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Complex Relationship of Body Mass Index with Mortality in Patients with Critical Limb Ischemia Undergoing Endovascular Treatment

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WHAT THIS PAPER ADDS

A complex relationship was found between body mass index (BMI) and long-term outcomes in patients with critical limb ischemia (CLI) after endovascular treatment of isolated infrapopliteal artery lesions. The 3 year overall survival rates were 33.3%, 61.2%, and 69.8% in underweight, normal, and overweight/obese patients, respectively. The survival rate was significantly lower in underweight patients and significantly higher in overweight/obese patients compared with patients of normal weight. Although underweight patients with CLI have a poor prognosis because of comorbidities, low BMI itself is an independent predictor of a poor prognosis in patients with CLI.

Objective: To investigate the relationship between body mass index (BMI) and long-term outcomes of patients with CLI after endovascular treatment (EVT).
Design: Retrospective multicenter study.
Subjects: 1088 consecutive patients (1306 limbs, mean age 72 ± 10 years) with CLI who underwent EVT for isolated infrapopliteal artery lesions were evaluated. These subjects were identified in the J-BEAT III registry.
Methods: The patients were divided into groups based on BMI <18.5 kg/m^2 (underweight, $n = 188$; 219 limbs), 18.5 to 24.9 kg/m^2 (normal weight, $n = 718$; 868 limbs), and >25.0 kg/m^2 (overweight/obese, $n = 182$; 219 limbs). The endpoints were overall survival and freedom from major adverse limb events (MALE).
Results: The median follow up period was 1.5 years (range: 1 month—8.7 years). The 3 year overall survival rates were 33.3%, 61.2%, and 69.8% in underweight, normal, and overweight/obese patients, respectively. The survival rate was significantly lower in underweight patients and significantly higher in overweight/obese patients compared with patients of normal weight (both $p < .0001$). The 3 year rates of freedom from MALE did not differ significantly among the three groups (36.4%, 45.4%, and 52.3%, respectively, $p = .32$). Age, BMI <18.5 kg/m^2, heart failure, aortic valve stenosis, renal failure, triglyceride levels, serum albumin <3.0 g/dL, anticoagulant treatment, non-ambulatory status, and Rutherford 6 classification all were significantly associated with overall survival.
Conclusions: BMI has a complex correlation with mortality in patients with CLI after EVT for isolated infrapopliteal artery lesions. Underweight patients with CLI have an extremely poor prognosis. Such patients have many other factors associated with mortality, but low BMI was identified as an independent predictor of a poor prognosis in patients with CLI. Similarly, normal weight patients had a small but significant increase in mortality compared with overweight/obese patients.

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INTRODUCTION

The "obesity paradox" emerges from the observation that mortality in patients with hypertension, heart failure,[1,2] and coronary artery disease[3] decreases as their body mass index (BMI) increases, despite the association of obesity with cardiovascular risk factors. BMI has also been found to be inversely related to mortality in patients with

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peripheral artery disease (PAD).[4,5] However, most patients in these reports presented with claudication alone, whereas patients with critical limb ischemia (CLI) are known to suffer a higher mortality (50—60% at 5 years) compared with those with uncomplicated claudication (20—30% at 5 years).[6]

In vascular surgery, an inverse relationship between obesity and mortality has been proposed in patients with CLI requiring lower extremity revascularization or amputation,[7,8] but this relationship is unclear in patients with CLI after endovascular treatment (EVT) as the primary therapy. EVT is now an alternative first line treatment for patients with CLI because its long-term outcome has been proven non-inferior to that of surgery.[9,10] EVT is also employed in inoperable cases because of age, comorbidities, and general condition. The purpose of this study was to investigate the relationship between BMI and long-term outcomes in patients with CLI following EVT.

SUBJECTS AND METHODS

Study design and population

The J-BEAT (Japanese Below the knee Artery Treatment Trial) III registry is a physician initiated, non-commercial, multicenter registry of consecutive patients with CLI undergoing EVT for isolated infrapopliteal artery lesions between April 2004 and March 2012 in Japan. A total of 1091 consecutive patients (1310 limbs) were identified retrospectively, with subsequent exclusion of three patients (four limbs) with no data for BMI. The patients were divided into three groups based on BMI as recommended by the World Health Organization (Fig. 1): <18.5 kg/m^2 (underweight, 188 patients, 219 limbs), 18.5 to 24.9 kg/m^2 (normal weight, 718 patients, 868 limbs), and >25.0 kg/m^2 (overweight/obese, 182 patients, 219 limbs). Weights and heights were measured at the time of admission.

