Biomedicine and Chemical Sciences 1(4) (2022) 264-269

35-BCS-1090-276

Content lists available at:
https://journals.irapa.org/index.php/BCS/issue/view/15

Biomedicine and Chemical Sciences

Journal homepage: https://journals.irapa.org/index.php/BCS

Changes in White Blood Cells, D-Dimer and Lactate Dehydrogenase Level in Covid-19 Patients: A Comparative Study

Mohammed Ali Mones[a*], Haider Abd Jabbar Al-Ammar[b], Aqeel Raheem AL-Barqawi[c], May Jaleel Abed[d]

[a,b] Department of Clinical Biochemistry, College of Medicine, University of Al-Qadisiyah, Al-Diwaniyah – Iraq
[b] Collage of Medicine, University of Al-Qadisiyah, Al-Diwaniyah – Iraq
[c] Collage of Medicine, Medical Chemistry Branch, University of Al-Qadisiyah, Al-Diwaniyah – Iraq

ARTICLE INFO

Article history:
Received on: July 9, 2022
Revised on: August 7, 2022
Accepted on: August 7, 2022
Published on: October 01, 2022

Keywords:
COVID-19
D-Dimer
LDH
White blood cells

ABSTRACT

Coronavirus is a new pandemic disease that began in Wuhan, China, and has since spread over the globe. The number of COVID-19 cases reported daily in Iraq has slowly increased. This study aims to investigate the effect of Covid-19 on the normal range of White Blood Cells (WBC), D-Dimer, and Lactate Dehydrogenase (LDH). This study looked at 65 patients who had tested positive for SARS-CoV-2 using polymerase chain reaction analysis. Patients with mild symptoms and a normal CT scan for the chest were separated into three groups: those with mild symptoms and a normal CT scan for the chest, those with intermediate disease presenting with fever and cough, other respiratory symptoms, and those with severe disease. At the time of the study, all patients' data were collected from Al-Diwaniyah Teaching hospital admission for parameters of White blood cell count, lactate dehydrogenase (LDH) levels, and D-Dimer levels, from December 27, 2020, to April 1, 2021. The WBC count, D-Dimer, and LDH in the patients with COVID-19 were higher than that of the control group (8.15 X109/L versus 390 ng/ml and 593 U/L), respectively, and the difference was highly significant ($p < 0.001$). There was no significant difference in WBC count and LDH among patients according to the severity ($p > 0.05$). A larger leukocyte count, D-Dimer, and LDH increased the risk of death. These signs can reliably predict a patient's prognosis while in the hospital. Our study's best lab marker was LDH.

Copyright © 2022 Biomedicine and Chemical Sciences. Published by International Research and Publishing Academy – Pakistan, Co-published by Al-Furat Al-Awsat Technical University – Iraq. This is an open access article licensed under CC BY:

(https://creativecommons.org/licenses/by/4.0)

1. Introduction

Wuhan City in China was the center of an unexpected outbreak of pneumonia in December 2019. Chinese scientists discovered a new coronavirus, dubbed SARS coronavirus two, in January 2020 and has since been renamed (SARS-CoV-2) (Kermali et al., 2020). COVID-19 confirmed cases reached over 90.000.000 on January 12, 2021, with over 1.900.000 deaths. Iraq is one of the top-ranked countries afflicted by COVID-19, with over 600.000 confirmed cases and over 12.000 deaths (Kaftan et al., 2021).

Due to genetic homologies between coronaviruses, COVID-19 had a clinical course and pathological findings that were similar to the (SARS) and (MERS) (Huang et al., 2020). WBCs or Leukocyte count is an Even in the presence of COVID-19, the most important predictor of a patient's health is their age (Dey & Mukherjee, 2021).

Leucocytes are white blood cells produced in the bone marrow and lymphoid tissue that help the immune system defend the body against foreign invaders and infectious illnesses (Togacar, Ergen & Sertkaya, 2019). A high WBC

*Corresponding author:** Mohammed Ali Mones, Department of Clinical Biochemistry, College of Medicine, University of Al-Qadisiyah, Al-Diwaniyah – Iraq

E-mail: **ch.majm91@gmail.com**

How to cite:

Mones, M. A., Al-Ammar, H. A. J., AL-Barqawi, A. R., & Abed, M. J. (2022). Changes in White Blood Cells, D-Dimer and Lactate Dehydrogenase Level in Covid-19 Patients: A Comparative Study. *Biomedicine and Chemical Sciences, 1(4)*, 264–269.

