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Prognosis after Lower Extremity Amputation in Patients with Diabetes

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ABSTRACT

Objectives : To evaluate rates of mortality and second lower extremity amputation (LEA) in patients with diabetes and to investigate predictors of survival and second LEA.

Design : A hospital-based retrospective cohort study.

Patients : Forty-two patients with diabetes who had undergone LEA and 168 who had not at three university hospitals in Japan from 1993 through 1998.

Methods : Follow-up until January 1, 2000, with clinical information abstracted from medical records.

Results : The patients who had undergone LEA were 31 men and 11 women with a mean age of 65.2 years and an average duration of diabetes of 19.4 years. During follow-up, 13 patients died and 13 underwent a second LEA. The crude mortality and second-LEA rates per 1,000 patient-years were 112.5 (95% confidence interval : 51.3 to 173.7) and 257.8 (147.6 to 368.1), respectively. The standardized mortality ratio was 5.4 (2.9 to 9.3). Life-table analysis showed that 1-year cumulative risks of death and second LEA were 20.0% (7.6% to 32.4%) and 27.6% (12.9% to 42.2%), respectively. Multivariate Cox proportional hazard models showed hazard ratios of death of 5.1 (2.3 to 11.2), unadjusted, and 4.2 (1.7 to 10.2), adjusted, for age, sex, and known duration of diabetes, and 4.0 (0.9 to 17.3) further adjusted for a significant potential confounder among patients who had undergone LEA compared with those who had not. The co-morbidity remaining in the model was a history of stroke, with a relative risk of 4.6 (1.3 to 16.4). Mortality in patients undergoing LEA was significantly higher for those 60 years or older and those with a history of stroke. The second-LEA rate was significantly higher for patients receiving dialysis and patients with a history of stroke.

Conclusions : Patients with diabetes are at high risk for LEA. Primary prevention of LEA is extremely important. (Jikeikai Med J 2003 ; 50 : 131-40)

Key words : amputation, diabetic foot, mortality, second amputation

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INTRODUCTION

An estimated 6.9 million Japanese have diabetes[1]. Although some studies have found a low incidence of lower extremity amputation (LEA) in Japanese patients with diabetes[2], LEA severely decreases patients' quality of life. Outcomes in Japanese patients who have undergone LEA have been studied[3–7], but the rate of second LEA and its predictors have not been well documented. The aims of this study were to evaluate mortality and rates of second LEA in patients with diabetes and to investigate predictors of survival and of second LEA.

RESEARCH DESIGN AND METHODS

Subjects

The setting of this study was three hospitals affiliated with The Jikei University School of Medicine. Forty-two patients with diabetes who underwent LEA once were identified through a review of all 24,910 operation records of the divisions of orthopedics and the divisions of plastic and reconstructive surgery in these hospitals from January 1993 through June 1998. The level of LEA was classified as follows: digits other than the great toe, the great toe, through metatarsals, transmetatarsal joints, through the ankle or the tarsus, below the knee, through the knee, above the knee, and the hip and hindquarter. "Major amputation" was defined as amputation through the ankle or tarsus or above. Amputations were major in 25 patients and minor in 17 patients. History of diabetes was determined by a review of operation records and medical records.

A total of 18,934 patients with diabetes who had visited the outpatient clinic of the three hospitals at least once in the same year as the LEAs were performed were extracted, with permission of the university hospital, from electronic hospital records for insurance claims. Diabetes was confirmed by medical records. Patients who had undergone LEA were excluded. Of these patients with diabetes, 168 were randomly selected to yield a 1-to-4 ratio for comparison with 42 patients who had undergone LEA.

Prognostic factors

The duration of diabetes, treatments for diabetes, the presence of diabetic complications, and co-morbidities, including hypertension, coronary artery disease, and stroke, were abstracted from the medical records. Diabetic retinopathy was classified as the progression of retinopathy to proliferative diabetic retinopathy or as worse. Diabetic nephropathy was classified as requiring dialysis or not. Diagnoses of hypertension, coronary artery disease, and stroke were recorded. For patients who had not undergone LEA, information about diabetic complications was collected from medical records from within 1 year of the LEA in the corresponding patient; information about co-morbidities was collected from when the corresponding individuals received LEA.

