Predictors of Delayed Wound Healing after Endovascular Therapy of Isolated Infrapopliteal Lesions Underlying Critical Limb Ischemia in Patients with High Prevalence of Diabetes Mellitus and Hemodialysis

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WHAT THIS PAPER ADDS
Acceptable limb salvage rates underlie wide use of endovascular therapy (EVT) for patients with critical limb ischemia secondary to isolated infrapopliteal lesions; however, delayed wound healing after revascularization remains a challenge. This study, involving 871 consecutive critically ischemic limbs, examines factors associated with delayed wound healing after EVT. Risk stratification based on these predictors allows wound healing rate estimation.

Objectives: Acceptable limb salvage rates underlie the widespread use of endovascular therapy (EVT) for patients with critical limb ischemia (CLI) secondary to isolated infrapopliteal lesions; however, post-EVT delayed wound healing remains a challenge. Predictors of delayed wound healing and their use in risk stratification of EVT in patients with CLI due to isolated infrapopliteal lesions are explored.

Methods: This was a retrospective multicenter study. 871 consecutive critically ischemic limbs were studied. There was tissue loss in 734 patients (age: 71 ± 10 years old; 71% male) who had undergone EVT between April 2004 and December 2012. The wound healing rate after EVT was estimated by the Kaplan—Meier method. The association between baseline characteristics and delayed wound healing was assessed by the Cox proportional hazard model.

Results: Diabetes mellitus and regular dialysis were present in 75% (553/734) and 64% (476/734) of patients, respectively; 67% of limbs (585/871) had Rutherford class 5 CLI; 8% (67/871) of wounds were located in the heel only; 25% (219/871) of limbs had Rutherford 6 (involving not only the heel); and 42% (354/871) of wounds were complicated by infection. The rate of freedom from major amputation at 1 year reached 88%, whereas the wound healing rate was 67%. Median time to wound healing was 146 days. By multivariate analysis, non-ambulatory status (hazard ratio [HR], 1.58; 95% confidence interval [CI] 1.31—1.91) serum albumin <3 g/dL (HR 1.42; 95% CI 1.08—1.86), Rutherford 6 (not only heel) (HR 1.68; 95% CI 1.33—2.14), wound infection (HR 1.24; 95% CI 1.03—1.50), EVT not based on angiosome concept (HR 1.28; 95% CI 1.06—1.55), and below the ankle (BTA) 0 vessel runoff after EVT (HR 1.45; 95% CI 1.14—1.86) were independent predictors of delayed wound healing.

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http://dx.doi.org/10.1016/j.ejvs.2015.01.017
Conclusions: Non-ambulatory status, low albumin level, Rutherford 6 (not only heel), wound infection, indirect intervention, and poor BTA runoff were independent predictors for delayed wound healing after EVT in patients with CLI secondary to infrapopliteal lesions, and their use in risk stratification allows estimation of the wound healing rate.

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Article history: Received 9 June 2014, Accepted 28 January 2015, Available online 4 March 2015

Keywords: Critical limb ischemia, Endovascular therapy, Angiosome concept, Wound healing, Risk factor stratification

INTRODUCTION

Critical limb ischemia (CLI), the most severe clinical manifestation of peripheral artery disease (PAD), is characterized by ischemic rest pain or the presence of ischemic tissue loss with or without gangrene. According to the Trans-Atlantic Inter-Society Consensus (TASC) II, the primary objectives of CLI treatment are to relieve ischemic pain, heal ischemic ulcers, prevent limb loss, improve patient function and quality of life (QOL), and prolong survival. When technically possible, revascularization, including bypass surgery (BSX) and endovascular therapy (EVT), are considered optimal treatments for patients with CLI in the latest PAD guidelines. Furthermore, EVT has become commonplace as the revascularization strategy for infrapopliteal lesions in patients with CLI because of comparable limb salvage rates to BSX and its less invasive nature. In the management of CLI with tissue loss, delayed wound healing not only lowers QOL but also increases medical costs, even if limb loss is successfully prevented.

