Sarcopenia is a prognostic factor for overall survival in patients with critical limb ischemia

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Background: **Sarcopenia has been proposed as a prognostic factor for various diseases. Patients with critical limb ischemia (CLI) have a very poor prognosis, but sarcopenia has not been reported as a prognostic factor for CLI patients. If sarcopenia is associated with the prognosis of CLI patients, it could help select the treatment plan. Therefore, we examined whether sarcopenia is a prognostic factor for CLI patients.**

Methods: **We performed a retrospective study of CLI patients diagnosed with Fontaine III or IV peripheral artery disease who underwent preoperative computed tomography imaging and revascularization between January 2002 and December 2009. The presence of sarcopenia was defined as skeletal muscle area of <114.0 cm^2 for men or <89.8 cm^2 for women using transverse computed tomography scans at the third lumbar vertebra. We compared the 5-year survival rate and clinical characteristics between patients with or without sarcopenia. We also screened possible prognostic factors for overall survival using hazard ratios (HRs) with 95% confidence intervals (CIs).**

Results: **Of 64 eligible patients, 28 patients had sarcopenia and 36 did not. There were significant differences in age, skeletal muscle area, body mass index, and the presence of smoking, cerebrovascular disease, and hemodialysis between patients with and without sarcopenia (all $P < .05$). The 5-year survival rate was significantly lower in patients with sarcopenia (23.5% vs 77.5%, $P = .001$). Prognostic factors for overall survival were the presence of sarcopenia (HR, 3.22; 95% CI, 1.24-9.11; $P = .02$), requirement for hemodialysis (HR, 4.30; 95% CI, 1.60-12.2; $P = .004$), and postoperative complications (HR, 5.02; 95% CI, 1.90-13.7; $P = .001$).**

Conclusions: **Our results suggest that sarcopenia is a prognostic factor for CLI patients. Exercise and nutritional interventions focusing on improving sarcopenia might be useful treatment options for CLI patients. (J Vasc Surg 2015;61:945-50.)**

The Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) study showed that bypass is an appropriate treatment for critical limb ischemia (CLI) patients with an expected survival of >2 years.[1] Some prognostic factors for CLI have been suggested during the past 15 years.[2-13] Meanwhile, several recent studies have suggested that sarcopenia, a reduction in skeletal muscle, is a prognostic factor for several diseases.[14-21] However, no studies have assessed whether sarcopenia is a prognostic factor for CLI patients.

The prognosis of CLI patients is poor, and the risk of cardiovascular and cerebrovascular events is high.[8,22] However, the relationship between sarcopenia and the prognosis of vascular disease is unclear. Sarcopenia is relatively easy to diagnose by preoperative computed tomography (CT) imaging. Therefore, if sarcopenia could predict the prognosis of CLI patients, it might help clinicians select the most appropriate treatment plan. In addition, if the mechanism underlying the association between sarcopenia and prognosis could be determined, treatments for sarcopenia, such as exercise, might improve the prognosis of CLI patients. From this context, the aim of this study was to determine the clinical significance of sarcopenia as a prognostic factor for CLI patients.

METHODS

The Kyushu University Investigational Review Board approved this study. Patient informed consents were not obtained because of limitations such as patient death, break in contact, and follow-up occurring in other hospitals. All information about this study protocol that is described in the subsequent "Patients" section was opened by bulletin according to the Kyushu University Investigational Review Board guidelines. Patients could be notified about this study and could ask whether they were included in the study. All patients were automatically included in this study without consent; however, patients could request to be excluded.

Patients. We conducted a retrospective study of patients with CLI diagnosed as Fontaine III or IV peripheral artery disease (PAD) who underwent revascularization at the Department of Surgery and Science, Kyushu University Hospital, Fukuoka, Japan, between January 2002 and December 2009. CLI patients underwent imaging studies,

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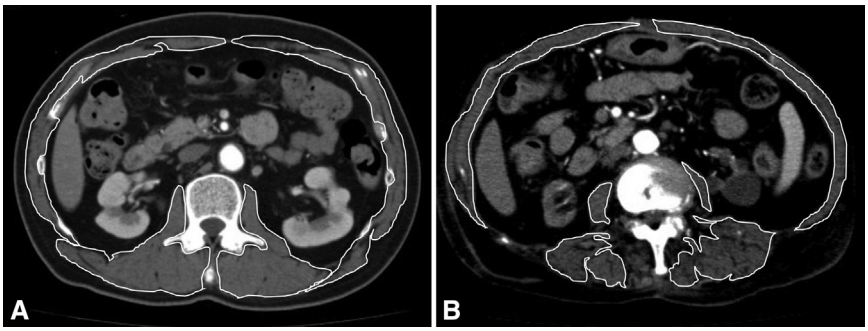

