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Navigating the intersection of COVID-19 and lower extremity acute limb ischemia: A retrospective cohort study of clinical characteristics and outcomes at Dr. Cipto Mangunkusumo Hospital

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Abstract

Acute limb ischemia (ALI), a critical condition threatening limb viability and patient survival, has demonstrated an increased incidence during the COVID-19 pandemic, primarily due to virus-associated thrombotic complications. The pandemic has also led to delays in the diagnosis and treatment of non-COVID conditions, including ALI. The aim of this study was to evaluate the clinical characteristics and outcomes of ALI patients treated at Dr. Cipto Mangunkusumo Hospital between 2018 and 2022, comparing outcomes before and during the COVID-19 pandemic. Patients were categorized into two cohorts: pre-pandemic (n=28) and pandemic (n=53), with March 2020 marking the onset of the pandemic period. Treatment outcomes—revascularization success, re-intervention, and mortality—were assessed using multivariate logistic regression. Among the 81 patients, 34.6% were treated before the pandemic and 65.4% during the pandemic. Revascularization success was significantly higher during the pandemic (relative risk (RR): 2.46; 95% confidence interval (CI): 1.16–5.24; p=0.013), whereas no significant differences were observed in re-intervention or mortality rates (both with p>0.05). A prior history of COVID-19 was not significantly associated with revascularization outcome (p=0.933). The use of fluoroscopic guidance was significantly associated with improved revascularization success (RR: 36.58; 95%CI: 6.54–204.6; p=0.001). Rutherford classification was a significant predictor of re-intervention success (p=0.022), while the presence of dyslipidemia and heart disease were independently associated with mortality (RR: 0.08–0.76, p=0.005, and RR: 2.24–25.18, p=0.001, respectively). In conclusion, fluoroscopy appears to enhance revascularization outcomes in the treatment of ALI. Comorbidities such as cardiovascular disease, and COVID-19 history should be taken into account when managing patients with ALI.

Keywords: Acute limb ischemia, COVID-19, revascularization, vascular surgery, fluoroscopic guidance

Introduction

Acute limb ischemia (ALI) is a vascular emergency defined as a sudden decrease in arterial perfusion to a limb, with symptom onset occurring within a 14-day window [1]. If not promptly recognized and treated, ALI can result in irreversible tissue loss, limb amputation, or death [2,3]. The European Society for Vascular Surgery (ESVS) classifies ALI based on the severity of ischemia

Received: March 19, 2025 - Accepted: July 3, 2025 - Published online: August 1, 2025

and the urgency of revascularization [1]. The most common etiologies include arterial thrombosis, embolism, and graft or stent occlusion, often arising in the setting of comorbidities such as atrial fibrillation, atherosclerosis, or previous peripheral revascularization [4,5]. Prior to the Coronavirus Disease 2019 (COVID-19) pandemic, ALI was estimated to affect 5–8% of individuals in Southeast Asia, with major amputation rates reaching 25% and in-hospital mortality rates ranging from 9% to 15% [4-6]. Treatment approaches for acute limb ischemia, including open surgery, endovascular procedures, and catheter-directed thrombolysis (CDT), are associated with significant healthcare expenditures, costing approximately USD 17,163.47, USD 20,620, and USD 30,675, respectively [7].

The COVID-19 pandemic has significantly disrupted healthcare systems, affecting the diagnosis and management of non-COVID conditions, including vascular emergencies like ALI [8,9]. COVID-19 is a multisystem disease marked by thromboinflammatory responses, including endothelial injury, cytokine overproduction, and hypercoagulability [10,11] Common laboratory abnormalities include elevated D-dimer [12], prolonged prothrombin time [13], decreased fibrinogen levels [14,15], thrombocytopenia [15], and an increased C-reactive protein to albumin ratio [16], all of which are linked to an increased risk of thrombosis [17].

Despite existing international reports on alterations to ALI during COVID-19, there is a paucity of literature on the effects of the COVID-19 pandemic on the incidence, presentation, management and outcomes among ALI patients in Indonesia. To date, the impact of the pandemic on ALI care in the Indonesian health care system in general has not been studied. Therefore, the aim of this study was to fill this gap by reviewing and comparing clinical profiles of Indonesian ALI patients before and during the COVID-19 pandemic.

Methods

Study design and setting

This retrospective cohort study analyzed medical records of ALI patients treated at Dr. Cipto Mangunkusumo Hospital from January 2018 to December 2022. Patients were divided into two groups: the pre-pandemic group (January 2018 to February 2020) and the pandemic group (March 2020 to December 2022). Data on demographics, clinical features, treatments, and outcomes were collected and compared between the two groups to assess the impact of the COVID-19 pandemic on ALI management and outcomes.

Sample size calculation and sampling method

The minimum sample size was calculated using a formula for comparing two proportions, with α=5% and β=20%. Based on a standard effect proportion (P_1) of 0.85 and an expected effect proportion (P_2) of 0.65, the required sample size was 40 subjects per group. This study used a consecutive sampling method. All eligible ALI patients during the study period were enrolled based on predefined inclusion and exclusion criteria. Patients were included if they: (1) were over 18 years old, and (2) were diagnosed with lower extremity ALI between January 2018 and December 2022. Patients were excluded if they: (1) had upper extremity ALI, as lower extremity ALI is more common, has well-established classification systems, and is more frequently managed with standardized revascularization approaches, (2) had incomplete medical records, or (3) received only conservative management for ALI (i.e., no intervention).

