

# Accuracy Of Serum Ferritin, C-Reactive Protein, Lactate Dehydrogenase And D. Dimers In Assessing Severity And Outcome Of COVID-19 Infection

Aziz-Un-Nisa<sup>1</sup>, Dur Muhammad<sup>2</sup>, Sultan Zaib<sup>3</sup>, Ibrahim Khan<sup>4</sup>, Imran Zaib<sup>5</sup>, Sehrish Saleem<sup>6</sup>

## Abstract

**Objective:** COVID-19 emerged as a pandemic. In the beginning, due to the rapid spread of the virus, it was difficult to understand fully its pathogenesis but various inflammatory markers were found to be raised. Along with the detection of the virus by polymerase reaction (PCR), studies of these markers not only help in diagnosis but also in assessing the prognosis of COVID-19 infection.

**Material and methods:** This cross-sectional study was conducted in the Capital Hospital, CDA Islamabad from 15 December 2021 to 30<sup>th</sup> June 2022. After obtaining consent, data on various inflammatory markers was recorded and analyzed by percentage/ frequency distribution. A chi-square test was applied and p-values were calculated (significant p-value= $<0.05$ ). Sensitivity, specificity, positive and negative predictive values, area under curve (AUC) and accuracy were calculated by using SPSS, version 23.

**Results:** A total of 185 COVID-19 PCR-positive patients were included in the study. 112(60.5%) were men and 73 (39.5%) were women. 165(89.2%) patients were  $> 40$  years of age. 117 (63.2%) patients had mild /moderate disease and 68(36.8%) had severe disease. 162 (87.5%) patients were discharged and 23 (12.4%) expired. AUC about the severity of disease was 0.603 for C- reactive protein (CRP), 0.593 for lactate dehydrogenase (LDH), 0.525 for D. dimers and 0.619 for ferritin. Accuracy about disease severity was as follows: CRP 57.4%, D. dimers 52.4 %, ferritin 57.9% and LDH 55.7%. AUC about the outcome of COVID-19 was 0.699 for CRP, 0.668 for LDH, 0.742 for D. dimers and 0.677 for ferritin. Accuracy of inflammatory markers about the outcome was as follows: CRP 45.9%, D. dimers 61.2%, LDH 48.1% and ferritin 46.9%.

**Conclusion:** Serum ferritin showed the highest accuracy (57.9%) in assessing the COVID-19 severity and D. dimer was more accurate (61.2%) in assessing disease outcome.

**Keywords:** COVID-19 infection, inflammatory markers, area under curve (AUC), accuracy.

<sup>1</sup> Physician and HOD Medicine, Capital Hospital, Islamabad; <sup>2,3,4,5</sup> Post-Graduate Trainee, Capital Hospital, Islamabad; <sup>6</sup> Stacionian, CPSP, Islamabad.

**Correspondence:** Dr Aziz-Un-Nisa, Physician and HOD Medicine, Capital Hospital, Islamabad. Email: drnisaabbasi@gmail.com

**Cite this Article:** Aziz-Un-Nisa, Muhammad, D., Zaib, S., Khan, I., Zaib, I., & Saleem, S. (2023). Accuracy Of Serum Ferritin, C-Reactive Protein, Lactate Dehydrogenase And D. Dimers In Assessing Severity And Outcome Of COVID-19 Infection. *Journal of Rawalpindi Medical College*, 27(3). <https://doi.org/10.37939/jrmc.v27i3.2207>.

