Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

From the New England Society for Vascular Surgery

Outcomes of acute limb ischemia in COVID-19

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ABSTRACT

Objective: The inflammatory cascade caused by severe acute respiratory syndrome coronavirus 2 infection may result in arterial thrombosis and acute limb ischemia (ALI) with devastating consequences. The aims of this study were to compare outcomes of ALI in the lower extremities in patients with and without coronavirus disease 2019 (COVID-19), and to determine if ALI development in the context of COVID-19 portends a worse prognosis compared with COVID-19 without ALI.

Methods: Queries were built on TriNetX, a federated network of health care organizations across the United States that provides de-identified patient data. International Classification of Diseases, 10th revision diagnostic codes were used to identify patients with acute limb ischemia of the lower extremities and COVID-19. The study timeframe was defined as January 20, 2020 to May 20, 2021. Statistical analyses, including propensity-score matching, were done through TriNetX's internal software. Outcomes looked at are rates of mortality, stroke, myocardial infarction, major adverse limb events, re-intervention, respiratory failure, sepsis, mental health complications, and acute renal failure. Baseline cohort characteristics were also collected.

Results: Patients with ALI with COVID-19 (ALI C19+; n = 526) were significantly less likely than patients with ALI without COVID-19 (ALI; n = 14,131) to have baseline comorbidities, including nicotine dependence (18% vs 33%; $P < .0001$). In contrast, ALI C19+ patients had significantly more comorbidities than hospitalized patients with COVID-19 without ALI (n = 275,903), including nicotine dependence (18% vs 10%; $P < .0001$). After propensity matching was performed, ALI C19+ patients had significantly higher rates of mortality (24.9% vs 9.2%; $P < .0001$), major adverse limb events (5.8% vs 2.9%; $P = .0223$), and acute renal failure (22.2% vs 14.9%; $P = .0025$) than patients with ALI. Compared with hospitalized patients with COVID-19 without ALI, ALI C19+ patients had higher propensity-matched rates of respiratory failure and being placed on assisted ventilation (32.9% vs 27%; $P = .0369$), sepsis (16.9% vs 12.2%; $P = .0288$), acute renal failure (22.1% vs 14.6%; $P = .0019$), and mortality (24.7% vs 14.4%; $P < .0001$).

Conclusions: Patients who developed ALI following COVID-19 present with significantly different demographics and comorbidities from those who develop ALI without COVID-19. After controlling for these variables, higher rates of major adverse limb events, acute renal failure, and mortality in patients with ALI with COVID-19 suggest that not only may COVID-19 precipitate ALI, but it may also exacerbate ALI sequelae. Furthermore, development of ALI in COVID-19 portends worse prognosis compared with patients with COVID-19 without ALI. (J Vasc Surg 2022;76:1006-13.)

Keywords: Acute limb ischemia; Arterial thromboembolism; Coronavirus; COVID-19; SARS-CoV-2

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in the United States on January 20, 2020, progress has been made in understanding its pathogenicity.

Current understanding of SARS-CoV-2 has proposed that it binds to angiotensin-converting enzyme (ACE) 2 receptors, causing significant inflammation. SARS-CoV-2 bound to these receptors on vascular endothelial cells causes endothelial injury and triggers a pro-inflammatory and hypercoagulable state.[1] Abdominal and thoracic aortic thrombosis, mesenteric ischemia, and acute cerebrovascular incident have also been described as manifestations of COVID-19 infection.[2] Acute limb ischemia (ALI), a vascular pathology with multifactorial etiology, is a known complication caused by the inflammatory cascade triggered by SARS-CoV-2 viral infection.[3,4] Although hypercoagulability is a rare cause of limb ischemia, the incidence of thromboembolic events in patients with COVID-19 is as high as 35% to 45%.[5] Several observational studies have found that patients with COVID-19 and ALI experience poor outcomes, including high rates of amputation and high failure rates of revascularization.[3,4] However, the

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Author conflict of interest: none.

Presented as an oral presentation at the Forty-eighth Annual Meeting of the New England Society for Vascular Surgery, Cape Neddick, ME, October 15-17, 2021.

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

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2022.04.038

characteristics of patients presenting with ALI following COVID-19 compared with characteristics of patients presenting with ALI alone have not been delineated. Furthermore, the degree to which COVID-19 exacerbates ALI sequelae, and the prognostic value of ALI development in COVID-19 compared with COVID-19 alone, has not been shown. As such, the purpose of this multicenter, retrospective cohort study was to compare the outcomes of ALI in patients with COVID-19 with patients with ALI without COVID-19.

METHODS

Data source. Data for this study was obtained from TriNetX's COVID-19 Research Network platform, a federated research network of electronic health record data from 63 health care organizations (HCOs) across the United States. The network provides access to real-time aggregate data from approximately 83.8+ million patients, including demographics, diagnoses, procedures, medications, lab values, and genomics. The HCOs that comprise the research network include primary care providers, specialists, and hospitals that care for both insured and uninsured patients. The geographical distribution of patients in the database are as follows: 18% from the Northeast, 14% from the Midwest, 26% from the South, and 30% from the West.

