Research Article

Impact of age dominating over the pre-existing comorbidities influencing the D-Dimer levels in SARS-COV-2 infection

Ibtisam Obaid Almatrooshi
Medical Laboratory Sciences, Gulf Medical University, Ajman, United Arab Emirates (UAE)
Nelofar Sami Khan* (iD)
Department of Biomedical Sciences, Gulf Medical University, Ajman, United Arab Emirates (UAE)

*Corresponding Author. Email: neloferkhan@gmu.ac.ae

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Abstract
COVID-19-related disease severity is more commonly seen in elderly patients with comorbidities, and hypercoagulability has been demonstrated to be involved in the disease progression. This study aimed to evaluate the level of D-Dimer in hospitalized SARS-COV-2 infected patients and to determine the influence of age, gender, Body Mass Index (BMI), and comorbidities on D-dimer value and correlate it with disease severity. This case-control retrospective study retrieved patient data on demographic characteristics, vital functions, comorbidities, disease severity [National Institutes of Health (NIH) classification], and D-dimer from medical records of Thumbay University Hospital, Ajman, United Arab Emirates. SPSS-Version-28 was used for data analysis; a Chi-Square test was done to compare the distribution of comorbidities and disease severity between demographic categories. An independent sample t-test and one-way ANOVA were done to compare mean levels of D-Dimer between two or more categories, respectively. The majority of patients were males, >40 years of age, overweight/obese, with 30% having one comorbidity and 20% having ≥2 comorbidities. Among the total, three-quarters had moderate, and one-quarter had severe disease conditions, irrespective of gender or BMI, with an increasing trend of severe cases in the older age group and with comorbidities. Increased D-dimer levels were seen in the majority of SARS-COV-2-infected hospitalized patients, with age as the primary determinant, irrespective of absence or presence of comorbidity, though the trend of higher prevalence of elevated D-dimer value in the multiple comorbid groups and more severe condition was observed. Supporting SAR-COV-2 as a coagulopathic condition, D-dimer concentrations can be a helpful marker of disease progression and can be considered to guide the clinical treatment.

Keywords: Coagulopathy, Comorbidity, COVID-19, D-dimer, SAR-COV-2 infection

INTRODUCTION

COVID-19, caused by the coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), is a deadly infectious disease primarily affecting the respiratory system. Until recently, more than 503 million infected cases of COVID-19 and 6.5 million deaths have been reported globally (National Institutes of Health, 2021). Around 86% of patients infected with SARS-CoV-2 tend to be asymptomatic or mildly symptomatic. Others may show severe respiratory problems because of the spread of the infection to the lungs, causing pneumonia. This severity is more commonly seen in elderly patients with comorbidities, most commonly hypertension, diabetes, and cardiovascular diseases (CVD) (Abu-Farha *et al.*, 2020).

SARS-CoV-2 causes a disease spectrum through various mechanisms, including altering coagulation parameters and increased D-dimer levels due to haemostatic abnormalities (Marietta *et al.*, 2020; Bikdeli *et al.*, 2020). Researchers have reported coagulopathy analysis in SARS-COV-2 patients (Long *et al.*, 2020; Zou *et al.*, 2020). Thrombotic complications and hypercoagulability were seen in patients who were admitted to the Intensive Care Units with severe symptoms (Thachil *et al.*, 2020). D-dimer and coagulation parameters were reported to be elevated in the non-surviving group of patients compared to the surviving group, suggesting

an association of coagulopathy with prognosis. Thus, an increased concentration of D-dimer is a strong indicator of mortality in SARS-COV-2 patients (Long *et al.*, 2020; Tang *et al.*, 2020).

SARS-CoV-2 appears not to possess intrinsic procoagulant effects, but the coagulopathy emanates from the inflammatory response and endothelial activation due to damage caused by the virus. SARS-CoV-2 brings about lung inflammation progressing into a cytokine storm in most severe cases. The severe pulmonary inflammation leads to vasculature activation and damage and may trigger pulmonary thrombosis, a hypercoagulation of blood affecting the circulatory system (McGonagle *et al.*, 2020).