Received January 19, 2023; accepted August 12, 2023; published online September 26, 2023

## 1. Introduction

Coronavirus (CoV) is a member of the family Coronaviridae of the order Nidovirales. Coronavirus disease 2019<sup>1</sup> is also more commonly referred to as (COVID-19). It is an enveloped single-stranded RNA virus, which is highly contagious, causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus infection was first reported in Wuhan<sup>2</sup>, Hubei province, China, in December 2019. WHO declared it a global pandemic in March 2020. It has a catastrophic effect on the world's population, resulting in more than 6 million deaths worldwide. Five SARS-CoV-2 variants<sup>3</sup> have been identified since the beginning of the pandemic which are: Alpha variant: originated in the United Kingdom (UK) in late December 2020  
Beta variant: first reported in South Africa in December 2020

Gamma variant: first reported in Brazil in early January 2021

Delta variant: first reported in India in December 2020

Omicron variant: first reported in South Africa in November 2021

The presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness and may prove fatal. Symptoms<sup>4</sup> may develop two days to two weeks after exposure to the virus. The common symptoms which may indicate COVID-19 include fever or chills, cough, difficulty in breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhoea. Among other reported symptoms sputum production, malaise, respiratory distress, and neurologic disorders which include dizziness, headache, stroke, encephalopathy/encephalitis, seizures, Guillain–

Barré syndrome and psychiatric dysfunctions are commonly reported.

The most common serious manifestation of COVID-19 upon the initial presentation is pneumonia. Other complications include acute respiratory distress syndrome, cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, and multi-organ failure. Approximately 5% of patients with COVID-19, and 20% of those hospitalized, experience severe symptoms necessitating intensive care.

The common complications among hospitalized patients include pneumonia (75%), ARDS (15%), AKI (9%), and acute liver injury (19%). Cardiac injury<sup>6</sup> has been increasingly noted, including troponin elevation, acute heart failure, dysrhythmias, and myocarditis. 10 to 25% of hospitalized patients with COVID-19 experience pro-thrombotic coagulopathy resulting in venous and arterial thromboembolic events. Neurologic manifestations include impaired consciousness and stroke. ICU case fatality reported that up to 40% of patients with comorbidities<sup>7</sup> like diabetes, hypertension, COPD, asthma and cardiac diseases were more severely affected than those with no morbidities.

COVID-19 infection can be diagnosed by taking nasal swabs in symptomatic patients. Three types of testing methods to determine SARS-CoV-2 infection are viral nucleic acid (RNA) detection through PCR, viral antigen detection and detection of antibodies to the virus. Other tests include a complete blood picture<sup>9</sup> which shows leukopenia, leukocytosis, and lymphopenia. Acute phase reactants like lactate dehydrogenase, ferritin, D. dimers levels and procalcitonin are commonly elevated. ECG findings may be suggestive of myocardial infarction, acute myocarditis and arrhythmias. LFTs, RFTs PT, APTT and INR are also deranged due to the involvement of the liver and kidney. IL-6 is an inflammatory mediator which is released from lymphocytes during severe inflammation and activates other inflammatory cells to release tumour necrotic factors (alpha) TNF alpha and other interleukins and causes cytokine cascade which further aggravates the inflammation causing cytokine storm syndrome<sup>10</sup>. Neutrophil/lymphocyte ratio predicts the severity of COVID-19 pneumonia<sup>11</sup>. Increased levels of IL-6 in covid 19 indicate the severity of the disease and development of cytokine storm syndrome. Chest X-

ray may show consolidations, commonly bilateral and usually involve lower zones of both lungs.

Pleural effusion is an uncommon finding. Chest computed tomography (CT) scanning in patients with COVID-19-associated pneumonia usually shows ground-glass appearance.

Treatment<sup>12</sup> of COVID-19 includes antiviral (Remdesivir), anti-inflammatory (steroids), antibiotics (to prevent secondary bacterial infection), monoclonal antibodies like (Tocilizumab, Baricitinib), anticoagulation<sup>13</sup> therapy like LMWH and factor 10 inhibitors like rivaroxaban (to prevent coagulopathies).

In our study, the accuracy of various inflammatory markers is being analyzed in the 185 Covid PCR-positive patients. The results from this study will provide regional data regarding the accuracy of these markers in assessing the severity as well as outcome of COVID-19 infection. This will be helpful in the future use of these markers for diagnosis as well as progression of disease.

