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Study of the Rule of D-Dimer in Prediction of Disease Severity in COVID-19- Infected Egyptian Patients

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ABSTRACT

Background: D-dimer level exceeding 1 µg/ml is identified as a risk factor for mortality in adult COVID-19 patients.

Objective: This study aimed to assess the role of D-dimer levels in predicting disease severity among COVID-19 infected patients in Egypt.

Patients and Methods: A cross-sectional study included 100 patients with confirmed COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) from oro-nasopharyngeal swabs, selected from the Isolation Departments of Menouf Fever Hospital and Sadat General Hospital. Fifty of them had severe COVID disease (Group I), and the other 50 (Group II) had mild to moderate COVID disease (i.e. hemodynamic stability without significant systemic illness). **Results:** Patients who died had a markedly higher mean D-dimer level compared to those still admitted (0.574 ± 0.305 mg/L) and those discharged (0.583 ± 0.466 mg/L), with significant differences between all groups except between those still admitted and those discharged (P=0.996). The ROC curve analysis for D-dimer levels showed strong diagnostic performance across different group comparisons. A cutoff of > 0.3 mg/L effectively distinguished cases from controls with an accuracy of 89.6%, sensitivity of 86.0%, and specificity of 80.0%. For distinguishing group I from group II, a cutoff of >1.3 mg/L yielded an accuracy of 88.6%, with 76.0% sensitivity and 92.0% specificity. A > 0.4 mg/L cutoff showed excellent accuracy (98.4%) in differentiating group I from group III, with 100% sensitivity and 84.0% specificity. Lastly, a > 0.3 mg/L cutoff achieved 80.7% accuracy in distinguishing group II from group III.

Conclusion: Elevated D-dimer levels were linked to severe disease progression, higher mortality, and increased inflammation. ROC curve analysis confirmed D-dimer's diagnostic value, with accurate cutoffs for distinguishing between patient groups. These findings align with broader research, supporting D-dimer testing as a useful tool for predicting severe outcomes and improving COVID-19 management.

Keywords: D-dimer, COVID-19, Egyptian patients, Prediction, Mortality rate.

INTRODUCTION

Since December 2019, the new coronavirus SARS-CoV-2 has caused a global outbreak of respiratory sickness known as COVID-19, impacting more than 100 nations [(1)]. The fundamental mechanism of SARS-CoV-2 infection is that the virus attach to the membrane-bound form of angiotensin-converting enzyme 2 (ACE2), which is then internalized by host cells. The severity of the sickness can range from asymptomatic or moderate episodes to serious respiratory infections like SARS and Middle East respiratory syndrome (MERS). Clinical signs include fever, cough, dyspnea, watery diarrhea, myalgia, severe lymphopenia, abnormal coagulation profiles, cardiovascular problems, and sudden death [(2)].

By the end of March 2020, there were over 600,000 confirmed COVID-19 cases worldwide. A significant challenge has been the overwhelming number of patients arriving at healthcare facilities, which strains available resources, particularly in critical care. Consequently, risk stratification measures are essential [(3)]. Early and effective indicators of clinical outcomes are critical for assessing the risk of COVID-19 patients. D-dimer, a marker produced by the synthesis and breakdown of cross-linked fibrin, indicating the activation of coagulation and fibrinolysis. Coagulopathy has been described, with increased D-dimer values found in 3.75–68% of COVID-19 patients [(2)]. Previous studies on community acquired pneumonia (CAP) and COPD patients shown that greater D-dimer levels are associated with more severe cases and can be used as a predictive biomarker [(4)]. A D-dimer level above 1 µg/ml is a risk factor for death in COVID-19 patients [(5)]. The present study aimed to assess the role of D-dimer levels in predicting disease severity among COVID-19 infected patients in Egypt.

PATIENTS AND METHODS

This cross-sectional study included 100 patients with confirmed COVID-19 infection by reverse transcription polymerase chain reaction (RT-PCR) from oro-nasopharyngeal swabs. They were selected from the Isolation Departments of Menouf Fever Hospital and Sadat General Hospital. Fifty of them had severe COVID disease (Group I), and the other 50 (Group II) had mild to moderate COVID disease (i.e. hemodynamic stability without significant systemic illness). Their ages ranged 25-35 years. Another 50 healthy volunteers of matched age and sex were included as a control group (Group III). Thus, we had three distinct groups.

Inclusion criteria: One or more of the following: respiratory distress, requiring oxygen support > 6 L/min due to hypoxemia. They also had hemodynamic instability symptoms and signs of systolic blood

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pressure < 90 mmHg, neurological impairment with a Glasgow Coma Scale score < 12, and signs of worsening organ dysfunction reflecting the severity of their condition.

Exclusion criteria: History of chronic respiratory diseases, cardiovascular conditions, liver or renal impairment, and any other severe comorbidities that could independently affect the severity of their COVID-19 symptoms. Additionally, individuals who refused to participate or did not provide informed consent. Pregnant women and those under the age of 18.

