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Original Research Article

A retrospective analysis of COVID-19 patients presented with vascular problems: a single center experience

Kartik Datta Kolli*, Subrammaniyan Rathinavel Pandian, Marun Raj Gnanasekaran, Manoj Prabakar Ravichandran, Kamaraj Raja, Ratnasri Ravipati

Department of Vascular Surgery, Saveetha Medical College and Hospital, Saveetha Nagar, Thandalam, Sriperumbudur, Tamil Nadu, India

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***Correspondence:**
Dr. Kartik Datta Kolli,
E-mail: karthikk2k7@gmail.com

ABSTRACT

Background: The aim of the study was to analyse clinical, biochemical parameters and treatment outcomes of COVID-19 patients with vascular disease.
Methods: Retrospective analysis of data of COVID patients from May 2020 until July 2021.
Results: 7 patients had arterial disease alone, 3 arterial and venous, 4 venous alone. Mean age of patients with arterial disease was 52. 80% were diabetic, 30% hypertensive, 30% thyroid disorders. 10% past CVA, 10% had past PAD history. 10% had history of tobacco consumption. 50% had severe and 20% had moderate COVID, 30% were post discharge. Mean duration of presentation was 20.1±18.6 days after COVID diagnosis; mean duration of symptoms 8.8±11.8 days. 50% femoro-popliteal segment and 20% iliac segment was involved. 10% each were subclavian, axillary and brachial occlusions. Mean±SD CRP, ESR and D-dimer at admission were 74.36±71.35, 97±38.5 and 1360±1538 respectively. 3 surgical, 1 medical intervention resulted in limb salvage in 4 patients (9.25 month follow up; 2 upper, 2 lower limb). 3 patients required trans-tibial or above amputations. Death occurred in 2 patients. The four patients with COVID induced VTE had no comorbidities, presented mean 5.75 days of symptom onset; COVID diagnosis mean 23.33 days prior. External iliac to popliteal vein was the most common pattern (75%). Mean CRP and ESR were lower than in the arterial cases. One patient underwent IVC filter placement and CDT; for another IVC filter was placed. All four were discharged uneventfully.
Conclusions: Patients who developed arterial disease mostly had comorbidities, more severe COVID disease and higher mean inflammatory markers.

Keywords: COVID-19, PAD, VTE, DVT, Acute limb ischemia

INTRODUCTION

Vascular disease, comprising of acute limb ischemia and venous thromboembolism, is a dreaded complication of COVID-19 infection.[1] Estimated prevalence of venous thromboembolism in patients with COVID-19 is 14.1%, while the incidence of acute limb ischemia in patients with COVID-19 who require hospitalization ranges from 3 to 15 percent.[2-4] COVID-19 can potentiate all 3 components of Virchow's triad thereby increasing the risk of thrombosis.[5] Using the angiotensin-converting enzyme 2 receptor (ACE-2), which is expressed on the surface of many cells, SARS-CoV-2 enters endothelial cells impairing their intrinsic antithrombotic properties and leading to endothelial dysfunction. It is postulated that viremia, hypoxia, the inflammatory response, increased expression of tissue factor, and elevated levels of neutrophil extracellular traps (NETs) promote endothelial activation.[6-8] The induction of a procoagulant state along with the reduction in plasminogen activators further results

in increased platelet reactivity.[9-11] Inflammatory cytokines and endothelial activation can lead to downregulation of antithrombin and protein C expression along with increase in the levels of plasminogen activator inhibitor; fibrinogen; factors V, VII, VIII, and X; and von Willebrand factor.[12] Increased platelet reactivity, NETosis, and alterations in the aforementioned hemostatic factors result in a hypercoagulable state.[13-18]

The excessive inflammatory response associated with SARS-CoV-2 infection plays an important role in the pathogenesis of thrombosis, including pulmonary microthrombosis and pulmonary intravascular coagulopathy.[19,20] In addition, fatigue, hypoxemia, being connected to medical devices (for hospitalized patients), or acute illness (including pulmonary involvement, myocarditis with associated heart failure, or other forms of severe disease) lead to limited mobility and venous stasis.[21,22] The risk of arterial and venous thrombosis is exponentially increased by the aforementioned mechanisms, adversely affecting the severity of COVID-19 infection.

