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Prediction of all-cause mortality in endovascularly treated patients with peripheral arterial disease of the lower extremities

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Abstract

Objectives: Lower extremity peripheral arterial disease (PAD) is associated with increased morbidity and mortality. The primary objective of the study was to identify nonspecific risk factors for 2- and 5-year all-cause mortality in endovascularly treated patients with PAD. The secondary objective was to develop a clinically applicable scoring system to estimate the probability of 2- and 5-year all-cause mortality based on our results.

Methods: We performed a retrospective study using data from patients with PAD who underwent endovascular treatment between January 2016 and December 2018. All data were collected from electronic medical records. A Cox proportional hazards regression model was used to examine the association between variables and all-cause mortality. Multivariate analyses were performed after adjusting for age, chronic limb-threatening ischaemia (CLTI), creatinine and fibrinogen in model 1, and for age, hypertension, diabetes mellitus, sex, smoking, dyslipidemia, CLTI, chronic obstructive pulmonary disease, malignancy, atrial fibrillation, heart failure with reduced ejection fraction, coronary artery disease, fibrinogen and creatinine in model 2. Variables associated with mortality with p-value <.02 in all analyses were included in the scoring system. The predictive performance of the scoring system was evaluated using the Area Under Curve (AUC) of Receiver Operating Characteristic curve.

Results: A total of 676 patients with a mean age of 68.6 ± 9.74 years were analyzed, 66.7% of patients had CLTI. The 2-year mortality rate was 22.3%; 29.5% in patients with CLTI and 8% in patients with claudications. The 5-year mortality rate was 48.8%; 60.5% in patients with CLTI and 25.3% in patients with claudications. CLTI presence, creatinine, age and fibrinogen were included in the scoring system. Based on the cut-off values of creatinine >102.4 umol/l, fibrinogen >5.41 g/L, age ≥68 years and CLTI presence, patients were categorized into five groups. For 2-year mortality, a score of 0 points corresponded to a 5.0% risk of death, 1 point to an 11.1% risk, 2 points to a 23.0% risk, 3 points to a 41.7% risk and a score of 4 points to a 63.1% risk of death (AUC 0.73; p = .000). For 5-year mortality, a score of 0 points corresponded to a 13.5% risk of death, 1 point to a 31.3% risk, 2 points to a 57.1% risk, 3 points to a 79.5% risk and a score of 4 points to a 91.9% risk of death (AUC 0.74; p = .000).

Conclusions: The all-cause 2-year mortality rate in patients with PAD was 22.3%, and the 5-year mortality rate was 48.8%. The strongest associations with 2- and 5-year mortality were observed for CLTI presence, creatinine, age and fibrinogen. The scoring system based on these variables predicts 2- and 5-year all-cause mortality risk in patients with PAD, with a probability approaching 75%.

Keywords

Lower extremity peripheral arterial disease, chronic limb-threatening ischaemia, all-cause mortality, creatinine, fibrinogen, age

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Introduction

Lower extremity peripheral arterial disease (PAD) is a widespread condition that affects over 230 million people worldwide[1]. It is the third leading cause of atherosclerotic morbidity, following coronary heart disease and stroke, and the primary cause of lower limb amputations.[2]

The most severe form is chronic limb-threatening ischaemia (CLTI). More than 20% of patients with claudication progress to CLTI within 5 years, with the strongest factors for progression being smoking, diabetes mellitus and renal failure.[3,4]

Despite its clinical significance, PAD remains understudied and underrecognized compared to other conditions such as stroke or myocardial infarction. Additionally, it is often underestimated by both healthcare providers and patients themselves. Consequently, many patients with PAD do not receive evidence-based therapies, even though their risk of stroke or myocardial infarction is at least as high as that of patients with coronary artery disease.

Since morbidity and mortality in these patients are closely linked to cardiovascular disease, pharmacological treatment primarily focuses on reducing cardiovascular risk. However, a study by Kochara et al.[4] revealed that over 40% of deaths in patients with PAD are attributed to non-cardiovascular causes, including infections, malignancies and pulmonary diseases.

Endovascular therapy may be beneficial for selected patients with limiting claudications that persists despite optimal pharmacotherapy and exercise therapy. On the other hand, early endovascular treatment is important for patients with CLTI to prevent amputation by restoring direct blood flow to the foot.[5]

The primary aim of the study was to identify nonspecific risk factors for 2- and 5-year all-cause mortality in endovascularly treated patients with PAD. The secondary aim was to develop a simple, clinically applicable scoring system to estimate the probability of 2- and 5-year all-cause mortality based on identified risk factors.

Patients and methods

We conducted a retrospective study using data of patients with PAD who underwent endovascular treatment between January 2016 and December 2018 at the East Slovak Institute of Cardiovascular Diseases in Slovakia. The study was approved by the Ethics Committee (approval number A2082024). Prior to undergoing endovascular treatment, all patients provided general informed consent for the processing of all their data.

Data collection

Sociodemographic data (age, sex, body mass index, smoking status), treatment details (anticoagulation therapy, antihypertensive therapy, statin therapy, proton pump inhibitor therapy), comorbidities (arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), atrial fibrillation, coronary artery disease, dyslipoproteinemia, malignancy, heart failure with reduced ejection fraction (HFrEF)), and selected laboratory parameters (LDL-cholesterol, HDL-cholesterol, creatinine, fibrinogen, estimated glomerular filtration rate (eGFR)) were collected from electronic medical records. Survival data were obtained from the Health Care Surveillance Authority Registry. This Register recorded the date of death without specifying the death cause.

