The perioperative and long-term fates of patients with chronic limb-threatening ischaemia who underwent secondary major amputations

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Abstract
This study investigated the perioperative and long-term fates of patients with chronic limb-threatening ischemia (CLTI) who underwent secondary major amputations. From April 2010 to December 2018, 1653 CLTI patients primarily underwent endovascular therapy (EVT). Of these patients, 138 who underwent secondary major amputations were included in this study. The primary outcome measure was the mortality. Prognostic factors associated with perioperative (30-day) and late mortality (after 30 days) were assessed. The 30-day mortality was 9.6%. Patients who died during the perioperative period had lower ejection fractions on echocardiography than those in the perioperative survivors (49.5 ± 14.9% vs 58.6 ± 12.4%, \(P = .018\)). None of the other clinical characteristics were significantly associated with perioperative death. Two-years postoperatively, 49.6%, 12.2%, and 4.3% of the patients had died, had contralateral amputations, and had additional above-knee amputations, respectively. In the alive patients who had not undergone additional amputation at 2 years, only 25.9% were ambulatory, whereas 51.7% and 22.4% were in wheelchairs and bedridden, respectively. An age \(\geq 80\) years and serum albumin <3.0 g/dL were significantly associated with late mortality (\(P = .032\) and \(P = .042\), respectively). In conclusion, the perioperative and long-term fates after secondary major amputation in CLTI patients who underwent EVT were considerably poor.

KEYWORDS
chronic limb-threatening ischaemia, endovascular therapy, mortality, secondary major amputation

Abbreviations: ABI, ankle brachial index; BTA, below the ankle; BTK, below the knee; CI, confidence interval; CLTI, chronic limb threatening ischaemia; DSA, digital subtraction angiography; EF, ejection fraction; ESC, European Society of Cardiology; ESVS, European Society of Vascular Surgery; EVT, endovascular therapy; GLASS, global limb anatomic staging system; HR, hazard ratio; MA, major amputation; SPP, skin perfusion pressure; TASC, Trans-Atlantic Inter-Society Consensus; WIfI, Wound, Ischaemia, and foot Infection.

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1 | INTRODUCTION

Chronic limb-threatening ischaemia (CLTI) is the most severe manifestation of peripheral artery disease (PAD) that is characterised by the presence of ischaemic rest pain, ulcers, or gangrene objectively attributable to arterial occlusive disease.\(^1\) The natural history of CLTI that does not undergo appropriate intervention is dire, with a high risk of major amputation.\(^2,3\) Major amputation is generally indicated when there is overwhelming infection present that threatens the patient’s life, when there is intractable rest pain that cannot be controlled, or when extensive necrosis has destroyed the foot.\(^4\) There is a high mortality risk for CLTI patients undergoing primary major amputations that is generally attributed to the relative older age and high prevalence of cardiovascular comorbidities.\(^5\)

CLTI is an absolute indication for revascularization,\(^1,4\) and in the recent decade, thanks to its minimally invasive nature, endovascular therapy (EVT) has been widely applied as a first-line revascularization strategy, contributing to an improvement in limb salvage rate.\(^6\) However, there is still a substantial proportion of CLTI patients who undergo secondary major amputations after EVT, and little is known about the prognosis and risk factors for secondary amputees.\(^7,8\)

Our study investigated (a) the perioperative and long-term fates of CLTI patients who underwent secondary major amputations after EVT and (b) the prognostic factors associated with perioperative and late mortality.

