Prognosis of critical limb ischemia patients with tissue loss after achievement of complete wound healing by endovascular therapy

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Objective: **Critical limb ischemia (CLI) patients with tissue loss have been recognized to have a poor survival rate. In this study, we aimed to determine whether the prognosis of CLI patients with tissue loss improves after complete wound healing is achieved by endovascular therapy.**

Methods: **We treated 187 CLI patients with tissue loss by endovascular therapy from April 2007 to December 2012. Among these patients, 113 patients who achieved complete wound healing were enrolled. The primary end point was survival rate at 3 years. The secondary end points were limb salvage rate and recurrence rate of CLI at 3 years.**

Results: **The mean follow-up period after achievement of complete wound healing was 32 ± 18 months. At 1 year, 2 years, and 3 years, the survival rates were 86%, 79%, and 74%; the limb salvage rates were 100%, 100%, and 100%; the recurrence rates of CLI were 2%, 6%, and 9%, respectively. On multivariate Cox proportional hazard analysis, age >75 years (hazard ratio, 3.18; 95% confidence interval, 1.23-8.24; $P = .017$) and nonambulatory status (hazard ratio, 2.46; 95% confidence interval, 1.08-5.65; $P = .035$) were identified as independent predictors of death for CLI patients with tissue loss even after complete wound healing was achieved. The Kaplan-Meier curve for the overall survival rate at 3 years showed that CLI patients of older age (>75 years) had a significantly decreased survival rate compared with CLI patients of younger age (≤75 years) (58% vs 87%; log-rank test, $P < .001$). In addition, nonambulatory CLI patients had a significantly poor survival rate relative to ambulatory CLI patients (40% vs 93%; log-rank test, $P < .001$).**

Conclusions: **The overall survival rate of CLI patients was acceptable and the recurrence rate of CLI was extremely low once complete wound healing was achieved. Nonambulatory status and age >75 years can serve as predictors of death even after complete wound healing is achieved. (J Vasc Surg 2015;61:951-9.)**

Critical limb ischemia (CLI) is the most advanced form of peripheral artery disease. CLI patients usually have a high prevalence of major amputation and death. The most important difference between CLI patients with tissue loss and peripheral artery disease patients with intermittent claudication is that the prognosis of CLI patients is associated with ischemic ulcers and gangrenes. For the treatment of CLI patients with tissue loss, both revascularization (to improve ischemia) and wound care are important. The limb salvage rates and major amputation-free survival rates of CLI patients at 1 year have been reported to be 58% to 92% and 54% to 80%, respectively.[1-4] However, these rates do not take into account whether the wound is completely healed. Most previous studies have investigated the survival rates or limb salvage rates of CLI patients, including wound healing patients and wound nonhealing patients.

The prognosis of CLI patients who have achieved complete wound healing remains unclear. In this study, we performed optimal revascularization and wound care for CLI patients with tissue loss to achieve complete wound healing. Our aims were to investigate the overall survival rate and limb salvage rate of these CLI patients and to determine the recurrence rate at 3 years after achievement of complete wound healing by endovascular therapy (EVT).

METHODS

Study population. We retrospectively analyzed CLI patients with tissue loss who achieved complete wound healing after EVT in our institution. The overall participant flowchart is shown in Fig 1. Between April 2007 and December 2012, 194 patients underwent EVT or surgical revascularization for CLI with tissue loss. After exclusion of nine patients (13 limbs) who underwent bypass surgery, 185 CLI patients were treated by EVT alone. Of these 185 CLI patients, 113 patients (124 limbs and 127 wounds) who achieved complete wound healing by December 2012 were enrolled. The patient's lower limb arteries (ie, femoral, popliteal, dorsalis, and posterior tibial arteries) were palpated, and the hemodynamic status was evaluated by the ankle-brachial index (ABI), skin perfusion pressure