For BSX, reports have documented 1 year wound healing rates in the 74–85% range, and median wound healing time of 173–186 days post procedure with regular dialysis, diabetes mellitus, low albumin level, non-ambulatory status, and Rutherford category 6 as predictors of delayed wound healing.

For EVT, the 1 year wound healing rate and median healing time were 54–86% and 97–145 days, respectively. Factors associated with delayed wound healing after EVT were diabetes mellitus, wound infection, below the ankle (BTA) runoff, and body mass index (BMI) < 18.5 kg/m².

Previous studies have been more limited in the outcomes examined and have not reported the risk stratification for wound healing, therefore in this study 871 limbs with ischemic tissue loss due to infrapopliteal lesions were analyzed to assess and risk stratify the wound healing rate and predictors after EVT.

MATERIALS AND METHODS

Study design

This study is a sub-analysis of J-BEAT (Japanese BElow the knee Artery Treatment registry: No. UMIN 000004917), a non-randomized multicenter study approved by the institutional review boards at all 14 participating cardiovascular and vascular institutions in Japan. The study protocol was developed in accordance with the Declaration of Helsinki and approved by the ethics committee of each participating hospital.

Participants

During the study period, 1316 limbs from 1078 CLI patients presenting with isolated infrapopliteal lesions were treated with plain balloon angioplasty. Patients with CLI without tissue loss (n = 321 limbs) were excluded from this analysis. Other exclusion criteria were (a) above ankle ischemic ulcer (n = 17 limbs); (b) failed EVT, defined as no below knee runoff vessel after EVT (n = 81 limbs); and (c) data missing on wound condition (n = 26 limbs). Finally, 871 limbs in 734 consecutive CLI patients who had undergone EVT for de novo infrapopliteal lesions were enrolled between April 2004 and December 2012.

The database excluded patients who were considered poor candidates for revascularization due to severe comorbidities and impairment at the functional (bedridden without intractable rest pain) and/or cognitive (dementia not requiring institutionalization) levels, or who refused revascularization. Although intervention was not attempted in patients with functionally unsalvageable limbs, non-ambulatory patients without cognitive problems were treated by angioplasty for limb salvage taking into consideration the patient’s preference, family cooperation, and lack of control of rest pain with analgesics.

Intervention

Indication and strategy for EVT were decided by consensus among vascular surgeons, interventional cardiologists, and interventional radiologists, depending on general condition, comorbidity and lower limb severity. Patients with >2 year life expectancy, and CLI patients with Rutherford 6 with good autogenous vein (diameter > 3 cm) were commonly selected for primary surgical bypass therapy.

All EVT procedures were performed under local anesthesia. Generally, a 3 or 4Fr sheath was used via an antegrade approach from the ipsilateral common femoral artery. After inserting the sheath, unfractionated heparin (5000 units) was routinely administered into the artery. A 0.014 inch guidewire was advanced into the culprit lesion and it was dilated using an optimally sized balloon catheter at the operator’s discretion. Basically, the diameter of the distal part of the healthy vessel was used as reference to decide balloon size. Stent, drug coated balloon, and atherectomy devices were not approved for use in infrapopliteal intervention in Japan.
Before endovascular intervention, the location of the non-healing ulceration/gangrene was confirmed and the angiosome based favorable target lesion was assessed by digital subtraction angiography. Angiosome oriented arterial recanalization was first attempted and if an angiosome based straight line was achieved other lesions with residual stenosis were not treated. However, if treatment of the angiosome based target lesions was unsuccessful, a non-angiosome oriented lesion was treated.

Antiplatlet therapy with aspirin (100 mg daily) and clopidogrel (75 mg daily) or cilostazol (100 mg twice daily) was started at least 1 week before EVT and continued for life.