Data collection and study variables

The independent variables were age, sex, referral status, Rutherford classification, affected lower extremity, pandemic status, COVID-19 infection, comorbidities, level of occlusion, and types of intervention. Dependent variables included the success of revascularization, the need for re-intervention, and in-hospital mortality. Age was defined as the patient's age at the time of ALI diagnosis, calculated from the date of birth and categorized as <60 years or ≥60 years. Sex was recorded as male or female. Referral hospital status indicated whether the patient had been transferred from another healthcare facility. Rutherford classification was determined through clinical examination and imaging findings and categorized into I, IIA, IIB, or III. The affected extremity was defined clinically and categorized as unilateral or bilateral lower limb involvement.

Pandemic status was categorized as pre-pandemic (before March 2020) or during the pandemic (March 2020 onward), based on the date of diagnosis. COVID-19 status was based on reverse transcription polymerase chain reaction (RT-PCR) test results recorded in the medical chart. Comorbidities included documented histories of hypertension, diabetes mellitus, obesity, dyslipidemia, chronic kidney disease, cardiovascular disease, malignancy, stroke, previous revascularization, or smoking.

The level of occlusion was determined by ultrasonography or computed tomography (CT) angiography and categorized as below-knee, femoropopliteal, or suprainguinal. Thrombectomy and catheter-directed thrombolysis (CDT) were defined as vascular interventions documented in operative notes. Fluoroscopy use refers to the application of fluoroscopic assistance during procedures. Amputation was defined as surgical removal of ischemic or infected tissue. Revascularization was considered successful if residual stenosis was <30% (for fluoroscopy-guided procedures) or if adequate backflow was achieved (for non-fluoroscopy procedures). Re-intervention was defined as any additional procedure performed within the same hospital stay due to medical indications. In-hospital mortality was recorded if the patient died during admission, regardless of cause.

Statistical analysis

Data were analyzed using SPSS for Mac version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics summarized subject characteristics. Bivariate analysis with the Chi-Square test assessed associations between variables, and those with $p<0.25$ were included in logistic regression to identify factors associated with revascularization outcomes. This threshold helps retain variables that may become significant after adjustment. Independent variables included age, sex, referral status, Rutherford classification, affected extremity, pandemic status, COVID-19 infection, comorbidities, level of occlusion, and intervention type. A p-value of <0.05 was considered statistically significant. Results were reported as relative risks (RR) with 95% confidence intervals (CI). Patients with incomplete or missing key data were excluded during the sampling process.

Results

Patients' characteristics

Data retrieved from Cipto Mangunkusumo Hospital medical records revealed 103 ALI patients between 2018–2022. Out of 81 patients, only those who met the inclusion and exclusion criteria were selected (**Figure 1**).

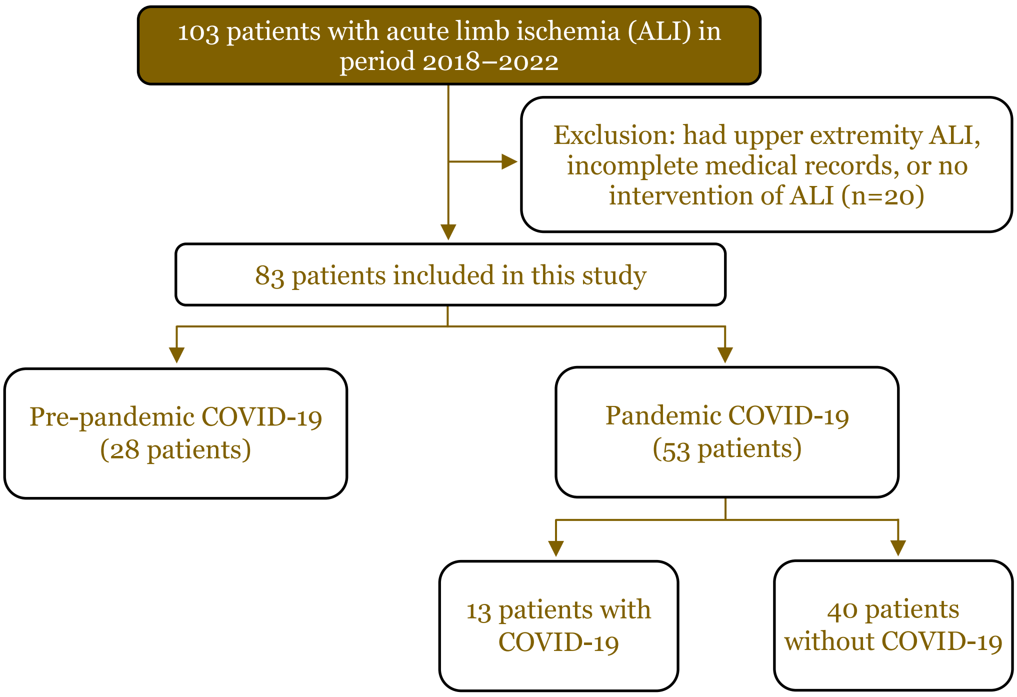

Figure 1. Flow diagram for the enrolment of study participants.

Among these, 28 (34.6%) patients were from the pre-pandemic period, and 53 (65.4%) were from the COVID-19 pandemic. Of all the patients during the COVID-19 pandemic, 13 (24.5%) had a confirmed history of COVID-19. Patient characteristics are presented in **Table 1**.

