Original Article

# Differences in Brain Natriuretic Peptide and Other Factors between Japanese Peripheral Arterial Disease Patients with Critical Limb Ischemia and Intermittent Claudication

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***Aim*: The goal of this study was to analyze differences in risk factors, including the level of brain natriuretic peptide (BNP) and the distribution of lesions, between cases of critical limb ischemia (CLI) and intermittent claudication (IC) among patients with peripheral arterial disease.**
***Methods*: Risk factors and clinical characteristics were prospectively investigated in 817 consecutive patients, including 185 patients with CLI and 632 patients with IC.**
***Results*: The patients in the CLI group were older than those in the IC group ($p<0.001$). The prevalence of diabetes and cerebral infarction and the proportion of women were higher in the CLI group ($p<0.05$). The plasma BNP levels in the CLI group were higher than those observed in the IC group (333±538 vs. 136±354 pg/mL, $p<0.001$). In contrast, the levels of homocysteine and fibrinogen were higher and the levels of albumin and the estimated glomerular filtration rate were lower in the CLI group ($p<0.05$). According to a multiple logistic analysis, the BNP level, diabetes, female gender, the albumin level, body mass index (BMI) and ankle-brachial pressure index (ABI) were associated with CLI ($p<0.05$). Aortoiliac artery lesions were less common, whereas femoropopliteal and below-the-knee (BK) lesions were more common, in the CLI group ($p<0.05$). The number of affected BK arteries was also higher in the CLI group ($p<0.001$). Correlations were found between the presence of aortoiliac lesions and smoking and a low HDL cholesterol level, while femoropopliteal lesions were found to correlate with age, BMI and hypertension and BK lesions were found to correlate with diabetes, age, female gender and BMI ($p<0.05$). The plasma BNP level correlated with the number of affected BK arteries ($p<0.05$).**
***Conclusions*: A high BNP level, diabetes, female gender, a low albumin level, ABI and BMI are risk factors for CLI. In this study, differences in the levels of anatomical lesions and correlated risk factors were found between the CLI and IC groups.**

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**Key words:** Critical limb ischemia, Intermittent claudication, Lesion characteristics, Brain natriuretic peptide

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## Introduction

Peripheral arterial disease (PAD) is a systemic disease with multiple atherosclerotic risk factors and poor long-term survival[1-4]. Among patients with PAD, there are disparities in clinical symptoms and risk factors between those with critical limb ischemia

(CLI) and those with intermittent claudication (IC). CLI is a severe stage of PAD associated with multiple risk factors, a danger of amputation and a poorer prognosis than IC[1, 5]. According to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC-II) report, diabetes, smoking, an ABI of $<0.7$, lipid abnormalities and an age $>65$ years are independent and likely additive risk factors for CLI[1]. However, these factors are also risk factors for IC, and the differences in risk factors between CLI and IC are unclear, particularly in Japanese patients with PAD.

The plasma brain natriuretic peptide (BNP) level has been reported to be a predictor of death, independent of traditional risk factors, in community populations[6] and vascular surgery patients[7]. This parameter tends to substantially increase in PAD patients compared to that observed in controls with moderate to high cardiovascular risk factors, such as hypertension, diabetes and hyperlipidemia[8]. However, differences in the plasma BNP levels between patients with CLI and IC have not yet been examined.

Clinical and epidemiological studies have shown the cardiovascular risk factors associated with PAD to differ according to the location of the disease[9, 10]. Hence, the distribution of lesions may be an additional important factor that differs between CLI and IC patients with PAD. Only a few studies have examined these differences and the relationships between risk factors and the distribution of lesions in patients with CLI and IC[11-13]. Therefore, the purpose of this study was to clarify the differences in clinical factors, including the plasma BNP levels, between PAD patients with CLI and IC and to examine the correlations between the distribution of lesions and risk factors in Japanese patients with PAD.

