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TITLE PAGES

Prognostic value of lower-limb perfusion single photon emission computed tomography-computed tomography in patients with lower-limb atherosclerotic peripheral artery disease

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ABSTRACT

Purpose: The purpose of this study was to estimate the severity of the participants' lower-limb ischemia by calculating the lower-limb-muscle-to-background ratio (LMBR) using lower-limb perfusion single photon emission computed tomography-computed tomography (SPECT/CT), and to evaluate the prognostic value of LMBR in peripheral artery disease (PAD) patients.

Materials and methods: This retrospective study consists of 38 patients with PAD (70 ± 12 y) and observed over one year were included in the analysis. All participants underwent lower-limb perfusion SPECT/CT. LMBR was calculated by dividing counts/volume in lower-limb muscle by mean counts/volume of background. All patients were divided into two groups based on their LMBR value and observed for the occurrence of major adverse event (MAE).

Results: The high and low LMBR groups consisted of 26 and 12 patients, respectively. The median LMBR in the high group was 9.59 (6.11–11.87) and while that in the low group was 4.35 (3.85–4.99). A significantly higher number of patients in the low LMBR group experienced MAE than in the high LMBR group (7 of 12 versus 1 of 26, $p < 0.001$).

Conclusion: This study demonstrated that the LMBR derived from lower-limb perfusion SPECT/CT may have a high prognostic value in patients with PAD.

Key Words: peripheral artery disease; lower-limb perfusion SPECT/CT; lower-limb-muscle-to-blood ratio; risk factors; prognosis

Introduction

Lower-limb atherosclerotic peripheral artery disease (PAD) is a highly prevalent disorder and mainly occurs in the elderly population. The number of patients with PAD is estimated to be over 200 million worldwide, with symptoms ranging from none to severe [1–3]. Since PAD has risk factors in common with coronary artery disease (CAD) and cerebrovascular disease (CVD), patients with PAD are likely to have these other comorbid conditions [3, 4]. Furthermore, patients with PAD, especially those with critical limb ischemia, have an increased risk for cardiovascular events, cerebrovascular events, lower-limb amputations, and death compared to the general population [4–7]. Previous reports have revealed that approximately 40% of patients with critical limb ischemia require lower-limb amputations within six months of their initial diagnosis and 20–25% die within a year [8, 9]. Therefore, accurately assessing the severity of lower-limb ischemia, risk stratifying patients, and implementing early optimal treatment may be crucial to improve the prognosis of PAD patients.

Traditionally, minimally-invasive imaging modalities, such as ultrasonography [10], computed tomography angiography (CTA) [11, 12], and magnetic resonance angiography (MRA) [13, 14], have been commonly used for the initial diagnosis of

PAD. However, ultrasonography only provides an evaluation of blood flow in the major vessels and is not useful for the assessment of microvessels. Both CTA and MRA are commonly used exclusively for morphological assessment of the major vessels. Unlike these modalities, lower-limb perfusion scintigraphy can evaluate lower-limb perfusion and ischemia. It has also been reported to be of high diagnostic accuracy and prognostic value for patients with PAD [15–20]. However, since conventional planar imaging has insufficient anatomical information, low-tracer-accumulation tissues, such as fat tissue and bones, cannot be eliminated from the analyses and this can cause an underestimation of lower-limb-muscle perfusion. Recently, single photon emission computed tomography-computed tomography (SPECT/CT) combined systems have been introduced into clinical use. Lower-limb perfusion SPECT/CT allows us to calculate lower-limb-muscle-to-background ratio (LMBR) and this parameter reflects exclusively lower-limb-muscle perfusion.

The aims of this study were to assess lower-limb-muscle perfusion by calculating LMBR with lower-limb perfusion SPECT/CT, and to evaluate the prognostic value of lower-limb perfusion SPECT/CT.

Materials and methods

Patient population

A total of 68 consecutive patients suspected to have PAD were included in this study and underwent lower-limb perfusion SPECT/CT between January 2010 and January 2015. The retrospectively enrolled patients who met the following criteria at the time of imaging: clinical diagnoses were confirmed based on clinical symptoms, a treadmill exercise test, ankle-brachial index (ABI), and angiography findings. Patients with Buerger's disease, collagen disease, cellulitis, osteomyelitis, and stasis dermatitis were excluded from this study. Furthermore, six censored participants were excluded from the study. We finally enrolled 38 patients in the present study (29 men and 9 women, 70 ± 12 years) (Fig. 1). Patients with hematologic malignancy were not included in this study. The study protocol was received and approved by the institutional review board (28-07-609).

Lower-limb perfusion SPECT/CT imaging

All patients underwent lower-limb perfusion SPECT/CT, using a SPECT/CT hybrid system, combining a dual-head gamma camera with a two-row multi-section computed tomography (CT) scanner: Symbia T2 (Siemens Healthcare Japan, Tokyo,

Japan). SPECT image acquisition was performed 15 min after intravenous injection of ^{99m}Tc-tetrofosmin 740 MBq at rest, without exercise stress. SPECT images were acquired over 10 min per bed position (30 projections over an orbit of 180°, 6° per step, and 20 sec per projection). Acquisition range was limited to within two bed positions from the toes; this includes the entirety of the lower legs and feet. An LEHR collimator was used for the acquisition and the matrix was 128 × 128 pixels. SPECT images were reconstructed using an iterative image reconstruction algorithm: Flash3D. The reconstruction parameters for number of subsets was 6 and for iterations was 8. Non-contrast-enhanced CT scan (tube voltage, 110 keV; tube current time product, 10–40 mA; detector configuration, 2 × 4 mm; matrix, 256 × 256 pixels; and reconstruction thickness, 5 mm) was also performed to enable CT attenuation correction and create SPECT/CT images.