Table 1. Clinical characteristics of acute limb ischemia (ALI) patients before and during the COVID-19 pandemic, and comparison between patients with and without COVID-19 infection

Variables	During pandemic (n=53)	Before pandemic (n=28)	*p*-value[a]	With COVID-19 (n=13)	Without COVID-19 (n=40)	*p*-value[a]
Age category						
<60 years	29 (54.7)	14 (50)	0.865	10 (76.9)	19 (47.5)	0.126
>60 years	24 (45.3)	14 (50)		3 (23.1)	21 (52.5)	
Sex						
Man	32 (60.4)	14 (50)	0.509	7 (53.8)	25 (62.5)	0.819
Woman	21 (39.6)	15 (50)		6 (46.2)	15 (37.5)	
Referral hospital						
No	18 (34)	21 (75)	0.001	7 (53.8)	25 (62.5)	0.819
Yes	35 (66)	7 (25)		6 (42.6)	15 (77.5	
Lower extremities are affected						
Unilateral	38 (71.7)	22 (78.6)	0.686	9 (69.2)	29 (72.5)	1.000
Bilateral	15 (28.3)	6 (21.4)		4 (30.8)	11 (27.5)	
Rutherford's classification						
I	2 (3.8)	0 (0)	0.359	0 (0)	2 (5)	0.954
IIA	13 (24.5)	4 (14.3)		4 (30.8)	9 (22.5)	
IIB	16 (30.2)	11 (39.3)		4 (30.8)	12 (30)	
III	22 (41.5)	13 (46.4)		5 (38.5)	17 (42.5)	
Hypertension						
No	21 (39.6)	15 (53.6)	0.334	6 (46.2)	15 (37.5)	0.819
Yes	32 (60.4)	13 (46.4)		7 (53.8)	25 (62.5)	
Diabetes mellitus						
No	29 (54.7)	18 (64.3)	0.553	7 (53.8)	22 (55)	1.000
Yes	24 (45.3)	10 (35.7)		6 (46.2)	18 (45)	
Obesity						
No	32 (60.4)	15 (53.6)	0.651	6 (46.2)	26 (65)	0.379
Yes	21 (39.6)	13 (46.4)		7 (53.8)	14 (35)	
Dyslipidemia						
No	30 (56.6)	13 (46.4)	0.523	7 (53.8)	23 (57.5)	1.000
Yes	23 (43.4)	15 (53.6)		6 (46.2)	17 (42.5)	
Chronic kidney disease						
No	44 (83)	27 (96.4)	0.165	11 (84.6)	33 (82.5)	1.000
Yes	9 (17)	1 (3.6)		2 (15.4)	7 (17.5)	
Heart disease						
No	34 (64.2)	18 (64.3)	1.000	10 (76.9)	24 (60)	0.334
Yes	19 (35.8)	10 (35.7)		3 (23.1)	16 (40)	
Malignancy						
No	49 (92.5)	27 (96.4)	0.432	13 (100)	36 (90)	0.561
Yes	4 (7.5)	1 (3.6)		0 (0)	4 (10)	
History of stroke						
No	48 (90.6)	26 (92.9)	0.541	11 (84.6)	37 (92.5)	0.586
Yes	5 (9.4)	2 (7.1)		2 (15.4)	3 (7.5)	
Revascularization history						
No	45 (84.9)	26 (92.9)	0.225	11 (84.6)	34 (85)	1.000
Yes	8 (15.1)	2 (7.1)		2 (15.4)	6 (15)	
Smoking history						
No	39 (73.6)	20 (71.4)	1.000	10 (76.9)	29 (72.5)	1.000
Yes	14 (26.4)	8 (28.6)		3 (23.1)	11 (27.5)	
Occlusion level						
Below knee	10 (18.9)	7 (25)	0.498	2 (15.4)	8 (20)	1.000
Femoropopliteal	23 (43.4)	14 (50)		5 (38.5)	18 (45)	
Suprainguinal	20 (37.7)	7 (25)		6 (46.2)	14 (35)	
Thrombectomy						
No	18 (34)	9 (32.1)	1.000	3 (23.1)	15 (37.5)	0.504
Yes	35 (66)	19 (67.9)		10 (76.9)	25 (62.5)	

Variables	During pandemic (n=53)	Before pandemic (n=28)	*p*-value[a]	With COVID-19 (n=13)	Without COVID-19 (n=40)	*p*-value[a]
Catheter directed thrombolysis						
No	51 (96.2)	27 (96.4)	0.727	13 (100)	38 (95)	1.000
Yes	2 (3.8)	1 (3.6)		0 (0)	2 (5)	
Amputation						
No	42 (79.2)	21 (75)	0.876	12 (92.3)	30 (75)	0.257
Yes	11 (20.8)	7 (25)		1 (7.7)	10 (25)	
Fluoroscopy						
No	29 (54.7)	22 (78.6)	0.061	7 (53.8)	22 (55)	1.000
Yes	24 (45.3)	6 (21.4)		6 (46.2)	18 (45)	

[a]Analyzed using the Chi-squared test
*Statistically significant at $p<0.05$

Outcomes of ALI patients in pre-COVID-19 pandemic and during the COVID-19 pandemic

Eighty-one patients were analyzed based on their pandemic status regarding the success of revascularization, mortality events, and re-intervention events, as presented in **Table 2**. A higher revascularization success rate was observed during the pandemic period (52.8%) compared to the pre-pandemic period (21.4%), with an RR of 2.46 (p=0.013). The improved outcome was potentially associated with the increased use of fluoroscopy-assisted procedures. However, no significant differences were observed in the incidence of re-intervention and mortality.

