Current and Past Obesity in Japanese Patients with Critical Limb Ischemia Undergoing Revascularization

Mitsuyoshi Takahara1,2, Osamu Iida3, Yoshimitsu Soga4, Akio Kodama5, Hiroto Terashi6, and Nobuyoshi Azuma7, on behalf of the SPINACH study investigators

1Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
2Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
3Cardiovascular Center, Kansai Rosai Hospital, Hyogo, Japan
4Department of Cardiology, Kokura Memorial Hospital, Fukuoka, Japan
5Division of Vascular Surgery, Department of Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan
6Department of Plastic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
7Department of Vascular Surgery, Asahikawa Medical University, Asahikawa, Japan

Aim: Recent studies suggested that past history of obesity or maximum body mass index (BMI) in the past was a strong prognostic predictor in a general population. The current study aimed to survey the distribution of current and maximum BMIs and to investigate their prognostic impact in patients with critical limb ischemia (CLI), whose prognosis was poor even after revascularization.

Methods: We analyzed a database of a prospective, multicenter registry in Japan, including 499 CLI patients undergoing revascularization. Their current and maximum BMIs were surveyed at registration. The distribution and the impact on the prognosis were explored.

Results: The estimated means (95% confidence intervals) of current and maximum BMIs were respectively 22.0 (21.7 to 22.3) and 25.3 (24.8 to 25.8) kg/m²; the difference was 3.3 (2.9 to 3.7) kg/m². The prevalence of current obesity (BMI ≥ 25 kg/m²) was 18% (15% to 22%), whereas 48% (43% to 53%) had ever been obese (maximum BMI ≥ 25 kg/m²). Past obesity was not rare even in currently lean subjects (BMI < 18.5 kg/m²), with the prevalence of 18% (7% to 29%). Current BMI, but not maximum BMI, was associated with the mortality risk; the adjusted hazard ratios per 5 kg/m² increase were 0.61 [0.46, 0.81] (P=0.001) and 1.07 [0.87, 1.31] (P=0.55), respectively.

Conclusion: The prevalence of current obesity was as low as 18% (15% to 22%) in Japanese CLI patients undergoing revascularization, whereas about a half were formerly obese. Maximum BMI was not independently associated with the mortality risk in the population.

Key words: Critical limb ischemia, Past obesity, Maximum body mass index, Prognosis

Introduction

Obesity is strongly associated with metabolic disorders including diabetes, dyslipidemia, and hypertension and has been well recognized as a risk factor for atherosclerotic cardiovascular diseases. In this context, it would be no surprise that obesity is common in patients with coronary artery disease (CAD); its prevalence was reported to be around a third in Japan. On the other hand, clinical studies on critical limb ischemia (CLI), another cardiovascular disease similarly rooted in atherosclerosis, suggested that the prevalence of obesity was much lower. However, body weight will be changed during a lifetime, and it remained unknown whether the majority of CLI patients had ever been free from obesity. CLI patients have an extremely high prevalence of various comorbidities; it is of clinical interest whether and how
these features would be associated with weight history. Furthermore, recent studies suggest that past obesity or maximum body mass index (BMI) in the past would be a strong prognostic predictor. However, no previous studies uncovered whether this would be true of a CLI population, whose prognosis is extremely poor even after revascularization. The current study aimed to survey the distribution of current and past BMI and to investigate their prognostic impact in CLI patients undergoing revascularization in Japan.

**Methods**

We used a clinical database obtained from the Surgical reconstruction versus Peripheral INtervention in patients with critical limb isChemia (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. 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.

The current analysis included a total of 499 patients in whom major amputation was never performed and revascularization was scheduled for ischemic wound with the Wound, Ischemia, and foot Infection (WIfI) classification system. Ischemia grade 2/3 or ischemic rest pain with the WIfI Ischemia grade 3. Skin perfusion pressures of 31–40 mmHg and ≤30 mmHg were treated as WIfI Ischemia grades 2 and 3, respectively. Surgical reconstruction and endovascular therapy were scheduled in 187 and 312 patients, respectively.

Data on maximum body weight were obtained from medical records and self-report. Current and maximum BMIs were calculated as current and maximum body weight (kg) divided by the square of current height (m), respectively. Data on maximum body weight were available in 380 patients (76%). Current obesity was defined as current BMI ≥ 25 kg/m², whereas past obesity was defined as maximum BMI ≥ 25 kg/m². Non-ambulatory status was determined when patients require personal assistance with transferring. The controlling nutritional status (CONUT) score, a laboratory assessment tool of nutritional status, was calculated from serum albumin level, total cholesterol level, and total lymphocyte count. Data on the history of intermittent claudication (claudication history) were obtained from medical records and self-report.