A thorough clinical history was taken, focusing on current COVID-19 symptoms, any previous illnesses, and any known contact with infected individuals. This was followed by a complete clinical examination, paying special attention to signs of respiratory distress, such as shortness of breath, cough, sore throat, and fever. Laboratory investigations included a complete blood count to assess hemoglobin concentration, red and white blood cell counts, the neutrophil-to-lymphocyte ratio, and platelet count. Liver function tests were also performed, including measurements of serum bilirubin, serum albumin, ALT, AST and prothrombin time and concentration. Renal function tests included blood urea and serum creatinine levels. Inflammatory markers such as CRP was assessed, along with a D-dimer assay using ELISA to check for coagulation abnormalities. Imaging studies were performed, including a chest X-ray to evaluate lung involvement and a CT scan of the chest without contrast to further assess pulmonary pathology.

Ethical consideration: After obtaining approval from The Ethical Committee of Menoufia University (10/2020 TROP25) and each patient gave informed permission. All patients and controls underwent several assessments. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Data were gathered, tabulated, and statistically analyzed using MEDCALC V.19.6.1 and SPSS version 25 on an IBM compatible personal computer. The statistics were separated into two sections: In descriptive statistics, the mean ± SD, median, and range were used to display quantitative data, while numbers (N) and percentages (%) were used to display qualitative data. Analytical statistics: The X^2-test, Fischer's Exact test, Student t-test (t), Pearson's correlation test, and ROC analysis were among the significant tests that were employed. A P-value of less than 0.05 indicates statistical significance.

RESULTS

The mean age was 53.3 ± 14.4 years for group I, 52.4 ± 16.8 years for group II, and 50.6 ± 16.5 years for group III, with no significant age differences among groups (P = 0.686). BMI significantly varied between groups (P < 0.001), with a mean BMI values of 27.0 ± 2.5 kg/m² for group I, 23.2 ± 3.5 kg/m² for group II, and 20.8 ± 1.9 kg/m² for group III. Tukey's test showed significant BMI differences between all groups (P < 0.001) (Table 1).

Table (1): Demographic and BMI data of study groups

Variable		Group I	Group II	Group III	F	P-value	Tukey's Test
Age (Years)	Range	21 - 80	19 - 90	19 - 77	0.377	0.686	
	Mean ± SD	53.300±14.417	52.380±16.787	50.580±16.469			
BMI (kg/m²)	Range	22.5 - 32.4	17.4 - 29.6	17.5 - 24.8	67.051	<0.001*	I & II: <0.001 * I & III: <0.001 * II & III: <0.001 *
	Mean ± SD	27.014 ± 2.519	23.192 ± 3.514	20.758 ± 1.886			

Sex distribution did not significantly differ among groups (P = 0.121), with group I had 56.0% males and 44.0% females, group II had 50.0% males and 50.0% females, and group III had 36.0% males and 64.0% females. Overall, the distribution was 47.3% males and 52.7% females. Smoking status differed significantly across groups (P = 0.006), with group I had 44.0% smokers, group II had 40.0% smokers, and group III had 16.0% smokers. The overall distribution was 33.3% smokers and 66.7% non-smokers (Table 2).

Table (2): Sex Distribution and smoking status among study groups

		Study group								Chi-Square	
		Group I		Group II		Group III		Total			
		N	%	N	%	N	%	N	%	X^2	P-value
Sex	**Male**	28	56.00	25	50.00	18	36.00	71	47.33	4.225	0.121
	Female	22	44.00	25	50.00	32	64.00	79	52.67		
Smoking	**Smoker**	22	44.00	20	40.00	8	16.00	50	33.33	10.320	0.006*
	Non-smoker	28	56.00	30	60.00	42	84.00	100	66.67		

The distribution of COPD between group I (44.00%) and group II (54.00%) showed no significant difference (P=0.317). Diabetes was present in 36.00% of group I and 34.00% of group II, with no significant difference (P=0.834). Hypertension was significantly more common in group I (56.00%) compared to group II (24.00%), with a P-value of 0.001. The prevalence of heart failure (6.00% in group I vs. 2.00% in group II), chronic kidney disease (6.00% in group I vs. 2.00% in group II), immunosuppressive therapy (2.00% in both groups), and malignancy (2.00% in both groups) was similar, with no significant differences (P > 0.05 for all comparisons) (Table 3 and Figure 1).