DOI: **https://doi.org/10.48112/bcs.v1i4.276**

count, also known as leukocytosis, indicates that the body is fighting an infection, and COVID-19 is no exception. According to research, people who test positive for COVID-19 but have no symptoms often have a high WBC count, particularly lymphocytes (Han et al., 2020). Significant links between WBC count and death have been discovered (Zhu et al., 2021).

D-Dimer Plasma coagulation results in the generation of soluble fibrin. D-Dimer is produced as a byproduct of crosslinked fibrin degradation. As a result, it is a sensitive biomarker for venous thromboembolism diagnosis (Shorr et al., 2002) D-Dimer levels are associated with coagulopathy, and high levels are a predictor of Covid-19 development (Magro, 2020). LDH is an intracellular enzyme found in cells in almost all organ systems (Yameny, 2021). This enzyme can be present in almost all live cells. Because it is linked to metabolic acidosis, it is an essential indication of cytokine storm in Covid-19 infection (Chhetri et al., 2020). During a 14-day follow-up, we evaluated the D-Dimer and LDH and their correlation with the modification of (WBC) in a group of 65 confirmed COVID-19 patients. We also wanted to see if there was a link between WBC, D-Dimer, LDH levels, and illness severity.

2. Materials and Methods

2.1. Study Population

The participants in the study were 125 persons ranging in age from 18 to 82 years, 65 COVID-19 patients from Iraq's Al-Diwaniyah Teaching Hospital, and 60 healthy controls. COVID-19 had 42 men and 23 women, compared to 31 men and 29 women in the healthy controls. Based on clinical symptoms, laboratory testing, and chest computed tomography (CT) scans, all of the cases were classified as mild, moderate, and severe as follows:

Mild: People with COVID-19 symptoms (fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but no shortness of breath, dyspnea, or abnormal chest imaging.

Moderate: Individuals with the moderate illness have an oxygen saturation (SpO2) of 94 percent on room air at sea level and show indications of lower respiratory disease during clinical examination or imaging.

Sever: Patients with COVID-19 with a SpO2 of 94 percent on room air at sea level, a PaO2/FiO2 of 300 mm Hg, a respiratory rate of >30 breaths/min, or lung infiltrates of >50 percent are deemed to have severe sickness. The clinical condition of these patients rapidly deteriorates. A nasal cannula or a high-flow oxygen device is used.

The control group consists of 60 uninfected people who have not previously displayed signs of coronavirus. A doctor makes the diagnostic and patient selection at Al-Diwaniyah Teaching Hospital who do not have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) and PCR negative. In the Elecsys immunoassay system, electrochemiluminescent immunoassay (ECLIA) was used. Between the Covid-19 and the control group, all of the parameters were evaluated and compared. This study was approved by the Ethics Committee of the Medicine College and the Ministry of Health. Under the Ministry of Health's guidance, a questionnaire was conducted with the permission of each person who participated in the study.

2.2. Statistical Analysis

The data were collected, summarized, analyzed, and presented using the statistical package for social sciences (SPSS) version 23 and Microsoft Office Excel 2010. Quantitative (numeric) data were initially tested for normality distribution using the Kolmogorov-Smirnov test. At the same time, qualitative (categorical) variables were reported as number and percentage as well as median (a measure of central tendency) and inter-quartile range (a measure of inter-quartile variation), while non-normally distributed numerical variables were expressed as median (a measure of central tendency) and standard deviation (an index of dispersion).

3. Results and Discussion

This research aimed to look at several blood parameters in COVID-19 patients who had been proven positive. Compared the severity of COVID-19 disease to a number of blood markers, We divided the patients into groups based on the severity of their illnesses in this study. Mild, moderate, severe, and categories were assigned to the patients. There were 16 miles, 28 intermediate, and 21 severe patients out of 65. The increasing age was an essential factor associated with poor outcomes with increased WBC, D-Dimer, and LDH.

