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Risk Stratification for 2-Year Mortality in Patients with Chronic Limb-Threatening Ischemia Undergoing Endovascular Therapy

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Aim: The latest Global Vascular Guidelines (GVG) recommend assessing the 2-year mortality risk in patients with chronic limb-threatening ischemia (CLTI) before revascularization. This study aimed to reveal whether the Wound, Ischemia and foot Infection (WIfI) classification, developed originally as a risk assessment tool for limb prognosis, would be useful in predicting the 2-year mortality risk in patients with CLTI in the era of GVG and WIfI.

Methods: We retrospectively analyzed 849 patients with CLTI who were primarily treated with endovascular therapy (EVT) between April 2010 and December 2016. The impact of baseline characteristics, including the WIfI classification on mortality risk, was investigated using the Cox proportional hazards regression model.

Results: During a mean follow-up of 19.3 months, 243 deaths were observed. The 2-year mortality rate was 32.3%. Multivariate analysis demonstrated that WIfI classification stages ($p=0.037$), in addition to male sex ($p=0.010$), age ($p<0.001$), non-ambulatory status ($p<0.001$), body mass index ($p=0.002$), and hemodialysis ($p<0.001$), were independent predictors for an increased risk of mortality, while the Rutherford classification was not.

Conclusions: WIfI classification stages were independently associated with mortality risk in patients with CLTI undergoing EVT, while the Rutherford classification was not. The WIfI classification would be a practical tool for planning the revascularization strategy in CLTI treatment.

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Key words: Chronic limb-threatening ischemia, Endovascular therapy, Risk stratification, WIfI classification, Mortality

Introduction

Chronic limb-threatening ischemia (CLTI) is a condition with rest pain, an unhealed ulcer, or gangrene that represents the most advanced manifestation of peripheral artery disease[1)]. CLTI has a poor prognosis, with a high mortality and amputation rate without appropriate revascularization. Guidelines recommend revascularization by either endovascular therapy (EVT) or bypass surgery; however, decision making for revascularization strategies varied among guidelines.

The latest Global Vascular Guidelines (GVG) proposed that patients with high surgical risk, who were defined as those with under 50% estimated 2-year life expectancy, are primarily recommended for EVT first[2)]. There are several risk stratification models for estimated 2-year life expectancy, and most models apply the classical Rutherford classification[3)] for wound assessment. These models for 2-year life

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expectancy were developed based on past studies and did not fit into recent real-world CLTI practice. Currently, the application of the Wound, Ischemia, and foot Infection (WIfI) classification system, developed originally as a risk assessment tool for limb prognosis[4], was recommended for the evaluation of CLTI by European guidelines[1] and GVG[2]. However, the predictive value of the WIfI system rather than the Rutherford classification for 2-year mortality for patients with CLTI has not been studied well in real-world practice.

Aim

The current study aimed to investigate the predictive value of the WIfI and Rutherford systems for 2-year mortality in patients with CLTI.

Methods

Participants

We retrospectively analyzed 849 de novo patients with CLTI who underwent primary EVT between April 2010 and December 2016. The wound severity was assessed retrospectively using the WIfI classification system, which consists of three factors that constitute and contribute to the risk of limb threat: wound (W), ischemia (I), and foot infection (fI)[4]. We excluded 51 patients whose WIfI classification could not be evaluated because of insufficient medical records of wounds and 13 patients with missing baseline data.

The current study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Kansai Rosai Hospital. This observational study was considered exempt from written informed consent of patients, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Instead, relevant information on the study was open to the public and opportunities for refusal were ensured.

