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PERIPHERAL

Prognostic Impact of Revascularization in Poor-Risk Patients With Critical Limb Ischemia

The PRIORITY Registry (Poor-Risk Patients With and Without Revascularization Therapy for Critical Limb Ischemia)

Osamu Iida, MD,[a] Mitsuyoshi Takahara, MD, PhD,[b] Yoshimitsu Soga, MD,[c] Nobuyoshi Azuma, MD, PhD,[d] Shinsuke Nanto, MD, PhD,[e] Masaaki Uematsu, MD, PhD,[a] on behalf of the PRIORITY Investigators

ABSTRACT

OBJECTIVES The authors sought to investigate the prognostic impact of revascularization for poor-risk CLI patients in real-world settings.

BACKGROUND Critical limb ischemia (CLI) is often accompanied with various comorbidities, and frailty is not rare in the population. Although previous studies suggested favorable outcomes of revascularization for CLI patients, those studies commonly included the healthier, that is, less frail patients.

METHODS This was a multicenter prospective observational study, registering patients who presented with CLI and who required assistance for their daily lives because of their disability in activities of daily living (ADL) and/or impairment of cognitive function. Revascularization was either planned (revascularization group) or not planned (non-revascularization group). The primary endpoint was 1-year survival, and was compared between the revascularization and non-revascularization groups, using the propensity score-matching method.

RESULTS Between January 2014 and April 2015, a total of 662 patients were registered, of those 100 non-revascularization patients were included. A total of 625 patients (94.4%) completed the 1-year follow-up. Death was observed in 223 patients (33.7%). After propensity score matching, the 1-year survival rate was 55.9% in the revascularization group versus 51.0% in the non-revascularization group, with no significant difference ($p = 0.120$). In the subgroups alive at 1 year after revascularization, health-related quality of life was significantly improved compared with baseline, whereas ADL scores were unchanged from baseline and still remained significantly worse than before CLI onset.

CONCLUSIONS The 1-year overall survival rate was not significantly different between the revascularization and non-revascularization groups in poor-risk CLI patients. (Poor-Risk Patients With and Without Revascularization Therapy for Critical Limb Ischemia; [PRIORITY Registry]; UMIN000012871) (J Am Coll Cardiol Intv 2017;10:1147–57) © 2017 by the American College of Cardiology Foundation.

From the [a]Cardiovascular Center, Kansai Rosai Hospital, Amagasaki, Japan; [b]Department of Diabetes Care Medicine, and Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Suita, Japan; [c]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Japan; [d]Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan; and the [e]Department of Cardiology, Nishinomiya Municipal Central Hospital, Nishinomiya, Japan. The PRIORITY study is sponsored by the following companies (in alphabetical order): Boston Scientific Japan K.K., HOKUSHINMEDICAL Co., Ltd., Japan, Orbusneich Foundation, Johnson & Johnson K.K., Medicon Inc., Medtronic Japan Co., Ltd, MSD K.K., Otsuka Pharmaceutical Co.,

ABBREVIATIONS AND ACRONYMS

ADL = activities of daily living

CI = confidence interval

CLI = critical limb ischemia

EQ-5D = EuroQol 5 Dimension

QOL = quality of life

SPP = skin perfusion pressure

Critical limb ischemia (CLI) is the most advanced form of peripheral arterial disease and has an extremely poor prognosis regarding both limb and life. It is reported that about one-half of patients without revascularization will either die or undergo major amputation within 1 year. Clinical guidelines, therefore, have recommended revascularization as the ultimate and optimal treatment for CLI (1–3). Indeed, a few well-designed prospective studies demonstrated a more favorable prognosis in patients undergoing revascularization (4–6).

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However, in these studies, much fewer patients with severe comorbidities were registered than there are expected to be in the real world (4,5). In clinical practice, CLI is commonly accompanied with various comorbidities, and frailty is not rare in the population. It remained unclear whether revascularization would bring similar prognostic advantages in these poor-risk CLI patients. Retrospective studies reported that frailty-related factors (e.g., ambulatory status) were strongly associated with poor prognosis in CLI patients undergoing revascularization, casting clinical doubt on the prognostic advantages of revascularization in a poor-risk population (6–8).

We therefore investigated the prognostic impact of revascularization for poor-risk CLI patients in real-world settings.

METHODS

This PRIORITY (Poor-Risk Patients With and Without Revascularization Therapy for Critical Limb Ischemia) registry was a prospective, multicenter observational study, registering adult patients (20 years or older) who presented with CLI due to chronic severe ischemia, and who required assistance in their daily lives because of their disability in activities of daily living (ADL) and/or impairment of cognitive function, between January 2014 and April 2015. The study subjects were enrolled in 37 participating centers all over Japan (Online Appendix). Management of CLI was left to the discretion of participating vascular surgeons and interventional cardiologists in each center, and revascularization was either planned (revascularization group) or not planned (non-revascularization group) at registration. The study was in accordance with the Declaration of Helsinki, and was approved by the ethics committee of each participating center. Written informed consent was obtained from every participant or, if impossible, from his/her family. This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR), which was approved by the International Committee of Medical Journal Editors (no. 000012871, Poor-Risk patients wIth and withOut RevascularIzation TherapY for critical limb ischemia [PRIORITY] Registry).