Data analysis

On lower-limb SPECT/CT images, 3D volumes of interest (VOI) were automatically drawn exclusively on the lower limb muscles, from the toes to the knee joints, of the patients based on the CT values of the muscles in each transaxial image to calculate the amount of tracer accumulation using Syngo MI Workplace (Siemens

Healthcare Japan, Tokyo, Japan). Specifically, all of the crural muscles, including the anterior tibial muscles, posterior tibial muscles, and peroneal muscles, and all of the foot muscles, including plantaris muscles, were included in the VOIs (Fig. 2a). Furthermore, two 3D VOIs were drawn in the bone marrow of both-side distal femur and mean counts per volume (CPV) (count/cm^3) of both-sides distal-femur bone marrow was calculated as a background (Fig. 2b). LMBR, which indicated the amount of perfusion in lower-limb muscles, was calculated by dividing CPV (count/cm^3) of PAD-side lower-limb muscles by mean CPV (count/cm^3) of the background. If patients had PAD on both sides, the lower LMBR between both sides was included in the analysis. In order to evaluate the clinical importance of LMBR, all of the patients were divided into two groups based on their LMBR values. The cut-off value was determined using a receiver operating characteristic (ROC) analysis based on the occurrence of major adverse event (MAE).

Interobserver reproducibility was evaluated by calculating the value of LMBR which was done by two experienced nuclear medicine specialists. Intraobserver reproducibility was evaluated by calculating the value of LMBR two times at an interval of one month which were done by the same nuclear medicine specialist. The

correlations of these values from each test were evaluated using a linear regression analysis. Neither the patient information nor the other specialists' results were accessible to any of the specialists.

Evaluation of prognosis

All patients were observed over one year after their initial lower-limb perfusion SPECT/CT for the occurrence of MAE, which were defined as amputations of the ischemic leg, cardiovascular events, cerebrovascular events, or all-cause mortality. The endpoint for this study was defined as either the occurrence of MAE or completion of one year of follow up after the lower-limb perfusion SPECT/CT. The relationship between the occurrence of MAE and various clinical parameters, including LMBR, therapeutic treatments, such as drugs, percutaneous transluminal angioplasty (PTA), and lower-limb bypass-surgery was also analyzed.

Statistical analysis

As all continuous variables were not distributed normally, the data were expressed as medians with 25^{th} and 75^{th} percentiles. Categorical variables were presented as counts (%).

Non-normally distributed continuous variables, such as age, ABI, and LMBR, were compared using the Mann-Whitney U-test. Categorical variables were compared using a Fisher's exact probability test for the bivariate data or Mann-Whitney U-test for Fontaine class and TASC class. Linear regression analysis was used to assess the interobserver and intraobserver variability of LMBR. The proportion of event-free patients was estimated by the Kaplan-Meier method and compared between high and low LMBR groups using the log-rank test. Variables with a significance level of $p < 0.05$ in the univariate Cox regression analysis were included in a multivariate Cox regression model to evaluate factors independently associated with the future occurrence of MAE.

A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using StatMate IV software version 4.01 (Advanced Technology for Medicine and Science, Tokyo, Japan).

Results

Clinical characteristics

Thirty-eight patients (age 70 ± 12 years; 29 men, 9 women) underwent lower-limb perfusion SPECT/CT for the assessment of LMBR. The patients' characteristics, including past history, Fontaine class, and ABI, are presented in Table 1. Based on Fontaine class, 1 patient was classified into stage I, 12 were stage II, 11 were stage III, and 14 were stage IV. Median ABI of the participants was 0.92 (0.76–1.07).

Inter- and intraobserver variability of LMBR

The linear regression analyses revealed excellent reproducibility of LMBR in inter- and intraobserver trials ($r = 0.970$, $p < 0.001$; $r = 0.976$, $p < 0.001$; respectively).

Patient categorization by LMBR value

Overall, the median LMBR value was 6.69 (5.27–10.57). Using ROC analysis, 26 patients were assigned to the high LMBR group, while the remaining 12 were assigned to the low group. The median LMBR was 9.17 (6.67–11.37) in the high group and 4.21 (3.90–5.21) in the low group. The cut-off value for high LMBR was 5.35 and the area under the ROC curve based on MAE occurrences was 0.92 (Fig. 3).