Coronary artery disease was defined as a history of typical angina, myocardial infarction confirmed by coronary angiography or CT-coronary angiography, either in the past or during hospitalization. COPD was defined as a previously diagnosed condition or active treatment of COPD. Hypertension was identified by systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current antihypertensive treatment. The diagnosis of diabetes mellitus was based on documentation and/or treatment with antidiabetic medications. Dyslipoproteinemia was defined by treatment with lipid-lowering drugs and/or LDL-cholesterol levels exceeding the recommended target (<1.4 mmol/L).[6] Heart failure with reduced ejection fraction (HfrEF) was defined as a left ventricular ejection fraction ≤40%, diagnosed either before or during hospitalization via echocardiography. Atrial fibrillation was confirmed either in pre-hospital documentation or by electrocardiographic evidence during hospitalization, without differentiation between paroxysmal, persistent or permanent types. Malignancy was defined as any malignancy in the perihospitalisation period and/or malignancy in the past. Intermittent claudications were characterized by aching, heaviness, burning, fatigue, cramping and/or tightness in the affected limb, with symptoms occurring after a reproducible amount of exercise. All patients with claudications had limiting and severe claudications despite at least 6 months of pharmacotherapy and exercise therapy.

CLTI was defined as the presence of ischaemic rest pain, a non-healing lower-limb wound lasting ≥2 weeks, or lower-limb gangrene. Chronic kidney disease was defined by documented chronic kidney disease with eGFR <60 mL/min/1.73 m^2. Non-smokers were defined as individuals with a lifetime history of smoking fewer than 100 cigarettes. Before endovascular treatment, blood samples were collected to determine biochemical parameters. All patients underwent lower limb arterial ultrasonography prior to endovascular treatment at our centre. During hospitalization, angiography and endovascular treatment were performed.

If the angiography finding was unsuitable for endovascular treatment (e.g. occlusion or severe stenosis of the common femoral artery, long occlusions and

multisegmental involvement), vascular surgeons were consulted immediately during angiography. Patients who were unsuitable for endovascular treatment were not included in the analysis. Endovascularly treated regions were divided into aortoiliac, femoropopliteal and crural region. The number of patent crural arteries after endovascular treatment was determined from the angiographic images, and types of endovascular treatment (angioplasty, stenting, drug eluting balloons, subintimal recanalization) were obtained from medical records.

Statistical analysis

Categorical variables were expressed as counts and percentages and compared using the Chi-square test. The normality of continuous variables was assessed using the Shapiro–Wilk test. Parametric data were presented as mean ± standard deviation, nonparametric data were presented as median with the 25th and 75th percentiles (lower and upper quartiles). Outliers were retained. The *t* test (for parametric data) and the Mann–Whitney U test (for nonparametric data) were used to compare continuous variables between groups.

A Cox proportional hazards regression model was used to examine the association between variables and all-cause mortality. Multivariate analyses were performed after adjusting for age, CLTI, creatinine and fibrinogen in model 1. In model 2, adjustments were made for age, hypertension, diabetes mellitus, sex, smoking, dyslipidemia, CLTI, COPD, malignancy, atrial fibrillation, HfrEF, coronary artery disease, fibrinogen and creatinine.

Variables associated with mortality with p-value <.02 in all analyses were included in the scoring system. Their independence was assessed using multicollinearity analysis (Variance Inflation Factor – VIF and Tolerance). Cut-off values for continuous variables were determined using a decision tree approach (CRT method, custom value 1). The decision tree identified the factors with the greatest impact on mortality. Continuous variables were binary coded using cut-off values, and a patient outcome score was assigned based on the sum of the values. Binary logistic regression was used to assess patient mortality depending on the outcome score. The predictive performance of the scoring system was evaluated using the Area Under Curve (AUC) of Receiver Operating Characteristic (ROC) curve. Statistical significance was set at $p < .05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

Results

A total of 676 patients (216 women and 460 men) with a mean age of 68.6 ± 9.74 years were analyzed, 66.7% of patients ($N = 451$) had CLTI. Treatment of one anatomical region was performed in 68.5% of patients ($N = 463$), treatment of two regions was performed in 30.9% of patients ($N = 209$), and treatment of three regions was performed in 0.59% of patients ($N = 4$).

The aortoiliac region was treated in 21.2% of patients ($N = 143$), the femoropopliteal region in 60.4% of patients ($N = 408$) and the crural region in 50.4% of patients ($N = 341$).

Angioplasty of the aortoiliac region was performed in 0.74% of patients ($N = 5$), angioplasty of the femoropopliteal region was performed in 9.80% of patients ($N = 66$); angioplasty of the crural arteries in 45.9% of patients ($N = 310$).

Stenting (including drug eluting stents) of the aortoiliac region was performed in 20.4% of patients ($N = 138$); stenting of the femoropopliteal region was performed in 28.6% of patients ($N = 193$); crural artery stenting in 0.89% of patients ($N = 6$).

Drug eluting balloons in the aortoiliac region were not used, in the femoropopliteal region they were used in 20.6% of patients ($N = 139$), in the crural region in 2.37% of patients ($N = 16$). Subintimal recanalization in any region was used in 9.48% od patients ($N = 64$).

The all-cause 2-year mortality rate was 22.3% ($N = 151$); 29.5% ($N = 133$) in patients with CLTI; and 8% ($N = 18$) in patients with claudications. The all-cause 5-year mortality rate was 48.8% ($N = 330$); 60.5% ($N = 273$) in patients with CLTI; and 25.3% ($N = 57$) in patients with claudications. Table 1 presents demographic factors, comorbidities, laboratory parameters, selected procedural factors and pharmacotherapy after endovascular treatment and compares living and deceased patients during 2- and 5-year mortality monitoring.

Table 2 shows the association between demographic characteristics, comorbidities, laboratory parameters, selected procedural factors and postprocedural treatment and 2-year all-cause mortality, and Table 3 demonstrates the association between these variables and 5-year all-cause mortality.

All patients were treated with antiplatelet therapy after the procedure, the duration of which was determined by the type of endovascular procedure, comorbidities, and concomitant treatment, with a minimum duration of 1 month.