## Methods

### Patients

The subjects included 817 consecutive patients who were referred to the Cardiovascular Hospital of Central Japan between January 1, 2006 and August 31, 2012. All patients had an ankle-brachial pressure index (ABI) of $\leq 0.90$ at their first visit for treatment of PAD. The final diagnosis of PAD was made based on clinical symptoms and the presence of aortoiliac, femoropopliteal or below-the-knee (BK) artery stenosis of $\geq 70\%$ on angiography or ultrasound. The classification of CLI and IC in the PAD patients was defined according to the TASC and TASC-II criteria[1, 14]. The patients were investigated prospectively. Prior to the start of the study, each patient received a full explanation of the treatment and examination methods and provided their written informed consent. The study protocol was approved by the Cardiovascular Hospital of Central Japan Medical Ethical Committee.

### Risk Factors

Diabetes mellitus, hypertension, cerebral infarction and coronary heart disease were examined as risk factors for arteriosclerosis. Diabetes was defined as a fasting plasma glucose level of $>126$ mg/dL on at least two measurements or the use of antidiabetic therapy[15]. Hypertension was defined as a blood pressure of $\geq 140/90$ mmHg recorded at least twice or treatment with antihypertensive agents. An electrocardiogram was recorded and echocardiography and brain CT were performed in each patient. A diagnosis of cerebral infarction was made if the patient had a history of this condition or lesions due to cerebral infarction were found on brain CT. Coronary heart disease was considered to be present when the patient had a history of this condition or exhibited positive signs on stress/rest myocardial perfusion scintigraphy or coronary angiography.

Blood was collected during fasting in the morning to measure the levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, uric acid, creatinine, glucose, glycosylated hemoglobin A1c, total protein, albumin, fibrinogen, lipoprotein (a), BNP and homocysteine. Lipid abnormalities were diagnosed based on an HDL cholesterol level of $<40$ mg/dL[1, 16], a triglyceride level of $\geq 150$ mg/dL[16, 17] and an LDL cholesterol level of $\geq 140$ mg/dL or the use of lipid-lowering agents[16].

The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation for creatinine, as modified by the Japanese Society of Nephrology: eGFR (mL/min/1.73 $m^2$) $= 194 \times (\mathrm{Scr})^{-1.094} \times (\mathrm{Age})^{-0287}$ ($\times 0.739$ if female)[18]. In patients receiving hemodialysis, the eGFR was calculated based on the serum creatinine level measured prior to hemodialysis.

In patients in whom angiography was performed, PAD was evaluated on digital subtraction angiography. The degree of stenosis was calculated using the automatic software program provided by the manufacturer (Phillips Med, Best, The Netherlands) for quantitative coronary angiography. A stenosis rate of $\geq 70\%$ on angiography indicated a diagnosis of significant stenotic lesions.

### Statistical Analysis

The data are expressed as the mean $\pm$ standard deviation. Continuous variables were compared between

**Table 1.** Baseline clinical characteristics and risk factors in patients with peripheral arterial disease

| Risk factor | CLI $n = 185$ (22.6%) | IC $n = 632$ (77.4%) | $p$-value |
|---|---|---|---|
| Age (year) | 74.3 ± 10.5 | 70.8 ± 9.2 | < 0.001 |
| ≥ 80 years (%) | 62 (33.5%) | 89 (14.3%) | < 0.001 |
| Gender (female) | 55 (29.7%) | 110 (17.4%) | < 0.001 |
| ABI | 0.45 ± 0.32 | 0.65 ± 0.22 | < 0.001 |
| BMI (kg/m$^2$) | 20.6 ± 4.1 | 22.3 ± 3.2 | < 0.001 |
| Risk factors | | | |
| Diabetes mellitus | 73 (39.5%) | 199 (31.5%) | 0.043 |
| Hypertension | 104 (56.2%) | 403 (63.8%) | 0.063 |
| Cerebral infarction | 55 (29.7%) | 99 (15.7%) | < 0.001 |
| Coronary heart disease | 56 (30.2%) | 225 (35.6%) | 0.179 |
| Smoking former or current | 139 (75.1%) | 434 (68.7%) | 0.077 |
| Alcohol intake | 71 (38.4%) | 292 (46.2%) | 0.060 |
| Laboratory data | | | |
| BNP (pg/mL) | 333 ± 538 | 136 ± 354 | < 0.001 |
| Albumin (g/dL) | 3.6 ± 0.5 | 4.0 ± 0.3 | < 0.001 |
| eGFR (mL/min/1.73 m$^2$) | 49.2 ± 25.4 | 53.7 ± 21.1 | 0.025 |
| Homocysteine (nmol/mL) | 18.5 ± 12.1 | 15.1 ± 11.6 | < 0.001 |
| Fibrinogen (mg/dL) | 385 ± 162 | 318 ± 92 | < 0.001 |
| Total-C (mg/dL) | 177 ± 42 | 179 ± 39 | 0.556 |
| LDL-C (mg/dL) | 119 ± 42 | 116 ± 70 | 0.588 |
| HDL-C (mg/dL) | 46.8 ± 15.8 | 47.2 ± 14.4 | 0.751 |
| Triglyceride (mg/dL) | 111 ± 86 | 152 ± 315 | 0.087 |
| Uric acid (mg/dL) | 5.7 ± 1.9 | 5.9 ± 1.6 | 0.162 |
| HbA1c (%) | 6.1 ± 1.1 | 6.0 ± 1.2 | 0.321 |
| Lipoprotein(a) (mg/dL) | 24.3 ± 19.1 | 26.9 ± 24.1 | 0.306 |