**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 inter-group difference was examined by the Welch's t test for continuous variables and the chi-square test for discrete variables. The association of BMI with the mortality risk was analyzed using the Cox proportional hazards model, whereas that with the risk of major amputation, major adverse limb events (a composite of major amputation and major re-intervention), and a composite of major amputation and any re-intervention was analyzed using the Fine and Gray’s proportional hazards regression model for subdistribution of competing risks, with adjustment for mortality. We also analyzed a subgroup with tissue loss at baseline, to investigate the association of BMI with the presence of tissue loss during the follow-up period in this subgroup, using the multinomial logistic regression model. In the model, the dependent variable was composed of the following three categories: alive without tissue loss (set as the baseline category), alive with tissue loss, and dead at each specific time point. Cases alive with major amputation were included in those alive with tissue loss. We additionally examined the prognostic impact of the CONUT score, as well as the baseline characteristics associated with past obesity, on these outcomes. Missing data were addressed by the multiple imputations by chained equations method. 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. They were 73 ± 10 years old, and 87% had ischemic tissue loss. The estimated means (95% confidence interval) of current and maximum BMIs were 22.0 (21.7 to 22.3) and 25.3 (24.8 to 25.8) kg/m², with the difference equal to 3.3 (2.9 to 3.7) kg/m². Current BMI was significantly correlated with the CONUT score (Pearson’s correlation coefficient r = -0.16, P<0.001), whereas maximum BMI was not (r = -0.02, P=0.69). The distributions of the variables are illustrated in Fig. 1A. Current BMI was ≥25 kg/m² in 18% (15 to 22%) and ≥30 kg/m²...
The current study demonstrated the distribution of current and past BMIs and their prognostic impact in CLI patients undergoing revascularization in Japan. The prevalence of current obesity in this study was as low as 18% (15% to 22%), which was considerably lower than that reported in previous studies of patients with CAD\(^2\). These findings support the idea that patient backgrounds would not be identical between a CLI population and a CAD population, although both CLI and CAD are rooted in atherosclerosis\(^6\). However, the low prevalence of current obesity did not mean that the majority of the CLI population was ever free from obesity. The current study revealed that almost a half had ever been obese. In addition, past obesity was not rare even in currently lean subjects. The CLI population experienced the BMI decrease by 3.3 (2.9 to 3.7) kg/m\(^2\) on average. Obesity accelerates the acquirement of metabolic disorders and increases the risk of atherosclerotic diseases\(^1\), and it is also well known that chronic inflammation, which could be linked to weight loss\(^17,19\), is involved in the progression of atherosclerosis\(^20\). The commonness of past obesity and subsequent weight loss in this population might reflect these involve-
Fig. 1. Distribution of maximum BMI by current BMI (left panel) and that of current BMI by maximum BMI (right panel) in the whole study population (A), the subgroup with diabetes mellitus (B), those with hypertension (C), those with dyslipidemia (D), and those on regular dialysis (E).

The horizontal width of bars indicates the proportion of respective categories of current (left panel) and maximum BMI (right panel). Error bars represent 95% confidence intervals. The mean current and maximum BMIs in each subgroup were estimated to be 22.3 (22.0 to 22.7) and 25.5 (25.0 to 26.1) kg/m² in those with diabetes mellitus, 22.1 (21.7 to 22.4) and 25.3 (24.8 to 25.8) kg/m² in those with hypertension, 22.2 (21.9 to 22.6) and 25.7 (25.2 to 26.3) kg/m² in those with dyslipidemia, and 22.0 (21.6 to 22.4) and 25.4 (24.8 to 26.0) kg/m² in those with regular dialysis, respectively.
ments during the developmental course of CLI.

The subsequent analysis showed that younger age, ambulatory status, and the history of intermittent claudication were associated with the past history of obesity. In contrast, the CONUT score, a laboratory nutritional assessment, was not associated with past obesity, whereas the score was significantly correlated with current BMI. The developmental course of CLI might be different between older and non-ambulatory CLI patients free from claudication history and younger and ambulatory ones with past history of intermittent claudication. Data on the natural course of CLI development were so far quite limited, and the association of obesity remained unclear. Future cohort studies will be needed to reveal the involvement of weight history in CLI development.