In univariate analysis and both multivariate analyses, the strongest associations with 2- and 5-year mortality were found for CLTI, creatinine, age and fibrinogen, which were statistically independent (age: VIF 1.10, Tolerance 0.91; CLTI: VIF 1.26, Tolerance 0.80; creatinine: VIF 1.03, Tolerance 0.97; fibrinogen: VIF 1.15, Tolerance 0.87). Based on the cut-off values of continuous variables (age, creatinine and fibrinogen) and the dichotomous variable CLTI, a predictive scoring model for 2- and 5-year mortality was developed. Each variable was scored as follows: creatinine >102.4 μmol/L: 1 point; fibrinogen >5.41 g/L:

Table 1. Patient demographic factors, comorbidities, laboratory parameters, selected procedural factors, and pharmacotherapy after endovascular treatment in living and deceased patients during 2- and 5-year mortality monitoring.

	All patients (*N* = 676)	Alive patients after 2-year follow-up (*N* = 525)	Dead patients after 2-year follow-up (*N* = 151)	p-value	Alive patients after 5-year follow-up (*N* = 346)	Dead patients after 5-year follow-up (*N* = 330)	p-value
Demographic factors							
Women (*N*., %)	216 (32.0%)	152 (29.0%)	64 (42.4%)	0.002	88 (25.4%)	128 (38.8%)	0.000
Age (years)¡	68.6 ± 9.74	70.0 ± 9.31	74.1 ± 9.26	0.000	65.5 ± 8.97	71.8 ± 9.48	0.000
Smokers + exsmokers (*N*., %)	576 (85.2%)	450 (85.7%)	126 (83.4%)	0.489	298 (86.1%)	278 (84.2%)	0.490
Body mass index (kg/m^2)¡	27.9 ± 5.79	28.0 ± 5.93	27.4 ± 5.24	0.219	27.7 ± 5.86	28.1 ± 5.72	0.566
Comorbidities							
CLTI	451 (66.7%)	318 (60.6%)	133 (88.1%)	0.000	178 (51.4%)	273 (82.7%)	0.000
Ankle-brachial index°	0.42 (0.22; 0.63)	0.43 (0.22; 0.62)	0.39 (0.20; 0.66)	0.521	0.46 (0.24; 0.63)	0.39 (0.20; 0.59)	0.341
Coronary artery disease (*N*., %)	346 (51.2%)	167 (31.8%)	67 (44.4%)	0.002	146 (42.2%)	200 (60.6%)	0.000
Chronic obstructive pulmonary disease (*N*., %)	95 (14.1%)	70 (13.3%)	25 (16.6%)	0.315	42 (12.1%)	53 (16.1%)	0.142
Malignancy (*N*., %)	57 (8.4%)	38 (7.2%)	19 (12.6%)	0.037	19 (5.50%)	38 (11.5%)	0.005
Atrial fibrillation (*N*., %)	116 (17.2%)	70 (13.3%)	46 (30.5%)	0.000	36 (10.4%)	80 (24.2%)	0.000
HfrEF	67 (9.9%)	41 (7.81%)	26 (17.2%)	0.001	17 (4.91%)	50 (15.2%)	0.000
Hypertension (*N*., %)	602 (89.1%)	461 (87.8%)	141 (93.4%)	0.053	296 (85.5%)	306 (92.7%)	0.003
Chronic kidney disease with eGFR<60 mL/min/1.73 m^2	131 (19.4%)	73 (13.9%)	58 (38.4%)	0.000	29 (8.4%)	102 (30.9)	0.000
Diabetes mellitus (*N*., %)	403 (59.6%)	306 (58.3%)	97 (64.2%)	0.189	174 (50.3%)	229 (69.4%)	0.000
Dyslipoproteinemia (*N*., %)	600 (88.8)	475 (90.5%)	125 (82.8%)	0.008	317 (91.6%)	283 (85.8%)	0.016
Pharmacotherapy after endovascular treatment							
Anticoagulation therapy (*N*., %)	148 (21.9%)	93 (17.7%)	55 (36.4%)	0.000	52 (15.0%)	96 (29.1%)	0.000
Beta-blockers (*N*., %)	383 (56.7%)	282 (53.7%)	101 (66.9%)	0.004	169 (48.8%)	214 (64.8%)	0.000
ACE-inhibitors/ARBs (*N*., %)	488 (72.2%)	388 (73.9%)	100 (66.2%)	0.058	271 (78.3%)	217 (65.8%)	0.000
Calcium channel blockers (*N*., %)	301 (44.5%)	233 (44.4%)	68 (45.0%)	0.902	142 (41.0%)	159 (48.2%)	0.067
Statins (*N*., %)	567 (83.9%)	450 (85.7%)	117 (77.5%)	0.013	300 (86.7%)	267 (80.9%)	0.032
Proton pump inhibitors (*N*., %)	140 (20.7%)	98 (18.7%)	42 (27.8%)	0.014	61 (17.6%)	79 (23.9%)	0.043
Preprocedural laboratory parameters							
Creatinine (μmol/l)°	82.8 (69.2; 108.5)	81.4 (68.0; 100.5)	97.9 (57.8; 151.0)	0.000	77.2 (66.0; 91.0)	94.3 (73.7; 130.5)	0.000
Fibrinogen (g/l)¡	4.37 ± 1.50	4.28 ± 1.44	4.87 ± 1.67	0.000	4.08 ± 1.28	4.75 ± 1.66	0.000
HDL-cholesterol (mmol/l)¡	1.10 ± 0.37	1.16 ± 0.37	1.12 ± 0.37	0.503	1.20 ± 0.39	1.09 ± 0.34	0.017
LDL-cholesterol (mmol/l)°	2.73 (2.02; 3.74)	2.80 (2.04; 3.76)	2.47 (1.93; 3.41)	0.213	2.88 (2.21; 4.02)	2.38 (1.85; 3.34)	0.001
Procedural factors							
Two or three regions of treatment	213 (31.5%)	142 (27.0%)	71 (47.7%)	0.000	79 (22.8%)	134 (40.6%)	0.000
Two or three patent crural arteries post-treatment	455 (67.3%)	365 (69.5%)	90 (59.6%)	0.001	249 (71.9%)	206 (62.1%)	0.001

Categorical data expressed as counts with percentages; °non parametric data expressed as median (25th, 75th percentiles); ¡parametric data expressed as mean ± standard deviation; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CLTI: chronic limb-threatening ischaemia; HR: hazard ratio; HDL: high-density lipoprotein; HfrEF: heart failure with reduced ejection fraction, LDL: low-density lipoprotein.

