Evaluation of Some Biomarkers in the Diagnosis and Severity Identification of Patients with COVID-19

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Abstract. This work shows how effective the biomarkers D dimer, C-reactive protein (CRP), and Lactate Dehydrogenase (LDH) were at diagnosing COVID-19 and how severe it was. A case-control research included (136) Covid-19 patients and (48) healthy people as a control group. Kits used to measure D dimer, CRP, and LDH. The outcomes are shown that there was a highly significant increase (P-value < 0.01) in the levels in COVID-19 patients compared to the control group for the biomarkers: D dimer, CRP, and LDH. There was a highly significant increase (P-value < 0.01) in COVID-19 patients with severe disease compared to other groups for the following biomarkers: D dimer and LDH. The study also showed that that the sensitivity values of the markers were 88%, 85%, and 79, for D-dimer, CRP, and LDH, D respectively; while specificity values were: 63%, 61%, and 66% respectively. These markers might be used in detection of COVID-19.

Keywords: COVID-19, SARS-CoV-2, D-dimer, CRP, LDH.

1 Introduction

SARS-CoV and Middle East respiratory syndrome coronavirus-2 (MERS-CoV) have generated epidemics in the previous two decades, with mortality rates of 9.5 percent and 34.4 percent, respectively. COVID19 has been identified as the third highly epidemic disease, having a lower mortality rate than SARS and MERS and a wide range of symptoms from one country to the next. Until the time of writing this study, more than 185 million cases have been officially registered as positive cases in about 222 countries all over the world, while the deaths exceed 4 million worldwide. The largest number of cases have been recorded in the United State of America (USA) with more than 34 million followed by India which recorded more than 30 million. The United States has the most deaths (about 600000), but Peru has the greatest mortality rate (approximately 5790 deaths per million of population) [1]. Inflammatory damage patterns in SARS and COVID-19 patients are comparable. Proinflammatory cytokines such as interleukin (IL)-1, IL6, IL12, interferon-gamma (IFN), IFN-induced protein 10 (IP10), macrophage inflammatory proteins 1A (MIP1A), and monocyte chemoattractant protein-1 (MCP1) have been associated to pulmonary infection and severe lung damage. These are identified in the serum of persons who have been diagnosed with SARS (D-dimer, CRP, and LDH).COVID-19 emergency warning indications include constant discomfort or pressure in the chest, difficulty breathing, disorientation, and pale lips or face, all of which require rapid medical attention. Pneumococcal infection develops as the situation worsens, and the incubation

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period has yet to be calculated because the virus was only recently discovered. Symptoms could develop as soon as three days after exposure or as late as 13 days later, according to the new information. According to recent studies, the incubation period is roughly five days on average [2].
The importance of the lab outcomes in detection and follow-up of Covid-19 patients cannot be overstated. The biomarkers for Covid-19 have been the subject of numerous studies. Complete blood count (CBC), tests studying coagulation and fibrinolysis flows such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) and D-dimers, and inflammation-related parameters are the most common routine assays requested by COVID-19 clients (procalcitonin, CRP, ESR, and ferritin). Because the virus has the potential to severely impair multiple key organs, including the liver, kidneys, and heart, doctors can determine the functioning processes of these organs by analysing biochemical indicators [3].

2 Materials and Methods

The work included (136) people diagnosed with Covid-19 (71 male and 65 female) and (48) healthy subjects as a control group. Who visited Al-Basra Teaching Hospital in Basra, Iraq? All patients in this research were diagnosed by specialist physicians and confirmed clinical and laboratory investigations, throughout the period from October 2020 to May 2020. The practical research was conducted at Southern Technical University in Basra's Medical Laboratory Technology department. D dimer (BioMérieux, France), CRP (Roche Diagnostics, Switzerland), and LDH (Roche Diagnostics, Switzerland) were also measured using kits (Roche Diagnostics, Switzerland).

2.1 Statiastical Analysis

The data is expressed in terms of averages and Std Dev. (SD). The t-test (for means) and the chi-square test were used to see if there were any differences between the groups (for frequencies). SPSS for Windows was used to conduct all statistical analyses (version 23, USA). ANOVA was employed as normal distribution based on $P < 0.05$ and $P > 0.05$ as the significant. and non-significant respectively.

3 Results and Discussion

3.1. Demographic Characteristics of the Study Groups

Table 1. Statistical distribution (frequency and percentage) of study groups (patients and control) by their age and gender.