Key Messages

- our study investigated (a) the perioperative and long-term fates of patients with chronic limb-threatening ischaemia (CLTI) who underwent secondary major amputations after endovascular therapy (EVT) and (b) the prognostic factors associated with perioperative and late mortality
- the perioperative and 2-year fates in CLTI patients following a secondary major amputation after EVT were noticeably poor
- the ejection fraction, evaluated using echocardiography, was significantly lower in the patients who died perioperatively, whereas older age and lower albumin levels were significantly associated with late mortality after secondary amputation

2 | MATERIALS AND METHODS

2.1 | Participants

We used a retrospective database of 1653 consecutive CLTI patients who primarily underwent EVT between April 2010 and December 2018 at the Kansai Rosai Hospital Cardiovascular Center, Amagasaki, Japan. Of these patients, 138 who underwent secondary major amputations were included in this analysis. This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Kansai Rosai Hospital. In accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, this observational study was considered exempt from acquiring written informed consent of the patients. Instead, the relevant information regarding the study was open to the public and all patients were afforded opportunities to refuse participation.

2.2 | EVT procedure

The ischaemia severity in the lower limb was assessed using the ankle-brachial index (ABI) and skin perfusion pressure (SPP). The locations of haemodynamically significant arterial lesions were generally evaluated using duplex ultrasound, and the details of the lesion morphology were additionally assessed by digital subtraction angiography (DSA) before any necessary revascularization was performed. EVT was indicated when a lesion showed ≥75% stenosis of the vessel diameter on diagnostic angiography and was haemodynamically significant. EVT was performed according to a generally accepted protocol. Aortoiliac lesions were treated using a primary stenting strategy. Regarding the femoropopliteal lesions, stents were implanted in cases of angioplasty failure that were complicated by severe dissection, residual stenosis, or significant pressure gradients (≥10 mm Hg). Below-the-knee (BTK) lesions were treated with plain angioplasty. Drug-coated balloon and atherectomy devices were not used as they were not approved in Japan during the study period.

2.3 | Major amputation procedure

Amputation techniques for BTK amputations are named according to the origin of the flap used to cover the tibia. The tibia should ideally be divided 10 to 12 cm distal to the tibial tuberosity.

However, a functional stump may still be possible with as little as 5 cm of residual tibia. The anterior incision extends from the medial to the lateral side, encompassing one half to
two-thirds of the leg circumference. The posterior flap length is approximately one-third of the leg circumference.9

2.4 | Follow-up protocol

The follow-up interval and modality were at the discretion of the physician, with the typical practice being every 2 to 4 weeks until the wound healed and then every 3 months thereafter, for as long as possible. At the time of follow-up, non-invasive tests including ABI, SPP, and duplex ultrasound were routinely conducted. Reintervention was clinically driven by the presence of recurrent symptoms or delayed wound healing accompanied by recurrent occlusion or stenosis as measured by the ABI, duplex ultrasound, and SPP. If a patient did not come to the hospital, telephone calls were made to check the limb status and the patient’s general health.

2.5 | Outcome measure

The primary outcome measure was all-cause mortality. The prognostic factors associated with the (a) perioperative (30-day) and (b) late mortalities (after 30 days) were assessed. The distributions of the fates of the ipsilateral and contralateral legs at 30 days and 2 years, as well as the mobility at 2 years, were also explored.

2.6 | Definitions

CLTI was defined according to the European Society of Cardiology/European Society for Vascular Surgery guidelines.1 Major amputation was defined as amputation proximal to the ankle. Nonambulatory status was defined as wheelchair dependence or a bedridden status, as assessed upon admission. Coronary artery disease was defined as the presence of symptoms or a history of myocardial infarction or any cardiac revascularization. The ejection fraction (EF) and laboratory examinations were assessed before secondary major amputation was performed. Primary wound healing was defined as complete epithelialisation of the wound at the amputation site within 30 days. Wounds were classified according to the Wound, Ischaemia, and Foot Infection (WIfI) classification.4 Each factor rating was further classified according to the severity (0: none; 1: mild; 2: moderate; and 3: severe) and combined with the WIfI clinical stage (1: very low risk; 2: low risk; 3: moderate risk; and 4: high risk) to estimate the 1-year amputation risk from pre-existing, expert consensus tables. Before revascularization, the global limb anatomic staging system (GLASS) was assessed using high-quality DSA according to the Global Vascular Guidelines.4 The WIfI and GLASS stages were retrospectively evaluated using the wound photographs and medical records at admission. To maximise the consistency of the evaluations, wound assessments were conducted independently by two wound specialists. Disagreements were resolved through discussion and consensus decisions. BTK and below-the-ankle (BTA) runoff were defined as the number of runoff vessels from the anteriotibial, peroneal, and posteriotibial arteries in BTK arteries, and dorsal, lateral, and medial planter arteries in BTA arteries. Technical success of EVT was defined as at least one runoff vessel through a BTA on final angiography.

