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COVID-associated acute limb ischemia during the Delta surge and the effect of vaccines

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ABSTRACT

Objective: Hypercoagulability is common in severe acute respiratory syndrome coronavirus 2 and has been associated with arterial thrombosis leading to acute limb ischemia (ALI). Our objective was to determine the outcomes of concurrent coronavirus disease 2019 (COVID-19) infection and ALI, particularly during the Delta variant surge and the impact of vaccination status.

Methods: A retrospective review was performed of patients treated at a single health care system between March 2020 and December 2021 for ALI and recent (<14 days) COVID-19 infection or who developed ALI during hospitalization for the same disease. Patients were grouped by year as well as by pre and post Delta variant emergence in 2021 based on the World Health Organization timeline (January to May vs June to December). Baseline demographics, imaging, interventions, and outcomes were evaluated. A control cohort of all patients with ALI requiring surgical intervention for a 2-year period prior to the pandemic was used for comparison. Primary outcomes were in-hospital mortality and amputation-free survival. Kaplan-Meier survival and Cox proportional hazards analysis were performed.

Results: Forty acutely ischemic limbs were identified in 36 patients with COVID-19, the majority during the Delta surge (52.8%) and after the wide availability of vaccines. The rate of COVID-19-associated ALI, although low overall, nearly doubled during the Delta surge (0.37% vs 0.20%; $P = .09$). Intervention (open or endovascular revascularization vs primary amputation) was performed on 31 limbs in 28 individuals, with the remaining eight treated with systemic anti-coagulation. Postoperative mortality was 48%, and overall mortality was 50%. Major amputation following revascularization was significantly higher with COVID-19 ALI (25% vs 3%; $P = .006$) compared with the pre-pandemic group. Thirty-day amputation-free survival was significantly lower (log-rank $P < .001$). COVID-19 infection (adjusted hazard ratio, 6.2; $P < .001$) and age (hazard ratio, 1.1; $P = .006$) were associated with 30-day amputation in multivariate analysis. Severity of COVID-19 infection, defined as vasopressor usage, was not associated with post-revascularization amputation. There was a higher incidence of re-thrombosis in the latter half of 2021 with the Delta surge, as reintervention for recurrent ischemia of the same limb was more common than our previous experience (21% vs 0%; $P = .55$). COVID-19-associated limb ischemia occurred almost exclusively in non-vaccinated patients (92%).

Conclusions: ALI observed with Delta appears more resistant to standard therapy. Unvaccinated status correlated highly with ALI occurrence in the setting of COVID-19 infection. Information of limb loss as a COVID-19 complication among non-vaccinated patients may help to increase compliance. (J Vasc Surg 2023;77:1165-73.)

Keywords: Acute limb ischemia (ALI); COVID-19

Since the beginning of 2020, the severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019 [COVID-19]) pandemic has had a devastating impact on

the United States, with over 82 million cases and over 1 million deaths.^{1,2} Although the primary manifestation of COVID-19 infection involves the pulmonary system, there

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has been documented involvement of various other organ systems, including cardiovascular, neurologic, renal, and hematologic.³

Hypercoagulable states have been shown to be associated with COVID-19 infection primarily in the venous system, with several studies documenting the presence of venous thromboembolisms and pulmonary embolisms in patients with COVID-19.^{4,5} It has been postulated that the prothrombotic state arises from underlying endothelial dysfunction and endotheliitis due to direct infection of the vascular endothelium by the COVID-19 virus, leading to thrombus formation.⁶⁻⁹ Several case reports and small multi-center studies have shown an elevated incidence of arterial thrombosis leading to acute limb ischemia (ALI) in COVID-19 infections with increased mortality, amputation rates, and intervention failure.¹⁰⁻¹⁵ However, most of these series were prior to the advent of vaccines.

The COVID-19 vaccines were approved by the United States Food and Drug Administration for emergency use in December of 2020.¹⁶ Shortly after the wide-availability of vaccines, in May of 2021, the World Health Organization identified the emergence of the Delta COVID-19 variant, putting an even larger strain on the health care system, with high numbers of breakthrough infection, increased virulence, and transmissibility.¹⁷ Currently, there is no study evaluating the association of the Delta variant COVID-19 infection with the incidence of ALI.