Patient prognosis

All 38 participants were observed over one year from their initial lower-limb SPECT/CT. Of the 38 participants, 8 (21%) experienced MAE during the one-year follow-up period. Amputations of the ischemic leg occurred in three patients, an acute myocardial infarction in one patient, a cerebral infarction in one patient, and death due to deterioration of heart failure in two patients, and sudden death due to unknown cause in one patient. Of the eight incidents of MAE, only a single case of fatal events occurred in the high LMBR group. In summary, the proportion of patients who experienced MAE was significantly higher in the low LMBR group than in the high group (7 of 12 vs. 1 of 26 patients, $p < 0.001$) (Fig. 4). A comparison of the clinical profiles of all participants who did and did not experience MAE is presented in Table 2. Table 3 shows the results of the univariate and multivariate Cox regression analyses for the occurrence of MAE. In the multivariate analysis, low LMBR was determined to be the most significant independent prognostic factor ($p = 0.013$).

Case presentations

Fig. 5 shows a typical case of a patient in the high LMBR group. This 70-year-old woman had PAD in Fontaine class III. The lower-limb catheter angiography revealed a 90% stenosis in the left superficial femoral artery and chronic total occlusion

in both anterior tibial arteries, posterior tibial arteries, and peroneal arteries. Lower-limb perfusion SPECT/CT showed moderate hypoperfusion in the left lower leg, mild hypoperfusion in the right lower leg, and severe hypoperfusion in both feet. Despite the many severe occlusions in major arteries, LMBR was high with a value of 7.31 on the left and 7.91 on the right. In this case, the patient remained MAE-free for the entire one-year follow-up period.

Fig. 6 shows a typical case of a patient in the low LMBR group. This 77-year-old man had PAD in Fontaine class IV. Lower-limb catheter angiography revealed 75% stenosis in the right common iliac artery, 90% stenosis in the right and left superficial femoral arteries, and chronic total occlusion in both anterior tibial arteries, posterior tibial arteries, and peroneal arteries. Consistent with the many severe occlusions in major arteries in both lower limbs, lower-limb perfusion SPECT/CT showed severe hypoperfusion in both lower legs and feet. The LMBR was low with a value of 4.03 on the right and 4.09 on the left. In this case, the patient died suddenly due to unknown cause 90 days after the initial lower-limb perfusion SPECT/CT. Since the patient had several comorbidities, such as hypertension, coronary artery disease, and

diabetes mellitus, and was repeatedly hospitalized due to deterioration of heart failure, it is speculated that the cause of the sudden death was a cardiovascular event.

Discussion

In the present study, LMBR was calculated with lower-limb perfusion SPECT/CT as an index indicating lower-limb-muscle perfusion and the prognostic value of LMBR was evaluated in patients with PAD. The results showed that LMBR was a valuable prognostic marker, with low LMBR indicating a poorer prognosis than high LMBR.

Assessment of lower-limb ischemia with lower-limb perfusion SPECT/CT

Lower-limb perfusion scintigraphy, which has exclusively planar imaging, is conventionally used for the diagnosis of PAD and the evaluation of lower-limb ischemia [15–20]. This modality is useful to estimate the efficacy of various treatments, such as medical therapies, percutaneous transluminal angioplasty, surgical revascularization, and angiogenic therapy [18–20]. However, conventional lower-limb perfusion scintigraphy provides solely planar images. While these planar images are sufficient to estimate the degree of global lower-limb perfusion, regional ischemia in each arterial territory could

not be evaluated due to lack of cross-sectional images. Unlike conventional lower-limb perfusion scintigraphy, lower-limb perfusion SPECT/CT has cross-sectional hybrid images and illustrates the relationships between obstructive lesions in each artery and ischemic regions in the lower-limb muscles [21]. Therefore, lower-limb perfusion SPECT/CT may have a higher diagnostic value than conventional lower-limb perfusion scintigraphy which has planar imaging without SPECT imaging.

Calculating LMBR with lower-limb perfusion SPECT/CT

Previously, Miyamoto et al. provided an index for lower-limb perfusion named "^{99m}Tc-tetrofosmin perfusion index" using lower-limb perfusion scintigraphy [19, 20]. This index was calculated by dividing lower-limb muscle counts per pixel by brain counts per pixel (muscle-to-brain ratio: MBR) [19, 20]. In this study, we devised a new index for lower-limb perfusion: LMBR derived from lower-limb perfusion SPECT/CT. This index is calculated by dividing CPV in the lower leg and foot muscles on the PAD-side by mean CPV in both-side distal-femur bone marrow. This calculation method was based on that of Miyamoto et al [19, 20]. In order to minimize the acquisition time of SPECT and radiation exposure in CT scanning, the acquisition range was limited to two bed positions and the background VOI, used for the calculation of LMBR, was set in the

distal-femur bone marrow. In this study population, since CPV in distal-femur bone marrow was stable with a value of 21.43 (16.23–26.55), this region is suitable as background for calculating LMBR.