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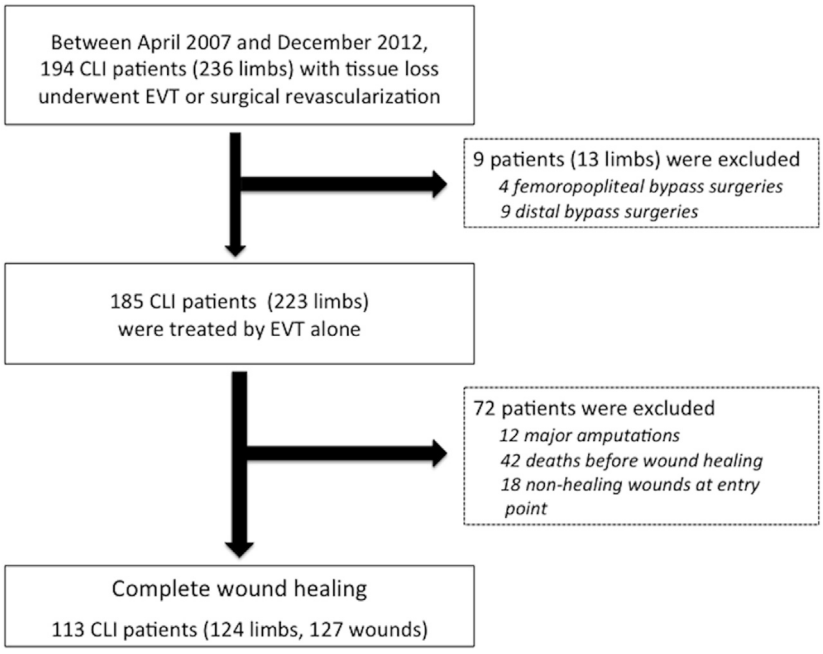


Fig 1. Overall participant flowchart of the study groups. *CLI,* Critical limb ischemia; *EVT,* endovascular therapy.

(SPP), and duplex ultrasound. SPP was measured on the dorsal and plantar sides of the foot. Flow in the lower limb artery was evaluated routinely before EVT with duplex ultrasound and digital subtraction angiography. We considered wounds to be completely healed when there was 100% epithelialization of tissue loss and wound care, including cleaning and ointment application, became unnecessary. Minor amputation wounds were left open and granulation was promoted. Thus, time to healing after minor amputation was also defined as complete epithelialization of ischemic lesions without wound care. A major amputation case was considered wound healing failure and excluded from this study. There were 72 patients who were excluded because of major amputation (n = 12), death before achieving complete wound healing (n = 42), and failure to achieve complete wound healing by December 2012 (n = 18). All the patients provided informed consent to undergo the procedure and for subsequent data collection. The study protocol was in accordance with the Declaration of Helsinki and approved by the Institutional Review Board.

Endovascular intervention. All endovascular procedures were performed under local anesthesia. Our EVT strategy was to provide visible blood flow to the wound as evaluated by digital subtraction angiography after EVT. We attempted revascularization based on the angiosome concept. If angiosome-based revascularization was difficult because of inability to cross the wire or balloon, and even if the wire and balloon crossed, we attempted to achieve indirect revascularization through the collateral network when blood flow to the wound was insufficient. Primary stenting with self-expandable stents was performed for the treatment of iliac lesions under intravascular ultrasound guidance. Provisional stenting was performed for femoropopliteal lesions. Balloon angioplasty was initially performed with an optimally sized balloon as assessed by intravascular ultrasound. If the results were suboptimal (ie, residual diameter stenosis >30% remained, or flow-limiting dissection after balloon angioplasty occurred), we implanted self-expandable stents. For infrapopliteal lesions, we performed an antegrade approach with a 4F sheath through the ipsilateral femoral artery, and we carried out balloon angioplasty only with a 100- or 120-mm-long balloon because the use of stents is not approved for below-the-knee intervention in Japan. Stents and atherectomy devices were not available for below-the-knee intervention. Oral dual antiplatelet therapy with aspirin (100 mg/day) plus either ticlopidine (200 mg/day) or clopidogrel (75 mg/day) was started before EVT and continued for ≥1 month thereafter. After sheath insertion, a bolus of 5000 units of heparin was administered intravenously.

Wound management and follow-up. After EVT, all patients received wound care at our foot care clinic once or twice a week after hospital discharge. Our foot care team included interventional cardiologists who actually performed EVT, a plastic surgeon, nurses specialized in foot care training, and a prosthetist who made customized shoes for depressurization to attempt offloading technique. We regularly checked the wound status and photographed the wound to monitor the healing process. The wound healing regimen was based on the "Tissue, Infection or Inflammation, Moisture imbalance, and Edge of wound" classification.[5] Infectious wounds were treated with the appropriate antibiotic therapy. The plastic surgeon

evaluated the need for incisional drainage, ostectomy, skin autografting, and free flap reconstruction and judged whether the wound was completely healed. ABI, SPP, and duplex ultrasound evaluations were performed when the healing course was insufficient. Angiography was performed when these noninvasive procedures suggested restenosis or occlusion of the target limb arteries. After achieving complete wound healing, patients were followed up at our foot care clinic every 3 months and assessed for wound recurrence. If the patients could not visit our clinic after achieving wound healing (eight patients; 7%), we conducted telephone interviews with the patients or their family members, who were highly educated about wound management at home, or with their primary physicians to obtain information and to know their wound status. We also have a palliative care team in our hospital that provides care not only to CLI patients but also mainly to cancer patients in our hospital as appropriate.

