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Mortality, Reamputation, and Preoperative Comorbidities in Patients Undergoing Dysvascular Lower Limb Amputation

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Background: Historically, mortality rates after major lower limb amputations (LLAs) have been very high. However, there are inconsistencies regarding the risk factors. The reamputation rate after major LLAs is largely unknown. The aim of this study is to report the 30-day and 1-year mortality and 1-year reamputation rates after major LLA and to identify potential risk factors.
Methods: An observational cohort study in which all patients undergoing dysvascular major LLA in 2012–2013 in 12 hospitals in the northern region of the Netherlands is included.
Results: Of total 382 patients, who underwent major LLA, 65% were male and the mean age (standard deviation [SD]) was 71.9 ± 12.5 years. Peripheral arterial disease was observed in 88% and diabetes mellitus (DM), in 56% of patients. No revascularization or prior LLA on the amputated side was observed among 26%, whereas 56% had no minor or major LLA on either limb before the study period. The 30-day and 1-year mortality rates were 14% and 34%, respectively. Patients aged 75–84 and >85 years had 3–4 times higher odds of dying within 1 year. Transfemoral amputations (odds ratio [OR], 2.2), history of heart failure (OR, 2.3), myocardial infarction (OR, 1.7), hemodialysis (OR, 5.7), immunosuppressive medication (OR, 2.8), and guillotine amputations (OR, 5.1) were independently associated with 1-year mortality. Twenty-six percent underwent ipsilateral reamputation within 1 year, for which no risk factors were identified.
Conclusions: The mortality rate in the first year after major LLA is high, particularly among those undergoing transfemoral amputations, which is likely to be indicative of more severe vascular disease. Higher mortality among the most elderly patients, those with more severe cardiac disease and who underwent hemodialysis reflects the frailty of this population. Interestingly, DM, revascularization history, and prior minor or major LLA were not associated with mortality rates.

INTRODUCTION

The vast majority of lower limb amputations (LLAs) is related to diabetes mellitus (DM) and peripheral arterial disease (PAD). These ‘‘dysvascular’’ amputations account for more than 90% of LLAs in the Western European countries.[1,2] LLAs are differentiated in minor and major amputations (i.e., ankle

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disarticulation and more proximal levels), with the latter being associated with more disability[3] and higher mortality rates.[4,5] Recent systematic reviews estimate the 30-day, 1-year, and 5-year mortality rates for major LLAs as 4–22%,[6] 47%,[7] and 52–80%,[5] respectively. Several studies indicate that older age, end-stage renal disease, and more proximal levels of amputations are associated with higher mortality rates.[5–7] The role of other comorbidities such as cardiovascular, pulmonary, and cerebrovascular diseases remains uncertain.[6] For example, cerebrovascular diseases were reported as being associated with higher mortality by some,[8,9] whereas others did not support this association and found different comorbidities as risk factors.[10] DM is observed among 40–50% of patients undergoing a major LLA,[11,12] but it remains unclear whether DM affects mortality rates among patients undergoing LLAs.[5] There is no consensus on whether DM and non-DM patients undergoing LLAs should be viewed as separate populations. Several recent studies report decreased incidence rates of major LLAs in the general and DM populations,[11–13] which may be attributed to improved treatment of PAD and DM in the past 2 decades.[14] Nonetheless, some patients undergo multiple minor and major amputations during their life time. Few studies have reported reamputation rates after major LLAs,[4,15] as most studies have focused on minor LLAs (including partial foot amputations)[16,17] and often report on DM populations only.[18,19]

We hypothesize that multivariate analysis of mortality rates with a larger set of comorbid conditions will improve the contemporary understanding of mortality risk, in the frail population that is confronted with dysvascular amputations. In addition, details pertaining to revascularization attempts, previous LLAs, the sequence of the performed amputations, and subsequent reamputations should be taken into account. The aim of this study is to report the 30-day and 1-year mortality and 1-year reamputation rates after major LLAs and to identify potential risk factors for these outcomes.