## 2. Materials & Methods

Our study was a cross-sectional study, conducted in the covid wards of the Capital Hospital, CDA Islamabad. The study was conducted after getting approval from the hospital ethical committee from December 2021 to June 2022. The purpose of the study was explained to the patients and verbal consent was obtained. All the required tests were done in the hospital as per entitlement and there was no financial implication on the patients.

A total of 185 patients from both male and female genders were included. Patients were 14 years of age or above. Patients with positive real-time polymerase chain reaction (PCR) were included in the study. Patients aged less than 14 years, covid PCR negative, pregnant females and patients with known malignancies were excluded from the study.

Serum ferritin, D. dimers, LDH and CRP levels were measured. Reference normal ranges were as follows: Ferritin <250 ng/ml, D. dimers <500 ng/ml, LDH <480 U/L, CRP <10 mg/dl. According to the National Institute of Health, Pakistan guidelines, patients with oxygen saturation > 90 % and with infiltrates involving < 50 % on chest x-rays were included in the mild/moderate disease group. Patients with SPO2 of <90 % and chest x-rays showing more than 50% of lung involvement

were included in the severe disease group<sup>14</sup>. Disease outcome in the form of discharged/expired was also noted. We calculated the sensitivity, specificity, positive and negative predictive values and in the end accuracy for every marker in terms of severity and outcome. Data was analyzed using the SPSS 23 system and areas under the curve were also calculated.

The chi-square test was applied as a test of significance and a p-value <0.05 was taken as significant.

### 3. Results

A total of 185 Covid-19 PCR-positive patients were included in our study. 112 (60.5%) patients were males and 73 (39.5%) were female. 89 % (n=165) of patients were > 40 years of age. 117 (63.2%) patients were suffering from mild/ moderate disease and 68 (36.8%) from severe disease. Of the 185 patients 162 (87.5%) were discharged. 12.4 % (n=23) of patients expired.

**Table 1** Studying the area under the curve about the severity of disease.

Test Result Variable(s)	Area Under the Curve				
	Area	Std. Error	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP before	<b>.603</b>	.043	.022	.518	.687
LDH before	<b>.593</b>	.044	.039	.508	.678
D. dimers before	<b>.525</b>	.045	.583	.437	.613
Ferritin before	<b>.619</b>	.043	.008	.536	.703

Markers	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	79.4%	41%	43.9%	77.4%	57.4%
D-Dimers	52.2%	52.6%	38.9%	65.6%	52.4%
Ferritin	80.6%	44.8%	45.8%	80%	57.9%
LDH	74.6%	44.8%	43.9%	75.4%	55.7%

**Table 2** Studying the accuracy of inflammatory markers in assessing the severity of COVID-19 infection.

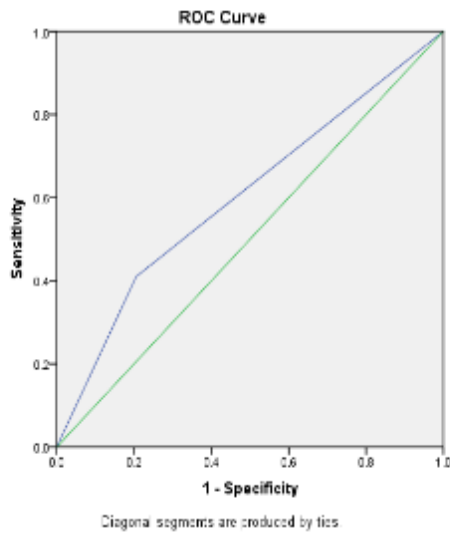
A comparison was made between various inflammatory markers and the severity of the disease. CRP was high in 69 patients in the mild/moderate-severe disease group and 54 patients in the severe disease group with a p-value of 0.003. LDH was high in 64 patients in the mild/moderate group and 50 patients of severe disease, with a p-value of 0.006. D. dimer was high in 55 patients in the first group and 35 patients in the severe disease group (p-value 0.317). Ferritin was high in 64 patients of mild/moderate disease and 54 patients in the severe disease group with a p-value of 0.000.