Comparison of LMBR with lower-limb-muscle ischemia

Fontaine classification is commonly used for the clinical stratification of lower-limb-muscle ischemia in patients with PAD [22]. The patient group in this study consisted of 1 class I, 12 class II, 11 class III, and 4 class IV patients. The median LMBR in Fontaine classes I, II, III, and IV were 9.17, 7.41 (6.55–12.11), 6.47 (5.20–10.06), and 5.14 (4.35–6.14), respectively. Therefore, LMBR is most likely related to the severity of symptoms caused by lower-limb ischemia. Previously, Miyamoto et al. reported an index for lower-limb perfusion: MBR derived from planar images of lower-limb perfusion scintigraphy [19, 20]. In this study population, the MBR of the patients in Fontaine classes I, II, III, and IV were 1.23, 1.04 (0.93–1.23), 1.22 (0.96–1.28), and 0.96 (0.92–1.10), respectively. While the MBR in Fontaine classes I–II did not differ from that in classes III–IV [1.10 (0.94–1.23) vs. 0.99 (0.92–1.27), p = 0.690], the LMBR in Fontaine classes III-IV was significantly lower than that in classes I-II [5.27 (4.13–9.42) vs. 8.38 (7.22–11.00), p =0.009]. MBR derived from planar images may underestimate

lower-limb muscle perfusion as the ROI used in this calculation includes tissues with low tracer accumulation such as fat tissue and bones. Therefore, LMBR derived from lower-limb perfusion SPECT/CT can more clearly stratify the severity of lower-limb ischemia than MBR derived from planar images.

Comparison of LMBR with angiographic findings

Of the 38 participants, 34 underwent angiography before the initial lower-limb perfusion SPECT/CT. TASC classification is commonly used for stratification of PAD severity [23]. In this study, in patients with aortoiliac disease, the median LMBR in TASC class none, A, B, and C were 7.27 (5.58–11.25), 5.57 (3.99–9.03), 6.88 (5.64–8.13), and 4.04, respectively; those with femoropopliteal disease, the LMBR in TASC class none, A, B, and C were 6.93 (5.74–9.71), 4.63 (4.14–5.11), 7.22 (4.21–11.07), and 14.47 (13.25–15.69), respectively; those with infrapopliteal disease, the median LMBR in TASC class none, A, B, and C were 10.67 (10.24–11.00), 5.98 (4.03–9.38), 6.84 (5.49–7.58), and 5.54 (4.04–11.63), respectively. Therefore, TASC classification was not related to the value of LMBR. This result might be due to the ignorance of the microcirculation, including collateral flow, in TASC classification. Angiographic findings might also overestimate

the severity of PAD compared to the severity of lower-limb ischemia derived from lower-limb SPECT/CT.

Prognostic value of LMBR for MAE in patients with PAD

Patient prognosis in cases with PAD, especially with critical limb ischemia, is poor, as they are at increased risk of CAD, CVD, lower-limb amputations, and death compared to the general population [4–7]. In this study, the proportion of patients who experienced MAE was significantly higher in the low LMBR group than in the high group (7 of 12 vs. 1 of 26 patients, $p < 0.001$). Kuśmierek et al. previously reported that patients with lower-limb hypoperfusion detected on lower-limb scintigraphy have a higher prevalence of CAD than the general population [24]. It is speculated that detecting lower-limb perfusion impairment by the scintigraphy and treating systemic atherosclerotic artery in early stage may avoid future adverse events such as CAD, CVD, and death.

ABI is also known to have a high prognostic value for adverse events caused by PAD [25, 26]. Doobay et al. reported that the hazard ratios of ABI for CAD, CVD, and all-cause mortality were 2.53, 2.45, and 3.97, respectively [25]. In this study, unlike

previous reports, ABI in patients who experienced MAE did not significantly differ from that of event-free patients [0.84 (0.71–1.08) vs. 0.88 (0.75–1.03), p = 0.938] and the hazard ratio of ABI for these events was extremely low with a value of 1.20. These results might be due to unreliable ABI values caused by simultaneous upper-limb arteriosclerosis and collateral-vessel formations in lower limbs. Therefore, the prognostic value of ABI may be less than previously expected in this study cohort. Even in such a complicated situation, LMBR had extremely high prognostic value. We believe that LMBR is indeed a reliable prognostic marker for future adverse events in patients with PAD.

Study Limitations

The main limitation of this study was the small patient sample size of 38 in total which limited the statistical reliability. Although several patient parameters such as diabetes mellitus and hypertension were not found to have prognostic value in this study, it is widely accepted that these factors are associated with MAE. However, as LMBR was the sole independent factor associated with MAE occurrences, we may infer that LMBR is indeed a strong predictor for MAE. Another limitation of this study was its short follow-up period. Of the 38 participants, 20 were observed in the 3 years after

initial examination and 13 (65%) experienced MAE. Amputations of the ischemic leg occurred in five patients, an unstable angina in one patient, acute myocardial infarctions in two patients, a cerebral infarction in one patient, a cerebral hemorrhage in one patient, and death due to deterioration of heart failure in two patients and sudden death due to unknown cause in one patient. Therefore, a longer period of observation may be required to reveal the actual prognostic performance of LMBR. A further limitation in the study was the lack of a control group and the lack of a group with mild lower-limb ischemia. As a result, the value of LMBR in the healthy, general population is unknown, as is the predictive value of LMBR in patients with milder PAD. Nonetheless, some patients in this study had a lower limb with no stenoses and using these limbs, it may be speculated that the lower limit for healthy LMBR is approximately 9.75 since their median LMBR was 11.57 (10.66–12.53). In this study, bone marrow was chosen as a background for the calculation of LMBR. Since there were no significant differences between the mean counts of right- and left-side bone marrow [right: 21.71 (15.84–26.78) vs. left: 21.19 (16.48–25.82), $p = 0.934$], it is speculated that the influence of stenotic lower-limb arteries might be eliminated. Although the most suitable background part has not been strictly examined, the CPV of bone marrow might be acceptable for the calculation of

LMBR and the prognostic value of LMBR seems to be extremely high. The participants included in this study mainly had serious PAD and 25 patients (66%) were classified into Fontaine class III or IV. Therefore, most of the patients in this study could not undergo stress tests. Because lower-limb perfusion SPECT/CT tests were performed at rest, the impact of muscle atrophy on the LMBR values might not be completely excluded. However, the influence of muscle atrophy may be minimized by calculating LMBR which is based on the accumulation per unit volume.

