

Additional Risk Stratification Using Local and Systemic Factors for Patients with Critical Limb Ischaemia Undergoing Endovascular Therapy in the Wifl Era

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WHAT THIS PAPER ADDS

The current guidelines describe the importance of assessing limb characteristics with Wifl (Wound, Ischaemia, and foot Infection) classification system to predict limb prognosis in patients with critical limb ischaemia (CLI). On the other hand, several reports have also suggested that systemic factors are associated with limb prognosis. This study, involving 735 *de novo* CLI patients, examines factors associated with wound healing after endovascular therapy. The risk stratification based on these factors and on Wifl allows further prediction of wound healing.

Objectives: While current guidelines describe the importance of assessing limb characteristics for predicting limb prognosis in patients with critical limb ischaemia (CLI), several reports have also suggested that systemic factors are associated with limb prognosis. The aim of this study was to evaluate whether systemic factors have the same impact on wound healing as limb characteristics in CLI patients undergoing endovascular therapy.

Methods: A total of 735 patients who were treated for the first time for CLI with tissue loss between April 2010 and December 2015 were extracted from a prospective registry and data for the Wound, Ischaemia, and foot Infection (Wifl) classification were searched retrospectively. The predictors of wound healing were explored with Cox proportional hazards regression.

Results: The one year wound healing rate was 60.2% in Wifl stage 1–3 patients and 53.6% in Wifl stage 4 ($p = .01$). In Wifl stage 1–3, no systemic factors were significantly associated with wound healing, whereas, in Wifl stage 4 patients, non-ambulatory status [hazard ratio (HR) 1.98; 95% confidence interval (CI) 1.37–2.84], haemodialysis (HR 1.90; 95% CI 1.33–2.72) and an albumin level under 3.0 g/dL (HR 1.53; 95% CI 1.02–2.31), were identified as independent risk factors for failure to achieve wound healing. If none or one of these risk factors were present, wound healing was comparable with Wifl 4 and Wifl 1–3 patients (67.7% vs. 63.6%, $p = .89$), whereas in patients with two or more risk factors wound healing was worse in Wifl 4 than in Wifl 1–3 patients (35.7% vs. 49.5%, $p = .01$).

Conclusion: Non-ambulatory status, haemodialysis, and a low albumin level were additional systemic risk factors for impaired wound healing in patients with Wifl stage 4. The wound healing rate in Wifl stage 4 patients with one or fewer of these risk factors was comparable to that in Wifl stage 1–3.

Keywords: Critical limb ischaemia, Endovascular therapy, Limb prognosis, Risk stratification, Wifl classification, Wound healing

Article history: Received 15 August 2018, Accepted 11 June 2019, Available online 10 August 2019

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INTRODUCTION

Recently, the Wound, Ischaemia, and foot Infection (Wifl) classification system, a predictor of limb prognosis in critical limb ischaemia (CLI) established by the Society for Vascular

Surgery (SVS), was introduced and widely applied in the authors' practice.^{1,2} In previous studies, the Wifl classification was associated with limb prognosis, including wound healing of diabetic foot ulcers.^{3,4}

Traditionally, systemic factors have been associated with limb prognosis after endovascular therapy (EVT).^{5–7} However, in practice, the impact of the Wifl classification for wound healing in individuals with CLI and whether systemic factors have the same impact as limb characteristics (e.g. Wifl clinical stages) have not been studied systematically. The

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<https://doi.org/10.1016/j.ejvs.2019.06.005>

aim of the current study was to study the prognostic impact of patient characteristics on the limb prognosis together with Wifl classification in CLI patients undergoing EVT.

MATERIALS AND METHODS

Participants

Our database was retrospectively analysed and data were included on 735 CLI patients first treated at the hospital who underwent initial EVT between April 2010 and December 2015 and who consented to follow up examination at a single cardiovascular centre. Patients who presented with acute limb ischaemia requiring emergency revascularisation were excluded. Patients with rest pain only, with missing baseline data, or who had not been evaluated with the Wifl score were also excluded (Fig. 1). Laboratory data and prescription forms were evaluated upon admission before EVT. An assessment of wound severity was performed retrospectively using the Wifl classification, which consists of three factors that constitute and contribute to the risk of limb threat: wound (W), ischaemia (I), and foot infection (FI).

For the wound, Grade 0 is no wound, Grade 1 a small, shallow ulcer on distal leg or foot without gangrene, Grade 2 a deeper ulcer with exposed bone, joint or tendon and/or gangrenous changes limited to toes, and Grade 3 is an extensive deep ulcer, full thickness heel ulcer, and/or calcaneal involvement and/or extensive gangrene. For ischaemia, Grade 0 means ankle brachial index (ABI) ≥ 0.80 or toe pressure (TP) ≥ 60 mmHg, Grade 1 means ABI of

0.60–0.79 or TP of 40–59 mmHg, Grade 2 means ABI of 0.40–0.59 or TP of 30–39 mmHg, and Grade 3 means ABI < 0.40 or TP < 30 mmHg. ABI is a standard method to assess limb ischaemia. However, ABI may be relatively high in calcified vessels. Therefore skin perfusion pressure (SPP) was also routinely measured, a widely accepted metric in Japan, as an alternative measurement to TP. When ABI was over 0.90 in spite of low SPP, SPP was used to define the ischaemia grade. When SPP grade ischaemia was used, TP pressure criteria were used as described previously.⁸

For foot infection, Grade 0 indicates no symptoms of infection, Grade 1 indicates local infection involving only skin and subcutaneous tissue, with Grade 2 local infection involving deeper than skin/subcutaneous tissue, and Grade 3 systemic inflammatory response syndrome.