Intervention Procedure

The severity of ischemia in the lower limb was assessed using the ankle-brachial index (ABI) and skin perfusion pressure (SPP). Locations of significantly hemodynamic arterial lesions were evaluated routinely by duplex ultrasound, and the morphological details of the lesions were assessed by digital subtraction angiography before any necessary revascularization. EVT was indicated when a lesion showed stenosis > 75% of the vessel diameter on diagnostic angiography and was hemodynamically significant. EVT was performed according to the generally accepted protocol. Aortoiliac lesions were treated using a primary stenting strategy. In femoropopliteal lesions, stents were implanted in cases of angioplasty failure, which were complicated with severe dissection, residual stenosis, or significant pressure gradients (10 mmHg or greater). Below-the-knee (BTK) lesions were treated with plain angioplasty. Drug-coated balloon and atherectomy devices were not used because these were not approved in Japan during the study period.

Follow-Up Protocol

The follow-up interval and modality were at the discretion of the physician, with the typical practice being every 2–4 weeks until the wound healed and then every 3 months for as long as possible, with the ABI, arterial duplex ultrasound, and SPP as needed. Reintervention was indicated for limbs with recurrent symptoms or delayed wound healing, accompanied by recurrent occlusion or stenosis as measured by the ABI, duplex ultrasound, and SPP. When patients presented with any of the abovementioned indications, reintervention was conducted as soon as possible.

Outcome Measure

The outcome measure of the current study was 2-year mortality and the aim was to explore the association of the WIfI classification with the outcome.

Definitions

Non-ambulatory status was defined as wheelchair dependence or a bedridden status, as assessed on admission. Coronary artery disease was defined as the presence of symptoms, a history of infarction, or a history of any cardiac revascularization. Severe valvular disease was defined as severe aortic stenosis or mitral regurgitation according to the latest guidelines[5] evaluated by cardiac ultrasonography. Left ventricular ejection fraction (EF) was also assessed by cardiac ultrasonography and a reduced EF was defined as < 40%[6].

Wounds were classified according to the WIfI scale as grade 0: no wound; grade 1: a small, shallow ulcer on the distal leg or foot without gangrene; grade 2: a deeper ulcer with exposed bone, joint, or tendon, and/or gangrenous changes limited to the toes; and grade 3: an extensive deep ulcer, full thickness heel ulcer, and/or calcaneal involvement and/or extensive gangrene. Ischemia was classified as grade 0: ABI ≥ 0.80, SPP ≥ 60 mmHg; grade 1: ABI 0.60–0.79, SPP 40–59 mmHg; grade 2: ABI 0.40–0.59, SPP 30–39 mmHg; and grade 3: ABI <0.40, SPP <30 mmHg.

The ABI is a standard method to assess limb ischemia. However, the ABI may be assessed as relatively high in calcified vessels. Therefore, we routinely used SPP, a widely accepted metric in Japan, as an alternative measurement to transcutaneous oxygen pressure (TcPO2). When the ABI was over 0.90 despite a low SPP, we substituted SPP for TcPO2 to define ischemia grades, following the method used in a previous study[7].

Foot infection was classified as grade 0: no symptoms of infection; grade 1: local infection involving only the skin and subcutaneous tissue; grade 2: local infection deeper than the skin/subcutaneous tissue; and grade 3: systemic inflammatory response syndrome.

Each factor rating was further classified by severity (0: none; 1: mild; 2: moderate; 3: severe), and combined with the WIfI clinical stage (1: very low risk; 2: low risk; 3: moderate risk; 4: high risk) to estimate the 1-year amputation risk from preexisting expert consensus tables[4]. These grades were evaluated retrospectively using photographs of the pedal wounds and medical records, including laboratory examinations at admission. To maximize the consistency of evaluations, wound assessments were conducted independently by two wound specialists. Disagreements were resolved by discussions and consensus.

