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Original Article

Incidence of lupus anticoagulant in hospitalized covid-19 patients

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Abstract: Background: Procoagulant profile of 2019-nCoV/SARS-CoV-2 has been well documented over the last year. Perturbance in coagulating factors has also been reported in Covid-19 patients, including increased d-dimers and reports of lupus anticoagulant (LA). Methods: The current study aimed to identify the incidence of positivity of lupus anticoagulant in Covid-19 patients and analyze the association between LA and D-dimer in predicting thrombosis and mortality in one-hundred and five hospitalized adult (age >14 years) patients and forty-three hospitalized pediatric (age <14 years) patients with a confirmed diagnosis of Covid-19 between June 2020 and September 2020. Results: Twenty-one (20%) adult patients were tested positive for PTT LA, of which nine (8.6%) turned out to be confirmed positive for LA through StaClot and DRVVT Ratio tests. Six (14%) pediatric patients were positive for PTT LA, and only one (2.3%) had positive StaClot. Median D-dimer at admission was positively correlated with age and CRP among adult patients and was significantly higher in expired cases (P=0.001). No association between any of the coagulation tests and thrombosis or mortality was observed in the pediatric cohort. Conclusion: We report an increased incidence of LA in Covid-19 patients, yet we didn't find any association between thrombotic events or mortality, probably due to the small sample size.

Keywords: Covid-19, D-dimers, thrombosis, lupus anti-coagulant

Introduction

A novel β coronavirus, 2019-nCoV/SARS-CoV-2 causing Coronavirus disease-19 (Covid-19) emerged in December 2019, caused mortality in over 1 million globally. 15-20% of Covid-19 patients suffer from a moderate to a severe clinical course requiring hospitalization [1]. This population of patients is at a higher risk of arterial and venous thromboembolic risk [2], which can be a potential cause of mortality in about one-third of these hospitalized patients [2, 3]. The viral infection leads to an inflammatory procoagulant state, eventually resulting in thromboembolism [2]. Changes in coagulation parameters were associated with poor patient outcomes and mortality [4]. Moreover, coagulopathy was reported in Covid-19 patients along with intra-alveolar fibrin deposition, which can lead to lethal respiratory failure [4-7]. In coagulopathy, almost all of the elements of the coagulation pathway, including procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic proteins, exhibit functional deficiency [8].

Likewise, the presence of antiphospholipid antibodies and their role in thrombotic risk for Covid-19 hospitalized patients was proposed [9-11]. Although the prevalence of lupus anticoagulant (LA) was found very high up to 35.5-45% in severe Covid-19 [12, 13], yet its association with thromboembolic events was not found in other studies [10, 14]. These discrepancies and conflicting reports on the role of LA in a hypercoagulable state in Covid-19 and its prognostic usefulness due to minimal available data demand further exploration [15]. Therefore, the current study aimed to evaluate the LA status in Covid-19 adult as well as pediatric patient population along with d-dimers to establish its usefulness as a prognostic factor.

Materials & methods

Patient population

We conducted a retrospective cross-sectional study on archived plasma samples, approved by the Institutional Review Board of King Faisal Specialist Hospital and Research Centre, Kingdom of Saudi Arabia, under approval #RAC-KFSHRC: 2201086. The study included one hundred and five adults (age >14 years) and forty-three pediatric (age ≤14 years) patients with a confirmed diagnosis of Covid-19, who were admitted to our hospital between June 2020 and September 2020 and had available archived samples. Excluded were samples with no approved consent from patients to enroll in any research study.

This study aimed to evaluate the incidence of positive LA antibodies as a cross-sectional study. All patients were tested for routine coagulation tests, PT, PTT, D dimer, and LA. Only clinical data for documented thrombosis and 30-day mortality were collected.

Laboratory testing

LA testing was carried out on all samples from our cohort regardless of the prolongation of PTT. A mixing study was done as part of the protocol for testing for LA. STA®-Staclot DRVV Screen and STA®-Staclot DRVV Confirm (Cat # 0334, 2 ml) kits were used for the detection of the LA in plasma by the diluted Russell's viper venom test. Three-step LA testing was carried out in dilute Russell's viper venom time (DRVVT)- and partial thromboplastin time (PTT)-based test system according to International Society on Thrombosis and Haemostasis (ISTH) guidelines [16]. All tests, including PT, PTT & D-dimer, were carried out on a STA-R Evolution analyzer (Stago, Asnières, France). For LA, we used Stago STA-Staclot DRVV Screen, STA-Staclot DRVV Confirm, PTT-LA, Staclot LA reagents. PT and PTT were tested using Stago reagent. C reactive protein (CRP) was measured using an automated chemistry analyzer COBAS 601 (Roche Diagnostics, Basel, Switzerland).