Conclusion

In this study, lower-limb perfusion was estimated by calculating LMBR using lower-limb perfusion SPECT/CT in patients with PAD. Furthermore, LMBR may have a high prognostic value for MAE in patients with PAD. A novel method for predicting the severity of lower-limb ischemia was employed and has the potential to be used extensively in clinical settings.

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Ethical Statement

The Ethics Committee at Nippon Medical School Hospital approved the study protocol (28-07-609). The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Conflict of Interest

Takanori Ikeda has received grant support through his institution from Daiichi Sankyo, Bristol-Myers Squibb, Boehringer Ingelheim; and honoraria for lectures from Bayer Healthcare, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Tanabe-Mitsubishi, and Ono Pharmaceutical. Regarding this study, all authors declare that there is no any potential conflict of interest.

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CAPTIONS FOR ILLUSTRATIONS

Fig. 1 Flow chart of patient inclusion and exclusion in the study

PAD peripheral artery disease; *SPECT* single photon emission computed tomography; *CT* computed tomography

Fig. 2 Three-dimensional muscle ROIs on lower- limb muscle and distal-femur bone marrow. a Three-dimensional muscle ROIs on lower- limb muscle. b Three-dimensional muscle ROIs on distal-femur bone marrow.

Fig. 3 Receiver operating characteristic analysis used for determining the cut-off LMBR value based on the occurrence of MAE.

The cut-off value for high LMBR was 5.35 and the area under the ROC curve was 0.92.

Fig. 4 Kaplan-Meier curve in reference to MAE stratified by LMBR value

The y-axis represents the cumulative event-free rate; the rate in the high LMBR group was significantly higher than in the low group (log-rank test, $p < 0.001$)

LMBR lower-limb-muscle-to-background ratio

Fig. 5 Representative images of lower-limb perfusion SPECT/CT in PAD patient in Fontaine class III assigned to high LMBR group

The images show moderate hypoperfusion in the left lower leg, mild hypoperfusion in the right lower leg, and severe hypoperfusion in both feet. Despite the many severe obstructions in major arteries in both lower limbs, LMBR is high with a value of 7.31 on the left and 7.91 on the right. This patient remained MAE-free for the entire one-year follow-up period

SPECT single photon emission computed tomography; *MIP* maximum intensity projection; *CT* computed tomography

Fig. 6 Representative images of lower-limb perfusion SPECT/CT in PAD patient in Fontaine class IV assigned to low LMBR group

The images show severe hypoperfusion in both lower legs and feet. Consistent with the many severe occlusions in major arteries in both lower limbs, LMBR is low with a value of 4.03 on the right and 4.09 on the left. This patient suddenly died at home 90 days after initial lower-limb perfusion SPECT/CT

SPECT single photon emission computed tomography; *MIP* maximum intensity projection; *CT* computed tomography

Table 1 Patient characteristics

Number of patients	N = 38
Age (years)	73 (66–77)
Male	29 (76%)
Fontaine class I/II/III/IV	1/12/11/14
ABI	0.92 (0.76–1.07)
TASC class none/A/B/C/D/no data	
Aortoiliac disease	21/10/2/1/0/4
Femoropopliteal disease	12/3/16/2/0/5
Infrapopliteal disease	6/6/12/10/0/4
Risk factors	
Diabetes mellitus	22 (58%)
Dyslipidemia	25 (66%)
Hypertension	32 (84%)
Smoking	22 (58%)
Obesity (BMI ≥ 25 kg/m^2)	9 (24%)
Comorbidity	
Coronary artery disease	19 (50%)
None/1VD/2VD/3VD	19/5/8/6
Cerebrovascular disease	6 (16%)

ABI ankle-brachial index; *BMI* body mass index; *VD* vessel disease

Table 2 Comparison of clinical profiles of all participants who did and did not experience MAE

	MAE n = 8 (21%)	No MAE n = 30 (79%)	P value
Age (years)	71 (70–76)	73 (65–77)	0.900
Male	6 (75%)	23 (77%)	0.712
Fontaine class I/II/III/IV	0/0/2/6	1/12/8/9	0.014
ABI	0.84 (0.71–1.08)	0.88 (0.75–1.03)	0.938
TASC class none/A/B/C/D/no data			
Aortoiliac disease	3/4/0/1/0/0	18/6/2/0/0/4	0.244
Femoropopliteal disease	2/0/5/0/0/1	10/3/11/2/0/4	0.758
Infrapopliteal disease	0/3/2/3/0/0	6/3/10/7/0/4	0.315
LMBR	4.35 (3.85–4.46)	8.89 (5.81–11.41)	< 0.001
Risk factor			
Diabetes mellitus	5 (63%)	17 (57%)	0.767