Patients with diabetes mellitus have a higher risk of developing a severe infection of SARS-CoV-2, and poor glycaemic control was observed, which indicates an increased need for hospitalization. Microvascular and macrovascular complications of diabetes mellitus were significantly correlated with elevated mortality risk in patients with SARS-COV-2 (Lim *et al.*, 2021). Similarly, various cellular and molecular mechanisms are postulated to understand the exacerbated impact of SARS-COV-2 in patients with pre-existing hypertension and CVD complications (Moccia *et al.*, 2020; Shibata *et al.*, 2020).

The precise molecular and cellular mechanisms underlying the increased coagulability of blood in SARS-COV-2 patients have not been fully understood. Literature has identified increased D-dimer levels as indicators and predictors of morbidity and mortality in severe cases. Therefore, there is a need to determine the effect of comorbidity on D-dimer levels of infected patients. This study aimed to evaluate and compare the level of D-Dimer in hospitalized SARS-COV-2 infected patients with and without comorbidities. Further, to determine the difference in the D-Dimer parameter among SARS-COV-2 patients according to age, gender, and Body Mass Index (BMI). Finally, to correlate the findings with disease severity.

MATERIALS AND METHODS

Study design
The research design is a case-control (retrospective) in which D-dimer levels of SARS-COV-2 infected hospitalized patients with comorbidities and without comorbidities were compared.

Study population
It included male and female adult hospitalized patients infected with SARS-COV-2, confirmed by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) whose d-dimer test was available in the records.

Study settings
The study was conducted at Gulf Medical University and Thumaby Hospital, Ajman, UAE, and included patients admitted between March to June 2021.

Ethical considerations
The study was approved by the Institutional Review Board of Gulf Medical University, Ajman. As the study used the data extracted from medical records implementing complete anonymization, it was exempted from specific patient consent.

Exclusion criteria
Patients with diseases influencing the D-dimer level, such as leukaemia, asthma, or pregnancy, were excluded from the study.

Sample size calculation
The required sample size for this study was 140, as calculated based on Hui Long et al. observation using Stephen Thompson's Equation (Long *et al.*, 2020).

Methods of data collection
Medical records from the Hospital Management System of SARS-CoV-2 patients from Thumbay Hospital, Ajman, were scanned. The details of 107 patients qualifying the inclusion criteria were enrolled retrospectively. Data on demographic characteristics, vital functions, comorbidities, disease severity, and D-dimer were retrieved. The reference range of D-dimer was up to 232 ng/mL, according to Thumbay Lab. The severity of SARS-CoV-2 was defined according to National Institutes of Health (NIH) clinical management, considered severe illness if a patient has SpO_2 <94% on room air at sea level and a respiratory rate of >30 breaths/min (National Institutes of Health, 2021).

Statistical analysis of data
Data were recorded on an Excel sheet and transferred to SPSS (Statistical Package for Social Sciences) Version 28. Continuous variables are expressed as mean and standard deviation, and categorical variables are expressed as counts and percentages. A Chi-Square test was done to compare parameters between different demographic categories. An Independent sample t-test was used for the comparison of the mean levels of D-Dimer among COVID-19 patients between two categories, and one-way ANOVA was used to find the difference in the mean between more than two categories.

RESULTS

The demographic distribution of 107 hospitalized patients enrolled in this study is shown in Table 1. The majority of the SARS-COV-19 patients were above 40

years of age (76; 71%), males (74; 69.2%), overweight (52; 48.6%), or obese (40; 37.4%).

Table 2 shows the distribution of comorbidities among patients, with 53(49.5%) as a control group having no comorbidity. Patients with only one comorbidity were 31 (29%) distributed as 15(14%) participants with diabetes mellitus (DM), 13(12.1%) with hypertension (HTN), and 3(2.8/%) with cardiovascular diseases (CVD). For those with a combination of two or more comorbidities, there were 23 (21.5%) of the patients.