Follow-up

To study rates of mortality and second LEA, follow-up was ended on the date of target events or on January 1, 2000, whichever was earlier. Information regarding whether the patient was alive or had undergone a second LEA was retrieved from medical records. If patients had transferred to other hospitals or clinics or had not visited the hospitals before January 1, 2000 for follow-up, they were sent a questionnaire asking about their present health status. Follow-up was completed for all subjects. To avoid ties in failure time, patients not undergoing LEA were randomly assigned a starting date for follow-up in the year when the corresponding patients underwent LEA.

The second-LEA rate included only second LEAs but not later ones, regardless of whether they were ipsilateral or contralateral.

Statistical analysis

Rates of mortality and second LEA were calculated as the numbers per 1,000 patient-years. Patient-years were calculated from the date of the first LEA to the closing date. Crude mortality rates were calculated for patients who had and had not undergone LEA. The standardized mortality ratios

for both groups were also calculated for comparison with the mortality rate of the general Japanese population in 1995[8]. The rates and ratios were calculated with a 95% confidence interval (CI)[9]. Life table analyses and log-rank tests were used.

To examine predictors of death and second LEA, log-rank tests were performed for variables of demographic characteristics, diabetic complications, and co-morbidities. Variables to be included in the final Cox model were selected with a stepwise procedure.

Statistical analysis of data was done with the SAS computer package (SAS Institute, Inc., Cary, NC, USA)[10]. The level of statistical significance was set at the type I error of 0.05.

Results

Patient characteristics

The 42 patients who had undergone LEA were 31 men and 11 women. The mean age and known diabetes duration at the start of follow-up were 65.2 years and 19.4 years, respectively. Patients who had undergone LEA tended to be older, to be males, and to have a shorter duration of known diabetes than did patients who had not undergone LEA (Table 1).

Mortality and second-LEA rates

Of the 42 patients who had undergone LEA, 13 died and 13 underwent a second LEA (Table 2) in the 115.6 patient-years of follow-up for survival and the 81.4 patient-years of follow-up for second LEA. For patients who had undergone LEA, the crude mortality

Table 1. Patient characteristics

	LEA	Non-LEA
n	42	168
Age (years)*	65.2±11.3	59.7±12.0
Sex (Male/Female)	31/11	105/63
Diabetes		
Known diabetes duration (years)*	19.4±11.3	9.7±8.6
Type of diabetes (Type 1/Type 2/Others or unknown)	0/37/5	4/160/4
Diabetes therapy (Diet/OHA/Insulin/Unknown)	3/9/22/8	34/69/53/12
Diabetic complications		
Retinopathy (PDR or worse/PPDR or better/Unknown)	14/12/16	29/67/72
Nephropathy (Dialysis/No dialysis/Unknown)	7/32/3	3/132/33
Co-morbidities		
Hypertension (Present/Not present/Unknown)	15/26/1	51/103/14
Coronary heart disease (Present/Not present/Unknown)	6/35/1	10/145/13
Cerebrovascular disease (Present/Not present/Unknown)	8/33/1	9/146/13
Level of amputation (Major/Minor)	25/17	N.A.

*mean±S.D.; OHA: Oral hypoglycemic agent; PDR: proliferative diabetic retinopathy; PPDR: preproliferative diabetic retinopathy

Table 2. Mortality and second-LEA rates

Mortality	LEA (*n*=42)	No LEA (*n*=168)
Observed patient-years for survival	115.6	542.5
Survival Status (Alive/Deceased/Unknown)	29/13/0	155/13/0
Crude mortality rates (/1,000 patient-years)	112.5 (51.3-173.7)	22.1 (9.6-34.6)
Adjusted mortality rates (/1,000 patient-years)	132.8 (14.5-251.1)	23.0 (10.5-35.5)
Standardized mortality ratio	5.4 (2.9-9.3)	1.4 (0.8-2.5)
Second LEA		
Observed patient-years for second LEA	81.4	N.A.
Second LEA (Yes/No/Unknown)	15/27/0	N.A.
Laterality (Ipsilateral/Contralateral)	9/4	N.A.
Second-LEA rate (/1,000 patient-years)	257.8 (147.6-368.1)	N.A.

