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ORIGINAL ARTICLE

Impact of infection severity on clinical outcomes in critical limb ischemia with tissue loss after endovascular treatment

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Abstract
Critical limb ischemia with infected wounds is known to have a poor prognosis and evaluation of infection severity using the Wound, Ischemia, and foot Infection classification system has been recommended. However, little is known about how infection severity influences the clinical outcomes of critical limb ischemia in patients with tissue loss. We investigated the impact of infection severity on the clinical outcomes in critical limb ischemia with tissue loss after endovascular treatment. In April 2007–August 2014, we enrolled 263 patients (328 limbs) who received endovascular treatment for critical limb ischemia with tissue loss. In the limbs examined, 369 individual wounds existed. We evaluated wound infection using the Infectious Disease Society of America (IDSA) classification. We also investigated wound healing rates at 12 months and limb salvage and major amputation-free survival rates at 2 years after endovascular treatment. Wound healing rates at 12 months for class 0, 1, 2, and 3 were 89, 81, 58, and 33%, respectively (log rank $P < 0.001$). Limb salvage and major amputation-free survival rates at 2 years were lower in patients with lower vs. higher IDSA classes (classes 0–3: limb salvage rate: 97, 90, 61, and 0%, respectively; $P < 0.001$; major amputation-free survival: 67, 61, 38, and 0%, respectively; $P < 0.001$). In Rutherford category 5, only wound healing rates at 12 months and limb salvage and major amputation-free survival rates at 2 years were stratified according to wound infection severity (wound healing rates: 87% in classes 0 and 1 and 65% in classes 2 and 3; $P < 0.001$; limb salvage rates: 93% in classes 0 and 1 and 69% in classes 0 and 2; $P < 0.0001$; major amputation-free survival rates: 61% in classes 0 and 1 and 46% in classes 2 and 3; $P < 0.001$). Wound infection severity affects clinical outcomes of critical limb ischemia with tissue loss, especially in critical limb ischemia with systemic inflammatory response syndrome. In Rutherford category 5, only clinical outcomes of critical limb ischemia were well-stratified according to infection severity. Wound infection affects clinical outcomes of patients with critical limb ischemia with tissue loss.

Keywords Infected wounds · Ischemia · Wound healing · Salvage · Amputation · Systemic inflammatory response syndrome

Introduction

Endovascular treatment (EVT) has been shown to be an effective treatment for critical limb ischemia (CLI). In addition, it is generally agreed that the prognosis of CLI with tissue loss is unfavorable due to lesion severity and patient backgrounds. Moreover, infected wounds in CLI patients contribute significantly to delayed wound healing and cause major amputation [1]. The achievement of wound healing is a key objective to improve quality of life. In clinical practice, the Rutherford classification system, which is essentially based on the extent of the wound with tissue loss, is often used to assess wound severity [2]. However, this classification system is insufficient to accurately assess wound severity because it is vague and lacks information on infection severity. Recently, the Wound, Ischemia, and foot Infection (WIfI) classification system has been recommended for the assessment of clinical outcomes in patients with CLI [3].

The Infectious Disease Society of America (IDSA) infection severity classification divides wound infection severity into four groups and it has been proposed that infection severity is associated with the amputation rate in the feet of

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patients with diabetes [4]. Infection can augment the need for perfusion both by increased metabolic activity and small vessel thrombosis attributable to angiotoxic enzymes. In clinical settings, however, little is known about the influence of infection severity in patients with CLI. The aim of this study was to clarify the clinical effect of infection severity as assessed by the IDSA classification in patients with CLI with tissue loss after EVT.

Methods

The study protocol was in accordance with the Declaration of Helsinki and was approved by the Saiseikai Yokohama City Eastern Hospital Institutional Review Board.

Study design and subjects

This study was a single-center, retrospective analysis of patients with CLI with tissue loss undergoing EVT. The patient flow chart is shown in Fig. 1. From April 2007 to August 2014, 263 consecutive patients with CLI with tissue loss (328 limbs) were treated at the Saiseikai Yokohama City Eastern Hospital and enrolled in this study. The 328 limbs presented with 369 individual wounds. In total, 36 patients were referred for bypass surgery, 16 patients were referred because of restenosis and delayed wound healing. However, 22 could not undergo the surgery because of conditions that left them with no vein for bypass. Thus, 14 patients underwent bypass surgery. Informed consent to undergo the procedure was obtained from all patients.

Patients were divided into four groups according to wound severity using the IDSA classification.[4] Infection severity was classified as follows: class 0, uninfected wound; class 1, local infection involving only the skin and the subcutaneous tissue; class 2, local infection with erythema of > 2 cm, or involving structures deeper than skin and subcutaneous tissues; and class 3, local infection with signs of systemic inflammatory response syndrome (SIRS) as manifested by two or more of the following: temperature of > 38 °C or > 36 °C, HR of > 90 beats/min, respiratory rate of > 20 breaths/min or PCO_2 of < 32 mmHg, and white blood cell count of > 12000 or 4000/cu mm or > 10% immature forms.

Patient evaluation and interventional procedure

As per the Trans-Atlantic Inter-Society Consensus guidelines, we defined patients with CLI as those with tissue loss associated with an absolute ankle pressure of < 70 mmHg or a toe pressure of < 50 mmHg [5]. The hemodynamic status of all wounds was evaluated using the ankle–brachial pressure index (ABI), skin perfusion pressure (SPP), and duplex ultrasound. Blood flow in the lower limb artery was evaluated routinely before EVT using duplex ultrasound imaging and angiography.

