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Original Article

Long-Term Outcomes of Acute Limb Ischemia: A Retrospective Analysis of 93 Consecutive Limbs

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Objective: To examine the medium- to long-term outcomes of acute limb ischemia (ALI), which are unclear at present.
Methods: We analyzed 93 consecutive limbs in 77 patients with ALI between January 2005 and December 2015 treated at our vascular center. We categorized the cases into four groups according to etiology (embolism, thrombosis, graft thrombosis, and dissection groups) to assess survival, limb salvage, and freedom from re-intervention rates.
Results: The mean age at onset was 72±15 years. The median follow-up length was 2.90 years. The Rutherford categories I, IIa, IIb, and III included 1, 38, 51, and 3 cases, respectively. Thromboembolectomy was performed in all patients in the embolism and thrombosis groups. In addition, endovascular treatment was performed in 25 (37.3%) patients, especially in the thrombosis group (81.3%). A major amputation could not be avoided in 10 patients. The 5-year limb salvage rates for categories IIa and IIb were 97.1% and 83.1%, respectively. The 5-year freedom from re-intervention rate was 89.2%. The survival rates at 1, 3, and 5 years were 87.9%, 75.2%, and 60.6%, respectively.
Conclusion: The 5-year survival rates of patients with ALI were equivalent to those with chronic limb threatening ischemia (CLTI). The intervention and long-term outcomes were distinguishable according to etiology.

Keywords: acute limb ischemia, 5-year survival rate, limb salvage rate

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Introduction

Acute limb ischemia (ALI) is the sudden onset of a decrease in blood supply to the limbs, which threatens viability, and immediate revascularization is required to salvage such limbs. The incidence of ALI is close to 1.5 cases per 10,000 persons per year.[1,2] ALI has various etiologies, such as embolism caused by atrial fibrillation, acute progression of peripheral artery disease (PAD), previous bypass graft occlusion, and aortic dissection. Other causes include popliteal artery aneurysm, hypercoagulability associated with chemotherapy or cancer, and iatrogenic causes. Revascularization in patients with ALI involves various approaches, such as surgical interventions, including thromboembolectomy and bypass surgery; endovascular interventions, including thrombolysis, angioplasty, and stenting; and both open and endovascular treatments (hybrid therapy). Presently, extensive improvements have been made in endovascular devices, the therapeutic range of endovascular treatment, and hybrid treatments. Although for these approaches, the 1-year limb salvage rate and survival rate are tough, not all patients with ALI have a good course for their history.[3–6] Numerous short-term surveillance approaches have been

reported; however, the long-term outcomes of ALI have not been sufficiently discussed yet. The aim of this study was to reveal the medium- to long-term survival rates of patients with ALI based on the etiology or severity, and to determine the clinical features of each etiology using the limb salvage or re-intervention rates.

Materials and Methods

A retrospective analysis of 93 consecutive limbs in 77 patients with ALI who were treated in our hospital, between January 2005 and December 2015, was performed. ALI was defined as any sudden onset of limb ischemia due to a decrease in limb perfusion within 2 weeks in accordance with the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II).[1] Two category III limbs were excluded, which were amputated primarily. Category III, which tried revascularization resolutely, was included. Physical findings, including pulselessness, a cold feeling, sensory loss, and motor loss, were examined. Blood flow in the lower extremity was evaluated using Doppler ultrasound. Contrast-enhanced computed tomography (CT) was performed whenever possible. The patients' clinical history, medication use, vascular intervention history, and laboratory data were assessed. The therapeutic range of prothrombin time-international normalized ratio (PT-INR) was defined as 2.0–3.0 for patients aged <70 years and 1.6–2.6 for patients aged ≥ 70 years.[7,8] Rutherford categories I–III were used for severity. The etiologies of ALI were classified as follows: embolism (embolism due to atrial fibrillation), thrombosis (atherothrombosis due to PAD), graft thrombosis (reconstruction graft thrombosis), dissection (aortic dissection), and examples of others: hypercoagulability associated with chemotherapy, active cancer, nephrosis, of iatrogenic case. The patients' long-term survival, re-intervention, and amputation data were extracted from medical records or through correspondence. The Kaplan–Meier method was used to analyze the limb salvage rate according to the Rutherford classification and etiology, freedom from re-intervention rate according to etiology, and survival rate according to the Rutherford classification and etiology. Re-intervention was defined as retreatment without amputation. The technical success of ALI treatment was defined as the restoration of antegrade flow to the lower extremity confirmed using intraoperative angiography, improvement of pulsation of dorsal and plantar arteries using intraoperative Doppler ultrasound, and significant relief from symptoms postoperatively.

