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ORIGINAL ARTICLE

COVID-19 Infection and Early Outcome of Acute Peripheral Vascular EventsA propensity Score Matching Analysis

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ABSTRACT

Background: COVID-19 infection is known for its induction of a prothrombotic state. Thromboembolic complications have gained increasing attention as a significant consequence of COVID-19 infection. The present study aimed to compare the short term outcome of thromboembolic events affecting the peripheral vascular system in patients with concomitant COVID-19 infection and patients without this infection.

Methods: The study included 177 covid-19 patients with peripheral vascular events. They comprised 62 patients with acute lower limb ischemia, 69 patients with lower limb DVT, 21 patients with thrombosed vascular access and 25 patients with occluded lower limb bypass graft. For comparison, we selected another 177 patients with peripheral vascular events without covid-19 infection. Patients were selected using a propensity score matching with 1:1 ratio. Patients were followed for 30 days after admission.

Results: Comparison between acute lower limb ischemia with and without covid-19 revealed that covid-19 patients had higher amputation rate (25.8 % versus 12.9 %, p=0.069) without statistical significance. However, multivariate regression analysis identified covid-19 infection as a significant predictor of limb amputation [OR (95% CI: 3.31 (1.15-9.6), p=0.027]. In DVT patients, covid-19 patients had significantly lower clinical improvement (75.4 % versus 91.3 %, p=0.012). In patients with vascular access thrombosis, covid-19 patients had lower secondary patency rates (61.9 % versus 71.4 %, p=0.52) without statistical significance. In patients with occluded lower limb bypass graft, covid-19 patients had markedly lower secondary patency rates despite falling short of statistical significance (68.0 % versus 88.0 %, p=0.088)

Conclusions: Covid-19 infection is related to worse outcome in many patients with peripheral vascular events particularly those with acute lower limb ischemia and DVT

Keywords: Acute lower limb ischemia; deep venous thrombosis; vascular access; COVID-19

INTRODUCTION

COVID-19 infection and its widespread clinical, economic and political impacts have dominated the global scene since its emergence in the last weeks of 2019. While the pandemic was early regarded as a predominately respiratory infection, It was soon realized that the medical professionals are confronted by a systemic disease with deceptive and lethal pathogenic mechanisms **[1].**

Among these mechanisms, COVID-19 infection is known for its induction of a prothrombotic state presumably caused by an interaction between the inflammatory mediators and the hemostatic factors **[**2**].** Noticeably, coagulopathy of COVID-19 infection is characterized by massive fibrin formation with less frequent antithrombotic activity and thrombocytopenia **[**3**].**

In this context, thromboembolic complications have gained increasing attention as a significant

consequence of COVID-19 infection particularly in the intensive care setting **[4].** Reportedly, COVID-19 patients have significantly higher rate of thromboembolic events when compared with non-infected counterparts **[5].** Elevation of D dimer, a biomarker indicating activated hemostasis and fibrinolysis is associated with higher mortality rate in COVID-19 patients reflecting the grave contribution of coagulopathy to COVID-19 prognosis **[6].**

To reduce the risks related to thromboembolic complications, use of low molecular weight heparin was recommended. Other options include fibrinolytic treatment and complement inhibition **[7,8].**

The present study aimed to compare the short term outcome of thromboembolic events affecting the peripheral vascular system in patients with concomitant COVID-19 infection and patients without this infection.

METHODS

The present retrospective study was conducted at Zagazig University Hospitals, Zagazig, Egypt and Department of Vascular University Hospitals Birmingham, United Kingdom in the period from May through December, 2020. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of both centers. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study included 177 covid-19 patients with peripheral vascular events. They comprised 62 patients with acute lower limb ischemia, 69 patients with lower limb DVT, 21 patients with thrombosed vascular access and 25 patients with occluded lower limb bypass graft.