DEFINITIONS. CLI was diagnosed when patients met at least 1 of the following criteria: 1) Patients had chronic ischemic foot rest pain with ankle pressure <50 mm Hg, toe blood pressure <30 mm Hg, or skin perfusion pressure (SPP) ≤30 mm Hg; 2) patients had ischemic foot ulcer or gangrene with ankle pressure <70 mm Hg, toe blood pressure <50 mm Hg, or SPP ≤40 mm Hg; or 3) other modality indicated apparent critical ischemia complicated with ischemic foot rest pain, ulcer, or gangrene (2).

ADL was assessed by the ambulatory status (ambulatory, in wheelchair, or bed-ridden), the modified Katz index of independence (9), and the Life-Space Assessment (10). The modified Katz index ranges from 0, indicating total dependence, to 6, indicating full independence, whereas the Life-Space Assessment score ranges from 0 ("totally bed-bound") to 120 ("traveled out of town every day without assistance"). Cognitive function was graded according to the Global Deterioration Scale (11), from stage 1 (no dementia) to stage 7 (late-stage dementia). Frailty was evaluated by 5-m gait velocity and grip strength. Health-related quality of life (QOL) was quantified using a validated Japanese version of EuroQol 5 Dimension (EQ-5D) in the original 3-level format, as well as the EQ Visual Analogue Scale (12,13). The EQ-5D health status was converted into a single index value with the score of 1 denoting "full health" and 0, "death," whereas EuroQol Visual Analogue Scale recorded a general health score ranging from 0, indicating "worst imaginable health

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state," to 100, indicating "best possible health state." ADL and QOL were assessed at registration (before revascularization), at 3 months after revascularization, and at 12 months after revascularization in the revascularization group, whereas they were assessed only at registration in the non-revascularization group. At registration, we also collected data regarding ADL before the onset of CLI, which were based on the medical records and the recollections of the patients and their family members.

ENDPOINTS. The primary endpoint was 1-year survival, that is, freedom from all-cause mortality. The secondary endpoints included amputation-free survival, defined as freedom from all-cause mortality and major amputation. We also assessed the cause of death. In the revascularization group, the technical success rate, the pre- and post-operative prevalence of rest pain, the incidence rate of perioperative complications, the incidence rate of lower extremity intervention (revascularization and major amputation) after registration, and the change of QOL and ADL were additionally evaluated.

STATISTICAL ANALYSIS. Data are presented as the mean $\pm$ SD for continuous variables and the number (percentage) for discrete variables, if not otherwise mentioned. A p value of <0.05 was considered as statistically significant. The intergroup difference in baseline characteristics was tested by the unpaired Student *t* test for continuous variables and the chi-square test for discrete variables.

When 1-year prognosis was compared between revascularization and non-revascularization, propensity score matching was performed to minimize the intergroup difference in baseline characteristics. The propensity score was developed using the logistic regression model in which the following variables were included: sex, age, body mass index, welfare, residence status, cognitive impairment, ADL (both at registration and before CLI onset), frailty, QOL, diabetes mellitus, regular dialysis, stroke, coronary artery disease, heart failure, medication, hemoglobin level, serum albumin level, left-ventricular ejection fraction, history of lower extremity revascularization, tissue loss, infection, bilaterality of CLI, and history of contralateral major amputation. Matching was based on the logit of the propensity score, within the caliper of 0.2 SD of the value. To maximize the statistical power to detect the intergroup prognostic difference, we extracted as many matched samples with the revascularization group to 1 sample without non-revascularization as possible. The sample size of 70 non-revascularization subjects versus 6 times as many paired revascularization subjects was calculated to have more than 80% of power to detect the difference of 10% in 1-year survival rate, on the hypothesis that 15% had their mortal lives saved by revascularization, whereas 5% had their lives claimed by revascularization, or vice versa.

The analysis after matching was performed on the stratification by the pairs, and weighted descriptive statistics were reported. The intergroup difference in baseline characteristics after matching was checked by the standardized difference. The 1-year incidence rate of survival and amputation-free survival was estimated by the weighted Kaplan-Meier method, and its intergroup difference was tested by the stratified log-rank test. As the sensitivity analysis, stratification on the propensity score and covariate adjustment using the propensity score were also performed. The 95% confidence intervals (CIs) of weighted mean, prevalence, and incidence rate in the matched population were obtained from 10,000-time bootstrap resampling.

Statistical analyses were performed by R version 3.1.0 (R Development Core Team, Vienna, Austria).

RESULTS

A total of 662 CLI patients were registered, and 625 patients (94.4%) completed the 1-year follow-up. Death was observed in 223 patients (33.7%).

Of the 662 registered participants, 562 had revascularization intended at registration (revascularization group), whereas the remaining 100 did not (non-revascularization group). In the revascularization group (n = 562), 30 patients (5.3%) underwent surgical reconstruction and 521 patients (92.7%) underwent endovascular therapy alone, whereas scheduled revascularization were not performed in the remaining 11 patients (2.0%), because of their deteriorated general conditions after registration.

