adenosine Kinase Attenuates Acute Lung Injury. Crit Care Med. 2016; 44(4): e181-9. doi: https://doi.org/10.1097/ccm.0000000000001370.
9. Boison D. Adenosine Kinase: Exploitation for Therapeutic Gain. Pharmacol Rev. 2013; 65(3): 906-43. doi: https://doi.org/10.1124/pr.112.006361.
10. Passos DF, Bernardes VM, da Silva JLG, Schetinger MRC, Leal DBR. Adenosine signaling and adenosine deaminase regulation of immune responses: impact on the immunopathogenesis of HIV infection. Purinergic Signal. 2018; 14(4): 309-20. doi: https://doi.org/10.1007/s11302-018-9619-2.
11. Lu J, Wei Z, Jiang H, et al. Lactate dehydrogenase is associated with 28-day mortality in patients with sepsis: a retrospective observational study. J Surg Res. 2018; 228: 314-21. doi: https://doi.org/10.1016/j.jss.2018.03.035.
12. Tao RJ, Luo XL, Xu W, et al. Viral Infection in Community Acquired Pneumonia Patients With Fever: A Prospective Observational Study. J Thorac Dis. 2018; 10(7): 4387-95. doi: https://doi.org/10.21037/jtd.2018.06.33.
13. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020; 58(7): 1021-28. doi: https://doi.org/10.1515/cclm-2020-0369.
14. Baroiu L, Lese AC, Stefanopol IA, et al. The Role of D-Dimers in the Initial Evaluation of COVID-19. Ther Clin Risk Manag. 2022; 18: 323-35. doi: https://doi.org/10.2147/tcrm.s357214.
15. Townsend L, Fogarty H, Dyer A, et al. Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response. J Thromb Haemost. 2021; 19(4): 1064-70. doi: https://doi.org/10.1111/jth.15267.
16. Arora J, Patel DR, Nicol MJ, et al. Vitamin D and the Ability to Produce 1, 25(OH)(2)D Are Critical for Protection from Viral Infection of the Lungs. Nutrients. 2022; 14(15): 3061. doi: https://doi.org/10.3390/nu14153061.
17. Saeed MAM, Mohamed AH, Owaynat AH. Cholecalciferol level and its impact on COVID-19 patients. Egypt J Intern Med. 2022; 34(1): 23. doi: https://doi.org/10.1186/s43162-022-00116-w.
18. Baiee HA, Hussein KH, Ismail IS, Abbas MK, Abd Hammadi AT. Epidemiological and clinical features of COVID-19 confirmed cases in Babel Governorate, Iraq. Med J Babylon. 2021; 18(4): 304-11. doi: https://doi.org/10.4103/MJBL.MJBL_15_21.
19. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020. 2020. No. WHO/nCoV/Clinical/2020.2. Available from:https://iris.who.int/bitstream/handle/10665/330854/WHO-nCoV-Clinical-2020.2-rus.pdf.

20. Lokwani DP. The ABC of CBC: Interpretation of Complete Blood Count and Histograms. JP Medical Ltd; 2013. doi: https://doi.org/10.5005/jp/books/11929.
21. Weiss C. Functions of the Blood. In: Schmidt RF, Thews G, Eds. Human Physiology. Springer Berlin Heidelberg; 1983:331-57. doi: https://doi.org/10.1007/978-3-642-96714-6_16.
22. Giusti G. Adenosine Deaminase. In: Bergmeyer HU, Ed. Methods of Enzymatic Analysis (Second Edition). Academic Press; 1974:1092-99. doi: https://doi.org/10.1016/B978-0-12-091302-2.50108-0.
23. Adam SS, Key NS, Greenberg CS. D-Dimer Antigen: Current Concepts and Future Prospects. Blood. 2009; 113(13): 2878-87. doi: https://doi.org/10.1182/blood-2008-06-165845.
24. Tripodi A. D-dimer testing in laboratory practice. Clin Chem. 2011; 57(9): 1256-62. doi: https://doi.org/10.1373/clinchem.2011.166249.
25. Lippi U, Guidi G. A new colorimetric ultramicromethod for serum glutamic-oxalacetic and glutamic-pyruvic transaminase determination. Clin Chim Acta. 1970; 28(3): 431-37. doi: https://doi.org/10.1016/0009-8981(70)90069-0.
26. Wu Y, Xiao YX, Huang TY, Zhang XY, Zhou HB, Zhang XX, Wu YE. What makes D-dimer assays suspicious-heterophilic antibodies? J Clin Lab Anal. 2019; 33(2): e22687. doi: https://doi.org/10.1002/jcla.22687.
27. Tang JYH. Detection of Microbiological Hazards. In: Andersen V, Lelieveld H, Motarjemi Y, Eds. Food Safety Management (Second Edition). Academic Press; 2023:835-50. doi: https://doi.org/10.1016/B978-0-12-820013-1.00002-4.
28. Laze B, Mitre A. Preliminary evaluation of Chorus System in comparison with mini-vidas system for detection of cytomegalovirus-IgM antibodies. International Journal of Research in Applied, Natural and Social Sciences. 2014; 2(1): 1-6. Available from: https://paper.researchbib.com/view/paper/12321.
29. Sadeghi-Haddad-Zavareh M, Bayani M, Shokri M, et al. C-Reactive Protein as a Prognostic Indicator in COVID-19 Patients. Interdiscip Perspect Infect Dis. 2021; 2021: 5557582. doi: https://doi.org/10.1155/2021/5557582.