Table 2. ALI patient outcomes before and during the COVID-19 pandemic

ALI patient outcome	During pandemic (n=53)	Before pandemic (n=28)	Relative risk (95%CI)	*p*-value[a]
Revascularization success				
Yes	28 (52.8)	6 (21.4)	2.46 (1.16–5.24)	0.013*
No	25 (47.2)	22 (78.6)		
Re-intervention success				
Yes	16 (30.2)	4 (14.3)	2.11 (0.78–5.72)	0.191
No	37 (69.8)	24 (85.7)		
Mortality				
Yes	25 (47.2)	13 (46.4)	1.02 (0.62–1.66)	1.000
No	28 (52.8)	15 (53.6)		

[a]Analyzed using the Chi-squared test
*Statistically significant at $p<0.050$

Outcomes of ALI patients with and without COVID-19 during the pandemic

Among 53 ALI patients treated during the COVID-19 pandemic, 13 had COVID-19. Outcomes between patients with and without COVID-19 are compared in **Table 3**. Revascularization success was similar (53.8% vs 52.5%, p=0.933), as were re-intervention rates (38.5% vs 27.5%, p=0.455) and mortality (46.2% vs 47.5%, p=0.933). No significant differences were found in outcomes between patients with and without COVID-19.

Table 3. Outcomes of ALI patients with and without COVID-19 during the pandemic

ALI patient outcome	With COVID-19 (n=13)	Without COVID-19 (n=40)	Relative risk (95%CI)	*p*-value[a]
Revascularization success				
Yes	7 (53.8)	21 (52.5)	1.03 (0.57–1.84)	0.933
No	6 (46.2)	19 (47.5)		
Re-intervention				
Yes	5 (38.5)	11 (27.5)	1.40 (0.60–3.28)	0.455
No	8 (61.5)	29 (72.5)		
Mortality				
Yes	6 (46.2)	19 (47.5)	0.97 (0.50–1.90)	0.933
No	7 (53.8)	21 (52.5)		

[a]Analyzed using the Chi-squared test
*Statistically significant at $p<0.050$

Relationship between ALI patient characteristics and outcomes before and during the COVID-19 pandemic

The analysis of ALI patient characteristics and outcomes revealed significant findings across revascularization success, re-intervention, and mortality, as detailed in **Table 4–6**. Thrombectomy and fluoroscopy were associated with significantly higher revascularization success (RR: 16.5; 95%CI: 2.38–114 and RR: 5.53; 95%CI: 2.88–10.6, respectively) (**Table 4**). Re-intervention, thrombectomy and fluoroscopy also demonstrated higher success (RR: 9.4; 95%CI: 1.34–67.3, and RR: 6.8; 95%CI: 2.5–18.4, respectively) (**Table 5**). Thrombectomy (RR: 0.45; 95%CI: 0.29–0.69) and fluoroscopy (RR: 0.53; 95%CI: 0.29–0.96) were associated with reduced mortality, while heart disease increased the risk of mortality (RR: 1.99; 95%CI: 1.27–3.11) (**Table 6**).

Table 4. Relationship between ALI patient characteristics with revascularization success during treatment before and due to the COVID-19 pandemic

Variables	Revascularization success (n=34)	Revascularization failed (n=47)	Relative risk (RR)	95%CI	*p*-value[a]
Age					
>60 years	14 (36.8)	24 (63.2)	0.79	0.47–1.34	0.513
<60 years	20 (46.5)	23 (53.5)	Reference	-	-
Sex					
Man	18 (39.1)	28 (60.9)	0.86	0.51–1.43	0.713
Woman	16 (45.7)	19 (54.3)	Reference	-	-
Referral hospital					
Yes	19 (45.2)	23 (54.8)	1.18	0.70–1.97	0.695
No	15 (38.5)	24 (61.5)	Reference	-	-
Lower extremities affected					
Bilateral	4 (19.0)	17 (81.0)	0.38	0.15–0.95	0.027*
Unilateral	30 (50.0)	30 (50.0)	Reference	-	-
Rutherford's classification					
III+IIB	24 (38.7)	38 (61.3)	0.73	0.43–1.25	0.418
IIA+I	10 (52.6)	9 (47.4)	Reference	-	-
Hypertension					
Yes	18 (40.0)	27 (60.0)	0.90	0.54–1.50	0.860
No	16 (44.4)	20 (55.6)	Reference	-	-
Diabetes mellitus					
Yes	16 (47.1)	18 (52.9)	1.23	0.74–2.04	0.575
No	18 (38.3)	29 (61.7)	Reference	-	-
Obesity					
Yes	12 (35.3)	22 (64.7)	0.75	0.44–1.30	0.419
No	22 (46.8)	25 (53.2)	Reference	-	-
Dyslipidemia					
Yes	19 (50.0)	19 (50.0)	1.43	0.85–2.40	0.250
No	15 (34.9)	28 (65.1)	Reference	-	-
Thrombectomy					
Yes	33 (61.1)	21 (38.9)	16.5	2.38–114	<0.001**
No	1 (3.7)	26 (96.3)	Reference	-	-
Fluoroscopy					
Yes	26 (86.7)	4 (13.3)	5.53	2.88–10.6	<0.001**
No	8 (15.7)	43 (84.3)	Reference	-	-

