The Incidence of Venous Thromboembolism among Hospitalized COVID-19 Positive Patients: A Multicenter Study

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Abstract

Background

Coagulation disorders are frequently encountered among coronavirus disease 2019 [COVID-19]-infected patients, especially among those with more severe symptoms. This study aims to determine the incidence and risk factors of venous thromboembolism [VTE] in COVID-19 patients.

Methods

The retrospective observational Cohort study was conducted from March to July 2020. All adult patients [>18 years old] with laboratory-confirmed COVID-19 were included. Laboratory data and real-time reverse transcriptase-polymerase chain reaction [rRT-PCR] for SARS-CoV-2 were obtained from medical records and correlated with those who developed VTE.

Results

In this study, 1024 patients were identified with confirmed COVID-19, of which 58 patients [5.7%] had VTE. In the bivariate analysis, VTE was associated with chronic kidney disease, hematological disorder, cancer, and high D-dimer>0.50 mg/l. The analysis of the data showed that the number of patients diagnosed with cancer was significantly higher in the VTE group [8 patients, 13.8%] than the non-VTE group [47 patients, 4.9%; p=0.003]. Patients with cancer were 2 times more likely to have VTE [adjusted odds ratio [1]=2.614; 95% CI=[1.048 – 6.519]; p=0.039]. The sensitivity analyses showed that individuals with high D-dimer>0.50 mg/l were more likely to have VTE.

Conclusion

VTE is more prevalent among individuals with chronic conditions, including cancer. Healthcare professionals should closely monitor individuals with high risk of developing VTE, including those with COVID-19 and chronic conditions, to prevent unwanted complications.

1. Introduction

In December 2019, the novel virus severe acute respiratory coronavirus 2 [SARS-CoV-2] was identified and sparked a worldwide pandemic [1, 2]. Symptoms associated with COVID-19 disease varied widely and ranged from asymptomatic or mild self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death [3, 4].

Coagulation disorders are frequently encountered among COVID-19-infected patients, especially among those with more severe disease symptoms. The incidence of these disorders is not well established [5]. Several laboratory tests could contribute to identifying venous thromboembolism [VTE] events in COVID-19-positive patients, especially in patients with severe respiratory symptoms [6, 7]. High D-dimer and mild thrombocytopenia are the most common laboratory values observed in this population [6, 7].

Many factors can affect blood hemostasis, thereby increasing the risk of thromboembolic events [8]. Factors that may induce vascular endothelial damage and increase the risk of VTE include older age, prolonged immobilization, dehydration, acute inflammatory state, presence of other cardiovascular risk factors or cardiovascular disease, previous history of VTE, classical genetic thrombophilia, mechanical ventilation, central venous catheterization, and surgery [8]. Daily assessment and initiation of anticoagulant prophylaxis are efficient strategies to reduce the risk of VTE [9, 10].

The aims of this study were to measure the incidence of VTE in all COVID-19-positive patients and to identify the risk factors for developing VTE in COVID-19-positive patients.

2. Methods

2.1. Setting and ethical approval

The study involved the following hospitals: Prince Sultan Medical Military City [Riyadh], King Abdullah Medical City [Makkah], King Fahad Medical City [Riyadh], Prince Mohammad Bin Abdulaziz Hospital [Riyadh], King Fahad Hospital of University [Khobar], and King Faisal Specialist Hospital and Research Center [Riyadh]. All centers are tertiary care hospitals with full-time availability of diagnostic modalities for diagnostic COVID-19 and VTE. Ethical approvals were obtained from the research ethics committee in each hospital.

2.2. Study population

Eligible patients were identified through the electronic pharmacy system. All admitted adult patients [>18 years old] with laboratory-confirmed COVID-19 with or without VTE were included. Confirmed cases included positive real-time reverse transcriptase polymerase chain reaction [rRT-PCR] test of nose/throat swab or sputum sample according to the WHO definition [11]. VTE was defined based on the ICD9-CM code. Exclusion criteria were patients discharged before 24 hours of admission and children or patients≤18 years old.