The risk of amputation was assessed with the four Wifl stages published previously (1, very low risk; 2, low risk; 3, moderate risk; 4, high risk) (Appendix Fig. 1, in Mills et al.¹). These grades were evaluated retrospectively using the photographs of foot wounds and medical records including laboratory examinations at registration. To minimise inappropriate wound assessment, the judgement was made by two wound specialists. When there was disagreement, the cases were discussed and appropriate evaluation was made.

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the hospital. Written informed consent was obtained from every participant.

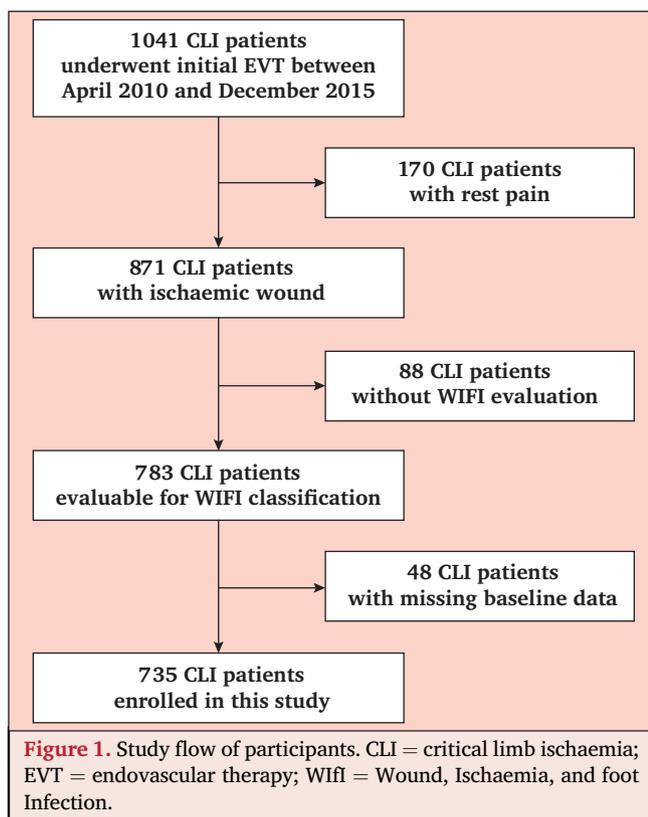
Study protocol

Briefly, the severity of ischaemia in lower limb was assessed using ABI and SPP. Wifl clinical stage 1 with Grade 1 ischaemia is generally not recommended for revascularisation at the outset under the latest guidelines. For these patients in this study, primary conservative therapy was carried out. If these wounds did not heal using primary therapy, revascularisation was subsequently considered.

The lower limb arteries were routinely evaluated by duplex ultrasound, and the presence of below the knee lesions was assessed by digital subtraction angiography before revascularisation. EVT was indicated when the lesion showed a stenosis $>75\%$ of the vessel diameter on diagnostic angiography and was haemodynamically significant. The endovascular treatment was done according to the generally accepted principles. Aorto-iliac lesions were managed by a primary stenting strategy. For femoropopliteal lesions, a stent was implanted in cases of angioplasty failure, which included severe dissection, residual stenosis, or a significant pressure gradient (≥ 10 mmHg). Below knee 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.

Wound care

Wound care is standardised in our institution. After wound irrigation, it undergoes an assessment. If examination alone



is insufficient or the wound defect is extensive (e.g. exposed bone, necrosis), sharp excisional debridement is routinely performed after revascularisation. The wound is covered with dressing materials suitable for the wound condition. Systemic antibiotics are prescribed only in cases of infection at the wound site or for other lesions. Negative pressure wound therapy is also used in cases with sufficient blood flow to the wound and no infection. After patient discharge, the general practitioner continues wound care, based on instructions from physicians, cardiologists, and plastic surgeons, and monitors the wound condition.

Follow up protocol

The follow up interval and modality were at the discretion of the physician, with typical practice being every two to four weeks until the wound healed and every three months for as long a period as needed, thereafter with ABI, arterial duplex ultrasound, and SPP. Re-intervention was indicated for limbs with recurrent symptoms accompanied by recurrent occlusion or stenosis as measured by ABI, duplex ultrasound, and SPP. When patients presented with any of the above indications, re-intervention was carried out as soon as possible.

Study outcomes

The primary endpoint of this study was twelve month wound healing. The endpoint measure was wound healing rate. The results were stratified according to the Wifl grade. Major adverse limb events (MALEs), amputation free survival (AFS), and re-intervention were also assessed as secondary endpoints.