As shown in Table 1, the non-revascularization group had a considerable difference in baseline characteristics from the revascularization group. In brief, the non-revascularization group were older and frailer, with more impaired cognitive function and ADL, and less frequently used cardio- and vasculo-protective medications, compared with the revascularization group. Stroke and foot infection were more prevalent in the non-revascularization group, whereas diabetes mellitus, regular dialysis, coronary heart disease, and a prior history of lower extremity revascularization were more common in the revascularization group. Ischemia was proved by ankle pressure (<50 mm Hg in rest pain or <70 mm Hg

TABLE 1 Baseline Characteristics in the Unmatched Population

	Revascularization Group (n = 562)	Non-Revascularization Group (n = 100)	Standardized Difference (%)	p Value
Male	59.3	41.0	37.1	<0.001
Age (yrs)	77 ± 10	82 ± 9	55.5	<0.001
Men	75 ± 10	78 ± 10	28.0	0.094
Women	79 ± 9	85 ± 8	68.2	<0.001
Body mass index (kg/m^2)	21.1 ± 3.7	20.2 ± 4.7	21.0	0.080
Data missing	1.4	5.0	20.4	0.047
Receiving welfare	8.4	9.0	2.3	0.987
Residence status				<0.001
Living with housemates	66.2	46.0	41.6	
Living alone	12.8	9.0	12.3	
Staying in nursing home	21.0	45.0	52.8	
Cognitive impairment (assessed by GDS)	3.3 ± 2.0	5.0 ± 2.0	88.3	<0.001
Dementia (GDS ≥4)	38.1	73.0	75.1	<0.001
ADL at registration (after CLI onset)				<0.001
Ambulatory status				<0.001
Ambulatory	35.2	16.0	45.2	
In wheelchair	46.3	43.0	6.6	
Bed-ridden	18.5	41.0	50.8	
Independence in ADL (Katz index)	2.8 ± 2.4	1.4 ± 2.0	64.7	<0.001
Width of life space (assessed by LSA)	19 ± 22	10 ± 17	43.4	<0.001
ADL before CLI onset				<0.001
Ambulatory status				<0.001
Ambulatory	60.9	36.0	51.3	
In wheelchair	27.8	37.0	19.8	
Bed-ridden	11.2	27.0	41.0	
Data missing	0.2	0.0	6.0	
Independence in ADL (Katz index)	3.9 ± 2.5	2.2 ± 2.5	66.9	<0.001
Data missing	0.4	0.0	8.5	1.000
Width of life space (assessed by LSA)	37 ± 33	18 ± 23	66.9	<0.001
Data missing	0.5	1.0	5.3	1.000
Grip strength				0.001
>15 kg in men, >10 kg in women	36.1	19.0	39.0	
≤15 kg in men, ≤10 kg in women	31.7	47.0	21.8	
Not measured	32.2	34.0	3.8	
5-m gait speed				<0.001
≤10 s	15.5	5.0	35.1	
>10 s	13.9	9.0	15.4	
Not assessed	70.6	86.0	37.9	
EQ-5D utility score	0.400 ± 0.256	0.259 ± 0.319	48.8	<0.001
Data missing	6.0	22.0	47.2	<0.001
EQ VAS	43 ± 22	39 ± 24	17.2	0.178
Data missing	9.4	24.0	39.8	<0.001
Diabetes mellitus	63.7	53.0	21.8	0.055
Regular dialysis	44.7	26.0	39.8	<0.001
Stroke	33.8	45.0	23.1	0.041
Coronary artery disease	51.4	33.0	38.0	<0.001
Heart failure	27.8	31.0	7.1	0.587
Medication at registration				<0.001
Renin-angiotensin system inhibitor	40.0	29.0	23.4	0.048
Beta-blocker	28.1	17.0	26.8	0.028
Statin	24.7	16.0	21.8	0.076
Antiplatelet agent	76.2	52.0	52.0	<0.001
Anticoagulant agent	23.0	14.0	23.2	0.061

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TABLE 1 Continued

	Revascularization Group (n = 562)	Non-Revascularization Group (n = 100)	Standardized Difference (%)	p Value
Hemoglobin (g/dl)	11.1 ± 1.9	11.0 ± 2.1	4.4	0.697
Data missing	0.0	2.0	20.2	0.018
Serum albumin (g/dl)	3.33 ± 0.63	3.08 ± 0.71	36.7	<0.001
Data missing	1.8	3.0	8.0	0.675
Left ventricular ejection fraction	61 ± 12	60 ± 15	7.4	0.570
Data missing	10.3	19.0	24.7	0.020
History of revascularization	30.8	17.0	32.8	0.007
Tissue loss	84.0	79.0	12.9	0.278
Infection (%)	29.7	44.0	29.9	0.007
AP-, ABI-, or SPP-proved ischemia*	80.1	72.0	22.5	0.069
Bilateral CLI	30.2	32.0	3.8	0.816
Contralateral major amputation	5.7	6.0	1.3	1.000

Values are % or mean ± SD. *Rest pain (Rutherford category 4) with ankle pressure <50 mm Hg, ankle-brachial pressure index ≤0.39, or skin perfusion pressure ≤30 mm Hg, and tissue loss (Rutherford category 5 or 6) with ankle pressure <70 mm Hg, ankle-brachial pressure index ≤0.59, or skin perfusion pressure ≤40 mm Hg.

ABI = ankle-brachial pressure index; ADL = activities of daily living; AP = ankle pressure; CLI = critical limb ischemia; EQ-5D = EuroQol 5 Dimension; EQ VAS = EuroQol Visual Analogue Scale; GDS = Global Deterioration Scale; LSA = Life-Space Assessment; SPP = skin perfusion pressure.

in tissue loss), ankle-brachial pressure index (≤0.39 in rest pain or ≤0.59 in tissue loss), or SPP (≤30 mm Hg in rest pain or ≤40 mm Hg in tissue loss) in 80.1% of the revascularization group and 72.0% of the non-revascularization group (p = 0.069).