**Table 3** Studying the area under the curve for the inflammatory markers about outcome.

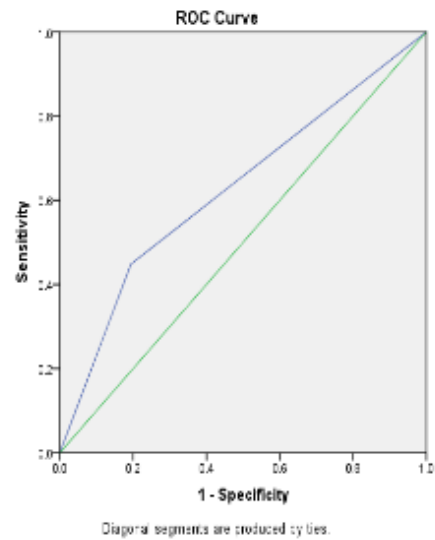
Test Result Variable(s)	Area Under the Curve				
	Area	Std. Error	Asymptotic Sig. <sup>b</sup>	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP before	.699	.045	.002	.610	.787
LDH before	.668	.052	.009	.566	.770
D. dimer before	.742	.047	.000	.650	.833
Ferritin before	.677	.049	.006	.580	.774

Markers	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	100%	38%	18.7%	100%	45.9%
D-Dimers	91.3%	56.9%	23.3%	97.8%	61.2%
LDH	91.3%	41.9%	18%	97%	48.1%
Ferritin	95.7%	40%	18.6%	98.5%	46.9%

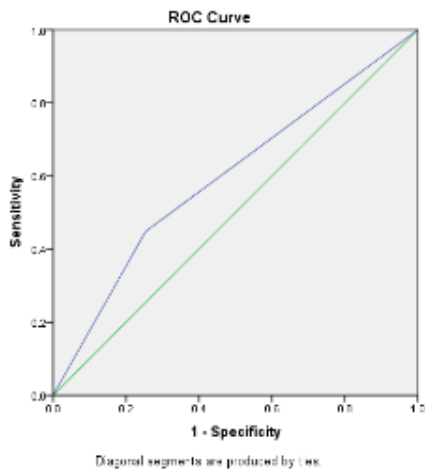
The curve of severity with CRP



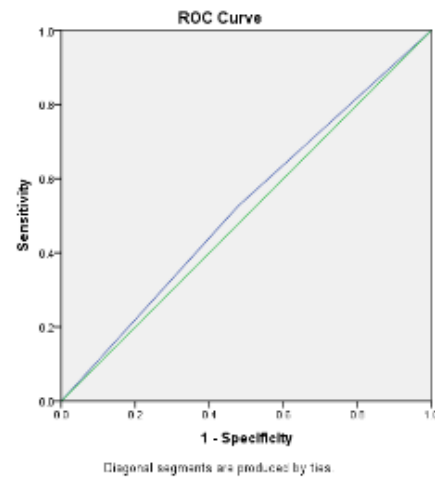
Curve of severity with ferritin



Curve of severity with LDH



The curve of severity with D. dimers

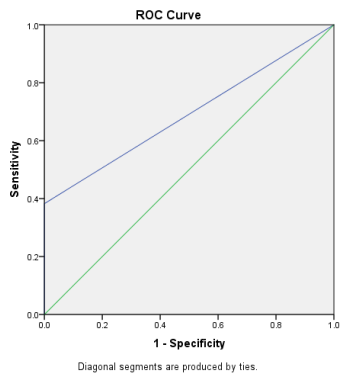


**Table 4** Studying the accuracy of inflammatory markers about outcome.

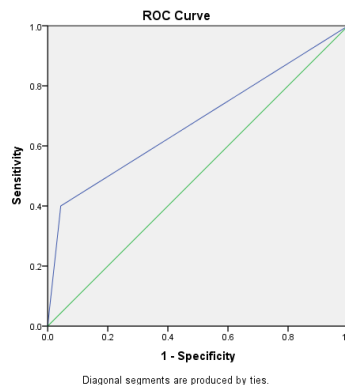
**Figure 1** ROC curve showing the relationship of disease severity with inflammatory markers

