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Original Article

Radiology Section

Association between Peripheral Arterial Thrombosis and COVID-19 using CT Angiography: A Retrospective Observational Study

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ABSTRACT

Introduction: Arterial thromboembolism is a major cause of morbidity and mortality in Coronavirus Disease 2019 (COVID-19) patients in both General Inpatient ward and Intensive Care Unit (ICU) settings. As COVID-19 is associated with coagulopathy or vasculopathy, it is necessary to investigate whether the peripheral vessels were also affected due to COVID-19-related thrombosis. Computed Tomography Angiography (CTA) is a quick, accurate, non invasive, and reliable method for assessing the location, extent and severity of arterial thrombosis.

Aim: To evaluate the association of acute peripheral arterial thrombosis in patients with COVID-19 infection and assess the differences in peripheral extremity clot burden using peripheral limb CTA.

Materials and Methods: A retrospective observational study was conducted in the Department of Radiology, Topiwala National Medical College and B.Y.L. Nair Charitable. Hospital, Mumbai, Maharashtra, India, from April 2020 to April 2021. A total of 70 patients with medical records of acute limb ischaemia, consisting of 35 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection-positive patients and 35 SARS-CoV-2 negative patients, who underwent peripheral CTA were included in the present study. For calculating arterial clot severity and extent in the peripheral extremities, three different systems were used. Age, sex, symptoms, co-morbidities, and CT thrombus burden score were analysed in both groups. The association between variables was analysed using the Chi-square test.

Results: The age range of patients presenting with acute limb ischaemia was 24-74 years (mean age=50 years). Claudication, pain and redness had a significant association with COVID-19 positive patients (p-value <0.001). It was also observed that proximal vessels had a slightly higher preponderance for thrombosis. A significant mean difference in arterial thrombus burden was observed in SARS-CoV-2 infection positive patients, with greater thrombus burden involving proximal vessels. In only the proximal vessels, the overall clot burden was 2.31±3.09 and 0.89±1.25 in the COVID-19 positive and negative groups, respectively (p-value=0.014). COVID-19 infected patients had a predilection for peripheral arterial thrombosis compared to controls, with a significant p-value of 0.034 in proximal upper limb involvement.

Conclusion: Computed tomography angiography is the preferred diagnostic modality for the evaluation of arterial thrombosis. Greater clot burden was seen in the proximal vessels of both upper and lower limbs in COVID-19 patients.

Keywords: Clot burden, Computed tomography, Coronavirus disease 2019, Distal predominant, Proximal only, Proximal predominant

INTRODUCTION

Coronavirus disease 2019 infection is not only characterised by respiratory symptoms, but it has now been proven to have cardiac, gastrointestinal, skin, renal and neurological manifestations [1]. Arterial thromboembolism is a major cause of morbidity and mortality in COVID-19 patients in both General Inpatient ward and ICU settings [2-4]. Arterial thrombosis has also been observed in COVID-19 patients, reported within the coronary arteries and within the brain [2,5,6]. CTA is a quick, accurate, non invasive and reliable method for assessing the location, extent and severity of arterial thrombosis. The estimated average prevalence of peripheral arterial thrombosis in COVID-19 patients is around 33%; however, no large-scale studies are available for the same [7].

Increased frequency of involvement of medium or large arteries was described by Dane B et al., (2022). They stated in their prospective study consisting of 82 patients, with three patients having arterial thromboembolism in the aorta or major branches, that thromboembolic findings occurred more frequently in patients with COVID-19 disease than without COVID-19 disease, with arterial thrombi involving medium or large arteries in five patients with COVID-19 disease [8]. Goldman IA et al., stated that there is a high incidence of arterial thrombosis in COVID-19 patients presenting with ischaemic leg symptoms (100% of cases in their cohort). They found that lower extremity arterial thrombus associated with COVID-19 is characterised by a greater thrombus burden and increased rate of amputation and death [9]. Both of the above studies had limitations, either in the form of a small sample size or a small proportion of patients with COVID-19 positive status. The present study focused on the effect of thrombus of medium and small arteries in upper as well as lower limbs.

The present study observed an increased number of patients presenting with peripheral extremity ischaemia and extensive arterial thromboses during the pandemic. These patients typically presented to the Emergency Department with new symptoms of swelling, pain, limb coldness, discoloration and claudication and underwent peripheral extremity CTA. On further evaluation, many of the patients were found to be positive for the COVID-19 virus. As COVID-19 is associated with coagulopathy or vasculopathy [10], the authors investigated whether the peripheral vessels were also affected due to COVID-19-related thrombosis, along with

its prevalence, demographic distribution, most common sites of involvement and severity.