Statistical Analysis

Unless otherwise noted, data are presented as the mean ± standard deviation for continuous variables and as percentages for discrete variables. The Cox proportional hazards regression model was used to determine the association of clinical characteristics with all-cause mortality. In addition to the WIfI classification, other clinical variables found to influence all-cause mortality in previous studies were included in the univariate analysis. The factors associated with all-cause mortality in the univariate analysis were examined by multivariate analysis. The hazard ratio (HR) and 95% confidence interval (CI) were reported. The predictive performance of the score was assessed by time-dependent receiver operating characteristic (ROC) curve analyses[8]. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS Version 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, USA: IBM Corp.), except for time-dependent ROC curve analyses, which were conducted using R version 3.1.0 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the patients' characteristics. The mean patient age was 74 ± 10 years, 506 (59.6%) were male, and 387 (45.6%) were non-ambulatory on admission. Notable comorbidities included diabetes mellitus (63.1%; 536/849), hemodialysis (51.8%; 440/849), a history of heart failure (9.4%; 80/849), and severe valvular disease (1.8%; 15/849). The average EF was 61.9 ± 11.8% and a reduced EF, defined as <40%, was observed in 5.4% of patients. Limb conditions are shown in **Table 2**. Before EVT, the mean ABI was 0.62 ± 0.22 and the SPP values at the dorsal and plantar surfaces were 27.5 ± 18.0 and 30.5 ± 17.9 mmHg, respectively. The WIfI clinical stage for amputation risk revealed 6.0% (51/849) stage 1 (very low risk), 22.5% (191/849) stage 2 (low risk), 26.0% (221/849) stage 3 (moderate risk), and 45.5% (386/849) stage 4 (high risk). The distribution of the arterial lesion locations is shown in **Table 2**. The first EVT was achieved successfully in 97.3% of patients. The post-EVT SPP was clearly improved to 42.7 ± 20.4 and 43.5 ± 20.6 at the dorsal and planter surfaces, respectively.

Prognosis of Patients with CLTI after EVT

During the follow-up period, 243 deaths were observed. The 2-year mortality rate was estimated to be 32.3% **(Fig. 1)**. The causes of death are shown in **Fig. 2**. The main causes of death were infectious disease (33.3%) and cardiovascular disease (30.9%). Among patients who died of infectious disease, 4.9% of patients died from infectious disease caused by CLTI, while the main cause of infectious disease was pneumonia (53%). Two patients died because of gastroenteritis, and one patient each died from infective endocarditis, pancreatitis, peritonitis, and urinary infection. Twenty-eight patients (34.5%) suffered from bacteremia with unknown cause.

In terms of limb prognosis according to the WIfI classification, the rates of major amputation were 2.0%, 4.2%, 4.1%, and 13.5% in WIfI stages 1, 2, 3, and 4, respectively.

Predictive Model for Mortality after EVT

The multivariate analysis demonstrated that WIfI clinical stages, male sex, older age, non-ambulatory status, lower body mass index (BMI), and hemodialysis were independently associated with an increased risk of mortality, while the Rutherford classification was not **(Table 3)**. The area under the time-dependent ROC curve of the multivariate model for 2-year mortality was 0.73 (95% CI, 0.69–0.77).

In addition, we also assessed the impact of each

Table 1. Baseline clinical characteristics of the study population

No. patients	849
Follow-up period, months	19.3 ± 18.0
Male	506 (59.6)
Age, years	74 ± 10
Body mass index, kg/m^2	21.2 ± 3.7
Non-ambulatory status	387 (45.6)
Hypertension	541 (63.7)
Dyslipidemia	271 (31.9)
Diabetes mellitus	536 (63.1)
Hemodialysis	440 (51.8)
Coronary artery disease	367 (43.5)
Severe valvular disease	15 (1.8)
Ejection fraction (EF), %	61.9 ± 11.8
Reduced EF < 40%	46 (5.4)

Data are expressed as the means ± standard deviations or numbers (percentages).

