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Risk stratification for low extremity amputation in critical limb ischemia patients who have undergone endovascular revascularization

A survival tree analysis

Hsuan-Li Huang, MD[a,b,c,*], Jyh-Ming Jimmy Juang, PhD[d], Chien-An Hsieh, MD[a], Hsin-Hua Chou, MD[a,e], Shih-Jung Jang, MD[a,e], Yu-Lin Ko, PhD[a,e]

Abstract

Patients with peripheral artery disease (PAD) are a heterogeneous population and differ in risk of mortality and low extremity amputation (LEA), which complicates clinical decision-making. This study aimed to develop a simple risk scale using decision tree methodology to guide physicians in managing critical limb ischemia (CLI) patients who will benefit from endovascular therapy (EVT).

A total of 736 patients with CLI, Rutherford classification (RC) stage ≥4, and prior successful EVT were included. Variables significantly associated with LEA by univariate analysis ($P < .05$) were selected and put into classification tree analysis using the Classification and Regression Tree (CART) model with a dependent variable, amputation, and depth of tree = 3. Four risk groups were generated according to the order of amputation rate. The amputation-free survival (AFS) times between groups were compared using the Kaplan–Meier curve with the log-rank test.

Patients were classified as high risk for amputation (G4) (WBC counts ≥10,000/μl, and platelet-lymphocyte ratio (PLR) ≥130.337); intermediate risk group 1 (G3) (WBC < 10,000/μl and RC stage before EVT > 5); intermediate risk group 2 (G2) (WBC count ≥ 10,000/μl, and PLR < 130.337) and low-risk group (G1) (WBC < 10,000/μl, RC before EVT ≤ 5). G2, G3, and G4 risk groups had shorter AFS time (range, 58.7 to 65.5 months) than the G1 risk group (100 months) ($P < .05$). Risk of LEA was significantly higher in the G4, G3, and G2 groups than in the G1 group ($P \leq .05$). The G4 group had the highest risk of amputation (odds ratio = 6.84, $P < .001$).

This simple risk scale model can help healthcare professionals more easily identify and appropriately treat patients with CLI who are at different levels of risk for LEA following endovascular revascularization.

Abbreviations: PAD = peripheral artery disease; LEA = low extremity amputation; CLI = critical limb ischemia; EVT = endovascular therapy; RC = Rutherford classification; CART = Classification and Regression Tree; PLR = platelet-lymphocyte ratio; NLR = neutrophil-lymphocyte ratio; CRP = C-reactive protein; AFS = amputation-free survival.

Keywords: amputation, critical limb ischemia, endovascular therapy, risk stratification

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H-LH and J-MJJ contributed equally to this work and should be considered co-first authors.

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[a] Division of Cardiology, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, [b] School of Post-Baccalaureate Chinese Medicine, Tzu Chi University, Hualien, [c] Division of Cardiology, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, [d] Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, [e] School of Medicine, Tzu Chi University, Hualien, Taiwan.

[*] Correspondence: Hsuan-Li Huang, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, 289 Jiang Kuo Road, Xindian District, New Taipei City 231, Taiwan (e-mail: huang304@gmail.com).

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1. Introduction

Atherosclerotic peripheral arterial disease (PAD) affects greater than 200 million people worldwide and is a common cause of vascular morbidity.[1] The risk of low extremity amputation (LEA) in patients with PAD are variable, ranging from low incidence in patients with claudication to poorer outcomes in patients with critical limb ischemia (CLI).[2] Without timely revascularization, CLI patients have an increased risk of mortality, morbidity, LEA, and reduced quality of life.[3,4] However, it is not clear why some symptomatic PAD patients are limited to claudication, while others develop CLI, raising the risk of tissue or limb loss.[2] Recent advances in medical care and increasing use of endovascular therapy (EVT) may have an influence on limb outcome in patients with PAD.[5–7] However, many patients are too fragile to withstand the intervention, and the risk benefit ratio in many patients is unfavorable.