Definitions

CLI was defined in accordance with the Trans-Atlantic Inter-Society Consensus (TASC) II guidelines.⁹ Non-ambulatory status was defined as wheel chair dependence or bed ridden, as assessed on admission. Hypertension was diagnosed as systolic blood pressure >130 mmHg, diastolic blood pressure >80 mmHg, or a history of treatment for hypertension. Dyslipidaemia was defined as serum low density lipoprotein (LDL) cholesterol > 100 mg/dL, high density lipoprotein (HDL) cholesterol < 40 mg/dL, triglycerides > 150 mg/dL, or history of treatment with lipid lowering drugs for dyslipidaemia. Coronary artery disease was defined as the presence of symptoms, a past history of myocardial infarction, or a history of any cardiac revascularisation. Regarding continuous variables, the cutoff values were chosen as in previous studies.^{7,10} A wound requiring surgery was defined as a wound that required invasive debridement or minor amputation. MALEs were defined as major amputation or major re-interventions (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) that occurred during the study period.¹¹ Major amputation was defined as amputation of the limb above the ankle. Any amputation at or distal to the Lisfranc ligament was not considered a limb salvage failure. Amputation data were obtained from outpatient clinic

follow up contact. AFS was defined as freedom from major amputation or death.

Complete wound healing was defined as complete epithelialisation of all wounds without death or major amputation. The date of wound healing was defined as the date when the wound was seen to completely epithelialised for the first time. In patients who underwent major amputation, the healing time was considered infinite as noted in a previous study.⁶

Statistical analysis

Unless mentioned otherwise, data are presented as median (interquartile range) for continuous variables and as percentages for discrete variables. Non-parametric analysis for continuous variables, the chi square test for discrete variables, and the Mann–Whitney test for ordinal variables were performed to assess differences in baseline characteristics between groups. Prognostic outcomes were assessed using the Kaplan–Meier method, and differences between groups were assessed with the log rank test when necessary. Cox proportional hazards regression and logistic regression analysis were used to determine the association between clinical characteristics and wound healing. Clinical variables found to influence wound healing in previous studies^{6,12,13} were included in the univariable analysis. Factors associated with wound healing in the univariable analysis were examined by multivariable analysis. The hazard ratio (HR) and 95% confidence interval (CI) were reported. The influence of the Wifl clinical stage for amputation risk on the association between baseline characteristics and outcome was evaluated by interaction effects. The study population was subsequently stratified in subgroups according to the number of independent risk factors defined by the multivariable analysis to assess the wound healing rate. The follow up index was evaluated for each patient group to avoid attrition bias.¹⁴ A *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

As shown in Table 1, 450 (61.2%) patients were male, the median age was 75 (68–81) years, and 215 patients (29.3%) were ≥80 years old. In all, 44.1% of the patients were non-ambulatory on admission. Notable comorbidities included diabetes mellitus (66.8%; 491/735) and haemodialysis (54.1%; 398/735). The median serum albumin was 3.4 (3.0–3.7) g/dL, with 24.2% (178/735) of the patients having a low albumin level (<3.0 g/dL). Regarding the limb condition (Table 2), the median ABI and the SPP at the dorsal and plantar surfaces before EVT were 0.64 (0.51–0.77), 24 (15–37) mmHg and 27 (19–40) mmHg, respectively. Regarding the Wifl clinical stage, 19.3% (142/735) of limbs were stage 1 (very low risk), 154 limbs (21.0%) were stage 2 (low risk), 168 limbs (22.9%) were stage 3 (moderate risk), and 271 limbs (36.9%) were stage 4 (high risk). Wounds requiring surgery were observed in 458 limbs (62.3%). The frequency

Table 1. Baseline clinical characteristics and follow-up ankle brachial index of the study population

	All	Wound healing +	Wound healing –
No. of patients	735	383	352
Male	450 (61.2)	229 (59.8)	221 (62.8)
Age, years	75 (68–81)	75 (68–81)	74 (68–81)
≥80	215 (29.3)	110 (28.7)	105 (29.8)
Body mass index, kg/m ²	21.1 (18.8–23.5)	21.6 (19.0–24.0)	20.8 (18.7–23.0)
<18.5	153 (20.8)	73 (19.1)	80 (22.7)
Non-ambulatory status	324 (44.1)	128 (33.4)	196 (55.7)
Hypertension	482 (65.6)	257 (67.1)	225 (63.9)
Dyslipidaemia	130 (17.7)	73 (19.1)	57 (16.2)
Diabetes mellitus	491 (66.8)	262 (68.4)	229 (65.1)
Haemodialysis	398 (54.1)	192 (50.1)	206 (58.5)
Coronary artery disease	325 (44.2)	161 (42.0)	164 (46.6)
Ejection fraction, %	64 (56–70)	65 (58–71)	64 (55–76)
<50%	114 (15.5)	50 (13.1)	64 (18.2)
Serum albumin, g/dL	3.4 (3.0–3.7)	3.5 (3.1–3.8)	3.3 (2.8–3.6)
<3.0 g/dL	178 (24.2)	69 (18.0)	109 (31.0)
Antiplatelet therapy	673 (91.6)	349 (91.1)	324 (92.0)
Antithrombotic therapy	156 (21.2)	68 (17.8)	88 (25.0)
Statin	166 (22.6)	88 (23.0)	78 (22.2)
Insulin	169 (23.0)	95 (24.8)	74 (21.0)
Oral hypoglycaemic agent	331 (45.0)	173 (45.2)	158 (44.9)
Follow up index	1.00 (0.96–1.00)	1.00 (1.00–1.00)	0.92 (0.10–1.00)