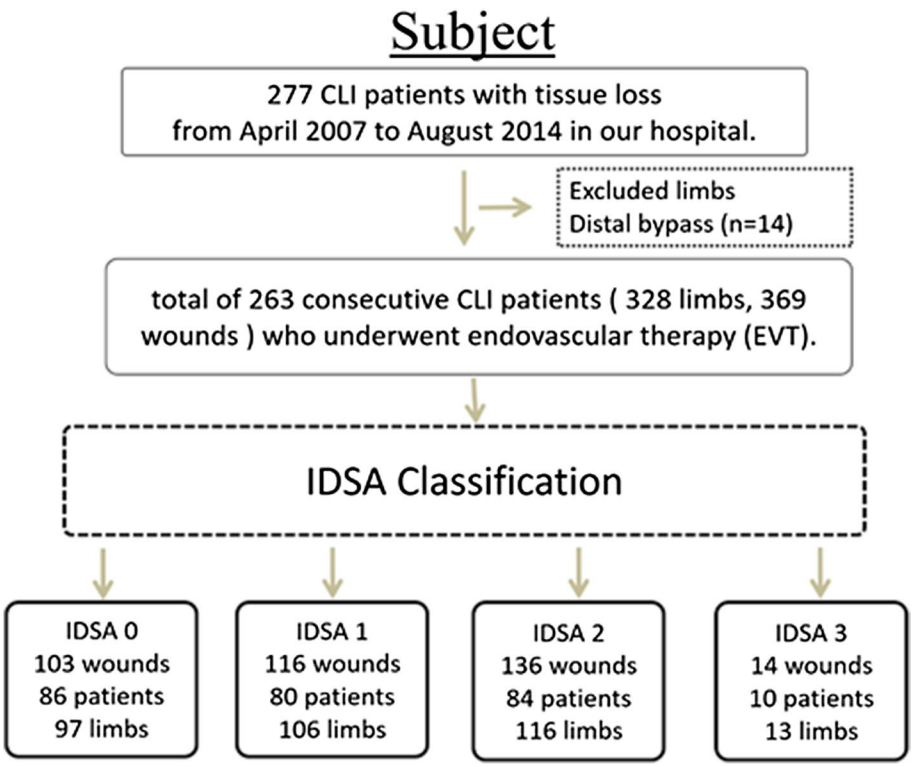


Fig. 1 Patient flow chart

Wounds that existed distally, from the metatarsophalangeal (MP) joint to the tips of the toes, were defined as minor tissue loss. On the other hand, wounds that existed proximally, from the MP joint toward the ankle, were defined as major tissue loss [1]. Indication of the EVT strategy was decided by consensus among interventional cardiologists and vascular surgeons, depending on the patient's general condition and condition of vessels for connecting the bypass. We chose EVT as the initial therapy when both treatments were possible. Our EVT strategy was to provide direct blood flow to the wounds as evaluated by digital subtraction angiography performed immediately after EVT, regardless of "direct" or "indirect" revascularization. All EVT procedures were performed under local anesthesia and a 0.014-in. guidewire was advanced into the culprit lesion and dilated using an optimally sized balloon catheter at the operator's discretion. Essentially, the diameter of the distal part of the healthy vessel was used as reference to decide balloon size. Stent, drug-coated balloon, and atherectomy devices were not approved for use in infrapopliteal intervention in Japan.

We performed primary stenting using self-expanding stents for the treatment of iliac lesions under intravascular ultrasound guidance via the ipsilateral femoral artery. Balloon angioplasty using an optimally sized balloon was performed for femoropopliteal lesions via the contralateral femoral artery. Self-expandable stents were implanted in patients with a residual diameter stenosis of $>30\%$, and/or flow-limiting dissection after balloon angioplasty. At the infrapopliteal level, we performed balloon angioplasty using long balloons (100–300 mm) only on the basis of angiographic measurements via the ipsilateral common femoral artery for an antegrade approach. Patients always received 5,000 U of heparin after sheath insertion; in addition, dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) were initiated before EVT and continued for at least a month.

Infected wound evaluation and management

Wound evaluation and wound management were decided on by our foot care team, which included interventional cardiologists, a plastic surgeon, nurses specialized in foot care training, and a prosthetist. Wound healing was evaluated and ulcers were managed using the "TIME" concept during follow-up. TIME is an acronym for the following: T, tissue; I, infection or inflammation; M, moisture imbalance; and E, edge of wound (non-advancing or undermined) [6]. Infected wounds were assessed using the IDSA classification at the initial visit. On admission, we checked for an inflammatory reaction and performed a cultivation test (of blood and the wound). We determined whether the wound culture was colonized by comparing with the results of the blood culture and the type of bacteria. When the blood culture was negative, we evaluated the result of the wound culture based on its general appearance, blood test results, phagocytosis of the bacteria on Gram staining, and the patient's wound infection status. Our interventions primarily included wound cleaning and debridement and the application of ointment. Blood flow evaluation was performed if the color of the lower limbs was bad or the natural course of the wound was taking an extended time and there was an absence of palpable pulses. The selection of antibiotics upon admission depended on the patient's physician. When antibiotic therapy was insufficient, the infection status was carefully assessed, and osteomyelitis or subcutaneous abscesses were investigated using magnetic resonance imaging (MRI) or ultrasound. Wound evaluation was decided on by our foot care team every week in our foot care clinic. If wound healing was insufficient, we used duplex ultrasound or angiography to evaluate target vessel restenosis. We considered referral for bypass surgery or a repeat EVT when target vessel restenosis was the cause of delayed wound healing. Debridement and minor amputation were executed to drain infected materials, remove infectious or necrotic tissue, and treat osteomyelitis to prevent major amputation. If the infected wounds threaten the patient's condition, in some cases, we performed debridement before EVT. However, basically we performed wound surgery (debridement or minor amputation) at the same time or immediately after EVT. Wounds were left open after minor amputations, and wounds were treated to induce granulation. Indications for incisional drainage, ostectomy, negative-pressure therapy auto-skin grafting, free-flap reconstruction, and midfoot or hindfoot amputations were decided by a plastic surgeon. For shallow wounds that needed epithelization, we mainly used an oil-based ointment (Isodine Sugar Paste Ointment; Shionogi Co, Ltd., Tokyo, Japan). For deep wounds that needed proliferation of granulation, we used a fibroblast growth factor (Fiblast Spray; Kaken Pharmaceutical Co, Ltd., Tokyo, Japan) as well as negative-pressure therapy to enhance granulation. In addition, we used off-loading techniques, with customized shoes for depressurization made by a prosthetist.

