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Importance of Evaluating D-Dimer, CRP, LDH, and RBS as Predictors in the Severity of COVID-19 Disease: Omicron Variant

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ABSTRACT

Background*: COVID-19 is associated with systemic inflammation, coagulation abnormalities, and metabolic disturbances that contribute to disease severity. Biomarkers such as D-dimer, C-reactive protein (CRP), and lactate dehydrogenase (LDH) have been identified as potential severity predictors, yet their combined diagnostic value and the influence of demographic factors remain incompletely characterized.* ***Objective****: To evaluate inflammatory, coagulation, and metabolic biomarkers in patients with moderate-to-severe COVID-19 and assess the influence of age and gender on these parameters.* ***Methods****: This cross-sectional study enrolled 260 hospitalized COVID-19 patients confirmed by quantitative reverse transcription polymerase chain reaction (RT-qPCR) and 50 healthy controls. Serum and plasma levels of D-dimer, CRP, LDH, and random blood sugar (RBS) were measured using fully automated apparatus methods. Statistical analysis included t-tests and analysis of variance to compare parameters across groups and demographic strata.* ***Results:*** *COVID-19 patients demonstrated significantly elevated D-dimer (863.17 ± 39.06 ng/ml, $p < 0.0001$), CRP (24.31 ± 2.08 mg/L, $p = 0.0055$), and LDH (443.09 ± 43.88 U/L, $p < 0.00001$) levels compared to controls. RBS levels were also significantly elevated ($p < 0.05$). Gender had no strong independent effect on these biomarkers; however, CRP showed significant age-related differences in males ($p < 0.05$), while LDH demonstrated significant age-related elevation in both sexes ($p < 0.001$). Diabetic COVID-19 patients exhibited substantially higher glucose levels independent of gender.* ***Conclusion:*** *D-dimer, CRP, and LDH are valuable biomarkers for assessing disease severity in moderate-to-severe COVID-19, with LDH showing pronounced age-dependent elevation. These markers may serve as useful indicators for monitoring clinical progression and identifying high-risk patients, particularly among diabetic populations.*

Keywords: COVID-19; Coagulation Disorders; Inflammation; Omicron Variant; Prognosis; Severity Assessment.

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INTRODUCTION

Recent global concern regarding coronavirus disease 2019 (COVID-19) has led to a formal declaration of its status as a public health emergency worldwide by the World Health Organization (WHO). Nov 2023 Updated analysis of cases could inform specific characteristic and risk factors for the severity of illness density[1]. Coronovirus disease 2019 (COVID-19), which is caused by the infection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a formidable global public health crisis in recent years [2] [3]. The first case of COVID-19 in Iraq was registered during March 2020 in the city of Al Najaf, and the spread of the virus has been dramatic across the

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country with a reported total number of around 51,300 infections and more than 7000 deaths based on daily reports announced by Iraqi ministry of health. This ubiquity was a difficulty for both clinicians and researchers. COVID-19 infection can result in a wide range of clinical outcomes, where according to World Health Organization interim guidance [4] [5], but fever and headache were less common, fever, dyspnea, dry cough, and exhaustion are among the most common COVID-19 symptoms, GI symptoms, skin lesions, anosmia, headaches, and sore throat, on the other hand, are considered minor symptoms [6].

Accurate diagnosis relies on a combination of molecular testing, clinical history, and medical imaging, Age, diabetes, CVD, CKD, COPD, malignancy, and stroke have all been linked to serious illness and poor outcomes [7]. CRP and D-Dimer, and LDH are inflammatory indicators that elevated in these patients, in addition, there is a high chance of mortality, which might have a detrimental impact on quality of life and everyday function [8,9]. Patients infected with COVID-19 are classified according to the 2019 Diagnosis and Treatment Program for Novel Coronavirus Pneumonia (trial version seven). Classification of COVID-19 as mild, moderate, severe, or critical in accordance with interim recommendations from the World Health Organization[1011].