*95% CI

and second-LEA rates for the entire follow-up period were 112.5 (95% C.I : 51.3 to 173.7) and 257.8 (147.6 to 368.1), respectively, per 1,000 patient-years. The standardized mortality ratios were 5.4 (2.9 to 9.3) (Table 2). Life-table analysis showed that the cumulative risks of death were 20.0% (7.6% to 32.4%) and 33.8% (18.7% to 48.8%), and those of second LEA were 27.6% (12.9% to 42.2%) and 43.2% (25.3% to 61.1%), respectively, for 1 and 3 years of follow-up (Fig. 1).

To exclude postsurgical mortality, the same analyses were performed excluding the 30 days immediately after the first LEA. The crude mortality rate and the second-LEA rate more than 30 days after the first LEA were 98.1 (40.1 to 156.0) and 371.2 (236.1 to 506.2), respectively, per 1,000 patient-years.

Patients who had undergone LEA had a significantly higher mortality rate than did patients who had not undergone LEA ($p<0.0001$; Fig. 1, upper panel). The unadjusted hazard ratio of death was 5.1 (95% CI : 2.3 to 11.2) using a Cox proportional hazard model. After adjusting for age, sex, and known duration of diabetes, the hazard ratio became 4.2 (1.7 to 10.2). After further adjusting for co-morbidities selected with a stepwise procedure, the relative risk of death was 4.0 (0.9 to 17.3) for patients who had undergone LEA compared with those who had not. The

