Endovascular interventions may save limbs in elderly subjects with severe lower extremity arterial disease

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Endovascular intervention, such as percutaneous transluminal angioplasty (PTA), improves claudication and saves limbs of patients with severe lower extremity arterial disease (LEAD).[1] A previous study showed that the mortality among octogenarians was as high as 29% regardless of the type of intervention and that revascularization was associated with high periprocedural mortality.[2] A previous study had already shown that reconstructive surgery for elderly individuals over 80 years old resulted in a significantly higher mortality rate than that for patients between 70 and 80 years old, whereas endovascular intervention and primarily conservative treatment had comparable prognoses.[3] Consistently, another study showed that the risks of both overall and amputation-free survival were significantly lower with endovascular treatment than with bypass surgery in patients with critical limb ischemia.[4] A systematic review and meta-analysis of 27 studies (15 cohort and 12 randomized controlled trials) with 1 642 patients suggests that conservative treatment may be considered for nonreconstructable patients with critical limb ischemia;[5] however, because a high risk of bias and serious inconsistencies were found in the included studies, the meta-analysis provided low-quality evidence. In contrast, a small cohort study with 49 patients suggests that amputation improved quality of life and health status in fragile elderly individuals.[6] The choice of endovascular interventions or conservative treatments for elderly individuals with severe LEAD is still under debate. Therefore, we conducted the present study to investigate the effect of old age (age ≥ 85 years) on prognoses in patients with severe LEAD undergoing PTA compared with patients under the age of 85 years.

This was a retrospective cohort study and enrolled consecutive patients with severe LEAD who underwent PTA at our hospital between 2013/1/1 and 2018/12/31. As we previously reported, our study was an all-comer study, and we excluded only patients with a nonsalvageable limb who refused amputation surgery.[7] The study was approved by the Mackay Memorial Hospital with Institutional Review Board number (20MMHIS034e), and the board waived the informed consent requirement for the study patients. We defined our primary study outcomes as all-cause mortality, cardiac-related mortality, major adverse cardiovascular events (MACEs) and major adverse limb events (MALEs) at the one-year follow-up. MACEs were defined as the composite of nonfatal myocardial infarction, nonfatal stroke, and cardiac-related death; MALEs were defined as amputation due to a vascular event above the forefoot, acute limb ischemia and clinically driven target vessel revascularization. The therapeutic strategies were reported previously, including the timing of PTA and the medication use.[7] Because the presence of acute limb

ischemia and Rutherford classification criteria were major risk factors for the study outcomes in patients with severe LEAD, we adjusted for both risk factors in the multivariate logistic regression analysis. Additionally, we showed that neutrophil-lymphocyte ratios were associated with the study outcomes in our previously report.[7] Therefore, we statistically adjusted for neutrophil-lymphocyte ratios in multivariate logistic regression analysis if the white blood cell count, neutrophil percentage or lymphocyte percentage was associated with the study outcomes in univariate logistic regression analysis. In multivariate logistic regression analysis, age as a continuous variable or age as a binary variable (age ≥ 85 or < 85 years) was adjusted separately. We considered two-tailed P values of 0.05 or lower indicative of significance.

Our study cohort consisted of 222 patients with a mean age of 73.6 years (standard deviation: 11.5), and 53.6% were male. Of these patients, 25 patients (11.3%) were at Rutherford stage III, 54 patients (24.3%) were at stage IV, 130 patients (58.6%) were at stage V, and 13 patients (5.9%) were at stage VI. The older group had lower ratios of comorbidities such as diabetes mellitus (44.4% $vs.$ 73.4%, P < 0.001) and chronic kidney diseases (17.8% $vs.$ 41.2%, P = 0.002), but other baseline characteristics were not significantly different. The presentation of acute limb ischemia was significantly higher in the elderly group (24.4% $vs.$ 9.6%, P = 0.012). The laboratory data did not differ significantly except that older individuals had lower values of body mass index (21.1 ± 3.6 $vs.$ 24.3 ± 4.1 kg/m^2, P < 0.001), serum creatinine (3.8 ± 3.6 $vs.$ 1.8 ± 1.5 mg/dL, P < 0.001), and triglycerides (94.7 ± 46.6 $vs.$ 165.4 ± 128.9 mg/ dL, P < 0.001) (shown in Table 1). With respect to the primary study outcomes, the older group had significantly higher ratios of all-cause mortality (37.8% $vs.$ 19.2%, P = 0.016), but cardiac-related mortality was not significantly different between the older and control groups (17.8% $vs.$ 10.2%, P = 0.192); moreover, no significant association was found in MALEs (8.9% $vs.$ 16.9%, P = 0.175), although a tendency toward a significant difference was found in MACEs (26.7% $vs.$ 14.1%, P = 0.070) (shown in Figure 1). In univariate logistic regression analyses, age as a continuous variable was associated with all-cause mortality (crude hazard ratio (cHR): 1.033, 95% CI: 1.006−1.060, P = 0.016) and