What is D-dimer? D-dimer is a soluble fragment produced when cross-linked fibrin is degraded by plasmin during fibrinolysis after fibrin formation, during fibrinolysis, plasmin breaks down this stabilized fibrin into soluble fragments, including D-dimed, which is generated only when cross-linked fibrin is present. Therefore, D-dimer reflects both coagulation and fibrinolytic activity. It is detected using specific monoclonal antibodies through various laboratory methods such as ELISA, latex agglutination, immunofluorescence, chemiluminescence assays, and point-of-care tests, each with specific advantages and limitations [12;13 ;14]. CRP is a propeptide, and an acute phase reactant synthesized in liver due to inflammatory processes; its gene has transcriptional regulation by cytokines IL1 and IL6[15 16].

LDH is an important biomarker associated with disease severity and has been linked to poor outcomes in several viral infections [17]. In covid-19 patients, LDH levels are significantly higher in severe cases composed to non-severe cases, sever infections can cause cytokine-mediated tissue damage, leading to the release of LDH from damaged cells into the bloodstream [18]. The lung dominant isoform LDH-3 may be released in greater amounts due to severe interstitial pneumonia and ARDS[19]. Elevated LDH also increases lactate production which may suppress immune responses and worsen disease progression[20]. Elevated LDH levels are inversely related to the blood oxygen saturation (P/F ratio) [6] ,meaning that the higher the LDH level, the more severe the hypoxemia in the patient. Although its elevation is commonly associated with severe lung disease, sources indicate that it is not solely a lung-specific indicator but rather a general response to damage to multiple tissues throughout the body[21;22,23]. CRP is also a strong predictor of mortality, particularly in certain groups such as diabetic patients with COVID-19, and its levels are often higher in males than in females [24].

References referred that combining these biomarkers, especially LDH and D-dimer, provides greater accuracy in predicting disease progression and identifying high-risk patients [25–27]. Elevated levels of these markers are also more likely in the elderly, smokers, and those with chronic conditions such as obesity, kidney disease, and diabetes [23,28;29].

Combining LDH and D-dimer helps improve the accuracy of predicting the course of COVID-19 by providing a more

comprehensive picture of the various metabolic processes affected in the body, as each reflects a different aspect of disease progression. While LDH is a key indicator of tissue and cell damage, particularly in severe interstitial pneumonia, D-dimer serves as a precise marker for coagulation disorders and vascular complications such as disseminated intravascular coagulation (DIC), Therefore, combining them allows for the simultaneous assessment of pneumonia severity and thrombotic risk [17,25].

Studies have shown that levels of these two factors are significantly higher in non-survivors compared to survivors, with LDH levels being up to twice the normal value and D-dimer levels triple the normal value [25]. Furthermore, concurrent elevations in several markers, including LDH and D-dimer, have been shown to be associated with significantly increased mortality rates and the need for mechanical ventilation such as NIV, HFNO, CPAP [17]. Statistically, LDH exhibits very high sensitivity, reaching 100% in some studies for predicting mortality, demonstrating a strong ability to identify high-risk cases. D-dimer, on the other hand, offers a good balance between sensitivity and specificity, at approximately 84.6% and 81.2%, respectively. Combining these parameters, especially with the addition of ferritin, raises the area under the curve (AUC) to 0.959, a very high degree of statistical accuracy in predicting mortality. In short, combining LDH and D-dimer reduces the likelihood of error in assessing case severity, as their combined elevation confirms the presence of tissue damage accompanied by coagulation system dysfunction, a hallmark of severe and fatal COVID-19 cases [17,25].

Diabetes also plays a significant role in modulating patients' responses to COVID-19 biomarkers, such as CRP, LDH, and D-dimer, by promoting inflammation, tissue damage, and coagulation disorders. Elevated levels of these markers in diabetic patients increase the risk of complications and death, making them sensitive indicators for monitoring disease severity, especially given the already high inflammatory and coagulation background in this population [24,30]. It is also important to distinguish whether these elevated levels are caused by the viral infection alone or are a result of the patient's pre-existing chronic conditions [25].