Any data on the TriNetX platform in aggregate form only contains de-identified data, adhering to the standard defined in Section §164.514(a) of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. TriNetX's de-identification process was attested through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule, superseding the need for TriNetX's previous waiver from the Western Institutional Review Board.[6] Written patient consent was waived. Because this study was not involved in the collection, use, or transmittal of individually identifiable data, this study was exempted from Albert Einstein College of Medicine and Montefiore Medical Center Institutional Review Board approval. This multicenter, retrospective cohort study followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.[7]

Study protocol. The study timeframe was defined as January 20, 2020, to May 20, 2021. The first reported case of SARS-CoV-2 in the United States was on January 20, 2020, and the first reported case of the Delta variant in the United States was towards the end of May 2021.[8,9] The emergence of the Delta variant was set as the end point of the study because of its markedly different pathogenicity from its parent strains.[8]

International Classification of Diseases, 10th Revision (ICD-10) codes were used to identify eligible patients as seen in Supplementary Table I (online only). ICD-10 codes were linked to the dates the events occurred. Mainly, ALI of the lower extremities was defined as thrombosis of the arteries of the lower extremities (I74.3), iliac artery (I74.5), or saddle embolus of the abdominal aorta (I74.01). COVID-19 positivity was defined as having a record of a positive SARS-CoV-2 test (9088) or diagnosis of COVID-19 (U07.1). Furthermore, patients were identified as having COVID-19 if they had records of unspecified coronavirus infection within the study timeframe (B34.2), pneumonia due to SARS-associated coronavirus (J12.81), and coronavirus as the cause of diseases classified elsewhere (B97.29). Previous electronic health record studies on COVID-19 included the latter ICD-10 codes (ie, B34.2, J12.81, B97.29) because there was no established code for COVID-19 early in the pandemic.

Patients with COVID-19 who developed ALI (ALI C19+) were identified by looking at the temporal relationship between the ICD-10 codes for ALI and COVID-19. Namely, these patients must have had a diagnosis of ALI either 1 day before, or within 1 week after COVID-19 diagnosis/positivity. This temporal relationship was decided upon because a prior study found ALI to develop around 1 week after COVID-19.[10] Furthermore, patients may have had an incidental COVID-19 finding if they were initially admitted for ALI; hence, including patients with diagnosis of ALI 1 day before COVID-19 diagnosis/positivity. Patients who developed ALI without concurrent COVID-19 were identified by excluding all patients who had a record of COVID-19. This meant that patients who had COVID-19 months prior to diagnosis of ALI were also excluded, reasoning that the long-term effects of COVID-19 have not been fully studied. Patients who were hospitalized for COVID-19 and did not develop ALI were identified by excluding any instance of ALI after COVID-19 diagnosis, again reasoning that the long-term effects of COVID-19 have not been fully studied.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter, retrospective, propensity score-matched study
- **Key Findings:** Patients with acute limb ischemia (ALI) with coronavirus disease 2019 (COVID-19) (n = 526) were compared with those without COVID-19 (n = 14,131). After propensity matching, patients with ALI with COVID-19 had a higher mortality rate (24.857% vs 9.178%; $P < .0001$), major adverse limb events (5.763% vs 2.868%; $P = .0223$), and acute renal failure (22.180% vs 14.914%; $P < .0001$).
- **Take Home Message:** These findings suggest that patients with ALI with COVID-19 have significantly different patient demographics and comorbidities than both patients with classical ALI and patients with COVID-19 without ALI and experienced higher rates of adverse clinical outcomes than patients with ALI without COVID-19.

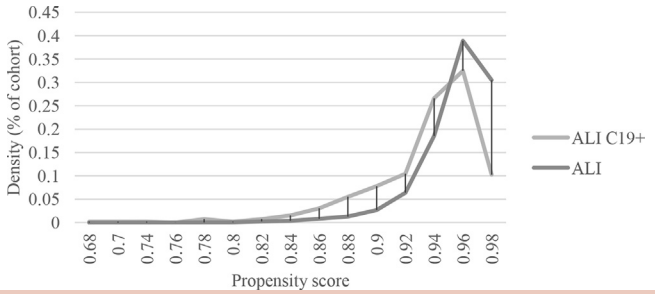

Fig 1. Propensity score density function of patients with acute limb ischemia with coronavirus 2019 (*ALI C19+*) vs patients with acute limb ischemia (*ALI*) before matching.

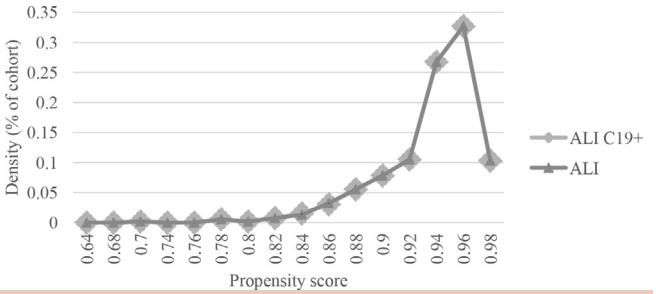

Fig 2. Propensity score density function of patients with acute limb ischemia with coronavirus 2019) ALI C19+ vs patients with acute limb ischemia (*ALI*) after matching.