This study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine.

Statistical analysis

Patient baseline data, which were categorized into the embolism, thrombosis, graft thrombosis, and dissection groups, are presented as percentage, median (interquartile range [IQR]), or mean $\pm$ standard deviation. The 5-year survival rate, limb salvage rate, and freedom from re-intervention rate were assessed using the Kaplan–Meier method. Holm's adjustment method was used to compare multiple groups. All statistical analyses were performed using JMP Pro 12.2.0 software (SAS Institute Inc., Cary, NC, USA). Holm's adjustment method was performed using R version 3.3.2 (The Comprehensive R Archive Network, 2016, https://cran.r-project.org/).

Results

Baseline characteristics

We evaluated 93 limbs in 77 Japanese patients. Forty-one patients were transported to the emergency room by ambulance. Fourteen patients were in-patients for other diseases, and 57 patients were male. **Table 1** shows the baseline data according to etiology. The mean patient age was 72 ± 15 years. The patient age was significantly lower in the dissection group than in the other groups. There was no sex difference in the embolism group, while male sex was more common in the other groups. The ischemic duration was defined as the time from the onset of symptoms to the start of the operation. The ischemic duration was relatively shorter in the embolism and dissection groups and was longer in the thrombosis group. With regard to comorbidities, 43 patients (55.8%) had atrial fibrillation, 54 (70.1%) had hypertension, 28 (36.3%) had dyslipidemia, 14 (18.2%) had diabetes mellitus, 14 (18.2%) had cerebral vascular disease, and 16 (20.1%) had coronary artery disease. All patients in the embolism group had atrial fibrillation. Hypertension was more common in the embolism and dissection groups than in the other groups. According to the Rutherford classification, 38 (40.9%) cases were category IIa and 51 (54.8%) were category IIb. Three (3.2%) cases were category III, which has been reported to show difficulty for limb viability rescue.[9]

Table 1 shows the frequencies of the different etiologies for ALI in our hospital. Embolism was the most frequent etiology (51 cases [54.8%]), followed by thrombosis (16 cases [17.2%]), graft thrombosis (10 cases [10.8%]), dissection (7 cases [7.5%]), and others (9 cases [9.7%]). Others included popliteal artery aneurysms, hypercoagulability associated with cancer, nephrosis, iatrogenic causes, and unknown causes.

Embolism

In the embolism group, all 38 patients had atrial fibrillation. Twenty-two patients (57.8%) were untreated.