Independent researchers collected demographic, angiographic, and procedural data from hospital charts or hospital databases according to pre-specified definitions. Follow up data were obtained from hospital charts or by contacting patients or referring physicians. The relevant review boards or ethics committees in all participating centers approved the study protocol. Written informed consent was obtained from each patient. This study is registered with the University Hospital Medical Information Network-Clinical Trial Registry (UMIN-CTR), as accepted by the International Committee of Medical Journal Editors (No. UMIN 000004917).

Endovascular intervention and follow up protocol

The EVT strategy was limited to the use of balloon angioplasty (without stenting), which was the only strategy permitted in Japan at the time of the study. Balloon angioplasty was performed with repeated dilation of each vessel by inflating optimally sized balloons for 1—3 min at nominal pressure. Satisfactory results were defined as persistent stenosis of <50% on angiography and achievement of one straight vascular route to the wound. Antiplatelet agents were administered prior to EVT and continued lifelong. Each patient was evaluated at 1, 3, and 6 months after EVT and then every 6 months after that. Repeat revascularization was performed when indicated by reappearance of symptoms with Rutherford[11] category 4, 5, or 6 and findings of ischemia with significant reduction of ankle-brachial index (ABI) or skin perfusion pressure.

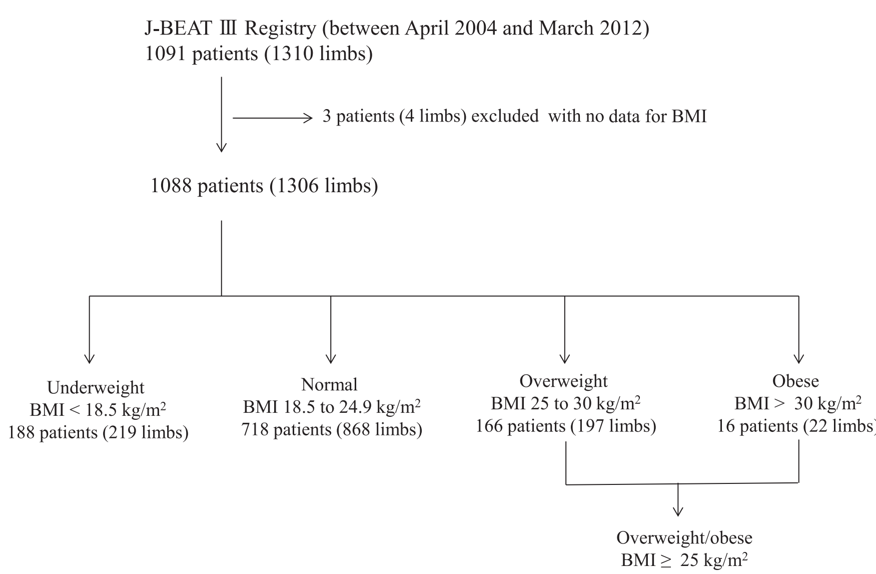


Figure 1. Patient flow charts. A total of 1091 consecutive patients (1310 limbs) who underwent endovascular treatment for isolated infrapopliteal artery lesions were identified retrospectively. Three patients (4 limbs) were excluded because they had no data for body mass index (BMI). The patients were divided into three groups based on BMI <18.5 kg/m^2 (underweight, 188 patients, 219 limbs), 18.5 to 24.9 kg/m^2 (normal weight, 718 patients, 868 limbs), and >25.0 kg/m^2 (overweight/obese, 182 patients, 219 limbs).

Study endpoints

The primary endpoint was overall survival. The secondary endpoint was freedom from major adverse limb events (MALE). Data from patients with normal BMI were used as a reference for comparison of mortality and freedom from MALE with those in the underweight and overweight/obese groups.

Definitions

CLI was defined as Rutherford category 4, 5, or 6. Isolated infrapopliteal artery lesions were detected by digital subtraction angiography. Patients with iliofemoral lesions with significant stenosis (>75% by angiography) or chronic total occlusion were excluded. MALE were defined as above the ankle amputation or any repeat revascularization of the index limb. Hypertension was defined as requiring treatment with oral antihypertensive agents or as systolic blood pressure >140 mmHg. Dyslipidemia was defined as requiring treatment with statins or a low density lipoprotein (LDL) cholesterol >140 mg/dL. Diabetes mellitus was defined as HbA1c >6.5%, spot glucose >200 mg/dL, or ongoing treatment with oral hypoglycemics and/or insulin injections. Coronary artery disease (CAD) was defined as stable angina or a history of percutaneous coronary intervention, coronary artery bypass graft surgery, or myocardial infarction. Heart failure was defined based on a history of hospital admission for heart failure or current heart failure symptoms. Aortic valve stenosis was defined as more than grade 3 severity measured by echocardiography. Cerebrovascular disease (CVD) was defined as a history of stroke or cerebral hemorrhage. Renal failure was defined as an estimated glomerular filtration rate <30 mL/min/1.73 m^2. Chronic obstructive pulmonary disease (COPD) was defined as ongoing or previous treatment for COPD or FEV1 <70% predicted. Anemia was defined as hemoglobin <13 g/dL for males and <11 g/dL for females. A Trans-Atlantic Inter-Society Consensus (TASC) 2000 D classification was defined as tibial or peroneal occlusions >2 cm or diffusely diseased tibial or peroneal vessels. Below the knee runoff was determined by digital subtraction angiography before EVT.