For the actual wound management procedure, all wounds were left open after intervention and were not sutured. Granulation and complete epithelialization were promoted by wound cleaning, ointment application, negative pressure therapy, and skin graft as necessary. Complete wound healing was defined as 100% epithelialization and without the need for wound care. Nonhealing wounds were defined as wounds that are almost completely epithelialized and functionally healed but still require ointment application. In some wounds, ointment application was continued for very small ulcerations; thus, the time to wound healing might take longer.

End points. The primary end point was the overall survival rate at 3 years after achievement of complete wound healing. The type of death was divided into cardiac death and noncardiac death. Death was regarded as cardiovascular of origin unless obvious noncardiovascular causes could be identified. The secondary end points were the limb salvage rate and CLI recurrence rate at 3 years after complete wound healing was achieved.

Definitions. CLI was defined according to the Trans-Atlantic Inter-Society Consensus (TASC) II guideline.[6] Ischemic tissue loss due to CLI was associated with an absolute ankle pressure <70 mm Hg or toe pressure <50 mm Hg. When these measurements could not be obtained because of intractable pain or a noncompressible artery with severe calcification, SPP was measured instead of ankle or toe pressure. SPP of <40 mm Hg was considered to indicate ischemic tissue loss.[7] Digital- or transmetatarsal-level amputation was considered minor amputation, and above-the-ankle amputation was considered major amputation. Limb salvage indicated freedom from major amputation. Nonambulatory status was defined as bedridden or wheelchair use as the patients cannot walk by themselves even with the aid of a cane or a circular walker. Nonambulatory patients did not use their own limbs to transfer. Patients who used a wheelchair because of wound pain were not considered to have a nonambulatory status. Wound recurrence was regarded as the re-formation of ulceration or gangrene with an insufficient hemodynamic status according to the TASC classification. A recurrent wound was not necessarily located at the same site or foot. Coronary artery disease included a history of documented angina pectoris, previous myocardial infarction, or percutaneous coronary intervention. Cerebrovascular disease signified a history of stroke, transient ischemic attack, carotid artery revascularization, or intracranial hemorrhage. Hypertension was defined as a casual blood pressure ≥140/90 mm Hg or the current use of antihypertensive drugs. Diabetes mellitus indicated treatment with insulin or oral hypoglycemic drugs or a casual plasma glucose level >200 mg/dL or hemoglobin A_{1c} level >6.5%. Dyslipidemia was defined as a fasting serum low-density cholesterol level ≥140 mg/dL, a high-density cholesterol level <40 mg/dL, a triglyceride level ≥150 mg/dL, or the use of cholesterol-lowering agents.

Statistical analysis. Continuous variables with normal distributions were expressed as mean ± standard deviation. Variables without normal distribution were expressed as median and interquartile range (ie, time to wound healing). Categorical variables were shown as counts and percentages. Continuous variables were compared by an unpaired *t*-test. Categorical variables were assessed by the Fisher exact test. Overall survival rate, limb salvage rate, and CLI recurrence rate were estimated by the Kaplan-Meier method, and the difference among groups was evaluated by the log-rank test. Cox proportional hazard analysis was used to identify the independent predictors of death after achievement of compete wound healing. All variables with $P < .05$ on univariate analysis were introduced in a multivariate Cox hazard model. A two-sided P value of $< .05$ was considered to indicate a statistically significant difference. All analyses were performed with SPSS software (version 19; IBM Corporation, Somers, NY).

RESULTS

Baseline characteristics. The characteristics of the 113 patients who achieved complete wound healing are listed in Table I. The patients had a mean age of 74 ± 11 years and consisted of 73 male patients (64.6%). The prevalence rates of diabetes mellitus, insulin use, and hemodialysis dependency were 68%, 24%, and 30%, respectively. Twenty patients (18%) had a nonambulatory status (bedridden, 2%; wheelchair use, 16%). After EVT, the ABI and SPP improved to 1.0 ± 0.15 and 60 ± 23, respectively.

