Clinical efficacy of endovascular therapy for patients with critical limb ischemia attributable to pure isolated infrapopliteal lesions

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Background: **Prognosis of endovascular therapy (EVT) for isolated infrapopliteal lesions has not been adequately studied. We investigated and risk-stratified long-term prognosis after EVT for critical limb ischemia (CLI) attributable to isolated infrapopliteal lesions.**

Methods: **Between March 2004 and October 2010, 884 patients (1057 limbs) with CLI attributable to isolated infrapopliteal lesions who underwent EVT with angioplasty alone were enrolled. Outcome measures were freedom from major adverse limb events with perioperative death (MALE+POD) and amputation-free survival. Cox proportional hazards models were used to assess independent predictors for these outcomes.**

Results: **Freedom from MALE+POD was 82 ± 1% and 74 ± 2% at 1 and 5 years, respectively. Risk factors associated with MALE+POD were age ≥80 years (adjusted hazard ratio [HR], 0.4; $P < .001$), nonambulatory status (HR, 2.0; $P < .001$), albumin <3.0 g/dL (HR, 1.4; $P < .0001$), Rutherford 6 (HR, 2.2; $P < .001$), C-reactive protein ≥3.0 mg/dL (HR, 2.1; $P < .001$), and below-the-ankle disease (HR, 2.0; $P < .001$). One- and 5-year amputation-free survival was 71 ± 2% and 38 ± 3%, respectively. Risk factors associated with major amputation/mortality were nonambulatory status (adjusted HR, 2.1; $P < .001$), body mass index <18.5 kg/m^2 (HR, 1.4; $P = .02$), albumin <3.0 g/dL (HR, 1.8; $P < .0001$), end-stage renal disease (HR, 1.4; $P = .004$), ejection fraction <50% (HR, 1.6; $P < .001$), Rutherford 6 (HR, 1.9; $P < .001$), C-reactive protein ≥3.0 mg/dL (HR, 1.7; $P < .0001$), and below-the-ankle disease (HR, 1.8; $P < .001$). In patients with more than four risk factors, both end points at 1 year were below the 71% suggested efficacy objective performance goal.**

Conclusions: **Long-term clinical outcomes were acceptable after EVT for patients with CLI due to pure isolated infrapopliteal lesion. Risk stratification by baseline characteristics is useful in estimating long-term prognosis. (J Vasc Surg 2013;57:974-81.)**

Developments in endovascular therapy (EVT) have raised expectations for improvement of the traditionally poor prognosis of critical limb ischemia (CLI) associated with infrapopliteal lesions.[1-4] In particular, primary angioplasty is now widely used for the treatment of infrapopliteal arterial lesions in CLI patients; according to the latest American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and European Society of Cardiology (ESC) Guidelines on the management of peripheral artery diseases, EVT is now considered the acceptable therapeutic modality to treat patients with CLI attributable to infrapopliteal lesions because of its favorable clinical outcome at a lower procedural cost compared with open bypass therapy (BSX).[5-8]

Despite its wide acceptance, the prognosis of EVT for isolated infrapopliteal lesions has not been adequately studied. To this end, outcomes combining life and limb prognosis, the commonest of which are amputation-free survival (AFS) and freedom from major adverse limb events (MALE) including amputation or major reintervention or perioperative death (POD), are regarded as inherent measures of prognostic effectiveness for revascularization of CLI patients. Moreover, based on analysis of three major randomized trials, Conte and colleagues have proposed a 71% rate as an objective performance goal (OPG) for both AFS and freedom from MALE+POD in catheter-based therapies.[9]

Prognosis of CLI patients undergoing EVT for pure isolated infrapopliteal lesions, therefore, would need to be compared against the aforementioned reference goals. However, common comorbidities in CLI patients profoundly influence prognostic outcomes.[10] Diabetes mellitus (DM) and end-stage renal disease (ESRD), for instance,[11] are both present in high proportions and are well known as independent predictors for poor prognosis in CLI patients; they are also independent risk factors for

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the progression to CLI especially when associated with infrapopliteal lesions.[12] Considerable inter-patient variation in prognosis of CLI patients with infrapopliteal lesion would be expected with poorer or better prognosis respectively in the presence or absence of particular comorbidities. Stratification of patients according to their prognostic risk, therefore, would be clinically relevant.

The aims of our current study were to (1) investigate prognostic risk factors associated with AFS and MALE+POD in CLI patients undergoing EVT for pure isolated infrapopliteal arterial lesions; and (2) assess the prognostic outcomes of these patients after stratification according to the number of risk factors present.