in-hospital mortality (cHR: 1.056, 95% CI: 1.006−1.108, P = 0.027) but not cardiac-related mortality (cHR: 1.012, 95% CI: 0.973−1.052, P = 0.559), MALEs (cHR: 0.979, 95% CI: 0.952−1.007, P = 0.146), or MACEs (cHR: 0.992, 95% CI: 0.959−1.026, P = 0.636). Age ≥ 85 $vs.$ < 85 years was associated with increased risks of all-cause mortality (cHR: 2.332, 95% CI: 1.302−4.177, P = 0.004), MACEs (cHR: 2.138, 95% CI: 1.074−4.256, P = 0.031), and in-hospital mortality (cHR: 3.694, 95% CI: 1.425−9.576, P = 0.007). Borderline significance was found for cardiac-related mortality (cHR: 2.101, 95% CI: 0.913−4.837, P = 0.081). No significant association was found regarding MALEs (cHR: 0.507, 95% CI: 0.179−1.439, P = 0.202) (shown in Table 1). In multivariate logistic regression analyses, the significant associations between age ≥ 85 years and the study outcomes became nonsignificant, including that of all-cause mortality (adjusted HR: 1.958, 95% CI: 0.937−4.090, P =0.074), cardiac mortality (adjusted HR: 1.628, 95% CI: 0.607−4.366, P = 0.333), MACEs (adjusted HR: 1.350, 95% CI: 0.604−3.015, P = 0.465) and in-hospital mortality (adjusted HR: 2.386, 95% CI: 0.442−12.881, P = 0.312) (shown in Table 2). The original nonsignificant association between age ≥ 85 years and MALEs changed after statistical adjustment for the confounders (adjusted HR: 0.141, 95% CI: 0.026−0.772, P = 0.024), and age ≥ 85 years was associated with a decreased risk of MALEs compared with age < 85 years.

Our study initially showed that elderly individuals aged 85 years or older had a significantly greater incidence of all-cause mortality but that cardiac-related mortality, MALEs and MACEs did not differ significantly between older individuals and younger individuals. In our cohort study, older patients had a lower prevalence of comorbidities such as diabetes mellitus and chronic kidney diseases than younger patients, which indirectly implied a survival bias in the elderly. Chronic kidney disease was considered a risk factor in patients with LEAD,[8] although it was not associated with amputation-free survival in the comparison between endovascular interventions and conservative treatments.[9] These older patients could have longer lives because they had a lower prevalence of comorbidities of cardiovascular diseases before they developed severe LEAD; in other words, the older patients were physiologically healthier than the younger patients

Table 1   Baseline characteristics and laboratory data in patients aged < 85 *vs.* ≥ 85 years.