**Follow up protocol**

All patients were followed up at 1 week, 1, 3, and 6 months after revascularization, and thereafter every 3 months. Overall and limb status, ankle—brachial index (ABI), and skin perfusion pressure (SPP) were routinely checked at follow up. SPP (Sensilase PAD 3000, Väsamed, Eden Prairie, MN, USA) was regularly measured at the dorsal and plantar sides of the foot. If a patient did not return to the hospital, limb status and patient’s general health were checked via phone interview (the last one applied in approximately 20% of cases).

**Wound management**

Wound status evaluation and wound care management were decided by plastic surgeons who evaluated and managed the ulcer using the TIME concept during follow up. TIME is an acronym for the following: T = tissue; I = infection or inflammation; M = moisture imbalance; E = edge of wound (non-advancing or undermined). Severity of wounds, especially of those infected, was carefully assessed by plastic surgeons who decided on indication for antibiotic therapy and amputation timing. Ulcer status and time to complete healing were recorded.

Repeat intervention was performed when delayed healing, worsening of the wound, or exacerbation of rest pain was recognized. A SPP <40 mmHg was defined as evidence of ischemia requiring re-intervention.

**Outcome measures and variables**

The outcome measures of this study were major amputation rate, complete wound healing rate, and median healing time after EVT. Factors associated with delayed wound healing after EVT were examined by multivariate analysis. Clinical variables found to influence wound healing in previous studies were inserted into the multivariate analysis.

The pre-procedural variables considered were age, sex, BMI, ambulatory status, Rutherford classification, presence of infection, diabetes mellitus, hypertension, dyslipidemia, regular hemodialysis, and serum albumin level as a nutritional marker.

The procedural variables considered in relation to outcome measures in this study were angiosome based EVT, the number of patent below knee and below ankle arteries after the procedure.

**Definitions**

Ischemic tissue loss was defined in accordance with TASC as tissue loss associated with ankle pressure <70 mmHg or a toe pressure <50 mmHg. When these measurements could not be obtained, SPP was measured. An SPP <40 mmHg was defined as indicating ischemic tissue loss. Major amputation means above ankle amputation. Complete wound healing was defined as achievement of complete epithelialization of all wounds without death or major amputation. Healing time was defined as time elapsed from initial EVT to complete epithelialization. Patients who died before wound healing was achieved were counted under delayed wound healing, with date of death as the cutoff date. In patients who underwent major amputation, the healing time was considered to be infinite. Delayed wound healing was defined as healing that took over 1 year, death before complete healing, or major amputation.

Wounds were classified according to the Rutherford classification. Rutherford 5 is minor tissue loss: non-healing ulcer, focal gangrene with diffuse pedal ischemia. Rutherford 6 is major tissue loss: extending above transmetatarsal level of functional foot, no longer limb salvageable or located at heel. In this study, Rutherford 6 was assigned to “not only heel” and “only heel” (Table 1).

Isolated infrapopliteal artery disease was defined as ischemia secondary to tibial lesions without any significant popliteal, femoral, iliac, and aortic lesions. Non-ambulatory status was defined as wheelchair bound or bedridden. The diagnosis of diabetes was based on World Health Organization criteria or on having been treated with insulin and/or an oral hypoglycemic agent. Hypertension was diagnosed as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg or having been treated for hypertension. Dyslipidemia was defined as serum low density lipoprotein (LDL) cholesterol ≥100 mg/dL or high density lipoprotein (HDL) cholesterol < 40 mg/dL or triglycerides ≥ 150 mg/dL, or having been treated for dyslipidemia.

