Journal of Cardiovascular Disease Research

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

Original research article

Analysis of c–reactive protein, lactate dehydrogenase, ferritin and d-dimer levels in COVID-19 patients: A retrospective study

[1]Dr. Koppukonda Ravi Babu, [2]Dr. Bonagiri Shanthi, [3]Dr. D Sridevi

[1]Associate Professor, Department of Biochemistry, Malla Reddy Institute of Medical Sciences Hyderabad India

[2]Professor and HOD, Department of Transfusion Medicine Nizam's Institute of Medical Sciences Hyderabad India

[3]Professor and HOD, Department of Biochemistry, Malla Reddy Institute of Medical Sciences, Hyderabad India

Corresponding Author:
Dr. Koppukonda Ravi Babu

Abstract

Background and Objectives: C-reactive protein (CRP) is an acute-phase protein that manifests in the blood within 6–10 hours in severe states of COVID-19 hyper inflammatory response, which results in a pathological dysfunction of innate host defense mechanisms. One of the biomarkers of inflammation in bacterial or viral infection is the iron storage form known as ferritin. In this retrospective study, our goal was to assess the diagnostic efficacy of CRP, ferritin, LDH, and D-dimer in identifying COVID-19 positive cases in India.

Methods: This research was carried out retrospectively at the Malla Reddy Institute of Medical Sciences in Hyderabad, India. A tertiary care teaching institution's electronic medical records from July 2020 and May 2021 were examined for the test results for CRP, LDH, ferritin, and D dimer in 172 patients overall.

Results: The results in ROC show that when all these parameters are combined, the area under the curve (AUC) of LDH and D-dimer is 0.62, that of LDH and C-reactive protein is 0.68, that of LDH and Ferritin is 0.96, and that of LDH, FERRITIN, D-DIMER, and C-reactive protein is 0.99. Before moving on to a final RT-PCR diagnosis, the severity of COVID-19 can be evaluated using a combination of common laboratory biomarkers (CRP, LDH, ferritin, and D- dimer) with a recognized sensitivity and specificity.

Conclusion: Prior to moving forward with a formal diagnosis by RT-PCR, a combination of common laboratory biomarkers (CRP, LDH, ferritin, and D-dimer) can be used to predict the diagnosis of COVID-19 with a recognized sensitivity and specificity.

Keywords: COVID-19, C-reactive protein, LDH, ferritin and D-dimer

Introduction

The coronavirus disease 2019 (COVID-19) is an intensely contagious illness that first surfaced in Wuhan, China, before spreading to other parts of the world [1]. The causal agent is the novel encompassed single straight positive-sense abandoned RNA coronavirus, also known as SARS-CoV-2 and with a preference for lung cells [2]. This novel HGN l strain was suggested to be produced from the creature by the hereditary analysis of SARS-CoV-2. A SARS-like coronavirus from bats and a coronavirus with an enigmatic origin recombined to form the root [3]. SARS-CoV-2 has the ability to spread quickly from one person to another, much more so than other human infections like the flu or plague, prompting the WHO to declare it a pandemic in 2020 [4].

Asymptomatic or only mild symptoms account for 80% of the disease's clinical presentations, while the remaining 20% can result in severe multi-organ failure and even death. The following symptoms may also be present: fever, headache, myalgia, generalized exhaustion, loss of taste or smell, sore throat, shortness of breath, and non-productive cough. Acute respiratory distress syndrome (ARDS), kidney failure, and heart failure are all conditions that can occur in some patients (15-20%) [5-7]. The clinical course and pathological findings of COVID-19 were comparable to those of the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) because of the genetic similarities between coronaviruses [8].

Diabetes was found to be 20% common among COVID-19 patients, according to reports [9]. Numerous markers, including serum ferritin, C-reactive protein, interleukin-6, fibrinogen, serum LDH, and D-dimer, have a direct impact on the severity of the disease and the patient's prognosis. The severity, progression, and mortality of COVID-19 are all correlated with hematological abnormalities. Patients

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

with COVID-19 have a very good history of lymphopenia, thrombocytopenia, and an abnormal coagulation profile [10-13].