Statistical analysis

Data for the normal BMI (reference) group were compared with those for the underweight and overweight/obese groups. Continuous variables are reported as means with standard deviation or medians with first and third quartiles, and are compared by unpaired *t* tests. Categorical variables are shown as numbers with percentages and are compared by the χ^2 test when appropriate or by Fisher's exact test. Event-free survival curves were calculated using the Kaplan—Meier method and compared by log-rank test. Subgroup analysis was performed based on established factors associated with mortality of patients with CLI to test the interaction between BMI and other factors. The hazard ratio (HR) and confidence interval (CI) for independent factors in Cox univariate analysis were calculated to determine suitability for inclusion in a Cox multivariate model (step-up procedure using the likelihood ratio). Factors with $p < .5$ in univariate analysis were used in multivariate analysis. Individual differences were considered to be significant at $p < .05$. All statistical analyses were performed using commercial software (JMP version 10.0; SAS Institute, Cary, NC, USA).

RESULTS

Patient and lesion characteristics

The characteristics of the patients are shown in Table 1. The patients had a mean age of 72 ± 10 years (range: 39—99 years). Underweight patients were more frequently female and non-ambulatory; had higher rates of aortic valve stenosis and Rutherford category 5 or 6; lower rates of hypertension and diabetes; and lower levels of serum triglyceride and albumin compared with patients with normal BMI. Overweight/obese patients had a higher prevalence of diabetes and higher levels of triglyceride, and were also younger than normal BMI patients. Among all 1088 patients, almost half had CAD, 73% had diabetes mellitus (predominantly Type 2), and 66% were in renal failure. The target lesions were mostly TASC 2000 D grade and had poor below the knee runoff, and 70% were chronic total occlusions. There were no major differences in lesion characteristics among the three groups (Supplementary Table).

Causes of death

The median follow up period was 1.5 years (range: 1 month-8.7 years); 35% (378/1088) of the patients died during this period. All cause mortality in overweight/obese patients was significantly lower than that in patients with normal BMI (23% [42/182] vs. 33% [238/718], $p < .01$), whereas that of underweight patients was significantly higher than that in normal BMI patients (52% [98/188] vs. 33% [238/718], $p < .001$). Cardiovascular death accounted for 38% (142/378) of all deaths and this rate did not differ significantly among the groups. Infection accounted for 31% (119/378) of all deaths and also did not differ significantly among the groups (Table 2).

Endpoints

Primary endpoints are presented as Kaplan—Meier curves in Fig. 2. The overall 3 year survival rates were 33.3%, 61.2%, and 69.8% in underweight, normal BMI, and overweight/obese patients, respectively. The rate was significantly lower in underweight patients and significantly higher in overweight/obese patients compared with patients with normal BMI (both $p < .0001$). Secondary endpoints are shown as Kaplan—Meier curves in Fig. 3. The rates for 3-year freedom from MALE were 36.4%, 45.4%, and 52.3%, respectively, and did not differ significantly among the groups ($p = .32$).

Subgroup analysis using Cox univariate and multivariate analyses

No interaction was found that had an effect on multivariate analysis of all cause mortality in subgroup analysis

Table 1. Patient characteristics according to BMI category.