The comparison of demographic characteristics between the patients with COVID-19 and the healthy controlled persons is shown in Table 1. There was no significant difference in mean age between the controlled group and patients with COVID-19, 48.52 ±16.02 years versus 51.74 ±15.27 years, respectively (p = 0.252). The controlled group included 31 (51.7 %) males and 29 (48.3 %).

Table 1
Comparison of demographic characteristics between patients with COVID-19 and healthy controlled persons

Characteristic	Control group n = 60	COVID-19 group n = 65	P-value
Age (years)			
Mean ±SD	48.52 ±16.02	51.74 ±15.27	0.252 I
Range	18 -82	21 -75	NS

n: the number of cases; SD: standard deviation; I: independent samples t-test; NS: not significant at P-value > 0.05.

Our results showed a significant increase was observed in the WBCs levels in patients with COVID-19 as compared with the controlled group 8.15 (5.92) and 6.30 (3.16), respectively, and the difference was highly significant (p < 0.001) as explained in Table 2. The current study's results were similar to the study (Javanian et al., 2020), .which has been previously reported that the WBCs count increased in patients with the COVID-19 disease. One of the fibrin breakdown products (FDPs) is D-Dimer. It has an 8-hour half-life and is detected in the blood around 2 hours after crossed-fibrin formation. It rises with age; the D-Dimer molecule consists of 2 crosslinked D fragments from fibrinogen, the smallest fibrinolysis-specific degradation product found in circulation (Zhang et al., 2018).

In this study, there was a significant (p<0.001) increase in the D-Dimer levels in patients with COVID-19 as they are compared with healthy individuals 390.00(618.00),277.74(172.54) respectively they are shown in Table 2, The results of the study have corresponded with other studies (Ye et al., 2020; Zhang et al., 2020a), which showed elevated levels in the D-Dimer levels in A group of patients with COVID-19. Patient mortality might be predicted by D-Dimer levels of more than 2.0 g/mL (a fourfold increase) upon admission, indicating that D-Dimer could serve as an early and useful indicator for managing Covid-19 patients (Zhang et al., 2020b). The virus may cause the LDH to enter the bloodstream by damaging cells with ACE2 (Cure & Cure, 2020). LDH elevations are related to cell damage, inflammation, or both. Cell lysis occurs, or cell membranes are damaged, and LDH will be released into the extracellular space (Chen et al., 2020).

Table 2
Comparison of markers of inflammation between patients with COVID-19 and healthy control subjects

Characteristic	Control group n = 60	COVID-19 group n = 65	P-value
WBC X109/L			
Median (IQR)	6.30 (3.16)	8.15 (5.92)	< 0.001 M
Range	3.5 -10.2	2.92 -21.17	HS
D-dimer (ng/ml)			
Median (IQR)	277.74 (172.54)	390.00 (618.00)	< 0.001 M
Range	48.3 -460.48	42.32 -7500	HS
LDH (U/L)			
Median (IQR)	188.00 (33.00)	593.00 (350.00)	< 0.001 M
Range	140 -255.16	169 -1623	HS

n: number of cases; IQR: inter-quartile range; I: independent samples t-test; M: Mann Whitney test; HS: highly significant at P-value ≤ 0.01

Table 3
Comparison of mean age of patients with COVID-19 according to the severity of disease

Severity of disease	Number of cases	Mean age (years)	SD	P-value
Mild	16	43.06	15.21	0.007 HS
Moderate	28	51.54	15.43	
Severe	21	58.62	11.88	
Total	65	51.74	15.27	

n: number of cases; SD: standard deviation; O: One-way ANOVA; HS: highly significant at P-value ≤ 0.01

Patients with severe disease increased WBC count. WBC count at admission is significantly correlated with death in COVID-19 patients; a higher level of WBC count (≥ 6.16×10^9/L) should be given more attention in the treatment of COVID-19 (Zhu *et al.*, 2021). A significant increase in WBCs may signify clinical worsening and an increased risk of a poor outcome (Henry et al., 2020). Cases of chest CT scans stratified COVID-19 severity by cases of patient severe, moderate, and mild. In the present study, a high D-Dimer elevation in the severe cases (847.00 (1947.00) as it is compared with mild and moderate cases 216.00 (108.25), 432.50 (523.25) is respectively shown in Table 4. The assay may be used early as a marker of severity before chest CT scans or as a complement to CT and clinical staging. The level was high in severe cases. There was a highly significant difference in D-Dimer level among patients according to severity (p < 0.001); the level was high in severe cases. The present study's consequences correspond with previous studies (Fazio et al., 2021; Soni et al., 2020), which show that COVID-19 patients frequently have increased levels of D-Dimer. Among patients admitted to the hospital with COVID-19, D-Dimer levels correlate with disease severity and serve as a good predictive sign for mortality.