Methodology

The Department of Biochemistry at Malla Reddy Institute of Medical Sciences in Hyderabad, India, conducted this retrospective study. A total of 172 patients were evaluated from a tertiary care teaching institution's electronic medical records between July 2020 and May 2021 for CRP, LDH, ferritin, and D dimer test values.

Inclusion criteria

- Men and women between the ages of 30 and 70.
- They either had close contact with previously confirmed COVID-19 positive patients or had one or more COVID-19 symptoms such as fever, cough, sore throat, dyspnea, muscle aches, and loss of smell or taste.

Exclusion criteria

- People with incomplete laboratory results, those with a history of kidney, liver, or diabetes mellitus, as well as those who are pregnant or have young children.

Results

Table 1: Study parameters

	COVID_AGE_M	LDH_M	FERRITIN_M	Ddimer_M	CRP_M
Mean	48.336	461.963	710.6539	1.2378	1.909
Std. Deviation	12.6903	265.6389	562.52025	1.75821	.9586
N	128	128	128	128	128
	FEMALE_AGE	**LDH_F**	**FERRITIN_F**	**D_DIMER_F**	**CRP_12_F**
Mean	53.0000	384.566	401.1734	.6989	1.473
Std. Deviation	13.15560	114.9663	374.28648	.96292	.9549
N	44	44	44	44	44
	AGE_M_F_COVID	**LDH_M_F**	**FERRITIN_M_F**	**Ddimer_M_F**	**CRP_M_F**
Mean	49.5291	442.163	631.4845	1.0999	1.798
Std. Deviation	12.93412	238.4908	537.19300	1.60769	.9738
N	172	172	172	172	172

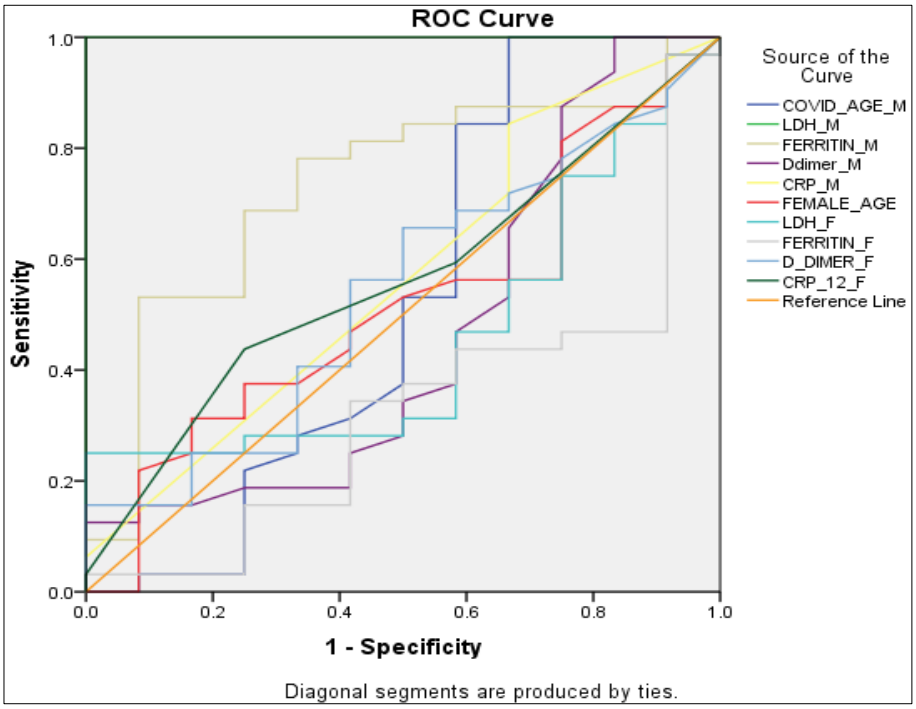

Fig 1: Study parameters

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

Table 2: COVID_AGE_M, Ddimer_M, CRP_M, FEMALE_AGE, D_DIMER_F, CRP_12_F has at least one tie between the positive actual state group and the negative actual state group