Study endpoint

We evaluated the following endpoints in patients with IDSA classes 0, 1, 2, and 3. The primary endpoint was complete wound healing after EVT within 12 months; the secondary endpoint was major amputation-free survival rate at 2 years after EVT. In this study, we studied the clinical outcomes in Rutherford category 5 only as a subanalysis to clarify the relationship between wound extent and infection because Rutherford category 6 was also known to have poorer outcomes than Rutherford category 5 in terms of wound healing and limb salvage rate. As an additional subanalysis, we evaluated the patients with ABI <0.4 prior to EVT. These

patients tend to have associated depressed immunity and progenitor cell counts. We studied the effectiveness of EVT for wound healing and limb salvage when stratified by infection severity in these patients with more advanced ischemia.

Definitions

Rutherford category 5 was defined as ischemic ulceration not exceeding ulcer of the digits of the foot. Rutherford 6 was defined as severe ischemic ulcers or Frank gangrene. Complete wound healing was defined as achievement of complete epithelization of all wounds without death or major amputation. Limb salvage was defined as freedom from major amputation, which included any amputation above the ankle. Target limb revascularization included any repeat endovascular interventions and surgical revascularizations. The angiosomes of the foot and ankle are defined by three main supply arteries. The posterior tibial artery supplies the plantar aspect of the toes, web spaces between the toes, sole of the foot, and inside of the heel. The anterior tibial artery continues as the dorsalis pedis artery, which supplies the dorsum of the ankle and the outside of the heel. Toe or transmetatarsal amputations were considered minor amputations. Time to healing after a minor amputation was also defined as complete epithelization of the ischemic lesions, with no further need for wound care, including wound cleaning and ointment application. Non-ambulatory status was defined as being wheelchair bound or bedridden. In this study, non-ambulatory status included patients who could not stand up and walk because of leg pain. Coronary artery disease was defined by documented angina pectoris, previous myocardial infarction, or a history of percutaneous coronary intervention. The diagnosis of diabetes mellitus was based on World Health Organization criteria or having been treated with insulin or oral hypoglycemic drugs, or as having casual plasma glucose of > 200 mg/dL or HbA1c of > 6.5%. Heart failure was defined by a history of hospitalization for heart failure or by the presence of current treatment for heart failure.

Statistical analysis

Continuous variables with a normal distribution are presented as means ± standard deviations and were compared using an unpaired *t* test. Continuous variables without a normal distribution are reported as median and interquartile range and were compared using the Mann–Whitney *U* test. Categorical variables are shown as percentages and were compared using Fisher's exact test. Comparisons of more than two groups of categorical variables were tested using the Chi-squared test.

Kaplan–Meier and log rank tests were used to compare groups in terms of wound healing, limb salvage, and major amputation-free survival. A two-sided *P* value of < 0.05 was considered to indicate a statistically significant difference. All statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

A summary of the baseline patient characteristics is reported in Table 1. There were no significant differences in patient background or comorbidities. C-reactive protein at the initial visit was higher in patients with IDSA classes 2 and 3 (classes 0–3: 0.5 ± 0.1, 1.5 ± 0.5, 3.2 ± 1.0, and 10.6 ± 8.1,

Table 1 Baseline patient characteristics

Variables[a]	IDSA 0 (*n* = 86)	IDSA 1 (*n* = 80)	IDSA 2 (*n* = 84	IDSA 3 (*n* = 10	*P* Value
Male	46 (54)	55 (69)	61 (73)	7 (70)	0.05
Age, years	75 ± 12	71 ± 11	70 ± 11	70 ± 10	0.29
Hypertension	69 (80)	61 (76)	59 (69)	7 (70)	0.41
Dyslipidemia	29 (30)	21 (26)	25 (29)	1 (10)	0.50
Diabetes mellitus	54 (62)	58 (73)	66 (78)	7 (70)	0.20
HbA1c, %	6.6 ± 1.7	6.7 ± 1.6	6.7 ± 1.6	6.6 ± 1.1	0.78
Pre-CRP mg/dl	0.5 ± 0.1	1.5 ± 0.5	3.2 ± 1.0	10.6 ± 8.1	<0.01
Hemodialysis	31 (36)	37 (46)	46 (54)	5 (50)	0.12
Coronary artery disease	22 (25)	19 (24)	22 (25)	3 (30)	0.42
Low ejection fraction < 40%	4 (4.7)	6 (7.5)	7 (8.3)	1 (10)	0.29
Non-ambulatory status					0.08
Wheel chair use	20 (23)	22 (27)	31 (36)	1 (10)	
Bed ridden	8 (9.3)	5 (6.3)	15 (17)	4 (40)	