Successful EVT was defined as < 25% residual stenosis without any flow reduction in target lesions on the final angiogram. Unsuccessful EVT was defined as failure to cross the lesion with guidewire or as ongoing flow reduction after
Table 2. Baseline characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics (n = 734)</th>
<th>Mean ± SD (n)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.9 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 80 years</td>
<td>155 (21)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>524 (71)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>21.6 ± 3.4</td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 18.5 kg/m²</td>
<td>135 (18)</td>
<td></td>
</tr>
<tr>
<td>Non-ambulatory status</td>
<td>329 (45)</td>
<td></td>
</tr>
<tr>
<td>Serum albumin</td>
<td>3.5 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Serum albumin &lt; 3.0 g/dL</td>
<td>165 (22)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>532 (72)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>287 (39)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>553 (75)</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>476 (64)</td>
<td></td>
</tr>
<tr>
<td>Lower limb characteristics (n = 871)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutherford classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutherford 5</td>
<td>585 (67)</td>
<td></td>
</tr>
<tr>
<td>Rutherford 6</td>
<td>286 (33)</td>
<td></td>
</tr>
<tr>
<td>Only heel</td>
<td>67 (8)</td>
<td></td>
</tr>
<tr>
<td>Not only heel</td>
<td>219 (25)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>364 (42)</td>
<td></td>
</tr>
<tr>
<td>EVT procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct intervention</td>
<td>546 (62)</td>
<td></td>
</tr>
<tr>
<td>Number of patent BTK runoff vessels after EVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>189 (22)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>312 (36)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>370 (42)</td>
<td></td>
</tr>
<tr>
<td>Number of patent BTA runoff vessels after EVT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>281 (32)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>373 (43)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>217 (25)</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; EVT = endovascular therapy; BTK = below the knee; BTA = below the ankle.

balloon angioplasty. At the time of final angiography, EVT success or failure was judged by the chief operator. Direct EVT referred to successful revascularization based on the angiosome concept, whereas indirect EVT was that achieved not based on this concept.15–17 Repeat EVT was defined as target limb EVT. The number of below knee runoff vessels was 0–3 based on anterior tibial, peroneal, and posterior tibial arteries. The number of below ankle runoff vessels ranged from 0 to 2 based on the dorsal pedis and lateral plantar arteries.

Statistical analysis

Data are expressed as mean and standard deviation for continuous variables or as percentage for dichotomous variables, unless otherwise mentioned. The survival rate and rates for major amputation and wound healing were assessed with the Kaplan–Meier method. Univariate and multivariate Cox proportional hazards regression models were used to investigate the un-adjusted and adjusted association of pre-procedural and procedural variables with complete wound healing, respectively. The developed risk stratification was identified from the variables independently associated with delayed wound healing in this study. The sensitivity and specificity for major limb amputation were calculated by time dependent receiver operating characteristic curve analyses.18 Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Variables with statistical significance in the multivariate model were determined as independent risk factors for outcome. A p value < .05 was considered significant. Statistical analyses were performed with SPSS version 15.0J (SPSS Inc., Chicago, IL, USA).

RESULTS

As shown in Table 2, the mean age was 71 ± 10 years, and 21% (155/734) of study participants were octogenarians; 524 patients (71%) were male. The average BMI was 21.6 ± 3.4, and the prevalence of emaciation (BMI < 18.5) was 18% (135/734). The mean serum albumin level was 3.5 ± 0.6 g/dL, with 22% (165/734) of patients having low albumin levels (< 3 g/dL). Notable comorbidities included diabetes mellitus (75%; 553/734), followed by regular dialysis dependence (64%; 476/734). Regarding limb condition, the mean SPP before and up to 48 hours after EVT was 31 ± 17 mmHg and 49 ± 22 mmHg, respectively (data not shown). The fact that over 60% of the patients were on dialysis, which was associated with calcification, may account for the falsely high ABI. Rutherford 5 was observed in 67% (585/871) of limbs, and Rutherford 6 in 286 limbs (33%). Among Rutherford 6 limbs, the wound was located in only the heel in 8% (67/871), and also elsewhere in 25% (219/871). Wound infection was complicated in 42% (364/871) of ischemic limbs. Aspirin was prescribed in 80% of patients. Thienopyridines and cilostazol were prescribed in 35% and 51% of patients, respectively. Statins were prescribed in 22% of patients with CLI (data not shown). Regarding the EVT procedure, direct intervention was performed in 62% of limbs (546/871).