	Age < 85 yrs $n = 177$	Age ≥ 85 yrs $N = 45$	P
Age, yrs	69.7 ± 9.4	88.9 ± 3.2	< 0.001
Male gender	94 (53.1%)	25 (55.6%)	0.867
Body mass index, kg/m^2	24.3 ± 4.1	21.1 ± 3.6	< 0.001
Heart rate at baseline, beats/min	86.7 ± 16.8	92.2 ± 19.7	0.058
Systolic BP at baseline, mmHg	147.5 ± 31.0	150.1 ± 30.0	0.603
Diastolic BP at baseline, mmHg	75.3 ± 4.2	75.5 ± 14.4	0.935
Current/past smoker	45 (25.4%)	8 (17.8%)	0.332
Alcohol intake	60 (33.9%)	9 (20.0%)	0.103
History of hypertension	117 (66.1%)	28 (62.2%)	0.726
History of diabetes mellitus	130 (73.4%)	20 (44.4%)	< 0.001
History of insulin use	26 (14.7%)	2 (4.4%)	0.078
History of dyslipidemia	38 (21.5%)	8 (17.8%)	0.683
History of kidney disease			0.002
Normal kidney function	104 (58.8%)	37 (82.2%)	
Chronic kidney disease	29 (16.4%)	7 (15.6%)	
End-stage renal disease	44 (24.9%)	1 (2.2%)	
History of CAD	69 (39.0%)	21 (46.7%)	0.396
History of myocardial infarction	12 (6.8%)	2 (4.4%)	0.741
History of carotid artery stenosis	3 (1.7%)	0	1.000
History of ischemic stroke	28 (15.8%)	7 (15.6%)	1.000
History of chronic heart failure			0.431
NYHA class I	7 (4.0%)	3 (6.7%)	0.431
NYHA class II	9 (5.1%)	3 (6.7%)	
NYHA class III	10 (5.6%)	5 (11.1%)	
NYHA class IV	5 (2.8%)	0	
Family history of premature CAD	2 (1.1%)	0	1.000
History of any cancer	8 (4.5%)	5 (11.1%)	0.145
History of amputation	13 (7.3%)	0	0.616
Above-knee amputation	6 (3.4%)	0	
Below-knee amputation	3 (1.7%)	0	
Forefoot amputation	4 (2.3%)	0	
Acute ischemic limb presentation	17 (9.6%)	11 (24.4%)	0.012
Rutherford classification			0.218
Class III	22 (12.4%)	3 (6.7%)	
Class IV	38 (21.5%)	16 (35.6%)	
Class V	106 (59.9%)	24 (53.3%)	
Class VI	11 (6.2%)	2 (4.4%)	
CHADS2 score			0.103
0	9 (5.1%)	0	
1	40 (22.6%)	6 (13.3%)	
2	61 (34.5%)	19 (42.2%)	
3	39 (22.0%)	11 (24.4%)	

Continued

	Age < 85 yrs n = 177	Age ≥ 85 yrs N = 45	P
4	22 (12.4%)	4 (8.9%)	
5	6 (3.4%)	5 (11.1%)	
Laboratory data			
Total cholesterol, mg/dL	160.2 ± 46.3	152.8 ± 46.5	0.357
High-density lipoprotein cholesterol, mg/dL	40.0 ± 18.1	44.4 ± 14.7	0.515
Low-density lipoprotein cholesterol, mg/dL	93.2 ± 34.8	101.3 ± 42.9	0.47
Triglyceride, mg/dL	165.4 ± 128.9	94.7 ± 46.6	< 0.001
Fasting glucose, mg/dL	180.2 ± 100.8	161.7 ± 101.9	0.279
Glycosylated hemoglobin	7.5% ± 2.0%	6.9% ± 1.9%	0.319
Creatinine, mg/dL	3.8 ± 3.6	1.8 ± 1.5	< 0.001
Creatinine clearance, mg/dL	31.3 ± 28.5	24.8 ± 12.3	0.022
Estimated glomerular filtration rate, mL/min per 1.732 m^2	37.9 ± 35.0	48.6 ± 30.7	0.064
Alanine transaminase, IU/L	23.1 ± 22.9	21.0 ± 12.2	0.546
Uric acid, mg/dL	5.8 ± 2.3	6.1 ± 2.4	0.437
White blood cell count, 10^3/µL	9561.0 ± 4971.5	9322.2 ± 4811.0	0.772
Neutrophil ratio	70.5% ± 12.8%	68.7% ± 17.8%	0.44
Lymphocyte ratio	17.1% ± 10.0%	17.3% ± 9.8%	0.9
Neutrophil-to-lymphocyte ratio	7.9% ± 10.3%	6.5% ± 5.9%	0.377
Medication at baseline			
Aspirin	69 (39.0%)	13 (28.9%)	0.230
Cilostazol	82 (46.3%)	26 (57.8%)	0.185
Clopidogrel	51 (28.8%)	10 (22.2%)	0.456
Oral anti-coagulant			
Pentoxyphylline	10 (5.6%)	1 (2.2%)	0.699
ACEI or ARB	9 (5.1%)	2 (4.4%)	1.000
Beta-blockers	32 (18.1%)	7 (15.6%)	0.828
Calcium channel blockers	40 (22.6%)	8 (17.8%)	0.549
Statin	34 (19.2%)	10 (22.2%)	0.677
Urate-lowering therapy	3 (1.7%)	2 (4.4%)	0.267