2.7 | Statistical analysis

Unless otherwise noted, data are presented as the mean ± SD and percentages for continuous and discrete variables, respectively. Patients who died during the perioperative period and those who lived were compared using an unpaired *t* test and the χ² test. The Cox proportional hazards regression model was used to determine the association between the clinical characteristics and late mortality risk. Patients who died in the perioperative phase were excluded from the late mortality analysis. The hazard ratio (HR) and 95% confidence interval (CI) were reported. A *P* value <.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York).

3 | RESULTS

3.1 | Baseline patient characteristics

The baseline characteristics of the study population are shown in Table 1. The mean age was 72 ± 11 years, 88 (63.8%) were male, and 94 (68.1%) were non-ambulatory on admission. Notable comorbidities included diabetes mellitus and haemodialysis (70.2% and 71.7%; 97/138 and 99/138, respectively). Before EVT, the mean ABI and SPP were 0.62 ± 0.19 and 21.9 ± 14.3 mm Hg, respectively. Regarding the WIfI clinical stage for amputation risk, 3.6%, 10.9%, 12.3%, and 63.8% (5/138, 15/138, 17/138, and 88/138, respectively) were stage 1 (very low risk), 2 (low risk), 3 (moderate risk), and 4 (high risk), respectively. Considering the WIfI clinical stage for amputation risk, 3.6%, 10.9%, 12.3%, and 63.8% (5/138, 15/138, 17/138, and 88/138, respectively) were stage 1 (very low risk), 2 (low risk), 3 (moderate risk), and 4 (high risk), respectively.

3.2 | Perioperative (30-day) fate after secondary major amputation

Figure 1 shows the perioperative fates of the CLTI patients who underwent secondary major amputations
after EVT. Perioperative death was observed in 9.6% of the patients. The main causes of death were infectious and cardiovascular disease (36.6% and 30.7%, respectively). Primary healing was observed in 57.1% of the patients, and 3.7% underwent additional ipsilateral amputation (n = 79 and n = 5, respectively). The