Data given as *n* (%) or median (interquartile range).

of wounds requiring surgery in each group was 187 limbs (40.3%) in Wifl stage 1–3 and 271 limbs (100%) in Wifl stage 4. Regarding the distribution of the arterial lesions, as demonstrated in Table 3, 92 limbs (12.5%) had aorto-iliac–

Table 2. Limb characteristics

	All	Wound healing +	Wound healing –
No. of patients	735	383	352
Ankle brachial index	0.64 (0.51–0.77)	0.65 (0.51–0.79)	0.63 (0.51–0.76)
Skin perfusion pressure, mmHg			
Dorsal surface	24 (15–37)	23 (15–36)	25 (15–38)
Plantar surface	27 (19–40)	28 (19–40)	26 (17–39)
Clinical stage in Wifl classification			
1 (very low risk)	142 (19.3)	84 (21.9)	58 (16.5)
2 (low risk)	154 (21.0)	78 (20.4)	76 (21.6)
3 (moderate risk)	168 (22.9)	97 (25.3)	71 (20.2)
4 (high risk)	271 (36.9)	124 (32.4)	147 (41.8)
Wound requiring surgery	458 (62.3)	242 (63.2)	216 (61.4)

Data given as *n* (%) or median (interquartile range). Wifl = Wound, Ischaemia, and foot Infection. Stage in Wifl classification is to predict one year amputation risk.

Table 3. Arterial lesion characteristics

	All	Wound healing +	Wound healing –
No. of patients	735	383	352
Lesion distribution			
Aorto-iliac–femoropopliteal	92 (12.5)	39 (10.2)	53 (15.1)
Isolated below the knee	320 (43.5)	181 (47.3)	139 (39.5)
Multilevel	323 (43.9)	163 (42.6)	160 (45.5)
Chronic total occlusion	589 (80.1)	313 (81.7)	276 (78.4)
Lesion calcification			
None	239 (32.5)	135 (35.2)	104 (29.5)
Unilateral	151 (20.5)	83 (21.7)	68 (19.3)
Bilateral	345 (46.9)	165 (43.1)	180 (51.1)

Data given as *n* (%).

femoropopliteal lesions, 320 limbs (43.5%) had isolated below the knee lesions, and 323 limbs (43.9%) had both types of lesions. Chronic total occlusion was observed in 80.1% of this population. Additionally, 345 limbs (46.9%) had bilateral calcified lesions. These characteristics were also observed in subgroups whether wound healing was completed in follow up period.

Prognosis of patients with critical limb ischaemia after EVT

Mortality, and the frequency of major amputation and MALEs, within 30 days after EVT, were 2.6% (18 patients), 2.0% (14 patients), and 3.3% (22 patients), respectively.

The one year AFS and freedom from MALEs were 78.3% and 93.1%, respectively, and the two year rates of them were 66.0% and 91.4%, respectively. At two years, 176 patients had died, 46 patients had undergone major amputation, and 66 patients had suffered from MALEs. The one year re-intervention rates in patients with Wifl stage 1–3 and stage 4 were 43.4% and 53.5%, respectively.

Wound healing rate and its predictors after EVT

The overall one and two year wound healing rates were 57.7% and 65.3%, respectively. A total of 383 patients achieved complete wound healing. Fig. 2 shows the cumulative two year wound healing rate after EVT according to the Wifl classification. The wound healing rate in patients with Wifl stage 1–3 and stage 4 were 60.2% and 53.6%, respectively, with Wifl stage 4 patients showing a significantly worse cumulative healing rate ($p = .01$). Tables 4 and 5 show the association between baseline characteristics and poor wound healing. Systemic factors were not associated with poor wound healing in patients with Wifl stage 1–3, whereas in those with Wifl stage 4, non-ambulatory status, haemodialysis, and a low albumin level (<3.0 g/dL) were associated with poor wound healing. The multivariable Cox