The aim of the study was to retrospectively analyze the clinical and biochemical characteristics and treatment outcomes in patients with COVID-19 infection complicated by vascular disease, with the goal to identify patterns of risk factors.

METHODS

This was a retrospective cross sectional study done at Saveetha Institute of Medical Sciences which is a tertiary health care center located in semi-urban locality in Tamil Nadu, India.

In the study, the characteristics of 14 patients who were managed by the department of vascular surgery from May 2020 to July 2021 were analyzed. Inclusion criteria were a diagnosis of COVID-19 and symptomatic peripheral arterial or venous thromboembolism. All the patients who matched the above criteria were included in the sample.

The data was analysed using Numbers software (Apple Inc, Cupertino). Statistical analysis consisted of indicators of distribution, mean and median, which were calculated using the aforementioned tool. Ethical committee approval was not required as the data was retrospective.

RESULTS

Out of 14 patients, 10 had arterial disease wherein 3 patients had a combination of arterial and venous disease while 7 patients had arterial disease alone. Venous disease alone was present in only 4 patients.

Arterial disease

Out of the 10 patients with arterial disease, 5 (50%) were male and 5 (50%) were female. Mean age was 52±11.69 years. 8 (80%) were diabetic and 3 (30%) were hypertensive. 3 (30%) had history of thyroid disease. 1 patient had history of tobacco abuse and past history of claudication. Another patient had past history of CVA. None had history of CAD.

One patient who had acute limb ischemia and DVT had past history of provoked DVT and pulmonary embolism. 7 patients out of the 10 were admitted in the hospital when vascular symptoms developed while 3 patients were discharged after admission for COVID-19 infection and presented to the OPD. 5 (50%) patients had severe COVID-19 infection and 2 (20%) were classified as having moderate COVID-19 infection, as defined by Oxygen saturation on room air (based on NIH COVID-19 treatment guidelines).[23]

Overall, the mean duration to presentation after COVID-19 diagnosis was 20.1±18.6 days (including post-discharge patients) (range: 5-50 days). Among the patients recently admitted, the mean duration to presentation was 11.14 days (range 5-40 days). The mean duration of vascular symptoms before presentation/referral to our department was 2 days among admitted patients (N=7) and 24.66 days among post discharge patients (N=3). Overall mean symptomatic duration before presentation/referral overall was 8.8 days (N=10).

Baseline patient characteristics are presented in Table 1.

Biochemical markers of inflammation and thrombosis, CRP and D-dimer, were routinely done at admission for all patients. Mean CRP (nephelometry) was 74.37 mg/dl, mean D-dimer at admission for the seven patients with acute presentations was 1527 ng/dl. Mean ESR was 107 mm/1st hour (Table 2).

Unilateral upper limb was involved in 3 (30%) patients and unilateral lower limb in 7 (70%) patients. There was no patient with bilateral limb involvement. In the three patients with venous involvement as well, DVT occurred in the same limb.

Among the seven lower limb cases, five were involving Fem-pop segment, two were involving iliac segment. One patient had an infra renal aortic thrombus which was managed with anticoagulation for 40 days before presenting to us with rest pain and impending gangrene of toe tips. On repeat CT Angiogram on presentation, the aortic thrombus had resolved, but there was an acute thrombus in the SFA.

Among the upper limb cases, one each were involving sub-clavian, axillary and brachial segment. The patient with sub-clavian occlusion had a cervical rib abutting the left sub-clavian artery.

Anatomical locations of segments involved (identified by CT angriogram) by acute or acute on chronic thrombus are presented in Table 3.

Interventions and outcomes of the ten arterial cases are documented in Table 4. To summarize the interventions and outcomes, total of nine patients underwent intervention.

Three patients underwent medical intervention alone due to severe COVID status, six patients underwent surgical intervention in addition to medical therapy. One patient had left against medical advise.