MATERIAL AND METHODS

Sample Collection

The present study was conducted on (260) individuals infected with COVID-19 SARS-CoV-2 variants (Omicron Variants) include two genders and ages between 16 to 79 years. Samples were taken from patients suspected to have COVID-19 (in whom cough, fever, headache, fatigue and gastrointestinal symptoms including diarrhea and vomiting had been identified) who had been subsequently confirmed by diagnosic PCR test. From among the 482 patients who tested positive for COVID-19 and the possible inclusion candidate, we enrolled 260 sick in-hospital patients with severe symptoms and complete laboratory records. Positive SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR) molecular assay. Data used in the study were gathered from patients with severe symptoms PCR This study also included a control group of (50) apparently healthy individuals of comparable ages and sexes. COVID-19 individuals were classified into two groups based on the severity of their symptoms (moderate, and severe) and third group consist with diabetic history (fever, cough, respiratory distress, anosmia & ageusia, and requiring for ventilation).

Estimation of plasma D-dimer, C-reactive protein, LDH and RBS

D-dimer, CRP, LDH and RBS levels were measured using automated analyzers according to the manufacturers' instructions. D-dimer was measured using the VIDAS® D-Dimer Exclusion™ II automated

immunoassay system (bioMérieux, Marcy-l'Étoile, France), a highly sensitive assay that when used in conjunction with assessment of clinical pretest probability enables safe exclusion of DVT and PE in low- and intermediate-risk outpatients within 20 minutes. The reference interpretation applied was 500 ng/mL for rule-in. CRP levels were assessed using the fully automated ABBOTT Afinion™ 2 Analyzer (Abbott Laboratories, Abbott Park, IL, USA) with dedicated Afinion™ CRP test cartridges (Product Code: 1116787 or equivalences). A rapid in vitro diagnostic assay is employed to quantitatively determine CRP in human blood; it aids clinicians by decreasing diagnostic uncertainty and directing antibiotic choices. Cut-off values of < 5.0 mg/L were considered negative; the measuring range was 5–200 mg/L for whole blood and 5–160 mg/L serum and plasma, respectively. Serum biochemistry parameters LDH and RBS were measured using the FUJI DRI-CHEM NX500i automatic biochemical analyzer (Fujifilm) according to the manufacturer's instructions.

Statistical Analysis

All experiments were performed in triplicate, and data were expressed as mean ± standard deviation (SE). Statistical analysis was carried out using SPSS. Differences between groups were analyzed using one-way analysis of variance (ANOVA), and T test. A p-value < 0.05 was considered statistically significant.

RESULTS

The results of this study showed a highly significant difference between the studied factors in patients compared to control groups, particularly D-dimer, which showed the highest significant increase compared to CRP and LDH (table 1 & table 2), This indicates that the disease strongly affects these biomarkers, causing increased coagulation activity, increased inflammatory activity, and tissue damage (lung tissue at the expense of other body tissues). Although the results comparing males and females in the groups showed gender differences in the severity of the biomarker elevations (table 6), there was no strong independent effect of sex on these biomarkers (table 3).

The results also showed significant differences in CRP selection for male patients in the age groups (under 40 years) and (41-59 years), while no significant difference was found for females (table 3). D-dimer test was not affected by age in either sex, while there was a significant age-related difference in the LDH test; the effect on this biomarker increased with age for both males and females p-value <0.001 (table 6). Diabetic patients, those with COVID-19 were particularly affected, as the results showed that their blood glucose levels were higher compared to those without DM (table 4). Diabetes strongly affects vital signs regardless of gender (table 5).

Table (1): Comparison between patients and control according to studied parameters.

Parameters	Study groups		t- test	p-value
	Patients (Mean ± SE)	Controls (Mean ± SE)		
D-dimer	863.17 ±39.06	202.60 ±24.65	6.49	0.0001*
CRP	24.31 ±2.08	3.20 ±0.36	2.81	0.0055*
LDH	443.09 ±43.88	154.10 ±10.17	4.68	0.00001*

Table (2): Comparison of biochemical parameters based on gender across study groups.