To minimize these baseline differences between the 2 groups, the propensity score matching was performed. The C statistic of the developed propensity score was 0.88 (95% CI: 0.84 to 0.91), indicating a substantial discriminatory ability. The matching procedure extracted 79 pairs, with as many patients in the non-revascularization group and 460 patients in the revascularization group. There was no remarkable difference in baseline characteristics between the matched groups (**Table 2**). The mean age was around 80 years, two-thirds had dementia, and two-thirds were nonambulatory before CLI onset. In the matched revascularization group, 1.7% underwent surgical reconstruction and 94.4% underwent endovascular therapy alone, whereas 3.9% eventually did not undergo revascularization.

SURVIVAL AND LIMB SALVAGE IN THE MATCHED POPULATION. **Figure 1A** demonstrates the 1-year life prognosis of the 2 groups. At 3 months, the survival rate was 83.1% (95% CI: 78.5% to 88.0%) in the revascularization group and 76.5% (95% CI: 69.3% to 84.0%) in the non-vascularization group, and there was a significant intergroup difference (p = 0.007 by the stratified log-rank test). However, at 1 year, the rate was 55.9% (95% CI: 51.8% to 63.9%) versus 51.0% (95% CI: 42.3% to 59.9%), with no significant difference (p = 0.120 by the stratified log-rank test). This nonsignificance was also confirmed by the sensitivity analysis with the stratification on the propensity score (p = 0.117), and covariate adjustment using the propensity score (p = 0.106). The leading causes of death were cardiac and vascular diseases, pneumonia, and sepsis in both groups (**Figure 1B**).

One-year life and limb prognosis in the matched population are shown in **Figure 2**. One-year amputation-free survival rate was estimated to be 44.3% (95% CI: 40.1% to 51.9%) in the revascularization group and 36.8% (95% CI: 28.2% to 45.1%) in the non-revascularization group, and there was a significant intergroup difference (p = 0.020 by the stratified log rank test).

To confirm the current findings, we also performed the analysis after limiting the study population to the patients whose ischemia was proved by ankle pressure (<50 mm Hg in rest pain or <70 mm Hg in tissue loss), ankle-brachial pressure index (≤0.39 in rest pain or ≤0.59 in tissue loss), or SPP (≤30 mm Hg in rest pain or ≤40 mm Hg in tissue loss). From this limited population (n = 522; n = 72 in the non-revascularization patients and n = 450 in the revascularization group), the matching procedure extracted 57 pairs, with as many patients in the non-revascularization group and 322 patients in the revascularization group. As shown in Online Figure 1, the 1-year survival rate was again not significantly different between revascularization and non-revascularization (p = 0.173), whereas the 1-year amputation-free survival rate was significantly higher in the revascularization group than in the non-revascularization group (p = 0.017).

CLINICAL OUTCOME IN THE MATCHED REVASCULARIZATION GROUP. We subsequently evaluated clinical outcomes regarding perioperative efficacy and safety, frequency of intervention, and change of ADL and QOL

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TABLE 2 Baseline Characteristics in the Matched Population

	Revascularization Group (n = 460)	Non-Revascularization Group (n = 79)	Standardized Difference (%)
Male	49.4	50.6	2.5
Age (yrs)	81 ± 10	80 ± 9	4.6
Males	77 ± 10	77 ± 9	2.3
Women	84 ± 8	83 ± 8	6.0
Body mass index (kg/m²)	20.2 ± 3.5	20.2 ± 4.8	0.6
Data missing	3.3	3.8	2.9
Receiving welfare	7.7	10.1	8.5
Residence status			
Living with housemates	48.0	43.0	9.9
Living alone	9.6	10.1	1.6
Staying in nursing home	42.4	46.8	9.0
Cognitive impairment (assessed by GDS)	4.7 ± 2.0	4.9 ± 2.1	8.0
Dementia (GDS ≥4)	68.3	68.4	0.1
ADL at registration (after CLI onset)			
Ambulatory status			
Ambulatory	18.2	16.5	4.6
In wheelchair	41.3	44.3	6.1
Bed-ridden	40.5	39.2	2.7
Independence in ADL (Katz index)	1.6 ± 2.1	1.5 ± 2.1	2.9
Width of life space (assessed by LSA)	12 ± 19	11 ± 18	6.2
ADL before CLI onset			
Ambulatory status			
Ambulatory	36.2	36.7	1.0
In wheelchair	37.0	36.7	0.7
Bed-ridden	26.7	26.6	0.3
Data missing	0.0	0.0	N/A
Independence in ADL (Katz index)	2.4 ± 2.5	2.4 ± 2.5	0.4
Data missing	0.0	0.0	N/A
Width of life space (assessed by LSA)	21 ± 27	19 ± 25	4.9
Data missing	0.0	0.0	N/A
Grip strength			
>15 kg in men, >10 kg in women	19.1	20.3	3.0
≤15 kg in men, ≤10 kg in women	45.3	44.3	1.9
Not measured	35.7	35.4	0.5
5-m gait speed			
≤10 s	5.4	5.1	1.4
>10 s	9.5	7.6	6.9
Not measured	85.1	87.3	6.5
EQ-5D utility score	0.264 ± 0.275	0.268 ± 0.325	1.2
Data missing	18.1	20.3	5.4
EQ VAS	38 ± 23	39 ± 24	2.5
Data missing	21.0	22.8	4.4
Diabetes mellitus	54.6	54.4	0.4
Regular dialysis	29.0	29.1	0.2
Stroke	41.6	43.0	2.9
Coronary artery disease	37.9	34.2	7.8
Heart failure	30.3	32.9	5.6
Medication at registration			
Renin-angiotensin system inhibitor	33.1	34.2	2.3
Beta-blocker	20.1	20.3	0.4
Statin	13.9	11.4	7.6
Antiplatelet agent	59.1	54.4	9.5
Anticoagulant agent	16.2	16.5	0.8