Another finding of clinical interest in the current study was the lack of an independent prognostic impact of maximum BMI. Previous studies reported that past obesity or maximum BMI was a strong prognostic predictor, which was in contrast to the current findings. Furthermore, those studies showed a positive association between maximum BMI and mortality risk, whereas maximum BMI was rather inversely associated with the mortality risk in the crude analysis in the current study. Although the true reasons remained unknown, past obesity and maximum BMI would have a different meaning between a general population and CLI patients. The current finding suggests that maximum BMI would not be a useful marker to predict life and limb prognosis in the population.

The association of current BMI with the mortality risk might be partially explained by the involvement of malnutrition. However, current BMI was associated with the mortality risk independently of the CONUT score, whereas the CONUT score, but not current BMI, had a significant association with limb-related prognosis. BMI might reflect some different aspects of systemic conditions than laboratory nutritional assessments.

The current study had some limitations. First, the maximum BMI, derived from maximum body weight, was based on self-report as well as medical records. So was the history of intermittent claudication. Recall of the history might be at risk of inaccuracy. In addition, since the data on height when body weight reached the maximum were unavailable, height at baseline was substituted to calculate the maximum BMI. Second, the SPINACH study did not collect the information on when body weight reached the maximum. Third, neither were detailed data available on the date of wound healing. Therefore, we were unable to assess the impact of BMI on the wound healing rate. Alternatively, we tentatively performed the multinomial logistic regression model to demonstrate the

| Table 2. Comparison between patients with and without past obesity |
|---------------------------------------------------------------|
| **Maximum BMI ≥ 25 kg/m²** | **Maximum BMI < 25 kg/m²** | **P value** |
| Age (years) | 72 [71 to 73] | 75 [74 to 76] | 0.002 |
| Male sex | 66% [60% to 73%] | 69% [63% to 75%] | 0.57 |
| Non-ambulatory status | 18% [13% to 23%] | 31% [26% to 37%] | 0.001 |
| Receiving welfare | 10% [6% to 14%] | 9% [5% to 12%] | 0.64 |
| Living alone | 14% [9% to 18%] | 18% [13% to 23%] | 0.19 |
| Staying at nursing home | 5% [2% to 8%] | 8% [5% to 12%] | 0.13 |
| Smoking history | 62% [55% to 68%] | 58% [52% to 64%] | 0.40 |
| Current smoking | 15% [10% to 19%] | 16% [11% to 21%] | 0.71 |
| Diabetes mellitus | 77% [72% to 83%] | 71% [65% to 77%] | 0.13 |
| Hypertension | 89% [84% to 93%] | 86% [82% to 91%] | 0.46 |
| Dyslipidemia | 74% [68% to 80%] | 67% [61% to 73%] | 0.11 |
| Regular dialysis | 53% [47% to 60%] | 52% [46% to 58%] | 0.74 |
| Heart failure | 19% [14% to 25%] | 18% [13% to 23%] | 0.70 |
| Coronary artery disease | 40% [33% to 46%] | 45% [38% to 51%] | 0.29 |
| Cerebrovascular disease | 26% [20% to 31%] | 22% [17% to 28%] | 0.42 |
| CONUT score (points) | 4.0 [3.7 to 4.3] | 4.0 [3.7 to 4.3] | 0.97 |
| Surgical reconstruction | 40% [33% to 46%] | 35% [29% to 41%] | 0.36 |
| Tissue loss | 90% [86% to 94%] | 84% [79% to 89%] | 0.098 |
| Claudication history | 60% [53% to 66%] | 48% [42% to 55%] | 0.021 |

Data are estimates and 95% confidence intervals.
Table 3. Association with prognostic outcomes