Parameters	Study groups				f-test	p-value
	Patients (Males) (Mean ± SE)	Patients (females) (Mean ± SE)	Controls (males) (Mean ± SE)	Controls (females) (Mean ± SE)		
D-dimer	763.40 ±131.57	964.90±139.23	161.81 ±26.07	146.00±13.01	11.69	0.000064*
CRP	35.62±4.75	28.52±5.25	3.21±0.36	3.37±0.30	9.66	0.000061*
LDH	458.72±64.07	365.11±51.66	154.16±10.69	161.83±10.43	15.31	0.000087*

Table (3): Age group comparation of biomarkers within each gender.

Gender	Comparison	Mean 1	Mean 2	Mean Diff	t-value	p-value	Significance
D-dimer	**Males**	<40 vs 41-59	1,124.9	1,234.6	-109.7	-0.42	0.676
		<40 vs >60	1,124.9	1,089.4	35.5	0.14	0.890
		41-59 vs >60	1,234.6	1,089.4	145.2	0.59	0.556
	Females	<40 vs 41-59	1,047.8	1,061.3	-13.5	-0.07	0.946
		<40 vs >60	1,047.8	892.7	155.1	0.99	0.324
CRP	**Males**	41-59 vs >60	1,061.3	892.7	168.6	0.97	0.335
		<40 vs 41-59	26.8	45.3	-18.5	-2.05	0.044*
		<40 vs >60	26.8	54.7	-27.9	-2.48	0.016*
		41-59 vs >60	45.3	54.7	-9.4	-0.76	0.449
	Females	<40 vs 41-59	32.4	38.9	-6.5	-0.64	0.524
		<40 vs >60	32.4	47.1	-14.7	-1.35	0.182
		41-59 vs >60	38.9	47.1	-8.2	-0.69	0.493
LDH	**Males**	<40 vs 41-59	263.3	438.8	-175.5	-1.65	0.127
		<40 vs >60	263.3	454.2	-190.9	-1.78	0.105
		41-59 vs >60	438.8	454.2	-15.4	-0.11	0.916
	Females	<40 vs 41-59	386.0	384.6	1.4	0.01	0.991
		<40 vs >60	386.0	467.4	-81.4	-0.60	0.560
		41-59 vs >60	384.6	467.4	-82.8	-0.60	0.560

Table (4): Comparison of biomarkers and blood glucose levels between diabetic patients and controls.

Parameters	Study groups		t- test	p-value
	Patients (Mean ± SE)	Controls (Mean ± SE)		
D-dimer	597.22 ± 37.84	142.22 ± 12.22	6.02	0.00001*
CRP	10.89 ± 1.22	3.37 ± 0.30	3.72	0.0006*
LDH	257.15 ± 18.11	154.17 ± 10.70	4.13	0.003*
RBS	220.80± 25.29	126.43± 5.28	2.08	0.041*

Table (5) : Gender differences in biomarkers levels among diabetic patients and controls.

Parameters	Study groups				f-test	p-value
	Patients (Males) (Mean ± SE)	Patients (females) (Mean ± SE)	Controls (males) (Mean ± SE)	Controls (females) (Mean ± SE)		
D-dimer	609.03±187.29	662.33±172.85	143±34.65	148.00±39.10	48.06	0.0068*
CRP	9.49±3.9	10.03±3.69	3.20±1.02	3.37±1.06	20.58	0.000096*
LDH	265.58±79.53	227.76±86.32	154.16±37.05	161.83±36.13	7.49	0.00020*
RBS	173.8± 25.29	169.25± 52.8	126.42± 19.75	131.42± 18.64	3.19	0.0304*

Table (6): Effect of age and sex on biochemical parameters.