### Table 1: Clinical characteristics of overall study population and patients with or without perioperative death

|                                | All (n = 138) | Perioperative death (+) (n = 13) | Perioperative death (−) (n = 125) | P value |
|--------------------------------|--------------|----------------------------------|----------------------------------|---------|
| **Patient characteristics**    |              |                                  |                                  |         |
| Male                           | 88 (63.8)    | 9 (69.2)                         | 79 (63.2)                        | .77     |
| Age (years)                    | 72 ± 11      | 76 ± 8                           | 72 ± 10                          | .18     |
| Body mass index (kg/m²)        | 20.7 ± 3.4   | 20.1 ± 2.6                       | 20.8 ± 3.5                       | .51     |
| Non-ambulatory status          | 94 (68.1)    | 9 (69.2)                         | 85 (68.0)                        | 1.00    |
| Hypertension                   | 83 (60.1)    | 8 (61.5)                         | 75 (60.0)                        | 1.00    |
| Dyslipidemia                   | 31 (22.4)    | 4 (30.8)                         | 27 (21.6)                        | .49     |
| Diabetes mellitus              | 97 (70.2)    | 10 (76.9)                        | 87 (69.6)                        | .76     |
| Haemodialysis                  | 99 (71.7)    | 11 (84.6)                        | 88 (70.4)                        | .35     |
| Coronary artery disease        | 67 (48.5)    | 8 (72.7)                         | 59 (47.2)                        | .13     |
| Cerebrovascular disease        | 31 (22.8)    | 2 (16.7)                         | 29 (23.4)                        | .73     |
| Ejection fraction (%)          | 57.8 ± 12.8  | 49.5 ± 14.9                      | 58.6 ± 12.4                      | .018    |
| Serum albumin (g/dL)           | 2.3 ± 0.5    | 2.4 ± 0.3                        | 2.3 ± 0.5                        | .76     |
| **Limb characteristics**       |              |                                  |                                  |         |
| Ankle-brachial index           | 0.62 ± 0.19  | 0.58 ± 0.19                      | 0.62 ± 0.19                      | .50     |
| Skin perfusion pressure (mm Hg)| 21.9 ± 14.3  | 20.3 ± 6.9                       | 22.0 ± 14.8                      | .76     |
| Rutherford classification      |              |                                  |                                  | 1.00    |
| 4 (Only rest pain)             | 0 (0)        | 0 (0)                            | 0 (0)                            |         |
| 5 (Minor tissue loss)          | 87 (63.0)    | 8 (61.5)                         | 79 (63.2)                        |         |
| 6 (Major tissue loss)          | 51 (37.0)    | 5 (38.5)                         | 46 (36.8)                        |         |
| **Clinical stage in WIfI classification** |      |                                  |                                  | .18     |
| 1 (Very low risk)              | 5 (3.6)      | 1 (7.7)                          | 4 (3.2)                          |         |
| 2 (Low risk)                   | 15 (10.9)    | 0 (0)                            | 15 (12.0)                        |         |
| 3 (Moderate risk)              | 17 (12.3)    | 0 (0)                            | 17 (13.6)                        |         |
| 4 (High risk)                  | 88 (63.8)    | 10 (76.9)                        | 78 (62.3)                        |         |
| **Lesion characteristics**     |              |                                  |                                  |         |
| GLASS                          |              |                                  |                                  | .40     |
| Stage 1                        | 5 (3.6)      | 0 (0)                            | 5 (4.0)                          |         |
| Stage 2                        | 37 (26.8)    | 3 (23.1)                         | 34 (27.2)                        |         |
| Stage 3                        | 69 (50.0)    | 8 (61.5)                         | 61 (48.8)                        |         |
| Not assessed                   | 27 (19.6)    | 2 (15.4)                         | 25 (20.0)                        |         |
| **Arterial lesion distribution** |           |                                  |                                  | .16     |
| Multi-vessel                   | 70 (50.7)    | 9 (69.2)                         | 61 (48.8)                        |         |
| Isolated below-the-knee        | 68 (49.3)    | 4 (30.8)                         | 64 (51.2)                        |         |
| Below-the-knee run-off vessels, n | 1.0 ± 0.8   | 1.1 ± 0.9                        | 1.0 ± 0.8                        | .85     |
| Below-the-ankle run-off vessels, n | 1.3 ± 1.1  | 1.3 ± 1.1                        | 1.3 ± 1.2                        | .89     |
| Technical success in EVT with at least 1 vessel run-off | 108 (78.3) | 9 (69.2) | 99 (79.2) | .48 |

Note: Data are given as n (%) or mean ± SD.
Abbreviations: EVT, endovascular therapy; GLASS, global limb anatomic staging system; WIfI, Wound, Ischaemia, and foot Infection.
remaining 28.6% (n = 41) of the patients did not achieve complete wound healing at the amputated site.

3.3 | Clinical features associated with perioperative mortality

As shown in Table 1, patients who died during the perioperative period had lower EF on echocardiography before undergoing secondary major amputation than the perioperative survivors (49.5 ± 14.9% vs 58.6 ± 12.4%, P = .018). Figure 2 shows the relationship between EF and perioperative mortality, demonstrating (A) sensitivity and specificity corresponding to an arbitrary cutoff value of EF and (B) perioperative mortality in a subgroup with EF lower than an arbitrary cutoff value of EF and those with EF higher than the cutoff value.