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
COVID_AGE_M	.526	.120	.792	.291	.761
LDH_M	1.000	.000	.000	1.000	1.000
FERRITIN_M	.732	.085	.019	.565	.899
Ddimer_M	.465	.108	.722	.254	.676
CRP_M	.568	.099	.493	.373	.762
FEMALE_AGE	.516	.097	.874	.326	.705
LDH_F	.458	.095	.673	.272	.645
FERRITIN_F	.326	.091	.077	.146	.505
D_DIMER_F	.540	.097	.683	.351	.730
CRP_12_F	.563	.092	.527	.381	.744

The test result variable(s): COVID_AGE_M, Ddimer_M, CRP_M, FEMALE_AGE, D_DIMER_F, CRP_12_F has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

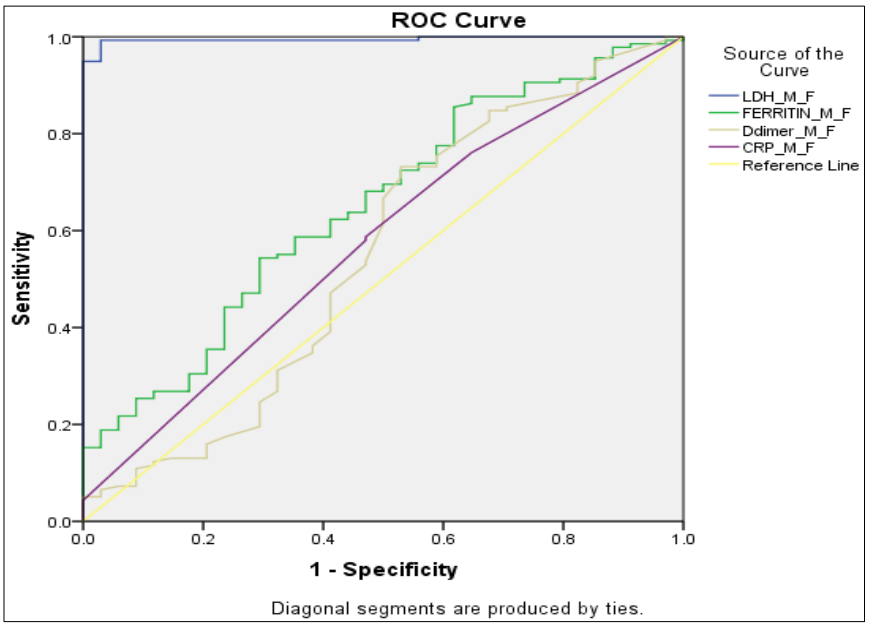

Fig 2: _AGE_M, Ddimer_M, CRP_M, FEMALE_AGE

Table 3: FERRITIN_M_F, Ddimer_M_F, CRP_M_F has at least one tie between the positive actual state group and the negative actual state group

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LDH_M_F	.995	.004	.000	.986	1.000
FERRITIN_M_F	.650	.052	.007	.548	.751
Ddimer_M_F	.551	.061	.355	.431	.672
CRP_M_F	.576	.055	.169	.469	.683

The test result variable(s): FERRITIN_M_F, Ddimer_M_F, CRP_M_F has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