METHODS

Setting and Population

Data were collected retrospectively in 12 hospitals – one academic and 11 general hospitals – in the northern region of the Netherlands, with a population of 1.7 million inhabitants.[20] In the Netherlands, general practitioners are tasked with providing primary medical care for residents registered in their practices. In 2012, the average pool of registered residents per general practitioner was 2,350 persons.[20] Patients are referred for specialist care in general hospitals or to the regional academic hospital for specialist care of higher complexity (after consultation with the general hospital). DM care is provided by an endocrinologist, who will also refer patients to appropriate specialists (e.g., vascular surgeon or ophthalmologist) when complications are expected and initiate multidisciplinary prevention and treatment of diabetic foot ulcers in particular. Similarly, vascular surgeons provide surveillance and treatment for patients with or at risk of PAD. Medical insurance is mandatory for all citizens, which ensures universal medical access for both primary and specialist care. As mandated by the central government, the infrastructure and health-care systems are designed such that in 95% of all medical emergency calls, ambulance response time is within 15 min. In the study region (provinces of Groningen, Friesland and Drenthe), the majority of the population resides within cities with a general hospital (within 5 km radius), the median distance from the residence city to a general hospital is 9.4 km[20] and the maximum distance from the most rural town to a general hospital is 38 km. Because centralized or regional medical registries are absent in the Netherlands, medical records of patients had to be accessed directly on site in each of the hospitals. Approval from the regional medical ethics committee was obtained before data collection (M15.176087). In addition, in each of the general hospitals, the local medical ethics committee(s) or the board of directors were informed and approved the study.

A major LLA was defined as an amputation through the ankle or more proximal level.[6,7,21,22] All major LLAs, performed from January 2012, through December 2013, were included. The choice to include patients undergoing an amputation in 2 consecutive years was in part to facilitate comparison of incidence rates over time with those of previous cohorts in the region in 1991–1992[23] and 2003–2004[24]. Data collection at the hospitals was performed from January 2015, through April 2017. Any major LLA among patients with a recorded diagnosis of DM and/or PAD at the time of or before major LLAs was included as dysvascular amputations. Additional details of the search strategy and inclusion are provided in Appendix A. Amputations due to trauma, cancer, complex regional pain syndrome type-1, iatrogenic complications, intractable leg lymphedema, and congenital syndromes were excluded. Sporadically, rapidly progressing *Staphylococcus aureus* and *Streptococcus* group A infections in otherwise healthy adults with no prior history of PAD/DM leading to LLAs were observed in the academic hospital. These patients were excluded because they represent a separate population than dysvascular amputation patients for whom the eventual cause of amputations may have been infection/sepsis control, but the underlying disease leading to an amputation had been PAD, DM, and related complications.

Variables

The primary outcome variables were the 30-day and 1-year postoperative mortality rates, for which time to death was calculated as the time (days) between the first major LLA during the study period (i.e., the index amputation) and date of death as stated in patients' medical records. The secondary outcome variable was reamputation, defined as subsequent major LLAs — either revision of the stump, conversion to more proximal level or contralateral amputations — within 1 year of the index amputation. Vascular surgical history, including percutaneous transluminal angioplasty (PTA), arterial bypass grafting, endarterectomy, and previous minor or major LLAs, was recorded and specified for having been performed either ipsilateral, contralateral, or bilateral to the side of the index amputation. A planned two-stage amputation among the dysvascular population is not the norm in the Netherlands, and to our knowledge, has not (or very rarely) been performed in the study region in the past 10 years. Guillotine amputations are reserved for emergency situations, for example, when time is of the essence for sepsis control or patients are too unstable for the longer operating time required for the standard amputation procedure. In this study, when guillotine amputations were performed, the definitive amputations performed several days later (if patients did survive) were not considered as reamputations. When multiple LLAs were performed in the study period, the most proximal level was used to determine the level of LLAs for the analyses of mortality rates. When major LLAs were performed on both limbs in the study period (either consecutively or in a single operation), amputations were labeled as bilateral. A primary LLA was defined as no recorded history of any vascular surgical procedure (i.e., PTA, bypass, or endarterectomy), minor or major LLAs on the side of the index amputation. Comorbidities were based on items from the Charlson Comorbidity Index[25] using the International Classification of Disease (ICD-9) codes, with several additional items, which are described in detail in Appendix A.

Statistical Analysis

Initially, we had planned a Cox regression analysis, but because of violation of the proportional hazards assumption, it was deemed inappropriate. Survival was analyzed using Kaplan-Meier estimation of cumulative mortality rates, for which the data were right censored. No missing data were imputed. Differences in observed mean days of survival after the amputation were analyzed using log-rank tests. Associations between patient characteristics for the outcomes 30-day and 1-year mortality and reamputation within 1 year were explored using χ^2 tests. Variables with $P < 0.2$ were included in the multiple logistic regression analyses using backward stepwise elimination. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the identified associations between the predictor variables and outcomes. Age was analyzed both as a continuous variable (not shown) and recoded into age categories to facilitate clinical interpretation. For the main analyses, statistical significance was set at $\alpha = 0.05$. Microsoft Excel 2016, IBM SPSS Statistics 24, and G*Power, version 3.1, were used for the analyses.