3.4 | Two-year fate after secondary major amputation

The 2-year follow-up rate was 83% (115/138). Two years after the secondary major amputation, 49.6% (n = 57) of the patients had died, and 12.2% and 4.3% (n = 14 and
n = 5, respectively) had contralateral and additional above-knee amputations, respectively (Figure 3). The main causes of death at 2 years were infectious and cardiovascular disease (43.8% and 21.0%, respectively). Of the patients who lived without undergoing additional amputations, only 25.9% were ambulatory, whereas 51.7% and 22.4% were in wheelchairs and bedridden, respectively (Table 2).

The univariate Cox regression analysis found that an age ≥80 years and serum albumin level <3.0 g/dL before major amputation were significantly associated with late mortality. The HRs were 1.81 and 4.34, respectively (95% CI 1.05-3.11 and 1.06-17.84, P = .032 and P = .042, respectively; Table 3).

### Table 2 Distribution of ambulatory status in 2-year survival patients

|                        | Ambulatory | Wheelchair | Bed-ridden |
|------------------------|------------|------------|------------|
| All (n = 58)           |            |            |            |
| Alive without any amputation, % (n = 39) | 24.1% (14/58) | 29.3% (17/58) | 13.8% (8/58) |
| Contralateral amputation, % (n = 14) | 0% (0/58) | 17.2% (10/58) | 6.9% (4/58) |
| Additional amputation, % (n = 5) | 1.7% (1/58) | 5.2% (3/58) | 1.7% (1/58) |

### Table 3 Univariate analysis for late mortality

|                                           | Unadjusted model |            |            |            |
|-------------------------------------------|------------------|------------|------------|------------|
| HR [95%CI]                                | P value          |            |            |            |
| Male                                      | 0.76 [0.45-1.27] | .29        |            |            |
| Age ≥80 years                             | 1.81 [1.05-3.11] | .032       |            |            |
| Non-ambulatory status                     | 1.09 [0.65-1.83] | .75        |            |            |
| Diabetes mellitus                         | 0.83 [0.50-1.34] | .48        |            |            |
| Haemodialysis                             | 1.76 [0.97-3.10] | .064       |            |            |
| Coronary artery disease                   | 1.44 [0.88-2.37] | .15        |            |            |
| Body mass index <18.5 kg/m²               | 1.16 [0.65-2.07] | .61        |            |            |
| Rutherford classification                 | 1.06 [0.63-1.79] | .83        |            |            |
| WIfI clinical stage                       | 1.12 [0.82-1.53] | .49        |            |            |
| Albumin <3.0 g/dL before amputation       | 4.34 [1.06-17.84] | .042       |            |            |
| Ejection fraction <50% before amputation  | 1.52 [0.88-2.61] | .13        |            |            |
| GLASS stage                               | 1.03 [0.64-1.66] | .90        |            |            |
| Isolated below-the-knee                   | 0.95 [0.62-1.66] | .95        |            |            |
| Below-the-knee run-off vessels            | 1.15 [0.83-1.59] | .41        |            |            |
| Below-the-ankle run-off vessels           | 0.89 [0.70-1.13] | .33        |            |            |
| Technical success in EVT with at least 1 vessel run-off | 0.78 [0.43-1.41] | .40        |            |            |

Note: Hazard ratios (HR) are presented together with the 95% confidence intervals (CI).
Abbreviations: EVT, endovascular therapy; GLASS, global limb anatomic staging system; WIfI, Wound, Ischaemia, and foot Infection.

### Discussion

Our study investigated the perioperative and 2-year fates of patients who underwent secondary major amputations after EVT. The cardiac condition, evaluated using the EF, was significantly lower in patients who died perioperatively, whereas an older age and lower albumin level were significantly associated with an increased late mortality risk. The perioperative and long-term fates after secondary major amputations in CLTI patients who underwent EVT was considerably poor.