[a]Categoric variables are presented as number (%) and continuous variables as mean ± standard deviation

respectively; $P < 0.01$). Validation of the WIfI classification is shown in Table 2. There were significant differences in the clinical stage after stratification by the WIfI classification. Positive rates of the blood culture were 0% for IDSA 0, 2.5% for IDSA 1, 12% for IDSA 2, and 23% for IDSA 3. In many cases, the wound cultures exhibited a lot of colonization and contamination unrelated to wound healing. *S. pyogenes*, *S. aureus*, methicillin-resistant *Staphylococcus aureus* and *P. aeruginosa* were causative bacteria mainly in blood cultures. There was no statistically significant difference associated with these outcomes because the number of patients was small.

Baseline lesion and wound characteristics are presented in Tables 3 and 4. There were no significant differences in target lesion sites or prevalence of chronic total occlusion among the four groups. Minor tissue loss was more common in patients with IDSA class 0 (classes 0–3: 90, 76, 43, and 29%, respectively; $P < 0.01$) and major tissue loss in patients with IDSA class 3 (classes 0–3: 9.7, 24, 57, and 71%, respectively; $P < 0.01$). Wounds in patients with IDSA classes 0 and 1 were more frequently located at the toe, and wounds in patients with IDSA class 3 were more frequently located at the body of the foot compared to those in other classes (classes 0–3; toe: 83, 79, 65 and 71%, respectively; $P < 0.01$).

Interventional results and wound management are reported in Table 5. Preprocedural ABI values were higher in each IDSA group than in the typical range for limb-threatening ischemia. Preprocedural SPP was lower in patients with IDSA class 3 (classes 0–3: 39 ± 19, 37 ± 21, 37 ± 20,

Table 2 Validation of WIfI classification

Variables	IDSA 0 ($n = 97$)	IDSA 1 ($n = 101$)	IDSA 2 ($n = 116$)	IDSA 3 ($n = 13$)	*P* Value
WIfI classification					<0.01
High	8 (8.3)	18 (18)	85 (73)	13 (100)	
Moderate	15 (16)	32 (32)	17 (15)	0 (0)	
Low	23 (25)	34 (34)	14 (12)	0 (0)	
Very low	51 (53)	17 (17)	0 (0)	0 (0)	

Table 3 Baseline lesion characteristics

Variables	IDSA 0 ($n = 97$)	IDSA 1 ($n = 101$)	IDSA 2 ($n = 116$)	IDSA 3 ($n = 13$)	*P* Value
Lesion characteristics					0.67
Aortoiliac	0 (0)	1 (0.9)	1 (0.7)	0 (0)	
Femoropopliteal	3 (3.1)	4 (4.0)	5 (4.3)	1 (7.7)	
I nfrapopliteal	41 (42)	44 (44)	55 (47)	4 (31)	
Aortoiliac + femoropopliteal	1 (1.0)	3 (3.0)	6 (5.2)	0 (0)	
Aortoiliac + infrapopliteal	3 (3.0)	0 (0)	1 (0.9)	0 (0)	
Femoropopliteal + infrapopliteal	41 (43)	48 (47)	42 (36)	6 (46)	
Aortoiliac + femoro-popliteal + infrapopliteal	7 (7.2)	3 (3)	10 (8.6)	2 (15)	
Chronic total occlusion lesion	60 (61)	72 (72)	69 (60)	8 (61)	0.27

Table 4 Baseline wound characteristics

Variables	IDSA 0 ($n = 103$)	IDSA 1 ($n = 116$	IDSA 2 ($n = 136$)	IDSA 3 ($n = 14$)	*P* Value
Wound characteristics					<0.01
Rutherford 5	93 (90)	88 (76)	58 (43)	4 (29)	
Rutherford 6	10 (9.7)	28 (24)	78 (57)	10 (71)	
Multiple wounds	22 (21)	45 (39)	59 (44)	9 (64)	<0.01
Location					
Toe	86 (83)	91 (79)	88 (65)	10 (71)	<0.01
Body of foot	3 (2.9)	7 (6.1)	18 (13)	5 (35)	<0.01
Heel	10 (9.7)	18 (16)	31 (23)	3 (21)	0.05
Crus	1 (1.0)	0 (0)	6 (4.4)	0 (0)	0.03

Table 5 Interventional results and wound management

Variables[a]	IDSA 0 ($n=97$)	IDSA 1 ($n=101$)	IDSA 2 ($n=116$)	IDSA 3 ($n=13$)	P Value
Preprocedural ABI	0.69 ± 0.22	0.71 ± 0.27	0.67 ± 0.27	0.65 ± 0.24	0.65
Preprocedural SPP, mm Hg	39 ± 19	37 ± 21	37 ± 20	13 ± 10	0.02
Postprocedural ABI	0.87 ± 0.20	0.90 ± 0.17	0.97 ± 0.18	0.89 ± 0	0.29
Postprocedural SPP, mmHg	50 ± 20	52 ± 19	51 ± 23	39 ± 0	0.49
Interventional results					
Blood flow to the wounds	76 (78)	81 (80)	78 (67)	8 (61)	0.06
Pedal loop patency	66 (68)	65 (64)	61 (52)	6 (46)	0.06
Angiosome concept	76 (78)	80 (80)	77 (66)	8 (61)	0.06
Re-intervention rate	27 (28)	42 (42)	46 (40)	2 (20)	0.14
Wound management					
Minor amputation	13 (13)	34 (34)	61 (53)	6 (46)	<0.01
Transmetatarsal level	0 (0)	2 (1.9)	12 (10)	3 (23)	0.08
Negative-pressure therapy	4 (4.1)	19 (19)	34 (30)	2 (15)	0.03
Auto-skin graft	0 (0)	8 (7.9)	10 (8.6)	0 (0)	0.09
Free-frap reconstruction	0 (0)	4 (4.0)	2 (1.7)	0 (0)	0.23