Table 3 demonstrates vital signs and other symptoms among the patients. Due to missing data on SPO$_2$ from two patients, only 24 out of 107 patients were considered to have severe illness according to NIH guidelines (National Institutes of Health, 2021). The most common symptoms at hospitalization were fever (86; 80.4%), cough (67; 62.6%), and dyspnoea (58; 54.2%). The least manifested symptoms were headache (16; 15%) and sore throat (9; 8.4%).

Table 4 shows the distribution of comorbidities among patients with respect to age, gender, BMI, and disease condition. In the control group with no comorbidity, 23 (74.2%) were £ 40 years, and 30 (39.5%) were above 40. In the two or more comorbidity groups, almost all the participants were more than 40 years of age.

Though the majority of patients were males, the percentage distribution of gender in control, one, and ≥2 comorbidities groups were almost similar, with no statistical difference.

Regarding the BMI, as the number of counts was less than five in two of the cells, the valid P value was not available. However, 63.5% of the overweight and 40% of the obese group had no comorbidity, and the remaining had one or two or more comorbidities.

Table 4 also shows moderate disease conditions among the majority of the patients with a clear trend of increasing the patients in the severe group with the increase in the number of comorbidities.

Table 5 represents the prevalence of disease severity and D-Dimer among various demographic subgroups of patients. Among the total, 77% have a moderate condition, and 23% have severe, with no significant difference in the trend, irrespective of age, gender, or BMI. Elevated D-dimer was seen in 70% of the total, with more in the higher age group and no significant difference due to gender or BMI. The mean value of D-dimer was significantly higher in severe patients (536; SD 551) compared to moderate condition patients (378; SD 366). Also, the mean D-dimer was significantly higher in older than 40 years of age compared to the younger age group with a P value ≤ 0.5. However, within the moderate or severe condition groups, there was no statistically significant difference with respect to gender or BMI.

Table 6 compares the comorbidity group to the control concerning disease severity and D-Dimer value.

Table 1. Demographic distribution of patients

Characteristics of patients	Groups	N=107 n (%)
Age	≤ 40	31 (29)
	> 40	76 (71)
Gender	Male	74 (69.2)
	Female	33 (30.8)
BMI	Normal	13 (12.1)
	Overweight	52 (48.6)
	Obese	40 (37.4)
	Not reported	2 (1.9)
Nationality	Middle East	31 (29)
	South Asians	72 (67.3)
	Others	2 (1.9)
	Not reported	2 (1.9)

Table 2. Distribution of comorbidities among patients (DM: Diabetes Mellitus; HTN: Hypertension; CVD: Cardiovascular Diseases)

Comorbidities of patients	N (%)
Control group (No Comorbidity)	**53 (49.5)**
Only one comorbidity	**31 (29)**
DM	15 (14)
HTN	13 (12.1)
CVD	3 (2.8)
Two or more comorbidities	**23 (21.5)**
DM & HTN	12 (11.2)
DM & CVD	3 (2.8)
HTN & CVD	1 (0.9)
DM & HTN & CVD	7 (6.5)
Total	**107 (100)**

Among the total patients, the mean D-dimer increases as the number of comorbidity increases, though the difference is not statistically significant. Also, the elevated D-dimer was equally seen in the control group (68%) and one comorbidity group (68%). However, in the ≥2 comorbidity group, more patients had high D-dimer (78.3%), and this trend is reflected in both the moderate and severe condition patients' groups.

Looking at the one comorbidity group, 65.2% of moderate and 75% of severe condition patients have elevated D-dimer values. Similarly, 73.3% of the moderate and 83.3% of severe condition patients have elevated D-dimer values. The valid P value to support the statistically significant difference is unavailable as the number of counts was less than five in some cells.