Statistical analysis

Descriptive statistics are provided as number (percentage) for discrete variables and median (range) for continuous variables due to the shape of the distribution. Chi-Square test or Fisher's exact test were applied to test for the significance of association between categorical variables. Mann-Whitney U test was used to test the difference between the medians for continuous variables. Spearman's correlation coefficient was utilized to measures the strength and direction of association between two continuous variables. *P* values less than 0.05 were considered statistically significant.

Results

Adult patient population (n=105)

The male to female ratio was 1:0.78, while 59 (56.2%) were male. The majority of the cases were below the age of 66 years. Median age at diagnosis among females was lower (46.5, range: 21-84) than males (56, range: 21-90); however, the difference was not statistically significant (P=0.069). One patient had pre-existing malignancy who developed LV thrombosis, and another patient developed portal vein thrombosis at the time of diagnosis. Demographic details are provided in **Table 1**. PTT (>40.4 sec) was prolonged in 55 (53%). PTT LA and DRVV Screening were done for all 105 patients (**Figure 1**). Five DRVV negative patients still went for the confirmatory tests as they had high clinical suspicion and co positivity for PTT-LA (>45 sec). Twenty-one (20%) PTT LA prolonged (ro5 seconds) patients were then tested for DRVV Ratio and StaClot. In this subgroup, Staclot was prolonged (r7.9 seconds) in seven (33.3%) cases. DRVV Ratio test turned out to be positive LA1/LA2 (ratio out to in only three (14.3%); two of whom were reported negative by StaClot (**Figure 1**, P=1.00). In all, nine (8.6%) patients were LA positive (Staclot LA ≥7.9 seconds and/or DRVVT Ratio D1.3. D-dimer was above 0.5 µg/mL in 74 (70.5%). All patients reported positive by DRVV Ratio, or StaClot tests had d-dimer values above 0.5 µg/mL. D-dimer at admission was found to be positively correlated with age (P<0.001) and CRP (P<0.001). CRP levels at presentation were available for six out of nine LA positive patients and were high (above 3.0) in all. CRP was increased in 91.1% of the patients (**Table 1**).

Thrombotic events and mortality: Only two (1.9%) thrombotic events were observed in our adult cohort. Both patients had above normal d-dimer at admission (>20 in one and 7.5 µg/

Table 1. Demographic and clinical characteristics of 105 non-pediatric patients with Covid-19 on admission

Characteristics	Values in patients	Test Values
Age, years (n=105)	53.0 (21.0-90.0) years	-
Male gender	59 (56.2%)	-
With malignancy	1 (0.1%)	-
On VTE Prophylaxis	97 (92.4%)	-
PTT LA, secs		41 (25-70)
<47	84 (80.0%)	
≥47	21 (20.0%)	
DRVV Screen, secs		40.0 (30-129)
<45	88 (83.8%)	
≥45	17 (16.2%)	
DRVV Confirmatory (n=21) secs		48.00 (38-87)
<45	9 (42.9%)	
≥45	12 (57.1%)	
DRVV Ratio (n=21)		1.14 (1.02-1.48)
<1.30	18 (85.7%)	
≥1.30	3 (14.3%)	
STACLOT (n=21), secs		6.20 (0-18.4)
<7.9	14 (66.7%)	
≥7.9	7 (33.3%)	
D dimer, µg/mL		0.98 (0.26-20.1)
≤0.5	31 (29.5%)	
>0.5	74 (70.5%)	
PT (n=102), secs		15.3 (12-44.1)
≤14.2	28 (27.5%)	
>14.2	74 (72.5%)	
PTT (n=103), secs		40.9 (30.2-85.4)
≤40.4	48 (46.6%)	
>40.4	55 (53.4%)	
CRP (n=56), mg/L		35.7 (0.6-301)
≤3.0	5 (8.9%)	
>3.0	51 (91.1%)	

Values are in median (range) for continuous and n (%) for discrete variables.

mL in the other, respectively). Nine patients from our cohort died during the admission, accounting for the mortality rate of 8.6%. Median D-dimer values at admission were found to be significantly higher in expired patients, P=0.001.