Diagnosis of COVID-19 infection was established on the basis of laboratory, clinical and radiological criteria recommended by the Egyptian Ministry of Health Guidelines. Only patients with positive PCR results were included in the study. Severity of Covid-19 illness was assessed according to the recommendations of Infectious Diseases Society of America/American Thoracic Society Criteria. Patients were classified to have severe disease if they have at least one of two major criteria (septic shock with need for vasopressors or invasive mechanical ventilation) or ≥ 3 minor criteria (respiratory rate ≥ 30 breaths/min, pao2/fio2 ratio ≤ 250, multilobar infiltrates, confusion/disorientation, uremia (bun level ≥ 20 mg/dl), leukopenia as a result to infection alone (WBC count<4,000 cells/ml), thrombocytopenia (platelets<100,000/ml), hypothermia (core temperature<36°C), hypotension requiring aggressive fluid resuscitation) [9].

Patients were excluded if they died of covid-19 complication or didn't receive the recommended management of their vascular complaints. For comparison, we selected another 177 patients with peripheral vascular events without covid-19 infection. Patients were selected using a propensity matching score with 1:1 ratio.

All patients were subjected to standard clinical vascular assessment and imaging studies to confirm the diagnosis. In all patients, appropriate treatment was started immediately after admission. Patients with ALI were treated with thrombectomy with Fogarty catheter with or without angioplasty. Postoperative anti-coagulation was achieved using full heparinization and post-discharge apixaban 5 mg twice daily. DVT was treated using apixaban in non-covid 19 patients and full heparinization in covid 19 patients. All patients received apixaban after discharge. Thrombotic AV access and occluded lower limb bypass graft were managed using catheter directed thrombolysis with or without angioplasty with or without surgical revision. Patients with occluded grafts received IV heparin for anti-coagulation followed by warfarin after discharge with bridging therapy. Covid-19 manifestations -if present- were treated according to Egyptian MOH protocol.

Patients were followed for 30 days after admission. In patients with ALI, the reported outcome included amputation and mortality rates. In DVT patients, outcome included clinical improvement (as indicated by chronic venous insufficiency questionnaire) and mortality rate. In patients with thrombosed vascular access, outcome was expressed as secondary patency and mortality rates. In patients with occluded lower limb vascular graft, the reported outcome included secondary patency, amputation and mortality rates.

Statistical analysis

Data obtained from the present study were presented as mean ± standard deviation (SD) or number and percent. Numerical data were compared using t test while categorical data were compared using Fisher's exact or chi-square test. Logistic regression analysis was used to identify predictors of outcome. P value less than 0.05 was considered statistically significant. All statistical tests were operated using SPSS version 26.0 (IBM, IL, USA).

RESULTS

The present study included 354 with peripheral vascular events. They comprised 177 covid-19 +ve patients and 177 covid-19 -ve patients. Comparison between acute lower limb ischemia

with and without covid-19 revealed that covid-19 patients had higher amputation rate (25.8 % versus 12.9 %, p=0.069) without statistical significance **(Table 1)**. However, multivariate regression analysis identified covid-19 infection as a significant predictor of limb amputation [OR (95% CI: 3.31 (1.15-9.6), p=0.027] **(Table 2).**

In DVT patients, covid-19 patients had significantly lower clinical improvement (75.4 % versus 91.3 %, p=0.012) **(Table 3)**. Logistic regression analysis identified male sex [OR (95% CI): 3.75 (1.16-12.1, p=0.027)] and covid-19 infection [OR (95% CI): 4.36 (1.44-13.2), p=0.009] as independent predictors of non-improvement. **(Table 4).**

In patients with vascular access thrombosis, covid-19 patients had lower secondary patency rates (61.9 % versus 71.4 %, p=0.52) without statistical significance **(Table 5)**. No variables could predict secondary patency on regression analysis **(Table 6)**.

In patients with occluded lower limb bypass graft, covid-19 patients had markedly lower secondary patency rates despite falling short of statistical significance (68.0 % versus 88.0 %, p=0.088) **(Table 7)**. No variables could predict secondary patency on regression analysis **(Table 8)**.