| Variable                          | Crude hazard ratio (Univariate model) | Adjusted hazard ratio (Multivariate model) |
|----------------------------------|--------------------------------------|-------------------------------------------|
| **Mortality**                    |                                      |                                           |
| Maximum BMI (per 5 kg/m²)        | 0.77 [0.66, 0.90] (P=0.001)          | 1.07 [0.87, 1.31] (P=0.55)                |
| Current BMI (per 5 kg/m²)        | 0.53 [0.43, 0.65] (P<0.001)          | 0.61 [0.46, 0.81] (P=0.001)               |
| Difference (per 5 kg/m²)         | 1.13 [0.92, 1.38] (P=0.23)           | N/I                                       |
| CONUT score (per 2 points)       | 1.37 [1.23, 1.51] (P<0.001)          | 1.26 [1.13, 1.41] (P<0.001)               |
| Age (per 10 years)               | 1.42 [1.23, 1.64] (P<0.001)          | 1.31 [1.12, 1.53] (P=0.001)               |
| Non-ambulatory status            | 2.80 [2.12, 3.71] (P<0.001)          | 1.97 [1.45, 2.66] (P<0.001)               |
| Claudication history             | 1.01 [0.77, 1.32] (P=0.95)           | N/I                                       |
| **Major amputation**             |                                      |                                           |
| Maximum BMI (per 5 kg/m²)        | 1.16 [0.81, 1.65] (P=0.43)           | N/I                                       |
| Current BMI (per 5 kg/m²)        | 0.92 [0.60, 1.40] (P=0.68)           | N/I                                       |
| Difference (per 5 kg/m²)         | 1.39 [0.86, 2.22] (P=0.18)           | N/I                                       |
| CONUT score (per 2 points)       | 1.44 [1.14, 1.83] (P=0.002)          | 1.33 [1.04, 1.70] (P=0.021)               |
| Age (per 10 years)               | 0.70 [0.53, 0.92] (P=0.012)          | 0.63 [0.46, 0.86] (P=0.003)               |
| Non-ambulatory status            | 2.33 [1.27, 4.26] (P=0.006)          | 2.25 [1.13, 4.51] (P=0.022)               |
| Claudication history             | 0.54 [0.29, 1.00] (P=0.049)          | 0.60 [0.32, 1.13] (P=0.12)                |
| **Major adverse limb events**    |                                      |                                           |
| Maximum BMI (per 5 kg/m²)        | 1.19 [0.94, 1.49] (P=0.15)           | N/I                                       |
| Current BMI (per 5 kg/m²)        | 1.12 [0.85, 1.50] (P=0.42)           | N/I                                       |
| Difference (per 5 kg/m²)         | 1.21 [0.87, 1.67] (P=0.26)           | N/I                                       |
| CONUT score (per 2 points)       | 1.23 [1.03, 1.46] (P=0.022)          | 1.23 [1.04, 1.46] (P=0.016)               |
| Age (per 10 years)               | 0.70 [0.57, 0.86] (P=0.001)          | 0.69 [0.56, 0.85] (P=0.001)               |
| Non-ambulatory status            | 1.50 [0.95, 2.36] (P=0.084)          | N/I                                       |
| Claudication history             | 1.26 [0.82, 1.94] (P=0.29)           | N/I                                       |
| **Composite of major amputation and any re-intervention** |                                      |                                           |
| Maximum BMI (per 5 kg/m²)        | 1.00 [0.86, 1.16] (P=0.98)           | N/I                                       |
| Current BMI (per 5 kg/m²)        | 1.03 [0.86, 1.23] (P=0.77)           | N/I                                       |
| Difference (per 5 kg/m²)         | 0.97 [0.79, 1.20] (P=0.81)           | N/I                                       |
| CONUT score (per 2 points)       | 1.08 [0.97, 1.19] (P=0.17)           | N/I                                       |
| Age (per 10 years)               | 0.87 [0.77, 0.99] (P=0.040)          | 0.87 [0.77, 0.99] (P=0.040)               |
| Non-ambulatory status            | 1.20 [0.89, 1.63] (P=0.23)           | N/I                                       |
| Claudication history             | 1.04 [0.80, 1.36] (P=0.77)           | N/I                                       |

Data are hazard ratios [95% confidence intervals] (P values) for mortality, major amputation, major adverse limb events, and a composite of major amputation and any re-intervention. Adjusted hazard ratios were derived from the multivariate model in which variables with significance in the crude hazard ratio (univariate model) were entered. Difference means maximum minus current BMI (i.e., decrease from maximum BMI). N/I, not included.