[a]Analyzed using the Chi-squared test
*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

Table 5. Relationship between ALI patient characteristics with re-intervention incidents during treatment before and due to the COVID-19 pandemic

Variables	Re-intervention success (n=20)	Re-intervention failed (n=61)	Relative risk (RR)	95%CI	*p*-value [a]
Age					
>60 years	7 (18.4)	31 (81.6)	0.61	0.27–1.37	0.331
<60 years	13 (30.2)	30 (69.8)	Reference	-	-
Sex					
Man	7 (15.2)	39 (84.8)	0.41	0.18–0.92	0.045*
Woman	13 (37.1)	22 (62.9)	Reference	-	-
Reference					

Variables	Re-intervention success (n=20)	Re-intervention failed (n=61)	Relative risk (RR)	95%CI	*p*-value [a]
Yes	13 (31)	29 (69)	1.72	0.77–3.87	0.272
No	7 (17.9)	31 (82.1)	Reference	-	-
Lower extremities affected					
Bilateral	5 (23.8)	16 (76.2)	0.95	0.39–2.30	1.00
Unilateral	15 (25)	45 (75)	Reference	-	-
Rutherford's classification					
III+IIB	17 (27.4)	45 (72.6)	1.74	0.57–5.30	0.239
IIA+I	3 (15.8)	16 (84.2)	Reference	-	-
Hypertension					
Yes	10 (22.2)	35 (77.8)	0.80	0.37–1.71	0.751
No	10 (27.8)	26 (72.2)	Reference	-	-
Diabetes mellitus					
Yes	8 (23.5)	26 (76.5)	0.92	0.42–2.00	1.000
No	12 (25.5)	35 (74.5)	Reference	-	-
Obesity					
Yes	8 (23.5)	26 (76.5)	0.92	0.42–2.00	1.000
No	12 (25.5)	35 (74.5)	Reference	-	-
Dyslipidemia					
Yes	10 (26.3)	28 (73.7)	1.13	0.53–2.42	0.952
No	10 (23.3)	33 (76.7)	Reference	-	-
CKD					
Yes	1 (10)	9 (90)	0.37	0.05–2.49	0.448
No	19 (26.8)	52 (73.2)	Reference	-	-
Heart disease					
Yes	6 (20.7)	23 (79.3)	0.77	0.33–1.78	0.723
No	14 (26.9)	38 (73.1)	Reference	-	-
Malignancy					
Yes	0 (0)	5 (100)	-	-	0.432
No	20 (26.3)	56 (73.7)	Reference	-	-
History of stroke					
Yes	1 (14.3)	6 (85.7)	0.56	0.87–3.56	0.834
No	19 (25.7)	55 (75.3)	Reference	-	-
History of revascularization					
Yes	2 (20)	8 (80)	0.79	0.21–2.90	1.000
No	18 (25.4)	53 (74.6)	Reference	-	-
Smoking history					
Yes	5 (22.7)	17 (77.3)	0.89	0.37–2.17	1.000
No	15 (25.4)	44 (74.6)	Reference	-	-
Occlusion level					
Supralinguinal	9 (33.3)	18 (66.7)	1.64	0.77–3.46	0.316
Femoropopliteal + below knee	11 (20.4)	43 (79.6)	Reference	-	-
Thrombectomy					
Yes	19 (35.2)	35 (64.8)	9.4	1.34–67.3	0.005**
No	1 (3.7)	26 (96.3)	Reference	-	-
Catheter-directed thrombolysis (CDT)					
Yes	3 (100)	0 (0)	-	-	0.016*
No	17 (21.8)	61 (78.2)	Reference	-	-
Amputation					
Yes	0 (0)	18 (100)	-	-	0.014*
No	20 (31.7)	43 (68.3)	Reference	-	-
Fluoroscopy					
Yes	16 (53.3)	14 (46.7)	6.8	2.5–18.4	<0.001**
No	4 (7.8)	47 (92.2)	Reference	-	-

[a]Analyzed using the Chi-squared test
*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

Table 6. Relationship between ALI patient characteristics with mortality during treatment before and due to the COVID-19 pandemic

Variables	Died (n=38)	Survived (n=43)	Relative risk (RR)	95%CI	*p*-value[a]
Age					
>60 years	19 (50)	19 (50)	1.13	0.71–1.80	0.764
<60 years	19 (44.2)	24 (55.8)	Reference	-	-
Sex					