An increase in D-Dimer indicated a hypercoagulable state in patients with Covid-19, which might be attributed to several reasons, one of the causes is that virus infections are usually accompanied by an aggressive pro-inflammatory response and insufficient control of an anti-inflammatory response (Wong et al., 2017). And another reason is that the hypoxia found in severe Covid-19 can stimulate thrombosis by increasing blood viscosity and a hypoxia-inducible transcription factor-dependent signaling pathway (Gupta et al., 2019; Tang et al., 2020).

It is known that D-specificity dimers for the diagnosis of venous thromboembolism are limited; however, the most sensitive change in coagulation parameters in COVID-19 is the increase in D-Dimer value, dimer's which indicates an increased risk for developing thrombosis. In addition, because the D-Dimer is known to be a mixture of weight fragments, tests can give results in weight for volume units or as fibrinogen equivalent units (FEU). Comparing findings from different tests may not be accurate (Conte et al., 2021). When plasmin cleaves fibrin to break down clots, one of the fragments produced is D-Dimers. The essays are frequently used as a diagnostic approach to rule out thrombosis. Any pathologic or non-pathologic event that promotes fibrin production or breakdown, on the other hand, increases plasma D-Dimer levels (Sproul et al., 2018; Linkins & Takach Lapner, 2017).

Fibrinogen is cleaved by thrombin, which leads to the production of fibrin monomer (FM). FMs rapidly react with each other by forming a two-stranded fibrous polymer. The polymers then aggregate laterally to form fibers. Activated factor XIII covalently binds adjacent D regions, which stretch the fibrin thread, increase the stiffness of the clot, and make it more resistant to lysis by plasmin. Other crosslinks also occur. During fibrinolysis, plasmin can Cleave the fibrin polymers between the adjacent D and E regions, but the covalently bound D regions cannot be separated. This results in fibrinolytic products. They are of various sizes, contain a "D-Dimer" motif, and when small enough, they are soluble (Hardy et al., 2020). In this study, increased LDH levels of LDH were observed in patients with COVID-19 as compared with the controlled group 593.00 (350.00) and 188.00 (33.00), respectively, as shown in Table 2.

The levels of LDH in patients with severe cases had higher levels of LDH 635.00 (383.50) as compared with mild and moderate cases 560.00 (301.00), 560.50 (273.25) Table 4. These outcomes were matched with (Lu et al., 2020), which found significant differences in the levels of LDH in severe, mild, and moderate cases. Upper and lower respiratory tract infection with SARS-COV-2 may trigger an early acute respiratory inflammatory response, releasing pro-inflammatory cytokines such as interleukin-1, followed by inflammasome activation and production of active mature interleukin-1, a mediator of pulmonary inflammation and fibrosis (Conti et al., 2020). Lung parenchymal cells and local inflammatory cells could be sources of high LDH levels (Kanchana et al., 2013); LDH levels that are high in the blood are an indirect indicator of lung tissue injury (Mura et al., 2007).

Table 4
Comparison of inflammatory markers according to the severity of disease

Characteristic	Mild	Moderate	Severe	P-value
	n = 16	n = 28	n = 21	
WBC	7.05 (4.77)	8.70 (5.98)	8.60 (5.48)	0.182 K NS
D-Dimer	216.00 (108.25)	432.50 (523.25)	847.00 (1947.00)	< 0.001 K HS
LDH	560.00 (301.00)	560.50 (273.25)	635.00 (383.50)	0.116 K NS

n: number of cases; K: Kruskal Wallis; HS: highly significant at P-value ≤ 0.01; NS: not significant at P-value > 0.05

ROC curve analysis was used to assess further the predicting power of the two diagnostic factors mentioned above. LDH showed higher sensitivity (0.969) in the ROC curve and the area under the curve (AUC) (0.986). However, D-Dimer showed higher sensitivity (0.422) in the ROC curve, the area under the curve (AUC) (0.677).WBC showed higher sensitivity (0.344) in the ROC curve, the area under the curve (AUC) (0.681), as shown in Table 5.