Table 4. Association with presence of tissue loss during follow-up period in a subgroup with tissue loss at baseline

| Variable                          | At 1 year | At 2 years | At 3 years |
|----------------------------------|-----------|------------|------------|
| **Crude relative risk ratio**    |           |            |            |
| (Univariate model)               |           |            |            |
| Maximum BMI (per 5 kg/m²)        | 0.90 [0.66, 1.24] (P=0.52) | 1.08 [0.74, 1.60] (P=0.68) | 0.86 [0.59, 1.24] (P=0.41) |
| Current BMI (per 5 kg/m²)        | 0.78 [0.55, 1.11] (P=0.16) | 0.82 [0.53, 1.26] (P=0.37) | 0.73 [0.49, 1.10] (P=0.13) |
| Difference (per 5 kg/m²)         | 1.07 [0.71, 1.62] (P=0.74) | 1.39 [0.88, 2.19] (P=0.16) | 1.04 [0.63, 1.72] (P=0.09) |
| CONUT score (per 2 points)       | 1.27 [1.04, 1.55] (P=0.017) | 1.57 [1.19, 2.06] (P=0.002) | 1.58 [1.15, 2.19] (P=0.006) |
| Age (per 10 years)               | 0.89 [0.68, 1.17] (P=0.40) | 0.82 [0.60, 1.10] (P=0.18) | 0.74 [0.53, 1.03] (P=0.073) |
| Non-ambulatory status            | 2.78 [1.56, 4.95] (P=0.001) | 3.86 [1.77, 8.43] (P=0.001) | 6.12 [2.58, 14.53] (P<0.001) |
| Claudication history             | 0.62 [0.37, 1.05] (P=0.078) | 0.74 [0.41, 1.33] (P=0.31) | 0.78 [0.42, 1.44] (P=0.42) |
| **Adjusted relative risk ratio** |           |            |            |
| (Multivariate model)             |           |            |            |
| CONUT score (per 2 points)       | 1.20 [0.98, 1.48] (P=0.076) | 1.49 [1.13, 1.98] (P=0.006) | 1.49 [1.06, 2.09] (P=0.024) |
| Non-ambulatory status            | 2.51 [1.39, 4.55] (P=0.002) | 3.21 [1.46, 7.05] (P=0.004) | 5.18 [2.13, 12.59] (P<0.001) |

Data are relative risk ratios [95% confidence intervals] (P values) for the presence of tissue loss at specific time points. Adjusted relative risk ratios were derived from the multivariate model in which variables with significance in the crude relative risk ratio (univariate model) were entered. Difference means maximum minus current BMI (i.e., decrease from maximum BMI).
association of BMI with the presence of wound (including both unhealed wounds and newly developed wounds) at specific time points. Fourth, the current study population was composed of Japanese CLI patients. In general, obesity is not so prevalent in Japan as in Europe or North America. Whether the current findings would be true in other countries remained unknown.

**Conclusion**

The current study demonstrated that the prevalence of current obesity was low in Japanese CLI patients undergoing revascularization, whereas almost a half of the patients had ever been obese. Past obesity was not rare even in currently lean subjects. Current BMI, but not maximum BMI, was associated with the mortality risk.

**Acknowledgments and Notice of Grand Support**

The SPINACH Study is sponsored by Abbott Vascular Japan Co., Ltd, Boston Scientific Japan K.K., Cook Japan Incorporated, Goodman Co., Ltd, Johnson & Johnson K.K., Kaken Pharmaceutical Co., Ltd, Kaneka Medix Corporation, Medicom Inc., Medikit Co., Ltd, Medtronic Japan Co., Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., St. Jude Medical Japan Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Terumo Corp., W.L.Gore & Associates Co., Ltd (in alphabetical order). The funding companies played no role in the design of the study, selection of the enrolled patients, revascularization procedures or equipment, or interpretation of the data.

**Declaration of Conflicting Interests**

The Authors declare that there is no conflict of interest.