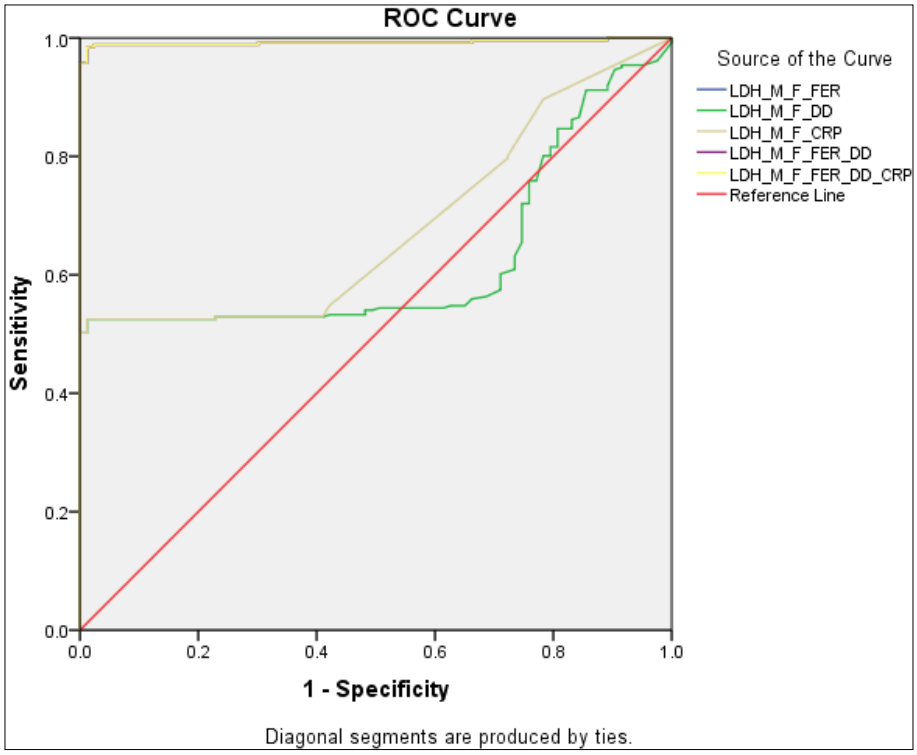

Fig 2: FERRITIN_M_F, Ddimer

Table 4: LDH_M_F_DD, LDH_M_F_CRP has at least one tie between the positive actual state group and the negative actual state group

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
LDH_M_F_FER	.959	.004	.000	.984	1.000
LDH_M_F_DD	.627	.030	.000	.568	.686
LDH_M_F_CRP	.681	.029	.000	.625	.738
LDH_M_F_FER_DD	.992	.004	.000	.984	1.000
LDH_M_F_FER_DD_CRP	.992	.004	.000	.984	1.000

The test result variable(s): LDH_M_F_DD, LDH_M_F_CRP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Table 5: Robust Tests of Equality of Means on variables

		Statistic[a]	df1	df2	Sig.
COVID_AGE_M	Welch	.002	1	14.568	.964
LDH_M	Welch	29.629	1	38.170	.000
FERRITIN_M	Welch	5.987	1	24.787	.022
Ddimer_M	Welch	.281	1	34.889	.600
CRP_M	Welch	1.051	1	22.196	.316
FEMALE_AGE	Welch	.024	1	20.159	.879
LDH_F	Welch	.012	1	27.331	.915
FERRITIN_F	Welch	2.707	1	16.547	.119
D_DIMER_F	Welch	1.391	1	41.718	.245
CRP_12_F	Welch	1.192	1	27.198	.285
LDH_M_F	Welch	29.629	1	38.170	.000
FERRITIN_M_F	Welch	5.987	1	24.787	.022
Ddimer_M_F	Welch	.281	1	34.889	.600
CRP_M_F	Welch	1.051	1	22.196	.316

a. Asymptotically F distributed.

Discussion

According to studies, COVID-19 individuals had a 20% prevalence of diabetes. Serum ferritin, C-reactive protein, interleukin-6, fibrinogen, serum LDH, and D-dimer are only a few of the indicators that directly affect the severity of the illness and the prognosis of the patient. Haematological abnormalities

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

are associated with COVID-19 severity, progression, and death. A very good history of lymphopenia, thrombocytopenia, and an abnormal coagulation profile exists in COVID-19 patients.