The ALI C19+ and ALI without COVID-19 cohorts were stratified into those who had an arterial revascularization procedure performed and those who did not. Arterial revascularization procedures included endovascular, bypass, and embolectomy/thrombectomy/endarterectomy techniques (Supplementary Table I, online only). We defined late surgical intervention as patients who did not have record of intervention within 1 week of ALI, but subsequently had an intervention during the follow-up period of 180 days. Because this was a rare outcome, we defined late surgical intervention as a composite of endovascular, bypass, and embolectomy/thrombectomy/endarterectomy techniques (Supplementary Table I, online only). The follow-up period was defined as 180 days, and outcomes followed were mortality, stroke, myocardial infarction, major adverse cardiovascular events (composite of mortality, stroke, myocardial infarction), major adverse limb events (MALE; amputations), acute renal failure, reintervention rates, respiratory failure or assisted ventilation, sepsis, and mental health complications (Supplementary Table I, online only).

Statistical methods. All statistical analyses, including 1:1 propensity-score matching, were performed with TriNetX's internal software, which uses R 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and Python 3.6.5 (Python Software Foundation, Centrum voor Wiskunde en Informatica Amsterdam, The Netherlands). Greedy nearest neighbor matching with a caliper width of 0.1 pooled standard deviations of the logit of the propensity scores in aggregate was used; standard difference less than 0.1 was considered well match.[11] Propensity matching was performed for age, sex, ethnicity, medications, and comorbidities (Supplementary Table II, online only). Propensity score distributions before and after matching were reported (Figs 1 and 2). Descriptive statistics were expressed as means with standard deviations. Unpaired *t* tests were used to compare means between the cohorts. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported, and *P*-values $< .05$ were considered statistically significant.

RESULTS

Characteristics of ALI C19+ patients compared with patients with ALI without C19. A total of 526 patients were identified in the group with ALI C19+ and 14,131 in the group with ALI without COVID-19 (Table I). 120 patients who had ALI following COVID-19 were not included because they did not meet the 1-week criteria. Unpaired *t* tests were performed between the two cohorts. The mean age for the groups was similar (65.2 ± 14.7 vs 65.6 ± 13.8; $P = .5109$). The gender distribution was not statistically different between the two groups (64% vs 59% male; $P = .0534$). Interestingly, there was a higher proportion of Hispanic patients in the ALI C19+ group (11% vs 4%; $P < .0001$) and a higher proportion of Caucasian patients in the COVID-19 negative group (64% vs 69%; $P = .0052$). There was no difference in the proportion of African Americans between the two groups (16% vs 13%; $P = .0508$).

There were many significant differences in baseline comorbid conditions between these two groups. Primary hypertension (51% vs 60%; $P < .0001$), chronic ischemic heart disease (28% vs 37%; $P = .0001$), chronic obstructive pulmonary disease (COPD) (14% vs 20%; $P = .0004$), psychiatric disorders (42% vs 50%; $P = .0004$), and neoplasms (19% vs 27%; $P < .0001$) were all seen at significantly higher rates in patients with ALI without COVID-19. In the ALI C19+ patients, significantly increased rate of type 2 diabetes mellitus (34% vs 30%; $P = .0420$) was seen. Nicotine dependence was seen at a two-fold higher rate in patients with ALI without COVID-19 (18% vs 33%; $P < .0001$).

Patients with ALI without COVID-19 were more likely to be on baseline aspirin (35% vs 49%; $P < .0001$, atorvastatin (29% vs 38%; $P < .0001$), ACE inhibitors (20% vs 29%; $P < .0001$), and beta blockers (41% vs 49%; $P = .0003$).

Outcomes of ALI C19+ patients compared with those without COVID-19. Propensity matching was performed in addition to unpaired *t* tests. Before propensity matching, patients with COVID-19 and ALI had worse outcomes at 180 days (Table II). There was a three-fold increase in mortality (24.715% vs 8.598%; OR, 3.490; $P < .0001$),

Table I. Characteristics of patients who developed acute limb ischemia (*ALI*) from coronavirus 2019 (*COVID-19*) vs those who developed ALI without COVID-19

	ALI C19+ (n = 526)	ALI (n = 14,131)	*P* value
Demographics			
Age, years	65.2 ± 14.7	65.6 ± 13.8	.5109
Male	64	59	.0534
Hispanic or Latino	11	4	**<.0001**
Black/African American	16	13	.0508
White	64	69	**.0052**
Comorbidities			
Primary hypertension	51	60	**<.0001**
Secondary hypertension	2	2	.6972
Atrial fibrillation and flutter	17	18	.6773
Type 1 diabetes mellitus	5	4	.5260
Type 2 diabetes mellitus	34	30	**.0420**
Overweight and obesity	19	16	.1097
Chronic ischemic heart disease	28	37	**.0001**
COPD	14	20	**.0004**
Asthma	7	7	.9350
Obstructive sleep apnea	7	9	.2067
Nicotine dependence	18	33	**<.0001**
Mental, behavioral, and neurodevelopmental disorders	42	50	**.0004**
Neoplasms	19	27	**<.0001**
Medications			
Aspirin	35	49	**<.0001**
Atorvastatin	29	38	**<.0001**
Simvastatin	6	8	.1454
Losartan	12	12	.8458
Oral hypoglycemic agents	15	16	.2787
Anticoagulants	56	56	.8458
ACE inhibitors	20	29	**<.0001**
Beta blockers	41	49	**.0003**