**References**

1) Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, Speizer FE and Hennekens CH: A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med, 1990; 322: 882-889
2) Japanese Coronary Artery Disease Study I: Current status of the background of patients with coronary artery disease in Japan. Circ J, 2006; 70: 1256-1262
3) Murata N, Soga Y, Iida O, Yamauchi Y, Hirano K, Kawsaki D, Fujihara M and Tomoi Y: Complex relationship of body mass index with mortality in patients with critical limb ischemia undergoing endovascular treatment. Eur J Vasc Endovasc Surg, 2015; 49: 297-305
4) Takahara M, Iida O, Fujita Y and Haneda M: Clinical characteristics of Japanese diabetic patients with critical limb ischemia presenting Fontaine stage IV. Diabetol Int, 2019; 10: 231-235
5) Takahara M, Okuno S, Nakamura I, Iida O, Tsujimura T, Hata Y, Fujita Y and Haneda M: Prospective study on clinical characteristics of Japanese diabetic patients with chronic limb-threatening ischemia presenting Fontaine stage IV. Diabetol Int, 2020; 11: 33-40
6) Mehta NK, Stenholm S, Eko IT, Aroma A, Heliovaara M and Koskinen S: Weight histories and mortality among finnish adults: the role of duration and peak body mass index. Epidemiology, 2014; 25: 707-710
7) Yu E, Ley SH, Manson JE, Willett W, Satija A, Hu FB and Willett W: Weight History and All-Cause and Cause-Specific Mortality in Three Prospective Cohort Studies. Ann Intern Med, 2017; 166: 613-620
8) Xu H, Cupples LA, Stokes A and Liu CT: Association of Obesity With Mortality Over 24 Years of Weight History: Findings From the Framingham Heart Study. JAMA Neuropathol, 2018; 1: e184587
9) Iida O, Takahara M, Soga Y, Kodama A, Terashi H and Azuma N: 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 Inter, 2017; 10: e005531
10) Ko T, Higashitani M, Uemura Y, Utsunomiya M, Yamaguchi T, Matsui A, Ozaki S, Tobita K, Kodama T, Morita H and Komuro I: Clinical Outcome and Diverse Risk Factors for Different Therapeutic Target Locations of Peripheral Artery Disease. J Atheroscler Thromb, 2020; 27: 769-779
11) Fukunaga M, Kawasaki D, Nishimura M, Yamagami M, Fujiwara R and Nakata T: Clinical Effects of Planned Endovascular Therapy for Critical Limb Ischemia Patients with Tissue Loss. J Atheroscler Thromb, 2019; 26: 294-301
12) Azuma N, Iida O, Takahara M, Soga Y and Kodama A: Surgical reconstruction versus peripheral intervention in patients with critical limb ischemia - a prospective multicenter registry in Japan: The SPINACH study design and rationale. Vascular, 2014; 22: 411-420
13) Mills JL, Sr., Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN and Anders G: The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WHI). J Vasc Surg, 2014; 59: 220-234 e221-222
14) Ignacio de Ulibarri J, Gonzalez-Madrono A, de Villar NG, Gonzalez P, Gonzalez B, Mancha A, Rodriguez F and Fernandez G: CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp, 2005; 20: 38-45
15) Takahara M, Iida O, Soga Y, Kodama A and Azuma N: Absence of Preceding Intermittent Claudication and its Associated Clinical Features in Patients with Critical Limb Ischemia. J Atheroscler Thromb, 2015; 22: 718-725
16) Takahara M, Iida O, Kohsaka S, Soga Y, Fujihara M, Shinke T, Amano T, Ikari Y, J ETV and investigators JP:
Diabetes mellitus and other cardiovascular risk factors in lower-extremity peripheral artery disease versus coronary artery disease: an analysis of 1,121,359 cases from the nationwide databases. Cardiovasc Diabetol, 2019; 18: 155
17) Bistrian BR, Schwartz J and Istfan NW: Cytokines, muscle proteolysis, and the catabolic response to infection and inflammation. Proc Soc Exp Biol Med, 1992; 200: 220-223
18) Plata-Salaman CR: Cytokines and anorexia: a brief overview. Semin Oncol, 1998; 25: 64-72
19) Suyoto PST, Aulia, B.: Low muscle mass and inflammation among patients with type 2 diabetes mellitus in Indonesia. Diabetol Int, 2019; 10: 219-224
20) Hansson GK: Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med, 2005; 352: 1685-1695
21) Miyashima M, Shoji T, Kakutani Y, Yamazaki Y, Ochi A, Morioka T, Shinohara-Mitsuki K, Fukumoto S, Shioi A, Inaba M and Emoto M: Inter-Arm Blood Pressure Difference in Diabetes Mellitus and Its Preferential Association with Peripheral Artery Disease. J Atheroscler Thromb, 2020; 27: 780-788
22) Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A and Hirsch AT: Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg, 2014; 60: 686-695 e682
23) Matsuo Y, Kumakura H, Kanai H, Iwasaki T and Ichikawa S: The Geriatric Nutritional Risk Index Predicts Long-Term Survival and Cardiovascular or Limb Events in Peripheral Arterial Disease. J Atheroscler Thromb, 2020; 27: 134-143
24) Azuma N, Takahara M, Kodama A, Soga Y, Terashi H, Tazaki J, Yamaoka T, Koya A and Iida O: 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