Fig 1. Representative transverse computed tomography (CT) images are shown of **(A)** a patient without sarcopenia and **(B)** a patient with sarcopenia. The images were taken at the third lumbar vertebra. The *white outline* shows the calculated skeletal muscle area.

including preoperative CT, angiography, and magnetic resonance angiography. PAD was categorized as Fontaine III or IV if the patient experienced pain at rest or had ulcers. Patients were excluded if they did not undergo CT because the quantity of their skeletal muscle could not be assessed.

Transverse CT images obtained at the third lumbar vertebra (L3) in the lower border were assessed in each patient. Skeletal muscles, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique abdominal muscle, and rectus abdominis muscle, were identified and quantified as previously described.[19,20,23] The cross-sectional areas (cm^2) of the skeletal muscles in the L3 region were measured by manual outlining on the CT images (Fig 1), and the areas were summed. The presence of sarcopenia was defined as a skeletal muscle area of <114.0 cm^2 for men and <89.8 cm^2 for women. These cutoff values were defined as below the fifth percentile of the standard value in healthy adults.[20,23] We also estimated the total skeletal muscle area using the method of Yoshizumi et al.[23]

The clinical characteristics, including smoking, diabetes mellitus, hypertension, dyslipidemia, ischemic heart diseases, cerebrovascular diseases, hemodialysis, and postoperative complications,[2-8] as well as survival time, were retrieved from the patients' medical records. We also developed a predictive score for sarcopenia based on patient characteristics. Overall survival (the primary end point) and clinical characteristics were compared between the two patient groups. Hazard ratios (HRs) for overall survival were calculated for each risk factor in univariate and multivariate analyses.

Follow-up strategy. All patients were examined in an outpatient clinic 1 month after revascularization, with subsequent assessments every 3 months if no problems developed. Some patients were seen in other hospitals. Patients with symptoms suggestive of vascular complications underwent additional medical examinations. Medical examinations consisted of an interview to assess symptoms, physical examinations, and measurement of the ankle-brachial pressure index. Patients with potential vascular complications also underwent CT and angiography as necessary.

Statistical analysis. The associations of continuous and categoric variables with clinically relevant outcome variables were assessed using the Student *t*-test and the Fisher exact test, respectively. The overall survival curves were analyzed using the Kaplan-Meier method and compared with the log-rank test. Univariate analysis of clinicopathologic factors and overall survival were performed using the log-rank test. Multivariate analyses of clinicopathologic factors and overall survival were performed using the Cox proportional hazards model. All analyses were performed using JMP 9.0 software (SAS Institute Inc, Cary, NC). Values of $P < .05$ were considered statistically significant.

RESULTS

Between January 2002 and December 2009, 108 patients with CLI underwent revascularization at the Department of Surgery and Sciences, Kyushu University Hospital, Fukuoka, Japan. The study excluded 44 patients (40.7%) because they did not undergo preoperative CT. Therefore, 64 patients (59.3%) with CLI underwent preoperative CT and were included in this study.

Of the 64 eligible patients, 28 (43.8%) had sarcopenia and 33 (56.2%) did not. The mean follow-up period was 3.5 ± 2.1 years in all 64 patients, 4.1 ± 2.2 years in patients without sarcopenia, and 2.7 ± 1.7 years in patients with sarcopenia. The clinicopathologic characteristics of patients with or without sarcopenia are summarized in Table I. There were significant differences in age, skeletal muscle area, estimated skeletal muscle area, body mass index (BMI), the proportions of smokers, patients with cerebrovascular disease, and patients who required hemodialysis in patients with and without sarcopenia (all $P < .05$). The other clinicopathologic characteristics and postoperative complications were not significantly different between patients with and without sarcopenia. The cancer-related mortality rate was significantly different between patients with and without sarcopenia ($P = .04$).