The wound characteristics, lesion characteristics, and interventional results of the 113 patients are summarized in Table II. Eleven patients (10%) had wounds on both legs and 13 (11%) had multiple wounds. Eighty patients (71%) were classified as Rutherford category 5, and 32 (28%) needed minor amputation to achieve complete wound healing. The median time to wound healing was 104 days [interquartile range, 32-202 days]. Isolated below-the-knee lesions were the culprit lesions in 63 patients (56%), whereas multilevel lesions were the culprit lesions in 41 patients (36%). The achievement rates of visible

Table I. Baseline characteristics of 113 critical limb ischemia (CLI) patients (127 wounds) who achieved complete wound healing

Variables	
Age, years	74 ± 11
Age >75 years	50 (44)
Sex: male	73 (65)
BMI	22 ± 3.8
BMI <18.5	21 (19)
Risk factors	
Hypertension	91 (81)
Dyslipidemia	39 (35)
Diabetes mellitus	77 (68)
Insulin use	27 (24)
Hemodialysis	34 (30)
History of smoking	41 (36)
Prior coronary artery disease	36 (32)
Prior cerebrovascular disease	29 (26)
Nonambulatory status	20 (18)
Bedridden	2 (2)
Wheelchair use	18 (16)
Laboratory data	
Serum albumin, g/dL	3.3 ± .6
C-reactive protein, mg/dL	2.6 ± 3.6
Creatinine, mg/dL	2.9 ± 3.2
HbA_{1c}, %	6.6 ± 1.8
Preprocedure ABI	0.51 ± 0.18
Preprocedure SPP, mm Hg	31 ± 11
Postprocedure ABI	1.0 ± 0.15
Postprocedure SPP, mm Hg	60 ± 23
Ejection fraction, %	59 ± 11
Low ejection fraction <40%	8 (7)
Medications	
Statin	53 (47)
ACE/ARB	70 (62)
Beta blockers	35 (31)
Antiplatelet drugs	
Aspirin	96 (85)
Thienopyridines	28 (25)
Cilostazol	76 (67)

ABI, Ankle-brachial index; *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BMI,* body mass index; *HbA_{1c},* glycosylated hemoglobin; *SPP,* skin perfusion pressure.
Continuous data are presented as mean ± standard deviation and categorical data as number (%).

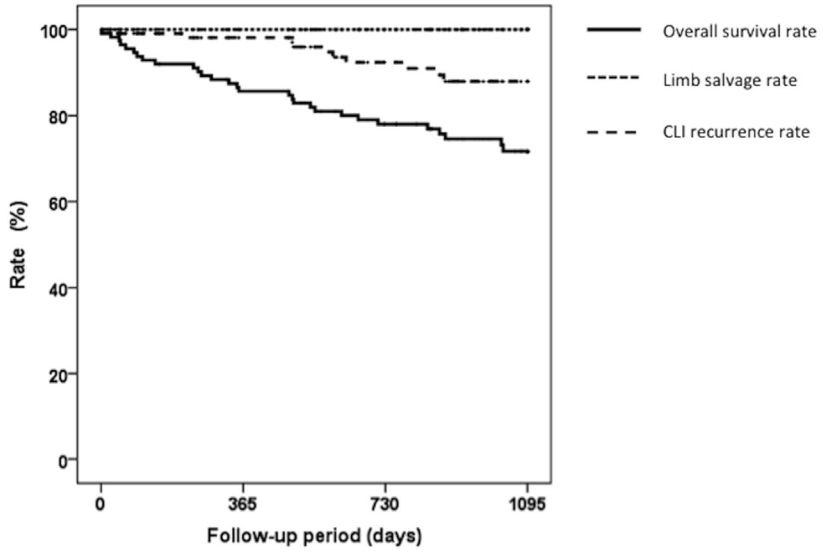
blood flow to the wound and revascularization based on the angiosome concept were 83% and 47%, respectively. The mean number of times EVT was performed before achievement of complete wound healing was 1.5 ± 1.2 times.

Outcome measures. The mean follow-up period was 32 ± 18 months. Five patients (4%) were lost to follow-up after transferring to other hospitals or losing contact. The overall survival rates at 1 year, 2 years, and 3 years were 86%, 79%, and 74%, respectively. The limb salvage rate was 100% at 3 years, and the recurrence rates of CLI at 1 year, 2 years, and 3 years were 2%, 6%, and 9%, respectively (Fig 2). Recurrence of CLI more frequently occurred at a site different from the original site (same site, two patients; different site, eight patients). In addition, 2 patients had recurrence in the form of Rutherford category 4, 7 patients in the form of Rutherford category 5, and 1 patient in the form of Rutherford category 6. In those who had recurrence, two patients died but the other eight patients achieved wound healing again. The incidence of noncardiac death (20%) was higher than that of cardiac death (6%) at 3 years. The most prevalent cause of noncardiac death was infectious disease (11 patients; 10%), followed by malignant disease (3 patients; 3%) and cerebrovascular disease (3 patients; 3%), renal failure (2 patients; 2%) and gastrointestinal bleeding (2 patients; 2%), and suffocation (1 patient; 0.9%).