Various inflammatory markers were also studied in disease outcomes. CRP was normal in 62 patients who were discharged and high in 100 patients in the discharged group. It was high in all 23 patients who expired (p-value 0.001). LDH was normal in 67 patients and high in 93 who were discharged but it was high in 21 patients out of 23 who expired (p-value 0.001%). D. Dimers was also high in 21 patients who expired (n=23) with a p-value of 0.000. Serum ferritin was normal in 64 patients and high in 96 patients who were discharged. It was high in 21 patients who expired, p-value of 0.000.

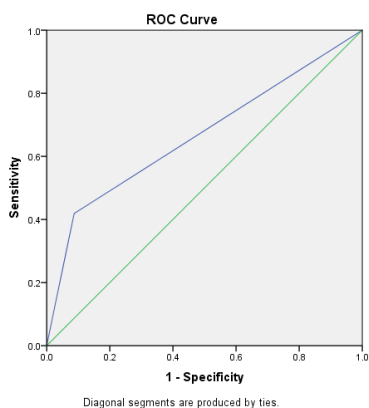
Curve of outcome with CRP



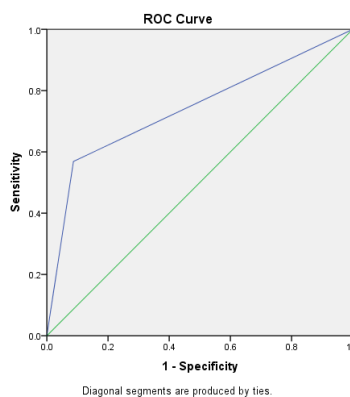
Curve of outcome with ferritin



Curve of outcome with LDH



Curve of outcome with D. dimers



**Figure-2** ROC Curve showing the relationship of disease outcome with inflammatory markers.

**5. Discussion**

Our research aimed to study the various inflammatory markers and compare them in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in assessing the severity of disease and outcome in COVID-19 patients. Our study showed that 70 patients (38.2%) were in

severe disease. We studied inflammatory markers in COVID patients and found that CRP, LDH and ferritin were significantly raised. The cut-off value for CRP was 10. CRP was significantly high in severe disease (n=56). Accuracy about disease severity was CRP 57.4%, D. dimers 52.4 %, ferritin 57.9% and LDH 55.7%. It is comparable in all four inflammatory markers under study.

Studies have shown that monitoring various inflammatory markers also helps in assessing the disease severity<sup>15</sup>. Studies have demonstrated that raised CRP may be an early predictor of the severity of COVID-19 infection<sup>16</sup>. Higher CRP levels were found in severe diseases as compared to milder forms. CRP is an inflammatory protein formed in the liver. CRP binds to damaged surfaces of the cells and results in the activation of the classical pathway of complement and may modulate the phagocytic activity<sup>18</sup>.

LDH is an important enzyme in anaerobic metabolism in almost all living organisms. A pooled analysis of nine studies has shown that high LDH levels were associated with a 6-fold increase in the odds of developing severe disease and a 16-fold increase in odds of mortality in patients with COVID-19.<sup>19</sup> Our study has also shown that elevated LDH levels were associated significantly with disease severity. Another study has demonstrated that COVID-19 patients with high levels of LDH on admission were more likely to develop ARDS<sup>20</sup>.