Table (3): Prevalence of comorbidities among study groups

		Study group						Chi-Square	
		Group I		Group II		Total			
		N	%	N	%	N	%	X^2	P-value
COPD	**Yes**	22	44.00	27	54.00	49	49.00	1.000	0.317
	No	28	56.00	23	46.00	51	51.00		
Diabetes	**Yes**	18	36.00	17	34.00	35	35.00	0.044	0.834
	No	32	64.00	33	66.00	65	65.00		
Hypertension	**Yes**	28	56.00	12	24.00	40	40.00	10.667	0.001*
	No	22	44.00	38	76.00	60	60.00		
Heart failure	**Yes**	3	6.00	1	2.00	4	4.00	1.042	0.307
	No	47	94.00	49	98.00	96	96.00		
Chronic kidney disease	**Yes**	3	6.00	1	2.00	4	4.00	1.042	0.307
	No	47	94.00	49	98.00	96	96.00		
Immunosuppressive therapy	**Yes**	1	2.00	1	2.00	2	2.00	0.000	1.000
	No	49	98.00	49	98.00	98	98.00		
Malignancy	**Yes**	1	2.00	1	2.00	2	2.00	0.000	1.000
	No	49	98.00	49	98.00	98	98.00		

Fever was present in 70.00% of group I and 78.00% of group II, with no significant difference (P=0.362). Headache was present in 44.00% of group I and 36.00% of group II, with no significant difference (P=0.414). Anosmia and loss of taste showed significant differences, with anosmia present in 62.00% of group I and 16.00% of group II (P<0.001), and loss of taste was present in 56.00% of group I and 12.00% of group II (P<0.001). Dyspnea was present in 36.00% of group I and 52.00% of group II, with no significant difference (P=0.107). Cough was present in 74.00% of group I and 72.00% of group II, with no significant difference (P=0.822). Diarrhea was present in 48.00% of group I and 38.00% of group II, with no significant difference (P=0.313). Epigastric pain was significantly more common in group I (86.00%) compared to group II (56.00%), with a P-value of 0.001. Hemoptysis was present in 22.00% of group I and 32.00% of group II, with no significant difference (P=0.260).

Table (4): Prevalence of symptoms among study groups

		Study group						Chi-Square	
		Group I		Group II		Total			
		N	%	N	%	N	%	X^2	P-value
Fever	**Yes**	35	70.00	39	78.00	74	74.00	0.832	0.362
	No	15	30.00	11	22.00	26	26.00		
Headache	**Yes**	22	44.00	18	36.00	40	40.00	0.667	0.414
	No	28	56.00	32	64.00	60	60.00		
Anosmia	**Yes**	31	62.00	8	16.00	39	39.00	22.236	<0.001*
	No	19	38.00	42	84.00	61	61.00		
Loss of taste	**Yes**	28	56.00	6	12.00	34	34.00	21.569	<0.001*
	No	22	44.00	44	88.00	66	66.00		
Dyspnea	**Yes**	18	36.00	26	52.00	44	44.00	2.597	0.107
	No	32	64.00	24	48.00	56	56.00		
Cough	**Yes**	37	74.00	36	72.00	73	73.00	0.051	0.822
	No	13	26.00	14	28.00	27	27.00		
Diarrhea	**Yes**	24	48.00	19	38.00	43	43.00	1.020	0.313
	No	26	52.00	31	62.00	57	57.00		
Epigastric pain	**Yes**	43	86.00	28	56.00	71	71.00	10.928	0.001*
	No	7	14.00	22	44.00	29	29.00		
Hemoptysis	**Yes**	11	22.00	16	32.00	27	27.00	1.268	0.260
	No	39	78.00	34	68.00	73	73.00		

Regarding thromboembolic events in group I, 6% of participants experienced deep venous thrombosis (DVT), compared to 2% in group II and none in group III. Similarly, pulmonary embolism (PE) was observed in 4% of participants in group I, 2% in group II, and 0% in group III (Table 5).

Table (5): Comparison of thromboembolic events among study groups

	Group I		Group II		Group III		Chi-Square	
	N	%	N	%	N	%	X^2	P-value
Deep venous thrombosis	3	6	1	2	0	0	1.031	0.310
Pulmonary embolism	2	4	1	2	0	0	0.340	0.560