Data are presented as mean ± SD or *n* (%). *Values are expressed as numbers (standard deviation) or numbers and percentages. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CAD: coronary artery disease; NYHA: New York Heart Association.

in our study. Age as a continuous or binary variable was not associated with all-cause mortality after we adequately adjusted for confounders in the statistical models. The major risk factors associated with all-cause mortality were Rutherford classifications, neutrophil-to-lymphocyte ratios, and alanine transaminase. A similar association can be found regarding cardiac-related mortality and MACEs, and the major risk factor associated with both outcomes was heart rate at baseline irrespective of whether age was presented as a continuous or binary variable. Age was not associated with MALEs in the univariate logistic regression analysis. Interestingly, the nonsignificant association between age and MALEs became significant after proper adjustment for the confounders and comorbidities in the multivariate logistic regression analysis. The factors associated with the decreased risks of MALEs were older age and body mass index, and the factors associated with the increased risks of MALEs in-
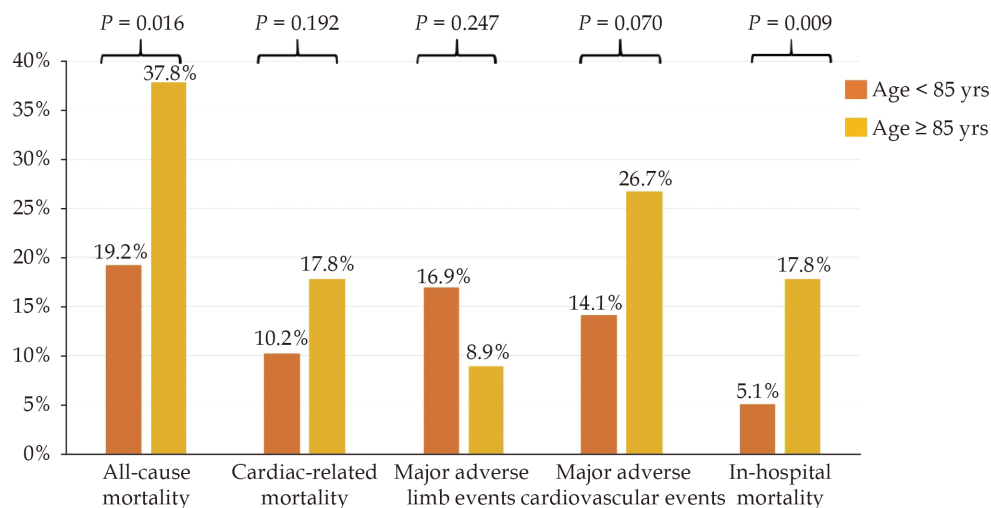
Figure 1   The crude incidence of all-cause mortality was significantly greater in patients aged ≥ 85 *vs.* < 85 years. The other study outcomes were comparable in the two groups.

cluded the Rutherford classification, medical history of chronic kidney diseases, and the serum values of total cholesterol and fasting glucose. As we previously explained, the older patients in our cohort were physiologically healthy compared with the younger patients, and the older patients with fewer prevalent comorbidities had a lower risk of incident MALEs. We thought that the selection bias in the elderly group explained the association of age with the decreased incidence of MALEs. We should not misinterpret age as a protective factor, but we should interpret the association between age and reduced MALEs as a good signal indicating that elderly patients still benefit from receiving endovascular intervention without the increased risks of mortality and MACEs compared with the younger patients.