ABI, ankle–brachial index; SPP, skin perfusion pressure

[a]Categorical variables are presented as number (%) and continuous variables as mean ± standard deviation

and 13 ± 10, respectively; $P=0.02$). The success rates for blood flow to the wounds and re-intervention rates did not statistically differ among the four groups. In addition, postprocedural ABI and SPP improved to a similar extent.

The need for minor amputation was lower for patients with IDSA class 0 than for the other classes (classes 0, 1, 2, and 3: 13, 34, 53, and 46%, respectively, $P<0.01$). The percentage of those treated with negative-pressure therapy was higher for patients with IDSA class 2 than for the other classes (classes 0, 1, 2, and 3: 4.1, 19, 30, and 15%, respectively, $P=0.03$).

Clinical outcomes according to infection severity

Wound healing rates at 12 months according to IDSA class are shown in Fig. 2. Wound healing rates at 12 months in patients with IDSA classes 0, 1, 2, and 3 were 89, 81, 59, and 33%, respectively (class 0 vs. 1, $P<0.001$; class 1 vs. 2, $P<0.001$; class 2 vs. 3, $P=0.03$). Limb salvage rates at 2 years in patients with IDSA classes 0, 1, 2, and 3 were 97, 90, 61, and 0%, respectively (class 0 vs. 1, $P=0.11$; class 1 vs. 2, $P<0.001$; class 2 vs. 3, $P<0.001$). Major amputation-free survival rates at 2 years in patients with IDSA classes 0, 1, 2, and 3 were 67, 61, 38, and 0%, respectively (class 0 vs. 1, $P=0.52$; class 1 vs. 2, $P<0.001$; class 2 vs. 3, $P<0.001$).

Effect of infection severity in Rutherford category 5

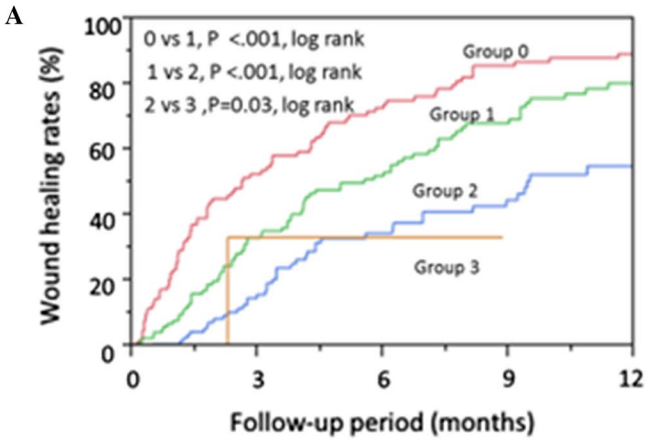
The subgroup analysis of Rutherford category 5 limbs excluded 105 limbs at Rutherford category 6 from the analysis. Wound healing at 12 months in Rutherford category 5 only in patients with IDSA classes 0 and 1 vs. those with classes 2 and 3 is shown in Fig. 3. The wound healing rate was significantly lower in class 2 or 3 than in class 0 or 1, even when limited to Rutherford category 5 only (87 vs. 65%; $P<0.001$). Furthermore, limb salvage and major amputation-free survival rates at 2 years were significantly lower in patients with IDSA classes 2 or 3 than in those with classes 0 or 1 (limb salvage rates: 93 vs. 63%; $P<0.001$; major amputation-free survival rates: 61 vs. 46%; $P<0.001$).

Effect of infection severity in patients with ABI < 0.4

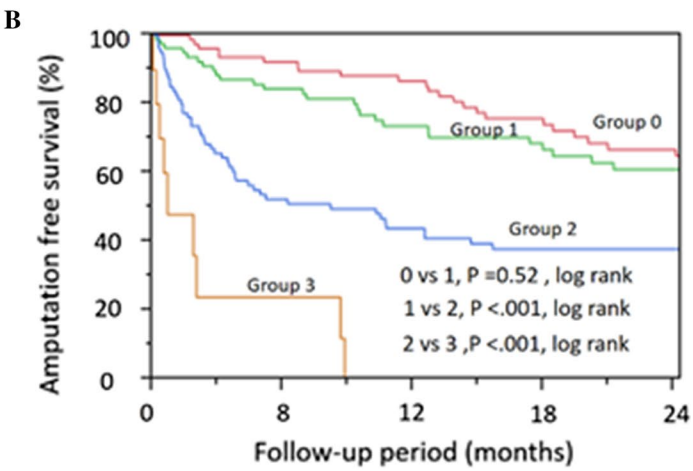
Figure 4 shows wound healing at 12 months in patients with ABI < 0.4, comparing those in IDSA classes 0 and 1 with those in classes 2 and 3. The wound healing rate was significantly lower for patients with IDSA classes 2 and 3 than for those with classes 0 and 1 (87 vs. 43%; $P<0.001$). Limb salvage and major amputation-free survival rates at 2 years were significantly lower for patients with IDSA classes 2 and 3 than for those with classes 0 and 1 (limb salvage rates: 88 vs. 38%; $P<0.001$; major amputation-free survival rates: 63 vs. 20%; $P<0.001$).