Patients with sarcopenia tended to be older, had a lower BMI and estimated skeletal muscle area, and a greater proportion had cerebrovascular diseases and required hemodialysis. Considering these results, we developed a predictive score for sarcopenia, which was calculated from the

Table I. Characteristics of patients with and without sarcopenia

Variable[a]	*Patients without sarcopenia (n = 36)*	*Patients with sarcopenia (n = 28)*	P
Age, years	69.2 ± 11.8	73.8 ± 9.6	.04[b]
Sex			.93[c]
Male	24 (66.7)	19 (67.9)	
Female	12 (33.3)	9 (32.1)	
Skeletal muscle area, cm^2	124.1 ± 19.3	91.0 ± 16.9	<.001[b]
Estimated, cm^2	136.1 ± 27.6	113.0 ± 24.7	<.001[b]
BMI, kg/m^2	23.1 ± 3.5	19.4 ± 2.3	<.001[b]
Serum albumin, g/dL	3.71 ± 0.58	3.85 ± 0.52	.30[b]
Fontaine/Rutherford			.94[c]
III/4	17 (47.2)	13 (46.4)	
IV/5, 6	19 (52.8)	15 (53.6)	
Smokers	21 (58.3)	8 (28.6)	.02[c]
Hypertension	21 (58.3)	15 (53.6)	.70[c]
Diabetes mellitus	18 (50.0)	12 (42.9)	.57[c]
Dyslipidemia	3 (8.3)	2 (7.1)	.86[c]
Ischemic heart disease	12 (33.3)	13 (46.4)	.29[c]
Cerebrovascular disease	5 (13.9)	11 (39.3)	.02[c]
Hemodialysis	5 (13.9)	10 (35.7)	.04[c]
Treatment			.41[c]
Endovascular therapy	6 (16.7)	7 (25.0)	
Bypass	30 (83.3)	21 (75.0)	
Graft type			
Vein	13 (43.3)	14 (66.7)	.10[c]
Prosthetic	15 (50.0)	6 (28.6)	.13[c]
Composite	2 (6.7)	1 (4.8)	.78[c]
Distal anastomosis			
Above knee	15 (50.0)	10 (47.6)	.87[c]
Below knee	15 (50.0)	11 (52.4)	.87[c]
Postoperative complications	10 (27.8)	9 (32.1)	.70[c]
Surgical site infection	2 (5.6)	2 (7.1)	.80[c]
Stroke	1 (2.8)	1 (3.8)	.86[c]
Pneumonia	0 (0)	1 (3.8)	.25[c]
Heart failure	2 (5.6)	2 (7.1)	.80[c]
Bleeding	1 (2.8)	1 (3.8)	.86[c]
Lymphorrhea	2 (5.6)	0 (0)	.21[c]
Others	2 (5.6)	2 (7.1)	.80[c]
Cause of death			
Ischemic heart disease	0 (0)	2 (14.3)	.27[c]
Acute heart failure	2 (25.0)	4 (28.6)	.86[c]
Cerebrovascular disease	1 (12.5)	1 (7.1)	.68[c]
Abdominal organ ischemia	0 (0)	1 (7.1)	.45[c]
Pneumonia	2 (25.0)	2 (14.3)	.53[c]
Acute respiratory failure	0 (0)	2 (14.3)	.27[c]
Sepsis	1 (12.5)	2 (14.3)	.91[c]
Cancer	2 (25.0)	0 (0)	.04[c]
Operative death	0 (0)	1 (3.6)	.25[c]

BMI, Body mass index.
[a]Values for continuous data are shown as means ± standard deviation, and categoric data are shown as number (%).
[b]Student *t*-test.
[c]Fisher exact test.

following conditions: age >65 years, BMI <22 kg/m^2, estimated skeletal muscle area below the fifth percentile of the value of healthy adults, the presence of cerebrovascular disease, and the requirement for hemodialysis. The score ranged from 0 to 5, and the prevalence of sarcopenia was 0% (0 of 12), 22.2% (4 of 18), 52.9 % (9 of 17), 87.5% (14 of 16), and 100% (1 of 1) for scores of 0 to 1, 2, 3, 4, and 5, respectively (Table II).

The overall survival curves of patients with and without sarcopenia are shown in Fig 2. The 5-year overall survival rates were 23.5% ± 0.18% for patients with sarcopenia and 77.5% ± 0.09% for patients without sarcopenia. The overall survival rate was significantly different between patients with and without sarcopenia ($P = .001$).