ACE, Angiotensin-converting enzyme; *C19+*, COVID-19-positive; *COPD*, chronic obstructive pulmonary disease.
Data are presented as percentage or mean ± standard deviation.
Boldface *P* values indicate statistical significance.

a two-fold increase in MALE (5.894% vs 2.696%; OR, 2.260; $P < .0001$), and a 2.5-fold increase in acute renal failure (22.053% vs 13.347%; OR, 1.837; $P < .0001$) in the ALI C19+ group. This trend remained significant after propensity matching, with a three-fold increase in mortality (24.857% vs 9.178%; OR, 3.273; $P < .0001$), two-fold increase in MALE (5.763% vs 2.868%; OR, 2.061; $P = .0223$), and a nearly two-fold increase in acute renal failure (22.180% vs 14.914%; OR, 1.626; $P = .0025$).

Outcomes for ALI C19+ patients versus those with ALI alone undergoing arterial procedures. Unpaired *t* tests, without propensity matching, were performed. After propensity matching, there were too few patients remaining in the ALI C19+ group for adequate statistical comparison.

There was a small proportion of patients in each group that initially underwent arterial procedures in this subset, with 89 patients in the ALI C19+ group and 2768 patients in the ALI group (Table III).

ALI C19+ patients were seen to have significantly higher rates of MALE (15.730% vs 8.020%; OR, 2.141; $P = .0093$) and acute renal failure (22.472% vs 14.884%; OR, 1.510; $P = .0492$).

Open reintervention with thromboendarterectomy, embolectomy, and/or thrombectomy was over eight-fold higher in ALI C19+ patients (31.461% vs 4.986%; OR, 8.748; $P < .0001$). Reintervention with bypass surgery was also seen at a significantly higher rate in ALI C19+ patients (11.236% vs 5.636%; OR, 2.119; $P = .0262$). There was no statistically significant difference in the rate of endovascular reintervention between the two groups.

Outcomes for ALI C19+ patients who did not undergo arterial procedures. Unpaired *t* tests, without propensity matching, were performed. After propensity matching, there were too few patients remaining in the ALI C19+ group for adequate statistical comparison. Major adverse cardiovascular events were seen at a greater than two-fold higher rate in the ALI C19+ group who did not undergo arterial interventions (33.410% vs 16.700%; OR, 2.503; $P < .0001$) (Table IV). In patients with COVID-19 without initial revascularization, there were significantly higher rates of MALE (3.432% vs 1.356%; OR, 2.586; $P = .0003$), acute renal failure (21.739% vs 12.756%; OR, 1.900; $P < .0001$). Interestingly, there was a significantly lower rate in ALI C19+ patients needing surgical intervention later (2.746% vs 5.573%; OR, 0.478; $P = .0108$).

Characteristics of ALI C19+ patients compared with hospitalized C19+ patients without ALI. Unpaired *t* tests were performed between the two cohorts. When compared with hospitalized C19+ patients who did not develop ALI (n = 275,903), ALI C19+ patients were significantly older (65.2 ± 14.7 vs 57.5 ± 19; $P < .0001$) (Table V). Furthermore, ALI C19+ patients were more likely to be male (64% vs 45%; $P < .0001$) and more likely to be white (64% vs 59%; $P = .0199$). However, a smaller proportion of ALI C19+ patients were Hispanic compared with patients with COVID-19 without ALI (11% vs 15%; $P < .0001$).

Furthermore, ALI C19+ patients had higher rates of primary hypertension (51% vs 40%; $P < .0001$), atrial fibrillation and flutter (17% vs 10%; $P < .0001$), type 1 diabetes mellitus (5% vs 3%; $P < .0010$), type 2 diabetes mellitus (34% vs 22%; $P < .0001$), chronic ischemic heart disease (28% vs 15%; $P < .0001$), COPD (14% vs 8%; $P < .0001$), nicotine dependence (18% vs 10%; $P < .0001$), and

Table II. Outcomes of acute limb ischemia (*ALI*) in patients with coronavirus 2019 (*COVID-19*) and without COVID-19