The results of the CRP, LDH, ferritin, and D-dimer levels showed substantial increases in individuals who were tested COVID-19 positive with RT-PCR as compared to those who were tested negative, according to Anand A. and Sandefur. According to a recent Italian study, RT-PCR may not always be necessary to detect COVID-19-positive patients because CRP and LDH levels are markedly elevated in COVID-19-positive individuals. According to other research, the severity of the disease was assessed using CRP, LDH, ferritin, and D-dimer, and a high level was linked to a bad prognosis and death. The majority of the cases included in the study were outpatients with mild presentations, so it's possible that the lack of association between D-dimer and increased risk of COVID-19 infection is due to the fact that D-dimer did not show up in the results of the multivariate logistic regression analysis. High levels of CRP, ferritin, and D-dimer are linked to poor outcomes in COVID-19, according to a recent met analysis [14, 15].

According to Lui *et al*., a Spearman correlation study revealed a favourable association between ferritin and CRP. With the use of the ROC technique, the specificity and sensitivity of the estimates of CRP, LDH, ferritin, and D-dimer in patients suspected of having COVID-19 have been calculated. The cut-off value for each marker in terms of predicting the existence of COVID-19 infection has also been estimated. CRP, LDH, and ferritin all had AUCs around 0.7 [16, 17].

For CRP and LDH, Mardani *et al*. found an AUC of 0.8, which is identical to our finding. Among these indicators, ferritin and LDH showed the best specificity, but sadly, they also had the lowest sensitivity. For ferritin, we established a cut-off value of 290 ng/mL; Tular Onur *et al*. reported a similar value. Our threshold for LDH was determined to be 278 mg/dL; this number was comparable [18, 19].

Li and co. For CRP, a cut-off value of 14 mg/L was found to be associated with a specificity and sensitivity of 0.77 and 0.56, respectively. These results are consistent with Cheng *et al*. The majority of studies recommended a threshold of 10 mg/L for CRP and 0.5 mg/L for D-dimer, despite the fact that there is no widespread consensus on such a number to assess the severity of COVID-19. CRP may be utilised to track the progression of the disease as well as a prognostic indicator [20, 21].

Hospitalization may be necessary for COVID-19 individuals with noticeably elevated D-dimer values, regardless of how severe their clinical symptoms are. High cost methods like RT-PCR and CT imaging are required for the diagnosis of COVID-19. However, in a place like Iraq where there is a lot of poverty and few medical resources, we may utilise these common, inexpensive laboratory tests to diagnose COVID-19 before using more expensive procedures, and combining these markers can increase the sensitivity of analysis [22-24].

Conclusion

Finally, it was found from the aforementioned study that, in order to predict the diagnosis of COVID-19 with a known sensitivity and specificity, a combination of common laboratory biomarkers (CRP, LDH, ferritin, and D-dimer) can be used.

Funding source:

None

Conflict of interest:

None

References

1. Pityana NB. A theological statement on the coronavirus pandemic: living the faith responsibly. Relig Theol. 2020;27(3-4):329-58.
2. Ambrose PM. High throughput genetics and characterization of an RNA Arbovirus, Sindbis virus, using accurate next-generation sequencing of viral evolution and RNA enrichment [dissertation]. Weill Medical College of Cornell University. ProQuest Dissertations Publishing; 2020.
3. Rangayasami A, Kannan K, Murugesan S, Radhika D, Sadasivuni KK, Reddy KR, *et al*. Influence of nanotechnology to combat against COVID-19 for global health emergency: a review. Sens Int. 2021;2:100079.
4. Ahire ED, Kshirsagar SJ. Immune responses induced by different vaccine platforms against coronavirus disease-19. Explor. Immunol. 2021;1:243-57.
5. Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, Rubio-Neira M, Guaman LP, Kyriakidis NC, *et al*. Clinical, molecular and epidemiological characterization of the SARS-CoV2 virus and the Coronavirus disease 2019 (COVID-19), a comprehensive literature review. DiagnMicrobiol Infect Dis. 2020 Sep;98(1):115094.
6. Kluge S, Janssens U, Welte T, Carstens SW, Marx G, Karagiannidis C. Recommendations for critically ill patients with COVID-19. Med Klin Intensivmed Notfmed, 2020;115(3):175-177. doi: 10.1007/s00063-020-00674-3.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