Variables	Died (n=38)	Survived (n=43)	Relative risk (RR)	95%CI	*p*-value[a]
Man	22 (47.8)	24 (52.2)	1.04	0.65–1.67	1.000
Woman	16 (45.7)	19 (54.3)	Reference	-	-
Reference					
Yes	18 (42.9)	24 (57.1)	0.84	0.52–1.33	0.592
No	20 (51.3)	19 (48.7)	Reference	-	-
Lower extremities affected					
Bilateral	14 (66.7)	7 (33.3)	1.67	1.08–2.57	0.064
Unilateral	24 (40)	36 (60)	Reference	-	-
Rutherford's classification					
III+IIB	28 (45.2)	34 (54.8)	0.86	0.52–1.43	0.759
IIA+I	10 (52.6)	9 (47.4)	Reference	-	-
Hypertension					
Yes	21 (46.7)	24 (53.3)	0.98	0.62–1.57	1.000
No	17 (47.2)	19 (52.8)	Reference	-	-
Diabetes mellitus					
Yes	19 (55.9)	15 (44.1)	1.38	0.87–2.19	0.250
No	19 (40.4)	28 (59.6)	Reference	-	-
Obesity					
Yes	19 (55.9)	15 (44.1)	1.38	0.87–2.18	0.250
No	19 (40.4)	28 (59.6)	Reference	-	-
Dyslipidemia					
Yes	14 (36.8)	24 (63.2)	0.66	0.40–1.08	0.138
No	24 (55.8)	19 (44.2)	Reference	-	-
CKD					
Yes	8 (80)	2 (20)	1.89	1.25–2.95	0.050
No	30 (42.3)	41 (57.7)	Reference	-	-
Heart disease					
Yes	20 (69)	9 (31)	1.99	1.27–3.11	0.006**
No	18 (34.6)	34 (65.4)	Reference	-	-
Malignancy					
Yes	2 (40)	3 (60)	0.84	0.28–2.53	1.000
No	36 (47.4)	40 (52.6)	Reference	-	-
History of stroke					
Yes	5 (71.4)	2 (28.6)	1.60	0.94–2.73	0.335
No	33 (44.6)	41 (55.4)	Reference	-	-
History of revascularization					
Yes	8 (80)	2 (20)	1.89	1.25–2.85	0.057
No	30 (42.3)	41 (57.7)	Reference	-	-
Smoking history					
Yes	12 (54.5)	10 (45.5)	1.24	0.77–1.99	0.555
No	26 (44.1)	33 (55.9)	Reference	-	-
Occlusion level					
Suprainguinal	13 (48.1)	14 (51.9)	1.04	0.64–1.69	1.000
Femoropopliteal+below knee	25 (46.3)	29 (53.7)	Reference	-	-
Thrombectomy					
Yes	18 (33.3)	36 (66.7)	0.45	0.29–0.69	0.001**
No	20 (74.1)	7 (25.9)	Reference	-	-
CDT					
Yes	2 (66.7)	1 (33.3)	1.44	0.63–3.33	0.913
No	36 (46.2)	42 (53.8)	Reference	-	-
Amputation					
Yes	6 (33.3)	12 (66.7)	0.66	0.33–1.32	0.298
No	32 (50.8)	31 (49.2)	Reference	-	-
Fluoroscopy					
Yes	9 (30)	21 (70)	0.53	0.29–0.96	0.035
No	29 (56.9)	22 (43.1)	Reference	-	-

[a]Analyzed using the Chi-squared test
**Statistically significant at $p<0.01$

In multivariate analysis (**Table 7**), the history of thrombectomy and fluoroscopy increased revascularization success with an RR of 19.22 (95%CI: 1.72–214.3) and 36.58 (95%CI: 6.54–204.6), respectively. In the characteristics of ALI patients for re-intervention, multivariate analysis demonstrated the Rutherford classification to be significant for patient reintervention, with an RR of 10.06 (95%CI: 1.40–72.34). In the characteristics of ALI patients on mortality at treatment, multivariate analysis showed a significant factor in dyslipidemia, heart disease, and fluoroscopy. Dyslipidemia and fluoroscopy reduce the risk of mortality with an RR of 0.24

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(95%CI: 0.08–0.76) and 0.25 (95%CI: 0.08–0.76), respectively, while heart disease increase the risk of mortality (RR: 7.52; 95%CI: 2.24–25.18).

Table 7. Multivariate risk factors for revascularization success, re-intervention success, and mortality in ALI patient characteristics during treatment before and due to the COVID-19 pandemic

Variables	Relative risk (RR)	95%CI	*p*-value
Revascularization success			
Lower extremities are affected			
Bilateral	0.14	0.02–1.13	0.063
Unilateral	Reference	-	-
Thrombectomy			
Yes	19.22	1.72–214.3	0.016*
No	Reference	-	-
Fluoroscopy			
Yes	36.58	6.54–204.6	<0.001**
No	Reference	-	-
Re-intervention success			
Rutherford's classification			
III+IIB	10.06	1.40–72.34	0.022*
IIA+I	Reference	-	-
Fluoroscopy			
Yes	4.05	0.90–22.43	0.066
No	Reference	-	-
Mortality			
Diabetes mellitus			
Yes	2.89	0.98–8.53	0.055
No	Reference	-	-
Dyslipidemia			
Yes	0.24	0.08–0.76	0.015*
No	Reference	-	-
Heart disease			
Yes	7.52	2.24–25.18	0.001**
No	Reference	-	-
Fluoroscopy			
Yes	0.25	0.08–0.76	0.015*
No	Reference	-	-

*Statistically significant at $p<0.05$
**Statistically significant at $p<0.01$

Discussion

There was a notable increase in the number of ALI cases at our hospital during the pandemic, nearly doubling the pre-pandemic rate. This rise warrants further exploration. While we hypothesize that COVID-19 played a key role in this surge, other contributing elements are likely to be involved. One significant factor was the rise in external hospital referrals, especially to tertiary hospitals, many of which were designated COVID-19 centers. This increase in referrals aligns with trends observed in other diseases during the pandemic, where COVID-19-related factors and referral processes led to higher admission rates at tertiary care centers [17]. Similar patterns have been observed in other specialties, such as obstetrics, where the pandemic led to a rise in referrals to tertiary care facilities [18]. Additionally, there was a learning curve at our center, which may have contributed to better recognition and management of ALI cases. However, it is important to note that while referrals increased, delays in non-COVID-19 patient transfers due to mandatory COVID-19 screenings may have worsened ALI outcomes, as patients experienced delays in receiving care [19,20].