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in the matched revascularization group. After revascularization, 31.0% had residual pain and 25.0% experienced perioperative complications, whereas 93.2% obtained initial technical success (Table 3). During the follow-up after registration, lower-limb intervention was performed as frequently as 2.4 (95% CI: 2.1 to 2.7) times per person-year in the group. In the subgroup alive for 1 year, ADL measures at 1 year were not significantly different from those at registration, and remained significantly poorer than those before CLI onset, although their QOL measures at 1 year were significantly better than those at registration (Table 4).

RISK STRATIFICATION ANALYSIS FOR PRIMARY OUTCOME. To explore for a subgroup in favor of revascularization, we additionally performed a risk stratification analysis. The screening analysis using the crude stratified Cox model suggested that the subgroup without the following risk factors were in favor of revascularization: old age, heart failure, and wound-free CLI (i.e., only rest pain) (Figure 3). We therefore classified the study population according to the accumulation of these risk factors. Consequently, as shown in Figure 4, revascularization was significantly negatively associated with mortality in the subgroup without any of the risk factors, whereas it was not in the subgroup with 1 or more of the risk factors. The impact of revascularization on mortality was significantly different according to the number of the risk factors (p for interaction = 0.004).

VALIDATION ANALYSIS WITH CONSIDERATION OF INTERINSTITUTION VARIABILITY. To validate the current findings, we additionally tried the propensity score-matching analysis with consideration of interinstitution variability. The propensity score was developed using the generalized linear mixed model with a logit link function in which interinstitution variability was treated as random effects. Consequently, the matching extracted 82 pairs, with as many patients in the non-revascularization group and 428 patients in the revascularization group. Although most baseline characteristics were similar between the matched groups, the following variables had the standardized difference of >10%: cognitive impairment assessed by the Global Deterioration Scale (4.6 ± 2.1 in the revascularization group vs. 4.9 ± 2.0 in the non-revascularization group), dementia (64.5% vs. 69.5%), heart failure (36.0% vs. 30.5%), use of beta-blockers (22.7% vs. 18.3%), use of antiplatelet agents (60.5% vs. 54.9%), history of revascularization (23.6% vs. 18.3%), tissue loss (77.1% vs. 81.7%), and contralateral major amputation (4.3% vs. 7.3%). As Online Figure 2 shows, the 1-year survival rate was not significantly different between the groups, whereas the 1-year amputation-free survival rate was significantly higher in the revascularization group. The subsequent risk stratification analysis demonstrated that the hazard ratio of revascularization for mortality was 0.5 (95% CI: 0.3 to 0.8) in the subgroup without any of the 3 risk factors (i.e., old age, heart failure, and wound-free CLI), whereas it was 0.8 (95% CI: 0.5 to 1.2) in those with 1, and 1.8 (95% CI: 0.7 to 4.4) in those with more than 1 of the risk factors.

TABLE 2 Continued

	Revascularization Group (n = 460)	Non-Revascularization Group (n = 79)	Standardized Difference (%)
Hemoglobin (g/dl)	11.0 ± 2.0	11.0 ± 2.1	1.0
Data missing	0.0	0.0	N/A
Serum albumin (g/dl)	3.12 ± 0.67	3.07 ± 0.71	7.8
Data missing	2.0	1.3	5.6
Left ventricular ejection fraction	60 ± 13	59 ± 16	7.6
Data missing	14.0	13.9	0.3
History of revascularization	21.6	20.3	3.4
Tissue loss	82.1	82.3	0.5
Infection	42.7	45.6	5.9
AP-, ABI-, or SPP-proved ischemia*	75.2	70.9	9.8
Bilateral CLI	32.2	32.9	1.5
Contralateral major amputation	5.6	7.6	7.9

Values are weighted mean ± SD or %. *Rest pain (Rutherford category 4) with ankle pressure <50 mm Hg, ankle-brachial pressure index ≤0.39, or skin perfusion pressure ≤30 mm Hg, and tissue loss (Rutherford category 5 or 6) with ankle pressure <70 mm Hg, ankle-brachial pressure index ≤0.59, or skin perfusion pressure ≤40 mm Hg.
N/A = not assessed because prevalence in both groups equaled to zero; other abbreviations as in Table 1.

DISCUSSION

This study investigated the prognostic impact of revascularization for poor-risk CLI patients in real-world settings. Patients in the non-revascularization group were older and frailer, with more impaired cognitive function and ADL, and used fewer cardiovascular protective drugs. Propensity score-matching analysis revealed that there was no significant differences in 1-year survival between the revascularization and non-revascularization groups. The 1-year amputation-free survival rate was higher in the revascularization group. In the subgroups alive at 1 year after revascularization, QOL scores were significantly improved compared with baseline, whereas ADL scores were unchanged from baseline and still remained worse than before CLI onset. In the risk stratification analysis, revascularization was associated with a significantly lower mortality risk in the subgroup that had ischemic wounds and did not have advanced age or heart failure.

