Duration from Wound Occurrence to Referral to a Vascular Center in Japanese Patients with Critical Limb Ischemia

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Objective: Clinical guidelines have long recommended referring patients with clerical limb ischemia (CLI) to a vascular specialist early in the course of their disease to plan for revascularization options. However, no data were so far available on how promptly CLI patients were referred to a vascular center in the real-world settings in Japan. This study aimed to survey the duration from wound occurrence to referral to a vascular center in CLI patients in Japan.

Materials and Methods: We analyzed a database of a prospective, multicenter registry in Japan, including 428 CLI patients presenting ischemic wounds and referred to vascular centers. The duration of the wound occurrence was surveyed at registration.

Results: The wound duration exceeded 1 month in 58.2% [95% confidence interval: 53.2% to 63.1%] of the patients, and 3 months (i.e., one season) in 15.9% [12.4% to 19.4%]. No clinical features were significantly associated with the wound duration. The wound duration was independently associated with the wound severity evaluated using the Wound, Ischemia, and foot Infection classification system (P=0.030).

Conclusion: A substantial number of CLI patients referred to vascular centers had a long duration of wounds, i.e., time from wound occurrence to the referral.

Keywords: critical limb ischemia, duration of wound, referral, wound severity

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Introduction

Critical limb ischemia (CLI) is the most advanced form of peripheral arterial disease and has an extremely poor limb prognosis. Most patients with CLI will ultimately need a revascularization procedure for limb salvage. Clinical guidelines have long recommended early recognition of tissue loss and/or infection and referral to a vascular specialist; CLI patients should be referred to a vascular specialist early in the course of their disease to plan for revascularization options.[1,2] However, no data were so far available on how promptly CLI patients were referred to a vascular center in the real-world settings in Japan. The current study aimed to survey the duration from wound occurrence to referral to a vascular center in CLI patients in Japan.

Materials and Methods

We used a clinical database obtained from the Surgical Reconstruction versus Peripheral Intervention in patients with CLI (SPINACH) study, a prospective, multicenter, observational study that registered patients who had CLI

due to atherosclerotic arterial disease in 23 centers (12 vascular surgery departments and 11 interventional cardiology departments) in Japan. CLI patients were registered at the referral to the participating centers between January 2012 and March 2013. The details of the SPINACH study are described elsewhere.[3,4] The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee at the principal research institution, Asahikawa University Hospital (no. 1023), and all the other centers registering patients. Written informed consent was obtained. In patients presenting ischemic wounds, the duration of the wound was assessed at registration. The current analysis included a total of 428 patients who presented ischemic wounds, satisfying the Wound grade 1 or higher and Ischemia grade 2 or higher of the Wound, Ischemia, and foot Infection (WIfI) classification system.[5] Patients who underwent pre-referral revascularization after the current wound occurrence were excluded. Surgical reconstruction and endovascular therapy were scheduled in 142 and 275 patients, respectively, whereas the remaining 11 patients were not indicated for revascularization. The duration of the wound was defined as the time from the wound occurrence to the referral, based on self-report and medical records. The data on the duration of the wound were available in 388 of 428 patients (90.1%). As mentioned elsewhere,[4] the WIfI classes of the study participants were retrospectively determined using the photographs of pedal wounds and medical records, including laboratory examinations, at registration. The judgment was first made at each participating center and was thereafter reviewed by an independent plastic surgeon. Disagreements were discussed and resolved in a subsequent committee attended by the plastic surgeon, a vascular surgeon, and an interventional cardiologist. Skin perfusion pressures of 31–40 mmHg and ≤30 mmHg were treated as WIfI Ischemia grades 2 and 3, respectively.[4] The pressure sensation of the foot was assessed by the Semmes–Weinstein 5.07 monofilament at the following four podalic sites: the distal great toe and the first, third, and fifth metatarsal heads.[6] Loss of pressure sensation was defined when patients were unable to feel correctly the pressure applied by the monofilament at any of the sites. Major cardiovascular diseases were defined as coronary artery disease and/or ischemic stroke. Prior history of lower limb revascularization and amputation was referred to as the treatments before the current wound occurrence, whether ipsilateral or not. Note again that this study did not include patients who underwent pre-referral revascularization after the current wound occurrence.