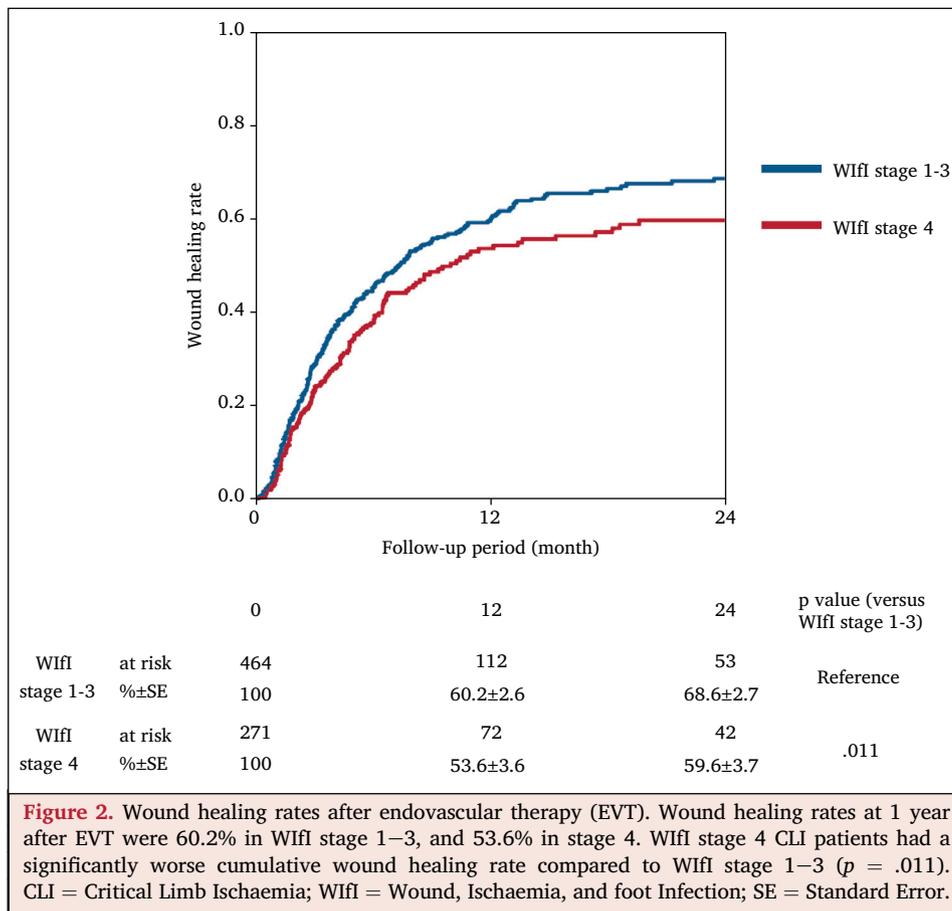


Table 4. Unadjusted association of baseline characteristics with poor wound healing in Wifi stage 1–3 vs. 4

	Unadjusted HR (95% CI) for poor wound healing				Interaction effect (p value)
	Wifi stage 1–3	p value	Wifi stage 4	p value	
Female	0.97 (0.76–1.25)	0.82	0.82 (0.56–1.18)	0.27	0.48
Age ≥ 80 years	0.83 (0.68–1.08)	0.15	0.97 (0.63–1.49)	0.90	0.53
Non-ambulatory status	1.26 (0.96–1.64)	0.09	2.00 (1.41–2.86)	<0.001	0.03
Diabetes mellitus	0.81 (0.63–1.06)	0.14	1.15 (0.78–1.69)	0.48	0.72
Haemodialysis	1.19 (0.93–1.52)	0.16	1.85 (1.32–2.63)	0.001	0.03
Coronary artery disease	1.04 (0.82–1.33)	0.71	1.14 (0.80–1.64)	0.47	0.92
BMI < 18.5 kg/m ²	1.05 (0.78–1.45)	0.72	1.20 (0.81–1.89)	0.40	0.88
Serum albumin <3.0 g/dL	1.15 (0.81–1.61)	0.45	1.85 (1.23–2.78)	0.003	0.06
Ejection fraction < 50%	1.41 (0.98–2.04)	0.07	1.23 (0.74–2.04)	0.42	0.64
Isolated below the knee lesion	0.80 (0.63–1.02)	0.07	1.05 (0.73–1.52)	0.76	0.18

BMI = body mass index; CI = confidence interval; HR = hazard ratio; Wifi = Wound, Ischaemia, and foot Infection.

regression analysis revealed that non-ambulatory status (HR 1.98; 95% CI 1.37–2.84; $p < .001$), haemodialysis (HR 1.90; 95% CI 1.33–2.72; $p < .001$), and a low albumin level (HR 1.53; 95% CI 1.02–2.31; $p = .04$) were independent factors that predict poor wound healing after EVT in Wifi stage 4 patients. In addition, Wifi stage 4 was associated significantly with decreased wound healing (HR 1.43; 95% CI 1.00–2.04; $p = .05$). The follow up index was added to the multivariate Cox regression analysis. Eventually, these three

factors were identified as independent factors associated with poor wound healing. According to the three factors, patients were divided into the following four groups: Wifi stage 1–3 with one or no factors, Wifi stage 4 with one or no factors, Wifi stage 1–3 with two or more factors, and Wifi stage 4 with two or more factors. Wifi stage 4 patients with two or more factors showed significantly worse wound healing than Wifi stage 1–3 patients with two or more factors (Fig. 3, $p = .013$). Furthermore, the wound healing

Table 5. Adjusted association between baseline characteristics and poor wound healing

	Adjusted HR (95% CI) for poor wound healing	p value	Interaction effect (p value)
<i>Non-ambulatory status</i>			0.04
In Wifl stage 1–3	1.24 (0.95–1.62)	0.12	
In Wifl stage 4	1.98 (1.37–2.84)	<0.001	
<i>Haemodialysis</i>			0.03
In Wifl stage 1–3	1.19 (0.93–1.52)	0.17	
In Wifl stage 4	1.90 (1.33–2.72)	<0.001	
<i>Serum albumin < 3.0 g/dL</i>			0.20
In Wifl stage 1–3	1.07 (0.75–1.52)	0.70	
In Wifl stage 4	1.53 (1.02–2.31)	0.04	
Wifl stage 4	1.43 (1.00–2.04)	0.05	

CI = confidence interval; HR = hazard ratio; Wifl = Wound, Ischaemia, and foot Infection.

rate was not significantly different between Wifl stage 1–3 patients with one or no factors and Wifl stage 4 patients with one or no factors ($p = .89$).