CLI: critical limb ischemia, IC: intermittent claudication, ABI: ankle-brachial pressure index, BMI: body mass index, BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, Total-C: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HbA1c: glycosylated hemoglobin A1c

patients with CLI and IC using the $t$-test, and proportions were compared using the chi-square test. The relationships between CLI and the risk factors were assessed using a multiple logistic analysis. The odds ratios (ORs) and confidence intervals (CIs) were calculated for individual factors using a univariate logistic analysis. Factors with a $p$-value of $< 0.05$ according to a univariate analysis were used in a multivariate logistic regression model to determine predictors of the risk factors for CLI. In the same way, the relationships between the atherosclerotic arterial lesion levels and the risk factors were assessed using a multiple logistic analysis with multivariate selection after a univariate analysis. A Pearson correlation analysis was used to evaluate simple correlations between the number of affected BK arteries and other risk factors, and a stepwise forward multiple regression analysis was used to examine the relationships between the number of affected BK arteries and the significant risk factors. The SPSS v.17.0 software program (SPSS Inc., Chicago, IL) was used for all calculations. A $p$-value of $< 0.05$ was considered to indicate a significant difference.

## Results

### Patient Characteristics

The subjects included 817 patients with PAD (185 patients with CLI and 632 patients with IC) 38-98 years of age (mean: 71.7 ± 9.7 years). The characteristics of the patients are shown in **Table 1**. The mean age of the patients in the CLI group was significantly higher than that of the patients in the IC group. The proportion of patients with CLI ≥ 80 years of age was higher than that of patients with IC. The rates of diabetes and cerebral infarction and the proportion of women were higher in the CLI group. The levels of BNP, homocysteine and fibrinogen were also

**Table 2.** Relationships between critical limb ischemia and risk factors in multiple logistic analyses with univariate and multivariate selection