Statistical analysis

Data are given as means and standard deviations for continuous variables or as percentages for discrete variables, if not otherwise mentioned. A P value of <0.05 was considered statistically significant, and 95% confidence intervals are reported when appropriate. The 95% confidence interval of a crude prevalence was calculated based on the binomial distribution. The association between the duration of the wound and the prevalence of respective clinical features was assessed using the generalized linear mixed model with a logit link function in which the log-transformed duration of the wound was entered as the fixed effects, and the inter-institution variability was treated as the random effects. The cumulative link mixed model with a logit link function was adopted to explore the association of the duration of the wound, as well as clinical features, with the WIfI severity. The duration of the wound was entered into the model as the fixed effects after its log-transformation. The inter-institution variability was entered as the random effect in the model. Finally, the impact of the duration of the wound on achieving a wound- and amputation-free survival after revascularization was investigated in the subgroup undergoing revascularization. The investigation was performed using the generalized linear mixed model with a logit link function, including survival with freedom from both wound and major amputation at 1, 3, 6, and 12 months after revascularization as the dependent variables, the log-transformed duration of wound as the fixed effects, and revascularization strategy (surgical or endovascular), time of follow-ups (1, 3, 6, or 12 months), and the inter-subject variability as the random effects. The WIfI Wound grade was, thereafter, additionally entered as the fixed effects to investigate whether the association of the duration of the wound with wound- and amputation-free survival was independent of the wound severity. The multiple imputation method was adopted for missing data. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

Results

Background characteristics of the study population are shown in **Table 1**. Mean age was 73±10 years; 29.0% were aged 80 years or older. The prevalence of diabetes mellitus and regular dialysis, major cardiovascular disease, and loss of pressure sensation was 73.6%, 53.7%, 52.8%, and 40.0%, respectively. In diabetic patients, 15.0% had hemoglobin A1c levels ≥8%, and 61.3% had a duration of diabetes ≥20 years. Before the current wound occurrence, 24.8% of the overall population underwent lower limb revascularization, whereas 12.1% had a history of lower limb amputation. The WIfI Wound grade 3 and Ischemia grade 3 accounted for 16.8% and 80.1%, respectively, whereas foot infection was observed in almost half of the population.

Table 1 Characteristics of the study population

N	428
Male sex	289 (67.5%)
Age (years)	73±10
≥ 80 years	124 (29.0%)
Non-ambulatory status	210 (49.1%)
Receiving welfare	46 (10.7%)
Living alone	68 (15.9%)
Staying in nursing home	35 (8.2%)
Albumin (g/dl)	3.5±0.6
<3 g/dl	72 (17.1%)
Diabetes mellitus	315 (73.6%)
HbA1c (%)	6.7±1.3
≥8%	47 (15.0%)
Duration of diabetes (years)	23±13
≥20 years	149 (61.3%)
Regular dialysis	230 (53.7%)
Major cardiovascular disease	226 (52.8%)
Aspirin use	278 (65.0%)
Thienopyridine use	147 (34.3%)
Cilostazol use	126 (29.4%)
Anticoagulant use	71 (16.6%)
Loss of pressure sensation	144 (40.0%)
Past history of intermittent claudication	213 (49.9%)
Past history of lower limb revascularization	106 (24.8%)
Past history of lower limb amputation	51 (12.1%)
WIfI classification: Wound	
W-1	157 (36.7%)
W-2	199 (46.5%)
W-3	72 (16.8%)
WIfI classification: Ischemia	
I-2	85 (19.9%)
I-3	343 (80.1%)
WIfI classification: foot Infection	
fI-0	222 (51.9%)
fI-1	104 (24.3%)
fI-2	89 (20.8%)
fI-3	13 (3.0%)

Data are mean±standard deviation, or number (percentage). Data were unavailable on albumin levels in 8 patients (1.9%), on HbA1c levels in 2 diabetic patients (0.6%), on duration of diabetes in 72 diabetic patients (22.9%), on pressure sensation in 68 patients (15.8%), history of claudication in 1 patient (0.2%), and history of amputation before the current wound occurrence in 6 patients (1.4%).