Table 5
The characteristics of receiver operator characteristics (ROC) curve analysis for WBC, D-Dimer, and LDH

Characteristic	LDH	D-Dimer	WBC
Cutoff	≤0.9	≤0.9	≤0.9
AUC	0.986	0.677	0.681
95CI%	0.963 to1.000	0.581 to 0.773	0.586 to 0.777
P-value	0.001	0.001	0.001
Sensitivity	0.969	0.422	0.344
Specificity	1	1	1
Accuracy	98%	67%	68%

AUC: area under the curve; CI: confidence interval; HS: highly significant at P-value ≤ 0.001

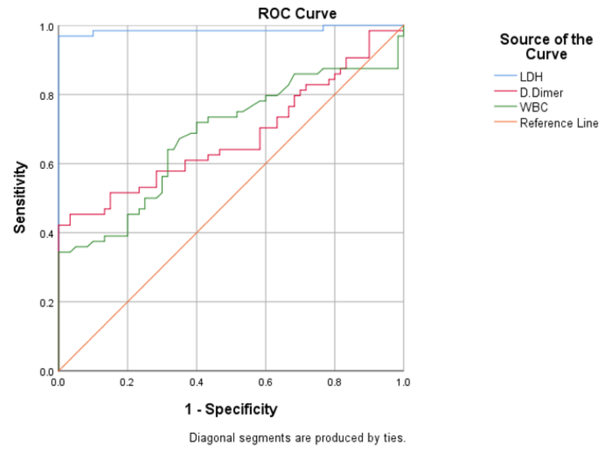

Fig. 1. ROC curve for lab parameters

4. Conclusion

A higher level of the leukocyte count, D-Dimer, and LDH were all linked to an increased risk of death. Patients' prognoses can be accurately predicted by monitoring these markers while in the hospital. LDH was the best laboratory marker in our study Our findings, taken together, can be useful in clinical practice, but they need to be confirmed by larger, multi-center investigations.

4.1. Recommendations

Measuring WBC, LDH, and D-Dimer, a larger sample size of patients with COVID-19. After a full recovery, a follow-up study for COVID-19 patients investigates WBC, LDH, and D-Dimer levels.

4.2. Limitation

Our study had some limitations. This study was conducted at a single centre with a limited sample size, time, lack of follow-up, and a small cohort of consenting patients. Furthermore, because many patients died in the hospital and outcomes were unknown at the time of writing, we only collected clinical data within three months for our analysis. COVID-19 is a fast-spreading virus with a wide range of severity. A bigger cohort study of COVID-19 patients worldwide would help better to identify the disease's clinical characteristics and risk factors.

4.3. Abbreviations

- AUC = area under the curve
- CT = computerized tomography
- ECLIA = Elecsys immunoassay system, electrochemiluminescent immunoassay
- FDPs = fibrin breakdown products
- FEU = fibrinogen equivalent units
- FM = fibrin monomer
- LDH = lactate dehydrogenase
- MERS = middle east respiratory syndrome
- ROC = receiver operating characteristic
- SARS = is a severe acute respiratory syndrome
- So2 = saturation oxygen
- SPSS = statistical package for the social sciences

- WBCs = White blood cells

Competing Interests

The authors have declared that no competing interests exist.

References

Chen, X. Y., Huang, M. Y., Xiao, Z. W., Yang, S., & Chen, X. Q. (2020). Lactate dehydrogenase elevations is associated with severity of COVID-19: a meta-analysis. Critical Care, 24(1), 1-3. **https://doi.org/10.1186/s13054-020-03161-5**

Chhetri, S., Khamis, F., Pandak, N., Al Khalili, H., Said, E., & Petersen, E. (2020). A fatal case of COVID-19 due to metabolic acidosis following dysregulate inflammatory response (cytokine storm). IDCases, 21, e00829. **https://doi.org/10.1016/j.idcr.2020.e00829**

Conte, G., Cei, M., Evangelista, I., Colombo, A., Vitale, J., Mazzone, A., & Mumoli, N. (2021). The meaning of D-dimer value in COVID-19. Clinical and Applied Thrombosis/Hemostasis, 27, **https://doi.org/10.1177/10760296211017668**

Conti, P., Ronconi, G., Caraffa, A. L., Gallenga, C. E., Ross, R., Frydas, I., & Kritas, S. K. (2020). Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents, 34(2), 327-331.