Our study has shown that ferritin was significantly raised in severe COVID-19 infection. A study from Italy has also demonstrated that ferritin levels over the 25th percentile were associated with a more severe pulmonary involvement, independently of age and gender but raised ferritin levels were not associated with disease outcomes<sup>21</sup>. Another study has shown that D. Dimers and ferritin were independent risk factors for COVID-19 severity<sup>22</sup>.

Our study has found that most of the patients were men (60.5%) and the majority were more than 50 years of age. The reduced susceptibility of females to viral infections may be attributed to the protection from the X chromosome and sex hormones, which play an important role in innate and adaptive immunity. Our results also demonstrate that COVID-19 is more likely to infect older men with chronic comorbidities. This may be the result of the weaker immune functions of these patients<sup>23</sup>.

Our study has demonstrated the significant relationship of all four inflammatory markers under study with the outcome of disease. AUC about the outcome of COVID-19 was 0.699 for CRP, 0.668 for LDH, 0.742 for D. dimers and 0.677 for ferritin. CRP was 100 % sensitive in assessing COVID-19 outcomes. D. dimer

was found to be the most accurate in assessing outcomes. (Table 4). Raised inflammatory markers signify severe inflammatory reactions ending in worse outcomes.

A study from Indonesia has identified CRP, neutrophil-to-lymphocyte ratio (NLR) and derived-NLR (d-NLR) values as independent risk factors for disease severity and death in COVID-19 patients.<sup>24</sup> A study from Pakistan has shown a significant increase in NLR and CRP levels (p=0.001) in patients who died from covid 19 infection<sup>25</sup>. Another retrospective study of 142 patients from India has shown that higher levels of inflammatory markers were associated with a worse outcome ferritin (p-value <0.001), c-reactive protein (p-value <0.001), interleukin 6 (p-value 0.007), procalcitonin (p-value 0.005) and lactic acid (p-value 0.004)<sup>26</sup>.

A study from Ankara, Turkey evaluated the role of various haematological markers in predicting covid-19 severity and concluded that almost all of the haematological parameters could be used as diagnostic biomarkers for covid-19 because the area under the curve (AUC) was higher than 0.50. The highest AUC among the parameters were of D.Dimer/fibrinogen ratio and neutrophil/ lymphocyte ratio.

Another study has demonstrated that inflammatory markers drawn within 48 hours of arrival correlated with clinical outcomes. However, these were not highly predictive of which patients would die or require intubation, ICU admission or renal replacement therapy<sup>28</sup>. A study has shown that CRP predicted the outcome in covid patients. CRP showed a sensitivity of 90.5%, specificity of 77.6%, positive predictive value of 61.3%, and negative predictive value of 95.4%. CRP was also an independent discriminator of severe/critical illness on admission with an AUC (0.783)<sup>29</sup>.

A retrospective study showed that ferritin was the last parameter to return to normal. CRP normalized about 5 days before ferritin. So ferritin is more useful in assessing the severity of the disease<sup>30</sup>.

Our study is real-time data from 185 patients. We studied the relationship of various inflammatory markers with covid 19 severity and its outcome in the form of discharged/expired patients. Raised inflammatory markers depicted the severity of covid 19

infection and we found that all of them were comparable in assessing the disease severity. D. dimer level at presentation in the hospital was found to be more accurate in assessing disease outcomes. This study also has certain limitations like all the tests were not done in all the patients. Despite that, our study may provide useful data on the region and we hope it will be helpful in the assessment of the severity and prognosis of covid 19 infection.

## 5. Conclusion

Our study has demonstrated that inflammatory markers are raised significantly in COVID-19 patients and correlate well with disease severity and outcome. Serum ferritin and D. dimer are the most accurate in depicting the severity and outcome of the disease respectively. This study was performed on covid PCR positive patients but results may apply to covid PCR negative patients too. More extensive studies may help us in further evaluating the role of inflammatory markers in the covid 19. This will help not only in diagnosing but also management of the disease.