Despite the use of revascularization therapy, the rate of death, and major amputation in the short and medium term remains high.[8] Moreover, it is difficult to determine which patients will benefit from EVT. Several scoring systems have been developed and biomarkers identified with the aim of improving the ability to predict functional status and to select patients who may benefit

from revascularization or those for whom primary amputation or palliation should be considered.[9–16] The present study used decision tree modeling to develop a simple risk-stratification scale to assess the benefit of EVT in CLI patients with different levels of risk for LEA.

2. Methods

2.1. Study population and design

Subjects for this study were derived from the Tzuchi Registry of ENDovascular Intervention for Peripheral Artery Disease (TRENDPAD), an ongoing, prospective, physician-initiated, single-center observational registry of patients who underwent EVT for symptomatic PAD starting in July 2005. For the present study, we interrogated the data of CLI patients from this database from July 2005 to December 2017. Included patients had CLI with Rutherford classification (RC) stage ≥4 and had undergone EVT. Patients who had acute limb ischemia, nonatherosclerotic PAD, or a life-threatening infection was excluded. Surviving patients with a follow-up duration <3 months were also excluded. The study was done in accordance with the Declaration of Helsinki, and the protocol was reviewed and approved by the hospital's Institutional Review Board (06-X17–067). All included patients provided signed informed consent.

2.2. Methods

Patients' demographic characteristics, medical comorbidities, and lesion location were recorded. Blood samples were obtained before the EVT or at admission including serum albumin, fasting blood sugar, glycohemoglobin, C-reactive protein (CRP) determined by high-sensitivity assay, complete blood cells and differential counts which will determine the neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). Total cholesterol, triglyceride, high, and low-density lipoprotein cholesterol were examined at admission or using most recent values within 2 months before procedure.

We defined EVT success as ≤30% residual stenosis by quantitative angiography with evidence of at least 1 patent tibial artery to the foot. Each artery of low extremity (iliac, femoropopliteal, anterior, and posterior tibial arteries as well as peroneal artery) having diameter stenosis > 50% was scored as 1 point. Lesion score was the sum of diseased low extremity vessels. LEA included major (limb loss above or below the knee) and minor (transmetatarsal or toe) amputation. The detailed complete baseline examinations, procedures for EVT, and follow-up protocol were conducted as described previously.[17,18]

Patients with tissue loss underwent wound debridement, free flap transplant, and hyperbaric oxygen therapy by the multidisciplinary healthcare team until their wounds healed. The main events (deaths, amputations, cardiovascular events, or re-EVTs) were documented at discharge and follow-up visits. If office follow-up visits were not feasible, alternate data sources included telephone interviews, medical records, the local electronic medical database, and the referring physician.

2.3. Decision tree analysis

Decision tree modeling was implemented using the Classification and Regression Tree (CART) model with a dependent variable, amputation, and depth of tree = 3. The CART model introduced by Breiman et al[19] reflects the 2 sides of the decision tree data analysis method and provides a mathematical framework for the fundamental properties of both classification and regression methodology. Significant variables identified by univariate regression analysis (Table 1, $P < .05$) were selected and entered into the CART model to identify the best predictors of risk. The most heterogeneous variable was selected for the first split, and the hierarchical process was repeated. In the present study, the decision tree was built with a root (WBC used initially), followed by the split node and leaf node. For selection, the branches of the tree and the specifications for tree growth were set using the CART method with a dependent variable, amputation, the minimum number of observations in a split = 100, and with the minimum of complexity parameters.