Cure, E., & Cure, M. C. (2020). Can dapagliflozin have a protective effect against COVID-19 infection? A hypothesis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14(4), 405-406. **https://doi.org/10.1016/j.dsx.2020.04.024**

Dey, J., & Mukherjee, S. (2021). Wireless COVID-19 telehealth: Leukocytes encryption guided by amino acid matrix. Wireless Personal Communications, 120(2), 1769-1789. **https://doi.org/10.1007/s11277-021-08534-9**

Fazio, S., Tufano, A., & de Simone, G. (2022, February). Sustained high D-dimer in outpatients who have recovered from mild to moderate coronavirus disease 2019 (COVID-19). In Seminars in Thrombosis and Hemostasis (Vol. 48, No. 01, pp. 115-117). Thieme Medical Publishers, Inc.. **https://doi.org/10.1055/s-0041-1729857**

Gupta, N., Zhao, Y. Y., & Evans, C. E. (2019). The stimulation of thrombosis by hypoxia. Thrombosis Research, 181, 77-83. **https://doi.org/10.1016/j.thromres.2019.07.013**

Han, H., Xu, Z., Cheng, X., Zhong, Y., Yuan, L., Wang, F., ... & Xia, Y. (2020). Descriptive, retrospective study of the clinical characteristics of asymptomatic COVID-19 patients. MSphere, 5(5), e00922-20. **https://doi.org/10.1128/mSphere.00922-20**

Hardy, M., Lecompte, T., Douxfils, J., Lessire, S., Dogné, J. M., Chatelain, B., ... & Mullier, F. (2020). Management of the thrombotic risk associated with COVID-19: guidance for the hemostasis laboratory. Thrombosis Journal, 18(1), 1-16. **https://doi.org/10.1186/s12959-020-00230-1**

Henry, B. M., De Oliveira, M. H. S., Benoit, S., Plebani, M., & Lippi, G. (2020). Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM), 58(7), 1021-1028. **https://doi.org/10.1515/cclm-2020-0369**

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... & Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet, 395(10223), 497-506. **https://doi.org/10.1016/S0140-6736(20)30183-5**

Javanian, M., Bayani, M., Shokri, M., Sadeghi-Haddad-Zavareh, M., Babazadeh, A., Yeganeh, B., ... & Ebrahimpour, S. (2020). Clinical and laboratory findings from patients with COVID-19 pneumonia in Babol North of Iran: a retrospective cohort study. Romanian Journal of Internal Medicine, 58(3), 161-167. **https://doi.org/10.2478/rjim-2020-0013**

Kaftan, A. N., Hussain, M. K., Algenabi, A. A., Naser, F. H., & Enaya, M. A. (2021). Predictive Value of C–reactive Protein, Lactate Dehydrogenase, Ferritin and D-dimer Levels in Diagnosing COVID-19 Patients: a Retrospective Study. Acta Informatica Medica, 29(1), 45-50. **https://doi.org/10.5455%2Faim.2021.29.45-50**

Kanchana, S., Kanchana, S., Vijitsopa, T., Thammakumpee, K., Yamwong, S., & Sawanyawisuth, K. (2013). Clinical factors predictive of pneumonia caused by pandemic 2009 H1N1 influenza virus. The American Journal of Tropical Medicine and Hygiene, 88(3), 461. **https://doi.org/10.4269%2Fajtmh.12-0132**

Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z., & Harky, A. (2020). The role of biomarkers in diagnosis of COVID-19–A systematic review. Life Sciences, 254, 117788. **https://doi.org/10.1016/j.lfs.2020.117788**

Linkins, L. A., & Takach Lapner, S. (2017). Review of D-dimer testing: good, Bad, and Ugly. International Journal of Laboratory Hematology, 39, 98-103. **https://doi.org/10.1111/ijlh.12665**