	BMI, kg/m^2 All (n = 1088)	Underweight <18.5 (n = 188)	Normal(Reference) 18.5 to 24.9 (n = 718)	Overweight/obese ≥25 (n = 182)
Patient characteristics				
Age, yrs	72 ± 10	73 ± 9	72 ± 10	68 ± 10†
≥ 80, n (%)	247 (23)	47 (25)	175 (24)	25 (14)†
Male, n (%)	756 (69)	117 (62)*	527 (73)	112 (62)†
Hypertension, n (%)	801 (74)	125 (66)*	534 (74)	142 (78)
Dyslipidemia, n (%)	452 (42)	64 (34)	299 (42)	89 (49)
Diabetes mellitus, n (%)	799 (73)	117 (62)*	533 (74)	149 (82)†
HbA_{1c} (%)	6.3 ± 1.5	5.9 ± 1.3*	6.3 ± 1.4	6.8 ± 1.7†
>6.4—8.4 %	319 (29)	41 (22)*	215 (30)	63 (35)
≥8.4 %	105 (10)	11 (6)	63 (9)	31 (17)†
Insulin therapy, n (%)	321 (37)	39 (27)*	213 (38)	69 (45)
History of smoking, n (%)	384 (35)	61 (32)	261 (36)	62 (34)
CAD, n (%)	543 (49)	97 (52)	352 (49)	94 (52)
Heart failure, n (%)	218 (27)	42 (30)	141 (27)	35 (24)
Aortic valve stenosis, n (%)	91 (9)	24 (14)*	58 (9)	9 (5)
CVD, n (%)	257 (24)	38 (20)	185 (26)	34 (19)
Renal failure, n (%)	713 (66)	124 (66)	481 (67)	108 (59)
Hemodialysis, n (%)	669 (61)	117 (62)	452 (63)	100 (55)
COPD, n (%)	93 (9)	23 (12)	57 (8)	13 (7)
LDL-cholesterol (mg/dL)	91 ± 32	88 ± 32	91 ± 32	97 ± 32†
Triglyceride (mg/dL), median (25, 75%)	101 (77, 139)	89 (64, 118)*	102 (77, 140)	121 (85, 173)†
Serum albumin (mg/dL)	3.6 ± 0.6	3.4 ± 0.6*	3.6 ± 0.6	3.6 ± 0.6
<3.0 g/dL, n (%)	168 (15)	39 (21)*	105 (15)	24 (13)
Anemia, n (%)	770 (71)	143 (76)	518 (72)	109 (61)†
Hemoglobin <8.0 g/dL, n (%)	36 (3)	9 (5)	23 (3)	4 (2)
CRP (mg/dL) median (25, 75%)	0.8 (0.2, 3.1)	1.2 (0.4, 3.1)	0.7 (0.2, 3.0)	0.7 (0.2, 3.3)
>3.0 mg/dL, n (%)	274 (25)	49 (26)	178 (25)	47 (26)
Drugs				
Aspirin, n (%)	860 (79)	138 (73)	572 (80)	150 (82)
Thienopyridine derivatives, n (%)	379 (35)	56 (30)	249 (35)	74 (41)
Cilostazol n, (%)	539 (50)	96 (51)	360 (50)	83 (46)
Anticoagulants, n (%)	222 (20)	43 (23)	152 (21)	27 (15)
Statins, n (%)	246 (23)	34 (18)	158 (22)	54 (30)
Beta-blockers n (%)	162 (20)	27 (19)	107 (20)	28 (19)
Lower limb characteristics				
Non-ambulatory, n (%)	432 (40)	90 (48)*	282 (39)	60 (33)
Rutherford classification				
4	226 (21)	25 (13)	152 (21)	49 (30)
5	566 (52)	105 (56)	375 (52)	86 (47)
6	296 (27)	58 (31)	191 (27)	47 (26)
ABI				
≥ 0.9, n (%)	339 (33)	46 (26)	224 (33)	69 (39)
<0.4, n (%)	49 (5)	9 (5)	34 (5)	6 (3)

Underweight to normal (reference): *$p < .05$.Overweight / obese to normal (reference): $^\dagger p < .05$.

using known factors associated with mortality of patients with CLI (Table 3). Potential risk factors and HRs for all cause mortality are shown in Table 4. Age, gender, BMI <18.5 or >25 kg/m^2, dyslipidemia, diabetes mellitus, HbA1c, CAD, heart failure, aortic valve stenosis, CVD, renal failure, hemodialysis, COPD, LDL-cholesterol, triglyceride levels, serum albumin <3.0 g/dL, hemoglobin <8 g/dL, C-reactive protein (CRP) >3.0 mg, medication with anticoagulants or statins, non-ambulatory status, Rutherford 5 or 6 classification, and ABI >0.9 or <0.4 were significant factors associated with overall survival. A Cox multivariate model (step-up procedure using the likelihood ratio) indicated that age, BMI <18.5 kg/m^2, heart failure, aortic valve stenosis, renal failure, triglyceride level, serum albumin <3.0 g/dL, medication with anticoagulants, non-ambulatory status, and a Rutherford 6 classification were significant factors associated with overall survival.

DISCUSSION

The major findings of this study are that (1) BMI has a complex relationship with 3 year overall mortality in patients with CLI after EVT for isolated infrapopliteal artery

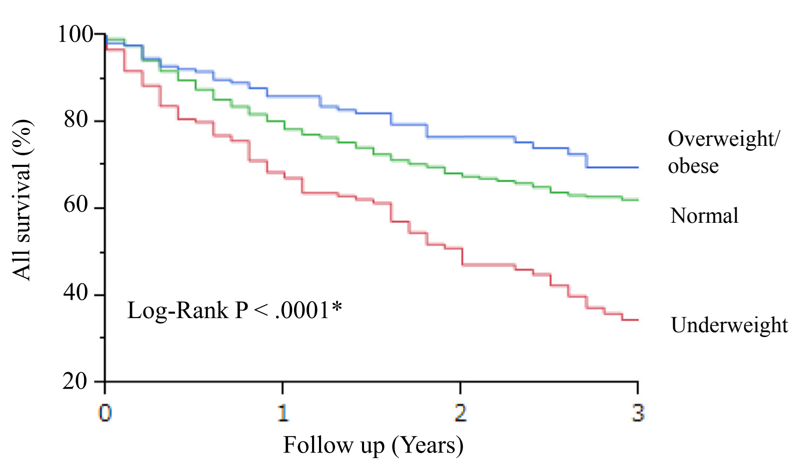
Table 2. Cause of death according to BMI category.