Table 1 Baseline and outcome parameters in acute lower ischemia patients with and without covid-19 infection

	Covid-19 +ve **N=62**	Covid-19 -ve **N=62**	P value
Age (years) mean ± SD	62.9 ± 9.6	60.1 ± 13.0	0.31
Male/female n	40/22	45/17	0.33
Rutherford stage n (%)			
I	-	-	0.75
IIA	31 (50.0)	28 (45.2)	
IIB	27 (43.6)	28 (45.2)	
III	4 (6.4)	6 (9.7)	
Covid-severity n (%)			
Severe	43 (69.4)	-	NA
Non-severe	19 (70.6)	-	
Outcome parameters n (%)			
Amputation	16 (25.8)	8 (12.9)	0.069
Mortality	8 (12.9)	6 (9.7)	0.57

Table 2 Predictors of limb amputation in ALI patients

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age	1.03	0.98-1.07	0.24	-	-	-
Sex	0.89	0.35-2.32	0.83	-	-	-
Rutherford stage						
IIb	4.7	1.44-15.32	0.01	5.19	1.55-17.35	0.008
III	20.6	4.07-104.4	<0.001	28.9	5.13-162.9	<0.001
Covid-19	2.3	0.92-5.98	0.074	3.31	1.15-9.6	0.027

Table 3 Baseline and outcome parameters in DVT patients with and without covid-19 infection

	Covid-19 +ve **N=69**	Covid-19 -ve **N=69**	P value
Age (years) mean ± SD	43.2 ± 15.4	45.5 ± 13.3	0.35
Male/female n	39/30	45/24	0.3
Predisposing factors n (%)			
Malignancy	17 (24.6)	15 (21.7)	0.69
Postsurgical	15 (21.7)	16 (23.2)	0.84
Contraceptive pills	26 (37.7)	29 (42.0)	0.58
Unprovoked	11 (15.9)	9 (13.0)	0.63
Site			

	Covid-19 +ve N=69	Covid-19 -ve N=69	P value
Iliofemoral	39 (56.5)	46 (66.7)	0.22
Femoropopliteal	30 (43.5)	23 (33.2)	
Covid-severity			
Severe	49 (71.0)	-	NA
Non-severe	20 (29.0)	-	
Outcome parameters n (%)			
Improved VEINES-QOL/Sym	52 (75.4)	63 (91.3)	0.012
Mortality	8 (11.6)	7 (10.1)	0.78

Table 4 Predictors of improved QOL in DVT patients

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age	0.99	0.96-1.03	0.77	-	-	-
Sex	2.67	0.93-7.7	0.068	3.75	1.16-12.1	0.027
Predisposing factors						
Unprovoked	Ref.					
Malignancy	3.4	0.82-14.08	0.091	3.66	0.81-16.5	0.092
Postsurgical	1.36	0.3-6.2	0.69	-	-	-
Contraceptive pills	0.21	0.03 – 1.39	0.11	-	-	-
Site	1.59	0.85-3.93	0.31	-	-	-
Covid-19	3.43	1.26-9.34	0.016	4.36	1.44-13.2	0.009

Table 5 Baseline and outcome parameters in thrombotic vascular access patients with and without covid-19 infection

	Covid-19 +ve N=21	Covid-19 -ve N=21	P value
Age (years) mean ± SD	56.9 ± 9.0	58.8 ± 8.7	0.49
Male/female n	8/13	11/10	0.35
Covid-severity			
Severe	15 (71.4)	-	NA
Non-severe	6 (28.6)	-	
Type of access n (%)			
Native	15 (71.4)	19 (90.5)	0.12
Synthetic	6 (28.6)	2 (9.5)	
Outcome parameters n (%)			
Secondary patency	13 (61.9)	15 (71.4)	0.52
Mortality	-	1 (4.8)	0.31