Items	Sub-groups	COVID-19 patients (N= 136)		Control Group (N= 48)		Chi Square (P value) Sig.
		Freq.	%	Freq.	%	
Age	17-31	6	4.4	0	0.0	4.13 (0.24) NS
	32-46	34	25.0	16	33.3	
	47-61	54	39.7	24	50.0	
	62-76	31	22.8	8	16.7	

Mean ± SD	**77-91**	**11**	**8.1**	**0**	**0.0**	
		54.13 ± 14.55		**51.46 ± 8.27**		**T-test = 1.12 (0.06) NS**
Gender	**Male**	**71**	**52.2**	**24**	**50.0**	**0.07 (0.79) NS**
	Female	65	47.8	24	50.0	

Table 1 showed statistical distribution (frequency and percentage) of study groups (patients and control) by their age and gender. This table explained that the highest percentage of the age subgroup is (47-61) years which constituted (39.7%) for the patient's group, and (50%) for the control group (figure 4.1), the same table revealed that the male percentage of patients are (52.2%), while gender is equally distributed among the control group (50% for each).

Table 2. Differences in the measurement of serum biomarkers between COVID-19 patients and control group

Biomarkers		**Patients (N= 136)**	**Control Group (N= 48)**	**T Test P value**
D dimer	**Mean**	**2418.01**	**466.33**	**7.18 0.000 HS**
	SD	**3093.01**	**409.10**	
CRP	**Mean**	**30.71**	**4.74**	**11.49 0.000 HS**
	SD	**24.10**	**6.35**	
LDH	**Mean**	**595.32**	**139.88**	**6.49 0.000 HS**
	SD	**811.59**	**58.38**	

HS: at P≤0.01; NS: at P≤0.05; SD: Std. Dev.

Table 2 shows the differences in the measurement of serum biomarkers between COVID-19 patients and the control group. This table exhibited that there is a highly significant increase (P-value < 0.01) in the levels in COVID-19 cases relative to the control for the following biomarkers: D dimer, CRP, and LDH.

3.2. Measurement of Biomarkers

Table 3. ANOVA table for Differences in the measurement of routine markers among patients' subgroups classified based on severity.

Biomarkers		**The severity of the Disease**			**F Test P-value**
		Mild (N= 42)	**Moderate (N=70)**	**Severe (N=24)**	
D dimer	**Mean**	**878.55 A**	**2843.98 B**	**3869.62 B**	**9.59 0.000 HS**
	SD	**1284.79**	**3425.50**	**3305.92**	
CRP	**Mean**	**23.40**	**33.94**	**34.10**	**2.87 0.06 NS**
	SD	**23.98**	**24.30**	**21.68**	
LDH	Mean	415.30 A	533.10 A	1091.86 B	6.17 0.000 HS
	SD	242.98	267.91	1793.71	

HS: at P≤0.01; NS: at P>0.05; SD: Std, Dev.; ANOVA: Analysis of Variance Different letters refer to a significant difference.

Table 3 Revealed differences in the measurement of serum biomarkers among different severity subgroups of COVID-19 patients. This table showed that there is a highly significant increase (P-value < 0.01) in COVID-19 people with severe illness compared to other groups for D dimer and LDH.

3.3. Receiver-Operating Characteristics of the Biomarkers

Table 4. ROC and AUC of the biomarkers for the diagnosis of breast cancer.

Biomarkers	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)	PPV	NPV
D-dimer	**0.81**	**0.01**	**6.34**	**88**	**63**	**83**	**73**
CRP	**0.66**	**0.08**	**6.34**	**85**	**61**	**63**	**53**
LDH	**0.84**	**0.06**	**375.74**	**79**	**66**	**82**	**06**

AUC; PPV; NPV.

The work also showed that that the sensitivity values of the markers were 88%, 85%, 79% for D-dimer, CRP, and LDH, D respectively; while specificity values were: 63%, 61%, 66% respectively (Table 4 and Fig 1)