Parameter	Subgroup	Mean	SE	F (Sex)	p (Sex)	F (Age)	p (Age)
D-Dimer	Male 41-59	650.07	82.95	0.05	0.82	0.45	0.64
	Male >60	846.90	147.91				
	Female <40	798.22	157.32				
	Female 41-59	765.45	81.75				
	Female >60	935.70	161.13				
CRP	Male 41-59	17.20	7.84	0.02	0.90	1.20	0.31
	Male >60	21.38	6.96				
	Female <40	8.36	2.38				
	Female 41-59	26.35	8.82				
	Female >60	26.43	12.39				
LDH	Male 41-59	229.33	29.13	1.85	0.18	12.50	<0.001*
	Male >60	313.86	25.70				
	Female <40	114.25	19.90				
	Female 41-59	207.30	23.40				
	Female >60	321.67	12.02				
RBS	Male 41-59	278.50	58.47	0.10	0.75	0.65	0.53
	Male >60	198.67	41.77				
	Female <40	189.78	53.50				
	Female 41-59	251.62	44.21				
	F>60	229.75	68.23				

DISCUSSION

The results of this study showed a very significant increase in D-dimer levels among patients, and this increase is associated with mortality rates. The average levels of this test were much higher in deceased patients compared to pandemic survivors, making this test a strong predictor of death [25]. In some cases, the increase reached nearly four times its normal values in the deceased, according to statistics [31]. D-dimer also showed a significant positive correlation with disease severity in Iraqi patients, making it a reliable marker and indicator for assessing disease progression [32]. Elevated D-dimer results in this study, for both sexes, reflect hypercoagulability. Sources indicate that 36.4% of patients in private medical clinics have abnormal levels of this indicator, necessitating treatment with anticoagulants to help reduce symptoms [33]. This supports theories that mortality is partly due to changes in microvascular structures that

facilitate clotting, with elevated D-dimer levels observed in cases of death [34].

Studies also review the importance of the D-dimer test in predicting the occurrence of pulmonary embolism (PE), Although CT scans are the best standard for diagnosing this condition, D-dimer is also an aid in assessing this condition, the severity of COVID, and mortality [34]. It is also used as a valuable tool for excluding the occurrence of venous thromboembolism [14]. Our study indicated that CRP levels increased significantly, and this increase, coinciding with an increase in D-dimer, was associated with higher mortality rates. However, the nature of the association between the two differed. Additional results also indicated an association between CRP and disease severity and mortality risk, although the strength of this association was weak in one of the studied samples, which may be attributed to the exclusion of mild cases [35]. On the other hand, another study concluded that both D-dimer and CRP levels were associated with increased mortality rates, with CRP being a stronger predictor of death, while D-dimer was more strongly associated with the occurrence of venous thromboembolism [36]. Platelet count and CRP levels were also found to be critical prognostic markers for determining COVID-19 severity, with an inverse relationship between them [37]. Studies show that CRP is a crucial biomarker for the early prediction of lung injury and clinical deterioration in COVID-19 patients[38].

CRP is an acute response protein rapidly secreted by the liver in response to inflammation or tissue damage. Its levels begin to rise within 6 to 8 hours and peak within 48 hours of symptom onset, making it an effective early indicator before the appearance of obvious clinical changes [35,38]. Elevated CRP levels are also associated with an increased risk of respiratory failure. A higher CRP level indicates a more severe disease course associated with acute lung injury and a worse prognosis [35,39]. Furthermore, it is linked to the so-called cytokine storm, resulting from an overactive immune system and the release of inflammatory cytokines that can lead to lung tissue destruction [15,38]. In this context, research findings indicate a significant correlation between CRP levels, disease severity, and mortality risk. One study demonstrated a strong correlation between CRP levels and disease severity in hospitalized patients, recommending quantitative CRP testing due to its speed and high accuracy [38]. Scientific discussions have also concluded that both CRP and LDH are significantly associated with disease severity and can be used individually or in combination as biomarkers to aid in diagnostic decision-making and patient assessment [15]. Laboratory results have shown that surgical intensive care patients have significantly higher CRP and LDH values, confirming their effectiveness as biomarkers for early prediction of disease severity [40].