METHODS

Participants. We retrospectively analyzed our prospectively maintained database including data on 2519 limbs in 2141 consecutive CLI patients who underwent EVT from April 2004 to June 2011 and who consented to follow-up at each of the 11 participating cardiovascular and vascular centers. To elucidate long-term clinical efficacy and stratify the risk for EVT outcomes, this study included patients with CLI attributable to pure isolated infrapoliteal lesions who underwent endovascular reconstruction. We excluded patients with involved popliteal and above popliteal revascularization. During this period, patients with CLI attributable to infrapopliteal lesions combined with either femoropopliteal lesions (47%, 1198 limbs in 1025 patients) or aortoiliac-femoropopliteal lesions (10%, 264 limbs in 232 patients) were excluded from this study. We also excluded 170 patients considered to be poor candidates for both forms of revascularization because of severe comorbidities and impairment at the functional, cognitive, and/or social (no family or professional career) levels; who refused revascularization; or who presented with acute limb ischemia requiring emergent revascularization or with functionally unsalvageable limbs. Finally, 1057 limbs from 884 consecutive CLI patients suffering from rest pain attributable to ischemia (Rutherford 4), or limb-threatening nonhealing ulceration/gangrene (Rutherford 5 or 6) attributable to pure isolated infrapopliteal lesions were included. During the study period, 375 CLI patients were treated with crural BSX by a vascular surgeon. Forty-four percent of limbs (n = 465) with isolated infrapopliteal lesion overlapped with a previous study.[10] The study protocol was developed in accordance with the Declaration of Helsinki and approved by the ethics committee of each participating hospital. This study was registered in the University Hospital Medical Information Network Clinical Trial Registry, which was approved by the International Committee of Medical Journal Editors (No UMIN000007016, Japanese Below-the-Knee Artery Treatment Registry II). All patients gave written informed consent prior to revascularization.

Study protocol. The study protocol was reported previously.[10] Briefly, lower limb severity was hemodynamically assessed by the ankle-brachial index and skin perfusion pressure (SPP). Lower limb arteries were routinely evaluated by duplex ultrasound, and presence of infrapopliteal lesions was assessed by digital subtraction angiography before revascularization. A group of vascular specialists including vascular surgeons and radiologists judged whether EVT was indicated for each patient. All endovascular procedures were conducted under local anesthesia. EVT was indicated when the lesion showed >75% diameter stenosis on diagnostic angiography and was hemodynamically significant. Selection of EVT approach was at operator's discretion. An antegrade approach with a 4F sheath from the ipsilateral common femoral artery was most commonly used. After inserting the sheath, unfractionated heparin (5000 U) was routinely injected into the artery. A 0.014-inch guidewire was advanced into the culprit lesion, and an optimally sized balloon catheter was introduced. Vessel diameter and lesion length were visually assessed using the balloon catheter as reference. A 100-mm- or 120-mm-long balloon (Shiden; Kaneka Medix Corporation, Osaka, Japan, or Amphillion; Medtronic, Minneapolis, Minn) was commonly used and balloon inflation was held at nominal pressure for at least 180 seconds to avoid flow limiting dissection. Bare-metal or drug-eluting stents and atherectomy devices were not used because of unavailability in Japan. Target lesion was chosen based on lesion and limb severity. In patients with tissue loss, target lesion was decided by the angiosome concept,[13] and easily treatable lesions were commonly selected in patients with rest pain. Dual antiplatelet therapy (aspirin at 100 mg/d and ticlopidine at 200 mg/d or cilostazol at 200 mg/d) was started at least 1 week prior to EVT and continued lifelong. Antibiotics were routinely administered if the ulcer was complicated with limb threatening severe infection as judged by a plastic surgeon who in these cases evaluated and managed the ulcer using the TIME concept (Tissue, Infection, Moisture Imbalance, Edge of Wound).[14]

All patients were followed up at 1 week, and at 1, 3, and 6 months after revascularization, and thereafter every 3 months. If a patient did not come to the hospital, telephone calls were made to check limb status and the patient's general health. At the time of follow-up, noninvasive testing, including ankle-brachial index, SPP, and duplex, was routinely conducted.

Study outcomes. The outcome measures were freedom from MALE+POD and AFS. We also assessed 30-day mortality and major amputation rate as safety outcomes, as proposed by the Society of Vascular Surgery.[9]

Definitions. The definitions of lower limb severity and the criteria for diagnosis of atherosclerosis risk factors have been reported previously.[11] Critical ischemic limb was defined in accordance with TransAtlantic Inter-Society Consensus (TASC) guideline.[2] When these measurements could not be obtained because of intractable rest pain or a noncompressible artery secondary to severe calcification, the SPP was measured; an SPP less than 40 mm Hg was defined as indicating a critical ischemic limb. Coronary artery disease and cerebrovascular disease was defined as the presence of symptom or past history of infarction or history of any revascularization. Below-the-ankle (BA) disease was defined as presence of a diseased arterial lesion at the dorsalis pedis or plantar artery. Treated lesion with widest limb perfusion area was identified as target lesion in this study. EVT procedural success was defined as obtaining one straight-line flow to the foot without occurrence of any flow limiting dissection. Reintervention including repeat angioplasty or bypass graft procedures were indicated for limbs with recurrent symptoms accompanied by recurrent stenosis greater than 50% as measured by duplex ultrasound or digital subtraction angiography. Perioperative death was defined as death occurring within 30 days. MALE was defined as major amputation or any major reintervention during the study period. Major reintervention included new bypass graft, jump, interposition graft revision, or the use of thrombectomy or thrombolysis in stents upon loss of primary assisted patency. Minor reintervention was defined as endovascular procedures (percutaneous transluminal angioplasty, atherectomy, stenting) without thrombectomy or thrombolysis, and minor surgical revisions (patch angioplasty). Major amputation was defined as surgical excision of the limb above the ankle. Any amputation at or distal to the Lisfranc level was not considered a limb salvage failure. Amputation data were obtained through outpatient clinic follow-up contact. AFS was defined as major amputation or death.