Table III reports the results of the univariate and multivariate analyses that were conducted to identify prognostic factors for overall survival. The univariate analyses showed that the presence of sarcopenia (HR, 4.24; 95% confidence interval [CI], 1.69-11.7; $P = .002$), hemodialysis (HR, 4.07; 95% CI, 1.68-9.75; $P = .002$), and postoperative complications (HR, 2.98; 95% CI, 1.23-7.10; $P = .02$) were significantly associated with overall survival. The

Table II. Distributions of the predicted scores for sarcopenia

Score	*0*	*1*	*2*	*3*	*4*	*5*
Patients without sarcopenia, No.	3	9	14	8	2	0
Patients with sarcopenia, No.	0	0	4	9	14	1
Prevalence rate, %	0.0	0.0	22.2	52.9	87.5	100.0

multivariate analysis showed these associations remained statistically significant for sarcopenia (HR, 3.22; 95% CI, 1.24-9.11; $P = .02$), hemodialysis (HR, 4.30; 95% CI 1.60-11.4; $P = .004$), and postoperative complications (HR, 5.02; 95% CI, 1.90-13.7; $P = .001$).

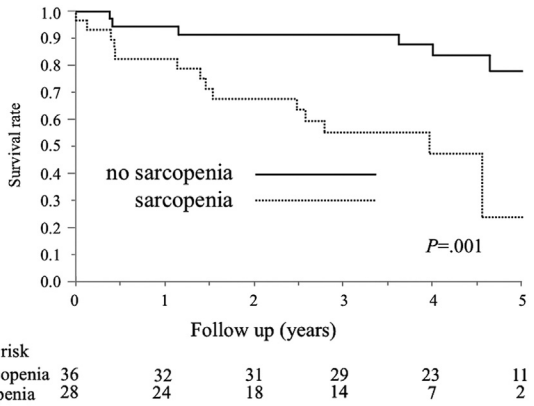

Fig 2. Kaplan-Meier curves show survival of patients with (*dotted line*) or without (*solid line*) sarcopenia ($P = .001$ by log-rank test).

DISCUSSION

The prognosis of CLI patients is very poor.[8] Prior studies have shown that hemodialysis and postoperative complications are associated with poor prognosis of patients with PAD,[8-13] whereas the current study revealed that sarcopenia is also associated with poor prognosis of CLI patients.

Although the 5-year survival rate of CLI patients with sarcopenia was poor (23.5%), the survival rate of patients without sarcopenia was much higher (77.5%) and similar to that of patients with intermittent claudication reported in Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).[8] Earlier studies demonstrated that hemodialysis is a critical risk factor for reduced survival in CLI patients,[23] which was also apparent in the present study (Table II). The BASIL study showed that bypass is an appropriate treatment for CLI patients with an expected survival of >2 years,[1] but the predictors of survival >2 years are still being discussed. The presence of sarcopenia and hemodialysis could possibly predict the prognosis of CLI patients. The current results suggest that patients without hemodialysis or sarcopenia could receive more aggressive treatments because they might be expected to survive longer, whereas patients with sarcopenia might require minimally invasive treatment because their survival is expected to be shorter.[1] For example, arterial bypass may be appropriate for patients without hemodialysis or sarcopenia because of the good long-term patency of this intervention.[1,24-26]

We believe that sarcopenia is a biomarker for overall debilitation and that measuring sarcopenia as an indication of the frailty of patients would be useful. Sarcopenia is associated with a variety of factors, including age, nutrition, comorbidities, and activities of daily living. A combination of factors, each with a small effect individually, could act together and result in sarcopenia.[27,28] To determine indications for surgical treatment, assessing the patient's general condition is important. Sarcopenia is associated with a poor general condition and could help the surgeon to select the appropriate treatment.

Age, BMI, the proportions of smokers, and patients with cerebrovascular disease were significantly different between patients with and without sarcopenia; unexpectedly, they were not prognostic factors in the current study (Table III) but could predict the presence of sarcopenia based on the predictive score developed in this study (Table II). Indeed, patients with high predicted scores, based on a combination of risk factors, were expected to have sarcopenia. These findings suggest that these factors have a very small influence on the patient's prognosis, even though sarcopenia is caused by such factors. Instead, it is possible that the accumulation of these risk factors contributes to the onset of sarcopenia rather than its prognosis. These results may also highlight the prognostic role of sarcopenia in CLI patients.

Obesity is a major risk factor, but the patients in our study generally had a low BMI. This might be related to the general characteristics of Japanese people, whereas the incidence of obesity is significantly higher in Western countries. "Sarcopenic obesity" is a syndrome characterized by low skeletal muscle area but high fat content. Patients with sarcopenic obesity have a high BMI, but their skeletal muscle area is quite low. Because the prevalence of sarcopenic obesity may be quite high in Western countries, measuring skeletal muscle area seems to be quite important, even in patients with a high BMI, considering the poor prognosis of patients with sarcopenic obesity.[29]

The cancer-related mortality rate was significantly higher in patients without sarcopenia than in those with sarcopenia. Although considering the causes of death is important, there was no clear tendency toward an increased incidence of a specific cause of death in patients with sarcopenia in this current study. Therefore, further studies may be needed to assess the most common causes of death in patients with sarcopenia.