There were significant differences in various hematological and biochemical parameters among the study groups**.** Platelet count was lower in group II (218.020 ± 52.256 × 10^3/µL) compared to group I (272.380 ± 65.325 × 10^3/µL, P = 0.018). White blood cell count was reduced in group III (6.902 ± 1.542 × 10^3/µL) compared to group I (9.028 ± 1.863 × 10^3/µL, P = 0.044). Lymphocyte count was higher in group II (2.641 ± 0.232 × 10^3/µL) than in group I (1.516 ± 0.145 × 10^3/µL, P < 0.001) and group III (2.280 ± 0.412 × 10^3/µL, P = 0.002). Neutrophil count was elevated in group I (7.072 ± 1.683 × 10^3/µL) compared to group III (4.033 ± 2.058 × 10^3/µL, P < 0.001). The neutrophil-to-lymphocyte ratio (NLR) was higher in group I (5.299 ± 1.151) versus groups II (3.066 ± 0.681, P < 0.001) and III (1.863 ± 0.354, P < 0.001). CRP levels were highest in group I (51.360 ± 11.871 mg/L) differing significantly from group II (16.620 ± 3.923 mg/L, P < 0.001) and group III (11.220 ± 2.771 mg/L, P < 0.001). Serum ferritin was higher in group I (381.880 ± 90.290 ng/mL) compared to group II (98.220 ± 22.427 ng/mL, P < 0.001) and group III (86.180 ± 20.552 ng/mL, P < 0.001). D-dimer levels were elevated in group I (1.800 ± 0.432 mg/L), differing significantly from group II (0.638 ± 0.151 mg/L, P < 0.001) and group III (0.234 ± 0.033 mg/L, P < 0.001). LDH was higher in group I (293.080 ± 47.664 units/L) compared to groups II (266.820 ± 32.199 units/L, P = 0.006) and III (162.680 ± 44.061 units/L, P < 0.001). Procalcitonin levels were also highest in group I (3.188 ± 0.773 ng/mL), with significant differences compared to group II (1.592 ± 0.313 ng/mL, P < 0.001) and group III (0.227 ± 0.069 ng/mL, P < 0.001). No significant differences were found in prothrombin time (P = 0.266). Serum creatinine and blood urea were higher in group I (1.074 ± 0.160 mg/dL and 40.120 ± 9.892 mg/dL) compared to group II (0.764 ± 0.187 mg/dL and 31.160 ± 4.400 mg/dL, P < 0.001 and P = 0.026, respectively). ALT, AST, total bilirubin, and serum albumin levels did not differ significantly among groups, except for total bilirubin (P = 0.029) and serum albumin, which were lower in group I (4.355 ± 0.619 g/dL) compared to group II (4.671 ± 0.304 g/dL, P = 0.004) and group III (4.441 ± 0.473 g/dL, P = 0.048) (Table 6).

Table (6): Comparison of laboratory parameters among study groups

Variable	Group I	Group II	Group III	F	P-value
Hemoglobin (Hb) (g/dL)	12.142± 1.876	12.640 ± 1.809	12.498 ± 1.519	1.087	0.340
Platelet Count (× 10^3)	272.380 ±65.325	218.020 ± 52.256	229.160 ± 55.927	4.230	0.016*
White Blood Cells (× 10^3)	9.028 ± 1.863	9.133 ± 1.325	6.902 ± 1.542	3.714	0.027*
Lymphocytes (× 10^3)	1.516 ± 0.145	2.641 ± 0.232	2.280 ± 0.412	14.049	<0.001*
Neutrophils (× 10^3)	7.072 ± 1.683	6.913 ± 1.447	4.033 ± 0.958	11.585	<0.001*
NLR	5.299 ± 1.151	3.066 ± 0.681	1.863 ± 0.354	36.983	<0.001*
CRP (mg/L)	51.360 ± 11.871	16.620 ± 3.923	11.220 ± 2.771	31.866	<0.001*
Serum Ferritin (ng/mL)	381.880 ±9.290	98.220 ± 22.427	86.180 ± 20.552	59.899	<0.001*
D-dimer (mg/L)	1.800 ± 0.432	0.638 ± 0.151	0.234 ± 0.033	104.991	<0.001*
LDH (units/L)	293.080 ± 47.664	266.820 ± 32.199	162.680 ± 4.061	135.899	<0.001*
Procalcitonin (ng/mL)	3.188 ± 0.773	1.592 ± 0.313	0.227 ± 0.069	470.566	<0.001*
Prothrombin %	90.300 ± 6.309	91.060 ± 5.032	89.180 ± 5.944	1.335	0.266
Serum Creatinine (mg/ dL)	1.074 ± 0.160	0.764 ± 0.187	0.786 ± 0.152	12.026	<0.001*
Blood Urea (mg/dL)	40.120 ± 9.892	31.160 ± 4.400	29.460 ± 4.987	5.598	0.005*
ALT (U/L)	27.040 ± 6.717	24.740 ± 5.731	25.180 ± 5.557	1.814	0.167
AST (U/L)	21.020 ± 5.020	20.760 ± 4.626	20.040 ± 4.853	0.331	0.719
Total Bilirubin (µmol/L)	0.709 ± 0.149	0.634 ± 0.151	0.597 ± 0.101	3.470	0.034*
Serum Albumin (g/L)	4.355 ± 0.619	4.671 ± 0.304	4.441 ± 0.473	5.750	0.004*

In this study, group I showed significant differences in D-dimer levels based on patient outcomes. The mean D-dimer level was highest among those who died (3.233 ± 0.462 mg/L), with a significant F-value of 6.072 (P =0.005). Post-hoc analysis revealed significant differences between deceased patients and those still admitted (P = 0.010) and between deceased patients and those discharged (P = 0.003). However, there were no significant differences in D-dimer levels based on CT chest CORAD classification, with an F-value of 0.778 (P = 0.465). In group II, D-dimer levels varied significantly by patient outcome (F=15.760, P<0.001). Patients who died had a markedly higher mean D-dimer level of 2.100 ± 0.000 mg/L compared to those still admitted (0.574 ± 0.305 mg/L) and those discharged (0.583 ± 0.466 mg/L), with significant differences between all groups except between those still admitted and those discharged (P=0.996). In contrast, D-dimer levels did not show significant variation across different CORAD classifications (F=0.111, P=0.953) (Table 7).