Among patient who received only medical therapy (N=3), two were given injection heparin infusion started at 1000 units per hour and both had worsening SIRS and acute limb ischemia progression despite anticoagulation. Both of them had DVT as well as acute limb ischemia and succumbed to the disease. The third patient, who had an acute SFA thrombus as well as DVT in CFV was started on Inj. Heparin infusion 1000 units/hour. He had symptomatic relief and palpable pedal pulses after two days.

Among patients who received surgical intervention in addition to medical therapy, two patients underwent upper limb trans-brachial embolectomies which resulted in limb salvage in both, with biphasic flow at wrist arteries and no symptoms. They were asymptomatic at 8th month follow-up.

Four lower limb surgical interventions were done including catheter directed thrombolysis (CDT) procedures in three patients (two for post-discharge patients with acute on chronic limb ischemia and one for a patient with persistent COVID at 40 days and acute iliac occlusion). One out of these three was salvaged without above ankle amputation at 3 month follow up (angioplasty done at check angiogram). One patient with iliac occlusion treated by CDT underwent through knee amputation with stump healing. In the third patient who underwent CDT followed by angioplasty there was improvement in ABI at discharge. However at two month follow-up, there was dry gangrene of the limb which had rapidly progressed to wet gangrene, necessitating amputation. In the fourth patient, open trans- femoral and trans- popliteal embolectomy was done with no infra popliteal flow. Therefore, below knee amputation was done for the patient and after two months, revision of the amputation had to be done. Overall, death occurred in 2 patients (20%); limb salvage without amputation occurred in 4 patients (40%) and improvement in amputation level with intervention occurred in 3 patients (30%). One patient (10%) left against medical advice (Table 5).

Arterial and venous disease

Three patients had ipsilateral acute limb ischemia as well as DVT.

All three patients were diabetic and had severe COVID-19 necessitating ICU admission and two of them had symptomatic limb swelling. All three were on thromboprophylaxis with Enoxaparin 40 mg SC OD. None of them were on antiplatelets. The mean day of presentation after COVID diagnosis was 6.33 days (5, 5, 6 days). Mean D-dimer and CRP at admission were 2390 ng/ml (678,312 and 4200 ng/ml) and 102.66 mg/dl (194, 79, 35 mg/dl). Two (66%) of the three patients died, while limb was salvaged with heparin infusion alone in one patient who survived. A trend of exponentially increasing D-dimer compared to admission value was noted in the patients who died. Both had a value in excess of 4200 ng/ml on the day of vascular surgery consultation. Of note, the patient who had an eventual outcome of limb salvage with Heparin infusion alone, had past history of post-surgical DVT with pulmonary embolism.

Venous disease

The four patients with venous thrombo embolism were all females. None of them had past or family history of VTE. None of them had any co-morbid conditions. One patient had an apparent provoking factor of major abdominal surgery for intestinal obstruction and COVID diagnosis when admitted for surgery. Two of these patients were admitted with active COVID, while the third had a history suggestive of COVID-19 infection with bilateral ground glass opacities involving both the lung fields on CT ten days prior to presentation at our center. She was neither diagnosed nor treated but had high antibody titer at presentation with unvaccinated status. Baseline characters of the patients with VTE are documented in Table 6. Baseline CRP, D-dimer and ESR of the patients are presented in Table 7. Anatomic segment involved (venous Doppler) is presented in Table 8. Two out of four (50%) patients received only IV anticoagulation while in two other patients, IVC filter placement was done followed by anticoagulation. All four patients were discharged on oral rivaroxaban and had no recurrence at follow up. Interventions and outcomes are documented in Table 9.

Table 1: Demographic characteristics of patients with arterial disease.

Characteristics	Values N (%)
Age (years)	52 (range: 39-70)
Gender	
Males	5 (50)
Females	5 (50)
Diabetes	8 (80)
Hypertension	3 (30)

Continued.

Characteristics	Values N (%)
Thyroid disease	3 (30)
Multiple co-morbids	2 (20)
Tobacco abuse	1 (10)
PAD history	1 (10)
CAD history	0 (0)
CVA history	1 (10%)
Mean duration of presentation after COVID diagnosis	20.1±18.6 days
Mean duration of presentation after COVID diagnosis, not including post discharge patients	11.14 days (range 5-40 days)
Mean duration of presentation after symptom onset, not including post discharge patients	2 days
Mean duration of presentation after symptom onset for post discharge patients	24.66 days
Mean duration of presentation after symptom onset overall	8.8 days

Table 2: Biochemical markers in patients with arterial disease.