	Before propensity matching			After propensity matching (for age, sex, ethnicity, comorbidities, and medications)		
180-day outcomes	ALI C19+, % (n = 526)	ALI, % (n = 14,131)	OR (95% CI); *P* value	ALI C19+, % (n = 523)	ALI, % (n = 523)	OR (95% CI); *P* value
Mortality	24.715 (130)	8.598 (1215)	**3.49 (2.838-4.291); *P* < .0001**	24.857 (130)	9.178 (48)	**3.273 (2.291-4.678); *P* < .0001**
Stroke	7.985 (42)	7.077 (1000)	1.139 (0.826-1.572); *P* = .4261	8.031 (42)	7.266 (38)	1.114 (0.706-1.759); *P* = .6417
Myocardial infarction	7.034 (37)	5.902 (834)	1.206 (0.857-1.697); *P* = .2808	7.057 (37)	5.163 (27)	1.399 (0.838-2.333); *P* = .1970
Major adverse limb event	5.894 (31)	2.696 (381)	**2.260 (1.550-3.295); *P* < .0001**	5.763 (30)	2.868 (15)	**2.061 (1.095-3.878); *P* = .0223**
Acute renal failure	22.053 (116)	13.347 (1886)	**1.837 (1.486-2.270); *P* < .0001**	22.180 (116)	14.914 (78)	**1.626 (1.184-2.232); *P* = .0025**

C19+, COVID-19-positive; *CI*, confidence interval; *OR*, odds ratio.
Boldface values indicate statistical significance.

Table III. Outcomes of patients with acute limb ischemia (*ALI*) with coronavirus 2019 (*COVID-19*) and without COVID-19, who initially underwent an arterial procedure for revascularization

180-day outcomes	ALI C19+, % (n = 89)	ALI, % (n = 2768)	OR (95% CI); *P* value
Major adverse cardiovascular events (death, myocardial infarction, cerebral infarction)	25.843 (23)	19.725 (546)	1.418 (0.874-2.300); *P* = .1549
Major adverse limb events (amputation)	15.730 (14)	8.02 (222)	**2.141 (1.190-3.850); *P* = .0093**
Acute renal failure	22.472 (20)	14.884 (412)	**1.510 (1.016-2.243); *P* = .0492**
Reintervention-endovascular	17.978 (16)	13.403 (371)	1.416 (0.815-2.459); *P* = .2145
Reintervention-thromboendarterectomy, embolectomy, thrombectomy	31.461 (28)	4.986 (138)	**8.748 (5.418-14.124); *P* < 0001**
Reintervention-bypass	11.236 (10)	5.636 (156)	**2.119 (1.077-4.173); *P* = .0262**

C19+, COVID-19-positive; *CI*, confidence interval; *OR*, odds ratio.
Boldface values indicate statistical significance.
One-to-one propensity matching was unable to be performed because of TriNetX's data obfuscation policy when patient sample sizes decrease below a specific threshold.

psychiatric disorders (42% vs 35%; *P* = .0026). However, ALI C19+ patients had lower rates of asthma compared with patients with COVID-19 who did not develop ALI (7% vs 10%; *P* = .0165).

ALI C19+ patients were more likely to be on baseline aspirin (35% vs 26%; *P* < .0001), atorvastatin (29% vs 18%; *P* < .0001), ACE inhibitors (20% vs 17%; *P* < .0001), and beta blockers (41% vs 30%; *P* = .0003) than patients with COVID-19 who did not develop ALI.

Outcomes of ALI C19+ patients compared with hospitalized C19+ patients without ALI. t tests with propensity-score matching were utilized. Following propensity matching for age, sex, ethnicity, comorbidities, and medications, ALI C19+ patients had higher 180-day rates of mortality (24.715% vs 14.449%; OR, 1.944; *P* < .0001), acute renal failure (22.053% vs 14.639%; OR, 1.650; *P* = .0019), respiratory failure or being placed on assisted ventilation (32.890% vs 26.996%; OR, 1.325; *P* = .0369), and sepsis (16.920% vs 12.167%; OR, 1.470; *P* = .0288) (Table VI). Rates of stroke, myocardial infarction, and psychiatric complications were not significantly different.

DISCUSSION

Prior studies have demonstrated that SARS-CoV-2 is associated with a hypercoagulable state caused by virally-induced vascular endothelial injury.[5,12,13] Due to this procoagulant state, there is a high risk for macro- and micro-thrombi formation in patients with COVID-19.[13,14] Many of the thromboembolic events associated with COVID-19 are venous in nature, but growing evidence has also shown an increased risk of arterial thrombotic events in patients with COVID-19, especially ALI.[3,15-17] Galyfos et al utilized pooled data from multiple case studies to show that COVID-associated ALI presents in patients with low incidence of comorbidities and is associated with a high mortality and amputation risk, but their conclusions were limited by low sample sizes.[18] Using national data, our study demonstrates that ALI C19+ patients face worse clinical outcomes compared with patients with ALI without a COVID-19 diagnosis, suggesting that COVID-19 may not only precipitate ALI but may be directly responsible for exacerbating ALI sequelae.