As demonstrated in **Table 2,** only 41.8% of the overall population had a ≤1-month duration of the wound. The 95% confidence interval of the prevalence was calculated to be 36.9% to 46.8%. In other words, 58.2% [95% confidence interval: 53.2% to 63.1%] had the duration of the wound longer than 1 month. Furthermore, the duration of the wound exceeded 3 months (i.e., one season) in 15.9% [12.4% to 19.4%] of the patients. None of the clinical features (including diabetes and regular dialysis, as well as a history of lower limb treatment) were significantly associated with the duration of the wound (**Table 3**).

The association of the duration of the wound with the WIfI classes is shown in **Table 4**. The duration of the wound was significantly associated with the WIfI Wound severity, even after adjustment for clinical features; the adjusted odds ratio was 1.22 [1.02 to 1.47] (P = 0.030). On the other hand, the duration of the wound was not significantly associated with the WIfI Ischemia or Foot Infection severity.

Finally, the duration of the wound was significantly inversely associated with achieving a wound- and amputation-free survival after revascularization, independently of revascularization strategy; the odds ratio of the wound duration with adjustment for revascularization strategy was 0.73 [0.54 to 1.00] per two-fold increase (P = 0.0495). However, the association was no longer significant after further adjustment for the WIfI Wound severity; the adjusted odds ratio was 0.78 [0.58 to 1.06] per two-fold increase (P = 0.11), whereas the WIfI Wound severity itself had a significant association (odds ratio: 0.33 [0.21 to 0.53], P < 0.001).

Discussion

The current study demonstrated that the duration of wound was longer than 1 month in 58.2% [53.2% to 63.1%] of the CLI patients and exceeded 3 months (i.e., one season) in 15.9% [12.4% to 19.4%], indicating that a substantial number of patients failed to be referred early to a vascular specialist. Although the true underlying causes for this delayed referral remained unexplored, limited awareness of the disease in both public and general physicians[7,8] might provoke the delay. The subsequent analysis showed that no clinical features were significantly associated with the duration of the wound, suggesting that a delayed referral would be a general issue encountered in every healthcare situation, rather than in some specific populations.

Intuitively, diabetic patients, especially with neuropathy, are more apt to leave their wounds uncared and be late in consulting doctors. However, the current study showed that the duration of the wound was not different between diabetic and non-diabetic patients, or between those with and without loss of pressure sensation, indicating that the delayed referral was similarly observed even in non-diabetic patients and those without neuropathy. Although the true reasons remained unknown, the delay might be caused mainly by the unawareness of family doctors, rather than by the nature of the disease. Another possible explanation is that patients free from diabetes and neuropathy might have had poorer knowledge on the risks of unhealed foot ulcers and their clinical significance.

Table 2 Duration of wound in overall population and by scheduled treatment strategy

Duration of wound	≤1 month	1–2 months	2–3 months	3–6 months	>6 months
Overall (n=428)	41.8% [36.9%–46.8%]	22.1% [17.9%–26.2%]	20.2% [16.0%–24.5%]	11.7% [8.5%–14.8%]	4.2% [2.2%–6.2%]
Surgical (n=142)	38.0% [28.9%–47.1%]	22.7% [15.4%–30.0%]	20.6% [12.9%–28.2%]	13.4% [7.3%–19.6%]	5.3% [1.3%–9.3%]
Endovascular (n=275)	44.3% [38.3%–50.3%]	21.0% [16.0%–26.0%]	19.9% [14.9%–24.8%]	11.1% [7.2%–14.9%]	3.7% [1.5%–6.0%]
Conservative (n=11)	36.4% [7.9%–64.8%]	27.3% [1.0%–53.6%]	18.2% [0.0%–41.0%]	9.1% [0.0%–26.1%]	9.1% [0.0%–26.1%]