Statistical analysis. Data are presented as mean ± SD for continuous variables and as percentages for dichotomous variables unless mentioned otherwise. Prognostic outcomes were assessed with the Kaplan-Meier method, and differences among groups with the log-rank test when necessary; their 1-year incidence is reported with the respective SE. Univariate Cox proportional hazards regression model was used to determine the unadjusted association of each variable with the outcomes. The statistically significant variables in the univariate analyses were entered into multivariate models to assess their independent impact on the outcome. We developed two multivariate models for each outcome: models into which all the significant explanatory variables in prior univariate models were entered (model 1), and those into which the variables were entered using a stepwise method (model 2). Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. We subsequently conducted risk stratification analysis for each outcome using a simple score based on the number of independent variables. A *P* value of <.05 was considered significant. Statistical analyses were performed using SPSS v. 15.0J (SPSS Inc, Chicago, Ill).

RESULTS

Table I shows baseline characteristics of the study population. Notable baseline characteristics included mean patient age of 71 ± 10 years, and high prevalence of DM (71%; 627/884) and ESRD on dialysis (62%; 546/884). Regarding limb status, 74% (781/1057) of limbs were complicated with tissue loss. Ninety percent of lesions were TASC 2000 D, and BA disease, defined as presence of a diseased arterial lesion at the dorsalis pedis or plantar artery, was observed in 63% of cases. Follow-up period was 17 ± 17 months (1.4 ± 1.4 years), and 330 of the 884 patients underwent major amputations or mortality, whereas MALE+POD was seen with 191 of 1057 limbs.

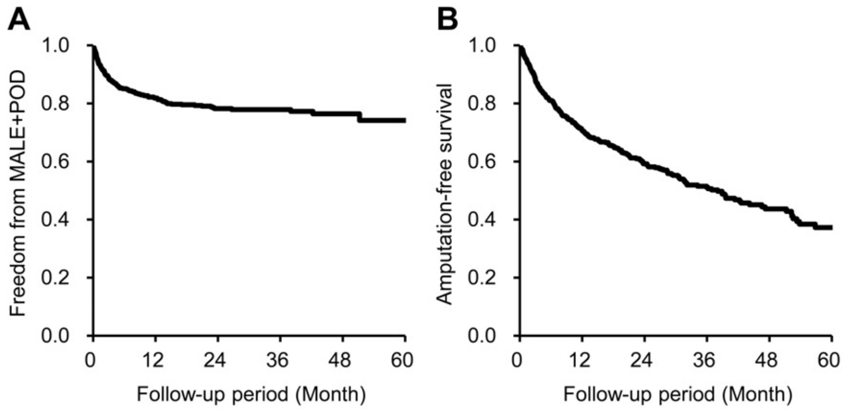
Table I. Baseline characteristics of study population

Variables	
Patients status (n = 884)	
Age, years	71 ± 10
Male sex	69% (612)
BMI	22 ± 3
Albumin, g/dL	3.5 ± 0.6
Nonambulatory	38% (338)
Risk factors	
Hypertension	73% (647)
Hyperlipidemia	61% (540)
Diabetes mellitus	71% (627)
Current smoking	36% (318)
ESRD (Cr ≥2.0 mg/dL)	64% (564)
EF, %	59 ± 14
Lower limb and lesion status (n = 1057)	
Tissue loss (Rutherford 5, 6)	74% (781)
Rutherford 6	19% (195)
CRP, mg/dL	2.7 ± 4.2
ABI before angioplasty	0.81 ± 0.25
SPP at dorsalis pedis side/plantar side, mmHg	32 ± 17/35 ± 19
TASC A/B/C/D	3% (32)/1% (13)/7% (67)/90% (945)
Lesion calcification	65% (682)
Target lesion length, mm	190 ± 96
Number of BTK run-offs before angioplasty/after angioplasty	0.50 ± 0.68/1.8 ± 0.8
BA disease before angioplasty	59% (627)

ABI, Ankle-brachial index; *BA,* below-the-ankle; *BTK,* below-the-knee; *BMI,* body mass index; *Cr,* creatinine; *CRP,* C-reactive protein; *EF,* ejection fraction; *ESRD,* end-stage renal disease; *TASC,* TransAtlantic Inter-Society Consensus; *SPP,* skin perfusion pressure.
Number of BTK run-offs before angioplasty was defined as the number of patent run-offs to the ankle.

Thirty-day safety outcomes. Procedural success, defined as obtaining one straight-line flow to the foot, was achieved in 95% (1009/1057) of limbs. Rate of perioperative death following EVT was 3% (26/884); 58% (15/26) of patients died from cardiovascular disease within 30 days. Cardiac death was the most frequent cause of death (50%; 13/26) in these CLI patients. In 31% (8/26), cause of death was attributed to infectious disease. Major amputation was conducted in 1% (14/1057) of limbs within 30 days.