| | Univariate selection | | | Multivariate selection | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value |
| Age (year) | 1.042 | 1.021-1.063 | <0.001 | 1.016 | 0.987-1.046 | 0.285 |
| Gender (female) | 2.011 | 1.343-3.012 | 0.001 | 2.005 | 1.109-3.62 | 0.021 |
| ABI | 0.051 | 0.025-0.104 | <0.001 | 0.077 | 0.029-0.205 | <0.001 |
| BMI | 0.863 | 0.814-0.914 | <0.001 | 0.909 | 0.839-0.984 | 0.019 |
| Risk factors | | | | | | |
| Diabetes | 2.281 | 1.280-4.062 | 0.005 | 1.815 | 1.068-3.082 | 0.028 |
| Hypertension | 0.588 | 0.333-1.039 | 0.067 | | | |
| Cerebral infarction | 2.198 | 1.453-3.324 | <0.001 | 1.893 | 0.839-4.268 | 0.124 |
| Coronary heart disease | 0.710 | 0.478-1.054 | 0.090 | | | |
| Smoking | 0.801 | 0.406-1.580 | 0.522 | | | |
| Alcohol intake | 0.939 | 0.863-1.021 | 0.123 | | | |
| Laboratory data | | | | | | |
| BNP | 1.001 | 1.000-1.003 | 0.024 | 1.002 | 1.001-1.006 | 0.038 |
| Albumin | 0.129 | 0.073-0.228 | <0.001 | 0.212 | 0.112-0.402 | <0.001 |
| eGFR | 0.991 | 0.982-0.999 | 0.026 | 1.000 | 0.990-1.012 | 0.880 |
| Homocysteine | 1.020 | 1.000-1.039 | 0.049 | 1.003 | 0.974-1.033 | 0.849 |
| Fibrinogen | 1.005 | 1.003-1.007 | <0.001 | 1.003 | 1.000-1.005 | 0.049 |
| High LDL-C | 1.089 | 0.725-1.625 | 0.690 | | | |
| Low HDL-C | 1.838 | 1.266-2.668 | 0.001 | 1.510 | 0.668-3.414 | 0.322 |
| High triglyceride | 0.544 | 0.281-1.055 | 0.711 | | | |
| Uric acid | 0.925 | 0.822-1.042 | 0.199 | | | |
| HbA1c | 0.960 | 0.788-1.169 | 0.684 | | | |
| Lipoprotein(a) | 0.995 | 0.985-1.005 | 0.306 | | | |

OR: odds ratio, CI: confidence interval, ABI: ankle-brachial pressure index, BMI: body mass index, BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HbA1c: glycosylated hemoglobin A1c

higher in the patients with CLI, whereas the eGFR and albumin levels were lower in the CLI group. According to the multiple logistic analysis, a female gender, ABI, body mass index (BMI), diabetes, the BNP level, the albumin level and the fibrinogen level were associated with CLI (**Table 2**). With respect to age, the non-adjusted odds ratio for CLI was significant from an age ≥75 to an age ≥90. After adjusting for the eight significant parameters in the logistic analysis, only an age ≥80 was found to be a significant risk factor for CLI (odds ratio: 2.43, 95% CI: 1.351-4.392, $p=0.003$).

**Regional Characteristics on Peripheral Angiography**

We performed angiography on 1,292 legs in 646 patients with PAD (152 patients with CLI and 494 patients with IC). The lesions were classified into three types: those located in the aortoiliac artery, femoropopliteal artery and BK arteries. The prevalence of aortoiliac artery lesions was lower, whereas that of femoropopliteal and BK lesions was higher, in the CLI group (**Fig. 1**). The number of affected BK arteries (anterior tibial, posterior tibial and peroneal arteries) was also higher in the CLI group than in the IC group (1.84±1.11 vs. 0.69±0.91, $p<0.001$). The relationships between CLI and the regional characteristics of each affected artery were analyzed using a multiple logistic analysis (**Table 3**), which provided an odds ratio of 4.33 for CLI associated with BK lesions.

**Regional Characteristics and Risk Factors**

The relationships between the three arterial lesion levels and the risk factors were analyzed using a multiple logistic analysis (**Table 4**). Lesions in the aortoiliac artery were correlated with smoking and a low HDL cholesterol level, while lesions in the femoropopliteal artery exhibited a correlation with age, a low ABI, a low BMI and hypertension and lesions in the BK arteries exhibited a correlation with diabetes, age, female gender, a low ABI and a low BMI. The num-