Table 1 Baseline characteristics of the patients

	Embolism	Thrombosis	Graft	Dissection
	38 patients	15 patients	9 patients	6 patients
	51 limbs	16 limbs	10 limbs	7 limbs
Age (mean±SD)	78.1±6.5	73.1±11.7	68.9±9.5	55.5±16.5
Male	22 (57.0%)	14 (93.3%)	8 (88.9%)	5 (83.3%)
Ischemic duration (median, IQR)	8 h (4–32)	60 h (10–90)	14.5 h (10–41)	6 h (5–14)
Atrial fibrillation	38 (100%)	2 (13.3%)	3 (33.3%)	0 (0.0%)
Hypertension	33 (86.8%)	7 (46.7%)	5 (55.6%)	5 (83.3%)
Dyslipidemia	15 (39.5%)	6 (40.0%)	4 (44.4%)	2 (33.3%)
Coronary artery disease	11 (28.9%)	1 (6.7%)	1 (11.1%)	0 (0.0%)
Cerebral vascular disease	7 (18.4%)	4 (26.7%)	0 (0.0%)	2 (33.3%)
Hemodialysis	1 (2.6%)	1 (6.7%)	2 (22.2%)	0 (0.0%)
Diabetes mellitus	9 (23.7%)	2 (13.3%)	3 (33.3%)	0 (0.0%)
Cancer	6 (15.8%)	5 (33.3%)	1 (11.1%)	0 (0.0%)
Rutherford I	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Rutherford IIa	23 (45.1%)	4 (25.0%)	3 (30.0%)	3 (42.9%)
Rutherford IIb	26 (51.0%)	12 (75.0%)	7 (70.0%)	3 (42.9%)
Rutherford III	1 (2.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)

SD: standard deviation; IQR: interquartile range

Twelve (31.5%) were treated with warfarin. Of the 12 warfarin-treated patients, nine (75.0%) were out of the therapeutic range for atrial fibrillation. Four patients (10.5%) stopped anticoagulation because of presurgery or bleeding complications. One patient who was prescribed direct oral anticoagulants (DOACs) stopped treatment at presurgery. Two cases were complicated, with superior mesenteric artery embolism. Surgical embolectomy was performed in all patients and endovascular intervention was added in 11 patients. Three patients needed a major amputation after primary surgery before discharge. Of these three patients, one was Rutherford category III with an ischemic duration of 10 days, one was Rutherford category IIb with severe pneumonia, and one was Rutherford category IIb with a saddle embolism.

Thrombosis

All 15 patients in this group were considered to have acute occlusion of a thrombus underlying PAD. Seven patients (46.7%) had hypertension. Four patients (26.7%) had cerebral vascular disease. Five patients (33.3%) had cancer. All patients underwent surgical thrombectomy first. Moreover, 13 (81.3%) patients underwent endovascular treatment. Iliac stenting was performed in eight patients, and superficial femoral artery stenting or ballooning was performed in four patients. Three patients underwent bypass surgery. A patient with a TASC D lesion involving the superficial femoral artery underwent a femoro–popliteal bypass. One patient with saddle embolism with an abdominal aortic aneurysm underwent bifurcated graft reconstruction.

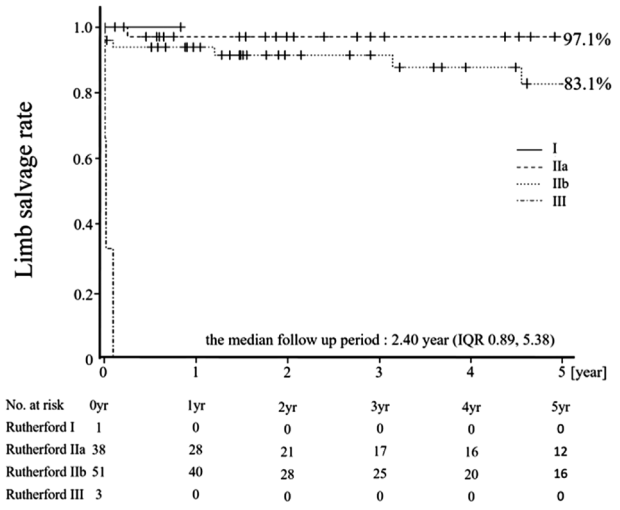
Graft thrombosis

All nine patients had undergone ipsilateral bypass surgery before ALI, including bifurcated graft reconstruction for Leriche syndrome or abdominal aortic aneurysm, axillo–femoral bypass after graft infection, femoro–popliteal bypass for claudication, and femoro–tibial bypass for chronic limb threatening ischemia (CLTI).

Thrombectomy was performed in all patients, re-bypass in three, endovascular treatment in four, and re-anastomosis in three. All patients were prevented from undergoing amputation during the primary intervention. One patient who underwent a femoro–tibial bypass for CLTI needed re-intervention 73 days after ALI and eventually underwent an amputation.