Table II. Wound characteristics, lesion characteristics, and interventional results of 113 critical limb ischemia (*CLI*) patients (127 wounds) who achieved complete wound healing

Variables	
Wound characteristics	
Bilateral CLI	11 (10)
Number of wounds	
1/2/3	100 (88)/12 (11)/1 (1)
Rutherford category 5/6	80 (71)/33 (29)
Wound location	
Toe	88 (70)
Plantar	3 (2)
Dorsal	13 (10)
Ankle	6 (5)
Heel	15 (12)
Infectious wound	42 (34)
Gangrene	46 (37)
Wound management	
Need minor amputation	32 (28)
Digital level	28 (25)
Transmetatarsal level	4 (4)
Aquacel Ag	22 (19)
Skin autograft	2 (2)
Negative pressure therapy	17 (15)
Free flap reconstruction	7 (6)
Time to wound healing, days	104 (32-202)
Target lesion site	
Aortoiliac	0 (0)
Femoropopliteal	9 (8)
Infrapopliteal	63 (56)
Aortoiliac + femoropopliteal	1 (1)
Aortoiliac + infrapopliteal	3 (3)
Femoropopliteal + infrapopliteal	32 (28)
Aortoiliac + femoropopliteal + infrapopliteal	5 (4)
Multilevel	41 (36)
Isolated infrapopliteal	63 (56)
Interventional results	
Femoropopliteal stenting	39 (85)
Mean number of stents per lesion	1.5 ± 0.9
Iliac stenting	9 (100)
Mean number of stents per lesion	1.3 ± 0.5
Achievement of blood flow to the wound	94 (83)
Revascularization based on angiosome concept	53 (47)
Mean number of times EVT was performed before achievement of wound healing	1.5 ± 1.2

EVT, Endovascular therapy.
Continuous data are presented as mean ± standard deviation and categorical data as number (%).



		0	365	730	1095
Overall survival	at risk	113	94	74	47
Limb salvage	at risk	113	94	74	47
CLI recurrence	at risk	113	93	69	40

Fig 2. Kaplan-Meier life-table analysis of the clinical outcomes of critical limb ischemia (*CLI*) patients with tissue loss after achievement of complete wound healing.

Predictors of death. Univariate Cox proportional hazard analysis showed that age >75 years, body mass index <18.5, diabetes mellitus, nonambulatory status, and albumin level <2.5 g/dL were associated with death after achievement of complete wound healing (Table III). Considering the correlation between body mass index and albumin level, the latter was excluded from the multivariate analysis to avoid multicollinearity. After introduction of these factors except for albumin level <2.5 g/dL into the multivariate Cox proportional hazard analysis, age >75 years (hazard ratio, 3.18; 95% confidence interval, 1.23-8.24; $P = .017$) and nonambulatory status (hazard ratio, 2.46; 95% confidence interval, 1.08-5.65; $P = .035$) were detected as independent predictors of death after achievement of complete wound healing. The Kaplan-Meier analysis revealed a significant difference in the survival rate between the two groups with vs without age >75 years (Fig 3, *A*; 58% vs 87%; log-rank test, $P < .001$) and ambulatory status vs nonambulatory status (Fig 3, *B*; 40% vs 93%; log-rank test, $P < .001$). In addition, there was no significant difference in the survival rate between CLI patients classified as Rutherford category 5 and CLI patients classified as Rutherford category 6 (Fig 3, *C*; 75% vs 73%; log-rank test, $P = .641$) after achievement of complete wound healing.

DISCUSSION

We report four major findings of the present study. First, the survival rate and limb salvage rate at 3 years of the CLI patients with tissue loss who achieved complete wound healing were >74% and 100%, respectively. Second, the recurrence rate of CLI was extremely low (<10% at 3 years). Third, an advanced age of >75 years and a nonambulatory status in CLI patients could be predictors of death even after achievement of complete wound healing. In fact, the survival rates of these patients were extremely lower than those of patients who were younger than 75 years or had no nonambulatory status. Fourth, Rutherford category 6 did not affect the poor survival rate after achievement of complete wound healing compared with Rutherford category 5.