Our data suggests a correlation between the COVID-19 pandemic and the rise in ALI cases, but the exact cause remains multifactorial. The increased incidence of ALI during the pandemic is consistent with findings from other studies. For instance, Gonzales-Urquijo reported that ALI occurred in 38.3% of COVID-19 patients, likely due to thrombosis and hypercoagulability associated with the virus [21,22]. Similarly, Pena *et al.* found that ALI was prevalent among COVID-19 patients, largely due to endothelial dysfunction, elevated cytokines, and hypercoagulability, all of which contribute to thrombosis in multiple locations [23].

In comparing the outcomes of ALI treatment before and during the pandemic, there was a significant increase in the success rate of revascularization (p=0.013) with more than twofold (RR: 2.46). The increased success of revascularization observed during the COVID-19 pandemic in our study may be partially attributed to the enhanced utilization of fluoroscopy-guided endovascular techniques. Fluoroscopy provides real-time imaging, enabling precise navigation and placement of catheters and guidewires during endovascular procedures [24]. However, this does not establish a direct cause-and-effect relationship. At our center, fluoroscopy and thrombectomy were applied in only about 50% of cases. This variability can be explained by factors such as the severity of ALI, the patient's overall health, and the procedural feasibility [25,26]. Other factors, such as enhanced operator skills, advances in endovascular technology, and perhaps earlier patient presentation, may have also contributed to the improved outcomes during the pandemic [27,28]. The inconsistent use of these techniques across cases highlights the need for further studies to explore the exact reasons for their limited application and to determine the true impact of fluoroscopy and thrombectomy on revascularization success.

No significant differences in re-intervention and mortality were found in this study, despite varied findings in previous research [29-32]. Predenciuc *et al.* [29] reported no difference in amputation risk between ALI patients with or without COVID-19, but mortality was significantly higher in the COVID-19 group, RR of 2.7 (95%CI: 1.42–5.31; p=0.002). Naouli *et al.* [30] observed a high rate of re-intervention and amputation, even after revascularization, with a mortality rate of 27.3%. Aimanan *et al.* also noted higher risks of amputation and death in COVID-19-related ALI due to hypercoagulability [31]. The study of Pham *et al.* showed different results from ALI patients with COVID-19, showing a higher mortality rate (24.9% vs 9.2%) than ALI patients without COVID-19 [32]. These variations may be due to differences in regional healthcare infrastructure, where some areas might have had more advanced treatment options or better access to critical care, while others faced resource limitations. Additionally, differences in patient demographics, including comorbidities and age, could also contribute to the divergent outcomes observed across studies. Moreover, the timing of interventions could have played a role. Early diagnosis and intervention, such as more aggressive use of revascularization techniques, may have improved outcomes in some centers, while delayed treatment in other settings could have led to worse outcomes.

In addition to comparative studies conducted on ALI patients during the pandemic, various case reports and case series have also documented an increase in the incidence of ALI and worsening of ALI in patients with COVID-19. For example, Surya *et al.* [33] reported a case of ALI that appeared after the diagnosis of COVID-19, while Primasari *et al.* [34] described a case of ALI with a sudden worsening and decreased perfusion of a COVID-19 patient who required immediate thrombectomy, but the therapy was unsuccessful. This is also theoretically supported by increased cytokines and coagulation factors in COVID-19 patients. Various studies show that COVID-19-induced coagulopathy increases prothrombotic and inflammatory biomarkers. Various pathological examinations of lung tissue or other organs also show evidence of microvascular inflammation along with microvascular thrombi [35]. Then, macrophages can also release procoagulant factors such as plasminogen activators, accompanied by an increase in angiotensin-converting enzyme 2 (ACE2) and activation of angiotensin II. The production of plasminogen activator inhibitor-1 also increases, accelerating vascular inflammation and thrombotic state [36,37]. In the study of Phan *et al.*, D-dimer, ferritin, lactate dehydrogenase, C-reactive protein, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were also found to increase [32]. Cytokine storm, complement activation, and endothelial injury have also been hypothesized to play an essential role in the venous and arterial thrombotic events associated with COVID-19 [38]. This appears to be related to a storm of inflammatory cytokines (interleukin-6 and interleukin-1-beta) contributing to a pro-coagulative and pro-adhesive state of dysfunctional endothelium [36].

The findings of this study revealed no significant differences between patients with and without COVID-19, while also showing a higher success rate of revascularization during the pandemic. Further research is warranted to explore the factors that play a role in these results and to compare them with findings from other studies.

In this study, several characteristics or factors influenced the outcome of ALI patients. In the outcome of revascularization success, it was found that a history of thrombectomy increased revascularization success by 16-fold, while fluoroscopy was associated with revascularization success by 5.5-fold. Similar results were also found in cases of re-intervention, as well as a reduced risk of mortality in patients. Thrombectomy is generally recommended as one of the initial therapies in ALI cases [39]. Thrombectomy was also associated with higher revascularization success rates in ALI patients compared to catheter-based thrombolysis (CDT). Thrombectomy also has a lower complication rate and a higher non-amputation rate when compared to CDT (93% vs 90.2%) [40,41]. Although thrombectomy is often linked to reduced re-intervention and mortality in ALI, this study did not show significant differences in these outcomes. This could be due to factors such as delayed presentation, comorbidities, or small sample size, which may have masked the potential benefits of thrombectomy in reducing re-intervention and in-hospital mortality. The use of fluoroscopy also increases the success of revascularization as one of the modalities that can be used to facilitate access to thrombectomy, as demonstrated by Angkoso *et al.* [42]. Fluoroscopy-guided thrombectomy techniques also increase efficacy and lower costs (more cost-effectively) for ALI patients [43].