As clinical guidelines have recommended, revascularization is positioned as the first-line therapy for CLI (1–3). This is because: 1) the effect of conservative treatments is insufficient, resulting in a high rate of major amputation; 2) the life prognosis in patients with major amputation is often reported to be poorer than controls; and 3) an acceptable limb salvage rate is proved by clinical studies of CLI patients undergoing revascularization. However, CLI patients often have various comorbidities with frailties in the real-world clinical settings. The beneficial effects of revascularization for CLI were suggested only by clinical studies including healthier and less frail CLI patients with longer life expectancy (4–7). It remained unclear whether poor-risk CLI patients would similarly receive prognostic benefits from revascularization. To the best of our knowledge, this is the first study to directly compare the 1-year prognosis of revascularization with that of conservative treatment in a poor-risk CLI population.

It is generally recognized that CLI leads to limb loss, resulting in deterioration of ADL, which ultimately increases the risk of mortality. Based on this recognition, there was an expectation that revascularization leading to limb salvage would limit the deterioration of ADL and lessen the risk of mortality. However, as the current study demonstrated, the mortality risk was not significantly reduced in poor-risk CLI patients undergoing revascularization. At the same time, no significant improvement of ADL was observed in the revascularization group. One possible explanation would be their originally impaired ADL. Their ADL was already so impaired before CLI onset that limb loss might have little influence on an additional decline in ADL, or an additional increase in mortality risk. In other words, limb salvage via revascularization might have few effects on the improvement of ADL or life prognosis in the population. Additionally, revascularization in poor-risk patients itself might increase the risk of its associated death. Despite a recent development and refinement of revascularization procedures for CLI, revascularization is still considerably invasive, especially in high-risk patients. Indeed, the incidence rate of local and systemic perioperative complications after revascularization in this study seemed higher than that reported in previous studies (14). Furthermore, hospitalization for revascularization might also have adverse effects on outcomes. Hospitalization itself is often associated with a substantial and sustained decline in ADL (15) and cognitive function (16), especially in patients with their ADL and cognitive function originally impaired. Adverse effects of revascularization and hospitalization might cancel out potential advantages of revascularization in poor-risk patients. Future studies are needed to

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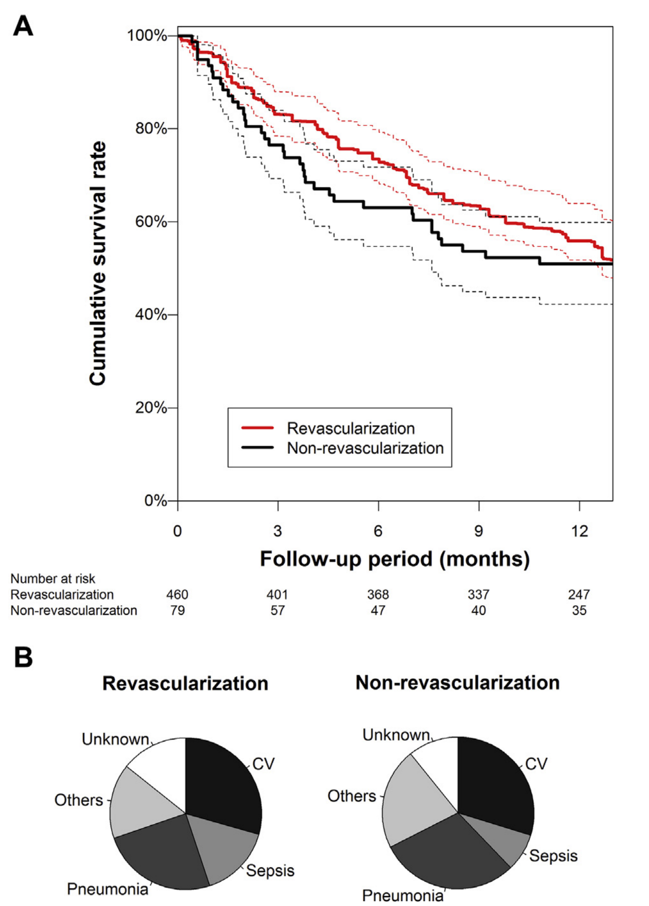
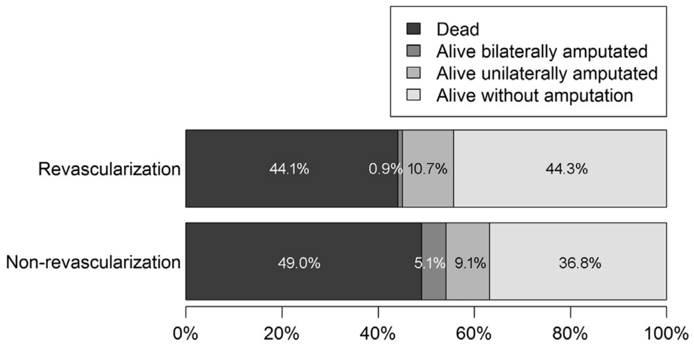
FIGURE 1 Life Prognosis of the Matched Population



(A) Weighted Kaplan-Meier estimation of survival rate during 1-year follow-up. **Dashed lines** = 95% confidence intervals, obtained from the 10,000-time bootstrap resampling. **(B)** Weighted proportion of cause of death. CV = cardiovascular.

FIGURE 2 1-Year Life and Limb Status of the Matched Population



Data are the weighted percentage of life and limb status. Amputation denotes major amputation.