Our analysis found that the demographics of patients who developed ALI following COVID-19 infection were

Table IV. Outcomes of patients with acute limb ischemia (*ALI*) with coronavirus 2019 (*COVID-19*) and without COVID-19, who did not initially undergo an arterial procedure for revascularization

180-day outcomes	ALI C19+, % (n = 437)	ALI, % (n = 10,186)	OR (95% CI); *P* value
Major adverse cardiovascular events (death, myocardial infarction, cerebral infarction)	33.410 (146)	16.700 (1897)	**2.503 (2.039-3.071); *P* < .0001**
Major adverse limb events (amputation)	3.432 (15)	1.356 (154)	**2.586 (1.509-4.433); *P* = .0003**
Acute renal failure	21.739 (95)	12.756 (1449)	**1.900 (1.504-2.400); *P* < .0001**
Intervention	2.746 (12)	5.573 (633)	**0.478 (0.268-0.854); *P* = .0108**

C19+, COVID-19-positive; *CI*, confidence interval; *OR*, odds ratio.
Boldface values indicate statistical significance.
One-to-one propensity matching was unable to be performed because of TriNetX's data obfuscation policy when patient sample sizes decrease below a specific threshold.

Table V. Characteristics of patients with coronavirus 2019 (*COVID-19*) who developed acute limb ischemia (*ALI*) versus hospitalized patients with COVID-19 who did not develop ALI

	C19+ with ALI (n = 526)	C19+ without ALI (n = 275,903)	*P* value
Demographics			
Age, years	65.2 ± 14.7	57.5 ± 19	**<.0001**
Male	64	45	**<.0001**
Hispanic or Latino	11	15	**<.0001**
Black/African American	16	14	.1426
White	64	59	**.0199**
Comorbidities			
Primary hypertension	51	40	**<.0001**
Secondary hypertension	2	1	.2644
Atrial fibrillation and flutter	17	10	**<.0001**
Type 1 diabetes mellitus	5	3	**.0010**
Type 2 diabetes mellitus	34	22	**<.0001**
Overweight and obesity	19	22	.0533
Chronic ischemic heart disease	28	15	**<.0001**
COPD	14	8	**<.0001**
Asthma	7	10	**.0165**
Obstructive sleep apnea	7	10	.0751
Nicotine dependence	18	10	**<.0001**
Mental, behavioral, and neurodevelopmental disorders	42	35	**.0026**
Neoplasms	19	21	.2981
Medications			
Aspirin	35	26	**<.0001**
Atorvastatin	29	18	**<.0001**
Simvastatin	6	5	.1454
Losartan	12	9	.8458
Oral hypoglycemic agents	15	13	.2787
Anticoagulants	56	34	.8458
ACE inhibitors	20	17	**<.0001**
Beta blockers	41	30	**.0003**

ACE, Angiotensin-converting enzyme; *C19+*, COVID-19-positive; *COPD*, chronic obstructive pulmonary disease.
Data are presented as percentage or mean ± standard deviation.
Boldface *P* values indicate statistical significance.

significantly different from the characteristic demographics of those who presented with ALI alone. Because TriNetX displays aggregate data from institutions throughout the nation, the unmatched comparisons capture the trend that patients who developed ALI following COVID-19 had significantly higher rates of mortality, MALE, and acute renal failure despite lower rates of comorbidities. Even after propensity matching, we found

Table VI. Propensity-matched outcomes of patients with coronavirus 2019 (*COVID-19*) who developed acute limb ischemia (*ALI*) vs patients with COVID-19 who did not develop ALI

180-day outcomes	ALI C19+, % (n = 526)	C19+, % (n = 526)	OR (95% CI); *P* value
Mortality	24.715 (130)	14.449 (76)	**1.944 (1.421-2.660); *P* < .0001**
Stroke	7.985 (42)	5.323 (28)	1.543 (0.941-2.530); *P* = .833
Myocardial infarction	7.034 (37)	6.464 (34)	1.095 (0.676-1.773); *P* = .7124
Acute renal failure	22.053 (116)	14.639 (77)	**1.65 (1.201-2.267); *P* = .0019**
Mental health complications	17.300 (91)	14.449 (76)	1.239 (0.889-1.726); *P* = .2057
Respiratory failure or Assisted ventilation	32.890 (173)	26.996 (142)	**1.325 (1.017-1.727); *P* = .0369**
Sepsis	16.920 (89)	12.167 (64)	**1.470 (1.039-2.080); *P* = .0288**

C19+, COVID-19-positive; *CI*, confidence interval; *OR*, odds ratio.
Boldface values indicate statistical significance.

that patients who developed ALI in the setting of COVID-19 had a two-fold higher rate of having MALE, 1.6-fold higher rate of having acute kidney injury, and 3.3-fold higher rate of death (Table II). Although acute kidney injury and mortality are not unique to ALI, major adverse limb events are. We can say then that, independent of comorbidities, patients who developed ALI in the setting of COVID-19 have roughly two-fold higher rates of major amputation compared with patients solely with ALI. These clinical outcomes are consistent with our understanding of how SARS-CoV-2 affects the vascular system and other organs. Patients with COVID-19 have been found to have abnormally elevated coagulation markers including D-dimer, partial thromboplastin time, prothrombin time, fibrinogen, fibrin degradation products, and interleukin-6.[5,15,19] Previous studies note that diffuse, small vessel platelet-fibrin thrombi and intravascular megakaryocytes were found in all major organs of patients with COVID-19, including the heart, lungs, kidney, liver, and mesenteric fat.[13] Menter et al also found that post-mortem examination of patients with COVID-19 showed renal tubular injury, interstitial edema, and fibrin thrombi in glomerular capillaries.[20] Other studies have also illustrated vascular pathological changes such as vascular endothelial shedding, intimal inflammation, and thrombosis in patients with COVID-19.[21] In addition, in the United States, studies have previously shown that with increasing revascularization rates, amputations have drastically decreased in cases of critical limb ischemia.[22,23] Unfortunately, in the case of patients with COVID-19, amputation may have been the best treatment option due to delayed presentation to medical care or rapidly progressing disease.[24]