2.4. Statistical analysis

All patient characteristics are summarized as the mean ± standard deviation (SD) for continuous data and n (%) for categorical variables. Area under the curve (AUC) was used to identify the cut-off values for lab data variables by Youden Index. The cut-off values were double confirmed by their clinical reference/normal values so that the cut-off values were clinically meaningful. Univariate analysis was performed to identify associations between amputation and patient characteristics using the Cox proportional hazards model. Results are presented as hazards ratio (HR) with corresponding 95% confidence intervals (95% CI) and *P* values. Four risk groups were generated according to the order of amputation rate. The AFS times between groups were compared using Kaplan–Meier curve analysis with the log-rank test. Statistical analyses were carried out using R version 3.4.3 and SAS version 9.4 for Windows.

3. Results

The data of a total of 736 patients were entered into the final analysis, including 542 patients without amputation and 194 patients with amputations (58 major and 136 minor amputations). Table 1 summarizes the demographic and clinical characteristics of the included patients. The study patients had a mean age of 71.96 years (SD = 11.48). Patients with LEAs were younger, heavier, taller, with more males, higher creatinine, higher HbA1C, higher platelet count, higher WBC count, more neutrophils, higher platelet-to-lymphocyte ratio, higher neutrophil-to-lymphocyte ratio, greater percentage of coronary artery disease and ESRD, lower HDL, lower hematocrit, lower eGFR, fewer lymphocytes, lower albumin, lower percentage of affected iliac arteries, and higher percentage of chronic kidney disease (*P*values < .05).

3.1. Decision tree analysis

Univariate analysis was used to select the significant variables associated with LEA, and significant variables were put into decision tree analysis (Fig. 1). Three variables were retained in the final tree: WBC, pre-EVT Rutherford classification (RC), and platelet-to-lymphocyte ratio. The decision tree generated 4 risk groups: high-risk patients (G4) (n = 150), intermediate risk group 1 (G2) (n = 63), intermediate risk group 2 (G3) (n = 77), and low-risk group (G1) (n = 446).

Kaplan–Meier curve analysis found that the G4, G2, and G3 risk groups had lower AFS time than the G1 risk group (mean AFS time = 18.0 month for G4, 10.8 months for G3, 78.9 months for G2, and 109.9 months for G1; *P* values < .001) (Fig. 2). The

Table 1

Patients' characteristics by amputation.