As with D-dimer and CRP, LDH levels are significantly elevated in this study, particularly in patients over 40 years of age (predominantly in males). This reinforces the notion that this enzyme is a strong predictor of mortality. Patients are classified as either normal or elevated based on their LDH levels, and these levels are also used to predict clinical progression and disease course [41]. The discussion highlights that COVID-19 is a viral disease associated with a local or systemic inflammatory response that can lead to multi-organ involvement. Studies confirm elevated LDH levels in most cases, especially severe cases, reflecting the degree of tissue damage and inflammation [42]. The results indicate that levels of both D-dimer and LDH [25].

The discussion also confirms a clear and significant relationship between LDH levels and COVID-19 severity, with findings consistent with theories suggesting that LDH levels increase proportionally with worsening disease severity [43]. Elevated LDH levels are

also associated with higher mortality rates, longer hospital stays, and increased need for intensive care unit (ICU) admission, particularly in patients with the delta variant, further highlighting the prognostic value of this biomarker [43]. The discussion also explores the role of both LDH and lactate as biochemical markers reflecting disease severity and mortality risk factors, referencing the Warburg effect, a metabolic reprogramming phenomenon where inflamed cells rely on metabolic pathways similar to those observed in cancer cells [39].

On the other hand, a meta-analysis concludes that elevated LDH levels are strongly associated with COVID-19 severity, including the occurrence of respiratory distress, the need for intensive care unit admission, and an increased risk of death [44,45]. One study also concludes that LDH has a sensitivity of 80.6% in predicting abnormal findings on chest X-rays in children, where biochemical changes precede imaging changes, thus reinforcing the importance of LDH as an early indicator of pathological changes [46]. Furthermore, the clinical characteristics of COVID-19 are similar to those of SARS, confirming that an LDH level above 283 U/L is an ideal indicator for identifying severe cases [47]. Some sources also reveal that LDH at admission is an independent risk factor for disease severity and mortality, exceeding the independence of the neutrophil-to-lymphocyte ratio (NLR) [48].

The results of this study, as well as other sources, confirm that the presence of chronic diseases such as diabetes and its lack of control significantly and negatively affects the course of COVID-19 [30]. These conditions increase the likelihood of the disease progressing to severe or critical stages and are considered among the most important risk factors associated with death. Studies have shown that diabetic patients are up to 2.75 times more likely to develop severe and critical cases compared to others. One study also recorded a very high mortality rate among diabetic patients infected with COVID-19, reaching 36.7%, compared to only 5.2% among diabetic patients not infected with the virus [49]; [50]. High blood glucose levels promote viral replication within immune cells (monocytes) and increase the expression of ACE2 receptors, which the virus uses to enter cells, Diabetes also leads to a stronger inflammatory response, stimulating the production of inflammatory cytokines such as TNF and IL-6, ultimately leading to lung cell death and respiratory deterioration [41] [40].

CONCLUSION

The present investigation demonstrates that moderate-to-severe COVID-19 infection is characterized by significant alterations in inflammatory, coagulation, and metabolic biomarkers. The marked elevation of D-dimer, CRP, and LDH levels reflects the underlying pathophysiological mechanisms of the disease, including systemic inflammation, endothelial dysfunction, tissue damage, and hypercoagulability. The age-dependent elevation of LDH, particularly pronounced in patients over 40 years of age, suggests that age is a critical determinant of tissue damage severity. Furthermore, the exacerbated biomarker elevation observed in diabetic patients indicates that pre-existing metabolic dysfunction substantially amplifies the inflammatory and coagulation responses to SARS-CoV-2 infection. These findings support the clinical utility of combining D-dimer, CRP, and LDH measurements as a comprehensive biomarker panel for early risk stratification, prognostic assessment, and monitoring of disease progression in COVID-19 patients.

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