Biochemical markers	Values	Range
Mean CRP (nephelometry) at admission	74.81 mg/dl	5-194
Mean D-dimer at admission (N=7, not including post discharge patients, laboratory upper reference 246 ng/dl)	1527 ng/ml	320->4200
Mean ESR (N=4, all four with acute presentations)	107 mm/1st hour	21-120

Table 3: Anatomical segment involved in patients with arterial disease.

Characteristics	Values
Lower limb (N=7)	Upper limb (N=3)
Iliac, 2	Subclavian, 1
Femoro popliteal, 5 (includes three acute on chronic presentations in post-discharge patients)	Axillary, 1
	Brachial, 1

Table 4: Interventions and outcomes in COVID patients with arterial disease.

Clinical COVID status at presentation	Presentation days after COVID diagnosis	Duration of complaints	Clinical findings	CT angio	Doppler	Intervention	Outcome
Severe	5	1	Fem-pop occlusion and acute, proximal, provoked DVT	-	Biphasic flow in left CFA, popliteal, monophasic in tibials (day of presentation). CFV hypoechoic thrombus.	Heparin 1000 units/hour infusion	Clinical deterioration over 4-5 days, needing intubation. Disease progression in the limb- iliac occlusion (seen 5 days after first). Death on day 7.
Moderate	7	4	Left subclavian occlusion with cervical rib	Thrombosis of LEFT SCA, AA, BA, RA, UA, IOA. Cervical rib	-	Left against advice	Left against advice

Continued.

Clinical COVID status at presentation	Presentation days after COVID diagnosis	Duration of complaints	Clinical findings	CT angio	Doppler	Intervention	Outcome
				abutting subclavian A.			
Post-COVID	50	30	Fem-pop occlusion-acute on chronic	PFA occlusion, distal SFA, popliteal, TP trunk occlusion	-	Thrombolysis with urokinase 40 hours, f/b distal popliteal, AT, TPT, PT angioplasty	Abi improvement, Rest pain decreased, over next two months. Toe wounds being managed conservatively for demarcation.
Post-COVID	45	30	Fem-pop occlusion	Distal femoral stenosis, p2 and 3 occlusion	-	Thrombolysis with urokinase 40 hours f/b distal femoral, AT, TPT, PT angioplasty	Immediate post op: improvement in ABI.
Post-COVID	28	14	Fem-pop subacute occlusion, no pedal flow	Mid SFA, Popliteal, TPT, AT thrombus	-	Femoro popliteal embolectomy, heparin post op infusion, BKA, Presented with rest pain and non-healing stump 2 months later, iliac occlusion, external iliac angioplasty done	Immediate post op: clinical improvement, biphasic AT, PT flow. Demarcation lowered, BKA done. After 2 months, disease progression inspite of anticoagulation and antiplatelets.
Severe	5	1	Acute iliac occlusion	Near total left CIA occlusion with thrombus. CFV thrombus.		Heparin 1000 units/hour infusion	Clinical deterioration over 4-5 days, needing intubation. Death on day 11.
Severe	6	1	Acute fem-pop occlusion	CFA, SFA partial lumen, Popliteal, AT, TPT thrombus LMPA non occluding PE.		Heparin 1000 units/hour infusion	Palpable AT, PT after 2 days. Pain relief.

Continued.

Clinical COVID status at presentation	Presentation days after COVID diagnosis	Duration of complaints	Clinical findings	CT angio	Doppler	Intervention	Outcome
Severe	40	2	Acute iliac disease, limb cold from mid thigh	CFA, PFA partial thrombotic occlusion		Catheter directed thrombolysis with Urokinase 48 hours	Through knee amputation after demarcation. Stump healed.
Severe	8	4	Brachial occlusion, no doppler flow in radial, ulnar	Mid, distal brachial, radial, lnar, interosseus occlusion,		Heparin infusion 1000 units/hr for two days followed by brachial embolectomy	Biphasic flow at discharge in radial and ulnar, symptomatic relief. Follow up until one year, no symptoms.
Moderate	7	1	Axillary occlusion	Complete thrombosis axillary A, brachial a. upto 2/3 of arm		Brachial embolectomy	Bi to triphasic flow at discharge in radial and ulnar arteries. Followed up until 8 months, no symptoms.