TABLE 3 Perioperative Efficacy and Safety of Revascularization

Procedural success	
Initial technical success	93.2 (89.2-95.9)
Pre- and post-operative pain	
Presence of pain before revascularization	84.0 (80.4-89.4)
Presence of pain after revascularization	31.0 (25.1-36.5)
Perioperative complication (n = 551)	
Total	25.0 (20.0-30.4)
Perioperative death	2.0 (0.5-4.0)
Stent occlusion	1.0 (0.4-2.2)
Distal embolism	0.3 (0.0-1.0)
Local infection	6.2 (3.0-8.8)
Local bleeding	3.5 (1.8-6.2)
Requirement of dialysis	3.6 (1.3-5.7)
Stroke	3.5 (0.8-5.8)
Ischemic heart attack	0.3 (0.0-0.8)
Pneumonia	4.8 (2.5-8.0)
Others	5.6 (2.5-7.9)

Values are weighted prevalence, % (95% confidence interval), in the matched cases of the revascularization group who underwent revascularization.

investigate whether a rehabilitation program for ADL and cognitive function could prevent an unnecessary decline in ADL and cognitive function during hospitalization, and could maximize clinical advantages of revascularization for CLI in the population.

One favorable finding for revascularization in the current study was a significant improvement of QOL scores in patients alive for 1 year after revascularization. Ischemic pain and unhealed wound, as well as limb amputation, are expected to be associated with a decline in QOL. Improvement of blood flow via revascularization was likely to lead to pain relief, wound healing, and freedom from major amputation, which might have resulted in improved QOL in the subgroup.

In the stratified analyses, old age, heart failure, and wound-free (i.e., rest pain-only) CLI were identified as risk factors modifying the prognostic impact of revascularization. The subgroup without any of these risk factors demonstrated significant superiority of revascularization in life prognosis, whereas those with any one of them received no significant beneficial effects of revascularization regarding 1-year survival. In general, the effect of revascularization is expected to have greater significance in younger patients because they are likely to have better longevity. On the other hand, the life prognosis is limited in older patients, and revascularization might make a small impact on their life prognosis. Older patients might have difficulty in overcoming the invasiveness of revascularization because their tolerance for invasive therapy is limited. Similarly, patients with heart failure, generally presenting poor life prognosis, were likely to have a low tolerance for

TABLE 4 ADL and QOL in Patients Alive at 1 Year After Revascularization

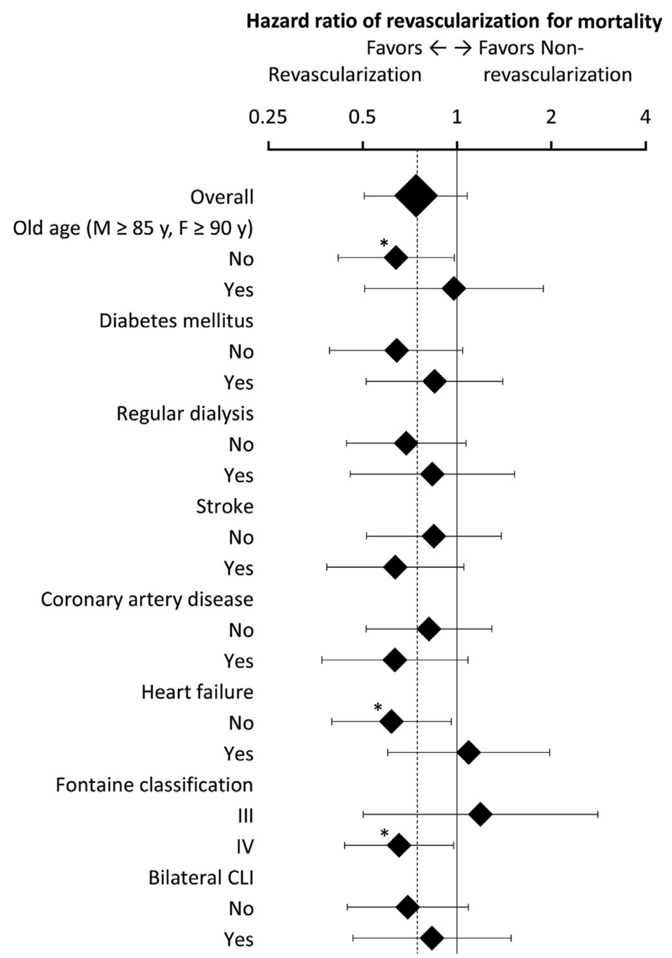
	At 1 Year	At 3 Months	At Registration	Before CLI Onset
Prevalence of ambulatory patients	32.5%	31.7%	27.4%	43.5%
Difference (vs. at 1 yr)	(Ref)	−0.7% (−3.8 to 3.1%)	−5.1% (−11.9 to 0.1%)	11.0% (5.8 to 17.6%)*
Independence in ADL (Katz index)	2.3 ± 2.4	2.3 ± 2.3	2.2 ± 2.3	2.8 ± 2.5
Difference (vs. at 1 yr)	(Ref)	0.0 (−0.1 to 0.2)	−0.1 (−0.4 to 0.1)	0.5 (0.2 to 0.8)*
Life space (assessed by LSA)	18 ± 25	19 ± 26	17 ± 23	27 ± 31
Difference (vs. at 1 yr)	(Ref)	1 (−2 to 2)	−1 (−5 to 2)	9 (6 to 13)*
EQ-5D utility score	0.434 ± 0.309	0.446 ± 0.303	0.316 ± 0.272	N/A
Difference (vs. at 1 yr)	(Ref)	0.012 (−0.017 to 0.052)	−0.118 (−0.164 to −0.076)*	-
EQ VAS	55 ± 25	51 ± 23	41 ± 23	N/A
Difference (vs. at 1 yr)	(Ref)	−4 (−6 to 0)*	−14 (−18 to −9)*	-