2.3. Study design and data collection

This retrospective observational cohort study was conducted from March to July 2020. Patients' data were retrospectively reviewed from the day of admission until hospital discharge or death. Clinical data were collected using a standardized data collection form. The following information was obtained: demographic data including [age, gender, body mass index], medication history, underlying comorbidities [acute coronary syndrome, heart failure, diabetic mellitus [DM], hypertension, dyslipidemia, chronic kidney dieses, hematological disease, cancer, thyroid dysfunction, lung or liver disease], vital signs, laboratory data, rRT-PCR for SARS-CoV-2, and coagulopathy results [fibrinogen, and D-dimer levels].

2.4. Outcomes

- The primary outcome was the incidence of VTE among hospitalized COVID-19-positive patients.

- The secondary outcome was identifying the risk factors associated with increased incidence of VTE among hospitalized COVID-19-positive patients.

2.5. Explanatory Variables

We hypothesized that predisposing factors, comorbid physical conditions, certain medications, and high D-dimer may affect the presence of VTE. Therefore, explanatory variables included the following: 1] predisposing factors: i. age [19-39, 40-49, 50-59, ≥60]; ii. sex; and iii. body mass index [underweight/normal [below 24.9]; overweight [25-29.9]; obese [≥30]]; 2] comorbid physical conditions: the presence of diabetes mellitus, hypertension, dyslipidemia, heart failure, ischemic heart disease, chronic kidney disease, dialysis, thyroid dysfunction, hematological disorders, lung disease, liver disease, and cancer; 3] medications: antiplatelet, anticoagulant, anti-diabetics, angiotensin-converting enzyme inhibitor [ACEIs] and angiotensin receptor blockers [*ARBs*], spironolactone, statin, diuretics, beta-blockers, calcium channel blockers, inhaled corticosteroid, and levothyroxine; and 4] high D-dimer>0.50 mg/l [yes, no] and high fibrinogen>200 mg/dl [yes/no]. We included all the explanatory variables in the explanatory variables. Nevertheless, we included only variables associated with VTE from the bivariate analysis in the multivariable analysis.

2.6 Statistical Analysis

Categorical variables were compared using a Chi-square test or Fisher's exact tests. Multivariable logistic regression methods were used to explore the risk factors associated with VTE. In the final model, the following variables were included: age, sex, diabetes, hypertension, dyslipidemia, heart failure, ischemic heart disease, chronic kidney disease, thyroid dysfunction, hematological disorders, and cancer as well as the use of ACEIs/ARBs, statins, beta-blockers, and levothyroxine. P-values of less than or equal to 0.05 were defined as statistically significant. The statistical analysis was conducted using STATA 16.

3. Results

3.1 Description of the Study Sample

The study sample comprised 1,024 patients with confirmed COVID-19 who were admitted in the study site hospitals between March and July 2020. Of the 1,024 patients, 58 patients [5.7%] had VTE. The majority of patients were males [n=653, 64%]. Patients aged 60 years or older were more represented than other age groups [36.8%; Table 1]. The most prevalent comorbidities were hypertension [43.7%] and diabetes [41%]. The most common medication classes were antihypertensive [46.2%], antidiabetics [20.9%] and statins [17.9%]. Details of patients' characteristics are reported in Table 1.

Comorbidities were similar in patients with and without venous thromboembolism with the exception of chronic kidney disease, thyroid dysfunction, hematologic disorders, and cancer, in which comorbidities were significantly higher in venous thromboembolism patients [p=0.032, p=0.002, p<0.001, p=0.003, respectively; Table 1]. With regard to medications history, VTE was significantly higher in patients using

ACEIs/ARBs, statin, and beta-blockers [p=0.004, p=0.047, p=0.045, respectively]. Furthermore, a higher percentage of patients with VTE had high D-dimer and fibrinogen than those without VTE [93.8% vs. 70.6%; p=0.001 and 52.6% vs. 31.9; p=0.008, respectively]. Table 1 shows the characteristics of hospitalized adults with COVID-19 by the presence of venous thromboembolism and relevant comparisons between the explanatory variables and the presence of VTE.

3.2 Factors Associated with VTE

Table 2 shows the results of the multivariable logistic regression, including adjusted odds ratios [AOR] and 95% confidence intervals [CI]. The multivariable logistic regression analysis identified only one factor associated with increased VTE incidence: patients diagnosed with cancer. An analysis of the data showed that the number of patients diagnosed with cancer was significantly higher in the VTE group [8 patients, 13.8%] than the non-VTE group [47 patients, 4.9%; p=0.003]. Patients with cancer were 2 times more likely to have VTE [AOR=2.614; 95% CI=[1.048 – 6.519]; p=0.039; Table 2]. Other factors that could be risk factors for the incidence of VTE included comorbidities such as diabetes, hypertension, dyslipidemia, and heart failure. However, these factors were not statistically significant between the two groups.