Wound healing is a meaningful end point after revascularization. However, only a few data are available regarding the rate of wound healing after revascularization.[4,8-10] Furthermore, all of these previous studies failed to investigate the effects of wound healing on survival rate and limb salvage rate. Conte et al[11] reported objective performance goals for the efficacy of catheter-based treatments in CLI patients. They set the amputation-free survival rate and limb salvage rate at 1 year as 71% and 84%, respectively. Romiti et al[12] reported a limb salvage rate of 82.4% and a survival rate of 68.4% at 3 years using meta-analysis of infrapopliteal angioplasty for CLI patients. Soderstrom et al[13] described long-term results after EVT, namely, a limb salvage rate of 75.3%, a survival rate of 47.5%, and an amputation-free survival rate of 37.7% at 5 years. In the present study, the limb salvage rate was 100% after achievement of complete wound healing with or without

Table III. Predictors of death after achievement of complete wound healing in univariate and multivariate Cox hazard models

	Univariate analysis	*Multivariate analysis*		
Variables	P *value*	*HR*	*95% CI*	P *value*
Age >75 years	<.001	3.18	1.23-8.24	.017
Sex: male	.103			
BMI <18.5	.018	2.15	.97-4.77	.060
Diabetes mellitus	.022	1.04	.46-2.31	.934
Hyperlipidemia	.128			
Hemodialysis	.236			
Current smoking	.053			
Nonambulatory status	<.001	2.46	1.08-5.65	.035
Albumin <2.5 g/dL	.044			
Infection	.291			
Number of wounds	.238			
Rutherford category 6	.642			

BMI, Body mass index; *CI,* confidence interval; *HR,* hazard ratio.

revascularization of the angiosome; thus, the major amputation-free survival rates at 1 year and 3 years were 86% and 74%, respectively. Our results showed that the prognosis of CLI patients who achieved complete wound healing was extremely good compared with previous studies. CLI patients are at high risk of coronary artery disease and cerebrovascular disease, which are the main causes of death. We routinely perform echocardiography and carotid duplex as screening tests as well as coronary angiography at the time of angiography of the lower limb artery. Percutaneous coronary intervention is planned as necessary. Peripheral artery disease is one of the systemic vascular diseases; thus, this holistic screening and intervention may have resulted in the good survival rate in our study. Our results suggest the possibility that wound healing plays an important role in improving the clinical outcomes of CLI patients. Recently, the Society for Vascular Surgery Lower Extremity Guidelines Committee has proposed a new classification system for CLI patients based on three major factors: wound, ischemia, and foot infection.[14] The committee suggested that wound healing depends on not only the degree of ischemia but also the severity of wound infection and wound depth. Thus, revascularization is only one of the treatments of CLI patients. Nevertheless, previous studies have reported no clinical improvement even after successful revascularization in both EVT and bypass surgery.[15-18] As wound healing appears to be closely associated with the improvement of the clinical outcomes of CLI patients, it is essential to clarify important aspects for achieving wound healing. In this study, major infection cases requiring open amputation or free flap reconstruction were initially sent to bypass surgery. If bypass was not possible because the patients had a high surgical risk or severe calcifications of the distal arteries, EVT followed by wound treatment was performed. However, the achievement of complete wound healing in these patients is low. In this study, only patients showing wound healing were enrolled. The rate of massive ischemic infection in the enrolled patients who eventually acquired complete wound healing by EVT alone was only 6% of the total cohort. Revascularization, wound management, and patient education have been suggested as important aspects to consider in the multidisciplinary therapy of CLI patients.[19-22] Chung et al[21] reported a significantly improved amputation-free survival with multidisciplinary care compared with standard wound care (593.3 ± 53.5 days vs 281.0 ± 38.2 days; log-rank test, $P = .02$). Moreover, Chung et al[21] showed that the time to wound healing tended to be shorter in the multidisciplinary care group than in the standard wound care group (444.5 ± 33.2 days vs 625.2 ± 126.5 days; log-rank test, $P = .74$). In the present study, the median time to achievement of wound healing was 104 days. The amount of time needed for revascularization was small, and we spent most of this time for wound care consisting of débridement, application of ointment, and use of negative pressure wound therapy. Whether complete wound healing can be achieved or the time to wound healing can be shortened depends critically on the wound management process. Thus, a more detailed assessment of how to achieve optimal wound care is necessary in the future.