Finally, we found that rates of MALE and acute renal failure were found to be higher in the ALI C19+ cohort that underwent arterial procedures than those without COVID-19 who underwent similar procedures. ALI C19+ patients also had higher rates of open reintervention (thromboendarterectomy, embolectomy, and/or thrombectomy) and bypass surgery. However, there was no difference in rate of endovascular reintervention between the groups. Successful revascularization has been documented to be relatively low in patients with COVID-19 compared with previously reported series.[3] Bellosta et al also postulated that their revascularization failure rate of almost 30% was due to the absence of forefoot microvasculature following intervention or potential sudden early recurrent thrombosis in their ALI C19+ patients. In addition, it is possible that poor clinical status of ALI C19+ patients prevented proper recovery following intervention, leading to postoperative complications. Early recognition of ischemic thrombotic events in patients with COVID-19 and more aggressive anticoagulant and thrombolytic treatment may help prevent such serious adverse events in ALI C19+ patients.

Given that COVID-19 appears to exacerbate ALI sequelae, it was important to characterize the ALI C19+ population and compare it with hospitalized patients with COVID-19 who do not develop ALI. Relative to hospitalized patients with COVID-19 who do not develop ALI, ALI C19+ patients notably had higher rates of hypertension and diabetes mellitus. This is consistent with existing knowledge that hypertension and diabetes mellitus are main risk factors for limb ischemia.[25] Furthermore, development of ALI appears to suggest worse prognosis in patients with COVID-19. In addition to mortality and acute renal failure, development of ALI led to higher rates of respiratory failure or assisted ventilation and sepsis.

There are certain limitations to this study. The TriNetX platform does not represent the general population, but rather only represents those who sought medical care at the 63 HCOs in the network. Patients who do not receive follow-up care at participating HCOs can also skew occurrence of outcomes. Propensity matching for some of our data set was limited by TriNetX's internal statistical analysis software and obfuscation policy. Safeguards against queries that could identify small subsets of cohorts are put in place to minimize the risk of patient re-identification.[26] There are also always inaccuracies inherent to electronic health record data collection, mainly coding or data entry errors. We attempted to minimize any errors with strict inclusion and exclusion

criteria, with particular focus on the temporality between the COVID-19 diagnosis and acute ischemic event. Lastly, the influence of thrombophylactic or therapeutic-anticoagulating regimes prior to development of ALI could not be assessed. As the pandemic progressed, many institutions developed their own guidelines with regards to stratifying patients with COVID-19 to receive thromboprophylaxis, therapeutic anticoagulation, or neither. Future studies should examine whether anticoagulation initiation in patients with COVID-19 prior to development of ALI affects outcomes.

CONCLUSIONS

Before and after controlling for covariates, rates of mortality, MALE, and acute renal failure were significantly higher in ALI C19+ patients than in patients with ALI alone. This suggests that COVID-19, independent of the patients' comorbidities, may directly exacerbate ALI sequelae. Furthermore, development of ALI suggests a worse prognosis in COVID-19 than in COVID-19 alone, with higher rates of mortality, renal failure, sepsis, and respiratory failure. Further studies are warranted to delineate a pathophysiologic link between COVID-19 and development of acute arterial thromboembolic events.

AUTHOR CONTRIBUTIONS

Conception and design: AP, EG, EL, JI
Analysis and interpretation: AP, AH, EG, EL, JI
Data collection: AP
Writing the article: AP, AH
Critical revision of the article: EG, EL, JI
Final approval of the article: AP, AH, EG, EL, JI
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: JI

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Submitted Nov 26, 2021; accepted Apr 10, 2022.

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Supplementary Table I (online only). International Classification of Disease, 10th Revision (*ICD-10*) codes used to identify eligible patients