1 point; age ≥68 years: 1 point; CLTI: 1 point. Patients were categorized into five groups based on their total score. For 2-year mortality assessment, a score of 0 points corresponded to a 5.0% risk of death, 1 point to an 11.1% risk, 2 points to a 23.0% risk, 3 points to a 41.7% risk and a score of 4 points to a 63.1% risk of death over next 2 years (p = .000). The model was validated with an AUC ROC of 0.73 (95% CI 0.68–0.77; p = .000; SE = 0.023), indicating a 73% probability of correctly predicting 2-year mortality risk (Figure 1).

When assessing the risk of 5-year mortality, a score of 0 points corresponded to a 13.5% risk of death, 1 point to a 31.3% risk, 2 points to a 57.1% risk, 3 points to a 79.5% risk

Table 2. The effect of demographic factors, comorbidities, laboratory parameters, selected procedural factors and pharmacotherapy on 2-year all-cause mortality after endovascular treatment of PAD patients.

	2-year all-cause mortality (univariate analysis) HR (95%CI; p)	2-year all-cause mortality (Model 1[a]) HR (95%CI; p-value)	2-year all-cause mortality (Model 2[b]) HR (95%CI; p-value)
Demographic factors			
Women	1.70 (1.23–2.35; 0.001)	1.21 (0.86–1.70; 0.276)	1.30 (0.92–1.85; 0.141)
Age (years)	1.08 (1.06–1.09; 0.000)	1.07 (1.05–1.09; 0.000)	1.06 (1.04–1.08; 0.000)
Smokers + exsmokers	0.82 (0.54–1.26; 0.373)	1.04 (0.67–1.62; 0.866)	1.03 (0.65–1.61; 0.916)
Body mass index (kg/m^2)	0.98 (0.96–1.01; 0.218)	0.97 (0.94–1.004; 0.083)	0.96 (0.93–0.99; 0.020)
Comorbidities			
CLTI	4.23 (2.59–6.92; 0.000)	2.26 (1.33–3.83; 0.003)	2.36 (1.36–4.12; 0.002)
Ankle-brachial index	0.73 (0.29–1.88; 0.517)	0.76 (0.31–1.84; 0.543)	0.62 (0.25–1.57; 0.314)
Coronary artery disease	1.35 (1.10–1.65; 0.005)	1.14 (0.91–1.42; 0.265)	1.06 (0.83–1.34; 0.660)
Chronic obstructive pulmonary disease	1.19 (0.78–1.83; 0.430)	1.83 (1.17–2.87; 0.008)	1.56 (0.98–2.49; 0.063)
Malignancy	1.64 (1.01–2.65; 0.044)	1.60 (0.97–2.61; 0.057)	1.46 (0.90–2.39; 0.130)
Atrial fibrillation	2.41 (1.71–3.41; 0.000)	1.43 (0.99–2.07; 0.059)	1.27 (0.86–1.86; 0.226)
HfrEF	2.15 (1.41–3.29; 0.000)	1.83 (1.19–2.82; 0.006)	1.59 (1.00–2.52; 0.050)
Chronic kidney disease with eGFR<60 mL/min/1.73 m^2	3.12 (2.25–4.33; 0.000)	1.71 (1.11–2.62; 0.014)	1.54 (0.98–2.41; 0.059)
Hypertension	1.89 (1.00–3.59; 0.052)	1.59 (0.83–3.02; 0.159)	1.34 (0.69–2.60; 0.394)
Diabetes mellitus	1.25 (0.90–1.74; 0.188)	0.97 (0.68–1.40; 0.887)	0.95 (0.66–1.37; 0.802)
Dyslipoproteinemia	0.55 (0.36–0.84; 0.006)	0.73 (0.48–1.13; 0.160)	0.74 (0.48–1.15; 0.179)
Pharmacotherapy after endovascular treatment			
Anticoagulation therapy	2.33 (1.67–3.24; 0.000)	1.48 (1.04–2.11; 0.032)	1.30 (0.81–2.08; 0.281)
Beta-blockers	1.65 (1.18–2.32; 0.004)	1.29 (0.91–1.83; 0.152	1.09 (0.74–1.61; 0.659)
ACE-inhibitors/ARBs	0.74 (0.53–1.03; 0.077)	1.10 (0.76–1.61; 0.597)	1.01 (0.68–1.50; 0.950)
Calcium channel blockers	1.04 (0.76–1.43; 0.806)	0.86 (0.61–1.20; 0.364)	0.81 (0.57–1.15; 0.235)
Statins	0.60 (0.41–0.88; 0.008)	0.69 (0.47–1.02; 0.059)	0.76 (0.38–1.51; 0.437)
Proton pump inhibitors	1.60 (1.21–2.84; 0.010)	1.37 (0.95–1.81; 0.093)	1.28 (0.87–1.87; 0.210)
Preprocedural laboratory parameters			
Creatinine (μmol/l)	1.003 (1.002–1.004; 0.000)	1.003 (1.002–1.004;0.000)	1.003 (1.002–1.004;0.000)
Fibrinogen (g/l)	1.22 (1.11–1.33; 0.000)	1.14 (1.03–1.27;0.014)	1.15 (1.03–1.28;0.014)
HDL-cholesterol (mmol/l)	0.77 (0.35–1.72; 0.526)	0.76 (0.33–1.81;0.556)	0.85 (0.35–2.09;0.727)
LDL-cholesterol (mmol/l)	0.84 (0.64–1.10; 0.209)	0.93 (0.71–1.22;0.606)	0.94 (0.71–1.25;0.680)
Procedural factors			
Two or three regions of treatment	2.15 (1.56–2.96; 0.000)	1.29 (0.86–1.94; 0.220)	1.34 (0.88–2.05; 0.168)
Treatment of aortoiliac region	0.53 (0.33–0.85; 0.008)	1.00 (0.52–1.85; 0.962)	0.85 (0.44–1.63;0.619)
Treatment of femoropopliteal region	1.56 (1.11–2.20; 0.011)	1.52 (0.99–2.33;0.056)	1.50 (0.98–2.31;0.064)
Treatment of crural arteries	2.02 (1.44–2.82; 0.000)	0.84 (0.52–1.34; 0.465)	0.97 (0.59–1.59;0.908)
Two or three patent crural arteries post-treatment	0.55 (0.40–0.78; 0.001)	1.05 (0.67–1.64; 0.824)	1.03 (0.65–1.63; 0.897)