Table (7): D-dimer level by CT chest CORAD classification and patient outcome

Group	CT Chest CORAD Classification	N	Mean ± SD (mg/L)	ANOVA F	P-value
Group I	CORAD 3	2	1.150 ± 0.495	0.778	0.465
	CORAD 4	12	1.933 ± 0.719		
	CORAD 5	36	1.792 ± 0.864		
	Outcome			**F** = 6.072	**P** = 0.005*
	Died	3	3.233 ± 0.462		
	Still admitted	18	1.800 ± 0.756		
	Discharge	29	1.652 ± 0.760		
	Tukey's Test				
	I & II				0.010*
	I & III				0.003*
	II & III				0.787
Group II	CORAD 1	15	0.673 ± 0.461	0.111	0.953
	CORAD 2	8	0.645 ± 0.695		
	CORAD 3	26	0.625 ± 0.432		
	CORAD 4	1	0.400 ± 0.000		
	Outcome			**F** = 15.760	**P** < 0.001*
	Died	2	2.100 ± 0.000		
	Still admitted	28	0.574 ± 0.305		
	Discharge	20	0.583 ± 0.466		
	Tukey's Test				
	I & II				< 0.001*
	I & III				< 0.001*
	II & III				0.996

In group I, D-dimer levels demonstrated a significant positive correlation with respiratory rate (r = 0.291, P = 0.040), serum ferritin (r = 0.294, P = 0.038), and procalcitonin (r = 0.396, P = 0.004). Negative correlations with age (r = -0.194, P = 0.176) and BMI (r = -0.237, P = 0.097) were observed but were not statistically significant. In Group II, significant positive correlations were identified with respiratory rate (r = 0.422, P = 0.002) and a significant negative correlation with ALT (r = -0.293, P = 0.039). No significant correlations were found with age, heart rate, or blood urea (Table 8).

Table (8): Correlation of D-dimer levels with clinical and laboratory parameters

Correlations				
	D-dimer(mg/L)			
	Group I		Group II	
	r	P-value	r	P-value
Age (Years)	0.194	0.176	0.254	0.075
BMI (kg/m)	0.237	0.097	-0.005	0.970
Heart rate (bpm)	0.128	0.377	0.231	0.106
SBP (mmHg)	0.042	0.772	-0.125	0.388
DBP (mmHg)	0.060	0.681	-0.168	0.243
Respiratory rate (Breath/min)	0.291	0.040*	0.422	0.002*
Oxygen saturation (%)	-0.152	0.291	-0.029	0.841
HB (g/dL)	-0.093	0.522	-0.274	0.055
Platelet count×10^3	-0.034	0.814	-0.137	0.344
White blood cells ×10^3	-0.118	0.415	0.150	0.297
Lymphocyte×10^3	-0.206	0.151	-0.111	0.442
Neutrophil×10^3	-0.133	0.357	0.105	0.467
NLR	-0.098	0.498	0.165	0.252
CRP (mg/L)	0.085	0.559	0.029	0.840
Serum ferritin (ng/mL)	0.294	0.038*	0.249	0.081
LDH (units/L)	0.239	0.095	-0.073	0.612
Procalcitonin (ng/mL)	0.396	0.004*	-0.243	0.089
Prothrombin time and concentration	-0.074	0.608	-0.213	0.137
Serum creatinine (mg/ dL)	0.099	0.493	-0.149	0.300
Blood urea (mg/ dL)	0.104	0.471	-0.152	0.291
ALT (U/L)	-0.072	0.621	-0.293	0.039*
AST (U/L)	-0.051	0.727	-0.151	0.294
Total bilirubin (µmol/L)	0.239	0.095	-0.202	0.159
Serum albumin (g/L)	-0.041	0.777	0.215	0.133

The ROC curve analysis for D-dimer levels showed strong diagnostic performance across different group comparisons. A cutoff of > 0.3 mg/L effectively distinguished cases from controls with an accuracy of 89.6%, sensitivity of 86.0%, and specificity of 80.0%. For distinguishing group I from group II, a cutoff of > 1.3 mg/L yielded an accuracy of 88.6%, with 76.0% sensitivity and 92.0% specificity. A > 0.4 mg/L cutoff showed excellent accuracy (98.4%) in differentiating group I from group III, with 100% sensitivity and 84.0% specificity. Lastly, a > 0.3 mg/L cutoff achieved 80.7% accuracy in distinguishing Group II from Group III (Table 8). Figure (1) Illustrated the ROC analysis for different study groups.