Freedom from MALE+POD and its associated factors (Fig 1, *A* and Table II). Freedom from MALE+POD was 82 ± 1%, 79 ± 2%, and 74 ± 2% at 1, 3, and 5 years, respectively. Predictors for MALE+POD were age ≥80 years (HR, 0.4; 95% CI, 0.3-0.7; *P* < .001) nonambulatory status (HR, 2.0; 95% CI, 1.5-2.7; *P* < .001), albumin <3.0 g/dL (HR, 1.4; 95% CI, 1.0-2.0; *P* < .0001), Rutherford 6 (HR, 2.2; 95% CI, 1.6-3.1; *P* < .001), CRP ≥ 3.0 mg/dL (HR, 2.1; 95% CI, 1.6-3.1; *P* <



	0	12	24	36	48	60
at risk	1057	497	267	136	70	29
%	100	81.9	78.2	77.9	76.4	74.1
SE	0.000	0.013	0.015	0.015	0.018	0.024

	0	12	24	36	48	60
at risk	884	422	232	118	60	24
%	100	70.6	59.2	51.1	43.7	37.3
SE	0.000	0.017	0.020	0.023	0.027	0.032

Fig 1. **A,** Freedom from major adverse limb events with perioperative death (*MALE+POD*) after angioplasty for 1057 critical ischemic limbs because of pure isolated infrapopliteal lesions. Overall freedom from MALE+POD was 82 ± 1%, 79 ± 2%, and 74 ± 2% at 1, 3, and 5 years, respectively. **B,** Amputation-free survival (AFS) after angioplasty for 884 patients with critical limb ischemia (CLI) due to pure isolated infrapopliteal lesions. AFS was 71 ± 2%, 51 ± 2%, and 37 ± 3% at 1, 3, and 5 years, respectively. *SE,* Standard error.

.001), and BA disease (HR, 2.0; 95% CI, 1.4-2.8; $P < .001$). Freedom from MALE+POD was stratified according to number of these risk factors (Fig 2). Note that since the HR of age ≥80 years was smaller than 1, we regarded age <80 years as a risk factor in the risk stratification. Freedom from MALE+POD was lower in the higher risk groups (1-year rates by number of risk factors: 0-1, 94 ± 1%; 2, 89 ± 2%; 3, 80 ± 3%; 4, 63 ± 5%; and 5-6, 40 ± 6%, respectively; $P < .001$).

AFS and its associated factors (Fig 1, *B* and Table III). Fig 1, *B* shows 5-year AFS. AFS was 71 ± 2%, 51 ± 2%, and 37 ± 3% at 1, 3, and 5 years, respectively. Results of the multivariate Cox proportional hazard regression analysis for AFS are shown in Table III. Nonambulatory status (HR, 2.1; 95% CI, 1.7-2.7; $P < .001$), BMI <18.5 kg/m^2 (HR, 1.4; 95% CI, 1.1-1.8; $P = .02$), albumin <3.0 g/dL (HR, 1.8; 95% CI, 1.4-2.3; $P <$ .0001), ESRD (HR, 1.4; 95% CI, 1.1-1.8; $P = .004$), ejection fraction <50% (HR, 1.6; 95% CI, 1.2-2.0; $P <$ .001), Rutherford 6 (HR, 1.9; 95% CI, 1.4-2.4; $P < .001$), CRP ≥3.0 mg/dL (HR, 1.7; 95% CI, 1.3-2.2; $P < .0001$), and BA disease (HR, 1.8; 95% CI, 1.4-2.3; $P < .001$) were associated with major amputation and mortality. Fig 3 shows the stratification of AFS according to number of these risk factors. The AFS was lower in the higher risk groups (1-year rates by number of risk factors: 0-1, 90 ± 2%; 2, 83 ± 3%; 3, 70 ± 4%; 4, 59 ± 5%; and 5-8, 25 ± 4%, respectively; $P < .001$).

Overall survival, limb salvage, and freedom from any reintervention rate up to 5 years (Supplementary Figs 1-3, online only). Overall survival was 78 ± 2%, 59 ± 2%, and 43 ± 3% at 1, 3, and 5 years, respectively. Limb salvage rate was 89 ± 1%, 86 ± 1%, and 85 ± 2% at 1, 3, and 5 years, respectively. Almost all major amputations were performed before 1 year. Freedom from any reintervention including minor or major reintervention was 66 ± 2%, 52 ± 2%, and 47 ± 3% at 1, 3, and 5 years, respectively. During the chronic phase, 5.4% (57/1057) of limbs underwent surgical conversion after initial EVT and re-angioplasty was done for 31% (328/1057) of limbs. Finally, MALE-free survival is shown in Supplementary Fig 4 (online only). MALE-free survival was 66 ± 2%, 49 ± 2%, and 33 ± 3% at 1, 3, and 5 years, respectively.

DISCUSSION

In this multicenter study including a large number of patients with CLI attributable to pure isolated infrapopliteal lesions, freedom from MALE+POD and AFS rate at 5 years after infrapopliteal angioplasty was 74 ± 2% and 37 ± 3%, respectively. After risk stratification analysis based on risk score assignment according to number of predictive end points, freedom from MALE+POD and AFS were lower in the higher-score groups. In the clinical setting, risk stratification based on these predictors before catheter revascularization would be useful in estimating future adverse outcome. To the best of our knowledge, this is the first study to assess risk stratification of standard outcomes following angioplasty in patients with CLI due to pure isolated infrapopliteal lesions.