7. Zhonghua Liu Xing Bing Xue Za Zhi. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. 2020;41(2):145-151. doi: 10.3760/cma.j.issn.0254-6450.2020.02.003.
8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5.
10. Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, The Lancet. 2020;395(10223):497-506.
11. Spiezia L, Boscolo A, Poletto F, *et al*. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure, Thrombosis and Haemostasis. 2020;120(6):998–1000.
12. Li Y, Zhao K, Wei H, *et al*. Dynamic relationship between D-dimer and COVID-19 severity, British Journal of Haematology. 2020;190(1):e24–e27.
13. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation, Blood, 2020;135(23):2033–2040.
14. Taj S, Kashif A, Arzinda Fatima S, Imran S, Lone A, Ahmed Q. Role of hematological parameters in the stratification of COVID-19 disease severity, Annals of medicine and surgery. 2021;62:68–72.
15. Hong H, Wang Y, Chung HT, Chen CJ. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. Pediatr Neonatol. 2020 Apr;61(2):131-132. doi: 10.1016/j.pedneo.2020.03.001.
16. Anand A, Sandefur J, Subramanian A. Three new estimates of India's all-cause excess mortality during the COVID-19 pandemic. Center for Global Development. July 20, 2021. Available from: https://cgdev.org/publication/three-new-estimates-indias-allcause-excess-mortality-during-covid-19-pandemic Accessed July 25, 2021.
17. Talele SG, Ahire ED, Surana KR, Sonawane VN, Talele GS. Corona Virus Disease (COVID-19): A past and Present Prospective. Asian Journal of Pharmaceutical Research. 2022;12(1):45-53.
18. Kluge S, Janssens U, Welte T, Carstens SW, Marx G, Karagiannidis C. Recommendations for critically ill patients with COVID-19. Med Klin Intensivmed Notfmed, 2020;115(3):175-177. doi: 10.1007/s00063-020-00674-3.
19. Kaftan AN, Hussain MK, Algenabi AA, Naser FH, Enaya MA. Predictive Value of C–reactive Protein, Lactate Dehydrogenase, Ferritin and D-dimer Levels in Diagnosing COVID-19 Patients: a Retrospective Study. Acta Informatica Medica. 2021 Mar;29(1):45.
20. Ahire ED, Sonawane VN, Surana KR. Role of drug repurposing in current treatment strategies against COVID-19; systemic review. Pharm Reson, 2020, 24-9.
21. Kadhim AS, Abdullah YJ. Serum levels of interleukin-6, ferritin, C-reactive protein, lactate dehydrogenase, D-dimer, and count of lymphocytes and neutrophils in COVID-19 patients: Its correlation to the disease severity. Biomedical and Biotechnology Research Journal (BBRJ). 2021 Jan 1;5(1):69.
22. Abdullah YJ, Kadhim AS, Khallaf SA, Alsaedi RZ. Serum levels of interleukin–6, ferritin, C-reactive protein, lactate dehydrogenase, D-dimer and count of lymphocytes and neutrophils in COVID-19 patients. Its correlation to the disease severity. Annals of the Romanian Society for Cell Biology. 2021 Mar 1:2220-8.
23. Shokr H, Marwah MK, Siddiqi H, Wandroo F, Sanchez-Aranguren L, Ahmad S, *et al*. Lactate Dehydrogenase/Albumin To-Urea Ratio: A Novel Prognostic Maker for Fatal Clinical Complications in Patients with COVID-19 Infection. Journal of Clinical Medicine. 2022 Dec 20;12(1):19.
24. Martinez Mesa A, Cabrera César E, Martín-Montañez E, Sanchez Alvarez E, Lopez PM, Romero-Zerbo Y, *et al*. Acute lung injury biomarkers in the prediction of COVID-19 severity: Total thiol, ferritin and lactate dehydrogenase. Antioxidants. 2021 Jul 29;10(8):1221.