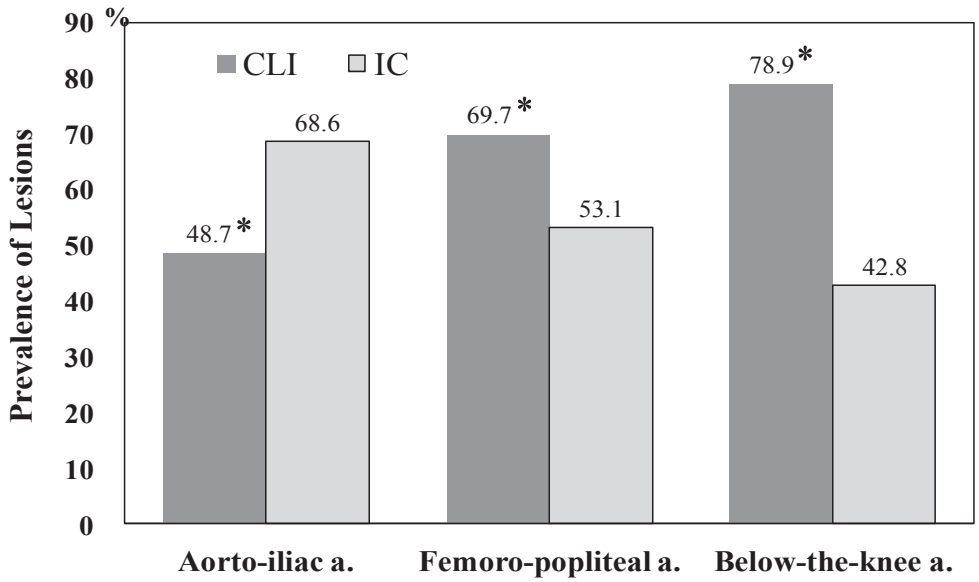


**Fig. 1.** Regional characteristics of the lesion levels on angiography in the patients with critical limb ischemia (CLI) and intermittent claudication (IC).

a.: artery, *$p<0.001$

**Table 3.** Relationships between critical limb ischemia and the three arterial lesion levels in a multiple logistic analysis

| Lesion site | OR | 95% CI | *p*-value |
|---|---|---|---|
| Aortoiliac artery | 0.717 | 0.451-1.140 | 0.159 |
| Femoropopliteal artery | 1.139 | 0.627-1.863 | 0.603 |
| Below-the-knee arteries | 4.331 | 2.588-7.249 | <0.001 |

OR: odds ratio, CI: confidence interval

ber of affected BK arteries demonstrated simple correlations with age, gender, ABI, BMI, smoking, diabetes, cerebral infarction, eGFR and the albumin level ($p<0.05$). A stepwise forward multiple regression analysis of the relationships between the number of affected BK arteries and these factors revealed significant positive correlations with diabetes, a female gender and age and significant negative correlations with the albumin level and eGFR (**Table 5**). The plasma BNP level had a tendency to be correlated with lesions in the BK arteries ($p=0.085$) and exhibited a significant negative correlation with lesions in the aortoiliac artery ($p=0.015$). The plasma BNP level also demonstrated a significant correlation with the number of affected BK arteries ($p=0.012$).

## Discussion

This is the first study to show differences in risk factors and lesion characteristics between Japanese PAD patients with CLI and IC. The mean age of the patients with CLI was significantly higher than that of the patients with IC. After adjusting for other significant parameters, only an age ≥80 was a significant risk factor for CLI, and the proportion of patients with CLI ≥80 years of age was higher than that of patients with IC. Increases in both the incidence and prevalence of PAD in association with increasing age are apparent based on epidemiology, as reported in the TASC-II study[1]. In a population-based study conducted in Sweden, the prevalence of CLI was 0.4% in subjects 60 to 90 years of age, with the prevalence of CLI being highest at 3.3% in those 80 to 84 years of age and a decline to 2.8% observed among the oldest subjects[19]. The findings of our study are consistent with these results.

We also found higher rates of diabetes and cerebral infarction, a higher proportion of women, higher serum levels of BNP, homocysteine and fibrinogen and lower values of eGFR and albumin in the patients

**Table 4.** Relationships between the three arterial lesion levels and risk factors in a multiple logistic analysis

| | Aortoiliac artery | | | Femoropopliteal artery | | | Below-the-knee arteries | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value | OR | 95% CI | *p*-value |
| Age (year) | | | | 1.029 | 1.007-1.051 | 0.009 | 1.039 | 1.016-1.063 | 0.001 |
| Gender(female) | | | | | | | 2.044 | 1.198-3.485 | 0.009 |
| ABI | | | | 0.168 | 0.068-0.411 | <0.001 | 0.216 | 0.089-0.523 | 0.001 |
| BMI | | | | 0.907 | 0.855-0.963 | 0.001 | 0.912 | 0.857-0.972 | 0.004 |
| Diabetes | | | | | | | 3.283 | 2.131-5.058 | <0.001 |
| Hypertension | | | | 1.519 | 1.016-2.246 | 0.042 | | | |
| Smoking | 2.175 | 1.384-3.415 | <0.001 | | | | | | |
| Low HDL-C | 1.583 | 1.009-2.483 | 0.046 | | | | | | |