3.3 Sensitivity Analysis

There was substantial missing data for D-dimer [n=155]. Therefore, we computed a separate multivariable logistic regression model that included the identified explanatory variables and the D-dimer on the presence of VTE [Table 3]. Most results were similar to the original results. However, we found a significant relationship between hematological disorders and the presence of VTE. Patients with hematological disorders were more likely to have VTE than their counterparts without such disorders [AOR: 9.064; p=0.006]. Furthermore, patients with high D-dimer were significantly more likely to have VTE [AOR: 6.874; p=0.002; Table 3].

Note: *significant *p*-value$\leq$0.05. ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; COVID-19: coronavirus disease 2019

Table 1 Characteristics of hospitalized adults [³18 years old] with COVID-19 by the presence of venous thromboembolism				
	Total [n=1024]	No VTE [n=966]	VTE [n=58]	*p*-value*
Demographics				
Age [years]				0.341
19-39	209/1008 [20.7%]	194/950 [20.4%]	15/58 [25.9%]	
40-49	191/1008 [18.9%]	185/950 [19.5%]	6/58 [10.3%]	
50-59	237/1008 [23.5%]	222/950 [23.4%]	15/58 [25.9%]	
≥60	371/1008 [36.8%]	349/950 [36.7%]	22/58 [37.9%]	
Missing	16	16	0	
Sex				0.970
Female	367/1020 [36%]	346/962 [36%]	21/58 [36.2%]	
Male	653/1020 [64%]	616/962 [64%]	37/58 [63.8%]	
Missing	4	4	0	
Body Mass Index				0.809
Underweight/Normal [Below 24.9]	131/622[21.1%]	123/576 [21.4%]	8/46 [17.4%]	
Overweight [25-29.9]	99/622 [15.9%]	91/576 [15.8%]	8/46 [17.4%]	
Obese [30 or above]	392/622 [63%]	362/576 [62.9%]	30/46 [65.2%]	
Missing	402	390	12	
Comorbidities				
Diabetes Mellitus	420 [41%]	395 [40.9%]	25 [43.1%]	0.739
Hypertension	447 [43.7%]	415 [43%]	32 [55.2%]	0.069
Dyslipidemia	55 [5.4%]	50 [5.2%]	5 [8.6%]	0.258
Heart Failure	40 [3.9%]	38 [3.9%]	2 [3.4%]	0.853
Heart Failure Preserved	21/120 [17.5%]	15/99 [15.2%]	6/21 [28.6%]	0.142

Table 1 Characteristics of hospitalized adults [³18 years old] with COVID-19 by the presence of venous thromboembolism				
Ischemic Heart Disease	115 [11.2%]	106 [11%]	9 [15.5%]	0.287
Chronic Kidney Disease	108 [10.5%]	97 [10%]	11 [19%]	**0.032**
Dialysis	19 [1.9%]	18 [1.9%]	1 [1.7%]	0.939
Thyroid Dysfunction	33 [3.2%]	27 [2.8%]	6 [10.3%]	**0.002**
Hematological Disorders	14 [1.4%]	10 [1%]	4 [6.9%]	**<0.001**
Lung Disease	60 [5.9%]	56 [5.8%]	4 [6.9%]	0.729
Liver Disease	20 [2%]	20 [2.1%]	0 [0%]	0.268
Cancer	55 [5.4%]	47 [4.9%]	8 [13.8%]	**0.003**
Smoker	27/333 [8.1%]	24/310 [7.7%]	3/23 [13%]	0.369
Medications				
Antiplatelet	89 [8.7%]	83 [8.6%]	6 [10.3%]	0.645
Anticoagulant	560 [54.7%]	514 [53.2%]	46 [79.3%]	**0.000**
Anti-diabetics	214 [20.9%]	197 [20.4%]	17 [29.3%]	0.105
ACEIs/ARBs	136 [13.3%]	121 [12.5%]	15 [25.9%]	**0.004**
Spironolactone	17 [1.6%]	16 [1.7%]	1 [1.7%]	0.969
Statin	183 [17.9%]	167 [17.3%]	16 [27.6%]	**0.047**
Diuretics	69 [6.7%]	65 [6.7%]	4 [6.9%]	0.961
Beta-blockers	126 [12.3%]	114 [11.8%]	12 [20.7%]	**0.045**
Calcium Channel blockers	142 [13.9%]	133 [13.8%]	9 [15.5%]	0.708
Inhaled Corticosteroid	62 [6.1%]	59 [6.1%]	3 [5.2%]	0.772
Levothyroxine	28 [2.7%]	22 [2.3%]	6 [10.3%]	**<0.001**
Laboratory Data				
High D-Dimer>0.50 mg/l	625/869 [71.9%]	580/821 [70.6%]	45/48 [93.8%]	**0.001**
High Fibrinogen>200 mg/dl	212/640 [33.1%]	192/602 [31.9%]	20/38 [52.6%]	**0.008**