Table 5: Outcomes summary in patients with arterial disease.

Outcome parameters	Observations
Death	2 (20%)
Limb salvage without amputation	4 (40%)
Upper limb	2 (2 out of 2 upper limbs intervened surgically)
Lower limb	2 (1 out of 4 lower limbs intervened surgically, 1 out of 3 lower limbs intervened with medical therapy alone)
Improvement in amputation level after intervention	3 (30%) (all lower limbs, 3 out of 4 lower limbs intervened surgically)
Left against advice, no intervention	1 (10%)

Table 6: Demographic characteristics of patients with venous disease.

Characteristics	Value
Age (years)	53.25 (range: 40-73)
Males	0 (0%)
Females	4 (100%)
Mean duration of presentation after COVID diagnosis	30
Mean duration of presentation after COVID diagnosis, not including post discharge patients	7.5 days (range 5-7 days)
Mean duration of presentation after symptom onset, not including post discharge patients	3 days
Mean duration of presentation after symptom onset for post discharge patients	7 days
Mean duration of presentation after symptom onset overall	5 days
Comorbidities	None
Past/ family history of VTE/ other provoking factors/ malignancy histrory	None

Table 7: Biochemical markers in patients with VTE.

Biochemical markers	Values	Range
Mean CRP (nephelometry) at admission	57.98 mg/dl	37-118
Mean D-dimer at admission	1712	608- >4200
Mean ESR	41.25 mm/1st hour	20-55

Table 8: Anatomical segment involved in VTE patients.

Outcome parameters	N (%)
External iliac to popliteal	3 (75)
CFV to popliteal	1 (25)
Pulmonary embolism (lobar artery) (in addition to DVT)	1 (25)
Portal, splenic, SMV thrombus (in addition to DVT)	1 (25)

Table 9: Interventions and outcomes in VTE.

Intervention	Outcomes			
Right acute, proximal. unprovoked DVT	(CTPA) lobar artery level PE	EIV- popliteal involved	IVC filter placement (Ind. inability to anticoag in v/o severe anemi. Blood transfused, f/b CDT and anticoagulation)	Decrease in limb swelling, discharged on rivaroxaban 15 mg bd. No recurrence at 3 month follow up.
Left acute, proximal, provoked DVT	(CTPA) No PE	CFV- popliteal	IV-oral anticoagulation	Decrease in limb swelling, discharged on rivaroxaban 15 mg bd. No recurrence at 2 month follow up.
Left acute, proximal, provoked DVT	CTPA No PE, portal, splenic and SMV thrombus with collaterals	EIV- popliteal involved	IVC filter placement (Ind. inability to anticoag in v/o severe anemia, f/b anticoagulation)	Decrease in limb swelling, discharged on rivaroxaban 15 mg bd. No recurrence at 2 month follow up.
Right acute, proximal, provoked DVT	CTPA not done	EIV- popliteal involved	IV- oral anticoagulation	Decrease in limb swelling, discharged on rivaroxaban 15 mg bd. No recurrence at 2 month follow up.

Table 10: Comparison with other case series of acute limb ischemia in COVID patients.

Parameters	Etkin et al.	Llonzo et al.	Indes et al.	Bellosta et al.	Present study
N (limb ischemia)	42	16	16	20	10
Mean/median age (years)	67 (median)	63.3	64 (median)	75	52 50 (median)
Comorbidites (% of patients)					
DM	35	56	53	15	80
SHTN	53	87	80	55	30
Thyroid disease	NR	NR	NR	NR	30
PAD	4	37.5	27	20	20
CKD	4	12	7	20	0
CAD	NR	NR	NR	NR	0
Multiple	45	NR	NR	NR	20
No past medical history	27	NR	NR	NR	10
D-dimer in ng/ml at presentation (median/ mean)	2673 (median)	4000	17,300 (median)	2200 (median)	895 (median) 1527 (mean)

Continued.