OR: odds ratio, CI: confidence interval, ABI: ankle-brachial pressure index, BMI: body mass index, HDL-C: high-density lipoprotein cholesterol

**Table 5.** Correlations between the number of affected below-the-knee arteries and other risk factors in a stepwise forward multiple regression analysis

| Risk factor | Units | $\beta$ | 95% CI | *p*-value |
|---|---|---|---|---|
| Diabetes | | 0.224 | 0.288 to 0.678 | <0.001 |
| Gender (female) | | 0.135 | 0.121 to 0.594 | 0.003 |
| Age | year | 0.131 | 0.004 to 0.024 | 0.006 |
| Albumin | mg/dL | −0.114 | −0.570 to −0.058 | 0.016 |
| eGFR | (mL/min/1.73 m$^2$) | −0.099 | −0.008 to −0.000 | 0.032 |

$R^2=0.135$, F for change in $R^2=4.617$, $p=0.032$
CI: confidence interval, eGFR: estimated glomerular filtration rate

with CLI compared to that observed in the patients with IC. In particular, diabetes has been reported to be a critically important risk factor for PAD and other cardiovascular diseases[20, 21]. Therefore, the recent American College of Cardiology Foundation/American Heart Association guidelines modified the age for consideration of ABI diagnostic testing to ≥65 years or ≥50 years in patients with a history of smoking or diabetes[22]. We previously reported that cerebral infarction is an independent risk factor for the progression of Fontaine stages in patients with PAD, in association with age, diabetes and a female gender[23]. Decreased physical capacity, sensory disturbance with respect to wounds and systemic atherosclerosis may also contribute to this risk[1, 23].

Our results provide the first evidence that the plasma levels of BNP are higher in patients with CLI than in patients with IC. Montagnana *et al.* found that the BNP levels were substantially increased in PAD patients compared to those observed in controls with moderate to high cardiovascular risk factors, such as hypertension, diabetes and hyperlipidemia[8]. The cardio-ankle vascular index is a novel indicator of arterial stiffness[24] and is independently associated with an elevated plasma BNP level in patients with hypertension[25]. In this study, the plasma BNP level also exhibited a significant correlation with the number of affected BK arteries. The presence of severe BK lesions was also associated with the BNP level and CLI. BNP is a hormone that is primarily secreted by cardiac myocytes and whose level is increased in patients with cardiac diseases[7]. The BNP expression occurs in various cells and tissue types[26]; however, the source of BNP in the patients evaluated in the current study was unclear. The BNP levels are also predictive of death, independent of traditional risk factors, in community populations[6] and vascular surgery patients[7]. Therefore, a higher plasma level of BNP may be an independent cause of CLI.

Hyperhomocysteinemia is an independent risk factor for atherosclerosis and a stronger risk factor for PAD than for coronary heart disease[27], thus exhibiting an association with death or severe vascular events in patients with PAD[20]. The results of the current study show that a high plasma homocysteine level is a risk factor for CLI as well as PAD. Malnutrition reflected by a low albumin level or low BMI compromises the ability to heal and subsequently prolongs the

stages of wound healing[28]. A low serum albumin concentration is a risk factor for a poor outcome after vascular surgery, in addition to CLI and coronary heart disease[29, 30]. Malnutrition and inflammation are also important risk factors for cardiovascular disease in hemodialysis patients[31, 32], while we have previously shown that a low BMI is a significant risk factor for a poor prognosis in patients with PAD[5]. The BMI exhibits a significant positive correlation with the levels of albumin and triglycerides and a negative correlation with the level of fibrinogen and chronic obstructive pulmonary disease[5], and the level of fibrinogen is particularly associated with the severity and potential for further development of PAD[33]. Therefore, malnutrition (a low albumin level or low BMI) and inflammation (a high fibrinogen level or chronic obstructive pulmonary disease) may be causes of an increased risk of CLI.