Outcome/revascularization procedure	Corresponding ICD-10/ procedure code	Notes
Mortality	Registered as deceased	
Stroke	I61-I63, G45.9	Ischemic and hemorrhagic stroke
Myocardial infarction	I21	
Major adverse limb events	1004982, 1005146, 1005298	Amputation procedures on pelvis, hip, femur, knee, leg and ankle joint
Acute renal failure	N17	
Major adverse cardiac events	Deceased, I61-63, G45.9, I21	Composite of death, stroke, and myocardial infarction
Respiratory failure or assisted ventilation	J96, 1014859	
Sepsis	A40, A41, R65.2	
Mental health complications	F43.1, F32, F33, G47, F41.1	PTSD, depressive episode, major depressive disorder (recurrent), sleep disorders, generalized anxiety disorders
Reintervention	Composite of revascularization procedures	
Embolectomy or thrombectomy, with or without catheter	34151	Renal, celiac, mesentery, aortoiliac artery, by abdominal incision
	34201	Femoropopliteal, aortoiliac artery, by leg incision
	34203	Popliteal-tibio-peroneal artery, by leg incision
Repair blood vessel, direct	35221	Intra-abdominal
	35226	Lower extremity
Repair blood vessel with vein graft	35251	Intra-abdominal
	35256	Lower extremity
	35281	Intra-abdominal
	35286	Lower extremity
Thromboendarterectomy, including patch graft, when performed	35302	Superficial femoral artery
	35303	Popliteal artery
	35304	Tibioperoneal trunk artery
	35305	Tibial or peroneal artery, initial vessel
	35306	Each additional tibial or peroneal artery
	35351	Iliac
	35355	Iliofemoral
	35361	Combined aortoiliac
	35363	Combined aortoiliofemoral
	35371	Common femoral
	35372	Deep femoral
Bypass graft, with vein	35533	Axillary-femoral-femoral
	35537	Aortoiliac
	35538	Aortobi-iliac
	35539	Aortofemoral
	35540	Aortobifemoral
	35556	Femoral-popliteal
	35558	Femoral-femoral
	35563	Ilioiliac
	35565	Iliofemoral

Supplementary Table I (online only). Continued.

Outcome/revascularization procedure	Corresponding ICD-10/ procedure code	Notes
	35566	Femoral-anterior tibila, posterior tibial, peroneal artery, or other distal vessels
	35570	Tibial-tibial, peroneal-tibial, or tibial/peroneal trunk-tibial
	35571	Popliteal-tibial, -peroneal artery or other distal vessels
In-situ vein bypass	35583	Femoral-popliteal
	35585	Posterior tibial, or peroneal artery
	35587	Popliteal-tibial, peroneal
Bypass graft, with other than vein	35621	Axillary-femoral
	35623	Axillary-popliteal or -tibial
	35637	Aortoiliac
	35638	Aortobi-iliac
	35646	Aortobifemoral
	35647	Aortofemoral
	35654	Axillary-femoral-femoral
	35656	Femoral-popliteal
	35661	Femoral-femoral
	35663	Ilioiliac
	35665	Iliofemoral
	35666	Femoral-anterior tibial, posterior tibial, or peroneal artery
	35671	Popliteal-tibial or peroneal artery
Arterial mechanical thrombectomy	37184	Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s); initial vessel
	37185	Primary percutaneous transluminal mechanical thrombectomy, noncoronary, non-intracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injection(s); initial vessel; second and all subsequent vessel(s) within the same vascular family
	37186	Secondary percutaneous transluminal thrombectomy (eg, nonprimary mechanical, snare basket, suction technique), noncoronary, nonintracranial, arterial or arterial bypass graft, including fluoroscopic guidance and intraprocedural pharmacological thrombolytic injections, provided in conjunction with another percutaneous intervention other than primary mechanical thrombectomy
Revascularization, endovascular, open or percutaneous, iliac artery, unilateral, initial vessel	37220	With transluminal angioplasty
	37221	With transluminal stent placement(s), includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, iliac artery, each additional ipsilateral iliac vessel	37222	With transluminal angioplasty
	37223	With transluminal stent placement(s), includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, femoral, popliteal artery(s), unilateral	37224	With transluminal angioplasty

(Continued on next page)

Supplementary Table I (online only). Continued.

Outcome/revascularization procedure	Corresponding ICD-10/ procedure code	Notes
	37225	With atherectomy, includes angioplasty within the same vessel, when performed
	37226	With transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37227	With transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, tibial, peroneal artery, unilateral, initial vessel	37228	With transluminal angioplasty
	37229	With atherectomy, includes angioplasty within the same vessel, when performed
	37230	With transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37231	With transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed
Revascularization, endovascular, open or percutaneous, tibial/peroneal artery, unilateral, each additional vessel	37232	With transluminal angioplasty
	37233	With atherectomy, includes angioplasty within the same vessel, when performed
	37234	With transluminal stent placement(s), includes angioplasty within the same vessel, when performed
	37235	With transluminal stent placement(s) and atherectomy, includes angioplasty within the same vessel, when performed

Supplementary Table II (online only). Covariates used in propensity matching

Covariate	Notes
Age	
Sex	
Ethnicity	
Comorbidities	Primary hypertension, secondary hypertension, atrial fibrillation, T1DM, T2DM, overweight/obesity, chronic ischemic heart disease, COPD, asthma, obstructive sleep apnea, nicotine dependence, mental/behavioral/neurodevelopmental disorders, neoplasms
Medications	Aspirin, atorvastatin, simvastatin, losartan, oral hypoglycemic agents, anticoagulants, ACE inhibitors, beta blockers

ACE, Angiotensin-converting enyme; *COPD*, chronic obstructive pulmonary disease; *T1DM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.