On the other hand, in Wifl stage 1–3 patients, each risk factor impaired wound healing with a HR 1.19 (95% CI 1.02–1.39) and in Wifl 4 patients by HR 1.79 (95% CI 1.45–2.20) (p for interaction = 0.001), as shown in [Appendix Table 1](#). In [Fig. 3](#), the wound healing rate was worse in patients with two or more factors than in patients with one or no factors in patients with Wifl stage 1–3 ($p = .009$).

The result of multivariable logistic regression analysis whether wound healing was completed at one year or not is also shown in [Appendix Table 2](#) and Kaplan–Meier estimates of outcomes in all Wifl stages in [Appendix Fig. 2](#).

DISCUSSION

Factors associated with wound healing after EVT were analysed in patients with CLI in a real world practice. This is the first study to perform a risk stratification of the wound healing rate based on Wifl stage and systemic factors following EVT in a real world CLI setting.

When comparing the data with recent studies, there were few differences in wound severity; however, the frequency in elderly patients and patients on haemodialysis was greater in the study population, indicating that CLI patients with worse or more advanced conditions were more frequently included in this study. The one year freedom from MALEs rate and the one year AFS in this study were acceptable in keeping with those in previous reports.^{2,5,15} Regarding the one year wound healing rate, the results are also comparable with the 55.9% in the

Japanese OLIVE study⁷ and the 37% reported by Darling et al.¹⁵

The Wifl classification was introduced by the SVS and has been widely used for decision making when treating CLI patients.¹ The Wifl classification is a novel classification system that stratifies the risk relating to limb prognosis. Three components of the wound condition, the degree of ischaemia, the severity of the wound and presence of infection, can distinguish ischaemic wounds more precisely than the traditional Rutherford or Fontaine classifications. Based on the findings of this study, the Wifl classification is clinically useful, and complete wound healing was more difficult to achieve when the Wifl stage was higher. However, the Wifl classification alone is not sufficient to predict the prognosis of CLI patients with many comorbidities. The risk stratified analysis revealed that the prognosis of Wifl stage 4 patients was strongly influenced by systemic factors, specifically, systemic complications, activity levels, and nutritional status, which can have an impact on clinical outcomes. The results suggest that by considering also the significant systemic factors, the predictive value of Wifl classification in wound healing would be even better. Regarding statistical analysis, Cox regression analysis was chosen to assess the outcome because wound healing time is also important in clinical settings. Multivariable logistic regression analysis was conducted to ascertain whether wound healing was completed at one year or not (shown in [Appendix Table 2](#)). Non-ambulatory status and haemodialysis were independent predictors of wound healing at one year, whereas a low albumin level was not.

With respect to non-ambulatory status, Lu et al.¹⁶ reported that mortality and complication rates were increased after EVT or bypass surgery in patients who could not walk independently. The latest guideline mentions that patients with extensive necrosis or infectious gangrene and those who are non-ambulatory with severe comorbidities may best be served by primary major amputation. In the current study, EVT was conducted for non-ambulatory patients who were ambulatory before the onset of CLI and would present with a change in ambulatory status after revascularisation.

Several studies have demonstrated that haemodialysis can influence survival and worsen the limb prognosis.⁸ For most patients on haemodialysis, treatment is difficult due to concomitant coronary artery disease, vulnerability to infection, and severe vascular calcification.

A low albumin level is a surrogate marker of malnutrition. In the OLIVE study,⁷ nutritional status was not a factor affecting lower limb prognosis. However, only 7% of patients in the OLIVE registry had an albumin level <3.0 g/dL, whereas 56% of patients in this study met this criterion. Thus, more patients with a poor nutritional status were enrolled, which may have contributed to a stronger impact of low albumin levels.

The current guidelines mention that the management of patients with CLI should consider Wifl classification system and it is well known that Wifl stage 4 has a poor prognosis.¹⁷ However, in the clinical setting there