MATERIALS AND METHODS

A retrospective observational study was conducted in the Department of Radiology, Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra, India, from April 2020 to April 2021. Institutional ethics committee approval was granted for this retrospective study with a waiver of informed consent {RADIO/468(14/10/2021) ECARP/2020/183}.

Inclusion criteria: Patients with medical records of acute limb ischaemia, consisting of 35 SARS-CoV-2 infection-positive patients and 35 SARS-CoV-2 negative patients who underwent peripheral CTA, were included.

Exclusion criteria: Patients with a history or imaging demonstrating chronic or prior peripheral arterial thrombosis, patients with a history of peripheral vascular disease, patients with chronic kidney disease, post-traumatic arterial thrombosis, and patients with a history of anaphylactic reactions to contrast agents were excluded from the study.

Study Procedure

Total 70 patient records were selected based on the inclusion criteria. As the required clinical details were available through the hospital management information system, matching was used to reduce the potential confounding from demographic characteristics, such as age and sex, between COVID-19 positive and negative patients. All CTA examinations were performed using the Philips Brilliance 64-Slice CT Scanner following the injection of 120 cc of Iomeprol 400 at 4-5 mL/sec. The cases were reviewed by two radiologists with over 10 years of experience, who were blinded to COVID-19 status. In cases of discrepancy, a third radiologist, with more than 30 years of experience, provided the final verdict.

Case scoring: In view of the non availability of verified large scale scoring systems for calculating arterial clot severity and extent in the peripheral extremities; we used three different systems, similar to Goldman IA et al., [9]. Vessels were categorised into two zones: proximal vessels (subclavian arteries, axillary arteries, brachial arteries, common iliac arteries, external iliac arteries, common femoral arteries, superficial femoral arteries, and popliteal arteries) and distal vessels (radial arteries, ulnar arteries, anterior tibial arteries, peroneal arteries, and posterior tibial arteries). Thrombosis or luminal narrowing of the palmar arteries, plantar arteries and digital arteries could not be assessed with a high confidence level in CTA and it produces false positives or inconclusive results. Hence, these parameters (thrombosis of arteries of hand only and thrombosis of arteries of feet only) were not included in the present study. A score of two was assigned for complete thrombosis of a vessel in any single cross section, and a score of one was assigned for partial thrombosis.

In the first system (proximal predominant), proximal vessels were given more importance, with each occluded proximal vessel awarded a value of 2 and each distal vessel given a value of 1. Vice versa, in the second system (distal predominant), each thrombosed distal vessel was given a value of 2 and each proximal vessel a value of 1. In the third system (proximal only), only proximal vessel thromboses were valued, and each vessel was given a value of 2.

To eliminate bias, imaging evidence favouring chronic thrombosis due to causes other than COVID-19, such as calcification within the walls and lumen of the vessel, narrowed arterial calibre, and presence of collaterals were not included in the study. Clinical history, hospital records, and prior imaging were used to determine whether the thrombus was acute or chronic. In the absence of prior imaging, the above-mentioned features were used to label vessels as chronically thrombosed.

Assessment parameters: Age, sex, symptoms and co-morbidities in both groups were analysed. CT thrombus burden score: The proximal and distal arteries of the upper and lower limbs were categorised, and a score was given as complete thrombosis (2), partial thrombosis (1) or no thrombosis (0), respectively.

STATISTICAL ANALYSIS

Data was entered into Microsoft Excel software (Windows 7; Version 2007) and analysed using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and Standard Deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical variables. The association between variables was analysed by using the Chi-square test for categorical variables. The p-value <0.05 was considered statistically significant.

RESULTS

The age group that presented with acute limb ischaemia ranged from 24 years to 74 years (mean age=50 years) [Table/Fig-1]. There was no significant gender predilection seen [Table/Fig-2].

Age (in years)	SARS-CoV-2 infection	
	Positive (n=35) n (%)	Negative (n=35) n (%)
≤30	3 (8.6)	-
31-40	7 (20)	9 (25.7)
41-50	10 (28.6)	9 (25.7)
51-60	5 (14.3)	7 (20)
>60	10 (28.6)	10 (28.6)
Mean±SD	50.14±13.46	50.63±12.47

[Table/Fig-1]: Comparison of age between study groups (N=70).
Chi-square test; p-value=0.458; Not significant

Gender	SARS-CoV-2 infection	
	Positive (n=35) n (%)	Negative (n=35) n (%)
Female	15 (42.9)	12 (34.3)
Male	20 (57.1)	23 (65.7)

[Table/Fig-2]: Comparison of gender between study groups (N=70).
Chi-square test; p-value=0.461; Not significant

Claudication, pain and redness had a significant association with COVID-19 positive patients [Table/Fig-3]. An association of hypertension in COVID-19 patients with acute thrombosis was found to be significant [Table/Fig-4].