Parameters	Etkin et al.	Llonzo et al.	Indes et al.	Bellosta et al.	Present study
Upper limb ischemia (% of patients)	16.6	25	20	5	20
Lower limb (% of patients)	83.3	75	80	95	80
Limb loss (%)	18	12.5	31	7	20
Mortality(%)	46	33	40	40	20

Note: NR= not reported.

DISCUSSION

Arterial disease

The incidence of acute limb ischemia in COVID-19 patients is reportedly higher than the incidence of acute limb ischemia in the general population and in patients with known PAD.[2,3,24,25] The profile of COVID patients affected by arterial disease has been studied by other case series- Etkin et al, Llonzo et al, Indes et al and Bellosta et al, comparison with these case series is represented in Table 10.[2,3,26,27]

Patient characteristics

The data from the present study compares closely with the past studies, except for lower age of patients. Most patients had at least one comorbidity, but in contrast to the other studies where hypertension was more prevalent, DM was the most common comorbidity in our study. There was no patient with chronic kidney disease. Only one patient (10%) in our study had no past medical history or risk factors. PAD history was present in almost the same proportion as in the studies done by Indes et al and Bellosta et al.[26,27]

In a systematic review of 31 articles describing 133 patients with COVID induced peripheral artery disease with gangrene, details of pre-existing co-morbidities were available for 119 patients; hypertension was the most common associated co-morbidity present in 61 patients (51.3%), followed by diabetes in 38 (31.9%), hypercholesterolemia in 21 (17.6%), prior CAD in 19 (16.0%), COPD in 6 (5.0%), chronic kidney disease in 4 (3.4%), atrial fibrillation and prior stroke in 2 subjects each and hypothyroidism (0.84%) in one patient.[26,27]

D-dimer and CRP

Median D-dimer value at presentation was lower when compared to other studies. Mean CRP was 75 mg/dl in our study while it was not reported by other studies.

ALI as presenting symptom

In their study, Etkin et al reported that acute limb ischemia was the initial presentation in 45% patients.[3] Similarly Mascia et al reported that COVID-19 infection was detected at or shortly after admission for acute limb ischemia in 48% of the patients.[29] However, in our study all the patients were symptomatic with COVID-19 infection before presentation and hence none who had ALI as a presenting symptom.

Timing of acute limb ischemia

ALI during hospitalization for COVID occurred in 7 (70%) patients in our study. Median duration of ALI presentation was 7 days (5-40 days range). This compares to median 13 days reported by Ahmet et al and median 11 days by Fournier et al.[4,30]

Our study included 3 patients who presented with subacute/acute on chronic limb ischemia 30-50 days after COVID-19 diagnosis. All three of them had mild disease not requiring oxygen supplementation. Similar presentations were described by Borrelli et al, Surya et al and Veerasuri et al.[31-33]

Thromboprophylaxis prior to presentation

Five out of the seven (71%) admitted patients were started on enoxaparin 40 mg sc once a day as thromboprophylaxis on admission, as per institutional protocol, as their D-dimers were elevated at admission. None of these patients were on antiplatelet agents. Out of three post discharge patients one was on antiplatelets plus rivaroxaban, one was on antiplatlets alone while one was not on any medication.

Diagnostic strategy

In the setting of the COVID-19 pandemic, the vascular imaging study used has depended upon the stability of the patient for transfer to the imaging suite, as well as consideration for allocation of resources.[34] In a review of a small cohort of 16 patients with acute upper or lower extremity ischemia, only 8 patients underwent confirmatory imaging studies.[26] However, in the present study, all patients had confirmatory imaging (9 CT angiograms and 1 bedside Doppler study).

Location of thrombus

Similar to other studies,the majority were lower limb ischemia cases. Concomitant DVT rate was higher in our study in comparision to Etkin et al (30% vs 16%).