	BMI, kg/m^2 All (n = 1088)	Underweight <18.5 (n = 188)	Normal (Reference) 18.5 to 24.9 (n = 718)	Overweight/obese ≥25 (n = 182)
All causes, *n* (%)	378 (35)	98 (52)*	238 (33)	42 (23) †
Cardiovascular death, *n* (%)	142 (38)	41 (42)	86 (36)	15 (36)
Myocardial infarction, *n* (%)	23 (6)	5 (5)	17 (7)	1 (2)
Heart failure, *n* (%)	69 (18)	22 (22)	41 (17)	6 (14)
Dysrhythmia, *n* (%)	15 (4)	5 (5)	7 (3)	3 (7)
Sudden death, *n* (%)	27 (7)	4 (4)	19 (8)	4 (9)
Aortic stenosis, n (%)	7 (2)	5 (5)*	1 (0.4)	1 (2)
Pulmonary embolism, *n* (%)	1 (0.2)	0 (0)	1 (0.4)	0 (0)
Cerebrovascular death, *n* (%)	19 (5)	3 (3)	10 (5)	6 (14) †
Cerebral infarction, *n* (%)	14 (4)	1 (1)	8 (3)	5 (12) †
Cerebral hemorrhage, *n* (%)	5 (1)	2 (2)	2 (0.8)	1 (2)
Other vascular death, *n* (%)	7 (2)	1 (1)	5 (2)	1 (2)
Nonvascular death, *n* (%)	209 (55)	53 (54)	136 (57)	20 (48)
Cancer, *n* (%)	20 (5)	6 (6)	13 (5)	1 (5)
Infection, *n* (%)	119 (31)	31 (32)	75 (32)	13 (31)
Sepsis, *n* (%)	73 (19)	14 (14)	50 (21)	9 (21)
Pneumonia, *n* (%)	38 (10)	16 (16)*	18 (8)	3 (10)
Other infection, *n* (%)	8 (2)	1 (1)	6 (3)	1 (2)
Gastrointestinal bleeding, *n* (%)	9 (2)	1 (1)	8 (3)	0 (0)
Others, *n* (%)	15 (4)	7 (7)	7 (3)	1 (2)
Unknown, *n* (%)	37 (10)	7 (7)	26 (11)	4 (10)

Sudden death: unobserved death that assumed to be related to a cardiovascular event.Underweight to normal (reference): *p < .05.Overweight / obese to normal (reference): †p < .05.

lesions; (2) this relationship was seen at 1 year follow up and became clearer over time; and (3) underweight patients with CLI have an extremely poor prognosis (overall 3 year survival of 33.3%).

An overweight/obesity status has been associated with development of cardiovascular disease in the general population and the prevalence has increased in recent years.[12] These conditions may also be associated with excess cardiovascular mortality in long-term outcomes.[13] Current guidelines for management of cardiovascular disease emphasize the importance of weight reduction for all overweight and obese patients for prevention and

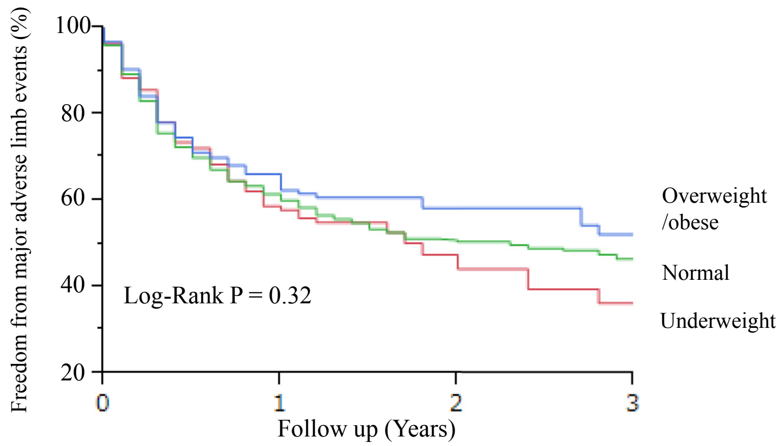


Patients at risk (survival rate ± SE* %)

	0	1	2	3
Underweight	188	102 (67.4±4)	54 (47.4±4)	24 (33.3 ±5)
Normal	718	465 (78.6±2)	276 (67.8±2)	156 (61.2 ±2)
Overweight/ obese	182	128 (86.1±3)	68 (76.8±4)	44 (69.8 ±4)

*SE: Standard error

Figure 2. Kaplan–Meier curves for overall survival according to body mass index (BMI) category. The 3 year overall survival rates were 33.3%, 61.2%, and 69.8% in underweight, normal, and overweight/obese patients, respectively. Compared with patients of normal weight, the 3 year survival rate was significantly lower in underweight patients and significantly higher in overweight/obese patients (both p < .0001).