Dyslipidemia	4 (50%)	21 (70%)	0.402
Hypertension	7 (88%)	25 (83%)	0.796
Smoking	7 (88%)	15 (50%)	0.132
Obesity (BMI ≥ 25 kg/m^2)	0 (0%)	9 (30%)	0.192
Comorbidity			
Coronary artery disease	4 (50%)	15 (50%)	1.000
None/1VD/2VD/3VD	4/0/4/0	15/5/4/6	0.215
Cerebrovascular disease	4 (50%)	4 (13%)	0.076
Treatment			
Sarpogrelate	2 (25%)	13 (43%)	0.592
Cilostazol	2 (25%)	19 (63%)	0.124
Aspirin	4 (50%)	11 (37%)	0.684
Prostaglandins	1 (13%)	11 (37%)	0.380
Clopidogrel	5 (63%)	12 (40%)	0.461
Angiotensin converting enzyme inhibitor and angiotensin receptor blocker	5 (63%)	16 (53%)	0.643

Calcium-channel blocker	3 (38%)	14 (47%)	0.686
β-blocker	3 (38%)	11 (37%)	0.712
Statin	4 (50%)	16 (53%)	0.690
PTA	3 (38%)	3 (10%)	0.177
Lower extremity bypass surgery	0	0	-
Hyperbaric oxygen therapy	5 (63%)	8 (27%)	0.139
Extracorporeal shock-wave therapy	1 (13%)	11 (37%)	0.380
Angiogenic therapy	0 (0%)	3 (10%)	0.460

ABI ankle-brachial index; *BMI* body mass index; *LMBR* lower-limb-muscles-to-background ratio; *MAE* major adverse event; *PTA* percutaneous transluminal angioplasty; VD vessel disease

Table 3 Univariate and multivariate Cox regression analysis for occurrence of MAE

	HR	95% CI	P value	HR	95% CI	P value
Age	1.725	0.348–8.552	0.504			
Male	0.977	0.197–4.844	0.978			
Fontaine class	5.004	0.537–46.601	0.157			
ABI	1.203	0.301–4.816	0.794			
Hypertension	1.287	0.161–10.259	0.812			
Dyslipidemia	0.448	0.112–1.793	0.256			
Diabetes mellitus	1.164	0.278–4.872	0.836			
Smoking	3.710	0.611–22.521	0.154			
Obesity (BMI ≥ 25 kg/m^2)	0.258	0.021–3.154	0.289			
Coronary artery disease	1.084	0.271–4.336	0.909			
Cerebrovascular disease	3.911	0.972–15.734	0.055			
Low LMBR	22.733	2.476–208.694	0.006	15.033	1.785–	0.013

					126.584	
Treatment after examination						
PTA	6.203	1.530–25.143	0.011	2.564	0.597–11.012	0.206
Cilostazol	0.238	0.048–1.180	0.079			
Prostaglandins	0.277	0.034–2.251	0.230			
ARB	1.350	0.323–5.651	0.681			
β-blocker	1.118	0.267–4.679	0.878			
Statin	0.821	0.205–3.284	0.780			

ABI ankle-brachial index; *BMI* body mass index; *CI* confidence interval; *HR* hazard ratio; *LMBR* lower-limb-muscles-to-background ratio; *MAE* major adverse event; *PTA* percutaneous transluminal angioplasty

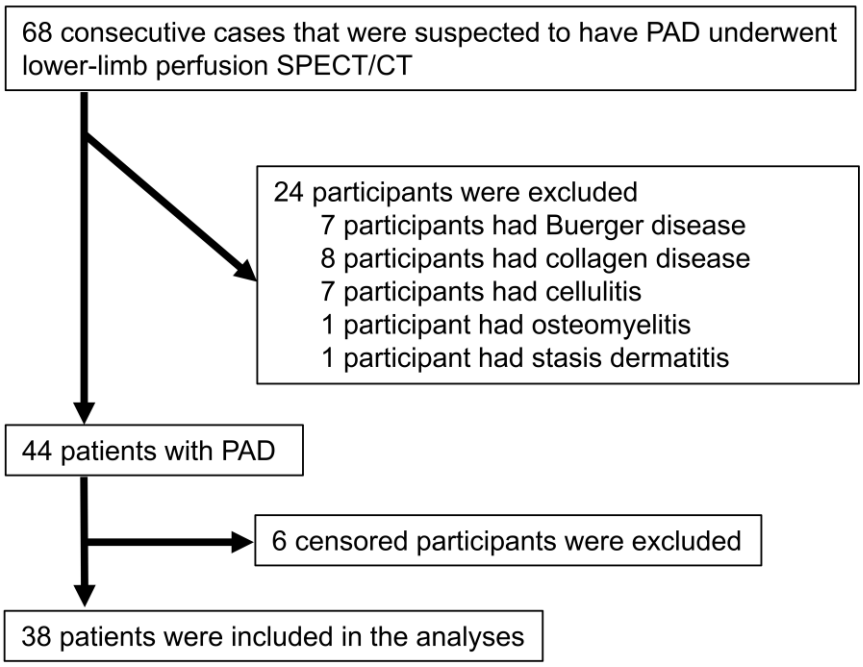
68 consecutive cases that were suspected to have PAD underwent lower-limb perfusion SPECT/CT
24 participants were excluded
7 participants had Buerger disease
8 participants had collagen disease
7 participants had cellulitis
1 participant had osteomyelitis
1 participant had stasis dermatitis
44 patients with PAD
6 censored participants were excluded
38 patients were included in the analyses