Data are the estimated proportions [95% confidence intervals] obtained using the multiple imputation methods. The original data on the duration of the wound were available in 388 of 428 patients (90.1%): 117 of 142 surgical patients (82.4%), 260 of 275 endovascular patients (94.5%), and 11of 11 conservative patients (100.0%). The duration of the wound were not different among scheduled treatment strategies (P=0.31 between surgical and endovascular, P=0.48 between surgical and conservative, and P=0.38 between endovascular and conservative, by the linear mixed model including log-transformed duration of wound as the dependent variable, treatment strategies as the fixed effects, and the inter-institution variability as the random effects).

Table 3 Association between duration of wound and clinical features

Duration of wound	≤1 month	1–2 months	2–3 months	3–6 months	>6 months	P
Male sex	69.8% [65.4%–74.3%]	66.1% [61.2%–71.0%]	64.0% [59.1%–68.8%]	62.8% [55.4%–70.1%]	82.4% [70.5%–94.2%]	0.84
Age ≥80 years	29.4% [24.7%–34.0%]	26.7% [21.4%–32.0%]	26.5% [21.4%–31.7%]	32.0% [25.5%–38.5%]	40.0% [30.2%–49.7%]	0.41
Non-ambulatory status	50.4% [45.4%–55.4%]	51.3% [45.6%–56.9%]	46.0% [41.0%–50.9%]	46.4% [40.2%–52.5%]	46.6% [33.2%–59.9%]	0.97
Receiving welfare	13.1% [9.7%–16.4%]	11.4% [6.8%–16.1%]	8.1% [4.6%–11.5%]	7.2% [1.6%–12.8%]	6.7% [0.0%–14.1%]	0.50
Living alone	16.5% [12.9%–20.1%]	18.2% [14.1%–22.3%]	15.7% [11.0%–20.3%]	14.0% [8.5%–19.6%]	3.3% [0.0%–18.2%]	0.52
Staying in nursing home	9.2% [6.3%–12.0%]	10.6% [7.6%–13.6%]	3.9% [1.7%–6.1%]	6.4% [3.4%–9.4%]	11.2% [7.6%–14.7%]	0.53
Albumin <3g/dl	18.8% [14.9%–22.7%]	15.2% [10.5%–20.0%]	16.8% [12.0%–21.6%]	20.4% [16.3%–24.5%]	3.3% [0.0%–12.2%]	0.89
Diabetes mellitus	73.5% [68.6%–78.4%]	73.1% [65.5%–80.8%]	71.3% [66.6%–76.1%]	78.1% [70.3%–85.9%]	75.5% [67.1%–84.0%]	0.61
HbA1c ≥8%	12.3% [9.0%–15.6%]	11.9% [8.5%–15.2%]	10.4% [7.4%–13.5%]	8.0% [5.4%–10.6%]	5.6% [3.2%–7.9%]	0.12
Duration ≥20 years	44.5% [37.9%–51.1%]	42.6% [29.6%–55.6%]	50.1% [42.5%–57.8%]	41.6% [35.9%–47.3%]	41.1% [20.3%–62.0%]	0.94
Regular dialysis	54.0% [48.5%–59.5%]	57.2% [50.7%–63.7%]	51.1% [44.3%–57.9%]	50.9% [39.8%–61.9%]	54.5% [45.0%–64.0%]	0.84
Major cardiovascular disease	57.6% [52.0%–63.2%]	53.8% [46.8%–60.8%]	36.5% [31.6%–41.4%]	59.2% [52.8%–65.5%]	61.1% [51.4%–70.8%]	0.55
Loss of pressure sensation	39.2% [33.8%–44.6%]	34.7% [28.1%–41.4%]	49.0% [40.8%–57.2%]	41.6% [31.3%–51.9%]	46.6% [27.6%–65.6%]	0.74
History of claudication	56.4% [51.6%–61.2%]	46.0% [38.8%–53.1%]	43.0% [38.0%–47.9%]	41.2% [33.3%–49.1%]	63.3% [56.5%–70.1%]	0.42
History of revascularization	25.6% [21.1%–30.1%]	28.8% [23.5%–34.1%]	24.0% [18.6%–29.4%]	19.2% [11.0%–27.4%]	14.4% [7.1%–21.6%]	0.25
History of amputation	13.5% [10.0%–17.0%]	11.5% [7.6%–15.3%]	11.1% [7.1%–15.1%]	16.0% [11.8%–20.1%]	7.7% [0.0%–16.2%]	0.88

Data are estimated prevalence with 95% confidence intervals, as well as P values for trend, obtained from the generalized linear mixed model with a logit link function.