In its effect on re-intervention, it was found that sex affected the need for re-intervention, with males requiring it less than females. This is in line with the study by Lancaster *et al.* [44], which demonstrated that women with peripheral arterial disease show a worse rate of functional decline and poorer clinical outcomes after invasive therapy than men. An ankle-brachial index (ABI) <0.4 was also found to be higher in women, and women with ALI were more likely to receive endovascular therapy than men and had a higher postoperative mortality rate than men [44]. Biological differences, including greater muscle mass and stronger collateral circulation in males, may lead to better initial outcomes and lower re-intervention rates compared to females [45].

In terms of comorbidities, chronic kidney disease and heart disease were associated with patient mortality, diabetes mellitus, and dyslipidemia in multivariate analysis. The relationship between these diseases is reciprocal, where all of them are associated with endothelial dysfunction in patients, either for the appearance of ALI or for ALI in these diseases. Therefore, our findings underscore the importance of risk assessment for dyslipidemia and heart disease in the management of ALI during the pandemic, which can guide clinical practice towards improving patient outcomes. Furthermore, concerning kidney disease, it is known that chronic kidney disease is associated with higher mortality, poorer treatment outcomes, and higher costs in patients with ALI [45]. In contrast, the endovascular procedure reduced the glomerular filtration rate by up to 15 mL/min ($p<0.001$), indicating the effect of ALI on renal function [46].

The research by Nishijima *et al.* supported the study's results on the influence of heart disease on ALI. Their study demonstrated the prevalence of ALI in patients requiring amputations ($p=0.042$) [47]. Diabetes mellitus is also a separate factor, such as the research by Ying *et al.*, which mentions the risk of ALI increasing up to 13.41 times in patients who have diabetes compared to those who do not, which also causes an increased risk of mortality. The risk increases with the longer duration of the patient's diabetes mellitus [48]. A case report also found worsening in patients with diabetes and heart disease [49].

Unlike previous studies that found significant differences in mortality risk between ALI patients with COVID-19 and those without COVID-19, this study reported that there was no significant difference in mortality risk, indicating potential variations in patient outcomes across different cohorts and settings during the pandemic. This suggests that the impact of COVID-19 on mortality risk in ALI patients may vary depending on various factors such as healthcare infrastructure, treatment protocols, and patient demographics. Although no formal modifications were made to ALI treatment protocols during the pandemic at our institution, the increased use of fluoroscopy, which was more consistently implemented during this period, may have enhanced procedural accuracy and outcomes. These findings underscore the importance of further research to elucidate the complex relationship between COVID-19 and ALI outcomes, which can inform more targeted interventions and improve patient care strategies during pandemics.

This study benefits from the use of longitudinal data spanning 2018 to 2022, which allows for meaningful comparison of ALI trends before and during the COVID-19 pandemic. However, the retrospective design may limit the applicability of the findings to broader populations. The wide confidence intervals observed in the multivariate analysis—such as the effect estimate for thrombectomy—suggest a lack of precision, likely due to the small sample size. These findings, though statistically significant, should be interpreted with caution. Future studies with larger sample sizes, longer follow-up periods, and broader outcome measures are needed to validate these findings. Additionally, further research should explore the underlying reasons for the limited use of fluoroscopy and thrombectomy and evaluate their true impact on revascularization outcomes in ALI patients.

Conclusion

A significant difference in revascularization success was observed between the pre-pandemic and pandemic periods. Thrombectomy and the use of fluoroscopy were associated with improved revascularization outcomes. The consistent use of fluoroscopic guidance is recommended to enhance procedural success. Modifiable risk factors such as dyslipidemia and cardiovascular disease should be addressed to reduce the risk of adverse outcomes. Although COVID-19 infection was not statistically associated with worse outcomes in this study, it remains a clinical concern due to its established link to increased thrombotic risk.

Ethics approval

The study was conducted appropriately with the Declaration of Helsinki and approved by the Health Research Ethics Committee, Faculty of Medicine, University of Indonesia - Dr. Cipto Mangunkusumo Hospital with Ethics Protocol No. 22-09-1147 and Certificate of Passing Ethics Review No. KET-1027/UN2.F1/ETIK/PPM.00.02/2022 dated September 26, 2022, and Approval for Research Permit from Dr. Cipto Mangunkusumo Hospital with letter No. LB.02.03/2.6.1/1237/2022 dated November 24, 2022.

Acknowledgments

The author would like to express sincere gratitude to the Director of Research and Development at the University of Indonesia for their generous grant support, which made this research possible.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study was funded by a Grant for Q1 Internationally Indexed Publication (PUTI Q1) from Universitas Indonesia in 2022.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems

How to cite

Muradi A, Fachriza I, Pratama D, *et al*. Navigating the intersection of COVID-19 and lower extremity acute limb ischemia: A retrospective cohort study of clinical characteristics and outcomes at Dr. Cipto Mangunkusumo Hospital. Narra J 2025; 5 (3): e2557 - http://doi.org/10.52225/narra.v5i3.2557.

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