Symptoms	COVID-19 infection		p-value
	Positive (n=35) n (%)	Negative (n=35) n (%)	
Gangrene	4 (11.4)	2 (5.7)	0.393
Claudication	21 (60)	2 (5.7)	**<0.001**
Pain	34 (97.2)	27 (77.1)	**0.012**
Blackening	13 (37.1)	9 (25.7)	0.303
Swelling	32 (91.4)	34 (97.2)	0.303
Redness	30 (85.7)	3 (8.6)	**<0.001**

[Table/Fig-3]: Comparison of symptoms between study groups (N=70).
Chi-square test; The p-value in bold font indicates statistically significant values

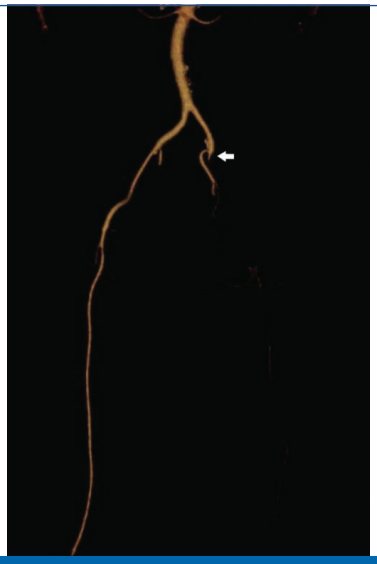
In a patient with a history of hypertension, the image shows a long segment of complete lumen occluding thrombus in distal right superficial femoral and popliteal arteries (white arrow) [Table/Fig-5]. A significant mean difference in arterial thrombus burden was observed in SARS-CoV-2 infection positive patients, with greater thrombus burden involving proximal vessels [Table/Fig-6]. Few images of angiogram are illustrated to show the clot burden [Table/Fig-7-9].

A greater risk of peripheral arterial thrombosis in upper limb was seen in COVID-19 positive patients; COVID-19 infected patients

had a predilection of peripheral arterial thrombosis compared to controls [Table/Fig-10].

Co-morbidities	COVID-19 infection		p-value
	Positive (n=35) n (%)	Negative (n=35) n (%)	
Diabetes mellitus	9 (25.7)	11 (31.4)	0.597
Hypertension	11 (31.4)	3 (8.6)	**0.016**
Fracture of shaft of femur	1 (2.9)	-	0.313
Carcinoma of breast	-	1 (2.9)	0.313
Mitral stenosis	-	1 (2.9)	0.313
Pancreatitis	1 (2.9)	-	0.313
Past history of thrombectomy	1 (2.9)	-	0.313

[Table/Fig-4]: Comparison of co-morbidities between study groups (N=70).
Chi-square test

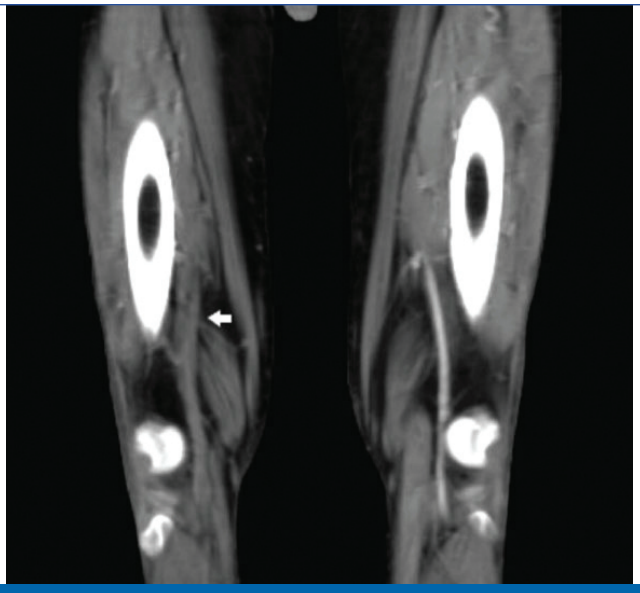


[Table/Fig-5]: Volume rendered image of bilateral limb angiogram.