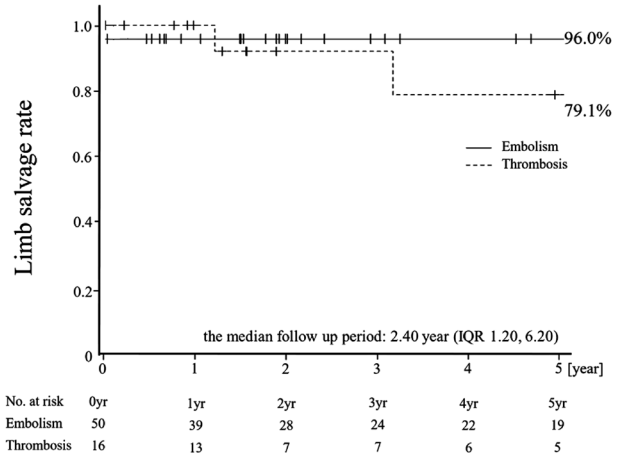
Dissection

The cause of ALI in this group was occlusion of the common iliac artery associated with proximal aortic dissection. The patient age was significantly lower in this group than in the other groups. One case was DeBakey category I, and a femoro–femoral bypass was performed in the patient after the central operation. Six cases were DeBakey category IIIb, and all these patients underwent extra-anatomical bypass surgery. Two patients needed an amputation before discharge, although all patients survived for over 90 days.



No. at risk	0yr	1yr	2yr	3yr	4yr	5yr
Rutherford I	1	0	0	0	0	0
Rutherford IIa	38	28	21	17	16	12
Rutherford IIb	51	40	28	25	20	16
Rutherford III	3	0	0	0	0	0

Fig. 1 The 5-year limb salvage rate according to the Rutherford classification.



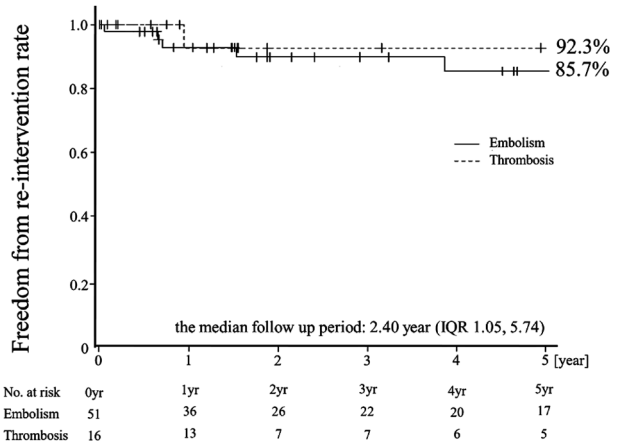
No. at risk	0yr	1yr	2yr	3yr	4yr	5yr
Embolism	50	39	28	24	22	19
Thrombosis	16	13	7	7	6	5

Fig. 2 The 5-year limb salvage rate according to etiology.

Limb salvage rate

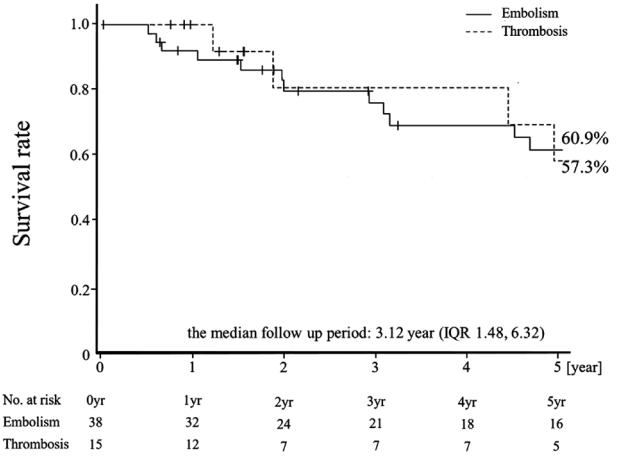
Follow-up data after ALI were available in 73 cases. We constructed Kaplan–Meier curves for the survival rate, limb salvage rate, and freedom from re-intervention rate. First, we analyzed the limb salvage rate according to the Rutherford classification (**Fig. 1**). The median follow-up period was 2.40 years (IQR 0.89 and 5.38). The limb salvage rate for category III was very low. All limbs in category III needed a major amputation within 90 days. The 5-year limb salvage rate for category IIb was 83.1%, and that for category IIa was 97.1%. There was no significant difference between categories IIa and IIb.