Variables of interest concerning thrombotic events and survival are described in **Table 2**. In PTT-LA positive patients, 4 (19%) patients expired while the remaining (n=17, 81%) were alive (P=0.076) at the last follow-up. In StaClot positive patients, only 1 (14.3%) patient expired while the remaining (n=6, 85.7%) were alive (P=1.0). The mortality among LA-positive cases was 22.2% (2 of 9).

One out of three patients reported positive by DRVV ratio test and negative by StaClot died with high D dimer. Another male patient having prolonged StaClot (aClo sec), negative for DRVV ratio with elevated d-dimer, expired. The only male patient with concurrent malignancy and higher d-dimer succumbed to Covid-19 and LV thrombosis. He was 39 years old with a d-dimer of 7.45 µg/mL, PTT-LA 45 sec, baseline PTT 85.4 sec, CRP: 68.5 mg/L.

Pediatric patient population (n=43)

Eighteen (41.9%) were male, with male to female ratio of 1:1.4. The majority of the cases were below the age of 8 years. Five (11.6%) had

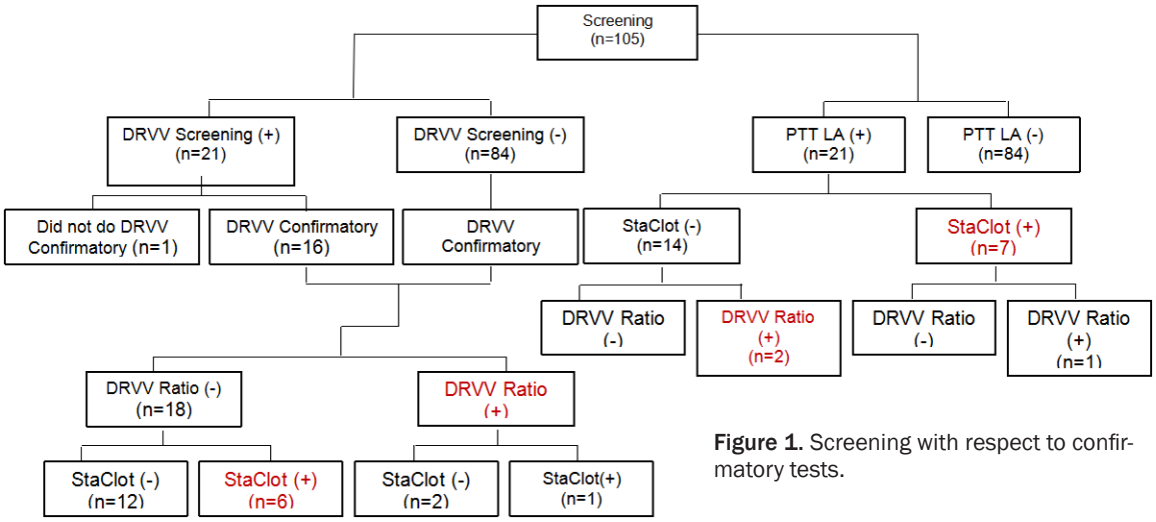

Figure 1. Screening with respect to confirmatory tests.

the malignant disease before the Covid-19 diagnosis. Patients' characteristics and their Hemostatic profile at admission are presented in **Table 3**. All patients underwent PTT LA and DRVV screening. Six (14%) were found to be positive for PTT LA. These six patients then underwent StaClot and DRVV ratio tests. StaClot was positive in only one (2.3%) case, while none of the patients had a DRVV ratio test positive. Twenty-six (60.5%) had their d-dimer above 0.5 ng/mL at admission. CRP was 2.4 mg/L in StaClot positive patient.

Median age at diagnosis was significantly lower (2.2 years, range, 0.06-13) in those patients who had a higher D-dimer (>0.5 µg/mL) compared to those with the lower values at diagnosis (7 years, range: 0.5-13, P=0.034).