Discussion

Our main findings in this study were as follows. First, greater infection severity was associated with a lower healing rate and poorer limb salvage and major amputation-free survival. Patients with SIRS had significantly poorer outcomes than did those classified otherwise.



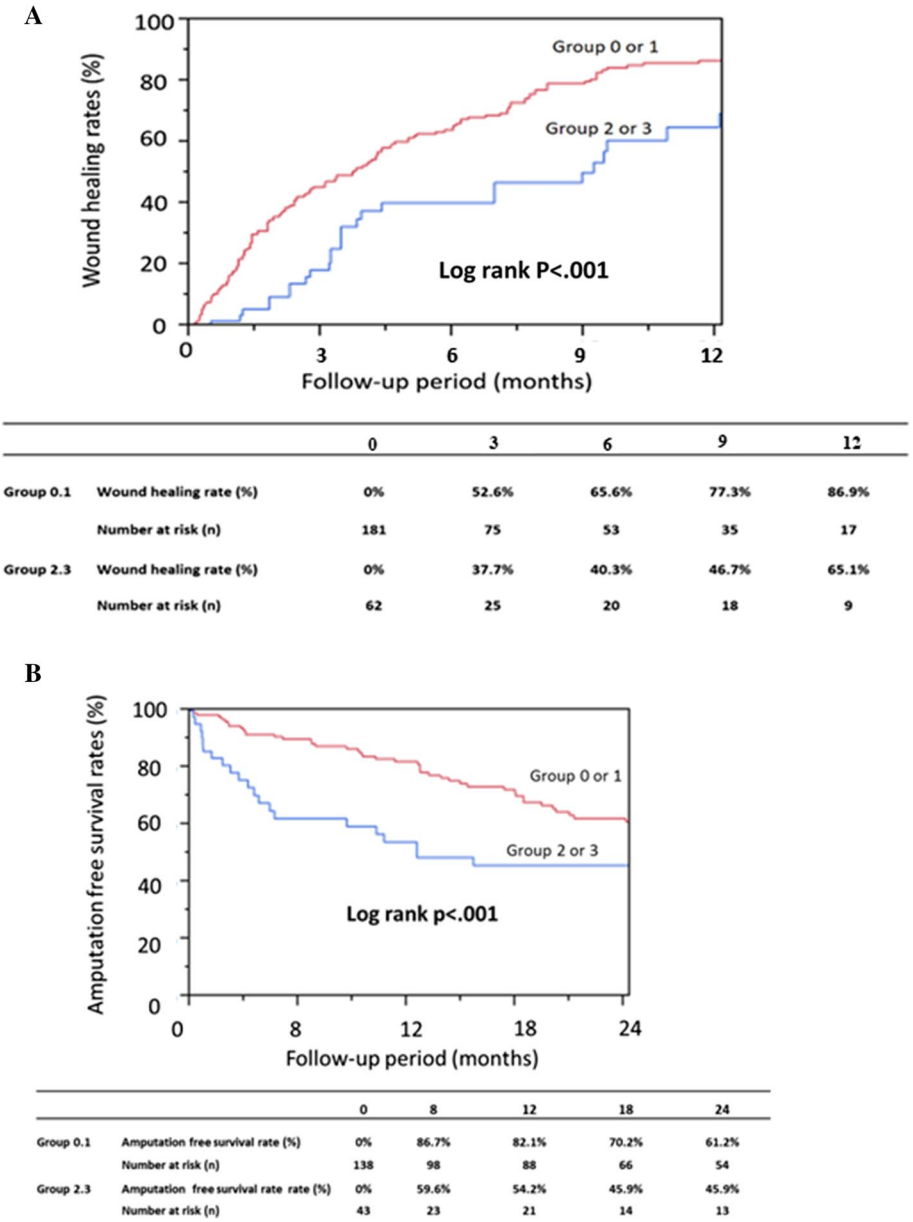
		0	3	6	9	12
Group 0	Wound healing rate (%)	0%	52.7%	74.1%	85.8%	89.3%
	Number at risk (n)	103	44	24	14	10
Group 1	Wound healing rate (%)	0%	33.3%	53.3%	69.5%	80.5%
	Number at risk (n)	116	67	47	25	13
Group 2	Wound healing rate (%)	0%	15.9%	34.6%	44.8%	57.8
	Number at risk (n)	136	77	44	30	17
Group 3	Wound healing rate (%)	0%	0%	0%	33%	
	Number at risk (n)	14	5	5	1	



		0	8	12	18	24
Group 0	AFS rate (%)	100%	92.3%	86.7%	74.1%	66.9%
	Number at risk (n)	84	71	59	43	37
Group 1	AFS rate (%)	100%	84.5%	73.7%	66.9%	61.0%
	Number at risk (n)	80	62	46	38	32
Group 2	AFS rate (%)	100%	52.4%	43.9%	38.0%	38.0%
	Number at risk (n)	85	40	31	21	15
Group 3	AFS rate (%)	100%	24%	0%		
	Number at risk (n)	10	3	1		

Fig. 2 **a** Wound healing rates at 12 months. **b** Amputation-free survival at 2 years according to wound infection severity

Second, in general, severely infected wounds were more frequent among Rutherford category 6 patients. However, in Rutherford category 5 patients, only the rates of wound