Variables	Total (N = 736)	Non-amputation (n = 542)	Amputation (n = 194)	HR (95%CI.)	*P* value
Age, year	71.96 ± 11.48	73.40 ± 11.56	67.93 ± 10.26	0.97 (0.96–0.98)	<.0001*
<65 years	207 (28.13)	133 (24.54)	74 (38.14)	Reference	.0004*
≥65years	529 (71.88)	409 (75.46)	120 (61.86)	0.59 (0.44–0.79)	
Weight (kg)	60.20 ± 10.62	59.25 ± 10.73	62.85 ± 9.87	1.02 (1.01–1.04)	.001*
Height (m)	1.59 ± 0.08	1.57 ± 0.08	1.61 ± 0.08	41.74 (7.71–225.90)	<.0001*
BMI, kg/m^2	23.79 ± 3.41	23.67 ± 3.52	24.15 ± 3.07	1.02 (0.98–1.06)	.28
Sex					
Male	385 (52.31)	269 (49.63)	116 (59.79)	0.73 (0.55–0.97)	.03*
Female	351 (47.69)	273 (50.37)	78 (40.21)	Reference	
Lesion score					
0-2	212 (28.80)	167 (30.81)	45 (23.20)	1.35 (0.97–1.88)	.08
3-5	524 (71.20)	375 (69.19)	149 (76.80)	Reference	
Numbers of BTK disease					
0	38 (5.16)	35 (6.46)	3 (1.55)	Reference	.02*
1	109 (14.81)	88 (16.24)	21 (10.82)	3.02 (0.90–10.13)	
2	215 (29.21)	160 (29.52)	55 (28.35)	3.97 (1.24–12.72)	
3	373 (50.68)	258 (47.60)	115 (59.28)	5.03 (1.59–15.86)	
BUN	33.31 ± 20.68	32.85 ± 20.88	34.58 ± 20.08	1.01 (0.99–1.01)	.08
Creatinine	3.48 ± 3.04	3.25 ± 2.94	4.12 ± 3.02	1.09 (1.04–1.13)	<.0001*
Cholesterol	161.29 ± 41.13	162.40 ± 40.52	158.43 ± 42.58	0.99 (0.99–1.00)	.08
Triglyceride	139.31 ± 82.18	139.86 ± 84.89	137.97 ± 74.99	1.00 (0.99–1.00)	.68
HDL	39.92 ± 12.97	40.49 ± 13.17	38.44 ± 12.39	0.98 (0.97–0.99)	.007*
LDL	94.36 ± 34.47	95.01 ± 33.71	92.59 ± 36.50	0.99 (0.99–1.00)	.14
HbA1C	7.32 ± 1.83	7.11 ± 1.70	7.90 ± 2.04	1.19 (1.11–1.28)	<.0001*
Hematocrit	33.01 ± 5.32	33.39 ± 5.37	31.97 ± 5.07	0.94 (0.92–0.97)	<.0001*
eGFR, ml/minute/1.73 m^2	42.43 ± 39.42	44.22 ± 39.22	37.44 ± 39.66	0.99 (0.99–0.99)	.008*
>60	199 (27.04)	155 (28.60)	44 (22.68)	Reference	.04*
≤60	537 (72.96)	387 (71.40)	150 (77.32)	1.43 (1.02–2.01)	
Platelet count, $10^3/\mu$l	248.72 ± 90.23	237.30 ± 90.40	280.37 ± 107.01	1.01 (1.00–1.01)	<.0001*
<250	425 (57.74)	343 (63.28)	82 (42.27)	Reference	<.0001*
≥250	311 (42.26)	199 (36.72)	112 (57.73)	2.33 (1.75–3.10)	
WBC count, $10^3/\mu$l	9101.82 ± 6900.28	8555.50 ± 7509.10	10628.14 ± 4482.16	1.00 (1.00–1.00)	<.0001*
<10.0	523 (71.06)	425 (78.41)	98 (50.52)	Reference	<.0001*