Our results and interpretation may conflict with previous studies showing that conservative treatments might be noninferior to endovascular interventions.[10–12] Some investigators thought that not all patients with critical limb ischemia should undergo revascularization and focused on patient selection to avoid unnecessary procedures.[11] Another investigator showed that one-year mortality rates were as high as 40% in patients who underwent endovascular interventions or conservative treatment; an individualized therapeutic strategy combined with a shared-decision process was suggested in elderly patients with critical limb ischemia.[12] The PRIORITY registry used propensity score matching to identify 539 patients with critical limb ischemia. In this registry, one-year mortality was 44.1% in patients who received revascularization versus 49% in patients who received conservative treatment, but no significant difference in mortality rate was found.[10] Compared with patients without risk factors, the patients with 2−3 poor risk factors seemed to have an increased risk of mortality after they received surgical or endovascular revascularization, but the difference was not significant.[10] The negative risk factors included old age (age ≥ 85 years in men or ≥ 90 years in women), heart failure, and wound-free resting pain.[10] In our study, most of our elderly patients were at Rutherford stage IV to VI, equal to the patients with two risk factors in the PRIORITY registry, but they still had comparable outcomes to the younger patients. The CRIT-ISCH registry was a prospective study to develop first-line treatment options in patients with critical limb ischemia.[9] In this comprehensive study, endovascular interventions significantly decreased the risk of amputation-free survival in patients with more severe angiographic stenoses or occlusions (Trans-Atlantic Inter Society Consensus (TASC II) type C or D),[13] and age >74 years was not associated with an increased risk of amputation-free survival.[9] The one-year mortality rate was 19% in patients who underwent endovascular interventions or conservative treatments, but endovascular interventions increased amputation-free survival by 3% compared with conservative treatment.[9] Given the

Table 2   The association between the study outcomes and variables in logistic regression analyses.

	Crude HR	95% CI	P	Adjusted HR	95% CI	P
All-cause mortality						
Age*, yrs	1.033	1.006–1.060	0.016	1.009	0.979–1.040	0.566
Age ≥ 85 vs. < 85 yrs*	2.332	1.302–4.177	0.004	1.958	0.937–4.090	0.074
Male gender	1.652	0.865–3.156	0.128	0.528	0.273–1.021	0.058
Body mass index, kg/m^2	0.918	0.850–0.990	0.027	0.946	0.867–1.031	0.208
Current/past smoker	0.925	0.558–1.532	0.762			
Alcohol intake	0.863	0.580–1.283	0.465			
History of hypertension	0.675	0.388–1.175	0.164			
History of diabetes mellitus	0.777	0.440–1.370	0.383			
Chronic kidney disease	1.055	0.756–1.474	0.752			
History of carotid artery stenosis	0.049	0.000–1058	0.553			
History of ischemic stroke	1.361	0.681–2.717	0.383			
History of chronic heart failure	1.035	0.799–1.339	0.797			
Atrial fibrillation	2.435	1.274–4.654	0.007	1.535	0.710–3.320	0.276
Presented with acute ischemic limb	4.133	2.257–7.567	< 0.001	1.813	0.827–3.976	0.137
Rutherford classification	2.073	1.330–3.233	0.001	2.008	1.163–3.467	0.012
Systolic BP at baseline, mmHg	0.995	0.986–1.005	0.325			
Diastolic BP at baseline, mmHg	1.013	0.992–1.033	0.226			
Heart rate at baseline, beats/min	1.026	1.011–1.042	0.001	1.015	0.996–1.034	0.125
Total cholesterol, mg/dL	1.001	0.995–1.007	0.765			
High-density lipoprotein cholesterol, mg/dL	0.995	0.961–1.031	0.796			
Low-density lipoprotein cholesterol, mg/dL	0.994	0.978–1.010	0.454			
Triglyceride, mg/dL	0.997	0.993–1.001	0.095			
Fasting glucose, mg/dL	0.999	0.997–1.002	0.708			
Glycosylated hemoglobin, %	1.106	0.917–1.333	0.291			
Creatinine, mg/dL	1.018	0.943–1.099	0.640			
Creatinine clearance	0.989	0.977–1.002	0.103			
Estimated glomerular filtration rate, mL/min per 1.732 m^2	0.998	0.989–1.006	0.585			
Alanine transaminase, IU/L	1.020	1.012–1.028	< 0.001	1.012	1.001–1.024	0.029
Uric acid, mg/dL	1.017	0.888–1.164	0.810			
White blood cell count, 10^3/μL	1.000	1.000–1.000	< 0.001			
Neutrophil ratio, %	1.052	1.026–1.079	< 0.001			
Lymphocyte ratio, %	0.917	0.884–0.952	< 0.001			
Neutrophil-to-lymphocyte ratio	1.030	1.016–1.044	< 0.001	1.031	1.011–1.052	0.002
Cardiac-related mortality						
Age*, yrs	1.031	0.994–1.069	0.100	1.012	0.973–1.052	0.559
Age ≥ 85 vs. < 85 yrs*	2.101	0.913–4.837	0.081	1.628	0.607–4.366	0.333
Male gender	0.987	0.340–2.863	0.980	0.588	0.250–1.385	0.224
Body mass index, kg/m^2	0.917	0.826–1.016	0.098	0.931	0.830–1.044	0.222
Current/past smoker	1.027	0.525–2.009	0.938			