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CLTI: chronic limb-threatening ischaemia; HR: hazard ratio; HDL: high-density lipoprotein; HfrEF: heart failure with reduced ejection fraction, LDL: low-density lipoprotein.
[a]Model 1: after adjustment including age, CLTI, fibrinogen and creatinine.
[b]Model 2: after adjustment including age, hypertension, diabetes mellitus, sex, smoking, chronic obstructive pulmonary disease, dyslipoproteinemia, CLTI, atrial fibrillation, HfrEF, malignancy, coronary artery disease, creatinine and fibrinogen.

and a score of 4 points to a 91.9% risk of death over the next 5 years (p = .000).

The model was validated with an AUC ROC of 0.74 (95% CI 0.70–0.77; p = .000; SE = 0.019), indicating a 74% probability of correctly predicting 5-year mortality risk (Figure 2). The predictive scoring system is presented in Table 4.

Creatinine emerged as the most significant factor associated with mortality in patients with CLTI. The 2-year mortality rate in patients with CLTI and creatinine >151.6 μmol/L (N = 58) was 60.3% (N = 35); in patients with creatinin 115.5–151.6 μmol/L (N = 51) was 39.2% (N = 20); and in patients with creatinine ≤115.4 μmol/L (N = 342) the 2-year mortality rate was 22.8% (N = 78).

Table 3. The effect of demographic factors, comorbidities, laboratory parameters, selected procedural factors and pharmacotherapy on 5-year all-cause mortality after endovascular treatment of PAD patients.

	5-year all-cause mortality (univariate analysis) HR (95%CI; p)	5-year all-cause mortality (Model 1[a]) HR (95%CI; p-value)	5-year all-cause mortality (Model 2[b]) HR (95%CI; p-value)
Demographic factors			
Women	1.60 (1.28–2.00; 0.000)	1.24 (0.98–1.57; 0.068	1.30 (1.03–1.65; 0.031)
Age (years)	1.06 (1.05–1.07;0.000)	1.05 (1.04-1.07; 0.000)	1.05 (1.03-1.06; 0.000)
Smokers + exsmokers	0.88 (0.66–1.19; 0.413)	1.16 (0.86–1.58; 0.340)	1.13 (0.83–1.54; 0.443)
Body mass index	1.01 (1.00–1.03; 0.480)	1.00 (0.98–1.02; 0.860)	0.99 (0.96–1.01; 0.163)
Comorbidities			
CLTI	3.30 (2.48–4.39; 0.000)	2.00 (1.47–2.72; 0.000)	2.00 (1.44-2.78; 0.000)
Ankle-brachial index	0.71 (0.38–1.31; 0.273)	0.87 (0.50–1.51; 0.622)	0.70 (0.39–1.26; 0.235)
Coronary artery disease	1.75 (1.41–2.19; 0.000)	1.16 (1.002–1.35; 0.047)	1.07 (0.92–1.25; 0.393)
Chronic obstructive pulmonary disease	1.23 (0.91–1.64; 0.175)	1.98 (1.43– 2.64; 0.000)	1.75 (1.27–2.40; 0.001)
Malignancy	1.74 (1.24–2.43; 0.001)	1.59 (1.12–2.25; 0.009)	1.46 (1.02–2.07; 0.037)
Atrial fibrillation	2.06 (1.60–2.66; 0.000)	1.35 (1.12–2.25; 0.009)	1.19 (0.90–1.57; 0.224)
HfrEF	2.18 (1.62–2.95; 0.000)	1.85 (1.36–2.52; 0.000)	1.58 (1.14–2.19; 0.006)
Chronic kidney disease with eGFR<60 mL/min/1.73 m^2	2.73 (2.16–3.46; 0.000)	1.47 (1.08–2.01; 0.015)	1.28 (0.93–1.76;0.136)
Hypertension	1.85 (1.22-2.80; 0.004)	1.58 (1.04–1.76; 0.027)	1.35 (0.87–2.08; 0.180)
Diabetes mellitus	1.73 (1.37–2.19; 0.000)	1.30 (1.00–1.64; 0.054)	1.28 (0.99–1.65; 0.060)
Dyslipoproteinemia	0.64 (0.47–0.88; 0.005)	0.82 (0.60–1.12; 0.204)	0.76 (0.55–1.05; 0.0.091)
Pharmacotherapy after endovascular treatment			
Anticoagulation therapy	1.85 (1.46–2.35; 0.000)	1.24 (0.97–1.60; 0.092)	1.15 (0.82–1.63; 0.415)
Beta-blockers	1.63 (1.30–2.05; 0.000)	1.30 (1.03–1.64; 0.026)	1.12 (0.87–1.46; 0.378)
ACE-inhibitors/ARBs	0.67 (0.53–0.84; 0.000)	0.85 (0.66–1.09; 0.202)	0.78 (0.60–1.01; 0.060)
Calcium channel blockers	1.20 (0.97–1.49; 0.102)	1.02 (0.81–1.27;0.878)	0.95 (0.75–1.21; 0.661)
Statins	0.71 (0.54–0.93; 0.014)	0.80 (0.61–1.06; 0.115)	0.87 (0.86–1.47; 0.400)
Proton pump inhibitors	1.37 (1.06–1.76; 0.015)	1.23 (0.95–1.60; 0.120)	1.23 (0.95–1.60; 0.116)
Preprocedural laboratory parameters			
Creatinine (μmol/l)	1.003 (1.002–1.004; 0.000)	1.003 (1.002-1.004; 0.000)	1.003 (1.002-1.004; 0.000)
Fibrinogen (g/l)	1.21 (1.12–1.31; 0.000)	1.17 (1.09–1.26; 0.000)	1.17 (1.09–1.26; 0.000)
HDL-cholesterol (mmol/l)	0.52 (0.29–0.93; 0.027)	0.56 (0.31–1.01; 0.054)	0.57 (0.31–1.07; 0.079)
LDL-cholesterol (mmol/l)	0.75 (0.62–0.90; 0.002)	0.81 (0.67–0.98; 0.026)	0.81 (0.67–0.98; 0.028)
Procedural factors			
Two or three regions of treatment	1.86 (1.50–2.32;0.000)	1.23 (0.93–1.63;0.145)	1.33 (1.00–1.78; 0.060)
Treatment of the aortoiliac region	0.71 (0.54–0.94; 0.018)	1.34 (0.92–1.94; 0.123)	1.34 (0.90–1.98; 0.148)
Treatment of the femoropopliteal region	1.23 (0.99–1.54; 0.067)	1.31 (0.99–1.74; 0.056)	1.35 (1.02–1.79; 0.057)
Treatment of crural arteries	1.86 (1.49–2.33; 0.000)	0.79 (0.58–1.08; 0.142)	0.85 (0.61–1.18; 0.327)
Two or three patent crural arteries after treatment	0.63 (0.50–0.80;0.000)	1.22 (0.89–1.67;0.217)	1.19 (0.86–1.64; 0.303)