≥10.0	213 (28.94)	117 (21.59)	96 (49.48)	3.49 (2.63–4.65)	
Neutrophil, %	70.53 ± 11.23	69.03 ± 11.32	74.74 ± 9.87	1.06 (1.04–1.07)	<.0001*
≤75%	462 (62.86)	370 (68.27)	92 (47.67)	Reference	<.0001*
>75%	273 (37.14)	172 (31.73)	101 (52.33)	2.58 (1.94–3.44)	
Lymphocyte, %	19.75 ± 9.56	20.81 ± 9.31	16.77 ± 9.61	0.94 (0.92–0.96)	<.0001*
CRP (mg/dl)	5.47 ± 7.16	4.51 ± 6.91	8.06 ± 7.19	1.06 (1.05–1.08)	<.0001*
≤10	521 (80.15)	458 (84.50)	119 (61.34)	Reference	<.0001*
>10	129 (19.85)	84 (15.50)	75 (38.66)	3.04 (2.21–4.17)	
Albumin	3.00 ± 0.66	3.07 ± 0.66	2.80 ± 0.62	0.49 (0.39–0.59)	<.0001*
Platelet to lymphocyte ratio	193.59 ± 151.55	188.14 ± 164.33	208.88 ± 106.71	1.00 (1.00–1.00)	<.0001*
Neutrophil to lymphocyte ratio	5.62 ± 8.02	5.06 ± 7.06	7.19 ± 10.11	1.03 (1.02–1.04)	<.0001*
RC stage before EVT					
≤5	577 (78.40)	458 (84.50)	119 (61.34)	Reference	<.0001*
>5	159 (21.60)	84 (15.50)	75 (38.66)	3.31 (2.47–4.44)	
Affected ABI	0.47 ± 0.18	0.47 ± 0.17	0.48 ± 0.18	1.23 (0.52–2.92)	.64
Iliac artery affected (%)	82 (11.14)	70 (12.92)	12 (6.19)	0.43 (0.24–0.78)	.005*
Superficial femoral artery or popliteal artery affected (%)	494 (67.12)	365 (67.34)	129 (66.49)	0.96 (0.71–1.29)	.79
Chronic atrial fibrillation (%)	121 (16.44)	95 (17.53)	26 (13.40)	0.82 (0.54–1.25)	.35
Hypertension (%)	619 (84.10)	459 (84.69)	160 (82.47)	0.77 (0.53–1.11)	.16
Coronary artery disease (%)	344 (46.74)	237 (43.73)	107 (55.15)	1.52 (1.14–2.01)	.004*
Congestive heart failure (%)	136 (18.48)	96 (17.71)	40 (20.62)	1.26 (0.89–1.79)	.20
Cerebral vascular accident (%)	166 (22.55)	117 (21.59)	49 (25.26)	1.24 (0.89–1.71)	.19
Chronic kidney disease (%)	537 (72.96)	387 (71.40)	150 (77.32)	1.43 (1.02–2.01)	.04*
ESRD (%)	313 (42.53)	209 (38.56)	104 (53.61)	1.87 (1.41–2.49)	<.0001*
Smoking (%)	266 (36.14)	187 (34.50)	79 (40.72)	1.27 (0.95–1.69)	.11
Lipemia (%)	332 (45.11)	253 (46.68)	79 (40.72)	0.76 (0.57–1.01)	.06
Major amputation					
Pre-EVT RC≤5	577 (78.4)	546 (80.53)	31 (53.44)	Reference	<.0001*
Pre-EVT RC>5	159 (21.6)	132 (19.47)	27 (46.56)	3.60 (2.08–6.24)	
Minor amputation					
Pre-EVT RC≤5	577 (78.4)	489 (81.50)	88 (64.71)	Reference	<.0001*
Pre-EVT RC>5	159 (21.6)	111 (18.50)	48 (35.29)	2.40 (1.60–3.41)	