DISCUSSION

SARS-Cov-2 caused an infectious disease primarily affecting the respiratory system. The disease's symp-

Table 3. Distribution of vitals and other symptoms among the patients

Vitals of patients	Categories	Prevalence N=107 n (%)
Pulse	≤100	65 (60.7)
	>100	42 (39.3)
Respiratory Rate	≤30	81 (75.7)
	>30	26 (24.3)
SpO$_2$	<94	24 (22.4)
	≥94	81 (75.7)
	Not reported	2 (1.9)

Other symptoms	Present n (%)	Absent n (%)
Fever	86 (80.4)	21 (19.6)
Cough	67 (62.6)	40 (37.4)
Dyspnoea	58 (54.2)	49 (45.8)
Headache	16 (15)	91 (85)
Sore Throat	9 (8.4)	98 (91.6)

toms included fever, difficulty breathing, cough, and invasive lung lesions. Dyspnoea and respiratory distress syndrome were the most severe symptoms seen in 54% and 75% of patients, respectively in the present study (Table 3).

The present findings showed gender disparity in disease prevalence, with 69.2% male and 30.8% female patients (Table 1), thus indicating that males were more likely than females to be COVID-19 patients. Several epidemiological studies globally reported similar outcomes with higher morbidity and mortality in males than females. This trend is attributed to elevated expression of angiotensin-converting enzyme-2 receptors for coronavirus in males than females. Additionally, sex-based immunological differences determined by sex hormones and the X chromosome increase the susceptibility of males to disease (Bwire, 2020). Other factors are lifestyle and behavioural differences in gender, like greater smoking levels in men than women. The irresponsible attitude of men overlooking their health, not taking preventive measures of frequent hand washing, wearing a face mask, and obeying stay-at-home orders, all result in more males getting COVID-19 infection, opined by Dr. Griffith from Vanderbilt University, Nashville, Tennessee (Griffith, *et al.,* 2020).

Furthermore, the present results (Table 1) demonstrated that the most infected age group was above 40 years (71%). This result was in line with other reports worldwide that the older population was hit with some of the worst effects of the pandemic because of the elevated prevalence of mental health issues, elaborated by a Psychologist from Erasmus University, Rotter-

dam, Netherlands (Van Jaarsveld, 2020) and physical health problems, explained at the molecular level by researchers from Glenn Center for Biology of Aging Research, Blavatnik Institute, Harvard Medical School, Boston, USA (Mueller, *et al.,* 2020).

Half of the patients had no comorbidity, 29% had only one, and 21.5% had two or more comorbidities (Table 2). The most common comorbidities were diabetes, and hypertension, similar trends commonly seen in many studies (Hannawi *et al.*, 2021; Sahni *et al.*, 2020; Mishra *et al.*, 2020). The higher prevalence of COVID-19 among overweight (49.5%) and obese (38%) individuals in the patient were in line with other reported studies revealing 39% increase in severe illness among obese patients (Sharma *et al.*, 2020). Higher BMI increases the risk of infection due to the suppression of immune response, as explained in the Bioscience report (Amin *et al.*, 2021). Obesity is highly prevalent in United Arab Emirates, and 60% of obese patients in this study had one or more comorbidities. In this patient population, elevated D-dimer was found in most cases (70%), but the distribution was not significantly different based on BMI (Table 4). However, many researchers found that obesity and being overweight increased the risk for thrombosis and severe covid-19 symptoms, reported by US Department of Health and Human Services/Centers for Disease Control and Prevention (Amin *et al.*, 2021; Kompaniyets *et al.,* 2021).

Most of the present studied patients had moderate disease symptoms; among the severe patients, more were older than 40. However, there was no statistically significant difference in the distribution of disease conditions as regards age, gender, or BMI (Table 5). Other studies from Wuhan, China, have also reported that most patients infected with the SARS-COV-2 virus develop mild to moderate symptoms and recover without needing specific treatment (Chen *et al.*, 2020).. It is also reported that severe symptoms are more likely to affect the elderly and those with other underlying medical complications, like hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer (Mishra *et al.,* 2020; Miri *et al.,* 2021; Yang et al., 2020). The trend of more severe condition cases with an increasing number of comorbidities was visible in the present study (Table 4).