		0	3	6	9	12
Group 0.1	Wound healing rate (%)	0%	52.6%	65.6%	77.3%	86.9%
	Number at risk (n)	181	75	53	35	17
Group 2.3	Wound healing rate (%)	0%	37.7%	40.3%	46.7%	65.1%
	Number at risk (n)	62	25	20	18	9

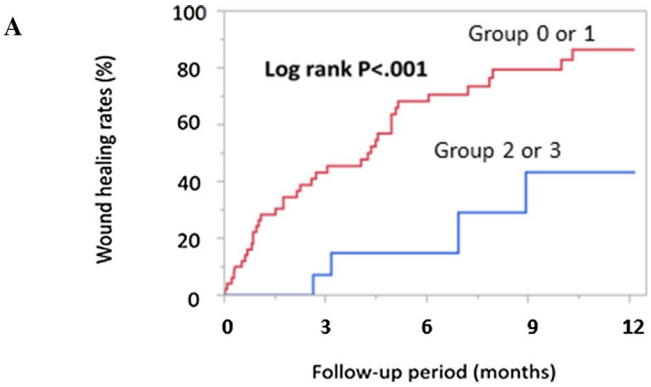
		0	8	12	18	24
Group 0.1	Amputation free survival rate (%)	0%	86.7%	82.1%	70.2%	61.2%
	Number at risk (n)	138	98	88	66	54
Group 2.3	Amputation free survival rate rate (%)	0%	59.6%	54.2%	45.9%	45.9%
	Number at risk (n)	43	23	21	14	13

Fig. 3 **a** Wound healing rates at 12 months in only Rutherford category 5 between IDSA 0 or 1 and 2 or 3. B, amputation-free survival at 2 years in only Rutherford category 5 between IDSA 0 or 1 and 2 or 3

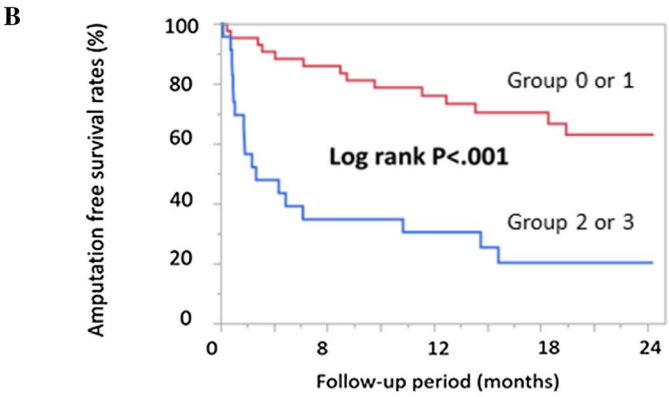
healing, limb salvage, and major amputation-free survival differed significantly by wound infection severity.

Patients with CLI are recognized to have poor prognoses [7]. Achieving wound healing is an important objective for patients with CLI to improve quality of life. Kobayashi et al. suggested that achieving wound healing was associated with improvement of clinical outcomes of CLI with tissue loss after EVT. Once wound healing was achieved, the overall survival rate at 3 years was 74% and CLI recurrence rate was only 9% [8]. These results suggest that wound healing is associated with improvement of clinical outcomes in patients with CLI.

A previous study reported that major tissue loss influenced wound non-healing in patients with CLI [9]. However, infection is also an important factor which is related to the failure of wound healing and major amputations in diabetic foot ulcers, and infection severity is normally stratified using the IDSA infection severity classification [10]. The IDSA classification has been prospectively validated as predicting the need for hospitalization (0% for no infection, 4% for mild, 52% for moderate, and 89% for severe infection) and for limb amputation (3% for no infection, 3% for mild, 46% for moderate, and 70% for severe infection) [4]. Results of the EURODIALE trial confirm that infection frequently triggers amputation in diabetic patients with a threatened limb. However, these results targeted diabetic feet, but not CLI [11].



		0	3	6	9	12
Group 0.1	Wound healing rate (%)	0%	42.9%	70.0%	79.2%	86.1%
	Number at risk (n)	51	27	14	7	4
Group 2.3	Wound healing rate (%)	0%	7.2%	14.9%	43.2%	43.2%
	Number at risk (n)	29	13	7	5	2



		0	8	12	18	24
Group 0.1	Amputation free survival rate (%)	100%	81.1%	76.2%	70.6%	63.2%
	Number at risk (n)	45	35	29	20	14
Group 2.3	Amputation free survival rate (%)	100%	62.3%	30.4%	20.3%	20.3%
	Number at risk (n)	23	24	7	5	2

Fig. 4 **a** Wound healing rates at 12 months in ABI less than 0.4 between IDSA 0 or 1 and 2 or 3. **b** Amputation-free survival at 2 years in ABI less than 0.4 between IDSA 0 or 1 and 2 or 3

Thus, despite the importance of infection in the path toward wound healing and major limb amputation in patients with lower extremity wounds and peripheral artery disease, infection severity was not mentioned in the Trans-Atlantic Inter-Society Consensus, Rutherford, or Fontaine classifications.

In the WIfI system, which contains information regarding the grade of wound status, ischemia, and foot infection, wound depth takes priority over wound size. However, data regarding the actual effects of infection severity on clinical outcomes of CLI with tissue loss are insufficient. To the best of our knowledge, the present study is the first to investigate the effects of infection severity on clinical outcomes of CLI with tissue loss.