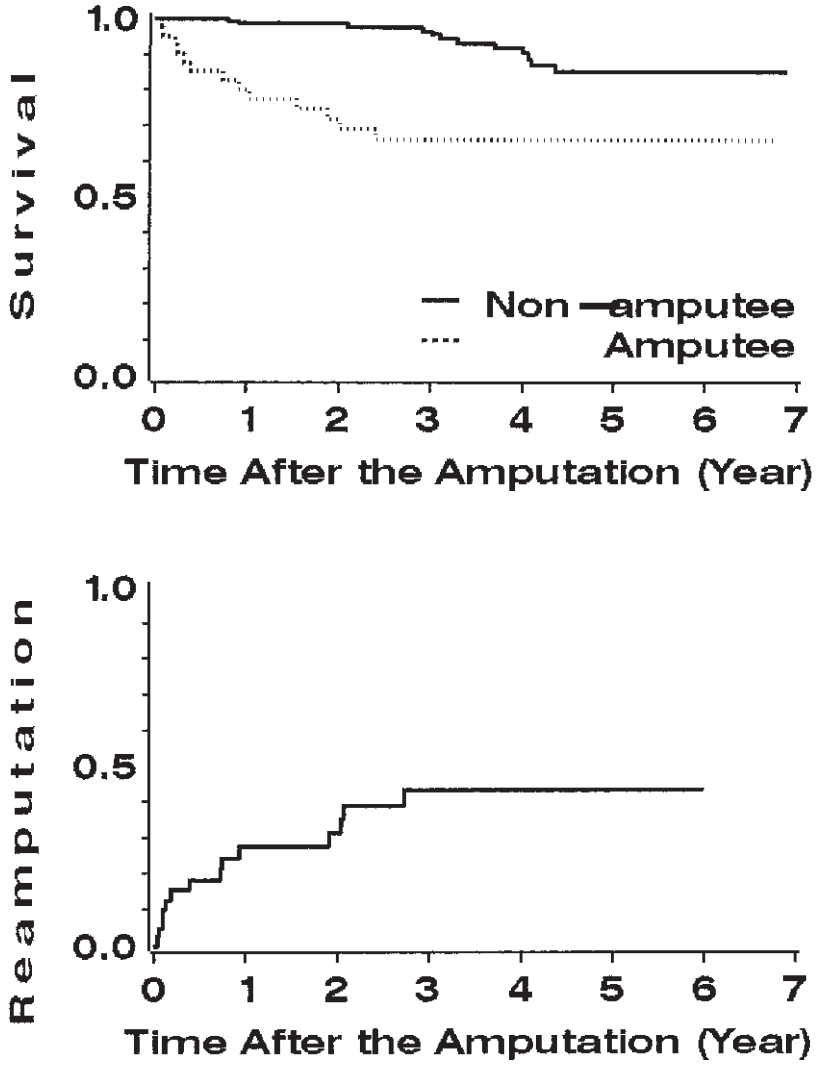

Fig. 1. Cumulative risk of death in patients with diabetes who had and had not undergone LEA (upper panel) and cumulative risk of second LEA (lower panel). The mortality rate was significantly higher in patients who have undergone LEA ($p<0.0001$).