Sarcopenia is easy to diagnose by CT, and CT can also provide other useful anatomic information. Some patients were diagnosed by angiography, and endovascular interventions could be performed at the same time without CT scans. The current study revealed that patients without sarcopenia had a good prognosis. Arterial bypass may be

Table III. Univariate and multivariate analyses of clinicopathological factors associated with overall survival after treatment of critical limb ischemia (CLI)

	Univariate analysis		*Multivariate analysis*	
Variable	*HR (95% CI)*	P[a]	*HR (95% CI)*	P[b]
Age, years	4.98 (0.65-48.9)	.13		
Sex, male/female	2.53 (0.94-8.77)	.06		
Fontaine, IV/III	1.05 (0.45-2.50)	.91		
Serum albumin, g/dL	0.77 (0.35-1.68)	.50		
BMI, kg/m^2	0.52 (0.06-4.09)	.54		
Presence/absence of				
Sarcopenia	4.24 (1.69-11.7)	.002	3.22 (1.24-9.11)	.02
Smoking	0.68 (0.26-1.62)	.39		
Hypertension	1.03 (0.43-2.53)	.95		
Diabetes mellitus	2.32 (0.95-6.21)	.07		
Dyslipidemia	1.20 (0.19-4.19)	.81		
Ischemic heart disease	1.97 (0.82-4.75)	.12		
Cerebrovascular disease	1.86 (0.70-4.49)	.20		
Hemodialysis	4.07 (1.68-9.75)	.002	4.30 (1.60-11.4)	.004
Post-op complications	2.98 (1.23-7.10)	.02	5.02 (1.90-13.7)	.001
Treatment, bypass/EVT	2.33 (0.67-14.7)	.21		

BMI, Body mass index; *CI,* confidence interval; *HR,* hazard ratio; *EVT,* endovascular therapy.
[a]Log-rank test.
[b]Cox proportional hazards model.

suitable in these patients because it offers better long-term patency than endovascular interventions.[1,20,24,25] Therefore, preoperative CT should be considered in such cases, and the surgeon should select an appropriate treatment plan that takes into account the patient''s status, including sarcopenia.

Prior reports[19,20,23] have described methods to diagnose sarcopenia by CT, and these methods were used in this study. We thought that skeletal muscle area at the L3 level is suitable because this level includes multiple muscles involved in daily living activities. For example, the erector spinae is involved in maintaining an erect position, and the iliopsoas is used in walking. Cutoff values for skeletal muscle area have not been adequately defined. We used the fifth percentile of the value of healthy adults because it is widely recognized as a standard value statistically and was used in prior study.[20] We believe that establishing cutoff values of skeletal muscle area for predicting sarcopenia is important and that skeletal muscle area should be examined in various patient populations, including other races and age groups, worldwide.

Prior studies have discussed the mechanism by which sarcopenia may affect the prognosis of patients with some diseases,[27-31] but not CLI. Skeletal muscle was recently reported to be an endocrine organ.[15] Moreover, adiponectin[32] and carnitine,[33] which target skeletal muscle, were reported to improve arteriosclerosis. It was thought that sarcopenia could reduce the effects of adiponectin and carnitine, exacerbating whole-body arteriosclerosis, which might contribute to the poor prognosis of CLI patients, including those with arteriosclerosis. Considering these issues, improving the prognosis of patients with CLI may be possible by treating sarcopenia as a whole-body disease. In TASC II, treadmill training was recommended for intermittent claudication patients but not for CLI patients.[8] Resistance training and nutritional therapy have been reported to improve sarcopenia.[33] Further studies are needed to evaluate whether a comprehensive treatment program, including revascularization, resistance training, and nutrition therapy, improves the prognosis of CLI patients.

CONCLUSIONS

The results of this study imply that sarcopenia is a possible prognostic factor for overall survival in patients with CLI. Exercise and nutritional interventions focusing on improving sarcopenia might be useful treatment options for CLI patients and are a topic for future research.

AUTHOR CONTRIBUTIONS

Conception and design: YuM, TM
Analysis and interpretation: YuM, ST
Data collection: YuM, YA
Writing the article: YuM, JO
Critical revision of the article: TM, KM, KS
Final approval of the article: YoM
Statistical analysis: YuM, TM
Obtained funding: Not applicable
Overall responsibility: YoM

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