The mean follow up after EVT was 21 ± 19 months. One year follow up was completed in 826 limbs (94.8%). A quarter of patients died within 1 year of EVT, and for the 1 year follow up 50% of the initial study population returned to the outpatient clinic and 20% were interviewed via phone calls; 5% of patients were lost to follow up.

Prognosis of patients with critical limb ischemia

Survival rate after EVT was 74.7% at 1 year, and 61.7% at 2 years.

Prognosis of critically ischemic limbs after EVT

The rate of freedom from major amputation for limbs in the Rutherford 5 category was 93% and 91% at 1 and 2 years after EVT, respectively. Rutherford 6 limbs had a worse prognosis than Rutherford 5 (1 year freedom from major amputation: 75%; 2 years: 74%; p < .001; Fig. 1).

Fig. 2 shows the cumulative wound healing rate after EVT according to limb stratification based on Rutherford category (Rutherford 5, Rutherford 6 [only heel], Rutherford 6 [not only heel]); 73% of limbs achieved wound healing 1 year after EVT for Rutherford 5. The wound healing rate after EVT was not significantly different between Rutherford
Predictors of delayed wound healing after EVT

As shown in Table 3, univariate analysis revealed significant association with delayed wound healing for the following variables: non-ambulatory status, albumin <3 g/dL, Rutherford 6 (not only heel), wound infection, indirect intervention, one below knee vessel runoff, and zero and one below ankle vessel runoff. In multivariate analysis, non-ambulatory status, albumin <3 g/dL, Rutherford 6 (not only heel), wound infection, indirect EVT, and zero below ankle vessel runoff were independent risk factors of wound healing after initial EVT.

Risk stratification for wound healing based on the multivariable Cox proportional hazard model

Patients were assigned to one of three risk groups based on number of risk factors (0 or 1 risk factor was defined as a low risk group; 2 or 3 as moderate; and 4, 5, or 6 as high), with risk factors including non-ambulatory status, low albumin level, Rutherford 6 (not only heel), wound infection, indirect EVT, and zero below ankle vessel runoff (Fig. 3). The cumulative wound healing rate at 12 months after EVT was as follows: low risk group, 79%; moderate, 62%; and high, 33% (p < .01 for each comparison). Limbs in the high risk group (number of risk factors = 4, 5, or 6) had a higher rate of major amputation than those in the low or moderate risk groups (number of risk factors = 0, 1, 2, or 3) (66.9% and 90.5% at 1 year after EVT; p < .01). The sensitivity and specificity for major limb amputation in the high risk group were calculated to be 32.4% and 89.5%, respectively.

DISCUSSION

Freedom from major amputation 1 year after EVT was achieved in 88% of patients with CLI secondary to isolated infrapopliteal lesions. On the other hand, the cumulative wound healing rate at 1 year after the initial EVT remained 66%. The median wound healing time after EVT was 146 days overall, and 350 days for Rutherford 6. Pre-operative factors associated with delayed wound healing were non-ambulatory status, low albumin level, wound extending to the transmetatarsal level, and wound infection. Angiome- some targeted EVT and number of below ankle runoff vessels were identified as procedure independent predictors for wound healing.
these predictors allows estimation of wound healing after EVT in patients with ischemic tissue loss.

In this analysis, only technically successful revascularization cases were enrolled. The rate of EVT failure was 8.5% (81/952). Comparison of intention to treat (i.e., including EVT failure cases) and as treated (i.e., excluding EVT failure cases) data revealed no significant difference between the two groups with respect to major amputation (85.7% and 87.6% at 1 year after EVT, \( p = 0.22 \)), and wound healing rate (66.7% and 63.7% at 1 year after EVT, \( p = 0.19 \)).

Previous studies have reported time to wound healing and wound healing rates after revascularization. After EVT for CLI with tissue loss, a 54–86% cumulative wound healing rate at 1 year was achieved (median time to wound healing: 97–145 days). The time to wound healing after bypass surgery (173–186 days) was longer than that for EVT because the proportion of Rutherford 6 was higher in BSX studies than EVT studies. In this study, wound healing for Rutherford 6 CLI took twice as many days as that for Rutherford 5.