Table 2 Estimates of adjusted odds ratios [AOR] and 95% confidence intervals [CI] of the explanatory variables associated with the presence of venous thromboembolism				
AOR	95% CI	P-value		
Age groups				
	19-39	Reference [1]		
	40-49	0.406	[0.147 – 1.121]	0.082
	50-59	0.78	[0.332 – 1.831]	0.567
	≥60	0.543	[0.229 – 1.289]	0.166
Sex				
	Female	Reference [1]		
	Male	1.41	[0.771 – 2.578]	0.265
Diabetes				
	Yes	0.891	[0.457 – 1.74]	0.736
Hypertension				
	Yes	1.37	[0.694 – 2.705]	0.365
Dyslipidemia				
	Yes	1.557	[0.553 – 4.382]	0.402
Heart Failure				
	Yes	0.923	[0.205 – 4.159]	0.917
Ischemic Heart Disease				
	Yes	1.19	[0.484 – 2.926]	0.705
Chronic Kidney Disease				
	Yes	1.772	[0.818 – 3.837]	0.147
Thyroid Dysfunction				
	Yes	1.872	[0.591 – 5.933]	0.287
Hematological Disorders				
	Yes	2.727	[0.71 – 10.477]	0.144
Cancer				
	Yes	2.614	[1.048 – 6.519]	**0.039**
ACEIs/ARBs				

	Yes	1.62	[0.683 – 3.842]	0.273
Statins				
	Yes	0.915	[0.413 – 2.027]	0.827
Beta-Blockers				
	Yes	0.752	[0.318 – 1.782]	0.518
Levothyroxine				
	Yes	2.189	[0.656 – 7.311]	0.203

Note: *significant *p*-value≤0.05. ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers.

Table 3 Adjusted odds ratios [AOR] and their 95% confidence intervals [CI] of the explanatory variables from multivariable logistic regression on the presence of venous thromboembolism [N=856]			
	AOR	95% CI	P-value
Age groups			
19-39	Reference [1]		
40-49	0.395	[0.124 – 1.252]	0.115
50-59	0.702	[0.27 – 1.821]	0.466
≥60	0.48	[0.181 – 1.277]	0.141
Sex			
Female	Reference [1]		
Male	1.442	[0.725 – 2.868]	0.297
Diabetes			
Yes	0.897	[0.441 – 1.825]	0.765
Hypertension			
Yes	1.226	[0.593 – 2.534]	0.582
Dyslipidemia			
Yes	1.592	[0.496 – 5.11]	0.435
Heart Failure			
Yes	1.397	[0.287 – 6.803]	0.679
Ischemic Heart Disease			
Yes	1.045	[0.382 – 2.859]	0.932
Chronic Kidney Disease			
Yes	1.818	[0.785 – 4.206]	0.163
Thyroid Dysfunction			
Yes	1.487	[0.396 – 5.586]	0.557
Hematological Disorders			
Yes	9.064	[1.876 – 43.801]	**0.006**
Cancer			
Yes	1.158	[0.294 – 4.569]	0.834
ACEIs/ARB2			

Yes	1.553	[0.579 – 4.169]	0.382
Statins			
Yes	1.536	[0.652 – 3.618]	0.327
Beta-Blockers			
Yes	0.786	[0.285 – 2.168]	0.642
Levothyroxine			
Yes	1.614	[0.39 – 6.685]	0.509
High D-Dimer			
Yes	6.874	[2.022 – 23.368]	**0.002**

Note: *significant *p*-value≤0.05.