Interventions

In most case series, aroung 50% of patients could undergo surgical (including endovascular) revascularization attempts.[34] However, our study, intervention was done for

90% of patients (revascularization attempted in 80% and systemic heparinisation given in 10%). No primary amputations were done. Limb salvage was possible in 40% patients, while improvement in level of amputation was possible in another 30% patients. Limb loss rate and mortality rate were 20% each.

In comparision in the large case series reported by Etkin et al revascularization was performed in 27% of patients, primary amputation in 10%, 57% were treated with systemic anticoagulation only, and 6% received systemic administration of tissue-plasminogen activator.[3] The rate of limb loss was 18% with mortality of 46%.

Of particular note, limb loss rate

In our study was 20% which was similar to Etkin et al, higher than Llonzo et al. and Bellosta et al, but lower than that in Indes et al. Mortality rate was lower compared to other studies.

The rate of major amputations in COVID-19 associated ALI is 4-5 times higher than with other non-COVID related vascular conditions.[34-37]

Venous disease

In our study, all the patients were females >40 years in age, with no co-morbid conditions. Only one patient had a provoking factor - recent major abdominal surgery for intestinal obstruction due to non-malignant jejunal stricture. She was started on enoxaparin 40 mg SC OD after the surgery but prophylaxis was discontinued after drop in Hemoglobin and history of bleeding hemorrhoids. At presentation three patients (75%) were classified as low risk group according to Boston University algorithm based on Modified Caprini score while, one patient (who underwent abdominal surgery and discontinued LMWH prophylaxis) was in the high risk group.[38,39]

In one large study of over 3000 admitted patients, most of whom received prophylactic-dose anticoagulation, risk factors for VTE on multivariate analysis were older age, male sex, Hispanic ethnicity, coronary artery disease, prior myocardial infarction, and higher D-dimer (>500 ng/ml) at hospital presentation.[40] VTE was associated with an increased mortality rate [adjusted hazard ratio (HR), 1.37; 95% CI 1.02-1.86]. Whereas, in our study, there were no such risk factors in any of the patients. Only one patient received prophylactic anticoagulation (inadequately, as discussed above). D-dimer at presentation was mean 1712 (range 608-4200) and all four patients survived. However, small sample size of our study precludes any valid conclusions.

Concomitant limb ischemia and DVT

In our study 30% of patients had concomitant DVT and limb ischemia which is higher than reported in the series by Etkin et al where 16% had DVT as well as acute limb ischemia.[3]

Limitations

Small sample size was a major limitation of this study. Studies with larger sample size are needed to identify the COVID-19 patients likely to be affected by arterial and venous disease.

CONCLUSION

Patients with ALI had comorbid conditions, mostly diabetes and presented on average in the second week after COVID-19 diagnosis. Biochemically, at admission, mean D-dimer was 6 times the reference range and mean CRP was nearly 15 times the normal limit. Lower limb arterial system was more commonly affected than the upper limb with Femoro Popliteal segment being most common site. Overall, Mortality rate was 20% and limb loss rate (defined as needing an above ankle amputation) was 20%. Among the patients with VTE none had comorbid conditions and most were otherwise at low risk of DVT. They presented on average in second week of COVID diagnosis. At admission, mean CRP was 12 times the normal limit and mean D-dimer was 7 times the reference range. External iliac to popliteal thrombosis was the most common anatomic pattern. One patient had concomitant pulmonary embolism (25%). There was no mortality in our study. Incidence of concomitant arterial disease and VTE was 30%, among the patients with arterial disease. All these patients were admitted in the ICU for severe COVID-19 infection, and had diabetes mellitus. At admission, Mean D-dimer and CRP values was 10 times and 20 times the reference range respectively reflecting severe thrombo-inflammatory activity. The mortality rate was 66%. COVID-19 patients who develop acute limb ischemia are likely to have comorbidities and high thrombo-inflammatory markers. Such a patient profile should keep clinicians on alert for possible symptoms and signs of ALI. Prompt diagnosis and management results in good probability of limb salvage, though less than in non COVID-19 ALI. Prolonged thromboprophylaxis might be required for COVID-19 patients with high risk profiles to prevent vascular complications.

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