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; CLTI: chronic limb-threatening ischaemia; HR: hazard ratio; HDL: high-density lipoprotein; HfrEF: heart failure with reduced ejection fraction, LDL: low-density lipoprotein.
[a]Model 1: after adjustment including age, CLTI, fibrinogen and creatinine.
[b]Model 2: after adjustment including age, hypertension, diabetes mellitus, sex, smoking, chronic obstructive pulmonary disease, dyslipoproteinemia, CLTI, atrial fibrillation, HFrEF, malignancy, coronary artery disease, creatinine and fibrinogen.

The 5-year mortality rate in patients with CLTI and creatinine levels >151.6 μmol/L ($N = 58$) was 96.6% ($N = 56$); in patients with creatinine levels 100.0–151.6 μmol/L ($N = 102$) was 69.6% ($N = 71$); in patients with creatinine 72.4–99.9 μmol/L ($N = 166$) was 52.4% ($N = 87$); and in patients with CLTI and creatinine ≤72.3 μmol/L ($N = 125$) the 5-year mortality rate was 47.2% ($N = 59$).

In patients without CLTI, age was the most significant factor influencing 5-year mortality. Among patients older than 68.0 years ($N = 77$), the mortality rate was 41.6% ($N = 32$), while in patients ≤68.0 years ($N = 148$) the 5-year mortality rate was 16.9% ($N = 25$).

No association was showed between treated region, number of treated regions, number of patent crural arteries,

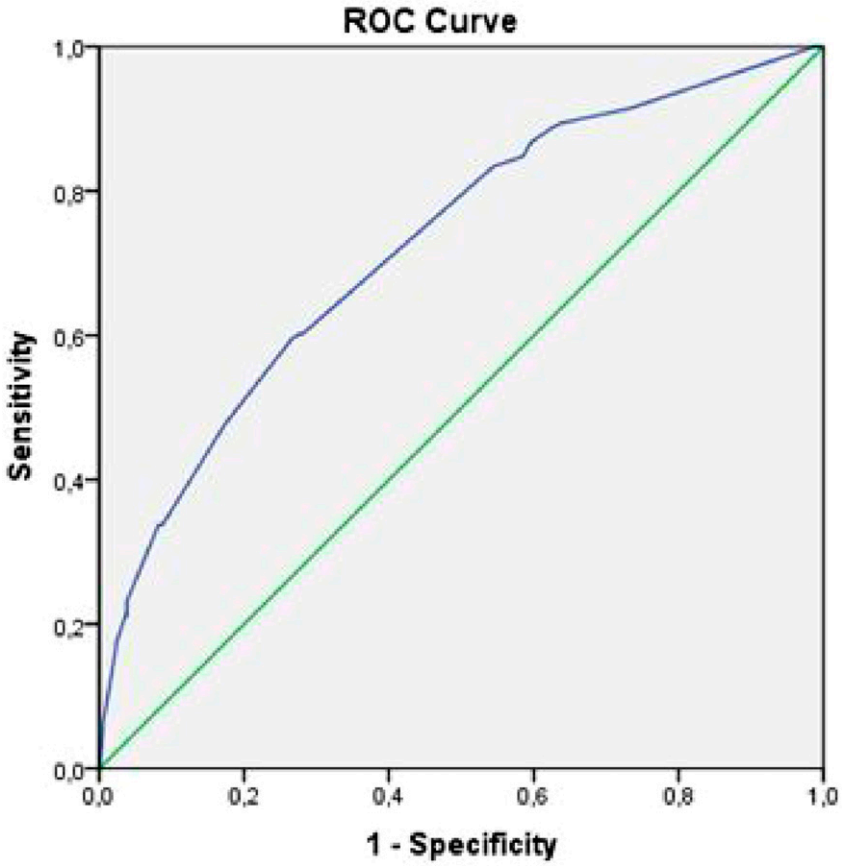

Figure 1. ROC curve of the 2-year mortality scoring system, based on a composite variable comprising CLTI, creatinine, age, and fibrinogen (AUC 0.73; 95% CI: 0.68–0.77; p = .000; SE 0.023).

treatment methods and 2- and 5-year mortality in univariate and both multivariate analyses simultaneously.