Figure 2 shows the limb salvage rate according to etiology. We analyzed the limb salvage rate according to etiology for all cases, except those involving category III, as the limb salvage rate of category III was very low. The median follow-up period was 2.40 years (IQR 1.20 and 6.20). The limb salvage rate in the embolism group was 96.0%, and



No. at risk	0yr	1yr	2yr	3yr	4yr	5yr
Embolism	51	36	26	22	20	17
Thrombosis	16	13	7	7	6	5

Fig. 3 The 5-year freedom from re-intervention rate according to etiology.



No. at risk	0yr	1yr	2yr	3yr	4yr	5yr
Embolism	38	32	24	21	18	16
Thrombosis	15	12	7	7	7	5

Fig. 4 The 5-year survival rate according to etiology.

all limbs were rescued in the long term. Limb loss in the thrombosis group was caused by the progression of PAD, and some of the patients needed limb amputation owing to critical limb ischemia in the follow-up period.

Freedom from re-intervention rate

Figure 3 shows the freedom from re-intervention rate according to etiology. The median follow-up period was 2.40 years (IQR 1.05 and 5.74). The 5-year freedom from re-intervention rate was 89.2%. Both the embolism and thrombosis groups needed re-intervention in the long term. Five patients with embolism needed re-intervention because of recurrence of left atrial thrombus caused by atrial fibrillation. All these patients received warfarin, but the therapeutic level was still insufficient. Patients with embolism had no further amputations during the period. The graft thrombosis group had one re-intervention in the early phase, eventually needing amputation because of sudden graft thrombosis associated with a femoro–tibial bypass for critical limb ischemia with digital necrosis. Un-

derlying critically threatened limbs were included in this group. The dissection group showed limb loss in the early phase, but primary patency was successful.

Overall survival rate

Figure 4 shows the survival rate according to etiology. The median follow-up period was 3.12 years (IQR 1.48 and 6.32). The 5-year survival rate in the embolism group was 60.2% and that in the thrombosis group was 57.3%. Although their basal characteristics were different, their survival rates were equivalent. The p-value in the log-rank test between the embolism and thrombosis groups was 0.77, after adjusting the p-value using Holm's method.

We also analyzed the survival rate according to the Rutherford classification. The 5-year survival rates for categories IIa, IIb, and III were 56.3%, 62.6%, and 66.7%, respectively. There was no relationship between the Rutherford classification and survival rate in our study.

Causes of death

There were 30 deaths in the follow-up period. The principal causes of death were identified in 21 cases. The most frequent cause of death was heart failure and sepsis, with five cases (16.7%) each. The other causes were cerebral failure (three cases [10.0%]), malignancy (three cases [10.0%]), renal failure (one case [3.3%]), gastrointestinal bleeding (one case [3.3%]), natural causes (three cases [10.0%]), and unknown causes (nine cases [30.0%]). Half of the patients in the graft thrombosis group were lost in the long term. The mean age at death for all patients was 79.8 ± 13.3 years. There was no difference in age at death between the embolism and thrombosis groups.

In the short-term period, there were two deaths; one patient who underwent a femoro–popliteal bypass occlusion died within 30 days due to dehydration and coagulopathy from severe acute pancreatitis, whereas the other who underwent valve replacement died within 90 days due to thrombosis resulting from intra-aortic balloon pumping. Infective endocarditis was noted in the latter, and the patient was considered to have a cardiopulmonary arrest on arrival. However, these causes of death were unrelated to ALI. None of the patients died due to ALI. The short-term mortality outcomes were considered acceptable.