Continued

	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Alcohol intake	1.056	0.638–1.751	0.831			
History of hypertension	0.694	0.319–1.511	0.358			
History of diabetes mellitus	1.246	0.524–2.963	0.619			
Chronic kidney disease	1.068	0.670–1.701	0.784			
History of carotid artery stenosis	0.049	0.000–52618	0.670			
History of ischemic stroke	0.737	0.221–2.455	0.619			
History of chronic heart failure	1.237	0.914–1.674	0.169			
Atrial fibrillation	2.436	0.977–6.072	0.056			
Presented with acute ischemic limb	3.769	1.579–8.998	0.003	1.815	0.646–5.101	0.258
Rutherford classification	1.346	0.778–2.327	0.288	1.294	0.684–2.448	0.429
Systolic BP at baseline, mmHg	0.999	0.986–1.013	0.928			
Diastolic BP at baseline, mmHg	1.021	0.993–1.049	0.151			
Heart rate at baseline, beats/min	1.039	1.018–1.061	< 0.001	1.029	1.006–1.054	0.014
Total cholesterol, mg/dL	1.002	0.994–1.010	0.619			
High-density lipoprotein cholesterol, mg/dL	0.989	0.940–1.040	0.664			
Low-density lipoprotein cholesterol, mg/dL	1.001	0.982–1.021	0.915			
Triglyceride, mg/dL	0.997	0.993–1.002	0.239			
Fasting glucose, mg/dL	1.000	0.996–1.004	0.835			
Glycosylated hemoglobin, %	1.108	0.867–1.416	0.414			
Creatinine, mg/dL	1.007	0.902–1.125	0.897			
Creatinine clearance	0.999	0.984–1.014	0.873			
Estimated glomerular filtration rate, mL/min per 1.732 m^2	1.004	0.994–1.015	0.448			
Alanine transaminase, IU/L	1.019	1.007–1.031	0.002	1.010	0.996–1.025	0.159
Uric acid, mg/dL	1.040	0.860–1.257	0.688			
White blood cell count, $10^3/\mu L$	1.000	1.000–1.000	0.018			
Neutrophil ratio, %	1.057	1.019–1.096	0.003			
Lymphocyte ratio, %	0.902	0.854–0.953	< 0.001			
Neutrophil-to-lymphocyte ratio	1.027	1.006–1.049	0.011	1.028	0.999–1.058	0.058
Major adverse limb events						
Age*, yrs	0.979	0.952–1.007	0.146	0.966	0.931–1.002	0.063
Age ≥ 85 *vs.* < 85 yrs*	0.507	0.179–1.439	0.202	0.141	0.026–0.772	0.024
Male gender	1.145	0.582–2.253	0.696	1.487	0.720–3.072	0.284
Body mass index, kg/m^2	0.941	0.864–1.025	0.160	0.897	0.806–0.998	0.046
Current/past smoker	1.009	0.553–1.841	0.977			
Alcohol intake	0.854	0.522–1.397	0.528			
History of hypertension	0.842	0.422–1.682	0.627			
History of diabetes mellitus	1.332	0.622–2.854	0.461			
Chronic kidney disease	1.499	1.028–2.184	0.035	1.588	1.023–2.465	0.039
History of carotid artery stenosis	2.110	0.289–15.434	0.462			
History of ischemic stroke	1.151	0.476–2.779	0.755			