Discussion

Our scoring system based on commonly available data and laboratory parameters can predict the 2- and 5-year mortality risk in patients following endovascular treatment for PAD, with a probability approaching 75%. The strongest associations with 2- and 5-year mortality in patients with PAD were observed for CLTI, creatinine, age and fibrinogen. In patients with CLTI, creatinine levels were the most significant factor associated with both 2- and 5-year mortality, while in patients with claudications, age was the strongest predictor of 5-year mortality.

As expected, patients with CLTI had a higher mortality rate than those with claudications, reflecting the greater comorbidity burden in these patients. CLTI patients were significantly older than patients with claudications (70.4 vs 64.8 years) and had a higher prevalence of coronary artery disease (56.8% vs 40.0%), atrial fibrillation (20.4% vs 10.7%), diabetes mellitus (71.8% vs 35.1%), HfrEF (11.5% vs 6.7%) and chronic kidney disease (23.7% vs 10.7%). The all-cause 2-year mortality rate in CLTI patients was more than three times higher than in non-CLTI patients (29.5% vs 8%), and the 5-year mortality rate was more than double (60.5% vs 25.3%), aligned with results from a Dutch national registry study.[7]

At the time of CLTI diagnosis, the mortality risk is approximately 18–25% at 1 year and around 60% at 5 years.[8–10] Mortality risk increases with declining kidney function. A study by Hata et al. reported a 32.3% 2-year mortality rate in patients with PAD, with 52% of these patients being treated with hemodialysis.[11]

Higher levels of creatinine and fibrinogen were significantly associated with increased mortality. Creatinine increases with decreased glomerular filtration and is a marker of kidney dysfunction; however, both creatinine and fibrinogen can also be associated with various diseases such as cardiovascular diseases, malignancies and inflammatory diseases.[12,13]

Kidney disease is a common comorbidity in PAD patients. In a study conducted by Xie et al., 27% of the study patients had chronic kidney disease.[14] After endovascular treatment, mortality was more than 50% higher in patients with eGFR <60 mL/min/1.73 m^2 and 5-year survival of these patients was lower compared to patients with higher

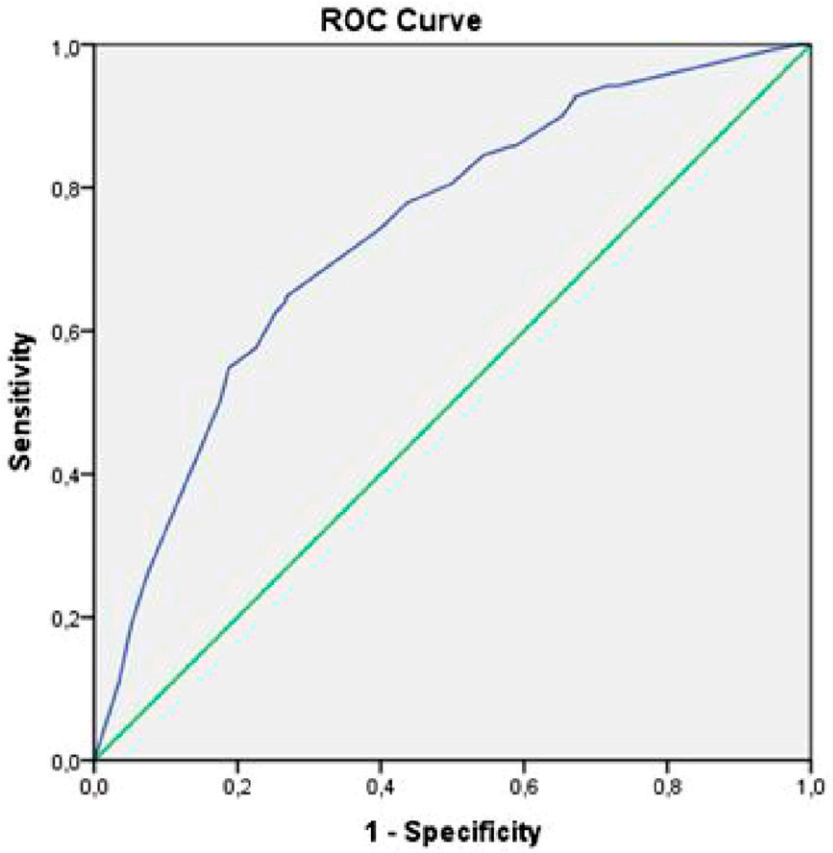

Figure 2. ROC curve of the 5-year mortality scoring system, based on a composite variable comprising CLTI, creatinine, age and fibrinogen (AUC 0.74; 95% CI: 0.70–0.77; p = .000; SE 0.019).

Table 4. Scoring system (CLTI, creatinine, age, fibrinogen) for predicting 2- and 5-year all-cause mortality after endovascular treatment of PAD patients.

Scoring system: CLTI = 1 point, age ≥68 years = 1 point, creatinine >102,4 μmol/l = 1 point, fibrinogen >5.41 g/L = 1 point					
	0 point	1 point	2 points	3 points	4 points
2-year mortality risk	5.0%	11.1%	23.0%	41.7%	63.1%
5-year mortality risk	13.5%	31.3 %	57.1 %	79.5 %	91.9 %

eGFR (49.9% vs 80.1%).[14] In our study group, 19.4% of patients (N = 131) had chronic kidney disease with eGFR <60 mL/min/1.73 m^2, and the 2-year mortality rate for these patients was 44.3% (N = 58), while the 5-year mortality rate was 77.9% (N = 102).