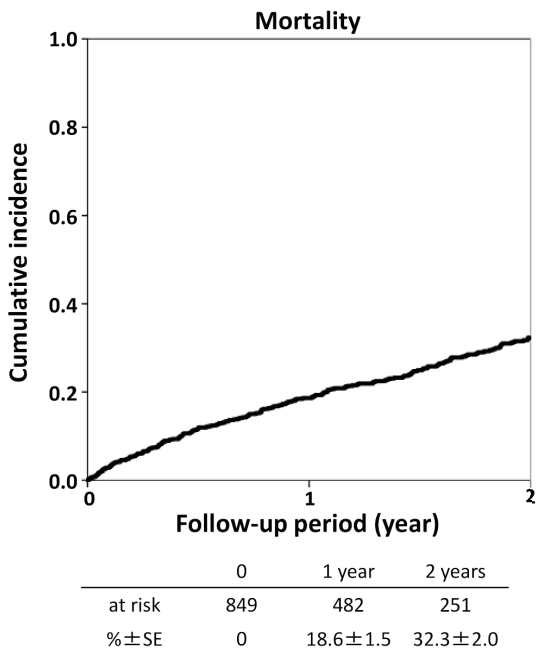

Fig. 1. Mortality after endovascular therapy

The 2-year mortality rate was estimated to be 32.3%.

Table 2. Baseline limb and arterial lesion characteristics of the study population

No. patients	849
Ankle-brachial index	0.62 ± 0.22
Skin perfusion pressure, mmHg	
Dorsal surface	27.5 ± 18.0
Plantar surface	30.5 ± 17.9
Rutherford classification	
4 (Only rest pain)	135 (15.9)
5 (Minor tissue loss)	525 (61.8)
6 (Major tissue loss)	189 (22.4)
Clinical stage in WIfI classification	
1 (Very low risk)	51 (6.0)
2 (Low risk)	191 (22.5)
3 (Moderate risk)	221 (26.0)
4 (High risk)	386 (45.5)
Lesion distribution	
Aorto-iliac	134 (15.8)
Femoro-popliteal	475 (55.9)
Below-the-knee	692 (81.5)

Data are expressed as the means ± standard deviations or numbers (percentages).
The Wound, Ischemia and foot Infection (WIfI) classification, see references nos. 4. The stages in WIfI classification is to predict 1-year amputation risk.

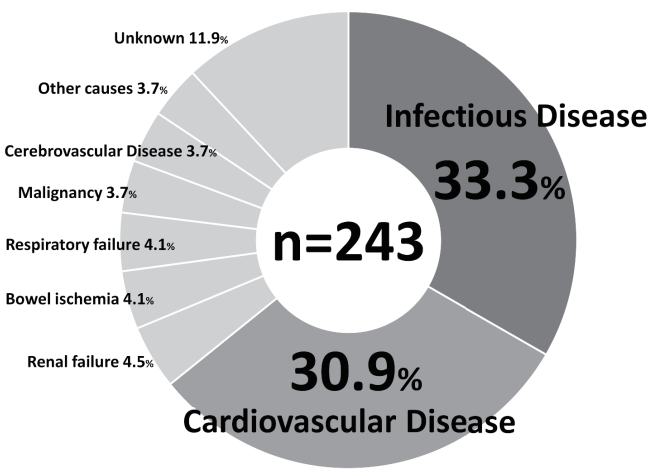

Fig. 2. The causes of death

During the follow-up period, 243 deaths were observed. The main causes of death were infectious disease (33.3%) and cardiovascular disease (30.9%).

component of the WIfI classification on outcomes as follows: wound (HR 1.32 [95% CI, 1.16–1.51], $p<0.001$) and foot infection (HR 1.18 [95% CI, 1.04–1.35], $p=0.013$) were independently associated with all-cause death, while ischemia (HR 1.01 [95% CI, 0.96–1.25] $p=0.17$) was not. Also, lesion distribution was not significantly associated with all-cause death as follows: aortoiliac (HR 0.81 [95% CI, 0.62–1.05], $p=0.11$), femoropopliteal (HR 1.14 [95% CI, 0.87–1.48], $p=0.30$), and BTK lesions (HR 1.07 [95% CI, 0.75–1.53], $p=0.70$).