Limbs at risk (event-free rate ± *SE %)

	0	1	2	3
Underweight	219	65 (57.9±4)	29 (44.3±5)	10 (36.4±6)
Normal	868	324 (60.1±2)	153 (50.6±2)	81 (45.4±2)
Overweight /obese	219	89 (62.6±4)	44 (58.4±4)	25 (52.3±5)

*SE: Standard error

Figure 3. Kaplan—Meier curves for major adverse limb events (MALE) according to body mass index (BMI) category. The 3 year rates of freedom from MALE were 36.4%, 45.4%, and 52.3% in the underweight, normal weight, and overweight/obese groups, respectively, and did not differ significantly among the groups ($p = .32$).

treatment.[14] However, longitudinal studies indicate that overweight and obese patients with established cardiovascular disease have a more favorable long-term prognosis.[1—3] This relationship has also been found in patients with peripheral arterial disease (PAD). Thus, Galal et al. followed 2392 patients with PAD after major vascular surgery, and found a significantly lower 4.4 year mortality in overweight patients (HR 0.73; 95% CI 0.64—0.84) and obese patients (HR 0.68; 95% CI 0.53—0.86) compared with underweight patients (HR1.42; 95% CI 1.00—2.01).[15] Other studies have found similar results.[4,5] However, this inverse association, which has been termed the "obesity paradox," has only been linked to patients with claudication and those requiring lower extremity revascularization or amputation.

Consistent with these results, the present findings show a clear complex relationship between BMI and mortality in patients with CLI. In the current study, patients with CLI who had isolated infrapopliteal artery lesions and underwent EVT as primary therapy were assessed. EVT for such lesions is not inferior to bypass surgery in long-term outcomes,[16,17] but bypass surgery remains the first line treatment for revascularization in patients with CLI in clinical practice. Physicians tend to select EVT for patients with a poor general condition who are high risk for general anesthesia. Therefore, the clinical characteristics in this study were more complicated than those in previous studies, including high rates of elderly patients (mean age 72 ± 10 years; 23% octogenarians), non-ambulatory cases (40%), and underlying diseases (heart failure 27%, coronary artery disease 49%, cerebrovascular disease 24%). Most patients also had diabetes (73%, predominantly Type 2), renal failure requiring hemodialysis (61%), and complicated infrapopliteal artery lesions that were occlusive and showed poor below the knee runoff on angiography. Underweight patients comprised 17% of the study population, whereas only 1% were obese. Interestingly, this distribution is opposite to that in studies in Western countries.[4,7,8,15] The complicated clinical characteristics may have contributed to the distribution in the current study, in addition to ethnic differences. Kumakura et al. found similar data in a Japanese cohort, in which 1.7% (11/652) of patients with PAD were obese,[5] and thus this distribution may be characteristic of Asian patients with PAD.

Age (per 10-year increment), HR 1.22 (95% CI 1.07—1.40); BMI <18.5 kg/m^2, HR 1.58 (95% CI 1.17—2.14); heart failure, HR 1.49 (95% CI 1.14—1.93); aortic valve stenosis, HR 1.57 (95% CI 1.05—2.36); renal failure, HR 2.17 (95% CI 1.62—2.92); serum albumin <3 g/dL, HR 1.62 (95% CI 1.19—2.20); medication with anticoagulants, HR 1.47 (95% CI 1.10—1.96); and non-ambulatory status, HR 2.26 (95% CI 1.73—2.96) emerged as negative factors associated with all cause mortality in a Cox multivariate model. These predictors are similar to those found in previous studies, except for anticoagulant therapy. Use of anticoagulants in patients with renal failure (including those undergoing hemodialysis) is controversial because of the increased risk of hemorrhage. The high prevalence of renal failure in the present study may be related to this result. At the same time, triglyceride levels (per 10 mg/dL) had a protective effect on all cause mortality, HR 0.97 (95% CI 0.95—0.996). A previous report[5] showed a positive relationship between BMI and triglyceride in patients with PAD. These authors suggested that malnutrition, represented by low triglycerides, may be a cause of increased risk in patients with lower BMI. This finding accords with the present results.