This study serves to determine the outcomes of concurrent COVID-19 infection and ALI, particularly during the Delta variant surge and the impact of vaccination status. We hypothesize that the hypercoagulable state induced by active COVID-19 infection leads to worsened outcome in instances of ALI, particularly in unvaccinated patients.

METHODS

This was a retrospective study evaluating the incidence of COVID-19-associated ALI across at a single health care, multi-hospital network between January of 2020 and March of 2022. The University of Pittsburgh Institutional Review Board approved this study (STUDY21100134). Informed consent was obtained for all patients undergoing intervention.

Data source and patient cohort. The electronic medical record (EMR) was queried for patients aged >18 years with ALI and a recent (<14 days) COVID-19 positive test or for those who developed limb ischemia during hospitalization for COVID-19.¹⁸ COVID-19 infection was confirmed by polymerase chain reaction testing or positive testing documentation from outside facilities. Patients presenting with ALI and negative COVID-19 testing or no COVID-19 testing were excluded. A control cohort of unmatched patients with ALI requiring surgical intervention for a 2-year period prior to the COVID-19

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective, cohort study of data collected from a single-institute, multi-hospital network
- **Key Findings:** The rate of coronavirus disease 2019 (COVID-19) associated acute limb ischemia (ALI), though low overall, nearly doubled during the Delta surge (0.37% vs 0.20%; $P = .09$). Major amputation following revascularization was significantly higher with COVID-19 ALI (25% vs 3%; $P = .006$) compared with the pre-pandemic group. COVID-19-associated limb ischemia occurred almost exclusively in non-vaccinated patients (92%).
- **Take Home Message:** The overall post-revascularization mortality and major amputation rates were significantly increased in the setting of concurrent COVID-19 infection. Unvaccinated status correlated highly with ALI occurrence in the setting of COVID-19 infection.

pandemic (2018-2019) was used for comparison of outcomes.

Baseline demographic information, imaging, interventions, and outcomes were obtained from the EMR. Clinical indicators of ALI were evaluated using the Rutherford scale of ALI based on the presence of limb pain, motor, or sensory deficit and pulse/doppler exam. Preoperative laboratory results and imaging were collected with the location of the occlusion documented. Vasculature patency was assessed using duplex ultrasound, computed tomography angiography (CTA), or digital subtraction angiography. Interventions were defined as either open surgical, endovascular, hybrid, primary amputation, or nonoperative based on operative reports and documentation. Postoperative outcomes and follow-up information were documented. Major adverse limb events include the need for subsequent major amputation and open or endovascular reintervention due to vessel re-thrombosis. Additional complications included initiation of vasopressor support or renal replacement therapy, cardiac failure defined by myocardial infarction, or pulmonary failure as represented by mechanical ventilation and mortality either during the index hospitalization or on subsequent readmission/follow-up. The initiation of postoperative vasopressor support was used as a surrogate for severity of COVID-19 infection in our study.

Outcomes. Primary outcomes were all-cause in-hospital mortality and 30-day amputation-free survival. The EMR, which is linked to the Social Security death index, was used to identify the death date as well as the amputation date. The cause of death was determined by documented death summaries and classified as COVID-

19-related (respiratory failure, multisystem organ failure, or septic shock secondary to initial COVID-19 infection), non-COVID-19-related (any other cause of death), or unknown. Thirty-day amputation-free survival was defined as not having a major amputation or death within 30 days of the index admission date. Major amputation was defined as either above-ankle amputation, or upper limb above-wrist amputation.

Secondary outcomes included hospital length of stay and major adverse limb events (rate of reintervention, and 30-day major amputation post-revascularization). Reintervention was defined as a return to the operating room due to recurrent ischemia or loss of patency after the primary intervention and was categorized as open surgical, endovascular, hybrid, or amputation.

Statistical analysis. Baseline characteristics for pre-COVID and COVID-19 cohorts were compared using the Pearson χ^2 and Fisher exact tests for categorical variables and presented as number (frequency %). For continuous variables, the Mann-Whitney and the Student *t* test were used and presented as mean (\pm standard deviation). Amputation-free survival at 30 days between the two groups was compared by Kaplan-Meier survival analysis with associated log-rank testing. Cox proportional hazard analysis was also utilized to assess for factors associated with amputation-free survival. The models generated adjusted hazard ratios (aHRs) with 95% confidence intervals (95% CIs). A *P*-value $\leq .05$ was determined to be statistically significant. All analyses were performed with Stata 17 (StataCorp, College Station, TX). Informed consent was obtained with consent to be treated, and all patients were de-identified.