Women with CLI have a higher mean age and rate of hypertension and are less likely to be current or former smokers[34]. A higher risk of multilevel disease is also observed in women, whereas men more often have isolated lesions[34]. We found that symptomatic conditions, including diabetes and hyperlipidemia, are more frequent and more severe in hospitalized women[23] while, Egorova *et al.* found that women are less likely to be admitted to the hospital for PAD but more likely to be hospitalized for CLI under emergency conditions[12].

The distribution of lesions is an additional factor that differs between PAD patients with CLI and IC. In this study, the prevalence of aortoiliac artery lesions was lower and that of femoropopliteal and BK lesions was higher in the CLI group. The number of affected BK arteries was also higher in the CLI group than in the IC group. It is well-known that distal PAD is associated with a more severe limb prognosis, particularly because achieving revascularization is more difficult and may not always be possible, leading to higher rates of amputation[9]. In the current study, a multiple logistic analysis of the relationships between the anatomical characteristics of the affected artery provided a high odds ratio of 4.33 for CLI associated with BK lesions. These results show that anatomical characteristics are important with respect to the progression of limb ischemia in patients with PAD.

Aortoiliac disease is associated with a younger age, male gender and cigarette smoking[35, 36], whereas infrageniculate disease is associated with a higher age, hypertension, renal failure and diabetes[35, 36]. Haltmayer *et al.* found that a current smoking status and the plasminogen level is significantly associated with hemodynamically relevant atherosclerosis in the aortoiliac and femoropopliteal segments, whereas no such associations are observed for lipid profiles or the level of fibrinogen[37]. In our study, the presence of lesions in the aortoiliac artery was found to be correlated with smoking and a low HDL cholesterol level, indicating that a low HDL cholesterol level is an important risk factor for aortoiliac artery lesions in patients with PAD. We also found that the presence of lesions in the femoropopliteal artery was correlated with age, a low ABI, a low BMI and hypertension. The TASC-II study reported that hypertension is associated with all forms of cardiovascular disease, including PAD. However, the relative risk for developing PAD is less for hypertension than for diabetes or smoking[1]. There are limited data regarding the association between hypertension and PAD according to lesion localization. Diehm *et al.* found no relationships between hypertension and lesion sites[35], whereas hypertension was found to be a significant risk factor for femoropopliteal artery lesions in our patients.

In this study, the presence of lesions in the BK artery was correlated with diabetes, age, a female gender, a low ABI and a low BMI. Diabetes is the most obvious risk factor for atherosclerotic involvement of the infragenicular arteries[35], and Haltmayer *et al.* found an association between diabetes and the crural arterial segments[37]. With regard to gender, Ortmann *et al.* found that women with CLI have a three-fold higher risk of occlusion than men[34]. As mentioned above, a low BMI is associated with malnutrition, inflammation and chronic obstructive pulmonary disease[5]. Malnutrition and inflammation are important risk factors for cardiovascular disease[31, 38], and chronic obstructive pulmonary disease is related to past and/or current smoking[39]. These relationships suggest that a low BMI may be related to the presence of severe artery lesions in patients with PAD.

The limitations of this study include the relatively small sample size, the analysis of a single facility and the lack of use of population-based data. Therefore, further studies are needed to determine the precise differences in risk factors and distribution of lesions between PAD patients with CLI and IC among hospitalized subjects and the general population.

## Conclusion

Patients with CLI have various systemic risk factors, with the rates of diabetes and cerebral infarction and the proportion of women being particularly higher among patients with CLI. The BNP level is another independent risk factor for CLI. In this study, the mean age and the homocysteine and fibrinogen

levels were higher, whereas the ABI, BMI and levels of albumin were lower, in the patients with CLI. The results of this study showed significant differences in the clinical status and characteristics of lesions between Japanese PAD patients with CLI and IC.

## Conflicts of Interest

None to declare.

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