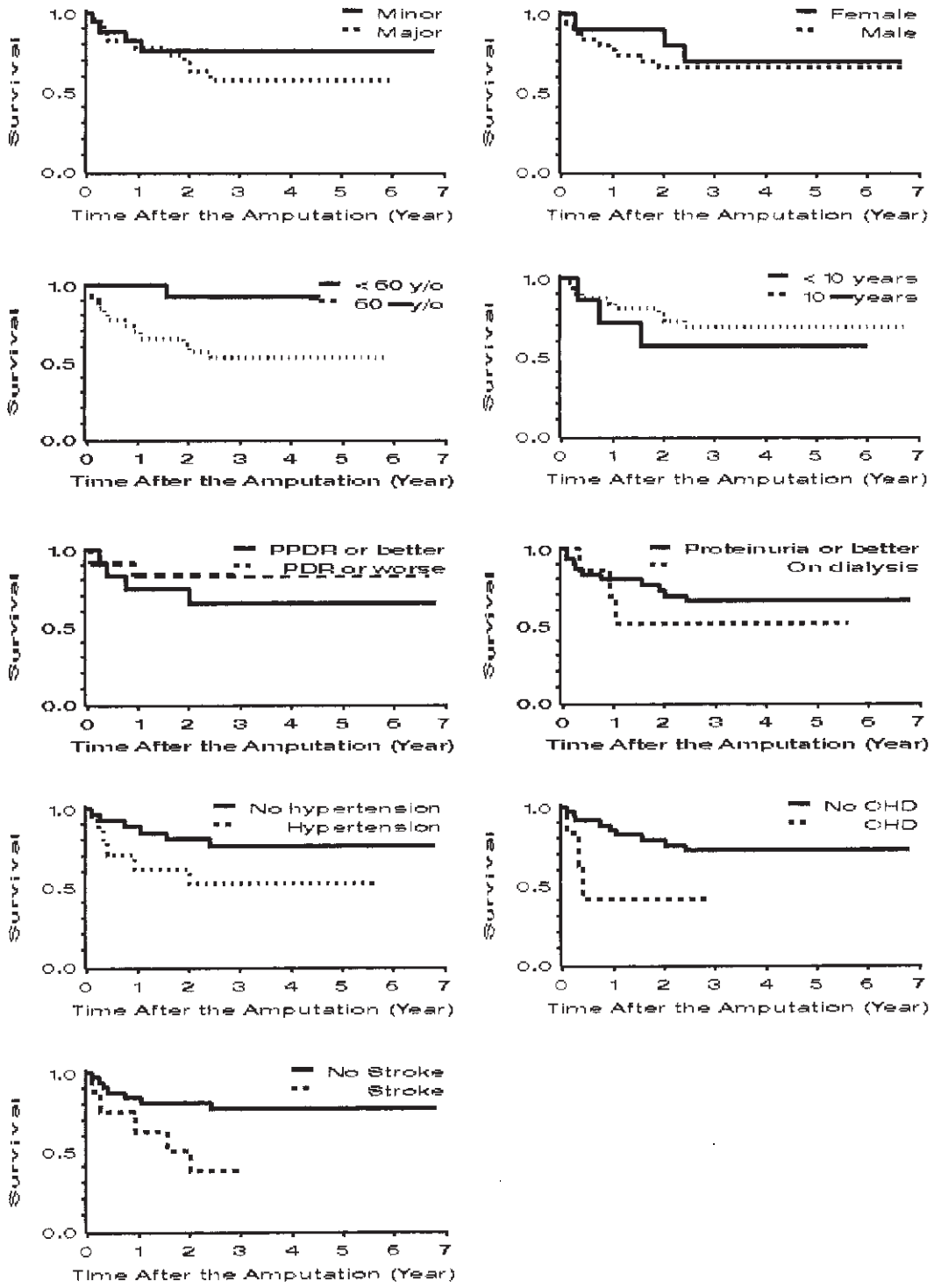

Fig. 2. The cumulative risk of death by characteristics in patients individuals who had undergone LEA. From the left to right, top to bottom, the survival curves are shown by : level of amputation, sex, age, duration of known diabetes, diabetic retinopathy, diabetic nephropathy, history of hypertension, history of coronary heart disease, and history of stroke. Mortality was significantly higher in patients 60 years or older ($p=0.02$) and in patients with a history of stroke ($p=0.03$). PPDR : preproliferative diabetic retinopathy ; PDR : proliferative diabetic retinopathy ; CHD : coronary heart disease.