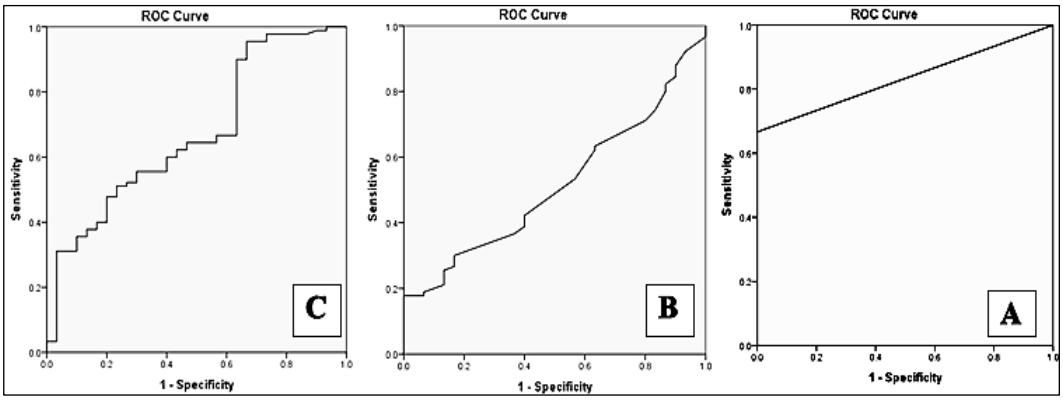

Fig 1. Diagonal segment of the ROC curve for (A) : D-dimer , (B) : CRP, (C) : LDH

The current study agrees with Rostami and Mansouritorghabeh [4] and Spiezia et al. [5] in terms of D-dimer. D-dimer was described as most effective lab results in Covid-19 people who need to be admitted to the hospital. No survivors had a considerably greater 2.12 µg/mL D-dimer according to Guan and his co-authors, who looked at 1099 people in lab with Covid-19 of 550 hospitals. Similarly, aberrant coagulation findings, particularly markedly high D-dimer, have been detected in deaths with Covid-19; a reflective investigation of 191 COV-Pat. showed 1g/mL Dimer when intended to hospital [7].

Although elevated D-dimer concentrations and dead-space ventilation may be caused by processes other than micro cloths, previous research suggests that intravascular disease plays a

key role in expanding dead space and producing hypoxemia in COVID-19-related ARDS [8]. According to Malik et al, greater D-dimer ranks are linked to a roughly threefold increased jeopardy of weak results in COVID-19 people [9].

Concerning CRP, the results agreed with Liu et al. they showed that CRP is raised in patients compared to control healthy people [10]; Patients with Covid-19 had high C-reactive protein (58.3 percent, 95 percent CI 21.8–94.7 percent), according to Rodriguez-Morales et al. (2020). RP is a sensitive biomarker of inflammation, infection, and tissue damage produced by the non-specific acute-phase protein IL-6 in the liver. CRP levels are generally low, but they spike dramatically during acute inflammatory responses [11]. CRP rises alone in conjunction with viral or bacterial infections. This work presents the balance of CRP in COVID-19 and detected CRP > 41.8 mg/L were more likely to cause more illness [12]. CRP levels are strongly related to the degree of inflammation and the severity of the condition. As a result, it is a significant biomarker in the diagnosis and assessment of infectious illness severity [9].

Regarding LDH, the results agreed with Liu et al., they showed that LDH was studied in 19 patients compared to control healthy subjects [10]; Rodriguez-Morales et al. counted the patients with Covid-19 showed high C-reactive protein (57.0%, 95%CI 38.0–76.0) [11]; Huang et al. reported that LDH levels were high in 73% of non-control; Liu et al. (2020C) found that CRP and LDH in 85% of non-control [13]; it was found that abnormal LDH levels observed, both at admission and hospitalization (LDH 37.6%), it is believed that lactate dehydrogenase (LDH) is released in large quantities of inflammatory and indicators of cell damage of the illness growth, activity, and movement [14].

CRP and LDH levels were found to be favourably linked with lung injury Murray scores in previous research [10]. Hypoalbuminemia, lymphopenia, and CRP ≥4 mg dL–1 revealed to be prognostic markers for pneumonia development to respiratory failure in MERS-CoV infected patients, while higher dehydrogenase was associated with severe acute respiratory syndrome (SARS-CoV) on entering to the hospital. As a result, a combination of hypoalbuminemia, lymphopenia, and elevated CRP and LDH concentrations in 2019-nCoV infected individuals to the hospital that might have acute lung problems [10].

Regarding D-dimer kits fluctuates between 93-95 percent [4]; Demelo-Rodrguez et al. also found that the D-dimer had a sensitivity of 95.7 percent, 29.3 percent specificity, and AUC of 0.729 with a cut-off point of 1.57 (μg/ml). Cui et al. studied the frequency of VTE in 81 ICU hospitalised people COVID-19 [16] and established such criteria for the detection of silent DVT [15]. They discovered that D-dimer with a cut-off point of 1.5 (μg/mL) had an 85% sensitivity and an 88.5 percent specificity for VTE prediction; Liu et al. calculated computed the optimal values markers that was 32.1 pg/ mL, 41.8 mg/L, and 0.07 ng/mL for IL-6, CRP, and PCT, respectively [10].