DM and ESRD, whose prevalence has dramatically increased worldwide, have been reported to significantly affect the development of CLI and to be risk factors for atherosclerotic involvement of infrainguinal, especially infrapopliteal, arteries. From recent trials, patients with

Table II. Association of baseline characteristics with MALE and POD

	Univariate model	*Multivariate model 1*	*Multivariate model 2*
Patients status			
Age ≥80 years	0.5 (0.3, 0.7)[a]	0.5 (0.3, 0.8)[a]	0.4 (0.3, 0.7)[a]
Male sex	0.9 (0.7, 1.2)[a]	–	–
BMI <18.5 kg/m^2	0.9 (0.6, 1.3)	–	–
Albumin <3.0 g/dL	2.4 (1.7, 3.3)[a]	1.5 (1.0, 2.1)[a]	1.4 (1.0, 2.0)[a]
Nonambulatory	2.6 (1.9, 3.4)[a]	1.9 (1.4, 2.6)[a]	2.0 (1.5, 2.7)[a]
Risk factors			
Hypertension	0.8 (0.6, 1.1)	–	–
Hyperlipidemia	0.9 (0.6, 1.2)	–	–
Diabetes mellitus	1.3 (1.0, 1.9)	–	–
Current smoking	1.0 (0.8, 1.4)	–	–
End-stage renal disease	1.5 (1.1, 2.1)[a]	1.3 (1.0, 1.9)	–
EF <50%	1.8 (1.3, 2.4)[a]	1.2 (0.9, 1.7)	–
Lower limb status			
Rutherford 6	3.7 (2.8, 5.0)[a]	2.2 (1.6, 3.1)[a]	2.2 (1.6, 3.1)[a]
CRP ≥3.0 mg/dL	3.4 (2.6, 4.6)[a]	2.1 (1.5, 2.9)[a]	2.1 (1.6, 3.0)[a]
TASC D	1.5 (0.9, 2.7)	–	–
BTK run-offs (vs 2 run-offs)	1.0 (Ref)	–	–
1 run-off	1.0 (0.5, 1.8)	–	–
0 run-off	1.0 (0.6, 1.8)	–	–
BA disease	2.1 (1.5, 2.9)[a]	2.0 (1.4, 2.8)[a]	2.0 (1.4, 2.8)[a]

BA, Below-the-ankle; *BTK,* below-the-knee; *BMI,* body mass index; *CI,* confidence interval; *CRP,* C-reactive protein; *EF,* ejection fraction; *ESRD,* end-stage renal disease; *HR,* hazard ratio; *MALE,* major adverse limb events; *POD,* perioperative death; *TASC,* TransAtlantic Inter-Society Consensus.
Data are HRs and 95% CIs.
[a]$P < .05$.

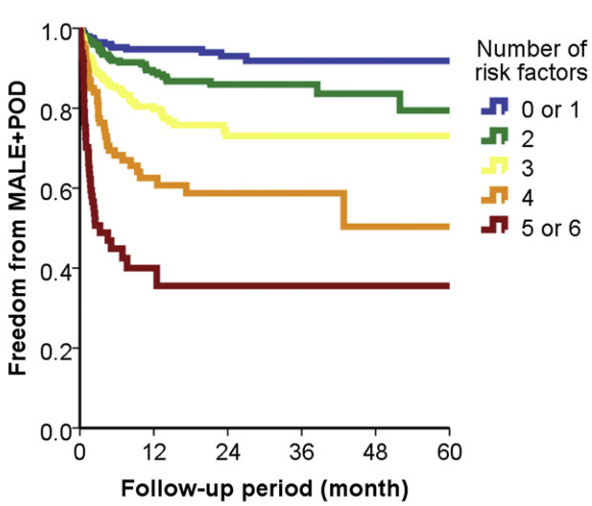


Fig 2. Risk stratification of major adverse limb events with perioperative death (*MALE+POD*) based on multivariable logistic analysis. Patients were assigned to groups based on the number of multivariable risk factors. Freedom from MALE+POD was lower in the higher-risk groups (1-year rates by number of risk factors: 94% for 0-1; 86% for 2; 75% for 3; 58% for 4; and 18% for 5 factors, respectively; $P < .001$).

CLI attributable to pure isolated infrapopliteal lesions appear to have more extensive distal disease including BA disease, poor initial pedal runoff leading to high incidence of major amputation, and severe comorbidities precluding surgical bypass compared with those patients with CLI attributable to multilevel disease.[3] Therefore, CLI attributable to pure isolated infrapopliteal lesion has been considered the most severe form of peripheral artery disease (PAD) in the overall population. Recently, because of the evolution of techniques and the availability of dedicated materials, the endovascular approach demonstrated improved clinical outcomes and, therefore, had been considered as first-line therapy in patients with CLI.[5,6] A recent meta-analysis of infrapopliteal angioplasty for the treatment of CLI by Romiti et al showed a limb salvage rate of 86% and a patient survival rate of 98%, which were comparable to those of bypass surgery.[4] Another study using propensity matching analysis to decrease confounder bias reported similar 5-year limb salvage and AFS rates between endovascular and surgical procedures for CLI attributable to infrainguinal lesions.[7] Therefore, infrapopliteal angioplasty is considered an acceptable therapeutic modality to treat patients with CLI attributable to infrapopliteal lesions, and it is most widely used in clinical practice. However, prognostic factors, including those derived from detailed laboratory examination, cardiac function evaluation, and angiographic features of infrapopliteal arteries, have not been systematically studied.