Subgroup analysis. To assess the effect of the emergence of the Delta variant and vaccination status on COVID-19-associated ALI, patients were grouped as pre-Delta (all cases from 2020 until May 2021) and post-Delta (June 2021 until December 2021) based on the World Health Organization timeline. For this subgroup analysis, we compared baseline characteristics using the same statistical methods described above. We also described characteristics and outcomes of individuals who presented with COVID-19-associated ALI after the emergence of the Omicron variant in 2022.

RESULTS

A total of 40 COVID-19-associated ischemic limbs in 36 patients were identified throughout the study period in comparison with 74 ischemic limbs in 68 patients in the pre-COVID-19 cohort. 18 of 40 limbs (45%) were initially admitted for COVID-19 infection, whereas the remaining 22 (55%) were admitted for ALI and found to be COVID-19-positive after testing or tested positive at home but did not meet hospitalization criteria based on their COVID-19 symptoms. The majority of subjects presented during the Delta surge (52.8%) and after the

wide availability of vaccines. COVID-19 variant information, however, was not available at the time of the study. A total of 13,522 cases of COVID-19 hospitalization were identified in the health care network between 2020 and 2021. The rate of COVID-19-associated ALI, though low overall, nearly doubled during the Delta surge (0.37% vs 0.20%; *P* = .09). A total of 212 cases of ALI were identified in the health care network between 2020 and 2021. The incidence of COVID-19-associated ALI during this study period was 17%. The average age of the COVID-19-associated ALI cohort was significantly older than the pre-COVID-19 group (69.1 ± 11.4 years vs 63.3 ± 14.4 years; *P* = .03). In both groups, the majority were male and non-Hispanic Whites, matching the demography of the western Pennsylvania patients (Table I). Within the COVID-19-associated ALI group, there was a 32.5% incidence of peripheral arterial disease, although the symptoms were not obtainable, as well as a significantly larger proportion who have had no prior history of vascular interventions (72% vs 59%; *P* < .001) as compared with the control. There was a higher proportion of patients with a history of stroke or transient ischemic attack within the COVID-19-associated ALI group (30% vs 12%; *P* = .02). There were no significant differences in the proportion of patients with a history of venous thromboembolism or hypercoagulable disorders between the two groups. The COVID-19-associated ALI group more often presented with Rutherford Class I ischemia on initial evaluation when compared with the unmatched control group (28% vs 8%; *P* = .03).

In the COVID-19-associated ALI group, intervention (open or endovascular revascularization vs primary amputation) was performed on 32 limbs in 28 individuals, with the remaining eight patients treated with systemic anti-coagulation. Of the 32 limbs undergoing interventions, 12 required adjunctive treatment during the index operation that was presumed to address underlying disease present within the native vasculature (stenting, balloon angioplasty or endarterectomy with and without patch angioplasty). Eleven of the 40 ischemic limbs were on pressors prior to any intervention or at the time of vascular intervention, with 45% that were treated with medical management. Only one patient was on veno-veno extracorporeal membrane oxygenation and was managed with anticoagulation alone. In the 10 ischemic limbs treated solely with endovascular intervention, all underwent catheter-directed intervention with the use of thrombolytic agents, and six interventions employed the use of catheter-directed aspiration as an adjunct. Of the combined hybrid and open interventions listed in Table II, there were four bypasses, with the remainder of interventions being thromboendarterectomies. All but one of the hybrid interventions involved concomitant stenting proximal to site of thrombectomy/bypass, with the remaining concluding with only a diagnostic angiogram. There

Table I. Baseline demographics of the pre-coronavirus 2019 (COVID-19) acute limb ischemia (ALI) cohort vs the COVID-19-associated ALI cohort