Serum albumin <3 g/dL was strongly associated with delayed wound healing in the current study. Azuma et al. also reported albumin <3 g/dL as a negative predictor for wound healing after bypass surgery; however, it is unknown whether hypoalbuminemia was caused by inflammation or malnutrition.

In previous reports, wound infection was associated with delayed wound healing. In this study, the major amputation rate after EVT was significantly different between wounds with, versus without infection (20% vs. 7%, respectively); the wound healing rate was also significantly different between the two groups (57% vs. 73%, respectively). Wounds extending to the transmetatarsal level and complicated by infection demonstrated poor outcomes: 1 year wound healing and amputation rates of 43% and 33%, respectively (data not shown). Rutherford category 6 with heel ulcer/gangrene was an independent predictor of delayed wound healing after BSX. In a previous report on diabetic ulcers, ulcer location influenced ulcer healing, with time to wound healing increasing progressively from toe to mid-foot to heel, which differs from the findings in this study. Size and depth of the wound were not recorded, rendering it difficult to compare previous reports on diabetic patients with the current results.
A high restenosis rate in infrapopliteal lesions after EVT using plain balloon angioplasty has been reported previously. A high restenosis rate in infrapopliteal lesions after EVT using plain balloon angioplasty has been reported previously. A high restenosis rate in infrapopliteal lesions after EVT using plain balloon angioplasty has been reported previously. Although infrapopliteal drug coated balloon angioplasty appeared to reduce restenosis as compared with traditional balloon angioplasty in one study with design limitations, in a high quality study, including independent angiographic and wound core laboratory assessments, a drug coated balloon did not improve either vessel or limb prognosis compared with plain balloon angioplasty. Further investigation is warranted to determine the population of patients who would benefit from intervention with drug coated balloons.

### Limitations

This was a sub-analysis of the J-BEAT trial, involving retrospective analysis of registry data. Only Japanese CLI patients, who are characterized by a high proportion of dialysis dependence, were included in this study. Patients with CLI who did not receive EVT were not included in this study; because of the retrospective nature of this study, the number of CLI patients who underwent primary surgical bypass could not be accurately determined. Although predictors for delayed wound healing by multivariate analysis using pre-procedural (some assessed at procedure time after choosing intervention modality) and post-procedural factors were examined, a risk score to predict which CLI patients would benefit most from EVT versus bypass surgery remains to be determined.

Heterogeneity in wound management practice among facilities was also a limitation in this retrospective analysis. Assessment of the success of EVT by attending physicians