Table (9): ROC curve analysis of D-dimer levels across study groups

Comparison	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Cases vs. Control	>0.3	86.0	80.0	89.6	74.1	89.6%
Group I vs. Group II	>1.3	76.0	92.0	90.5	79.3	88.6%
Group I vs. Group III	>0.4	100.0	84.0	86.2	100.0	98.4%
Group II vs. Group III	>0.3	72.0	80.0	78.3	74.1	80.7%

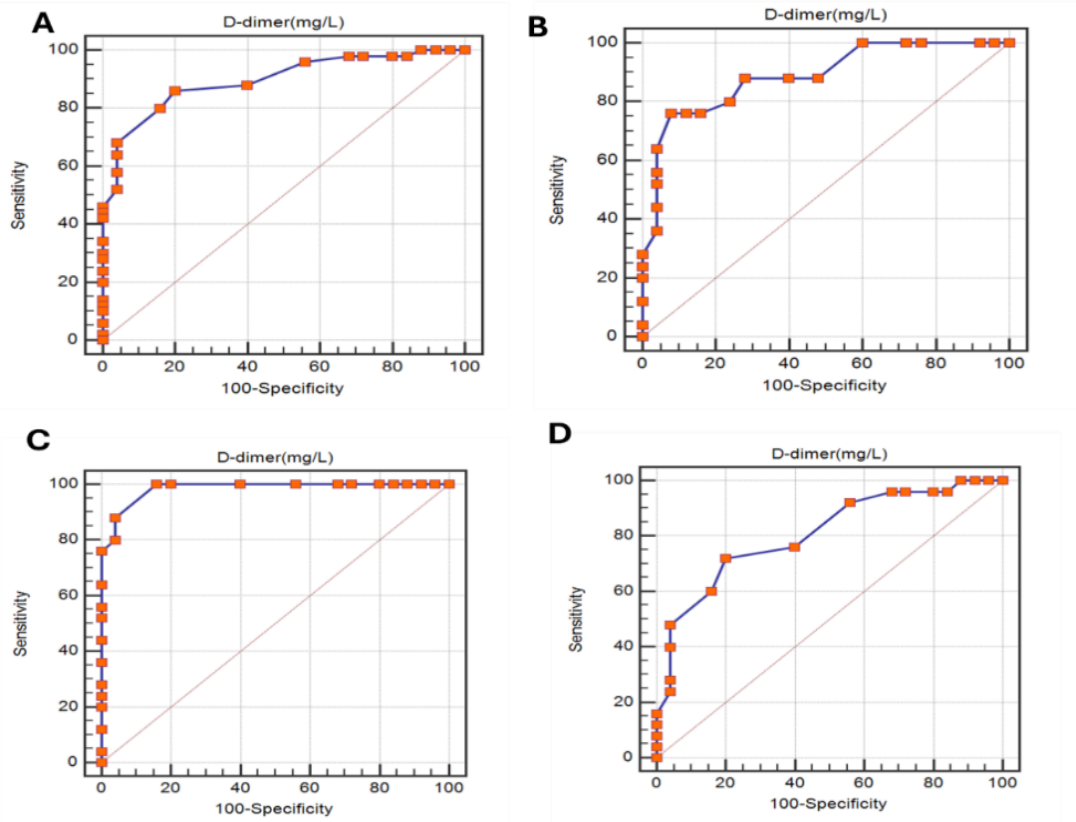

Figure (1): ROC curve depicting d-dimer levels for differentiation between study groups and controls.

DISCUSSION

There was no statistically significant difference between the studied groups regarding age or sex distribution. However, there was a significant difference in BMI across the groups (P<0.001), with group I had the highest mean BMI (27.014 kg/m²), followed by group II (23.192 kg/m²), and group III (20.758 kg/m²). Tukey's test confirmed that these differences were statistically significant between each pair of the included groups (P < 0.001). According to **Gao *et al.*** [6] out of 6910695 eligible people (mean BMI 26.78 ± 5.59 kg/m²), 13 503 (0.20%) were admitted to the hospital, 1601 (0.02%) to an intensive care unit, and 5479 (0.08%) passed away following a positive SARS-CoV-2 test. Poorer results and a higher risk of serious illness are associated with a higher BMI. Obesity is associated with chronic inflammation and altered immune responses, which can exacerbate the severity of COVID-19.

There was a statistically significant difference between the studied groups regarding the prevalence of smoking (P=0.006). Group I had the highest prevalence of smokers (44%) followed by group II (40%) and finally group III (16%). The total proportion of smokers was 33.33%, indicating that smoking status varied considerably between groups, which could be relevant for understanding differences in disease outcomes. Our results are in alignment with **Gallus *et al.*** [3] who reported that Compared to never-smokers, current and previous smokers had a 30–50% higher chance of developing COVID-19. Smoking significantly worsens the progression and severity of COVID-19. The chronic damage smoking inflicts on the respiratory system impairs mucociliary function and weakens lung defenses, making smokers more susceptible to severe respiratory infections [3].