Values are %, weighted mean ± SD, %, or difference (95% confidence interval), in the matched cases of the revascularization group who were alive for 1 year after registration. *$p < 0.05$ vs. at 1 year.
Abbreviations as in Tables 1 and 2.

invasiveness, and the advantages of revascularization might be limited in the population. In addition to these 2 systemic risk factors, wound-free (i.e., rest pain-only) CLI was identified as another modifying factor. Although its true mechanisms remained unclear, one possible explanation might be a nutritional impact of unhealed wounds. Nutritional status, substantially influencing life prognosis, is generally deteriorated by chronic inflammatory responses. Patients with unhealed wounds likely suffer from chronic inflammatory responses, and wound healing, that, relief of inflammation, is expected to restore their nutritional status. Accordingly, in wound-complicated CLI patients (Rutherford category 5 or 6), revascularization would bring prognostic advantages partly through this nutritional recovery by wound healing. By contrast, wound-free patients (Rutherford category 4), not suffering from wound-induced nutritional waste, could hardly derive these nutritionally beneficial effects from revascularization. Consequently, in wound-free patients, overall advantages of revascularization would be smaller than in wound-complicated patients, and be less likely to outweigh adverse effects of revascularization. Another possible explanation might be the severity of systemic ischemia. Patients with Rutherford category 4 often have severer limb ischemia than those with Rutherford category 5 or 6, indicating their more severe progression of atherosclerosis. The severity of atherosclerosis and consequent ischemia in systemic organs might be similarly greater in patients with Rutherford category 4 than in those with Rutherford category 5 or 6, which would affect subsequent prognosis.

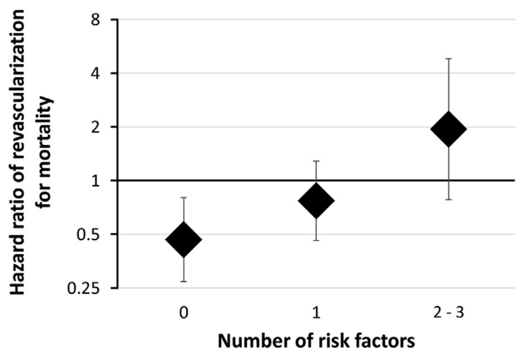
STUDY LIMITATIONS. First, this study was not a randomized controlled trial. However, alternatively,

FIGURE 3 Impact of Revascularization on Mortality in Subgroups



Data are hazard ratios of revascularization for mortality and their 95% confidence intervals, calculated from the Cox proportional hazards model with stratification on the propensity score. *$p < 0.05$. CLI = critical limb ischemia; F = female; M = male.

FIGURE 4 Accumulation of Risk Factors and Impact of Revascularization on Mortality



Data are hazard ratios of revascularization for mortality and their 95% confidence intervals, calculated from the Cox proportional hazards model with stratification on the propensity score. Risk factors were old age (≥85 years in men and ≥90 years in women), heart failure, and wound-free critical limb ischemia (i.e., only rest pain).

we prospectively collected data on factors associated with revascularization, to perform propensity score matching. We believe that these procedures could reduce biases as much as possible. Second, QOL and ADL data were limited. QOL and ADL during the follow-up were not assessed in the conservative treatment group. It remained to be studied whether subsequent QOL and ADL would be different between those with and without revascularization. Also, QOL and ADL assessments were not independently adjudicated or in a blinded fashion to revascularization or no revascularization therapies. Third, the current study did not collect angiographic data or details of revascularization procedures. Fourth, although efforts were made to provide patients with the best possible medical therapy under the national medical insurance system, treatment was at the discretion of physicians during the follow-up period, and the data were not collected in the current study. Additionally, details of adjunctive therapies for ischemic wounds were not collected in this study. Although these were generally managed based on the TIME (tissue [nonviable or deficient], infection/inflammation, moisture [imbalance], and edge [nonadvancing or undermined]) concept (17), the management was at the discretion of physicians. Fifth, this study population was Asian, and the study was conducted under the medical insurance system in Japan. Future studies with other ethnic groups in other countries will be needed to validate the current findings.

CONCLUSIONS

One-year life prognosis was not significantly different between revascularization and non-revascularization groups in poor-risk CLI patients. The risk stratification analysis suggested that revascularization was associated with a significantly lower mortality risk in the subgroup who had ischemic wounds and did not have advanced age or heart failure.

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ADDRESS FOR CORRESPONDENCE: Dr. Osamu Iida, Kansai Rosai Hospital, Cardiovascular Center, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan. E-mail: iida.osa@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Whether revascularization would bring prognostic advantages in poor-risk patients with CLI has not been systematically studied.

WHAT IS NEW? The current prospective multicenter study compared the 1-year overall survival rate between revascularization and non-revascularization groups in CLI patients who required assistance for their daily lives because of their disability in ADL and/or impairment of cognitive function. Consequently, the 1-year overall survival rate was not significantly different between the revascularization and non-revascularization groups in poor-risk CLI patients.

WHAT IS NEXT? Further investigations will be needed to evaluate the difference in quality of life between revascularization and non-revascularization groups, and to validate risk-stratification strategies in the population.

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KEY WORDS critical limb ischemia, mortality, revascularization

APPENDIX For a list of the participating centers and principal investigators as well as supplemental figures, please see the online version of this paper.