4 Conclusion

D dimer, CRP, and LDH levels are higher in COVID-19 patients, and D-dimer and LDH levels are higher in patients with severe COVID-19 infection. In the diagnosis of COVID-19, D-dimer and CRP had quite high sensitivity and specificity.

References

[1] Mohamadian, M., Chiti, H., Shoghli, A., Biglari, S., Parsamanesh, N., & Esmaeilzadeh, A. (2021). COVID-19: Virology, biology, and novel laboratory diagnosis. The journal of gene medicine, 23(2), e3303.

[2] Hafeez A, Ahmad S, Siddqui S, Ahmad M, Mishra S. A (2020) Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments, and Prevention. EJMO.; 4(2): 116-125 .

[3] Kumar D, Malviya R, Kumar Sharma P. (2020) Corona Virus: A Review of COVID-19. EJMO;4(1):8–25.

[4] Rostami, M., & Mansouritorghabeh, H. (2020). D-dimer level in COVID-19 infection: a systematic review. Expert review of hematology, 13(11), 1265–1275.

[5] Spiezia, L., Boscolo, A., Poletto, F., Cerruti, L., Tiberio, I., Campello, E., Navalesi, P., & Simioni, P. (2020). COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thrombosis and haemostasis, 120(6), 998–1000.

[6] Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., Liu, L., Shan, H., Lei, C. L., Hui, D., Du, B., Li, L. J., Zeng, G., Yuen, K. Y., Chen, R. C., Tang, C. L., Wang, T., Chen, P. Y., Xiang, J., Li, S. Y (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. The New England journal of medicine, 382(18), 1708–1720 .

[7] 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 : JTH, 18(6), 1324–1329.

[8] Grasselli, G., Tonetti, T., Protti, A., Langer, T., Girardis, M., Bellani, G., Laffey, J., Carrafiello, G., Carsana, L., Rizzuto, C., Zanella, A., Scaravilli, V., Pizzilli, G., Grieco, D. L., Di Meglio, L., de Pascale, G., Lanza, E., Monteduro, F., Zompatori, M., Filippini, C (2020). Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. The Lancet. Respiratory medicine, 8(12), 1201–1208.

[9]. Malik, P., Patel, U., Mehta, D., Patel, N., Kelkar, R., Akrmah, M., Gabrilove, J. L., & Sacks, H. (2021). Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. BMJ evidence-based medicine, 26(3), 107–108.

[10] Liu, Y., Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., Wang, Z., Li, J., Li, J., Feng, C., Zhang, Z., Wang, L., Peng, L., Chen, L., Qin, Y., Zhao, D., Tan, S., Yin, L., Xu, J., Zhou, C.Liu, L. (2020A). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Science China. Life sciences, 63(3), 364–374.

[11] Rodriguez-Morales, A. J., Cardona-Ospina, J. A., Gutiérrez-Ocampo, E., Villamizar-Peña, R., Holguin-Rivera, Y., Escalera-Antezana, J. P., Alvarado-Arnez, L. E., Bonilla-Aldana, D. K., Franco-Paredes, C., Henao-Martinez, A. F., Paniz-Mondolfi, A., Lagos-Grisales, G. J., Ramírez-Vallejo, E., Suárez, J. A., Zambrano, L. I., Villamil-Gómez, W. E., Balbin-Ramon, G. J., Rabaan, A. A., Harapan, H., Dhama, K., (2020). Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease, 34, 101623.

[12] Liu, F., Li, L., Xu, M., Wu, J., Luo, D., Zhu, Y., Li, B., Song, X., & Zhou, X. (2020B). Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, 127, 104370.

[13] Huang C, Wang Y, Li X. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet;395: 497e506.

[14] Farhana A, Lappin SL. Biochemistry (2021) Lactate Dehydrogenase. [Updated 2021 May 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557536/

[15] Demelo-Rodríguez, P., Cervilla-Muñoz, E., Ordieres-Ortega, L., Parra-Virto, A., Toledano-Macías, M., Toledo-Samaniego, N., García-García, A., García-Fernández-Bravo, I., Ji, Z., de-Miguel-Diez, J., Álvarez-Sala-Walther, L. A., Del-Toro-Cervera, J., & Galeano-Valle, F. (2020). Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. Thrombosis research, 192, 23–26.

[16] Cui, S., Chen, S., Li, X., Liu, S., & Wang, F. (2020). Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. Journal of thrombosis and haemostasis : JTH, 18(6), 1421–1424.