In the present study, patients with infected wounds penetrating to bone and spreading to the whole body had poorer clinical outcomes. To control infection, we checked every type of bacterial cultivation and felt that we administered adequate levels of antibiotics at the time of admission since patients with CLI are generally more compromised. However, preventing SIRS necessitates eradication of the primary infection site as well as the consideration of various treatment options (minor amputation, drainage, and negative-pressure therapy) to cure infected wounds after sufficient

revascularization. Recognizing infection severity during the initial evaluation enables the prediction of poor wound healing and necessitates aggressive wound management.

A previous study reported that wound infection was associated with delayed wound healing.[1,2] The OLIEVE registry, which was designed for Japanese patients, showed that body mass index of < 18.5 and wound infection were significant risk factors for delayed wound healing of ischemic ulcers [12]. In this study, even if the wound appeared to be small (i.e., Rutherford category 5), amputation rates at 24 months in patients with IDSA classes 0, 1, 2, and 3 were 3.4, 7.7, 21, and 75%, respectively. This result suggested that the severity of infection affected clinical outcomes, as found in a previous study of IDSA classification [4]. In particular, the prognoses of patients with SIRS were worse than those in other infection severity categories. Therefore, in severely infected patients, we must consider the possibility of primary amputation to save lives. In addition, if an infection is settled, but the wound is large, the risk of infection in the chronic phase will be increased, and it will be necessary to maintain blood flow for a long time.

A disadvantage of infrapopliteal balloon angioplasty is its high restenosis rate.

A previous study reported that restenosis rates 3 and 12 months after infrapopliteal angioplasty were 73 and 82%, respectively [13].

A severely infected wound requires a greater blood supply and longer patency time to achieve complete wound healing. Previous studies have reported that the restenosis rates and time to wound healing of bypass surgery were better than those of EVT; thus, for obviously comprehensive infected wounds at first impression, bypass surgery may be more effective if patients have suitable distal arteries through which to connect the bypass [14–16]. In a study on wounds in which 42% were infectious, Pomposelli et al. reported actuarial graft patency, limb salvage, and patient survival at 18 months of 82, 87, and 80%, respectively [17].

On the other hand, our study found that wound healing rates at 12 months in IDSA classes 0, 1, 2, and 3 were 89, 81, 59, and 33%, respectively. Although all patients with ABI < 0.4 were classified into high- or moderate-risk WIfI categories regardless of their infection status, our subanalysis showed that there was a significant difference in clinical outcomes according to the severity of infection even for severe ischemic limbs only. These results suggest that when patients have a low-risk IDSA classification and direct blood flow to the wounds is demonstrated on angiography after EVT, wound healing rates are acceptably similar to those after bypass surgery. However, it is difficult to achieve complete wound healing in high-risk patients. In the present study, wound healing rates at 12 months in patients with CLI in IDSA classes 2 or 3 were lower than those in classes 0 or 1, despite the fact that there was no significant difference in the rate of successful EVT between the four groups. The IDSA 3 group included cases that involved intervention to maintain the blood flow of the broken end at the time of the major amputation as well as patients for whom it was hoped that saving the limb was possible, even if the wound was above the ankle. In fact, these high-risk patients died before wound healing was complete, leading to a further decrease in the wound healing rates. Although bypass surgery should be considered early for high-risk patients, some patients could not tolerate surgery due to severe background conditions (both general and lesion-related) that left them with no vein for bypass. In addition, it was previously reported that it was difficult to properly evaluate the range of osteomyelitis using MRI if the lower limb blood flow was insufficient [18]. Therefore, even when primary amputation was performed, there were cases in which additional amputation was necessary because wound healing could not be achieved. For such patients, it was sometimes necessary to repeat EVT to maintain blood flow to the wound site for wound healing.

Given this, advances in EVT technology are essential. Recently, new devices, such as interwoven nitinol stent, drug-coated balloons, and directional atherectomy, which are not yet widely available in Japan, have resulted in a decrease in repeat EVT rates [19–21]. These devices may contribute to improving future outcomes after EVT in high-risk patients.

Several limitations should be considered. First, this study was a single-center retrospective study that included only Japanese patients with CLI. Therefore, the results may not be generalizable to other populations. Most importantly, the number of limbs was too small to investigate and evaluate possible correlations between the IDSA classification with wound healing and major amputation; there were only 13 patients in group 3. Actual clinical outcomes should be evaluated by studies that include a larger number of patients. Second, the choice of antibiotics and infection control used after admission depended on the patient's physician. Third, the sample was limited to patients with CLI after EVT. If the wound status deteriorated, we considered attempting a second session and referring the patient for bypass surgery. However, this study excluded all patients who underwent bypass surgery, and the real validation ability could not be fully evaluated. Fourth, hyperbaric oxygen therapy was not available at our facility. Fifth, ABI less than 0.4 might not be able to assess severe ischemia accurately. However, SPP and toe pressure might not be suitable for evaluation of ischemia as well as ABI because the infected wounds tend to have high SPP value and this study included only patients with tissue loss. Finally, newer technologies such as drug-eluting balloons and atherectomy devices were not used in this study because these technologies were unavailable in Japan [19–21].

Conclusion

Assessing infection severity is necessary to decide the most appropriate method with which to initially treat a patient with CLI. In daily clinical practice, patients with CLI are normally evaluated using the Rutherford classification system. This system is based on wound extent, but not on wound infection severity. Apart from successful revascularization, various factors are associated with wound healing. Of course, primary amputation and bypass surgery should be considered if patients are in life-threatening condition due to severe infection of the foot or if the healing course is delayed after EVT. The correct assessment of infection wound is essential to achieve wound healing and amputation-free survival in patients with CLI with tissue loss.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial relationships or other conflicts of interest relevant to the contents of this paper.

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