Recent evidence has shown that elevated creatinine is associated with cardiovascular mortality, non-cardiovascular mortality and with poorer prognosis in patients with various malignancies.[15] Elevated baseline creatinine has been identified as a predictor of mortality following cardiac surgery, and linear correlation between serum creatinine and all-cause mortality has been documented in patients after percutaneous coronary intervention, independent of acute myocardial infarction, cardiac death and stroke.[16,17] Creatinine also serves as a predictor of mortality in patients after acute stroke and in those hospitalized with COVID-19.[18,19] In patients with colorectal cancer, renal cell carcinoma, ovarian cancer, and sarcomas, elevated creatinine levels have been linked to poorer survival outcomes, likely due to excessive muscle catabolism and cachexia.[20] Elevated serum creatinine is also thought to be associated with highly active malignancy.[15] Additionally, both PAD and malignancy are associated with chronic low-grade inflammation, which may induce intrarenal vascular dysfunction, resulting in elevated creatinine levels.[15]

Fibrinogen is a critical protein in the coagulation cascade, and its ability to induce the synthesis of

proinflammatory cytokines and modulate the immune response makes it a key component of the acute phase response. It plays an essential role in bleeding, thrombosis and inflammation.[21] Elevated plasma fibrinogen levels have been positively associated with cardiovascular diseases, including coronary artery disease, stroke and mortality from both vascular and nonvascular causes.[12,22] A meta-analysis performed by Cui et al. confirmed a significant association between elevated fibrinogen and both total and cardiovascular mortality.[23] In patients undergoing peritoneal dialysis, higher fibrinogen levels were associated with increased cardiovascular and all-cause mortality.[24] Fibrinogen has been identified as a biomarker in various malignancies, including ovarian cancer, gastric cancer, renal cell carcinoma, hepatocellular carcinoma and sarcomas. It promotes cancer cell adhesion to platelets, facilitates cancer cell migration, aids in their adherence to distant organs, enhances angiogenesis and helps protect cancer cells from immune surveillance, which explains why elevated fibrinogen levels in patients with cancer can be associated with poorer overall survival.[25]

To improve the prognosis of PAD patients, treatment should be individualized with a person-centred approach. Priority should be given to intensive cardioprotection and nephroprotection, the use of antidiabetic drugs with cardiovascular and nephroprotective benefits, management of infections and comorbidities and with multidisciplinary collaboration in healthcare.

Analysis of the REACH registry found that treatment with at least two preventive therapies (including aspirin, statins and/or angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs)) is associated with a 65% reduction in the risk of all-cause mortality in patients with PAD who do not have a prior history of cardiovascular disease.[26]

In our study group, 83.9% of all patients were treated with statins and 72.2% of patients were treated with ACE inhibitors/ARBs. Among CLTI patients, 81.1% were treated with statins, and 71.1% received ACE inhibitors/ARBs, which means that protective treatment was not used sufficiently. These results led to an intensification of treatment of our patients with PAD according to current guidelines.[5]

Cardiovascular risk can be reduced by cholesterol-lowering therapy, which includes statins, ezetimibe, bempedoic acid, PCSK9 inhibitors and inclisiran.[5] The combination of aspirin and low-dose rivaroxaban also has proven to be beneficial.[5] Regardless of blood pressure levels and in the absence of contraindications, ACEIs/ARBs may be considered in all patients with PAD to reduce cardiovascular events.[5] Sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists offer both cardioprotective and nephroprotective benefits. They are recommended for patients with type 2 diabetes mellitus and PAD, regardless of baseline or target glycated haemoglobin levels or concomitant glucose-lowering therapies.[5,27]

Furthermore, finerenone, a nonsteroidal mineralocorticoid receptor antagonist, has demonstrated a reduction in the risk of renal function decline and cardiovascular events in patients with chronic kidney disease associated with type 2 diabetes mellitus and is currently being investigated in non-diabetic patients with chronic kidney disease.[27]

The most common types of malignancy in patients with PAD are those related to smoking. While there are no formal recommendations for routine cancer screening, some authors suggest screening in selected patient groups, such as those with anaemia or recurrent arterial occlusions.[28]

Patients with PAD are at risk of infectious complications and hospitalization for infection. The association between PAD and infection has been confirmed for cellulitis, pneumonia, bloodstream infection and urinary tract infection.[29] Infection may also be related to invasive procedures such as revascularization. Moreover, immune responses may be impaired due to long-term chronic inflammation, diabetes mellitus and smoking.

Our predictive scoring system offers the advantage of utilizing commonly available variables, such as the presence of CLTI, creatinine levels, age and fibrinogen levels, making it suitable for patients with potentially underdiagnosed comorbidities. However, incorporating additional variables could improve the accuracy of the scoring system. Among laboratory parameters, albumin and neutrophil to lymphocyte ratio may provide further improvement in the accuracy of the scoring system.[30]

Our study has limitations that could have affected the results. Data were evaluated retrospectively. Patients were treated at a single centre, which may have introduced selection bias. Claudication patients included in this study reported limiting and severe claudications; therefore, the results of the study may not be generalizable to patients with non-limiting claudications who were treated with exercise and pharmacotherapy. Similarly, the study only considered PAD patients who underwent endovascular treatment. Patients with CTLI treated with open revascularization and patients with CLTI without the possibility of revascularization treated with amputation were not included in the study.

Other limitations include small sample size, and underrepresentation of women. Furthermore, the analysis combined male and female patients as well as those with and without CLTI. The heterogeneity of patients (different treatment regions, different treatment methods, simultaneous treatment of more than one region) are limitations to the optimal assessment of the impact of treatment method and treatment region on patient mortality. Causes of deaths were not assessed because of the low autopsy rate in our population.

Conclusions

After endovascular treatment of patients with lower extremity peripheral arterial disease, the 2-year all-cause mortality rate was 22.3%; 29.5% in patients with CLTI and 8% in patients with claudication. The 5-year all-cause mortality rate was 48.8%; 60.5% in patients with CLTI and 25.3% in patients with claudication. The strongest associations with 2- and 5-year mortality in patients with PAD were observed for CLTI, creatinine, age and fibrinogen. Creatinine emerges as the most significant nonspecific risk factor associated with mortality in CLTI patients, while age is a risk factor for 5-year mortality in patients without CLTI. The scoring system based on CLTI presence, creatinine, age and fibrinogen predicts the 2- and 5-year mortality risk in patients with lower extremity arterial disease with a probability approaching 75%. Future studies aimed at refining risk estimation could improve the prognosis of patients after endovascular treatment by early diagnosis of associated diseases and targeted management of high-risk patients.

Authors' contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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