In this study, age >75 years and nonambulatory status were found to be independent predictors of death even after complete wound healing was achieved. Our multivariate analysis using "age >80 years" or "age >85 years" instead of age >75 years revealed no statistically significant difference. Thus, age >75 years was considered an independent predictor of death in CLI patients even after complete wound healing. Chung et al[21] similarly suggested that a baseline nonambulatory status was an independent predictor of major amputation or death, or both. However, nothing can be done to improve these two factors. In our opinion, the purpose of EVT and achievement of complete wound healing is to improve the quality of life (QOL) of the elderly or nonambulatory CLI patients. Almost all CLI patients with tissue loss have foot pain, which is occasionally difficult to relieve; thus, wound healing serves as the optimal care for CLI patients with tissue loss. When CLI patients have an ulcer or gangrene in the "nonfunctioning" limb, particularly in nonambulatory patients, and there is no hope for limb salvage, early major amputation may prevent a protracted course and death. In addition, it has been reported that intensive medical therapy was associated with good survival and fewer major adverse limb events.[23-25] In the present study, the usage rates of statin, angiotensin-converting enzyme/angiotensin receptor blocker, and beta blockers were 47%, 62%, and 31%, respectively, which were considered insufficient. To improve the survival rate of high-risk CLI patients, careful attention to their medical status must be given. Rutherford category 6 has been reported as an independent predictor of major amputation or death in CLI patients.[9,26] Feiring et al[26] reported that the mortality of CLI patients with Rutherford category 6 was significantly poor compared with CLI patients with Rutherford category 5. On the other hand, the present study suggested no statistically