Variables	SARS-CoV-2 infection		p-value
	Positive (n=35) (Mean±SD)	Negative (n=35) (Mean±SD)	
Proximal only	2.31±3.09	0.89±1.25	**0.014**
Proximal weighted	3.40±3.52	1.41±1.73	**0.004**
Distal weighted	3.32±3.18	1.50±1.99	**0.005**

[Table/Fig-6]: Comparison of overall arterial thrombus clot scores between study groups (N=70).
Chi-square test; p-value *Significant; Data was divided into buckets with frequency of each bucket specified; Therefore, Chi-square test was used

[Table/Fig-7]: Maximum intensity projection image of upper limb angiogram at the level of arch of aorta reveals partial lumen occluding thrombus in proximal left subclavian artery (white arrow), with clot burden score of 01.



[Table/Fig-8]: Maximum intensity projection image of right lower limb angiogram at the level of knee, shows short segment thrombosis of the right popliteal artery (white arrow).

[Table/Fig-9]: Maximum intensity projection image of right upper limb angiogram, revealing a short segment complete thrombosis in distal brachial artery (white arrow).

Variables	SARS-CoV-2 infection		p-value
	Positive (n=35) n (%)	Negative (n=35) n (%)	
Proximal upper limb	12 (34.3)	5 (14.3)	**0.050**
Proximal lower limb	8 (22.9)	10 (28.6)	0.584
Distal upper limb	9 (25.7)	2 (5.7)	**0.021**
Distal lower limb	10 (28.6)	13 (37.1)	0.445
Total upper limb	14 (40)	6 (17.1)	**0.034**
Total lower limb	13 (37.1)	18 (51.4)	0.228

[Table/Fig-10]: Comparison of overall arterial thrombus between study groups (N=70).
Chi-square test

DISCUSSION

In the present retrospective study consisting of 70 patients, with an equal number of COVID-19 positive and negative patients, there was a higher risk of overall thrombotic complications in the peripheral extremities with greater thrombus burden in COVID-19 positive patients. The present study results align with studies by Dane B et al., and Goldman IA et al., which revealed a higher propensity

of peripheral arterial thrombosis in COVID-19 with a greater clot burden [8,9].

As compared to the literature search of 31 articles conducted by Rastogi A et al., which found pain, paraesthesia, and gangrene as the most common symptoms [11]. The present study had pain, redness and claudication as the most common presenting symptoms. The geriatric population affected with COVID-19 disease has a higher prevalence of presenting with symptoms of acute limb ischaemia, as depicted by Rastogi A et al., in their study, with a mean age of 65.4 years [11]. Similar findings were obtained in the present study with a mean age group of 50.14 years.

Kharroubi SA and Diab-El-Harake M found that males had higher rates of mortality, hospitalisation and clinical complications from COVID-19 compared to females [12]. However, no sex predilection was found in the present study.

The present study also found a higher risk of thromboembolic affection of the peripheral extremities in patients with COVID-19, who have a background history of hypertension. Corroborative evidence of an increased risk of disease progression in COVID-19 positive patients with hypertension was found in several cohort studies conducted by Grasselli G et al., Li J et al., and Zhou F et al., [13-15].

Kumar A et al., searched the PubMed for case-control studies in English and included 33 studies (16,003 patients) in their analysis. They found diabetes to be significantly associated with mortality of COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37-2.64; p-value <0.01). Diabetes in patients with COVID-19 is associated with a two-fold increase in mortality and severity of COVID-19 compared to non diabetics. In the present retrospective study among 20 patients with diabetes mellitus, 11 were found in SARS-CoV-2 infection negative patients and nine in positive patients, showing no significant association of diabetes mellitus with higher thromboembolic risk [16].

Limitation(s)

Limitations of the current study include the small sample size and single-institution retrospective nature. This cohort describes patients presenting in the Emergency Department with symptoms of acute limb ischaemia, who underwent CTA of the peripheral extremities. As all patients with thromboembolism did not undergo CTA due to contraindications such as acute kidney injury or chronic kidney disease, the prevalence is underestimated.

CONCLUSION(S)

A positive association between COVID-19 and peripheral arterial thrombosis with a greater thrombus burden characterised by a predilection for proximal arteries is seen. In conclusion, COVID-19 disease may present with peripheral extremity microthrombi. Radiologists should raise concern for COVID-19 infection when identifying thromboembolic findings during and after the pandemic, allowing prompt diagnosis and treatment of this condition, thus preventing limb loss.

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