Figure 1

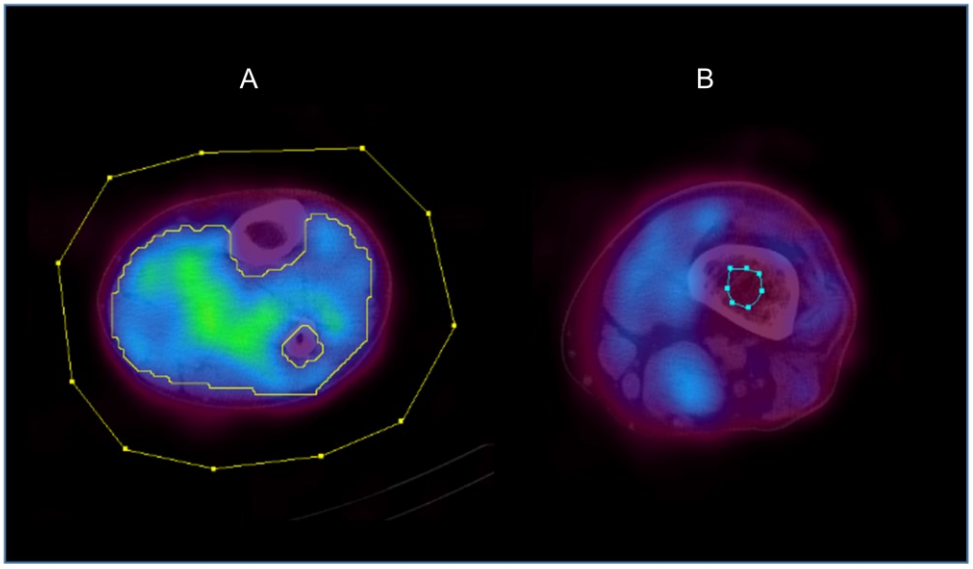

Figure 2

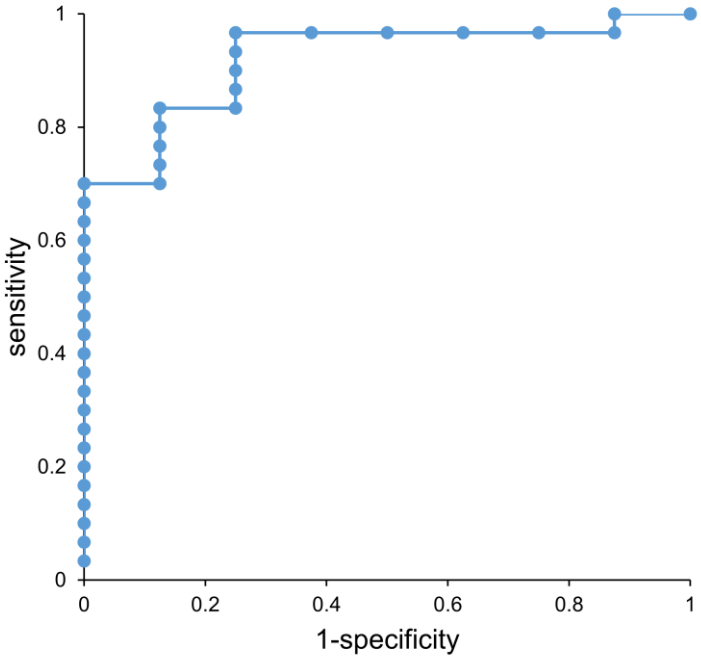

Figure 3

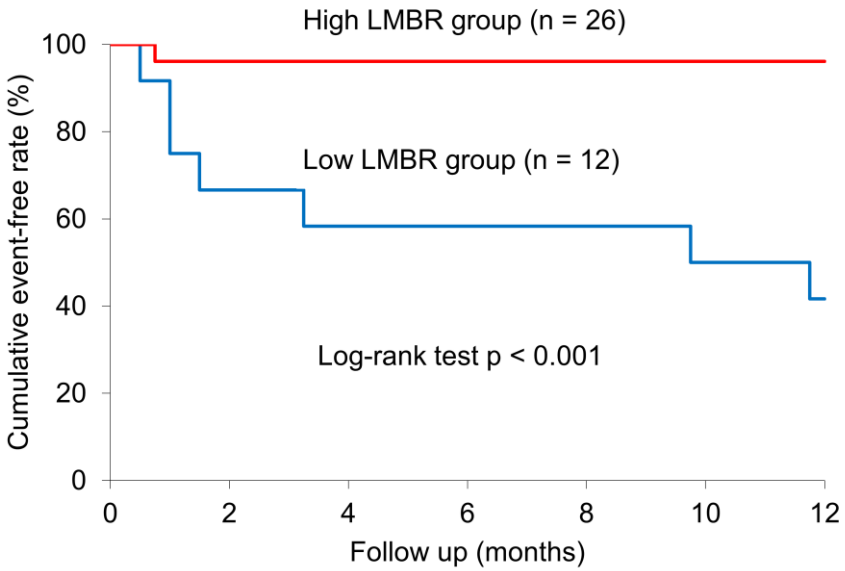
High LMBR group (n = 26)
Low LMBR group (n = 12)
Log-rank test p < 0.001
Cumulative event-free rate (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
Follow up (months)