4. Discussion

In this multicenter retrospective study, we described the incidence and risk factors for VTE in COVID-19 patients and found that approximately 5.7% of patients had VTE. However, cancer was the only identified risk factor for increased incidence of VTE. COVID-19 can cause consequences of disorders. Some patients may develop a severe proinflammatory state that can be associated with coagulopathies. Although the mechanism is not clear, it may be caused by generalized inflammatory process, endothelial dysfunction, immobility, and disseminated intravascular coagulation [12].Studies have shown that VTE is reported more in critically ill patients with high D-dimer levels, where no anticoagulation was used [13].

Our results indicate that the incidence of thromboembolic complications is quite low compared to a previously published study, which reported the rate of VTE in hospitalized COVID-19-infected patients to be as high as 20% [14]. However, our results are more consistent with a multicenter study conducted in Saudi Arabia, which reported a rate of 1.5% of VTE in COVID-19-infected patients and indicated that all events except one occurred in the ICU [15].

Another study reported that approximately 46.1% of patients developed deep venous thrombosis [DVT] and the risk factors associated with increased prevalence included CURB-65 scores [3-5], Padua scores, and D-dimer levelsin hospitalized patientsIn addition, elderly individuals as well as those with declined lymphocytes counts, enlarged APTT, and higher D-dimer had risk predictors for VTE [16].

The only identified significant factor for VTE in the current study is cancer. Patients with cancer were two times more likely to have VTE. About 13.8% of the VTE group had cancer. Paredes-Ruiz et al. conducted a prospective observational study in a non-hematologic cancer patient [2]. The authors found that the incidence of VTE in patients with COVID-19 was 10% at 90 days [17]. Meanwhile, a lower risk of VTE in cancer patients was reported in one study that compared rates to non-cancer patients with COVID-19 [14% vs. 18% at 28 days]; this percentage is more consistent with our results [18]. Our findings showed a

higher incidence rate of VTE associated with cancer in patients with COVID-19 compared to others study that showed an incidence rate of 7% [12].

Li et al. found that not only active cancer was considered a risk factor associated with VTE in COVID-19 patients, but also recent anti-cancer therapy and high-risk VTE cancer subtypes were risk factors [15]. Pre-admission anticoagulant/antiplatelet therapy was shown to possibly reduce the risk [19].

Almost one third of deaths reported were related to VTE in COVID-19 patients, and poor prognosis was more described in cancer patients [12]. Being elderly is considered a risk for VTE, as others have described [20]. Although our study showed that 37.9% of patients who developed VTE were older than 60 years, this risk factor was shown to be insignificant in multivariable logistic regression [16].

Additional factors that could be considered to be linked with VTE include comorbidities such as diabetes, hypertension, dyslipidemia, and heart failure. However, our analysis showed no significant findings related to these factors.

Our study limitations include the deficiency of some reported risk factors [e.g., Padua/CURB-65 score]. In addition, mortality, ICU admission, pre-admission anticoagulant/antiplatelet use, previous history of VTE, type of cancer, and anticoagulant doses and bleeding status during admission were not reported. Furthermore, laboratory data were not uniformly available and were not collected in each patient according to a standardized timing or protocols.

In conclusion, this study's findings showed that, in COVID-19 patients, VTE is associated with chronic physical conditions, especially cancer. Healthcare professionals should closely monitor individuals with chronic physical conditions and COVID-19 to minimize the risk of VTE and further complications.

Declarations

Funds

No funding was received for conducting this study.

Contributions

The role of each author can be specified as follows:

All authors contributed to the study conception and design. Material preparation, data collection Ab.S.A, Az.A, M.A, T.A, M.J.A, F.A.A, A.B.A, S.H.A and data analysis were performed by A.M.M. The first draft of the manuscript was written by H.A, B.A, S.A and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

A.A, HA,A.M.A assisted in the study design, performed acquisition of data, laboratory and statistical analyses and drafted the manuscript;

Conflict of interest

All authors declare that they have no known financial interests or personal relationships that could influence the work reported in this paper.

Ethical approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from research Ethics Committee of each hospital.

Consent to participate

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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