Characteristics were summarized as mean ± SD for continuous data and n (%) for categorical ones by amputation.

The univariate association was performed using the Cox proportion hazard model and represented as derived hazards ratio (HR) with corresponding 95% CI and *P* values.

* $P < .05$, indicated significantly associated with amputation.

BMI = body mass index, BTK = below-the-knee, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, HbA1C = glycated hemoglobin, CRP = C-reactive protein, EVT: endovascular therapy, ABI = ankle brachial pressure index, ESRD = end-stage renal disease, RC = Rutherford class.

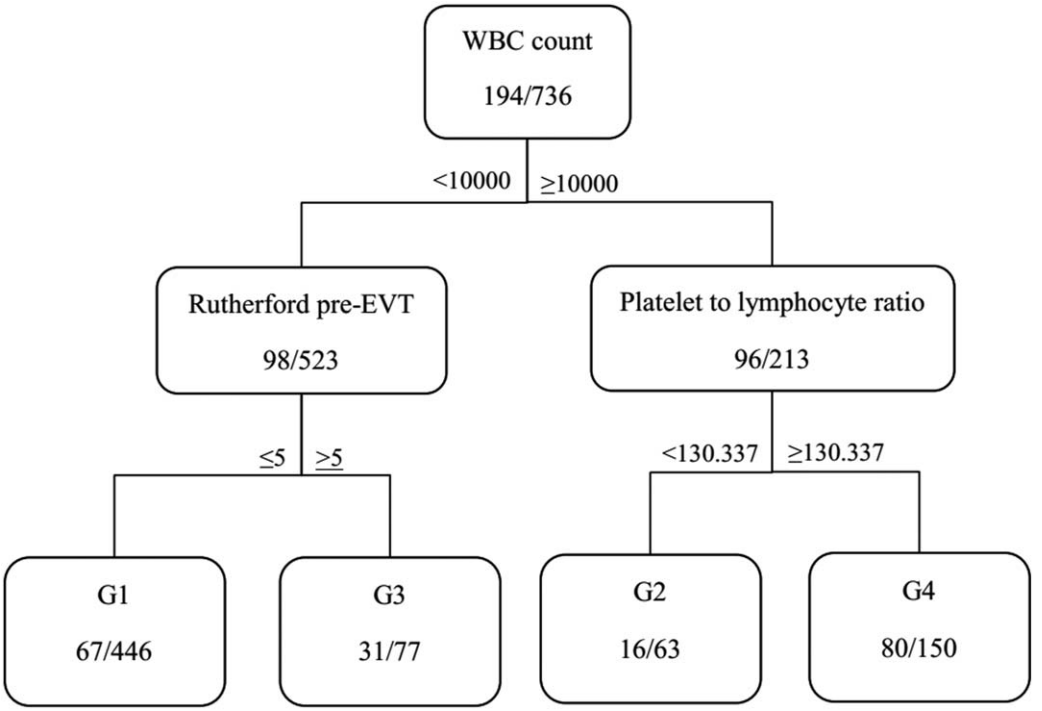

Figure 1. Predictors of amputation and risk stratification in all subjects. Significant variables by univariate analysis ($P < .05$) were selected and put into the following classification tree analysis. The decision tree was built with a root based on WBC levels (<10,000/μl and ≥10,000/μl). For selection, the branches of the tree and the specifications for tree growth was set using the CART method with a dependent variable, amputation, and the depth of tree = 3. Three variables retained in the final tree (WBC, Rutherford pre-EVT, and platelet to lymphocyte ratio). Four risk groups were generated according to the order of amputation rate (G1, G2, G3, and G4).

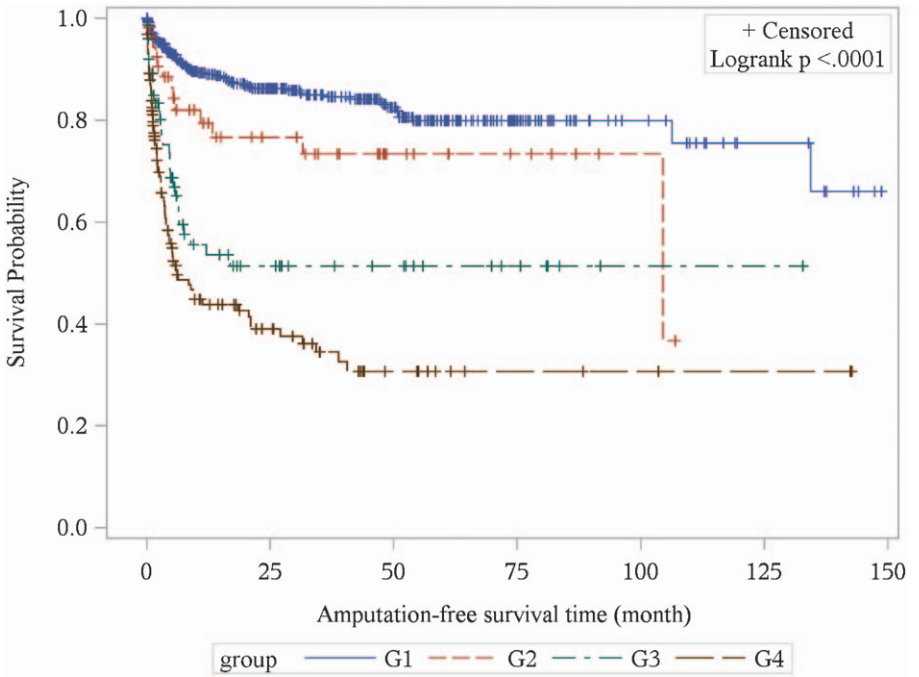

Figure 2. Kaplan–Meier curves are estimating for amputation-free survival according to 4 different risk groups in all subjects. G1: WBC < 10000, Rutherford pre-EVT ≤ 5; G2: WBC < 10000, Rutherford pre-EVT > 5; G3: WBC ≥ 10000, platelet to lymphocyte ratio < 130.337; G4: WBC ≥ 10000, platelet to lymphocyte ratio ≥ 130.337.