There was a statistically insignificant difference between the studied groups regarding the prevalence of COPD and diabetes (P=0.317 and P=0.834, respectively). However, hypertension was much more prevalent in group I, affecting 56% of patients vs 24% in group II (P=0.001) demonstrating a considerable differential in prevalence. Other comorbidities including heart failure, chronic renal disease, immunosuppressive medication, and malignancy, demonstrated comparable frequencies between the groups with no significant differences (P > 0.05 for all). These findings concur with those of **Batlle *et al.*** [4] who found that patients with pre-existing hypertension who also had a SARS-CoV-2 infection were more likely to be admitted than those without hypertension. Obesity and hypertension are 50% and 48% more common in hospitalized COVID-19 patients, respectively. On the other hand, several research found that individuals with COPD had greater viral loads, more inflammatory markers, and more respiratory symptoms. According to an immunohistochemical investigation, COPD patients' bronchial epithelial and alveolar macrophage expression of IFN-β was considerably lower than that of controls [5].

In the present study, fever, headache, dyspnea, cough, diarrhea, and hemoptysis were reported at similar rates in both groups, with no significant differences observed (P > 0.05 for all). However,

anosmia and loss of taste were significantly more common in group I, with 62% and 56% of patients affected respectively, compared to 16% and 12% in group II (P < 0.001 for both). Additionally, epigastric pain was significantly more prevalent in group I, affecting 86% of participants versus 56% in group II (P=0.001). These results agree with an enormous meta-analysis, 39.2% of the 138,897 COVID-19-positive patients had taste impairment (95% CI: 35.34–43.12%) [7]. Another study reported that anosmia was seen in 22% to 68% of COVID-19 patients [8]. These similarities reinforce the relevance of anosmia and taste dysfunction as common symptoms in COVID-19 and highlight the potential differences in symptom prevalence between different patient groups according to the disease severity.

Our results revealed several significant hematological and biochemical differences among the groups studied. Group I had a significantly lower platelet count and higher neutrophil count, NLR, CRP, serum ferritin, D-dimer, LDH, and procalcitonin levels compared to groups II and III, indicating more severe inflammatory and thrombotic responses. Lymphocyte count was significantly higher in group II, while white blood cell count was lower in group III. Serum creatinine and blood urea levels were also significantly higher in group I, suggesting potential renal involvement. Additionally, serum albumin was significantly lower in group I compared to the other groups. Total bilirubin was significantly different between groups I and III. Prothrombin time, ALT, AST, and most liver function tests showed no significant differences. These findings concur with those of **Awale *et al.*** [9] who found that TLC increased steadily throughout the course of the hospital stay and with the severity of the illness. Leukocytosis was linked to increased severity and even death in the COVID-19 patients, according to another meta-analysis conducted by **Henry *et al.*** [10] According to the current investigation, the lymphocyte count was found to be normal in mild instances, but it was shown to be further declining as the illness severity rose. However, **Bellman *et al.*** [11] retrospective research of 259 COVID-19 patients revealed that anemia and disturbed homeostasis were prevalent in hospitalized patients, and that the hemoglobin levels of mild and severe illness differed statistically significantly. Significant inflammation was identified as the cause of anemia. However, no change was seen in the current investigation.

Group I had considerably higher D-dimer levels than group II (P < 0.001) and group III (P < 0.001), indicating a strong statistically significant difference between the groups under study. These elevated levels in group I suggest a higher degree of coagulation activity, which is commonly associated with more severe disease progression and complications in COVID-19 patients. Our study revealed that D-dimer levels in group I were significantly higher in patients who died (3.233 ± 0.462 mg/L), with an F-value of 6.072 (P = 0.005). Significant differences were found between deceased patients and those still admitted (P = 0.010) or discharged (P = 0.003), but not by CT chest CORAD classification. In group II, D-dimer levels were also markedly higher in those who died (2.100 ± 0.000 mg/L), with significant differences across patient outcomes (F = 15.760, P < 0.001), except between admitted and discharged patients (P = 0.996). These findings are consistent with those of **Yao *et al.*** [12] who discovered that the sole factor linked to higher chances of death was D-dimer > 2.0 mg/L at admission [OR 10.17 (95% CI 1.10–94.38), P = 0.041]. Of the patients, 74.6% (185/248) had D-dimer elevation (≥ 0.50 mg/L). **Zhan *et al.*** [13] evaluated the predictive usefulness of D-dimer for the incidence, mortality, and severity of venous thromboembolism (VTE) events in COVID-19 patients by a thorough meta-analysis. For severity, mortality, and VTE in COVID-19, they discovered that the pooled sensitivity of the D-dimer prognostic performance was 77% (95% CI: 73%-80%), 75% (95% CI: 65%-82%), and 90% (95% CI: 90%-90%), respectively, while the specificity was 71% (95% CI: 64%-77%), 83% (95% CI: 77%-87%), and 60% (95% CI: 60%-60%). D-dimer has a moderate ability to predict severe and fatal COVID-19 patients. **Soni *et al.*** [14] also found that 80.1% of hospitalized patients had D-dimer increase (≥0.50 μg/mL). Subsequent fatalities were significantly predicted by a D-dimer level ≥2.01 μg/mL (P < 0.01; HR, 3.165; 95% CI, 2.013–4.977). Of the 75 (96%) cases that resulted in death, 72 had high D-dimer levels (≥ 0.50 μg/mL).