Table 3. Subgroup analysis based on factors associated with mortality of patients with CLI.

	n	HR	95 % CI Upper	Lower	*p*-value
Total					
Underweight	188	1.95	1.54	2.47	<.001
Normal	718	1.00	reference		
Overweight/obese	182	0.66	0.47	0.91	.01
Age					
Age < median					
Underweight	81	1.89	1.33	2.70	<.001
Normal	350	1.00	reference		
Overweight/obese	112	0.66	0.43	1.03	.07
Age ≥ median					
Underweight	107	2.01	1.47	2.76	<.001
Normal	368	1.00	reference		
Overweight / obese	70	0.69	0.42	1.14	.145
Gender					
Male					
Underweight	117	2.11	1.56	2.85	<.001
Normal	527	1.00	reference		
Overweight/obese	112	0.75	0.50	1.12	.16
Female					
Underweight	71	1.66	1.12	2.45	.01
Normal	191	1.00	reference		
Overweight/ obese	70	0.50	0.28	0.90	.02
Ambulatory Status					
Non-ambulatory					
Underweight	90	1.72	1.27	2.34	<.001
Normal	282	1.00	reference		
Overweight/obese	60	0.86	0.55	1.32	.48
Ambulatory					
Underweight	98	2.04	1.40	2.97	<.001
Normal	436	1.00	reference		
Overweight/obese	122	0.60	0.36	0.99	.047
Albumin Level					
<3.0 g/dL					
Underweight	39	1.97	1.23	3.15	.005
Normal	105	1.00	reference		
Overweight/obese	24	0.82	0.40	1.67	.59
≥ 3.0 g/dL					
Underweight	149	1.89	1.44	2.48	<.001
Normal	613	1.00	reference		
Overweight/obese	158	0.64	0.44	0.93	.64
Heart failure					
No					
Underweight	99	1.95	0.40	2.71	<.001
Normal	391	1.00	reference		
Overweight/obese	108	0.73	0.48	1.12	.15
Yes					
Underweight	42	1.90	0.40	2.71	<.001
Normal	141	1.00	reference		
Overweight/obese	35	0.41	0.20	0.85	.02
Aortic valves stenosis					
No					
Underweight	144	1.79	1.36	2.35	<.001
Normal	599	1.00	reference		
Overweight/obese	164	0.62	0.43	0.88	.008
Yes					
Underweight	24	2.03	1.12	3.68	.02
Normal	58	1.00	reference		

Continued

Table 3-*continued*

	n	HR	95 % CI Upper	Lower	*p*-value
Overweight/obese	9	0.86	0.30	2.48	.78
Renal failure					
Yes					
Underweight	124	1.97	1.51	2.59	<.001
Normal	481	1.00	reference		
Overweight/obese	108	0.66	0.44	0.98	.04
No					
Underweight	64	2.06	1.30	3.34	.003
Normal	237	1.00	reference		
Overweight/ obese	74	0.81	0.45	1.47	.49

HR: hazard ratio, CI: confidence interval

Although BMI >25 kg/m^2 was not significantly associated with mortality in the Cox multivariate model but was significantly associated with mortality in the Cox univariate model, the Kaplan—Meier curves and 0.73 of adjusted odds ratio support BMI >25 kg/m^2 as a possible positive predictor of survival.

The 3 year overall survival of normal weight patients was 61.2%, similar to that of 65% for all patients with CLI in a recent meta-analysis. That of overweight/obese patients was slightly higher (69.8%), whereas that of underweight patients was extremely low (33.3%). This complex relationship between BMI and all cause mortality was seen at 1 year follow up and has become clearer over time. These findings emphasize the markedly poor prognosis of underweight patients among all patients with CLI. Although underweight patients had a higher incidence of severe manifestations associated with mortality of patients with CLI in their baseline characteristics (Table 1), subgroup analysis showed a complex relationship of BMI with mortality in all subgroups (Table 3), lessening the probability that other differences in baseline characteristics had a large impact. In contrast, freedom from MALE at 3 years did not differ significantly among the three groups.

The pathophysiology of the adverse effects of low BMI on mortality is unclear. Death because of aortic valve stenosis and pneumonia were significantly higher in underweight patients (Table 2), but all other causes of death did not differ significantly among the BMI categories. Increases in both cardiovascular and non-cardiovascular death have been reported in underweight patients with heart failure[18] or coronary artery disease.[19] Similar results were found in patients with CLI, with most of the causes of death becoming more frequent as BMI decreased. Several investigators[20,21] have noted that the adverse effect of low BMI on mortality is manifest only in patients with cardiorespiratory failure. The high mortality in underweight patients with CLI who have severe systemic comorbidities and poor general condition could be associated with very low levels of cardiorespiratory failure. More than half of the deaths in patients with CLI are reported to be caused by cardiovascular events.[6] In the present study, cardiovascular events were the major cause of death, at 38%; followed by infection, which had a notably high rate of 31%. These