Higher age is the only factor significantly associated with the elevated D-dimer and higher mean D-dimer compared to the younger group, and no influence of gender, BMI, or comorbidity was observed (Table 5), with a similar result reported in another study that included data from 45 Dutch hospitals (Henkens *et al.*, 2022). A high D-dimer concentration indicates an increased risk of abnormal blood clotting and has been associated with the progression of SARS-COV-2 disease (Henkens *et al.*, 2022). The study conducted in a

Table 4. Distribution of comorbidities among patients with respect to age, gender, and BMI

Comorbidities	Total N=107 n (%)	Age in years ≤40 N=31 n (%)	Age in years >40 N=76 n (%)	P Value	Gender Male N=74 n (%)	Gender Female N=33 n (%)	P Value	BMI Normal N=13 n (%)	BMI Overweight N=52 n (%)	BMI Obese N=40 n (%)	P Value	Condition Moderate N=81 n (%)	Condition Severe N=24 n (%)	P Value
Control (No comorbidity)	53 (49.5)	23 (74.2)	30 (39.5)	0.002	38 (51.4)	15 (45.5)	0.837	3 (23.1)	33 (63.5)	16 (40.0)	-	43 (81.1)	10 (18.9)	0.600
1 Comorbidity	31 (29.0)	7 (22.6)	24 (31.6)		21 (28.4)	10 (30.3)		6 (46.2)	10 (19.2)	15 (37.5)		23 (74.2)	8 (25.8)	
≥2 Comorbidities	23 (21.5)	1 (3.2)	22 (28.9)		15 (20.3)	8 (24.2)		4 (30.8)	9 (17.3)	9 (22.5)		15 (71.4)	6 (28.6)	

Table 5. Prevalence of disease severity and D-Dimer among various demographic subgroups of patients (A P-Value less than 0.05 considered to be significant);*Total number of patients ranged from 103 to 107 in different categories due to 2 missing each from BMI and SpO$_2$

Demographic Characteristics of patients		No. of Patients N*	Condition Moderate n (%)	Condition Severe n (%)	P-Value	Mean D-Dimer Moderate Mean (SD)	P-Value	Mean D-Dimer Severe Mean (SD)	P-Value	D-Dimer Total	D-Dimer ≤232 n (%)	D-Dimer >232 n (%)	P-Value
Total		105	81 (77.1)	24 (22.9)	0.001	378 (366)	-	536 (551)	-	422 (426)	32 (30)	75 (70)	0.001
Age	≤40	31	26 (83.9)	5 (16.1)	0.232	265 (134)	0.404	315 (140)	0.05	271 (133)	14 (45.2)	17 (54.8)	0.028
	>40	74	54 (73.0)	20 (27.0)		435 (429)		581 (594)		484 (486)	18 (23.7)	58 (76.3)	
Gender	Female	33	26 (78.8)	7 (21.2)	0.672	343 (218)	0.447	424 (159)	0.324	358 (208)	10 (30.3)	23 (69.7)	0.952
	Male	72	54 (75.0)	18 (25.0)		396 (422)		574 (631)		451 (492)	22 (29.7)	52 (70.3)	
Body Mass Index	Normal	13	11 (84.6)	2 (15.4)	0.605	367 (175)	0.818	407 (192)	0.824	373 (169)	3 (23.1)	10 (76.9)	0.802
	Over weight	50	36 (72.0)	14 (28.0)		333 (184)		598 (712)		424 (433)	15 (28.8)	37 (71.2)	
	Obese	40	31 (77.5)	9 (22.5)		366 (357)		462 (184)		385 (330)	13 (32.5)	27 (67.5)	