Table 6 Predictors of secondary patency in thrombotic vascular access patients

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age	1.03	0.96-1.11	0.42	-	-	-
Sex	0.87	0.24-3.15	0.83	-	-	-
Type of access	2.4	0.5-11.5	0.27	-	-	-
Covid-19	1.54	0.42-5.6	0.51	-	-	-

Table 7 Baseline and outcome parameters in occluded lower limb bypass graft patients with and without covid-19 infection

	Covid-19 +ve N=25	Covid-19 -ve N=25	P value
Age (years) mean ± SD	65.9 ± 4.4	67.3 ± 7.8	0.44
Male/female n	16/9	17/8	0.77
Covid-severity			
Severe	18 (72.0)	-	NA
Non-severe	7 (28.0)	-	
Type of graft n (%)			
Native	15 (60.0)	13 (52.0)	0.57
Synthetic	10	12 (48.0)	
Type of bypass n (%)			
Below knee	16 (64.0)	18 (72.0)	0.54
Above knee	9 (36.0)	7 (28.0)	
Outcome parameters n (%)			
Secondary patency	17 (68.0)	22 (88.0)	0.088
Amputation	3 (12.0)	2 (8.0)	0.64
Mortality	1 (4.0)	1 (4.0)	NA

DISCUSSION

The present retrospective study tried to illustrate the detrimental effect of COVID-19 infection on a variety of acute peripheral vascular events. In our study, COVID-19 infection was associated with higher amputation rate in ALI patients. These conclusions are in line with the findings of **[10]** who noted that COVID-19 infected patients with critical limb ischemia had worse limb salvage rates when compared to non-infected counterparts. Also, the study of Stabile et al. **[11]** noted a significantly higher amputation rate in COVID infected patients with critical limb ischemia during the lockdown period in comparison to previous periods. Likewise, the propensity score matching analysis of Goldman et al **[12]** reported that COVID-19 patients with limb ischemia had significantly higher clot burden and amputation rate. The higher rate of amputation in infected patients is probably related to the COVID-19 induced infectious angiitis demonstrated by a recent pathological study **[13].**

In patients with DVT, logistic regression analysis identified male sex and covid-19 infection as independent predictors of postoperative non-improvement which is a novel findings. Most previous studies focused on the risk factors associated with increased prevalence of DVT in COVID-19 patients and no study to the best of our knowledge assessed the relation between COVID-19 infection and treatment outcome **[14-17]**.

In patients presented with vascular access thrombosis in the current study, no significant differences were noted between COVID-19 -ve and COVID-19 +ve patients regarding patency and mortality rates. Probably, the effects of COVID-19 coagulopathy in hemodialysis patients is alleviated by the long-term anti-thrombotic prophylaxis used in those patients. However, in contrast with our findings, the study of **[18]** reported higher mortality rates among hemodialysis patients in 2020 in comparison to 2018 and 2019.

In our study, patients COVID-19 patients admitted with thrombosed lower limb vascular grafts experienced a trend towards lower patency rate in comparison to non-infected patients.

CONCLUSION

The present study documented the effect of COVID-19 co-infection on treatment outcome of miscellaneous peripheral vascular events. The study noted that COVID-19 infection was associated with higher rate of amputation in patients with ALI and lack of clinical improvement in DVT patients.

- **Conflict of Interest**: None.
- **Financial Disclosures:** None.

Supplementary materials: The table 8 is available online

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Supplementary Table

Table 1 Predictors of secondary patency in occluded lower limb bypass graft patients

	Univariate analysis			Multivariate analysis		
	OR	**95%CI**	**P**	**OR**	**95%CI**	**P**
Age	1.02	0.91-1.014	0.8	-	-	-
Sex	0.88	0.22-3.54	0.85	-	-	-
Graft type	4.8	1.09-20.9	0.039	5.73	0.78-42.3	0.087
Bypass type	3.5	0.87-13.9	0.078	1.14	0.17-7.42	0.89
Covid-19	3.45	0.79-15.01	0.099	4.61	0.89-23.8	0.068