If such poor knowledge on foot ischemia underlies the delay, raising medical and public awareness of the disease could be a realistic solution to accelerate their referral to a vascular center.

Another paradoxical finding of the current study was that a history of lower limb revascularization was not associated with a shortened duration of wound. Generally, patients with history of lower limb revascularization, i.e., those previously diagnosed with peripheral artery disease, are more likely suspected of having the risk of foot

Table 4 Association of clinical features with wound severity

	WIfI: Wound severity		WIfI: Ischemia severity		WIfI: foot Infection severity	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Male sex	0.88 [0.59–1.32]	0.96 [0.62–1.48]	1.01 [0.60–1.70]	1.00 [0.57–1.74]	0.73 [0.48–1.10]	0.79 [0.51–1.23]
Age ≥80 years	0.85 [0.56–1.29]	0.87 [0.55–1.38]	1.28 [0.73–2.24]	1.38 [0.74–2.58]	0.89 [0.58–1.35]	0.86 [0.54–1.36]
Non-ambulatory status	1.95 [1.32–2.89]*	1.72 [1.11–2.65]*	0.84 [0.51–1.38]	0.98 [0.56–1.71]	1.48 [1.00–2.18]	1.18 [0.76–1.83]
Receiving welfare	1.16 [0.63–2.13]	1.09 [0.55–2.15]	0.63 [0.31–1.31]	0.72 [0.32–1.62]	0.76 [0.40–1.45]	0.68 [0.34–1.38]
Living alone	1.18 [0.70–1.98]	1.14 [0.64–2.03]	0.91 [0.47–1.78]	0.99 [0.46–2.10]	0.87 [0.51–1.49]	0.88 [0.48–1.59]
Staying in nursing home	1.14 [0.56–2.33]	0.74 [0.33–1.66]	0.75 [0.31–1.79]	0.82 [0.31–2.17]	1.23 [0.60–2.54]	1.14 [0.51–2.57]
Albumin <3 g/dl	2.83 [1.69–4.74]*	2.64 [1.54–4.54]*	0.88 [0.45–1.70]	0.94 [0.47–1.90]	1.99 [1.20–3.29]*	1.82 [1.07–3.11]*
Diabetes with HbA1c <8%	1.28 [0.82–1.99]	1.23 [0.66–2.29]	0.71 [0.39–1.27]	1.37 [0.62–3.04]	1.76 [1.11–2.79]*	1.27 [0.68–2.35]
Diabetes with HbA1c ≥8%	2.15 [1.11–4.16]*	2.26 [1.01–5.04]*	1.26 [0.46–3.45]	2.51 [0.76–8.27]	1.77 [0.90–3.50]	1.26 [0.54–2.93]
Duration of diabetes ≥20 years	0.96 [0.60–1.54]	0.68 [0.36–1.29]	0.62 [0.36–1.05]	0.60 [0.29–1.26]	1.66 [1.05–2.62]*	1.34 [0.77–2.33]
Regular dialysis	0.95 [0.65–1.39]	0.91 [0.59–1.40]	0.87 [0.53–1.42]	1.09 [0.62–1.91]	1.06 [0.72–1.57]	1.02 [0.66–1.59]
Major cardiovascular disease	0.94 [0.64–1.38]	0.94 [0.63–1.41]	0.92 [0.56–1.50]	0.95 [0.56–1.62]	0.80 [0.54–1.18]	0.72 [0.47–1.08]
Loss of pressure sensation	1.93 [1.21–3.07]*	1.88 [1.05–3.34]*	0.54 [0.32–0.93]*	0.59 [0.32–1.09]	1.92 [1.22–3.04]*	1.81 [1.09–3.02]*
History of claudication	0.75 [0.50–1.10]	0.91 [0.60–1.38]	1.21 [0.73–1.99]	1.04 [0.61–1.78]	0.74 [0.50–1.11]	0.93 [0.60–1.43]
History of revascularization	0.83 [0.53–1.29]	0.63 [0.37–1.07]	0.89 [0.50–1.56]	1.17 [0.60–2.31]	0.84 [0.53–1.32]	0.59 [0.34–1.03]
History of amputation	1.76 [0.99–3.10]	1.88 [0.96–3.69]	0.48 [0.25–0.95]*	0.46 [0.20–1.03]	1.88 [1.06–3.31]*	2.12 [1.09–4.12]*
Duration of wound (per 2-fold increase)	1.19 [1.00–1.42]*	1.22 [1.02–1.47]*	0.80 [0.64–1.00]	0.80 [0.64–1.01]	1.00 [0.83–1.19]	0.96 [0.79–1.15]