Figure 4

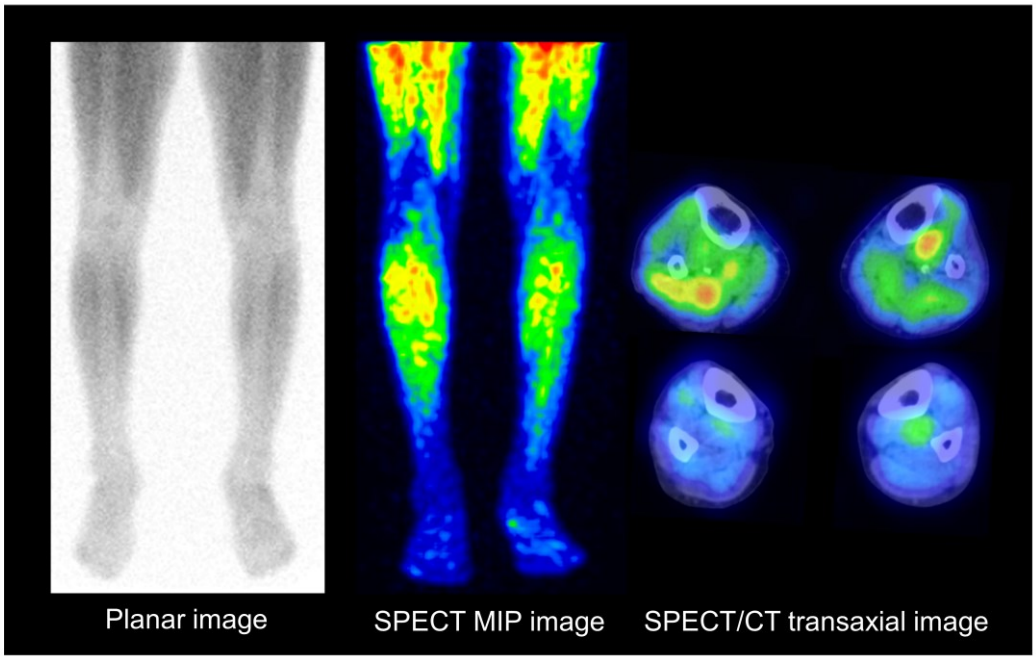

Figure 5

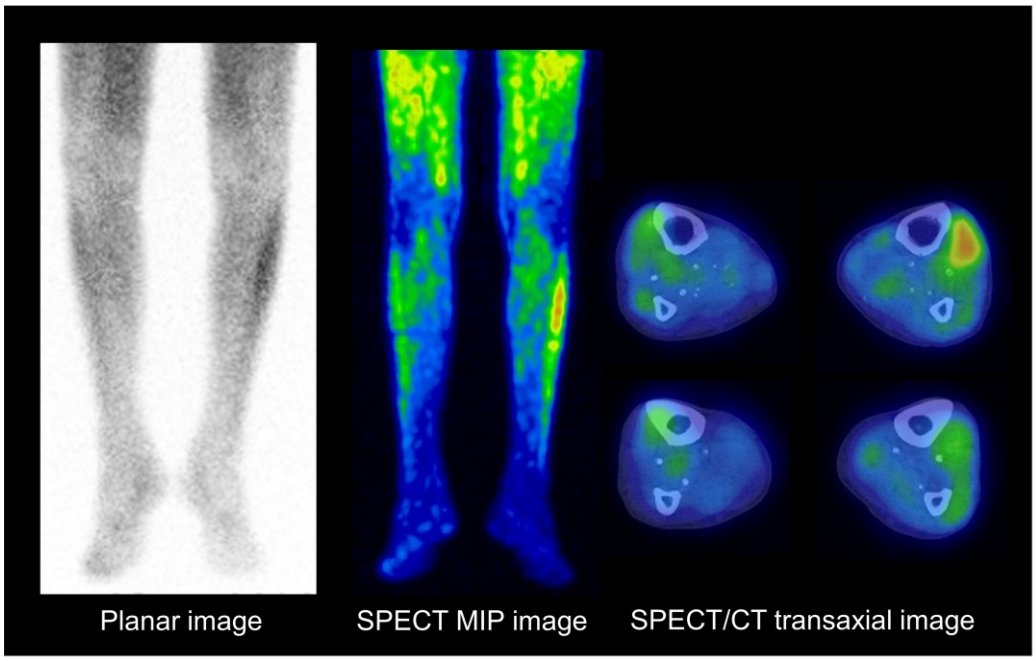

Figure 6