Continued

	Crude HR	95% CI	P	Adjusted HR	95% CI	P
History of chronic heart failure	1.211	0.922–1.591	0.169			
Atrial fibrillation	1.280	0.495–3.307	0.610			
Presented with acute ischemic limb	0.976	0.344–2.770	0.963	0.745	0.201–2.763	0.660
Rutherford classification	4.227	2.339–7.636	< 0.001	7.642	3.438–16.984	< 0.001
Systolic BP at baseline, mmHg	0.991	0.980–1.002	0.105			
Diastolic BP at baseline, mmHg	0.984	0.960–1.008	0.196			
Heart rate at baseline, beats/min	0.999	0.980–1.018	0.926			
Total cholesterol, mg/dL	0.988	0.979–0.997	0.010	0.989	0.979–0.999	0.043
High-density lipoprotein cholesterol, mg/dL	1.006	0.980–1.034	0.639			
Low-density lipoprotein cholesterol, mg/dL	0.987	0.974–1.001	0.071			
Triglyceride, mg/dL	1.000	0.998–1.003	0.844			
Fasting glucose, mg/dL	1.003	1.000–1.006	0.037	1.004	1.001–1.008	0.018
Glycosylated hemoglobin, %	1.171	0.978–1.403	0.086			
Creatinine, mg/dL	1.044	0.957–1.138	0.337			
Creatinine clearance	0.995	0.981–1.009	0.496			
Estimated glomerular filtration rate, mL/min per 1.732 m^2	0.990	0.978–1.002	0.089			
Alanine transaminase, IU/L	1.002	0.987–1.017	0.816			
Uric acid, mg/dL	0.906	0.765–1.073	0.251			
White blood cell count, $10^3/\mu L$	1.000	1.000–1.000	0.006			
Neutrophil ratio, %	1.047	1.017–1.079	0.002			
Lymphocyte ratio, %	0.933	0.894–0.974	0.001			
Neutrophil-to-lymphocyte ratio	1.016	0.992–1.040	0.190	0.972	0.933–1.012	0.172
Major adverse cardiovascular events						
Age*, yrs	1.016	0.986–1.046	0.300	0.992	0.959–1.026	0.992
Age ≥ 85 *vs.* < 85 yrs*	2.138	1.074–4.256	0.031	1.350	0.604–3.015	0.465
Male gender	1.012	0.422–2.426	0.978	0.735	0.371–1.456	0.377
Body mass index, kg/m^2	0.923	0.849–1.004	0.062	0.939	0.858–1.029	0.178
Current/past smoker	1.523	0.945–2.454	0.084			
Alcohol intake	1.111	0.731–1.690	0.621			
History of hypertension	0.753	0.391–1.452	0.398			
History of diabetes mellitus	1.318	0.638–2.723	0.456			
Chronic kidney disease	0.937	0.623–1.411	0.756			
History of carotid artery stenosis	0.049	0.000–7539	0.620			
History of ischemic stroke	1.044	0.436–2.503	0.923			
History of chronic heart failure	1.191	0.913–1.553	0.198			
Atrial fibrillation	2.479	1.169–5.257	0.018	1.597	0.678–3.764	0.284
Presented with acute ischemic limb	2.592	1.222–5.497	0.013	2.088	0.905–4.818	0.085
Rutherford classification	1.257	0.806–1.960	0.314	1.181	0.723–1.928	0.506
Systolic BP at baseline, mmHg	0.998	0.988–1.009	0.715			
Diastolic BP at baseline, mmHg	1.008	0.985–1.031	0.506			
Heart rate at baseline, beats/min	1.025	1.008–1.042	0.004	1.025	1.005–1.045	0.015
Total cholesterol, mg/dL	1.003	0.997–1.010	0.342			