## CONFLICTS OF INTEREST- None

**Financial support:** None to report.

**Potential competing interests:** None to report

## Contributions:

A.U.N - Conception of study

A.U.N, S.Z, I.K - Experimentation/Study Conduction

A.U.N, D.M - Analysis/Interpretation/Discussion

A.U.N - Manuscript Writing

A.U.N, I.Z - Critical Review

S.S - Facilitation and Material analysis

## References

- Bordi L, Nicastrì E, Scorzolini L, Di Caro A, Capobianchi MR, Castilletti C, Lalle E; on behalf of INMI COVID-19 study group and Collaborating Centers. Differential diagnosis of illness in patients under investigation for the novel coronavirus (SARS-CoV-2), Italy, February 2020. *Euro Surveill.* 2020 Feb;25(8):2000170. doi: 10.2807/1560-7917.
- Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. *J Adv Res.* 2020 Mar 16;24:91-98. doi: 10.1016/j.jare.2020.03.005.
- England PH. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing. 2021 Aug 6;23.
- Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, Haroon S, Price G, Davies EH, Nirantharakumar K, Sapey E, Calvert MJ; TLC Study Group. Symptoms, complications and management of long COVID: a review. *J R Soc Med.* 2021 Sep;114(9):428-442. doi: 10.1177/01410768211032850.
- Sheraton M, Deo N, Kashyap R, Surani S. A Review of Neurological Complications of COVID-19. *Cureus.* 2020 May 18;12(5):e8192. doi: 10.7759/cureus.8192.
- Chavez S, Long B, Koyfman A, Liang SY. Coronavirus Disease (COVID-19): A primer for emergency physicians. *Am J Emerg Med.* 2021 Jun;44:220-229. doi: 10.1016/j.ajem.2020.03.036.
- Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, Hosein Z, Padda I, Mangat J, Alfat M. Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med.* 2020;2(8):1069-1076. doi: 10.1007/s42399-020-00363-4.
- Goudouris ES. Laboratory diagnosis of COVID-19. *Jornal de pediatria.* 2021 Feb 22;97:7-12.
- Terpos E, Ntanasis-Stathopoulos I, Elalamy I, Kastritis E, Sergentanis TN, Politou M, Psaltopoulou T, Gerotziafas G, Dimopoulos MA. Hematological findings and complications of COVID-19. *Am J Hematol.* 2020 Jul;95(7):834-847. doi: 10.1002/ajh.25829.
- Hu B, Huang S, Yin L. The cytokine storm and COVID-19. *Journal of medical virology.* 2021 Jan;93(1):250-6.
- Imran MM, Ahmad U, Usman U, Ali M, Shaikat A, Gul N. Neutrophil/lymphocyte ratio-A marker of COVID-19 pneumonia severity. *Int J Clin Pract.* 2021 Apr;75(4):e13698. doi: 10.1111/ijcp.13698.
- Stasi C, Fallani S, Voller F, Silvestri C. Treatment for COVID-19: An overview. *Eur J Pharmacol.* 2020 Dec 15;889:173644. doi: 10.1016/j.ejphar.2020.173644.
- Bradbury CA, McQuilten Z. Anticoagulation in COVID-19. *Lancet.* 2022 Jan 1;399(10319):5-7. doi: 10.1016/S0140-6736(21)02503-4.
- <https://www.nih.org.pk/wp-content/uploads/2020/05/Clinical-Management-Guidelines-for-COVID-19-infection-V3-29-5-2019578.pdf>
- Abbas, S., Hayat, A., Majeed, N., Jaffar, S., Asghar, J., & Ali, S. (2020). COMPARISON OF INFLAMMATORY MARKERS WITH DIFFERENT LEVELS OF SEVERITY OF COVID-19 DISEASE. *Pakistan Armed Forces Medical Journal*, 70(2), S455-58.
- Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. *Journal of medical virology.* 2020 Nov;92(11):2409. doi: 10.1002/jmv.26097
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX; China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
- Young B, Gleeson M, Cripps AW. C-reactive protein: a critical review. *Pathology.* 1991 Apr;23(2):118-24. doi: 10.3109/00313029109060809.
- Henry BM, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, Lippi G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled

- analysis. *Am J Emerg Med.* 2020 Sep;38(9):1722-1726. doi: 10.1016/j.ajem.2020.05.073.
20. Zhou Y, Ding N, Yang G, Peng W, Tang F, Guo C, Chai X. Serum lactate dehydrogenase level may predict acute respiratory distress syndrome of patients with fever infected by SARS-CoV-2. *Ann Transl Med.* 2020 Sep;8(17):1118. doi: 10.21037/atm-20-2411.
  21. Umair, M., Kim, D. & Choi, M. Impact of climate, rising atmospheric carbon dioxide, and other environmental factors on water-use efficiency at multiple land cover types. *Sci Rep* **10**, 11644 (2020). <https://doi.org/10.1038/s41598-020-68472-7>
  22. M Hussein A, Taha ZB, Gailan Malek A, Akram Rasul K, Hazim Kasim D, Jalal Ahmed R, Badraden Mohamed U. D-Dimer and Serum ferritin as an Independent Risk Factor for Severity in COVID-19 Patients. *Mater Today Proc.* 2021 Apr 13. doi: 10.1016/j.matpr.2021.04.009.
  23. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. *Front Med.* 2020 Apr;14(2):126-135. doi: 10.1007/s11684-020-0767-8.
  24. Prasetya IB, Cucunawangsih, Lorens JO, Sungono V, El-Khobar KE, Wijaya RS. Prognostic value of inflammatory markers in patients with COVID-19 in Indonesia. *Clin Epidemiol Glob Health.* 2021 Jul-Sep;11:100803. doi: 10.1016/j.cegh.2021.100803.
  25. Asghar MS, Khan NA, Haider Kazmi SJ, Ahmed A, Hassan M, Jawed R, Akram M, Rasheed U, Memon GM, Ahmed MU, Tahniyat U, Tirmizi SB. Hematological parameters predicting severity and mortality in COVID-19 patients of Pakistan: a retrospective comparative analysis. *J Community Hosp Intern Med Perspect.* 2020 Oct 29;10(6):514-520. doi: 10.1080/20009666.2020.1816276.
  26. Parimoo A, Biswas A, Baitha U, Gupta G, Pandey S, Ranjan P, Gupta V, Barman Roy D, Prakash B, Wig N. Dynamics of Inflammatory Markers in Predicting Mortality in COVID-19. *Cureus.* 2021 Oct 27;13(10):e19080. doi: 10.7759/cureus.19080
  27. Şan İ, Gemcioğlu E, Davutoğlu M, Çatalbaş R, Karabuğa B, Kaptan E, Erden A, Küçükşahin O, Ateş İ, Karaahmetoğlu S, Hasanoğlu İ, İnan O, Ünal BN, Erdemir E, Kahraman FA, Güner R. Which hematological markers have predictive value as early indicators of severe COVID-19 cases in the emergency department? *Turk J Med Sci.* 2021 Dec 13;51(6):2810-2821. doi: 10.3906/sag-2008-6.
  28. Barrett B, Pamphile S, Yang F, Naeem F, Kim J, Annam J, Borczuk R, Yellin S, Bass C, Fowler S, Mosheyev M, Mayer YJ, Friedman BW. Inflammatory markers are poorly predictive of clinical outcomes among hospitalized patients with COVID-19. *Am J Emerg Med.* 2021 Aug;46:595-598. doi: 10.1016/j.ajem.2020.11.038.
  29. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, Ye L, Xiong J, Jiang Z, Liu Y, Zhang B, Yang W. Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019. *Clin Infect Dis.* 2020 Nov 19;71(16):2174-2179. doi: 10.1093/cid/ciaa641
  30. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia. *Lab Invest.* 2020 Jun;100(6):794-800. doi: 10.1038/s41374-020-0431-6