Table 4. Cox univariate and multivariate (step-up procedure using likelihood ratio) analysis

	n	Univariate				Multivariate			
		HR	95 % CI Upper	Lower	*p*-value	HR	95 % CI Upper	Lower	*p*-value
Age (per 10 yrs)	1088	1.18	1.07	1.31	.001	1.22	1.07	1.40	.004
Male (vs. female)	1088	0.90	0.73	1.12	.34	-			
BMI									
<18.5 kg/m^2		1.95	1.54	2.47	<.001	1.58	1.17	2.14	.003
18.5 to 24.9 kg/m^2		1.00	reference			1.00	reference		
≥25 kg/m^2		0.66	0.47	0.91	.01	0.88	0.59	1.32	.54
Hypertension	1088	0.96	0.76	1.20	.70	-			
Dyslipidemia	1088	0.66	0.53	0.81	<.001	n.e.			
Diabetes mellitus	1088	0.80	0.64	0.99	.04	n.e.			
HbA1c (per 1 %)	1087	0.92	0.86	0.996	.04	n.e.			
Insulin therapy	863	0.99	0.79	1.25	.94	-			
History of smoking	1088	0.93	0.75	1.16	.52	-			
CAD	1088	1.41	1.14	1.73	.001	n.e.			
Heart failure	816	1.72	1.36	2.17	<.001	1.49	1.14	1.93	.003
Aortic valve stenosis	998	2.06	1.52	2.78	<.001	1.57	1.05	2.36	.03
CVD	1088	1.69	1.36	2.09	<.001	n.e.			
Renal failure	1088	2.01	1.59	2.55	<.001	2.17	1.62	2.92	<.001
Hemodialysis	1088	1.97	1.57	2.47	<.001	n.e.			
COPD	1088	1.85	1.35	2.52	<.001	n.e.			
LDL-cholesterol (per 10 mg/dL)	1049	0.91	0.88	0.94	<.001	n.e.			
Triglycerides (per 10 mg/dL)	1088	0.96	0.94	0.98	<.001	0.97	0.95	0.996	.02
Serum albumin <3.0 g/dL	1081	2.24	1.77	2.85	<.001	1.62	1.19	2.20	.002
Hemoglobin <8.0 g/dL	1082	2.19	1.38	3.47	.001	n.e.			
CRP >3.0 mg/dL	1065	1.83	1.48	2.28	<.001	n.e.			
Aspirin	1088	1.25	0.97	1.62	.09	n.e.			
Thienopyridine derivatives	1088	0.83	0.67	1.03	.10	n.e.			
Cilostazol	1088	0.92	0.75	1.12	.41	-			
Anticoagulants	1088	1.54	1.23	1.94	<.001	1.47	1.10	1.96	.009
Statins	1088	0.68	0.52	0.89	.004	n.e.			
Beta-blocker	824	1.19	0.90	1.58	.23	-			
Non-ambulatory	1088	3.01	2.45	3.70	<.001	2.26	1.73	2.96	<.001
Rutherford classification	1088								
4		1.00	reference			1.00	reference		
5		1.71	1,26	2,31	.001	1.13	0.77	1.68	.53
6		2.94	2.15	4.03	<.001	1.83	1.20	2.78	.005
ABI		1040							
≥0.9		0.68	0.53	0.86	.002	n.e.			
0.4–0.9		1.00	reference						
<0.4		1.44	0.93	2.23	.10	n.e.			

HR: hazard ratio, CI: confidence interval, n.e.: number excluded by step-up procedure

results may be explained by the high prevalence of tissue loss in the present cohort.

Limitations

The study had a retrospective design despite use of a prospectively maintained database. Also, the cohort excluded patients with CLI who underwent bypass surgery or medical therapy. Although there was an opportunity to recognize patients with severe COPD because all the patients in this study were treated in the hospital at least once, and a full medical history was taken at that time, pulmonary function tests were not performed in all patients, which may have resulted in an underestimate of the prevalence of COPD (9%) in the present study compared with previous studies.[15] Classification according to BMI is based only on weight relative to height, and no data were available for body fat distribution, such as waist circumference or waist to hip ratio, which may be better predictors of cardiovascular events. Also, changes in body weight over time were not taken into account so the relationship of weight change with outcomes remains to be elucidated.

CONCLUSIONS

BMI was found to be related in a complex fashion to mortality in patients with CLI who underwent EVT for isolated infrapopliteal artery lesions. This relationship was observed at 1 year follow up and became clearer over time. Underweight patients with CLI had an extremely poor prognosis compared with those of normal BMI and overweight/obese patients with CLI. Underweight patients with

CLI had many factors associated with mortality, but low BMI emerged as a novel independent predictor of a poor prognosis.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2014.10.014

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