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### Table 3: Univariate and multivariate analyses: predictors of delayed wound healing after EVT in patients with CLI due to isolated infrapopliteal lesions.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis HR (95% CI)</th>
<th>p</th>
<th>Multivariate analysis HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 80 years</td>
<td>0.93 (0.75—1.14)</td>
<td>0.519</td>
<td>0.88 (0.71—1.10)</td>
<td>0.282</td>
</tr>
<tr>
<td>Male</td>
<td>0.95 (0.79—1.14)</td>
<td>0.630</td>
<td>0.98 (0.79—1.20)</td>
<td>0.855</td>
</tr>
<tr>
<td>BMI &lt; 18.5 kg/m²</td>
<td>1.69 (1.35—2.17)</td>
<td>0.778</td>
<td>1.02 (0.80—1.28)</td>
<td>0.863</td>
</tr>
<tr>
<td>Non-ambulatory status</td>
<td>1.25 (1.03—1.51)</td>
<td>&lt;0.001</td>
<td>1.58 (1.31—1.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.04 (0.82—1.29)</td>
<td>0.979</td>
<td>0.98 (0.80—1.19)</td>
<td>0.852</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.96 (1.63—2.38)</td>
<td>0.905</td>
<td>0.97 (0.81—1.16)</td>
<td>0.779</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1.00 (0.83—1.20)</td>
<td>0.359</td>
<td>1.08 (0.87—1.32)</td>
<td>0.460</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>0.86 (0.72—1.02)</td>
<td>0.078</td>
<td>1.11 (0.91—1.34)</td>
<td>0.282</td>
</tr>
<tr>
<td>Albumin &lt;3 g/dL</td>
<td>1.09 (0.90—1.33)</td>
<td>&lt;0.001</td>
<td>1.42 (1.08—1.86)</td>
<td>0.010</td>
</tr>
<tr>
<td>Tissue Loss (versus Rutherford 5)</td>
<td>1.00 (Ref.)</td>
<td></td>
<td>1.00 (Ref.)</td>
<td></td>
</tr>
<tr>
<td>Rutherford 6 (only heel)</td>
<td>1.16 (0.98—1.38)</td>
<td>0.051</td>
<td>1.11 (0.79—1.56)</td>
<td>0.538</td>
</tr>
<tr>
<td>Rutherford 6 (not only heel)</td>
<td>1.72 (1.33—2.22)</td>
<td>&lt;0.001</td>
<td>1.68 (1.33—2.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1.38 (1.00—1.92)</td>
<td>&lt;0.001</td>
<td>1.24 (1.03—1.50)</td>
<td>0.021</td>
</tr>
<tr>
<td>Indirect intervention</td>
<td>2.22 (1.78—2.77)</td>
<td>&lt;0.001</td>
<td>1.28 (1.06—1.55)</td>
<td>0.008</td>
</tr>
<tr>
<td>BTK runoff after EVT (versus 3 runoffs)</td>
<td>1.00 (Ref.)</td>
<td></td>
<td>1.00 (Ref.)</td>
<td></td>
</tr>
<tr>
<td>2 runoff vessels</td>
<td>1.63 (1.36—1.96)</td>
<td>0.480</td>
<td>0.92 (0.72—1.16)</td>
<td>0.502</td>
</tr>
<tr>
<td>1 runoff vessel</td>
<td>1.44 (1.20—1.72)</td>
<td>0.018</td>
<td>1.04 (0.81—1.33)</td>
<td>0.718</td>
</tr>
<tr>
<td>BTA runoff after EVT (versus 2 runoffs)</td>
<td>1.00 (Ref.)</td>
<td></td>
<td>1.00 (Ref.)</td>
<td></td>
</tr>
<tr>
<td>1 runoff vessel</td>
<td>1.08 (0.86—1.35)</td>
<td>0.021</td>
<td>1.14 (0.93—1.41)</td>
<td>0.190</td>
</tr>
<tr>
<td>0 runoff vessel</td>
<td>1.29 (1.04—1.61)</td>
<td>&lt;0.001</td>
<td>1.45 (1.14—1.86)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BMI = body mass index; EVT = endovascular therapy; BTK = below the knee; BTA = below the ankle; HR = hazard ratio; CI = confidence interval.
was not blinded, which might introduce bias. Information on wound nature (ulcer and gangrene), width and depth, or on wound brush and pedal arch status after EVT was not collected. The data in this study were not separated into training and test sets to develop and to assess, respectively, the validity of predictive risk stratification. The current findings therefore should be externally validated in settings with similar sample characteristics. It remains to be determined if the developed model can be validated in the general population sampled independently. Information on medical therapy used after revascularization was collected only for antiplatelet and statin medication. Compliance and discontinuation rates or other details of medication use during follow up could not be determined.

CONCLUSIONS
The wound healing rate was acceptable after EVT and similar to those in earlier studies. Non-ambulatory status, low albumin level, Rutherford 6 (not only heel), wound infection, indirect intervention, and poor below ankle runoff were independent predictors for delayed wound healing after EVT in CLI patients due to infrapopliteal lesions. Risk stratification allows estimation of wound healing rate.

CONFLICT OF INTEREST
None.

FUNDING
None.

REFERENCES
Predictors of Delayed Wound Healing after EVT

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