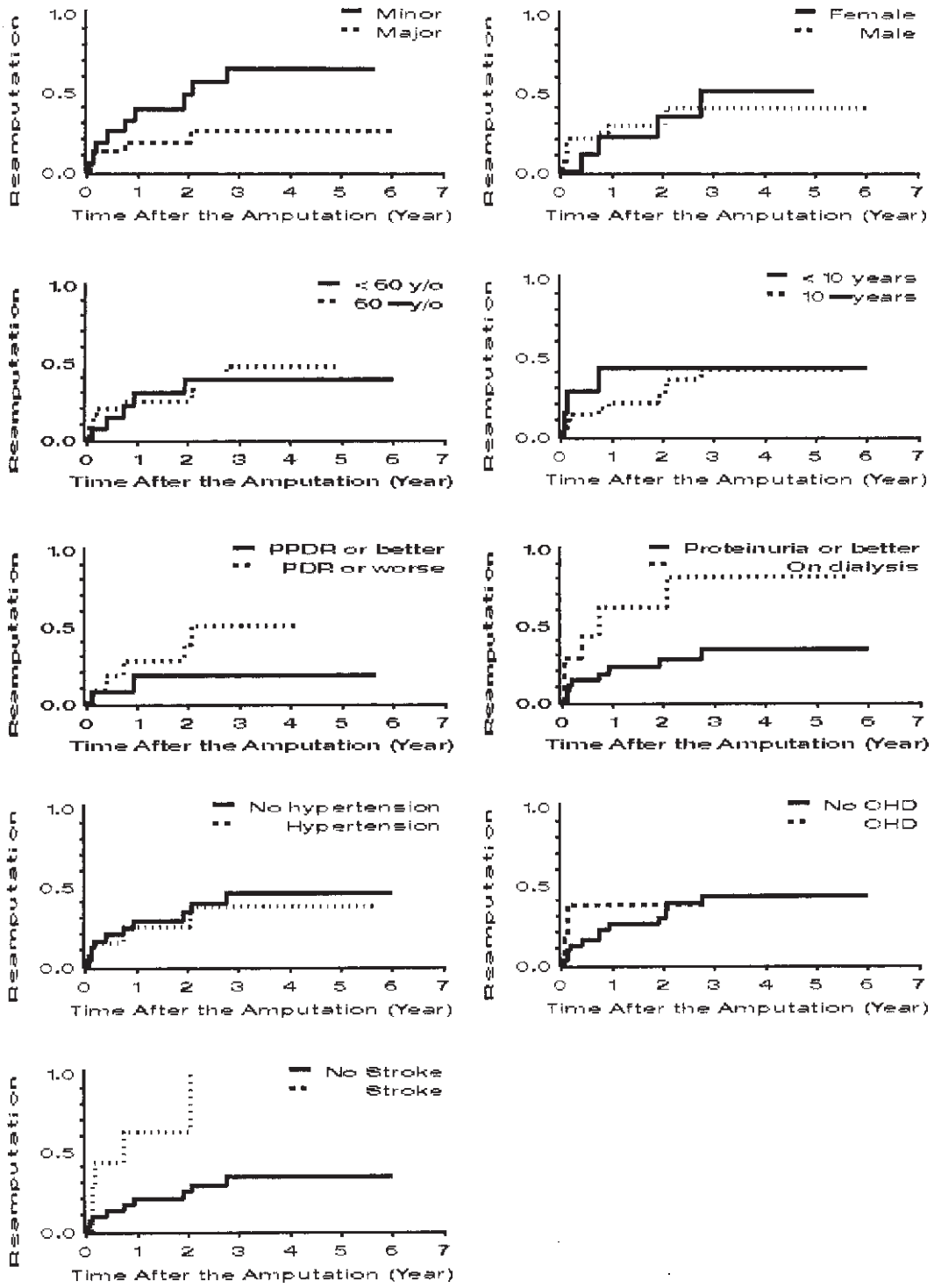

Fig. 3. The cumulative risk of second LEA by characteristics. From the left to right, top to bottom, the survival curves are shown by : level of amputation, sex, age, duration of known diabetes, diabetic retinopathy, diabetic nephropathy, history of hypertension, history of coronary heart disease, and history of stroke. Mortality was significantly higher in patients receiving dialysis ($p=0.01$) and in patients with a history of stroke ($p=0.03$). PPDR : preproliferative diabetic retinopathy ; PDR : proliferative diabetic retinopathy ; CHD : coronary heart disease.

co-morbidity remaining in the model was a history of stroke, with a relative risk of 4.6 (1.3 to 16.4). The same analysis restricted to the period after the 30th day from the first LEA produced similar results.

Predictors of death and second LEA

Life-table analysis showed that mortality rate after LEA was significantly higher in patients 60 years or older ($p=0.02$) and in patients with history of stroke ($p=0.03$, Fig. 2). The variables of age, sex, level of LEA, known diabetes duration, retinopathy, nephropathy, hypertension, coronary heart disease, and stroke were not selected with the stepwise procedure for a multivariate Cox proportional hazard model.

Life-table analysis showed that the second-LEA rate was significantly higher in patients receiving dialysis ($p=0.01$) and in patients with a history of stroke ($p=0.003$, Fig. 3). No variables of clinical characteristics showed statistical significance for a multivariate Cox proportional hazard model with the stepwise procedure.

Discussion

This study investigated the rates of mortality and second LEA in Japanese patients with diabetes who had undergone LEA. The 1- and 3-year cumulative risks of death were 20.0% and 33.8%, respectively. Previous studies of LEA in diabetes in various countries (Table 3) have consistently found a high risk of death, comparable to the results of the present study. We found that 1- and 3-year cumulative risks of second LEA were 27.6% and 43.2%, respectively, which were also comparable to findings of earlier studies (Table 4).

Although these data were essential for setting priorities for health policy and estimating the needs of facilities, they must be interpreted with caution.

Table 3. Studies since 1992 of mortality after LEA in patients with diabetes

Reference	Year*	Mortality rate		Location	Number of patients
Stewart[18]	1992	Median	44 months	Scotland	445
Deerochanawong[20]	1992	Median	22 months	U.K.	48
Eneroth[21]	1992	1-year	41%	Sweden	70
		2-year	51%		
Lee[13]	1993		55.5/1,000 py**	U.S.A.	156
Apelqvist[22]	1993	1-year	20%	Sweden	123
		3-year	41%		
		5-year	73%		
Lavery[23]	1996		36.3/1,000 py	The Netherlands	3,133
Lavery[24]	1997		32.9/1,000 py	U.S.A.	4,861
Ebskov[25]	1998	1-year	32%	Denmark	3,516
	1998	3-year	55%		
Pohjolainen[26]	1998	1-year	38%	Finland	287
		2-year	53%		
		5-year	80%		
Frykberg[27]	1998	Median	19 months	U.S.A.	27
Larsson[28]	1998	1-year	15%	Sweden	189
		3-year	38%		
		5-year	68%		
Faglia[29]	2001	1-year	~70%	Italy	27
		3-year	~50%		
Present study	2003	1-year	20.0%	Japan	42
		3-year	33.8%		