Data are odds ratios (ORs) and their 95% confidence intervals. Adjusted ORs were obtained from the multivariate model in which all variables listed in the table were entered. Asterisks indicate P<0.05.

ischemia. The current study, however, suggested that they were not always referred to a vascular center earlier. Some patients might distinctly remember the burden and cost of the peripheral interventions they previously underwent, and might be reluctant to experience such treatments again. Such unwillingness might obstruct timely consultation. In other patients, information on the history of revascularization might not be properly shared with family doctors or care providers; the information might not be utilized for differential diagnosis in primary care.

The duration of the wound was independently associated with an increased wound severity, evaluated by the WIfI classification Wound grade. As is well documented, ischemic wounds have a progressive nature, often requiring timely revascularization.[1,2] Although the causal relationship between the duration of the wound and the wound severity remained to be proven, a delayed referral to a vascular center, until which ischemic wounds would be deteriorated, could increase the wound severity at referral. Furthermore, the duration of the wound was inversely associated with achieving a wound- and amputation-free status after revascularization. This inverse association was no longer significant after adjustment for the wound severity, indicating that the association would be explained by the wound severity. As is well recognized, CLI presenting severe tissue loss is still associated with poor limb prognosis even after successful revascularization procedures.[9,10] It is also of note that the severity in tissue loss and the prolonged time to heal both increase resource utilization and costs, which is a considerable health care burden.[11,12]

Efforts to promote a prompt referral, shortening the duration of the wound, would potentially minimize wound severity, help achieve wound- and amputation-free status after revascularization, and reduce the health care burden. Future prospective studies are needed to validate the efficacy.

The current study had some limitations. First, the duration of the wound was based on self-report as well as medical records. Recall of the history might be at risk for inaccuracy. Second, information on the primary wound care before the referral was unavailable. The reasons why CLI patients were not referred early to a vascular center also remained unknown. Third, the SPINACH study collected data on renal failure, neuropathy, and major cardiovascular disease, but not on other diabetes-related micro- or macro-angiopathies (e.g., retinopathy and carotid artery disease), which are expected to be commonly seen in this population.[13,14] Data on primary foot care and patient education were also unavailable in the study. Fourth, the current study included only CLI patients referred to the vascular centers; no data were available on patients who developed CLI but were never referred to the vascular centers.

Conclusion

A substantial number of CLI patients referred to vascular centers had a long duration of ischemic wounds, i.e., time from wound occurrence to the referral. The duration of the wound was an independent risk factor for the wound severity, and CLI patients with a longer wound duration were less likely to achieve a wound- and amputation-free status after revascularization. There was still space for promoting a prompt referral of CLI patients to a vascular center in real-world settings in Japan.

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The authors declare that they have no conflict of interest.

Additional Note

Informed consent has been obtained from participants.

Author Contributions

Study conception: MT, OI, YS, AK, NA
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