Table 3. Univariate and multivariate cox regression analysis for predictors of mortality

	Univariate		Multivariate	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Male	1.34 [1.04-1.75]	0.027	1.43 [1.09-1.87]	0.010
Age (per 1 year increase)	1.03 [1.02-1.04]	<0.001	1.04 [1.02-1.05]	<0.001
Non-ambulatory status	2.13 [1.65-2.75]	<0.001	1.83 [1.40-2.39]	<0.001
Diabetes mellitus	0.83 [0.64-1.08]	0.16		
Hemodialysis	2.01 [1.54-2.62]	<0.001	2.21 [1.68-2.90]	<0.001
Coronary artery disease	1.17 [0.91-1.51]	0.21		
BMI (per 1.0 kg/m² increase)	0.91 [0.88-0.95]	<0.001	0.94 [0.90-0.98]	0.002
Aorto-iliac lesion	0.81 [0.62-1.05]	0.11		
Femoro-popliteal lesion	1.14 [0.87-1.48]	0.30		
Below-the-knee lesion	1.07 [0.75-1.53]	0.70		
Rutherford classification	0.87 [0.97-1.48]	0.087		
WIfI clinical stage	1.22 [1.06-1.42]	0.007	1.18 [1.01-1.38]	0.037

Hazard ratios (HR) are presented together with the 95% confidence intervals (CI).
BMI: body mass index.
The Wound, Ischemia and foot Infection (WIfI) classification, see references nos. 4. The stages in WIfI classification is to predict 1-year amputation risk.

Discussion

In the current study, we analyzed the predictive variables for 2-year mortality in patients with CLTI undergoing EVT. The multivariate analysis demonstrated that WIfI stages in addition to systemic factors suggested in previous reports were identified as independent predictors for all-cause mortality, while the Rutherford classification was not.

In the current study, the 2-year mortality was 32.3%, reflecting poorer outcomes than the Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial, whose 2-year mortality was 26.8%[9]. The reason for this discrepancy could be attributed to the slightly older patients in this study (average age, 74 years versus 73 years in the BASIL trial) and the high frequency of patients with hemodialysis (52% in this study versus 7% in the BASIL trial).

Whereas the WIfI classification was developed originally as a risk assessment tool for limb prognosis, the current study revealed that the classification was independently associated with the mortality risk. On the other hand, contrary to previous reports[9-11], the Rutherford classification, a classical one, was not. The reason may be attributed to the vagueness of the definition for the Rutherford classification 5 or 6. The WIfI classification might be superior to the Rutherford classification in risk stratification because it is defined exactly and incorporates the additional factors of ischemia and foot infection.

In the GVG[2], the flowchart for treatment of CLTI indicates that risk stratification should be conducted according to wound and patient characteristics, including the WIfI classification. However, the specific factors to predict patient risk are not documented. The risk stratification model from this study predicts long-term mortality using the WIfI classification, developed originally as a risk assessment tool for limb prognosis, as well as specific medical history, physical findings, and activities of daily living; therefore, the model is more practical for determining the revascularization strategy than the classical model using the Rutherford classification.

Study Limitations

This study has some limitations. First, this was a retrospective, single-center study. We retrospectively assessed the WIfI clinical stage using the photographs of pedal wounds and medical records, including laboratory examinations at registration. Although efforts were made to obtain consistent and accurate wound evaluations, some error is inevitable. Second, we analyzed only patients who underwent EVT. Therefore, we could not assess the perioperative mortality for bypass surgery. Finally, this is a post-hoc stratification. Although the predictive model identified from this analysis was reasonable in our clinical setting, post-hoc findings should be regarded as hypothesis-generating and thus require external validation before being more broadly accepted.

Conclusions

The current study revealed that the WIfI clinical stages, in addition to male sex, age, non-ambulatory status, BMI, and hemodialysis, were independently associated with an increased risk of mortality in patients with CLTI undergoing EVT, while the Rutherford classification was not. The WIfI classification would be a practical tool for planning the revascularization strategy in CLTI treatment.

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Disclosures

None.

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