*Date of publication, **age-adjusted mortality rate, py : patient-years, ADA : American Diabetes Association

Table 4. Studies since 1992 of second-LEA rate in patients with diabetes

Reference	Year*	Laterality	Second-LEA rate		Location	Number of patients
Deerochanawong[20]	1992	Ipsilateral	3-year	32%	U.K.	48
		Contralateral	3-year	6%		
Larsson[28]	1998	Either	1-year	14%	Sweden	189
			3-year	30%		
			5-year	49%		
Faglia[29]	2001		3-year	0%	Italy	27
Present study	2003	Either	1-year	27.6%	Japan	42
			3-year	43.2%		

*Date of publication

First, prognosis might be strongly affected by the indication of surgical procedure, conservative therapy, and preventive care for the diabetic foot before or after LEA. Because this study was retrospective, decision making for LEA and other treatments was not standardized. Second, the prognosis may also be affected by the subjects' other characteristics, such as age. Finally, the definition of LEA and its outcome may not be comparative. Despite such a lack of comparability, on the basis of repeated observations of poor prognosis, we cannot overemphasize the importance of the problem ; as Logan said, "feet have hearts too"[11].

The relevant question then becomes to what extent is the poor prognosis due to LEA and to what extent to diabetes ? We found a standardized mortality ratio of 5.4, after a mean follow-up period of 2.8 years. Ebskov has reported mortality ratios of 8.4 for the first year and 4.1 for the second year after LEA[12]. Apelqvist et al. have reported mortality ratios of 5.0, 4.4, and 3.9 for the first, second, and third years after the first LEA[22]. The standardized mortality ratio is useful because it takes into account age- and sex-specific mortality in the general background population. We found that patients who had undergone LEA were 5.1 times more likely to die than were patients who had not undergone LEA. However, the difference in mortality was no longer significant after significant co-morbidity had been adjusted for. One interpretation of this result is that co-existing cardiovascular diseases contribute to the poor prognosis after LEA. Few previous reports[13,14] have provided such a comparison.

We found that the mortality rate after LEA was higher in patients 60 years or older or with a history of stroke and that the rate of second LEA was higher in patients receiving dialysis or with a history of stroke. Although these factors may also reflect on the indication of LEA, it is still useful for identifying patients at high risk for death after LEA. We did not find any differences in mortality or second-LEA rates between major and minor amputation, which have been suggested by other studies[14,15].

Our study had four major limitations : small sample size ; possible inaccuracy of clinically relevant information, including glycemic control ; lack of information on causes of death ; and its having been hospital-based. The small sample size was due, at least in part, to the low incidence of LEA in Japanese patients[16]. Our subjects were abstracted from a large number of operation records, which yielded the largest published series of Japanese patients with diabetes who had undergone LEA. Clinical information may not have been accurate because it was collected retrospectively. For example, glycemic control, which could be measured with glycosylated hemoglobin, was not analyzed, because glycosylated hemoglobin assay requires standardization[17]. However, this limitation is, again, hard to overcome. Because of the low incidence of LEA, prospective studies are impractical despite the possibility of providing more accurate information than do retrospective studies. In our study, we could not collect information about all causes of death. Other studies have suggested that major causes of death are cardiovascular diseases[14,18] and infection[18], but additional

studies of causes of death are needed. Because our study was performed at three university hospitals, bias may have been present and either overestimated prognosis owing to high quality of care or underestimated prognosis owing to referral of difficult cases.

Little data is available about diabetic foot problems in Asia[19]. Our description of mortality patterns and clinically significant results is the first step toward decreasing the rate of LEA in Japanese patients with diabetes.

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