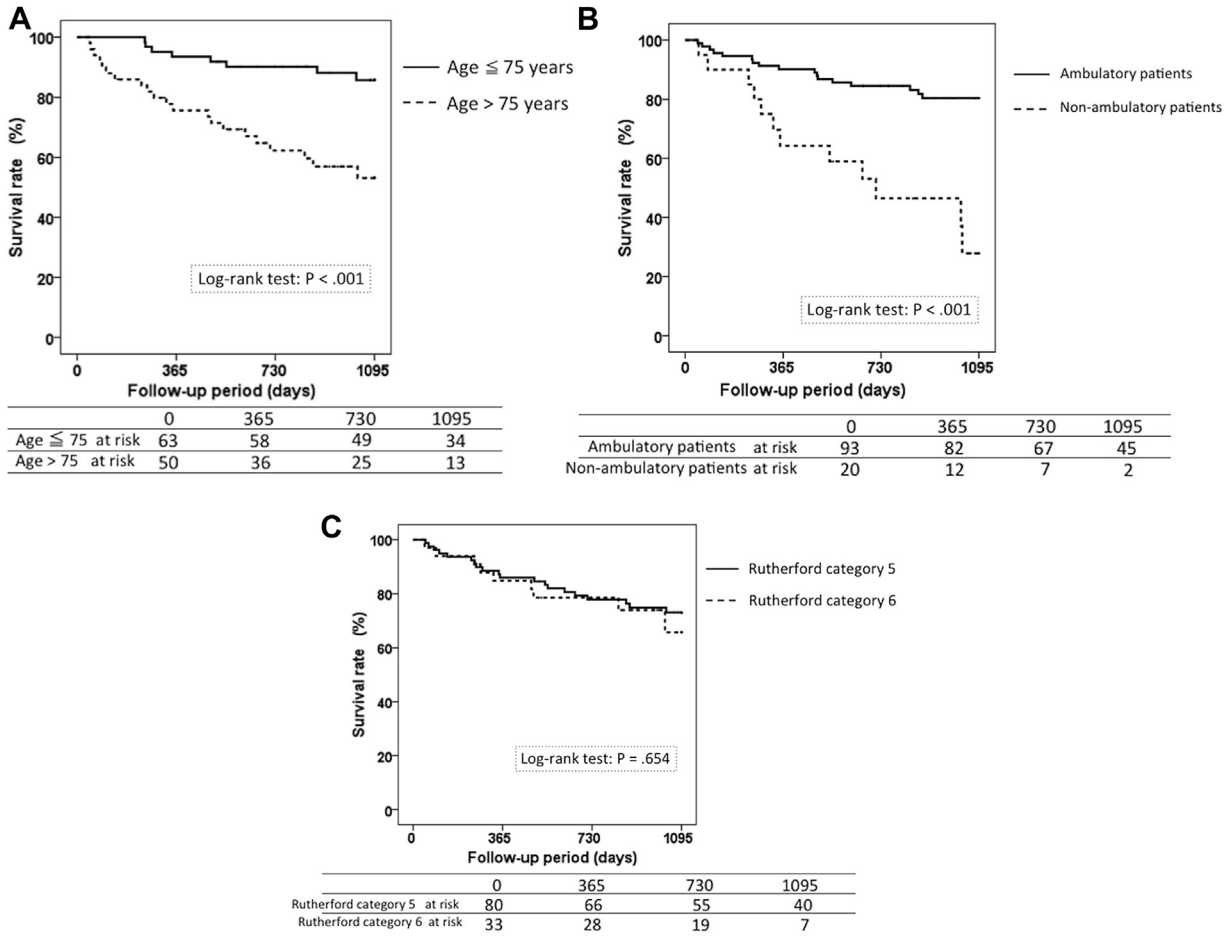


Fig 3. A, Survival rates of critical limb ischemia (CLI) patients at 3 years of follow-up according to age >75 years and <75 years. **B,** Survival rates of ambulatory CLI patients and nonambulatory CLI patients at 3 years of follow-up. **C,** Survival rates of CLI patients with Rutherford category 5 and Rutherford category 6 at 3 years of follow-up.

significant difference in the survival rate of CLI patients with vs without Rutherford category 6 after achievement of complete wound healing. Thus, once wound healing is achieved, the prognosis of CLI patients with Rutherford category 6 may not be inferior to that of CLI patients with Rutherford category 5. However, achievement of complete wound healing is reportedly difficult in CLI patients with Rutherford category 6.[9,10] It is therefore crucial to evaluate the possible treatment approaches to achieve complete wound healing in CLI patients with Rutherford category 6 in the future.

Advanced technologies should also be developed and used for improving wound healing rates.[27,28] Several studies have reported the use of new technologies such as drug-eluting balloons, stents, or debulking devices for improving patency rates.[29-31] However, we should also evaluate whether these devices can improve the clinical outcomes of CLI patients and not focus only on the patency rates. The most important aspect in the therapy of CLI patients is the treatment of the wounds themselves in addition to the narrowed vessels. Achieving complete wound healing eventually leads to the improvement of the limb salvage and survival rates. As there is a scarcity of studies investigating the efficacy of multidisciplinary therapy for CLI patients, more investigations into highly effective multidisciplinary therapy for CLI patients should be undertaken to improve not only the affected vessels but also the wound healing rate.

Limitations. First, this analysis was retrospectively conducted in a single center and the sample size was relatively small. However, few centers perform EVT and foot care by the same physicians; therefore, it was difficult to conduct a large-scale multicenter study. Second, in the present study, only wound healing patients were enrolled and wound nonhealing patients were excluded. Patients with wound healing may overall be much healthier or have better social support systems than patients with nonhealing wounds that may contribute to improved survival. In addition, we had a small number of patients who were not followed up, and therefore there was the lack of

face-to-face wound follow-up among these patients to confirm wound healing and recurrence. Third, although all of the patients achieved complete wound healing, the treatment course of wound healing was not standardized. More effective treatment strategies may be associated with shortening of the time to wound healing. However, little is known about the effects of time to wound healing on the clinical outcomes of CLI patients. Further investigation is needed to establish more effective wound care strategies. Fourth, although improvement of the QOL of CLI patients is important, we did not have data regarding QOL assessment using simple questionnaires such as EuroQol score, which assesses the patient's mobility, self-care, usual activity, pain or discomfort, and anxiety or depression.[32] Finally, we excluded all of the bypass cases; therefore, we could not compare the differences in the effects of wound healing achieved by EVT or bypass on the future survival rate. However, to the best of our knowledge, there are no studies that have compared the clinical outcomes of CLI patients after achievement of complete wound healing between EVT and bypass; thus, further research is warranted.

CONCLUSIONS

The clinical outcomes of CLI patients with tissue loss are known to be poor. However, the present study showed that the survival rate and limb salvage rate of CLI patients with tissue loss become acceptable after complete wound healing is achieved. Moreover, the prevalence rate of CLI recurrence was extremely low once wound healing was achieved. However, it seems apparent that older patients (age >75 years) and nonambulatory patients have poor survival rates even after achieving complete wound healing. Equally important to improving the survival rate of CLI patients is the improvement of their QOL. Wound healing is a valuable end point for CLI patients to improve their QOL. Therefore, focus should also be placed on how optimal wound care and ischemia treatment can be provided. As the importance of a multidisciplinary treatment approach cannot be underscored, more novel studies to investigate the types of multidisciplinary therapy that can considerably improve the wound healing rate and patients' QOL must be carried out, particularly for older CLI patients (age >75 years) and nonambulatory CLI patients.

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AUTHOR CONTRIBUTIONS

Conception and design: NK
Analysis and interpretation: YI, KH
Data collection: HI, MY
Writing the article: NK, YI
Critical revision of the article: KH, MN
Final approval of the article: NK, MN
Statistical analysis: RT
Obtained funding: TM
Overall responsibility: NK

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