Discussion

ALI needs immediate revascularization; otherwise, it may result in a major amputation and may greatly limit daily activity. In this study, we mainly analyzed the long-term outcomes of ALI according to the Rutherford classification or etiology. Re-intervention was required in both the embolism and thrombosis groups; however, only the thrombosis group needed a major amputation in the long term. There was no significant difference in the survival rate.

Accordingly, in our vascular center, we initially performed surgical embolectomy for embolism. Thrombectomy for thrombosis was also performed, as most thromboses in patients with PAD involved a central fresh thrombus lesion that extended from a severe stenotic lesion, and then, stenting or ballooning was performed according to the stenotic lesion. In Western countries, thrombolysis, especially the use of recombinant tissue-type plasminogen activator (rt-PA), is one of the primary approaches for a central thrombus, and several outcomes have been reported.[5,10–12] However, rt-PA is not permitted for ALI in our country, and therefore, we performed thrombectomy to shorten the occluded lesion and to save stents.

Embolism is the most common cause of ALI, and it was responsible for 52.6% of cases in our hospital, which is similar to the rate reported in a previous study.[13] All the treated cases of embolism of the lower extremities were caused by atrial fibrillation, except in one patient who had embolism due to infective endocarditis and one due to lung cancer. We excluded these cases from the analysis because they were treated without revascularization. In our study, two cases were complicated, with superior mesenteric artery embolism. To prevent thrombus formation, anticoagulation is the most popular therapy for atrial fibrillation. Nevertheless, in the embolism group, 75.0% of patients who were treated with warfarin were out of the therapeutic level with regard to PT-INR. Most patients with ALI with atrial fibrillation showed subtherapeutic levels.[13] Daily medication is a minimum requirement, and knowledge about ALI for patients with atrial fibrillation would help with earlier admission. In our study, only one patient was prescribed DOACs; however, treatment was stopped at presurgery. Therefore, no DOAC-medicated patients showed ALI in our study period. As DOACs are considered not to require monitoring, not to cause a hypercoagulable state, not to be affected by foods, and to reduce the risk of bleeding, they may be more appropriate in preventing embolism instead of warfarin. Medication compliance would be improved with DOACs for the reasons mentioned previously. There is a possibility of changing warfarin to DOACs, and a previous report has shown that DOACs prevent ALI in patients with atrial fibrillation.[14]

As the incidence of atrial fibrillation increases with age, the risk of embolism is the highest among senior citizens.[15] The mean age at embolism development was high in our study. The mortality of patients with atrial fibrillation is considered high during the first year after diagnosis. The chance of death associated with cerebral vascular disease or cardiac failure increases in patients with atrial fibrillation.[16,17] To prevent ALI and other embolism-relat-

ed issues, anticoagulation should be considered even for elderly patients with atrial fibrillation.

Embolism may be resolved with revascularization embolectomy alone because the characteristic of the vascular lumen is more normal for embolism than for thrombosis. Although some cases have indicated that hybrid therapy is better, embolism can extend to the infrapopliteal arteries or show calcified stenosis. Hybrid therapy involving surgical embolectomy with a guidewire would result in accurate and conscientious manipulation. Although re-embolism occurred in the long term, a major amputation was rare. We are strictly lecturing the necessity of anticoagulation to prevent re-embolism. This information may have helped prevent amputation in the patients with embolism.

We did not encounter other causes of embolism, such as infective endocarditis or tumor revascularization in the study period; however, these causes cannot be overlooked and should be considered when performing echocardiography or when an unidentified infection is suspected.