Thrombotic events and mortality: No thrombotic event was recorded in the pediatric cohort. Mortality was recorded in one patient who was an 18-month-old boy with malignancy, had d-dimer 0.64 µg/mL, and PT and PTT were within normal limits. The patient was negative for PTT LA and was not further tested for DRVV ratio or StaClot.

Discussion

The Covid-19 pandemic is still not under control, with surging morbidity and mortality despite measures to contain it. Therapeutic interventions for critically ill patients should be reviewed critically, including identifying prognostic factors in disease pathogenesis. In critically ill patients, coagulation parameters perturbance has been linked with poor patient outcomes and mortality [4]. Evidence regarding coagulopathy in Covid-19 patients has been documented; however, the role of different coagulation parameters as prognostic factors in Covid-19 patients has not been fully established. The current study aimed to analyze the coagulation parameters in hospitalized adult and pediatric patient population suffering from Covid-19 and correlate these with age, thrombosis, and mortality.

Harzallah *et al.* [13], Bowles *et al.* [11] and Helms *et al.* [6] reported high LA in Covid-19 patients. In our study, we found positive LA in 8.6% adults & 2.3% pediatric patients, which is much lower than what had been reported by Bowles *et al.,* who analyzed a cohort of 216 Covid-19 positive patients and reported the presence of LA by both DRVVT and LA-sensitive PTT in 18 of 34 patients (53%).

In our cohort, three patients (14.3%) had a DRVV ratio of ≥1.30, and 20% of patients had PTT LA >45 sec. Bowles et al. reported similar result by DRVVT alone in 7 (21%), while by LA-sensitive PTT alone in 6 (18%). In our patients, results of both tests didn't show any correlation with thrombosis or mortality. However, Helms *et al.* reported sixty-four thrombotic complications in 150 Covid-19 patients, while 50 patients out of 57 tested positive for LA via PTT. They also reported significantly elevated baseline d-dimers which is similar to our finding [6]. Similarly, Carmine *et al.* reported no association between LA and mortality in a cohort of 192 patients suffering from Covid-19, although 95 patients were positive for LA [3].

Table 2. Non-Pediatric patients' outcome with respect to variables of interest

Characteristics (n=105)	Thrombosis (+) (n=2)	*P*-Value	Expired (n=9)	*P*-Value
Age, years	41.0 (39.0-43.0)	0.411	59.0 (35.0-85.0)	0.284
Gender		1.0		1.0
Male	1 (1.7%)		5 (8.5%)	
Female	1 (2.2%)		4 (8.7%)	
VTE Prophylaxis		1.0		0.524
Negative	None		1 (12.5%)	
Positive	2 (2.1%)		8 (8.2%)	
D dimer, seconds		1.0		0.055
≤0.5	None		None	
>0.5	2 (2.7%)		9 (12.2%)	
PTT LA, seconds		1.0		0.076
<47	2 (2.4%)		5 (6%)	
≥47	None		4 (19%)	
DRVV Screen, seconds		1.0		0.159
<45	2 (2.3%)		6 (6.8%)	
≥45	None		3 (17.6%)	
DRVV Confirmatory (n=21)		-		1.0
<45	None		2 (22.2%)	
≥45	None		2 (16.75)	
DRVV Ratio (n=21)		-		0.489
<1.30	None		3 (16.7%)	
≥1.30	None		1 (33.3%)	
STACLOT (n=21), seconds		-		1.0
<7.9	None		3 (21.4%)	
≥7.9	None		1 (14.3%)	
PT (n=102), seconds		1.0		1.0
≤14.2	None		2 (7.1%)	
>14.2	1 (1.4%)		6 (8.1%)	
PTT (n=103), seconds		1.0		0.298
≤40.4	1 (2.1%)		6 (12.5%)	
>40.4	1 (1.8%)		3 (5.5%)	
CRP (n=56), mg/L		1.0		1.0
≤3.0	None		None	
>3.0	2 (3.9%)		5 (9.8%)	
DRVV Ratio/StaClot		-		0.614
Both (-)	-		2 (16.7%)	
DRVV Ratio (+)	-		1 (50%)	
StaClot (+)	-		1 (16.7%)	
Both (+)	-		None	
D dimer, seconds	13.8 (7.5-20.1)	0.025*	8.3 (0.61-20.1)	0.001*
PTT LA, seconds	44.5 (44-45)	0.194	45 (28-70)	0.126
DRVV Screen, seconds	41 (40.0-42.0)	0.826	43.0 (34.0-129.0)	0.048*
DRVV Confirmatory (n=21)	-	-	53.5 (42.0-87.0)	0.517
DRVV Ratio (n=21)	-	-	1.05 (1.03-1.48)	0.275
STACLOT (n=21), seconds			4.45 (1.4-11.0)	0.763
PT (n=102), seconds	20.9	-	15.6 (12-20.9)	0.940
PTT (n=103), seconds	62.5 (39.5-85.4)	0.390	39.5 (33.3-85.4)	0.709
CRP (n=56)	40.6 (12.6-68.5)	0.812	68.5 (4.0-301.0)	0.824

