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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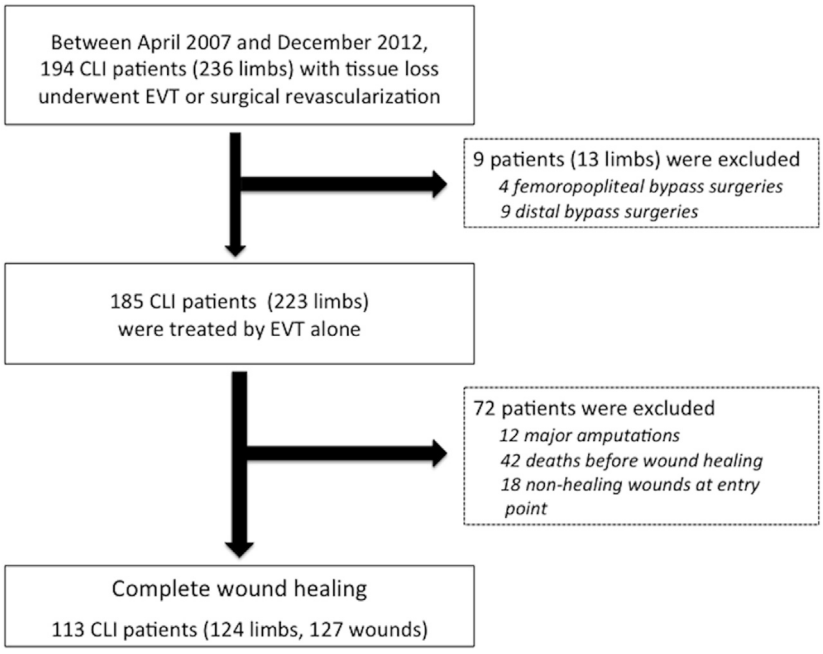

Fig 1. Overall participant flowchart of the study groups. *CLI,* Critical limb ischemia; *EVT,* endovascular therapy.

(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