	Pre-COVID-19 ALI n = 74 (64.9%)	COVID-19 ALI n = 40 (35.1%)	P-value
Age, years	63.3 (14.4)	69.1 (11.4)	.029
Gender			
Male	45 (61)	29 (72)	.23
Female	29 (39)	11 (28)	
Ethnicity			
White	65 (88)	36 (90)	.032
Black	7 (9)	0 (0)	
Hispanic	0 (0)	1 (2)	
Other/unknown	2 (3)	3 (8)	
Smoking			
Non-smoker	26 (35)	18 (46)	.38
Current smoker	19 (26)	6 (15)	
Previous smoker	29 (39)	15 (38)	
Intravenous drug use	4 (5)	0 (0)	.30
History of VTE	6 (8)	3 (8)	1.00
Hypertension	48 (65)	32 (80)	.13
CAD	28 (38)	13 (32)	.68
CHF	4 (5)	5 (12)	.27
Diabetes	25 (34)	16 (40)	.54
CKD	8 (11)	6 (15)	.56
ESRD	3 (4)	2 (5)	1.00
History of stroke/TIA	9 (12)	12 (30)	.024
HLD	29 (39)	14 (35)	.69
History of hypercoagulable disease	6 (8)	3 (8)	1.00
Malignancy	10 (14)	7 (18)	.59
COPD	15 (20)	11 (28)	.48
History of vascular intervention			
None	44 (59)	29 (72)	<.001
Endoscopic	30 (41)	6 (15)	
Open	0 (0)	5 (12)	
History of amputation			
None	65 (88)	35 (88)	.67
Minor amputation	6 (8)	2 (5)	
Major amputation	3 (4)	3 (8)	
Anticoagulation	17 (23)	8 (20)	.81
Aspirin	34 (46)	17 (42)	.84
Antiplatelets	26 (35)	8 (20)	.13
Rutherford classification			
Class I	6 (8)	11 (28)	.025

(Continued)

Table I. Continued.

	Pre-COVID-19 ALI n = 74 (64.9%)	COVID-19 ALI n = 40 (35.1%)	P-value
Class IIa	30 (42)	13 (32)	
Class IIb	34 (47)	13 (32)	
Class III	2 (3)	3 (8)	

CAD, Coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HLD, hyperlipidemia; TIA, transient ischemic attack; VTE, venous thromboembolism.
Data are presented as number (%) or mean (standard deviation).

was a significantly higher proportion of subjects who received either nonsurgical management or primary amputation (30% vs 0%; $P < .001$) in the COVID-19-associated ALI group as compared with the control, with the majority of the nonoperative and primary amputation patients intubated at the time of ALI diagnosis (70%). There were 37 ischemic lower extremities and three ischemic upper extremities in our cohort. The majority of the thrombus were located proximally (17/40) (ie, iliac/femoral or subclavian/axillary/brachial) as opposed to distally (12/40) (ie, popliteal/tibial or radial/ulnar), with the remaining being multi-level in nature (9/40), occurring mainly during the Delta surge (6/9). There were, however, no differences in the management or outcomes when stratifying by occlusion location (Supplementary Table I, online only). There was also a significantly longer length of stay (19.3 ± 14.1 days vs 10.4 ± 9.3 days; $P < .001$), as well as a higher rate of 30-day major amputation (25% vs 3%; $P < .001$) within the COVID-19-associated ALI group as compared with the control (Table II).

Postoperative in-hospital mortality was 48%, and overall mortality was 50% in the COVID-19-associated ALI cohort. Almost all deaths in the COVID-19-associated ALI cohort were COVID-19-related, with only one patient having a non-COVID-19-related mortality. This individual survived their index COVID-19 hospitalization, with the cause of death being hemorrhagic shock secondary to gastrointestinal bleeding. Patients who were treated nonoperatively had a higher mortality rate when compared with others who received some form of intervention (63%). Among the eight nonsurgically managed patients, five were deceased secondary to COVID-19 pneumonia, and the remaining three did not require any major amputations. The 30-day amputation-free survival in the COVID-19-associated ALI group was 45%, which was significantly lower than the pre-COVID-19 cohort (89%) by Kaplan-Meier analysis (Fig). On multivariate analysis, COVID-19 infection was associated with increased 30-day amputation (aHR, 6.2; 95% CI, 2.3-16.8; $P < .001$) and in-hospital mortality (aHR, 10.1; 95% CI,

Table II. Treatment and postintervention outcomes of pre-coronavirus disease 2019 (COVID-19) acute limb ischemia (ALI) vs COVID-19-associated ALI

	Pre-COVID-19 ALI n = 74 (64.9%)	COVID-19 ALI n = 40 (35.1%)	P-value
Treatment type			
Open	21 (28)	11 (28)	<.001
Endovascular	19 (26)	10 (25)	
Hybrid	34 (46)	7 (17.5)	
Medical only	0 (0)	9 (22)	
Amputation	0 (0)	3 (7.5)	
Reintervention	7 (16)	7 (17.5)	.88
Total length of stay, days	10.4 (9.3)	19.3 (14.1)	<.001
In-hospital mortality	6 (8)	19 (48)	<.001
Postintervention amputation	11 (14.9)	7 (17.5)	.54
30-day amputation	2 (3)	11 (28)	.001
30-day mortality	8 (11)	17 (42)	<.001

Data are presented as number (%) or mean (standard deviation).