From analysis of three major randomized trials, age over 80 years and tissue loss, and presence of DM were associated with MALE+POD. In the present study, after multivariate analysis, age over 80 years, nonambulatory status, albumin <3.0 g/dL, ejection fraction <50%, Rutherford 6, CRP >3.0 mg/dL, and BA disease were independently associated with the outcome. However, the opposite results were obtained when studying the influence of patient age on MALE+POD. We performed

Table III. Association of baseline characteristics with major amputation and mortality

	Univariate model	*Multivariate model 1*	*Multivariate model 2*
Patients status			
Age ≥80 years	1.1 (0.8, 1.4)	–	–
Male sex	0.9 (0.7, 1.1)	–	–
BMI <18.5 kg/m^2	1.6 (1.2, 2.1)[a]	1.4 (1.0, 1.8)[a]	1.4 (1.1, 1.8)[a]
Albumin <3.0 g/dL	2.8 (2.2, 3.5)[a]	1.8 (1.4, 2.3)[a]	1.8 (1.4, 2.3)[a]
Nonambulatory	3.0 (2.4, 3.8)[a]	2.1 (1.7, 2.7)[a]	2.1 (1.7, 2.7)[a]
Risk factors			
Hypertension	1.0 (0.8, 1.3)	–	–
Hyperlipidemia	0.7 (0.5, 0.8)[a]	0.8 (0.7, 1.0)	–
Diabetes mellitus	0.9 (0.7, 1.2)	–	–
Current smoking	0.9 (0.7, 1.2)	–	–
ESRD	1.5 (1.2, 1.9)[a]	1.4 (1.1, 1.8)[a]	1.4 (1.1, 1.8)[a]
EF <50%	2.0 (1.6, 2.6)[a]	1.6 (1.2, 2.0)[a]	1.6 (1.2, 2.0)[a]
Lower limb status			
Rutherford 6	2.9 (2.3, 3.7)[a]	1.9 (1.4, 2.4)[a]	1.9 (1.4, 2.4)[a]
CRP ≥3.0 mg/dL	2.7 (2.1, 3.2)[a]	1.7 (1.3, 2.2)[a]	1.7 (1.3, 2.2)[a]
TASC D	2.0 (1.2, 3.2)[a]	1.7 (1.0, 2.8)	–
BTK run-offs (vs 2 run-offs)	1.0 (Ref)	–	–
1 run-off	1.2 (0.9, 2.2)	–	–
0 run-off	1.4 (0.7, 1.9)	–	–
BA disease	1.9 (1.4, 2.4)[a]	1.8 (1.4, 2.3)[a]	1.8 (1.4, 2.3)[a]

BA, Below-the-ankle; *BMI,* body mass index; *BTK,* below-the-knee; *CI,* confidence interval; *CRP,* C-reactive protein; *EF,* ejection fraction; *ESRD,* end-stage renal disease; *HR,* hazard ratio; *TASC,* TransAtlantic Inter-Society Consensus.
Data are HRs and 95% CIs.
[a]$P < .05$.

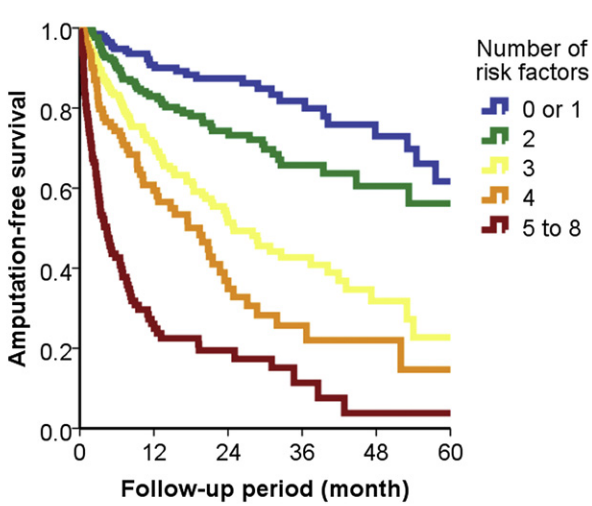


Fig 3. Risk stratification of amputation-free survival (AFS) based on multivariable logistic analysis. Patients were assigned to groups based on the number of multivariable risk factors. AFS was lower in the higher-risk groups (1-year rates by number of factors: 90% for 0-1; 82% for 2; 71% for 3; 57% for 4; 38 % for 5; and 3% for 6-8 factors, respectively; $P < .001$).

an additional analysis comparing background characteristics of patients aged over 80 years and those aged less than 80 years. As a result, we found that DM and dialysis, both of which strongly affect survival and major amputation rate, were more prevalent in patients aged less than 80 years than those aged over 80 years. Younger CLI patients had more advanced atherosclerosis because of more frequent presence of comorbidities, and more severe infrapopliteal artery lesions subsequently lead to worse limb outcomes. Cardiac function and BMI <18.5 were not predictors for MALE+POD. In the TASC guideline, cardiac failure or poor nutritional status were reported as negative predictors for wound healing status and should be evaluated and treated appropriately. However, in this study, the latter factors did not appear to significantly affect limb prognosis, and we posit that patients with these risk factors died before they could undergo major amputation or major reintervention. MALE has several limitations as an end point and has been reconsidered as such in the era of endovascular treatment. Also, an end point including complete wound healing might be preferable as limb end point after revascularization.