In general, the goals of major amputation for CLTI patients with either failed or successful revascularization are as follows: (a) relief of refractory ischaemic pain; (b) removal of all diseased, necrotic, or grossly infected tissue in the lower extremity; (c) achievement of primary healing; and, if the patient is capable, (d) preservation of independent ambulatory ability.4 A recent systematic review reported that the early perioperative mortality in CLTI patients who underwent major amputations ranged from 4% to 22%.5 The risk factors for perioperative mortality were inconsistent among the studies; however, age, end-stage renal and cerebrovascular disease, systemic inflammation at the time of amputation, and a bedridden status were determined as perioperative risk factors in most, but not all, studies.4,10,11 We propose that the inconsistent results among the studies could be because of the heterogeneity of the patients’ attributes, level of amputation, and treatment pathways. The incidence of perioperative mortality in this study was comparable to that of previous studies,2 although this study focussed on secondary amputation following EVT. The true reason why the aforementioned variables did not correlate with the perioperative mortality in this study population remains unknown; however, it might be because of the study population was limited to those who underwent secondary amputation or because there was a high prevalence of patients who were undergoing haemodialysis therapy. In contrast, we found that a low EF was associated with perioperative mortality. We also found that the WIfI and GLASS stages were not associated with perioperative mortality. To the best of our knowledge, previous studies have not assessed these parameters and this is the first study demonstrating an association between the cardiac condition, the WIfI classification, and GLASS stages.
with regard to the perioperative mortality. The association with a lower EF indicates that patients with poor cardiac function could not tolerate the perioperative invasiveness of major amputation under general anaesthesia. When a secondary major amputation is planned in clinical practice, its indication and the level and condition of the limb undergoing major amputation are generally discussed. Our study suggests discussing the cardiac condition, rather than the limb severity, might also be important when assessing the perioperative death risk.

At 2 years postoperatively, approximately half of the patients had died and only a quarter of the living patients who did not undergo additional amputation remained ambulatory. We found that an older age and hypoalbuminaemia before secondary major amputation influenced the 2-year mortality risk. The presence of cardiovascular disease, other comorbidities, and frailty in older patients increases the late mortality risk. Hypoalbuminaemia is generally caused by malnutrition and inflammation, both of which are correlated with mortality risk in PAD patients. Several studies elucidated that (a) many PAD patients were malnourished, (b) the proportion of malnourished patients was significantly higher in those with tissue loss than in those with claudication and rest pain, and (c) the prevalence of systemic inflammation was higher in PAD patients than those with other vascular diseases. Malnourishment causes immune dysfunction, whereas systemic inflammation accelerates atherosclerosis. In this population, hypoalbuminaemia may reflect this vicious cycle and may be associated with an increased late mortality risk.

4.1 | Clinical implications

Our study, which reflected the latest practices, clarified the importance of a detailed systemic assessment in CLTI patients when planning and performing secondary major amputations. Although the indication for major amputation is generally determined by the ischaemic wound severity, to manage patients’ perioperative and late mortality risks, it is also important to assess the cardiac function, age, and albumin levels.

4.2 | Limitations

This study has several limitations. First, it was a single-centre, retrospective study with a relatively small sample size. Second, it did not include amputees who had undergone surgical bypass therapy. Thus, there may have been selection bias in the data interpretation. Further studies that include these patients are required to confirm these results. Third, not all of the patients who were included in this study were followed up for the full 2 years; thus, the 2-year fate may have either been under- or over-estimated. Fourth, the WIfI clinical stage was evaluated retrospectively using photographs of the ischaemic wounds and medical records, including the laboratory findings at registration. Although efforts were made to obtain consistent and accurate wound evaluations, some amount of error was inevitable. Fifth, because we collected the variables retrospectively, unknown and unevaluated confounders could have affected the study outcomes, especially other comorbidities, medications, and procedural details including devices used. Sixth, data on the reasons why secondary major amputation was performed were not collected. Finally, because of a very small number of patients with EF lower than 20% to 30% (n = 0 for EF < 20% and n = 3 for EF < 30%), the multivariate risk analysis was practically impossible in the current study population. The latest heart failure guideline states that reduced EF is defined as less than 50%, and the number of patients with EF < 50% in the study population was sufficient to conduct this analysis. We therefore tentatively defined impaired EF as cutoff value less than 50% in the current study. Also, impact of CRP and HD on perioperative mortality would be involved in a complex manner. The current sample size might be too small to detect these involvements.