30-Day Kaplan Meier Amputation Free Survival Estimates

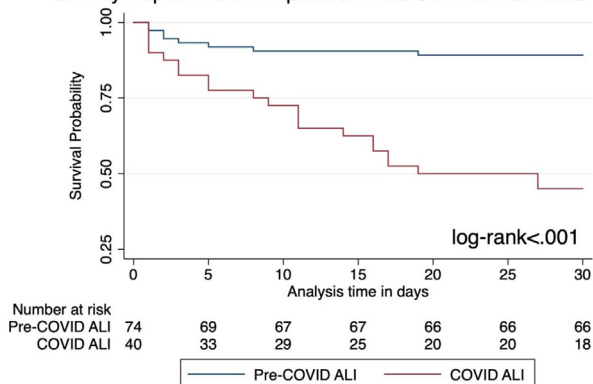


Fig. Thirty-day Kaplan-Meier amputation-free survival curve. ALI, Acute limb ischemia; COVID-19, coronavirus disease 2019.

2.7-37.4; $P = .001$). Increased age was also a determinant of 30-day amputation and in-hospital mortality (Supplementary Tables II and III, online only). Severity of COVID infection, defined by vasopressor usage in our cohort, was not associated with post-revascularization amputation ($P = .68$) or nonoperative management ($P = .5$).

Subgroup analysis. Since the beginning of 2021 with implementation of COVID-19 vaccines, there have been 26 ischemic limbs, with 19 (73%) presenting during the Delta surge. There was a significantly lower proportion of subjects who exclusively underwent endovascular revascularization as compared with the months prior to the surge (0% vs 41%; $P < .001$). The instances of COVID-19-associated ALI occurred almost exclusively in non-vaccinated patients, with only two vaccinated individuals presenting during the Delta surge with concurrent

infection and limb ischemia, both of whom received two doses of the Pfizer vaccine without any clinical evidence of vaccine-induced thrombotic thrombocytopenia (Table III). Furthermore, there was also a higher incidence of re-thrombosis during the Delta surge, as reintervention for recurrent ischemia of the same limb was more common when compared with the first half of 2021 (Table IV), although not statistically significant (21% vs 0%; $P = .55$).

A total of four ALIs in four individuals were identified during the Omicron surge (January 2022-March 2022), which was a drastic, though nonsignificant, drop-off compared with the Delta surge (0.19% vs 0.37%; $P = 1.00$). Only one subject had been vaccinated with two doses of the Pfizer vaccine. One patient underwent open revascularization, and three patients underwent endovascular revascularization. There were no major amputations or mortalities at 30 days within this subgroup.

DISCUSSION

The results of this study demonstrated that limb ischemia in the setting of acute COVID-19 infection is associated with significant mortality as well as an increased risk of limb loss despite revascularization. Thirty-six ischemic limbs were identified between 2020 and 2021 during the COVID-19 pandemic, with a near two-fold increase in incidence during the more virulent and severe Delta variant surge compared with previous variants (0.37% vs 0.21%). The overall incidence of ALI in the setting of COVID-19 infection for our study was similar at 0.27%, compared that seen at various New York City hospital systems early in the pandemic at approximately 0.4%.^{19,20} Our study demonstrated a drastic change in the outcomes of revascularization in ALI when associated with concurrent COVID-19 infection. The majority of ischemic events in the COVID-19-

Table III. Baseline demographics of pre-Delta coronavirus disease 2019 (*COVID-19*) acute limb ischemia (*ALI*) vs Delta *COVID-19* *ALI* cohorts