Thrombosis was the second major cause of ALI. The progression of arteriosclerosis can result in the development of unstable plaques, and an acute event can occur when a plaque ruptures. Ischemic duration was longer in the thrombosis group than in the embolism group. This might be associated with the fact that collateral blood supply can reduce the progression of ischemia. As thrombotic lesions can cause calcification and stenosis in patients with PAD, surgical thrombectomy alone may not always be successful in improving blood flow. We performed surgical thrombectomy with stenting for the iliac artery, with ballooning for the iliac arteries or superficial femoral artery. In some cases, we considered bypass surgery depending on the lesion length. One patient with SFA TASC D underwent bypass surgery. In the long term, disease progression may lead to re-intervention. In this study, re-intervention was required in three cases.

The new insights of this study include the long-term outcomes of patients with ALI. Most articles have reported around 1-year overall survival or limb salvage.[3] In our study, the 5-year survival rate was equivalent between the embolism (60.9%) and thrombosis (57.3%) groups, which was approximately equivalent to those of CLTI in previous reports.[1,18] The mean age at death was approximately 80 years, and most deaths were associated with chronic heart failure, cerebral vascular disease, and sepsis. These causes of death were similar to those in patients with CLTI, which is not closely related to ALI.

According to the Rutherford classification, the 5-year survival rate of Rutherford IIa, IIb, and III were approximately equivalent. All limbs of categories I and IIa were rescued from the onset of primary ischemia, although limbs of category III needed a major amputation. Category IIb was the boundary for limb salvage, suggesting that category IIb is the fundamental category for limb salvage.

One patient died from gastrointestinal bleeding, which might have been associated with anticoagulation. Conversely, anticoagulation may not influence the adverse event of death in patients with ALI. A systemic approach is required to prevent death, and appropriate anticoagulation is needed for embolism or antiplatelet therapy for thrombosis.

We treated embolism and thrombosis using thromboembolectomy, removed emboli or extended acute thrombus, and performed angioplasty if the intimal lesion persisted. Some patients could achieve technical success by thromboembolectomy alone; however, we should consider that some thrombi might be difficult to remove, such as old thrombi or debris from plaques. Recently, the benefits of thrombolysis and thromboembolectomy have been considered to be equivalent.[6,19] However, bleeding has been reported as a complication due to thrombolysis in numerous reports.[6,10,20,21] Thromboembolectomy still remains the gold standard for ALI, and hybrid therapy combined with angioplasty could achieve successful revascularization. The disease etiology detected from pre- and intraoperative findings can help determine the treatment strategy.

The location or volume of the thrombus would be useful information, which indicates the ischemic area. In this study, we attempted the evaluation of these points. As the time for examination was limited and immediate revascularization was required, a localized ultrasound test was performed. A contrast-enhanced CT scan was useful in evaluating the approximate location of ischemic limbs. However, we could not precisely detect that the nonenhanced area equals the occlusion area. It was difficult to evaluate the location of the thrombus correctly using a contract-enhanced CT scan or intraoperative findings.

The present study has some limitations. This was a single-center retrospective study. Therefore, some data were not available and there might have been bias. However, the long-term outcomes were good, as the response rate was 94.8%, excluding four cases. Also, some groups had a small number of patients. This was a consecutive retrospective study of patients with ALI with multifarious etiologies and lesser frequency. As the follow-up period was from 2005 to 2015, some cases had incomplete outcome data.

The long-term outcomes of Asian patients with ALI have not been adequately reported, and the current study provides extensive information on these patients. This can be considered as strength of our study.

Conclusion

In conclusion, we assessed the long-term outcomes of patients with ALI. Category IIb is the fundamental category for limb salvage. The 5-years survival rates of patients with ALI were equivalent to those with CLTI. The limb salvage and freedom from re-intervention rates were high. The intervention and long-term outcomes were distinguishable according to each etiology. Therefore, etiology-based treatment should be selected. Anticoagulation for atrial fibrillation is still an issue.

Disclosure Statement

Umetsu M and other co-authors have no conflict of interest.

Author Contributions

Study conception: DA
Data collection: MUm
Analysis: MUm
Investigation: MUm
Writing: MUm
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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