30. Yuan X, Huang W, Ye B, et al. Changes of hematological and immunological parameters in COVID-19 patients. Int J Hematol. 2020; 112(4): 553-59. doi: https://doi.org/10.1007/s12185-020-02930-w.
31. Berzuini A, Bianco C, Migliorini AC, Maggioni M, Valenti L, Prati D. Red blood cell morphology in patients with COVID-19-related anaemia. Blood Transfus. 2021; 19(1): 34-36. doi: https://doi.org/10.2450/2020.0242-20.
32. Cossarizza A, De Biasi S, Guaraldi G, Girardis M, Mussini C. SARS-CoV-2, the Virus that Causes COVID-19: Cytometry and the New Challenge for Global Health. Cytometry A. 2020; 97(4): 340-43. doi: https://doi.org/10.1002/cyto.a.24002.
33. Kurt C, Altunçeki Ç Yildirim A. Contribution of Erythrocyte Sedimentation Rate to Predict Disease Severity and Outcome in COVID-19 Patients. Can J Infect Dis Med Microbiol. 2022; 2022: 6510952. doi: https://doi.org/10.1155/2022/6510952.
34. Pu SL, Zhang XY, Liu DS, Ye BN, Li JQ. Unexplained elevation of erythrocyte sedimentation rate in a patient recovering from COVID-19: A case report. World J Clin Cases. 2021; 9(6): 1394-401. doi: https://doi.org/10.12998/wjcc.v9.i6.1394.
35. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180(7): 934-43. doi: https://doi.org/10.1001/jamainternmed.2020.0994.
36. Sekar S, Sivalingam J. Cerebrospinal fluid (CSF) adenosine deaminase (ADA) activity in patients with meningitis. Int J Sci Res (Ahmedabad). 2017; 6(10): 186-89. Available from: https://www.worldwidejournals.com/international-journal-of-scientific-research-(IJSR)/fileview.php?val=October_2017_1506781138__67.pdf.
37. Geiger JD, Khan N, Murugan M, Boison D. Possible Role of Adenosine in COVID-19 Pathogenesis and Therapeutic Opportunities. Front Pharmacol. 2020; 11: 594487. doi: https://doi.org/10.3389/fphar.2020.594487.
38. Al Talib HM. The Role of Adenosine Deaminase Levels in The Diagnosis of COVID-19 Infection. HIV Nursing. 2022; 22(2): 3217–20. Available from: https://hivnursing.net/index.php/hiv/article/view/916.
39. Yuan X, Lee JW, Bowser JL, Neudecker V, Sridhar S, Eltzschig HK. Targeting Hypoxia Signaling for Perioperative Organ Injury. Anesth Analg. 2018; 126(1): 308-21. doi: https://doi.org/10.1213/ane.0000000000002288.
40. Danese E, Montagnana M. An Historical Approach to the Diagnostic Biomarkers of Acute Coronary Syndrome. Ann Transl Med. 2016; 4(10): 194. doi: https://doi.org/10.21037/atm.2016.05.19.
41. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146(1): 110-18. doi: https://doi.org/10.1016/j.jaci.2020.04.006.
42. Lim MA, Pranata R, Huang I, Yonas E, Soeroto AY, Supriyadi R. Multiorgan Failure With Emphasis on Acute Kidney Injury and Severity of COVID-19: Systematic Review and Meta-Analysis. Can J Kidney Health Dis. 2020; 7: 2054358120938573. doi: https://doi.org/10.1177/2054358120938573.
43. Serin I, Sari ND, Dogu MH, et al. A new parameter in COVID-19 pandemic: initial lactate dehydrogenase (LDH)/Lymphocyte ratio for diagnosis and mortality. J Infect Public Health. 2020; 13(11): 1664-70. doi: https://doi.org/10.1016/j.jiph.2020.09.009.
44. Cichoż-Lach H, Michalak A. Liver injury in the era of COVID-19. World J Gastroenterol. 2021; 27(5): 377-90. doi: https://doi.org/10.3748/wjg.v27.i5.377.

45. Feng G, Zheng KI, Yan QQ, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. J Clin Transl Hepatol. 2020; 8(1): 18-24. doi: https://doi.org/10.14218/jcth.2020.00018.
46. Yao Y, Cao J, Wang Q, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J Intensive Care. 2020; 8: 49. doi: https://doi.org/10.1186/s40560-020-00466-z.
47. Logothetis CN, Weppelmann TA, Jordan A, Hanna C, Zhang S, Charkowick S, Oxner A. D-Dimer Testing for the Exclusion of Pulmonary Embolism Among Hospitalized Patients With COVID-19. JAMA Netw Open. 2021; 4(10): e2128802. doi: https://doi.org/10.1001/jamanetworkopen.2021.28802.
48. Tomaszewska A, Rustecka A, Lipińska-Opałka A, Piprek RP, Kloc M, Kalicki B, Kubiak JZ. The Role of Vitamin D in COVID-19 and the Impact of Pandemic Restrictions on Vitamin D Blood Content. Front Pharmacol. 2022; 13: 836738. doi: https://doi.org/10.3389/fphar.2022.836738.
49. Luan YY, Yin CH, Yao YM. Update Advances on C-Reactive Protein in COVID-19 and Other Viral Infections. Front Immunol. 2021; 12: 720363. doi: https://doi.org/10.3389/fimmu.2021.720363.