	Pre-Delta <i>COVID-19</i> <i>ALI</i> n = 17 (47.2%)	Delta <i>COVID-19</i> <i>ALI</i> n = 19 (52.8%)	<i>P</i> -value
Age, years	71.6 (12.1)	66.4 (11.2)	.19
Gender			
Male	14 (82)	12 (63)	.27
Female	3 (18)	7 (37)	
Ethnicity			
White	15 (88)	17 (89)	.79
Hispanic	1 (6)	0 (0)	
Other/unknown	1 (6)	2 (11)	
Vaccination status	0 (0)	2 (11)	.49
Smoking			
Non-smoker	8 (47)	9 (50)	1.00
Current smoker	2 (12)	3 (17)	
Previous smoker	7 (41)	6 (33)	
History of PAD	6 (35)	6 (32)	1.00
History of VTE	3 (18)	0 (0)	.09
Hypertension	15 (88)	14 (74)	.41
CAD	7 (41)	5 (26)	.48
CHF	4 (24)	1 (5)	.17
Diabetes	8 (47)	6 (32)	.50
CKD	6 (35)	0 (0)	.006
ESRD	1 (6)	1 (5)	1.00
History of stroke/TIA	6 (35)	6 (32)	1.00
HLD	9 (53)	3 (16)	.03
History of hypercoagulable disease	2 (12)	1 (5)	.59
Malignancy	4 (24)	2 (11)	.39
COPD	5 (29)	5 (26)	1.00
History of vascular intervention			
None	12 (71)	14 (74)	.88
Endoscopic	2 (12)	3 (16)	
Open	3 (18)	2 (11)	
History of amputation			
None	14 (82)	17 (89)	.79
Minor amputation	1 (6)	1 (5)	
Major amputation	2 (12)	1 (5)	
Anticoagulation	4 (24)	4 (21)	1.00
Aspirin	9 (53)	7 (37)	.50
Antiplatelets	6 (35)	1 (5)	.03
Multiple limbs affected	1 (6)	7 (37)	.04
Rutherford classification			
Class I	5 (29)	6 (32)	.59
Class IIa	6 (35)	4 (21)	
Class IIb	4 (24)	8 (42)	
Class III	2 (12)	1 (5)	

CAD, Coronary artery disease; *CHF*, congestive heart failure; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *ESRD*, end-stage renal disease; *HLD*, hyperlipidemia; *PAD*, peripheral arterial disease; *TIA*, transient ischemic attack; *VTE*, venous thromboembolism. Data are presented as number (%) or mean (standard deviation).

Table IV. Treatment and postintervention outcomes of pre-Delta coronavirus 2019 (COVID-19) acute limb ischemia (ALI) vs Delta COVID-19 ALI cohorts

	Pre-Delta COVID-19 ALI n = 17 (47.2%)	Delta COVID-19 ALI n = 19 (52.8%)	P-value
Treatment type			
Open	4 (24%)	6 (32%)	.01
Endovascular	7 (41%)	0 (0%)	
Hybrid	1 (6%)	6 (32%)	
Medical only	4 (24%)	5 (26%)	
Amputation	1 (6%)	2 (11%)	
Reintervention	3 (17.6%)	4 (21%)	.79
Reintervention type			
Open	3 (100%)	1 (25%)	.05
Hybrid	0 (0%)	3 (75%)	
Postintervention amputation	2 (12%)	4 (22%)	.66
Total length of stay, days	19.6 (13.9)	18.6 (12.4)	.82
In-hospital mortality	6 (35%)	12 (63%)	.18
30-day amputation	3 (18%)	8 (42%)	.13
30-day mortality	7 (41%)	9 (47%)	.75
Data are presented as number (%) or mean (standard deviation).			

associated ALI cohort were de novo, in patients without a history of vascular disease or prior vascular interventions when compared with the control ALI cohort (72% vs 59%), highlighting the viremia-induced hypercoagulability that has been documented in the literature.²¹⁻²³ Although there have been multiple studies reporting the instances and outcomes of COVID-19-associated thrombotic events, most of these studies were published at the beginning of the pandemic and in small patient cohorts.^{15,19,23-25} To the authors' knowledge, this is a unique institutional series evaluating the outcomes of COVID-associated limb ischemia with a particular focus on the Delta variant surge.

It is important to highlight the potential preventive effects of appropriate vaccination in our patient cohort, as COVID-associated ALI occurred almost exclusively among the unvaccinated subjects. The overall effects of the Delta wave during the COVID-19 pandemic have been highlighted by Manzur-Pineda et al, with an increase in the overall rate of thrombotic events, the majority of which were venous in nature.²⁶ Furthermore, similar to the vaccination status of our cohort (92% unvaccinated), COVID-related thrombotic complications occurred almost exclusively within the unvaccinated population (94%) in their study. This could potentially serve as an important basis for the promotion of public health initiatives and improvement in vaccination rates in local communities.