Lu, Y., Sun, K., Guo, S., Wang, J., Li, A., Rong, X., ... & Wang, S. (2020). Early warning indicators of severe COVID-19: A single-center study of cases from Shanghai, China. Frontiers in Medicine, 7, 432. **https://doi.org/10.3389/fmed.2020.00432**

Magro, G. (2020). Cytokine Storm: is it the only major death factor in COVID-19 patients? Coagulation role. Medical Hypotheses, 142, 109829. **https://doi.org/10.1016%2Fj.mehy.2020.109829**

Mura, M., Andrade, C. F., Han, B., Seth, R., Zhang, Y., Bai, X. H., ... & Liu, M. (2007). Intestinal ischemia-reperfusion-induced acute lung injury and oncotic cell death in multiple organs. Shock, 28(2), 227-238. **https://doi.org/10.1097/SHK.0b013e318033e927**

Shorr, A. F., Thomas, S. J., Alkins, S. A., Fitzpatrick, T. M., & Ling, G. S. (2002). D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ill patients. Chest, 121(4), 1262-1268. https://doi.org/10.1378/chest.121.4.1262

Soni, M., Gopalakrishnan, R., Vaishya, R., & Prabu, P. (2020). D-dimer level is a useful predictor for mortality in patients with COVID-19: Analysis of 483 cases. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 14(6), 2245-2249. https://doi.org/10.1016/j.dsx.2020.11.007

Sproul, E., Nandi, S., & Brown, A. (2018). Fibrin biomaterials for tissue regeneration and repair. In Peptides and proteins as biomaterials for tissue regeneration and repair (pp. 151-173). Woodhead Publishing. https://doi.org/10.1016/B978-0-08-100803-4.00006-1

Tang, N., Bai, H., Chen, X., Gong, J., Li, D., & Sun, Z. (2020). Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. Journal of thrombosis and haemostasis, 18(5), 1094-1099. https://doi.org/10.1111/jth.14817

Togacar, M., Ergen, B., & Sertkaya, M. E. (2019). Subclass separation of white blood cell images using convolutional neural network models. Elektronika ir Elektrotechnika, 25(5), 63-68. https://doi.org/10.5755/j01.eie.25.5.24358

Wong, J. P., Viswanathan, S., Wang, M., Sun, L. Q., Clark, G. C., & D'elia, R. V. (2017). Current and future developments in the treatment of virus-induced hypercytokinemia. Future Medicinal Chemistry, 9(2), 169-178. https://doi.org/10.4155/fmc-2016-0181

Yameny, A. A. (2021). Lactate dehydrogenase level as a COVID-19 biomarker. Journal of Bioscience and Applied Research, 7(1), 29-34. https://dx.doi.org/10.21608/jbaar.2021.173662

Ye, W., Chen, G., Li, X., Lan, X., Ji, C., Hou, M., ... & Yang, L. (2020). Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respiratory research, 21(1), 1-7. https://doi.org/10.1186/s12931-020-01428-7

Zhang, H., Wang, X., Fu, Z., Luo, M., Zhang, Z., Zhang, K., ... & Chen, Y. (2020a). Potential factors for prediction of disease severity of COVID-19 patients. MedRxiv. https://doi.org/10.1101/2020.03.20.20039818

Zhang, L., Long, Y., Xiao, H., Yang, J., Toulon, P., & Zhang, Z. (2018). Use of D-dimer in oral anticoagulation therapy. International Journal of Laboratory Hematology, 40(5), 503-507. https://doi.org/10.1111/ijlh.12864

Zhang, L., Yan, X., Fan, Q., Liu, H., Liu, X., Liu, Z., & Zhang, Z. (2020b). D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. Journal of thrombosis and haemostasis, 18(6), 1324-1329. https://doi.org/10.1111/jth.14859

Zhu, B., Feng, X., Jiang, C., Mi, S., Yang, L., Zhao, Z., ... & Zhang, L. (2021). Correlation between white blood cell count at admission and mortality in COVID-19 patients: a retrospective study. BMC Infectious Diseases, 21(1), 1-5. https://doi.org/10.1186/s12879-021-06277-3