Our results revealed that in group I, D-dimer levels significantly correlated with respiratory rate (r = 0.291, P = 0.040), serum ferritin (r = 0.294, P = 0.038), and procalcitonin (r = 0.396, P = 0.004). In group II, significant correlations were found with respiratory rate (r = 0.422, P = 0.002) and a negative correlation with ALT (r = -0.293, P = 0.039). These findings are consistent with a meta-analysis of 5350 individuals from 25 studies, which found that high CRP, PCT, and D-dimer levels were strongly related with an increased risk of poor outcomes in COVID-19 patients. Elevated CRP was associated with poor outcomes [RR 1.84, p < 0.001] and severe COVID-19 [RR 1.41]. Elevated PCT was significantly linked with poor outcomes (RR 3.92, p < 0.001), death (RR 6.26), and severe COVID-19 (RR 3.93). Elevated D-dimer was related with poor outcomes (RR 2.93, p < 0.001), death (RR 4.15), and severe COVID-19 (RR 2.42). Patients who had negative outcomes showed considerably higher blood ferritin levels, with a standardized mean difference of 0.90 [15].

Correlations of D-dimer levels with respiratory rate, serum ferritin, and procalcitonin in group I suggest that D-dimer may be an important marker of systemic inflammation and respiratory distress in these patients. The positive correlation with respiratory rate aligns with the idea that increased D-dimer levels are associated with worsening respiratory function, potentially indicating more severe disease or complications like pulmonary embolism. Similarly, the correlations with serum ferritin and procalcitonin, both markers of

inflammation and infection, highlighted D-dimer's role in reflecting the inflammatory response in severe cases.

In our study, the ROC curve analyses for D-dimer across different cutoff values showed varying performance metrics in distinguishing between the groups. At a cutoff of > 0.3 mg/L, the accuracy was 89.6% for cases vs. controls, while a cutoff of >1.3 mg/L distinguished group I from group II with 88.6% accuracy. A cutoff of >0.4 mg/L was highly effective in distinguishing group I from group III, with an accuracy of 98.4%. Finally, a cutoff of > 0.3 mg/L showed moderate effectiveness in differentiating group II from group III, with an accuracy of 80.7%. These results highlighted the utility of D-dimer as a biomarker across different clinical contexts.

Numerous studies indicate that COVID-19 individuals had higher risks of thrombotic events, including pulmonary embolism (PE), deep vein thrombosis (DVT), and disseminated intravascular coagulation (DIC). Mortality and a poor prognosis for patients were linked to the prevalence of these coagulopathies [12-14]. The diagnostic utility and precision of D-dimer in COVID-19 were assessed in a meta-analysis research conducted in 2021. The findings revealed a pooled sensitivity of 90% for DVT prediction (95% CI: 90–90%), 77% for disease severity (95% CI: 73–80%), and 75% for mortality (95% CI: 65–82%) of D-dimer. 71% (95% CI: 64–77%), 83% (95% CI: 77–87%), and 60% (95% CI: 60–60%) were the respective specificities [15]. 697 COVID-19 participants participated in a different trial that evaluated PTE, d-dimer, and CTPA. Approximately one-third of patients who were hospitalized had PTE and had noticeably elevated D-dimer values. According to their findings, a D-dimer limit of 0.5 mg/L offers a 98.2% sensitivity and a 5.7% specificity for the presence of PTE [13].

The diagnostic utility of D-dimer for VTE and PE in 79 COVID-19 patients was examined by **Artifoni *et al.* [17].** VTE and PE were confirmed by lower limb duplex ultrasonography and CTPA, respectively. They revealed that DVT patients had a markedly elevated D-dimer. For VTE and PE, the D-dimer cutoff point of 1 mg/L had an NPV of 90% and 98%, respectively. When considering a threshold of 3 mg/L, the PPV for VTE rose to 67% from 44%. Additionally, **Leonard-Loranat *et al.* [18]** looked at a research that had the same goal. A CT angiography was used for the confirmation. According to their results, a d-dimer level above 2.6 mg/L has a 100% sensitivity and a 67% specificity, making it strongly indicative of PE. Another investigation found that the cutoff point of 2.6 mg/L had a specificity of 59.5% and a sensitivity of 89.7%.

CONCLUSION

This study highlighted D-dimer's significant role as a biomarker for assessing COVID-19 severity in Egyptian patients. Elevated D-dimer levels were linked to severe disease progression, higher mortality, and increased inflammation. Correlations with respiratory distress, serum ferritin, and procalcitonin suggest its utility in reflecting systemic inflammation and thrombotic activity. ROC curve analysis confirmed D-dimer's diagnostic value, with accurate cutoffs for distinguishing between patient groups. These findings align with broader research, supporting D-dimer testing as a useful tool for predicting severe outcomes and improving COVID-19 management.

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