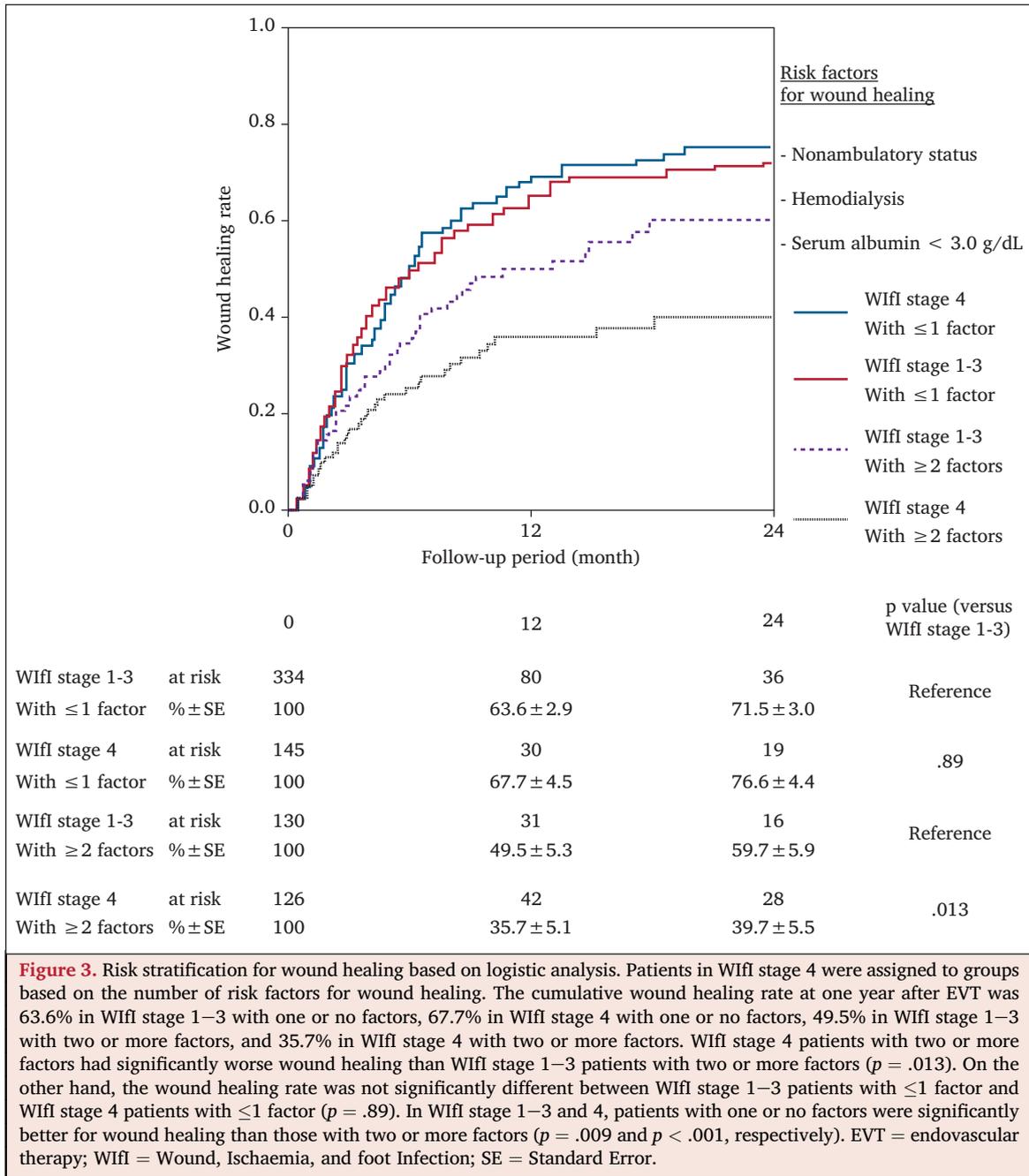


Figure 3. Risk stratification for wound healing based on logistic analysis. Patients in Wifl stage 4 were assigned to groups based on the number of risk factors for wound healing. The cumulative wound healing rate at one year after EVT was 63.6% in Wifl stage 1–3 with one or no factors, 67.7% in Wifl stage 4 with one or no factors, 49.5% in Wifl stage 1–3 with two or more factors, and 35.7% in Wifl stage 4 with two or more factors. Wifl stage 4 patients with two or more factors had significantly worse wound healing than Wifl stage 1–3 patients with two or more factors ($p = .013$). On the other hand, the wound healing rate was not significantly different between Wifl stage 1–3 patients with ≤ 1 factor and Wifl stage 4 patients with ≤ 1 factor ($p = .89$). In Wifl stage 1–3 and 4, patients with one or no factors were significantly better for wound healing than those with two or more factors ($p = .009$ and $p < .001$, respectively). EVT = endovascular therapy; Wifl = Wound, Ischaemia, and foot Infection; SE = Standard Error.

are patients with Wifl stage 4 who can achieve complete wound healing. Patients who did not have three risk factors detected in this study could achieve wound healing after EVT.

Limitations

This study has some limitations. First, it was a retrospective single centre study and the Wifl clinical stage was assessed retrospectively. In addition, the Wifl classification was originally proposed for patients with diabetic foot ulcers. In this study, validation of the Wifl classification cannot be evaluated in CLI patients without diabetes mellitus. However, a previous study has suggested the usefulness of the Wifl classification in patients without diabetes mellitus.¹⁸

Second, only patients who underwent EVT were analysed and patients who underwent bypass surgery were excluded.

Third, evaluation of the timing of wound healing was limited. For inpatients, the exact time required for epithelialisation can be assessed, but whether a wound has healed can only be confirmed when an outpatient visits the hospital.

Fourth, 88 patients were excluded because some data to define the Wifl clinical stages were missing.

Finally, this is a *post hoc* stratification. Although three predictive factors identified from this analysis were reasonable in the clinical setting, *post hoc* findings should be regarded as hypothesis generating and thus require external validation before being more broadly accepted.