5 | CONCLUSION

The perioperative and long-term fates of CLTI patients who underwent secondary major amputations after EVT were substantially poor. The EF, evaluated using echocardiography, was significantly lower in patients who died during the perioperative period, whereas an older age and lower albumin level were significantly associated with an increased late mortality risk.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Tomoe Ogaki and Yosuke Hata: Researched data. Tomoe Ogaki, Osamu Iida, and Yosuke Hata: Wrote the manuscript. Natsumi Yamauchi, Chika Yokoi, and Mitsuyoshi Takahara: Contributed to the discussion
and reviewed/edited the manuscript. **Toshiaki Mano** and **Yuji Asada**: Reviewed/edited the manuscript.

**DATA AVAILABILITY STATEMENT**
The data that support the findings of this study are available from the corresponding author upon reasonable request.

**ETHICS STATEMENT**
This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Kansai Rosai Hospital. In accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan, this observational study was considered exempt from acquiring written informed consent of the patients.

**REFERENCES**
1. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European stroke organization (ESO); the task force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J*. 2018;39:763-816.
2. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg*. 2000;31:S1-S296.
3. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg*. 2007;33(suppl 1):S1-S75.
4. Conte MS, Bradbury AW, Kolh P, et al. GVG Writing Group for the Joint Guidelines of the Society for Vascular Surgery (SVS), European Society for Vascular Surgery (ESVS), and World Federation of Vascular Societies (WFVS). Global Vascular Guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58:S1-S109.
5. van Netten JJ, Fortington LV, Hinchcliffe RJ, Hijmans JM. Early post-operative mortality after major lower limb amputation: a systematic review of population and regional based studies. *Eur J Vasc Endovasc Surg*. 2016;51:248-257.
6. Agarwal S, Sud K, Shishhebhor MH. Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: from 2003-2011. *J Am Coll Cardiol*. 2016;67:1901-1913.
7. Iida O, Nakamura M, Yamauchi Y, et al. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. *Circ Cardiovasc Interv*. 2013;6:68-76.
8. Iida O, Takahara M, Soga Y, et al. Three-year outcomes of surgical versus endovascular revascularization for critical limb ischemia: the SPINACH study (surgical reconstruction versus peripheral intervention in patients with critical limb ischemia). *Circ Cardiovasc Interv*. 2017;10:e005531.
9. Adams CT, Lakra A. Below knee amputation. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2020 PMID: 30521194.
10. Stern JR, Wong CK, Yerovinkina M, et al. A meta-analysis of long-term mortality and associated risk factors following lower extremity amputation. *Ann Vasc Surg*. 2017;42:322-327.
11. Fortington LV, Geertzen JH, van Netten JJ, Postema K, Rommers GM, Dijkstra PU. Short and long term mortality rates after a lower limb amputation. *Eur J Vasc Endovasc Surg*. 2013;46:124-131.
12. Azuma N, Takahara M, Kodama A, et al. Predictive model for mortality risk including the wound, ischemia, foot infection classification in patients undergoing revascularization for critical limb ischemia. *Circ Cardiovasc Interv*. 2019;12:e008015.
13. Yokoyama M, Watanabe T, Otaki Y, et al. Impact of objective malnutrition status on the clinical outcomes in patients with peripheral artery disease following endovascular therapy. *Circ J*. 2018;82:847-856.
14. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891-975.

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