Table 2

Risk group analysis for derivation and validation sets using Cox proportion hazard model.

	Derivation	Validation
	HR (95%CI)	HR (95%CI)
Low Risk (G1)	Reference	Reference
Intermediate Risk 1 (G2)	1.77 (0.97–3.19)	1.61 (0.56–4.65)
Intermediate Risk 2 (G3)	**3.89 (2.52–5.99)**	**4.24 (1.88–9.54)**
High Risk (G4)	**6.17 (4.45–8.55)**	**4.24 (2.34–7.68)**

Derivation sets including all 736 subjects.
Validation sets were randomly selected with per 30% subjects from the derivation sets.
Numbers in bold indicated $P < .05$.
HR = hazards ratio.

LEA rates from the classification tree were derived as 15.0%, 23.6%, 39.5%, and 52.5% for G1, G2, G3, and G4, respectively.

The Cox proportional hazards model showed that the risk of LEA was significantly higher in G4 and G3 as compared with G1, except for G2 (G4: HR = 6.17, $P < .0001$; G3: HR = 3.89, $P < .0001$; G2: HR = 1.77, p = 0.06) (Table 2). Repeated validation sets showed a consistent significant difference of LEA risk between G4 versus G1 or G4 versus the lower-risk groups (P values $< .05$)

To make a decision tree for major amputation alone, we excluded the CLI patients with minor amputation. Subsequently, we have performed the univariate analysis to compare the difference between non-amputation and major amputation groups, and then re-examined the decision tree with the significant variables identified by univariate analysis. As shown in Supplementary Figure 1, http://links.lww.com/MD/D173, 2 variables were retained in the final tree: WBC and platelet-to-lymphocyte ratio. The decision tree generated 3 risk groups: high-risk patients (G3) (n = 3), intermediate risk group (G2) (n = 32), and low-risk group (G1) (n = 23). This decision tree exhibited that Rutherford pre-EVT score maybe not an important factor to predict the occurrence of major amputation in CLI patients after the surgery. This result indicated that WBC and platelet-to-lymphocyte ratio could also predict major amputation.

4. Discussion

The present study developed a simple risk stratification scale using decision tree methodology to predict the likelihood of LEA in patients with CLI after treatment with EVT. One strength of the newly developed scale is that the risk model is easy to set using clinical records upon admission and hence may be more translatable to the general clinic than risk models based on data from controlled clinical studies.

Prior studies have investigated potential factors that can predict the success of revascularization in treating CLI patients.[9–11,13–16,20–27] Results of studies designed to assess the risk of LEA in CLI patients following bypass surgery have also been reported previously.[13–15,21–25] Findings of the present study are consistent with several of these previous studies that also identified that WBC, PLR levels, and RC at hospital admission were important risk factors for LEA.[10,13,14]

The majority of the studies that evaluated the risk of LEAs were retrospective in design and used univariate and multivariate analysis to identify risk factors, and subsequently gave each risk factor a number based on the multivariate analysis coefficient.[14,15,25] The Society of Vascular Surgery developed the WIfI (wound, ischemia, and foot infection) classification based on 3 major factors that impact amputation risk and clinical management.[21,23] These risk scales were validated and were able to assist the clinician in outcome analysis for various forms of wounds and arterial revascularization procedures in this challenging patient population.[23] However, these scales are not readily used in clinical practice because they require several types of clinical records to complete the dataset.