The results of our study fall in line with the previously documented findings with a 30-day major amputation rate of 28% as well as a 30-day mortality rate of 42%, both of which were significantly higher than the control ALI group from 2 years prior. Etkins et al²⁰ reported an overall in-hospital mortality of 46% and Faries et al¹⁹ noted an in-hospital mortality of 33%. This was further reflected in the significant decrease in 30-day amputation-free survival when compared with the control ALI group (45% vs 89%). The results are even more striking when separated based on the emergence of the Delta variant, with no incidents of post-revascularization reintervention or amputation in the post-vaccination era (January 2021-May 2021) prior to the emergence of the Delta variant (0% vs 21%). This may highlight the increased virulence and lethality of the Delta variant, which has been demonstrated in the mortality data by the Centers for Disease Control and Prevention.¹⁷ Among our cohort of COVID-19-associated ALI, there were six limbs (15%) where acute ischemia was the sole initial manifestation of their underlying COVID-19 infection, as has been previously reported.^{14,27} It was interesting to note that the 30-day major amputation rates for our study population varied dramatically when comparing between patients with COVID-19 and non-COVID-19 ALI at 28% vs 3% ($P = .001$). Although Kahlberg et al reported a secondary major limb amputation rate of 5.4% in their cohort out of Milan during their 2-month study period,²⁸ Faries et al noted a more comparable major amputation rate of 28% at 6 months in their patients with COVID-19-associated ALI.¹⁹ Furthermore, Goldman et al also noted a similar amputation rate of 25% among their cohort of patients with COVID-19 in their 3-month study period.²⁵ This could potentially be caused by the change in the virus itself, as a large portion of major 30-day amputations originated since the emergence of the Delta variant (73%).

The results of our multivariate Cox regression models showed that the only significant predictors for in-hospital mortality and 30-day amputation when controlling for other variables (ie, age and gender) were COVID-19 infection and age. There was also a notable change in the treatment algorithm for ALI that has emerged since the pandemic, with a significant increase in nonoperative management and primary amputation within our COVID-19 cohort (30% vs 0%), and a shift away from endovascular revascularization during the Delta surge (0% vs 41%) (Table II). This highlights the tenuous presentation status of patients with COVID-19 and a shift towards a more palliative/conservative treatment model in severe cases of this particular variant. Furthermore, the elevated mortality rate seen with COVID-19-associated ALI occurred almost exclusively due to complications from their index COVID-19 infection (ie, multi-system organ failure or respiratory decompensation) and could also be largely preventable with

appropriate vaccination. As new variants emerge, their impact on the incidence and outcomes of COVID-19-associated ALI remains to be seen. Preliminary data from our institution during the Omicron emergence demonstrates a decreased rate of reintervention after index revascularization as well as a decreased rate of major amputation and mortality when compared with the Delta variant.

There are several limitations to our study. First, given the retrospective nature, the total number of COVID-19-associated ischemic limbs were likely larger than those reported in our study. This could in part be due to the substantial rate of false negatives among polymerase chain reaction tests leading to exclusion of ischemic limbs with negative COVID-19 tests during our study period.²⁹ Although it had become standard protocol among the vascular division to test all patients presenting with ALI for COVID-19 during the peak of the pandemic as well as the Delta surge, additional patients could still have been missed because of subclinical undiagnosed COVID-19 infection with concurrent ALI, and also based on the search criteria in our EMRs, as those whom both COVID-19 and limb ischemia were not documented were excluded. Particularly at the beginning of the pandemic, critically ill patients with acute arterial thrombosis may have had their ischemic events attributed to increasing vasopressor support or systemic illness without exploration or documentation defined limb ischemia. Although hypercoagulable testing was not routinely performed on the COVID-19-associated ALI cohort as active COVID-19 infection, once discovered, was suspected to be the most likely cause of their underlying limb ischemia, there were no difference in the history of previously documented hypercoagulability disorder between our cohorts. Given the unequal distribution of COVID-19 cases within the United States, our small cohort size may be a result of stricter public health restrictions and the lower population density of western Pennsylvania. The rarity of the events also prevents adequate matching from our control group, although despite the lower rate of vascular disease comorbidities, there was still a significantly lower rate of amputation-free survival within our COVID-19-associated ALI group. Finally, given our temporal restriction of 14 days between ALI and COVID-19 symptoms/testing, there may be a significant number of delayed ALI after COVID-19 infection that may have been excluded and will need to be further investigated in the future.