dedicated COVID hospital in North India reported that SARS-COV-2 patients have very high peak D-dimer concentrations in diabetic patients compared to non-diabetic (Mishra *et al.*, 2020). Another study from the University Hospital Center of Oujda (Morocco) also reported very high D-dimer levels among diabetic patients compared to non-diabetic patients. Adding that D-dimer level >2885 ng/mL was a strong predictor of mortality in diabetic patients(Miri *et al.*, 2021). Similar results were also reported in hypertensive patients. A study conducted on COVID 19 patients hospitalized at the Central Hospital of Wuhan, China, reported hypertension and elevated D-dimers increased mortality in patients (Yang *et al.*, 2020). High D-dimer among hypertensive patients compared to non-hypertensive is reported in another study from Hospital of Jianghan University, Wuhan, China (Xia *et al.*, 2021). Another study conducted on COVID-19 patients from three hospitals in Hubei Province, China, showed higher levels of D-dimers among those with CVD compared to those without. Also, D-dimer levels were directly related to the disease severity among COVID-19 patients with non-survivors had higher level compared to survivors pointing to think about anticoagulant treatment among severe cases (Li *et al.*, 2020). Also reported from Central People's Hospital of Yichang, Hubei, high prevalence of comorbidities and D-dimer among the severe patient group compared to non-severe group (Zhang *et al.*, 2021).

The present sample of patients was small, and sequential D-dimer values were unavailable in the laboratory records. Therefore, in the present results, despite showing a higher prevalence of elevated D-dimer value in the multiple comorbidity group, a statistically significant difference compared to the control was not seen. However, the D-dimer value was high in most SARS-COV-2-infected hospitalized patients, irrespective of other factors.

Conclusion

The present study concluded that D-dimer levels in SARS-COV-2-infected hospitalized patients increased, irrespective of the presence or absence of comorbidity with age as the main determinant influencing D-dimer elevation, though the trend of higher prevalence of elevated D-dimer value in the multiple comorbid groups was observed. This study supports that SAR-COV-2 is a coagulopathic condition with D-dimer representing a direct link between SAR-COV-2 infection and disease progression. D-dimer assays are frequently used in clinical practice. Therefore, without other results, D-dimer concentrations can be a helpful marker of disease progression. The information on elevated D-dimer may also be considered to guide clinical treatment. It is recommended to elaborate the study, including more data from other hospitals allocated for SARS-COV-2 patients. The lab reporting for D-dimer and complete coagulation parameters conducted sequentially at different phases of the disease will give an accurate picture of the association between coagulopathy and SARS-COV-2 disease. Due to the unavailability of data on coagulation parameters, this study was confined to only the D-dimer value measured at the time of patient admission.

Table 6. Comparison of D-Dimer value between the comorbid groups to the control concerning patient condition as moderate or severe

Patient Condition Category	Number of Patients	D-Dimer (ng/mL)		D-Dimer (ng/mL)		
		Mean (SD)	P-Value	≤ 232 n(%)	>232 n(%)	P-Value
Total Patients	Control (N=53)	366 (228)		17 (32.1)	36 (67.9)	
	1 Comorbidity (N=31)	445 (567)	0.330	10 (32.3)	21 (67.7)	0.627
	≥2 Comorbidities (N=23)	521 (543)		5 (21.7)	18 (78.3)	
Moderate Condition Patient	Control (N= 43)	354 (228)		14 (32.6)	29 (67.4)	
	1 Comorbidity (N=23)	366 (379)	0.583	8 (34.8)	15 (65.2)	0.533
	≥2 Comorbidities (N=15)	467 (612)		4 (26.7)	11 (73.3)	
Severe Condition Patient	Control (N=10)	422 (235)		3 (30.0)	7 (70.0)	
	1 Comorbidity (N= 8)	672 (921)	0.652	2 (25.0)	6 (75.0)	-
	≥2 Comorbidities (N= 6)	548 (240)		1 (16.7)	5 (83.3)	

versity, for their guidance in statistical analysis.

Conflict of interest
The authors declare that they have no conflict of interest.

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