Conte et al identified that two clinical factors, namely age over 80 years and presence of tissue loss, affect AFS. In the current study, we found that nonambulatory status, BMI <18.5, albumin <3.0 g/dL, end-stage renal disease, ejection fraction <50%, Rutherford 6, CRP >3.0 mg/dL, and BA disease were independently associated with AFS. Nonambulatory status indicates impaired ADLs, whereas BMI <18.5 and albumin <3.0 g/dL suggest poor nutrition. These three variables can be regarded as general status factors. Contrary to data derived from the analysis performed by Conte et al, age over 80 years was not an AFS predictor in this study. In younger CLI patients, more advanced systematic atherosclerosis and more severe infrapopliteal artery lesions were independent factors for MALE and also, in general, older age was a risk factor for survival. AFS is a combined end point including survival and amputation, which probably offsets patient longevity and limb prognosis.

On the other hand, critical ischemic limbs with CRP ≥3.0 mg/dL are likely to reflect substantial inflammation often accompanying infection. Therefore, CRP level, as well as Rutherford 6, seems to reflect limb status. BA disease is an anatomic feature that often remains unimproved even after intensive interventions including EVT. Although we have reported that BA runoff plays an important role as the outflow vessel affecting vessel patency after infrapopliteal angioplasty, BA disease was found as a novel predictive factor for AFS, and we posit that BA disease negatively affects vessel patency leading to high occurrence of reintervention and major amputation. The observation that general status factors, limb status factors, and anatomic factors were independently associated with AFS is not only of pathogenetic but also of clinical interest, and suggests that the management of CLI patients requires systemic evaluations in addition to local treatment.

Regarding efficacy of infrapopliteal angioplasty, overall 1-year AFS was 71%, which was equivalent to the results presented by Conte et al.[9] Also, after risk stratification, patients with more than four predictors did not meet the 71% OPG for 1-year AFS in catheter-based therapies. In terms of freedom for MALE+POD, the 1-year result of 81% surpasses the OPG of 71%. In this study, major reintervention did not include re-endovascular procedure; hence, a better outcome was obtained. Limbs with more than four predictors did not meet the 71% OPG for 1-year AFS in catheter-based therapies. Finally, preprocedure stratification of outcomes as derived from this study plays an important role in therapeutic modality decision making.

Limitations. This was a retrospective and nonrandomized study despite use of a prospectively maintained database with a large number of consecutive CLI patients with pure isolated infrapopliteal lesions. Patients considered unsuitable for revascularization or treated with BSX were not managed by the physicians involved in the study and, therefore, data on them were not collected and analyzed. In addition, the actual number of patients with completely healed wounds was not determined. Selection of medication, especially of antiplatelet therapy, was at the physicians's discretion, leading to possible selection bias. Although most patients were treated as part of an endovascular-first approach, some were referred for an endovascular procedure because of the lack of bypass target, lack of adequate vein conduit, and severe comorbidities precluding surgical bypass surgery. Therefore, a heterogeneous patient population with different comorbidities and disease distribution was included in this study. However, in the clinical setting, CLI attributable to pure isolated infrapopliteal lesion is the most severe form in the PAD population, and infrapopliteal angioplasty has been most widely used for treatment of CLI patients. Overall AFS rate at 1 year in this study was 71%, which was comparable to the OPG defined by Conte et al, documenting satisfactory results in this setting with only traditional plain angioplasty. Several clinical, limb, and anatomic status factors were associated with prognosis after infrapopliteal angioplasty, and this could simplify the estimation of future AFS occurrence after an endovascular approach. Also, risk stratification for adverse outcomes would be essential in endovascular revascularization, as it may inform the decision-making process. These results are in good agreement and match our daily clinical practice. The results, however, cannot be generalized to surgical intervention. Newer stratification in the era of next-generation devices for infrapopliteal intervention warrants further prospective investigation against bypass results.

CONCLUSIONS

Long-term clinical outcomes were acceptable after EVT with angioplasty for patients with CLI attributable to pure isolated infrapopliteal lesions. Risk stratification based on outcome predictors allows estimation before catheter revascularization of future occurrence of MALE+POD and AFS in CLI patients attributable to pure infrapopliteal lesions.

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AUTHOR CONTRIBUTIONS

Conception and design: OI, YS, YY, KH, DK, TY
Analysis and interpretation: OI, MT
Data collection: OI, YS, KH, YY, DK, TY
Writing the article: OI, YS, MT
Critical revision of the article: OI
Final approval of the article: OI, YS, KH, DK, TY, MT, MU
Statistical analysis: MT
Obtained funding: Not applicable
Overall responsibility: OI