CONCLUSIONS

In our evaluation of COVID-19-associated ALI in the University of Pittsburgh Medical Center health system, ALI observed with the Delta variant appeared more frequently and more resistant to standard therapy, as demonstrated by the higher rate of reintervention. The overall post-revascularization mortality and major

amputation rates were significantly increased in the setting of concurrent COVID-19 infection. In our clinical experience, unvaccinated status correlated highly with ALI, suggesting a potential protective effect of vaccination against thrombotic limb-threatening ischemia. Whether the protection is due to the vaccination status or other correlative factors needs to be clarified. Increased awareness of limb loss as a COVID-19 complication among nonvaccinated individuals may help to increase compliance and vaccination rates in the community.

AUTHOR CONTRIBUTIONS

Conception and design: BX, NS

Analysis and interpretation: BX, DS, MB, NA, RK, EA, US, RC, ME, MM, NS

Data collection: BX, DS, MB, NA, RK, EA

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Final approval of the article: BX, DS, MB, NA, RK, EA, US, RC, ME, MM, NS

Statistical analysis: BX, DS

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Overall responsibility: BX

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). Management and outcomes of coronavirus 2019 (COVID-19)-associated acute limb ischemia (ALI) by thrombus location

	Proximal n = 17 (44.7%)	Distal n = 12 (31.6%)	Multi-level n = 9 (23.7%)	P-value
Limb				
Lower extremity	15 (88)	11 (92)	9 (100)	.78
Upper extremity	2 (12)	1 (8)	0 (0)	
Treatment type				
Open	7 (41)	1 (8)	3 (33)	.09
Endovascular	1 (6)	4 (33)	5 (56)	
Hybrid	3 (18)	3 (25)	1 (11)	
Medical only	5 (28)	3 (25)	0 (0)	
Amputation	2 (12)	1 (8)	0 (0)	
Reintervention	3 (18)	2 (17)	2 (22)	1.00
30-day amputation	4 (24)	4 (33)	3 (33)	.81

Data are presented as number (%).

Supplementary Table II (online only). Multivariate Cox proportional hazard model for 30-day amputation

	Hazard ratio	95% CI	P-value
COVID-19 infection	6.2	2.3-16.8	<.001
Age	1.1	1.0-1.1	.006
Gender ^a	0.6	0.2-1.5	.268
History of vascular intervention ^b			
Endoscopic	0.4	0.11-1.5	.168
Open	1.4	0.4-5.4	.63
Rutherford classification ^c			
Class IIa	2.7	0.7-10.8	.156
Class IIb	2.8	0.7-11.7	.158
Class III	3.6	0.5-23.9	.186
Treatment type ^d			
Endovascular	0.3	0.1-1.7	.179
Hybrid	1.3	0.4-4.1	.591
Medical only	0.9	0.2-4.1	.984
Amputation	4.5	0.5-42.9	.196

CI, Confidence interval; COVID-19, coronavirus 2019.
^aMale gender is the reference group.
^bNo history of vascular interventions is the reference group.
^cRutherford Class I is the reference group.
^dOpen surgical treatment is the reference group.

Supplementary Table III (online only). Multivariate Cox proportional hazard model for in-hospital mortality

	Hazard ratio	95% CI	P-value
COVID-19 infection	10.1	2.7-37.4	.001
Age	1.1	1.0-1.1	.047
Gender ^a	0.7	0.2-2.4	.581
History of vascular intervention ^b			
Endoscopic	0.1	0.1-0.6	.019
Open	0.7	0.1-3.7	.684
Rutherford classification ^c			
Class IIa	3.2	0.7-14.1	.126
Class IIb	7.5	1.4-40.3	.019
Class III	7.9	1.1-60.1	.047
Treatment type ^d			
Endovascular	2.2	0.3-14.7	.415
Hybrid	3.6	0.9-14.9	.074
Medical only	3.2	0.6-16.1	.16
Amputation	0.6	0.1-6.6	.662

CI, Confidence interval; COVID-19, coronavirus 2019.
^aMale gender is the reference group.
^bNo history of vascular interventions is the reference group.
^cRutherford Class I is the reference group.
^dOpen surgical treatment is the reference group.