Continued

	Crude HR	95% CI	P	Adjusted HR	95% CI	P
High-density lipoprotein cholesterol, mg/dL	0.984	0.950–1.020	0.385			
Low-density lipoprotein cholesterol, mg/dL	1.004	0.991–1.017	0.575			
Triglyceride, mg/dL	0.999	0.995–1.002	0.434			
Fasting glucose, mg/dL	0.998	0.995–1.002	0.401			
Glycosylated hemoglobin, %	1.185	0.975–1.440	0.088			
Creatinine, mg/dL	0.973	0.877–1.080	0.610			
Creatinine clearance	1.004	0.993–1.016	0.463			
Estimated glomerular filtration rate, mL/min per $1.732/m^2$	1.006	0.997	1.014	0.174		
Alanine transaminase, IU/L	1.009	0.997–1.020	0.143			
Uric acid, mg/dL	1.047	0.905–1.213	0.536			
White blood cell count, $10^3/\mu L$	1.000	1.000–1.000	0.240			
Neutrophil ratio, %	1.026	0.999–1.054	0.062			
Lymphocyte ratio, %	0.955	0.920–0.992	0.017			
Neutrophil-to-lymphocyte ratio	1.016	0.993–1.039	0.176	1.010	0.978–1.043	0.533
In-hospital mortality						
Age*, yrs	1.056	1.006–1.108	0.027	0.995	0.934–1.061	0.885
Age ≥ 85 *vs.* < 85 yrs*	3.694	1.425–9.576	0.007	2.386	0.442–12.881	0.312
Male gender	1.147	0.330–3.990	0.830	0.766	0.211–2.776	0.685
Body mass index, kg/m^2	0.795	0.681–0.928	0.004	0.858	0.711–1.036	0.112
Current/past smoker	0.828	0.323–2.121	0.694			
Alcohol intake	0.896	0.457–1.757	0.749			
History of hypertension	0.761	0.290–1.999	0.579			
History of diabetes mellitus	0.685	0.261–1.798	0.442			
Chronic kidney disease	0.931	0.509–1.700	0.815			
History of carotid artery stenosis	0.049	0.000–> 9999	0.742			
History of ischemic stroke	1.114	0.320–3.876	0.865			
History of chronic heart failure	0.752	0.394–1.438	0.389			
Atrial fibrillation	2.120	0.691–6.503	0.189			
Presented with acute ischemic limb	9.256	3.564–24.043	< 0.001	3.874	1.070–14.024	0.039
Rutherford classification	4.564	1.934–10.774	0.001	6.867	2.189–21.541	0.001
Systolic BP at baseline, mmHg	0.981	0.965–0.998	0.031	0.989	0.969–1.009	0.272
Diastolic BP at baseline, mmHg	1.018	0.985–1.052	0.292			
Heart rate at baseline, beats/min	1.043	1.020–1.067	0.000	1.025	0.984–1.067	0.243
Total cholesterol, mg/dL	0.994	0.982–1.005	0.291			
High-density lipoprotein cholesterol, mg/dL	0.956	0.880–1.038	0.280			
Low-density lipoprotein cholesterol, mg/dL	0.993	0.967–1.020	0.613			
Triglyceride, mg/dL	0.998	0.993–1.004	0.537			
Fasting glucose, mg/dL	1.000	0.996–1.005	0.884			
Glycosylated hemoglobin, %	1.058	0.757–1.479	0.741			
Creatinine, mg/dL	1.001	0.870–1.152	0.988			

Continued

	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Creatinine clearance	0.976	0.949−1.004	0.093			
Estimated glomerular filtration rate, mL/min per 1.732 m^2	0.999	0.985−1.014	0.931			
Alanine transaminase, IU/L	1.019	1.008−1.030	0.001	1.002	0.984−1.202	0.843
Uric acid, mg/dL	1.124	0.914−1.381	0.268			
White blood cell count, 10^3/μL	1.000	1.000−1.000	0.001			
Neutrophil ratio, %	1.115	1.052−1.182	< 0.001			
Lymphocyte ratio, %	0.869	0.802−0.942	0.001			
Neutrophil-to-lymphocyte ratio	1.038	1.018−1.059	< 0.001	1.052	1.021−1.084	0.001

*Age as a continuous variable and age ≥ 85 *vs.* < 85 years were adjusted separately. HR: hazard ratio; BP: blood pressure.

debate regarding hard outcomes in patients with severe LEAD, soft outcomes such as cost effectiveness may be used as alternatives. A study by Peters, *et al.*[14] included 195 patients aged over 70 years, and the authors evaluated the effect of endovascular interventions on improvement of the quality-adjusted life-years and incremental cost-effectiveness ratios compared with the effect of conservative treatment. The results indicated that performing endovascular interventions for patients with critical limb ischemia was cost effective. As optimal treatments are not always the same for elderly patients with severe LEAD,[3,9,12] we should select the appropriate treatment according to the patients' condition and preferences. We suggest that age was not the only predictor of the prognosis in patients with severe LEAD according to our study results, and we should choose vascular interventions on the basis of the comorbidities, severity and angiographic findings of LEAD,[9] presence of ischemic wounds,[10] life expectancy and patient preferences.[12]

Selection bias was noted in the present study when we divided the patients by age. The older patients had lower ratios of comorbidities, and they seemed healthier than the controls. The selection bias of the older group partially explained the lower risks of the study outcomes in our study. Though our study was limited by the nature of the cohort study, we may still support a role of endovascular intervention for older patients with severe LEAD. Although life inevitably comes to an end, we believe that endovascular interventions can still save a limb in older patients with severe LEAD without a trade-off between limb salvage and procedural risks.

CONFLICT OF INTEREST

None.

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