Values are in median (range) for continuous and n (%) for discrete variables. *Significant at 5%.

Table 3. Demographic and clinical characteristics of 43 pediatric patients with Covid-19 on admission

Characteristics	Values in patients	Test Values
Age, years (n=43)	5 (0.06-13) years	-
Male gender	18 (41.9%)	-
On VTE Prophylaxis	6 (14%)	-
With malignancy	5 (11.6%)	-
D dimer (n=43) μg/mL		0.6 (0.26-20.1)
≤0.5	17 (39.5%)	
>0.5	26 (60.5%)	
DRVV Screen (n=43), secs		37 (29-65)
<45	37 (86%)	
≥45	6 (14%)	
DRVV Confirmatory (n=6), secs		44.5 (41-62)
<45	3 (50%)	
≥45	3 (50%)	
DRVV Ratio (n=6)		1.1 (1.04-1.26)
<1.3	6 (100%)	
≥1.3	None	
STACLOT (n=6), secs		5.25 (1.2-10.8)
<7.9	5 (83.3%)	
≥7.9	1 (16.7%)	
PT (n=42), secs		15.1 (12.4-26.2)
≤14.2	11 (26.2%)	
>14.2	31 (73.8%)	
PTT (n=43), secs		39.5 (26.6-59.5)
≤40.4	25 (58.1%)	
>40.4	18 (41.9%)	
CRP (n=23), mg/L		5.2 (0.2-297.8)
≤3	9 (39.1%)	
>3	14 (60.9%)	

Values are in median (range) for continuous and n (%) for discrete variables.

We are reporting two (2.1%) venous thromboembolism in our adult population, which is similar to what was observed by Bowles *et al.,* who reported pulmonary embolism in 1 patient, clinically suspected thrombosis in another [11]. Reyes *et al.* reported a significant difference of thrombotic events in patients with and without LA which is contrary to our findings [17]. These discrepancies can be due to differences in selection criteria of patients or the method of LA detection.

Interference with CRP is a concern since most of these critically ill patients have raised levels of CRP. Elevated CRP levels give false positive results for dRVVT and aPTT, the higher incidence of LA in other studies is perhaps due to the presence of interferences like CRP. In our cohort, only 2% had a correlation with CRP. However, a prevailing notion between the researchers is that an increase in LA (false positive) can be due to marked elevation of C-reactive protein [18], which doesn't correlate with thrombotic events.

In the current study, we found a positive correlation between D-dimer and mortality and thrombosis in the adult patient population. However, no such association was seen in the pediatric population, yet a higher d-dimer value was significantly associated with lower age at diagnosis. In our study, the incidence of thrombotic events was too low to draw a conclusions. Moreover, studies found a 3.7-68% increase in D-dimer in Covid-19 patients [19], where elevated D-dimers were associated with poor prognosis and D-dimer >1 μg/mL with mortality in Covid-19 patients [20]. Similarly, in the current study, only two thrombotic events were observed, both patients having high d-dimer. We found a significant correlation between high d-dimers at admission and mortality with a trend between LA and mortality, yet it was not statistically significant. One of the limitations of this study is that we could not test for other antiphospholipid antibodies.

Conclusion

We report a relatively higher incidence of LA in Covid-19, primarily adult patients, yet we didn't find any association between thrombotic events and lupus anticoagulant. While a trend was found between LA and mortality in our cohort, it was not statistically significant. Larger cohorts are required to establish the association between LA and other antiphospholipid antibodies in Covid-19 patients with thrombosis.

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Disclosure of conflict of interest

None.

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