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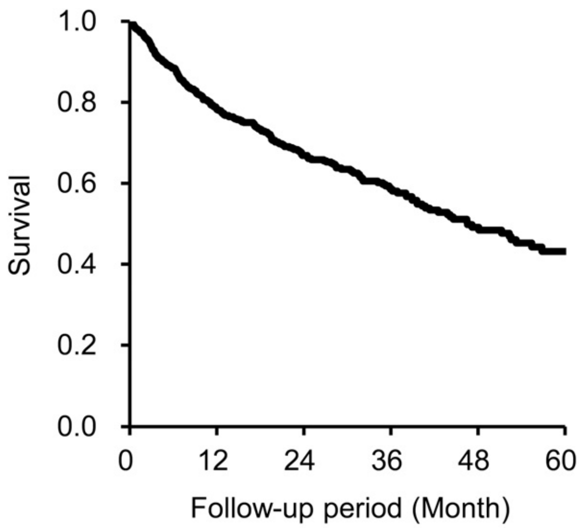
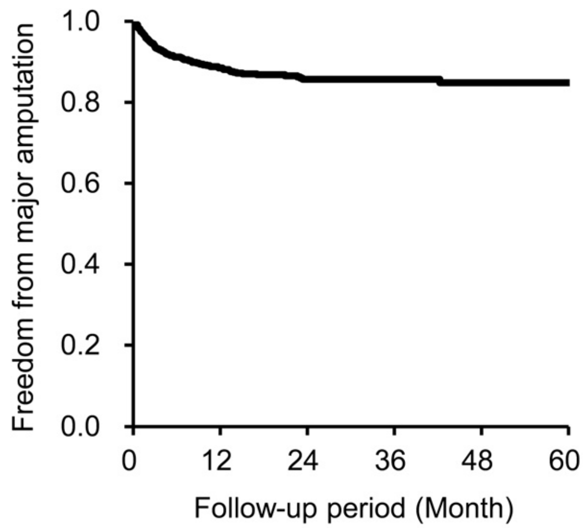


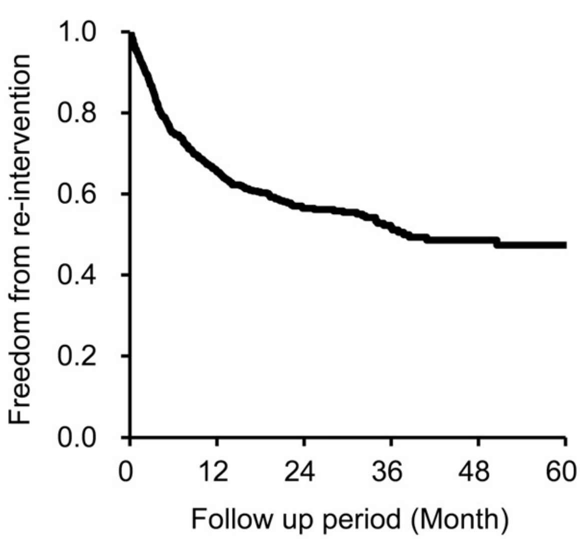
	0	12	24	36	48	60
at risk	884	484	265	137	72	32
%	100	78.2	66.9	58.5	49.1	43.2
SE	0.000	0.015	0.019	0.023	0.028	0.033

Supplementary Fig 1 (online only). Overall survival after angioplasty for the 884 patients with critical limb ischemia (CLI) because of pure isolated infrapopliteal lesions. Overall survival was 78 ± 1%, 59 ± 2%, and 43 ± 2% at 1, 3, and 5 years, respectively. *SE,* Standard error.



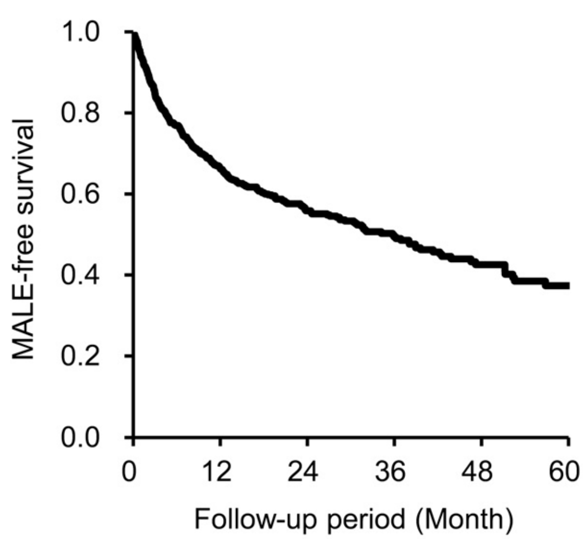
	0	12	24	36	48	60
at risk	1057	524	282	142	72	32
%	100	88.5	85.7	85.7	84.8	84.8
SE	0.000	0.011	0.013	0.013	0.016	0.016

Supplementary Fig 2 (online only). Limb salvage rate after angioplasty in 1057 critical ischemic limbs. Limb salvage rate was 89 ± 2%, 86 ± 2%, and 85 ± 2% at 1, 3, and 5 years, respectively. Almost all major amputations were performed before 1 year. *SE,* Standard error.



	0	12	24	36	48	60
at risk	1057	399	199	92	43	15
%	100	65.5	56.5	51.7	48.6	47.4
SE	0.000	0.017	0.019	0.023	0.025	0.027

Supplementary Fig 3 (online only). Freedom from any reintervention. Freedom from any reintervention including minor or major reintervention was 66 ± 1%, 56 ± 1%, and 47 ± 2% at 1, 3, and 5 years, respectively. *SE*, Standard error.



	0	12	24	36	48	60
at risk	884	408	222	114	58	25
%	100	66.2	55.8	49.4	42.6	37.4
SE	0.000	0.017	0.020	0.022	0.026	0.031

Supplementary Fig 4 (online only). Major adverse limb event (*MALE*)-free survival. MALE-free survival was 66 ± 2%, 49 ± 2%, and 33 ± 3% at 1, 3, and 5 years, respectively. *SE*, Standard error.