The Finnvasc risk scale, derived from the Finnish Vascular Registry by Biancari et al showed that the combined endpoint for 30–day postoperative mortality and major amputation was increased in patients with ≥3 of the risk factors.[25] Schanzer et al developed the PREVENT III risk scale, which includes 5 factors (dialysis, tissue loss, age ≥75 years, hematocrit ≤30, and advanced coronary artery disease) to predict 1-year AFS in CLI patients after autologous infra-inguinal bypass.[15] Using the variables of surgical site infection, vasculopathy, prior LEA, and WBC >11,000, Lipsky et al developed a risk scale to predict the risk of LEA in hospitalized patients with diabetic foot infections. Those authors found that the LEA rates ranged from 0% in patients with a score of zero to 50% in patients with scores of ≥21.[14] Brizuela Sanz et al developed the ERICVA model to estimate the 1-year AFS in CLI patients receiving either open or endovascular revascularization. Factors associated with major amputation and/or death in that model were cerebrovascular disease, prior contralateral major amputation, diabetes mellitus, dialysis, chronic obstructive pulmonary disease, cancer, hematocrit <30%, neutrophil/lymphocyte ratio >5, the absence of arterial Doppler signal at the ankle, emergency admission, and RC 6.[13]

Our analysis in the present study differs from the models described above in that it used decision tree methodology to identify the combination of factors that can help to determine whether a patient has low, medium, or high risk for amputation following EVT. Since multiple risk factors can exist in the same patient, risk factor analysis should ideally consider the factors in combination rather than isolation.[26] A disadvantage of multivariable-derived risk schemes is the degree of complexity and the necessity of using complex mathematical functions that preclude ease of use.[26] The decision tree method utilized in the present study can detect interactions between variables, just as in multivariate regression analysis. However, the decision tree is relatively easy to apply and calculate, which allows its potential use in a wide variety of clinical conditions such as oncology, cardiology, infections, and neurology.[26] Moreover, the accuracy of decision tree models has been found to be close to that of more complex models derived from logistic regression analysis.[26]

Thrombocytosis and lymphocytopenia both correlate with the degree of host systemic inflammation, which commonly encountered in patients with CLI. The PLR reflects a novel marker incorporating both hematologic indices and has been reported as an independent factor for LEA.[10,27] PLR, a readily applicable blood test, played an additional role of risk stratification in this CART decision tree model.

4.1. Limitations

The risk model developed in the present study has several limitations that are typical of all risk models. The current model was designed within a specific local population, and it is unclear how accurate it will be in a different population or patients.

Additional studies recruiting patients from different hospitals or geographic areas should be conducted. Also, any risk model may lose validity over time as surgical indications, new treatments, and new technologies are developed. In addition, the clinical profiles of patients may alter over time. Interpretation of results of the present study is also limited by data being from only a single site and the retrospective design. Finally, we did not enroll CLI patients treated with surgical bypass; further study is warranted to validate this risk model in outcome prediction of CLI patients treated with different revascularization strategy.

5. Conclusions

The CART decision tree model, using the clinical status (RC stage) and readily available markers (WBC and PLR levels), is a quick risk scale to reliably assess the risk of LEA in CLI patients following EVT. The use of this risk-scale may help clinicians decide whether patients would benefit by receiving EVT or if the patient should be managed differently.

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Author contributions

Conceptualization: Hsuan-Li Huang, Jyh-Ming Jimmy Juang, Chien-An Hsieh, Yu-Lin Ko.
Data curation: Hsuan-Li Huang, Jyh-Ming Jimmy Juang, Chien-An Hsieh, Hsin-Hua Chou, Shih-Jung Jang, Yu-Lin Ko.
Formal analysis: Hsuan-Li Huang, Hsin-Hua Chou, Shih-Jung Jang, Yu-Lin Ko.
Writing – original draft: Hsuan-Li Huang, Chien-An Hsieh.
Writing – review & editing: Hsuan-Li Huang.

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