CONCLUSIONS

In this study, not only Wifl classification but also three systemic factors including non-ambulatory status, haemodialysis and low albumin level were associated with wound healing in CLI patients. These results suggest that systemic factors should be considered for stratification of limb prognosis of CLI patients.

CONFLICT OF INTEREST

None.

FUNDING

None.

ACKNOWLEDGEMENTS

We acknowledge the expertise of Drs Mitsutoshi Asai, Masaharu Masuda, Takashi Kanda, Yasuhiro Matsuda, and Shota Okuno at Kansai Rosai Hospital in their performance of the catheterisation procedures.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2019.06.005>.

REFERENCES

- Mills Sr JL, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, et al. The society for vascular surgery lower extremity threatened limb classification system: risk stratification based on wound, ischemia, and foot infection (Wifl). *J Vasc Surg* 2014;**59**: 220–34.
- Causey MW, Ahmed A, Wu B, Gasper WJ, Reyzelman A, Vartanian SM, et al. Society for Vascular Surgery limb stage and patient risk correlate with outcomes in an amputation prevention program. *J Vasc Surg* 2016;**63**:1563–73.
- Weaver ML, Hicks CW, Canner JK, Sherman RL, Hines KF, Mathioudakis N, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (Wifl) classification system predicts wound healing better than direct angiosome perfusion in diabetic foot wounds. *J Vasc Surg* 2018;**68**:1473–81.
- Hicks CW, Canner JK, Mathioudakis N, Sherman R, Malas MB, Black 3rd JH, et al. The Society for Vascular Surgery Wound, Ischemia, and foot Infection (Wifl) classification independently predicts wound healing in diabetic foot ulcers. *J Vasc Surg* 2018;**68**:1096–103.
- Iida O, Nakamura M, Yamauchi Y, Kawasaki D, Yokoi Y, Yokoi H, et al. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. *Circ Cardiovasc Interv* 2013;**6**:68–76.
- Shiraki T, Iida O, Takahara M, Soga Y, Yamauchi Y, Hirano K, et al. Predictors of delayed wound healing after endovascular therapy of isolated infrapopliteal lesions underlying critical limb ischemia in patients with high prevalence of diabetes mellitus and hemodialysis. *Eur J Vasc Endovasc Surg* 2015;**49**:565–73.
- Iida O, Nakamura M, Yamauchi Y, Fukunaga M, Yokoi Y, Yokoi H, et al. 3-Year outcomes of the OLIVE registry, a prospective multicenter study of patients with critical limb ischemia: a prospective, multi-center, three-year follow-up study on endovascular treatment for infra-inguinal vessel in patients with critical limb ischemia. *JACC Cardiovasc Interv* 2015;**8**:1493–502.
- Iida O, Takahara M, Soga Y, Kodama A, Terashi H, Azuma N, et al. SPINACH investigators. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: the SPINACH study (surgical reconstruction versus peripheral intervention in patients with critical limb ischemia). *Circ Cardiovasc Interv* 2017;**10**:e005531.
- Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society Consensus for the management of peripheral arterial disease (TASC II). *Eur J Vasc Endovasc Surg* 2007;**33**(Suppl. 1):S1–75.
- Shiraki T, Iida O, Takahara M, Okamoto S, Kitano I, Tsuji Y, et al. Predictive scoring model of mortality after surgical or endovascular revascularization in patients with critical limb ischemia. *J Vasc Surg* 2014;**60**:383–9.
- Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg* 2009;**50**:1462–73. e1-3.
- Azuma N, Uchida H, Kokubo T, Koya A, Akasaka N, Sasajima T, et al. Factors influencing wound healing of critical limb ischemia foot after bypass surgery: is the angiosome important in selecting bypass target artery? *Eur J Vasc Endovasc Surg* 2012;**43**:322–8.
- Kawarada O, Fujihara M, Higashimori A, Yokoi Y, Honda Y, Fitzgerald PJ. Predictors of adverse clinical outcomes after successful infrapopliteal intervention. *Catheter Cardiovasc Interv* 2012;**80**:861–71.
- von Allmen RS, Weiss S, Tevaearai HT, Kuemmerli C, Tinner C, Carrel TP, et al. Completeness of follow-up determines validity of study findings: results of a prospective repeated measures cohort study. *PLoS One* 2015;**10**:e0140817.
- Darling JD, McCallum JC, Soden PA, Meng Y, Wyers MC, Hamdan AD. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (Wifl) classification system following infrapopliteal endovascular interventions for critical limb ischemia. *J Vasc Surg* 2016;**64**:616–22.
- Lu K, Farber A, Schermerhorn ML, Patel VI, Kalish JA, Rybin D, et al. The effect of ambulatory status on outcomes of percutaneous vascular interventions and lower extremity bypass for critical limb ischemia in the Vascular Quality Initiative. *J Vasc Surg* 2017;**65**: 1706–12.
- Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. Editor's choice - 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018;**55**:305–68.
- Beropoulos E, Stavroulakis K, Schwindt A, Stachmann A, Torsello G, Bisdas T. Validation of the Wound, Ischemia, foot Infection (Wifl) classification system in nondiabetic patients treated by endovascular means for critical limb ischemia. *J Vasc Surg* 2016;**64**:95–103.