RESULTS

Patient Characteristics

A total of 382 patients undergoing a major LLA in 2012—2013 were identified (Table I), and 65% of them were male. The mean age (SD) at the time of the index amputation was 71.9 ± 12.5 years. At 30 days for 2 patients (0.5%) and at 1 year for 16 patients (4%), outcome data were unavailable, and dates of last documented contact were used for time to censored events. PAD was observed in 88% of the patients (Table I), and DM was present in 56% of the patients. Among those with PAD, 52% also had DM. Among 7 patients (1.8%), the reason for amputation was an acute arterial occlusion without any prior history of either PAD or DM at the time of the index amputation. Fifty-four patients (14%) were treated in the regional academic hospital, the remaining 86% were geographically distributed by place of residence in the 11 general hospitals. Fifteen guillotine amputations (4%) were performed. Hypertensive disease was the most common comorbidity and was observed in 73% of the patients. Twenty-six percent had no history of any revascularization or amputation on the side of the index amputation (i.e., primary LLAs). Fifty-six percent of the patients had no previous minor or major LLA on either limb, whereas

Table I. Characteristics of patients undergoing major lower limb amputations

		30 days			1 year		
Variable	Baseline	Alive	Dead	P[a]	Alive	Dead	P[a]
Total	382 (100)	326 (85)	54 (14)		236 (62)	130 (34)	
Age, years (mean, SD)	71.9 (12.5)	71.6 (12.6)	73.7 (12.1)	0.25	69.4 ± 12.2	75.6 ± 12.4	<0.01
Age, categories							
0−54	42 (11)	38	4	0.15	30	12	<0.01
55−64	66 (17)	56	9		50	14	
65−74	96 (25)	88	8		76	17	
75−84	122 (32)	97	24		56	59	
>85	56 (15)	47	9		24	28	
Gender (male)	247 (65)	213	32	0.39	163	76	0.04
Prior LLA (either limb)							
No minor/major LLA	212 (56)	176	35	0.05	126	75	0.26
Prior minor LLA	131 (34)	120	11		89	39	
Prior major LLA	39 (10)	30	8		21	16	
Level of amputation[b]							
Transtibial	176 (46)	159	17	0.04	122	49	<0.01
Knee disarticulation	25 (7)	21	3		17	6	
Transfemoral	179 (47)	144	34		95	75	
Primary LLA[c]	100 (26)	80	18	0.17	51	43	0.02
Bilateral amputation	17 (5)	15	2	0.76	12	4	0.38
Guillotine amputation	15 (4)	10	5	0.03	6	8	0.09
Smoking status (ever)	289 (76)	247	40	0.79	187	89	0.02
Medical history							
Peripheral arterial disease	336 (88)	285	49	0.49	204	118	0.22
DM	216 (56)	190	26	0.54	134	77	0.38
DM type I	26 (7)	23	3		13	13	
DM type II, oral medication	74 (19)	64	10		48	22	
DM type II, insulin use	116 (30)	103	13		73	42	
Cerebrovascular disease	104 (27)	93	11	0.21	58	39	0.26
Cardiac disease							
Hypertension	277 (73)	231	45	0.06	162	106	0.01
Myocardial infarction	101 (26)	86	15	0.83	24	44	0.01
CABG	82 (21)	69	12	0.87	43	35	0.05
Heart failure	102 (26)	77	24	<0.01	45	53	<0.01
Chronic pulmonary disease	112 (29)	93	18	0.47	65	41	0.42
Renal disease	128 (34)	103	25	0.03	68	58	0.01
Hemodialysis	28 (7)	21	7	0.09	10	18	<0.01
Autoimmune disease	49 (13)	42	7	0.99	25	24	0.03
Immunosuppressive medication	90 (24)	75	15	0.45	44	46	<0.01
Alcohol abuse	65 (17)	52	12	0.25	42	19	0.43
Revascularization (ipsilateral)							
PTA	148 (39)	125	23	0.55	95	46	0.36
Bypass graft	134 (35)	117	17	0.53	90	38	0.09
Endarterectomy	100 (26)	92	8	0.04	75	20	<0.01

Values are indicated as number of patients (%) unless indicated otherwise.

CABG, coronary artery bypass grafting; DM, diabetes mellitus; LLA, lower limb amputation; PTA, percutaneous transluminal angioplasty.

[a] χ^2 tests for categorical variables and t tests for age between patients alive and dead at 30 days and 1 year after amputation.

[b] Most postproximal level of amputations performed within study period, ankle disarticulation ($n = 1$) and hip disarticulation ($n = 1$) are not included.

[c] With no ever recorded vascular surgical procedure or a minor/major LLA on the side of the index amputation.

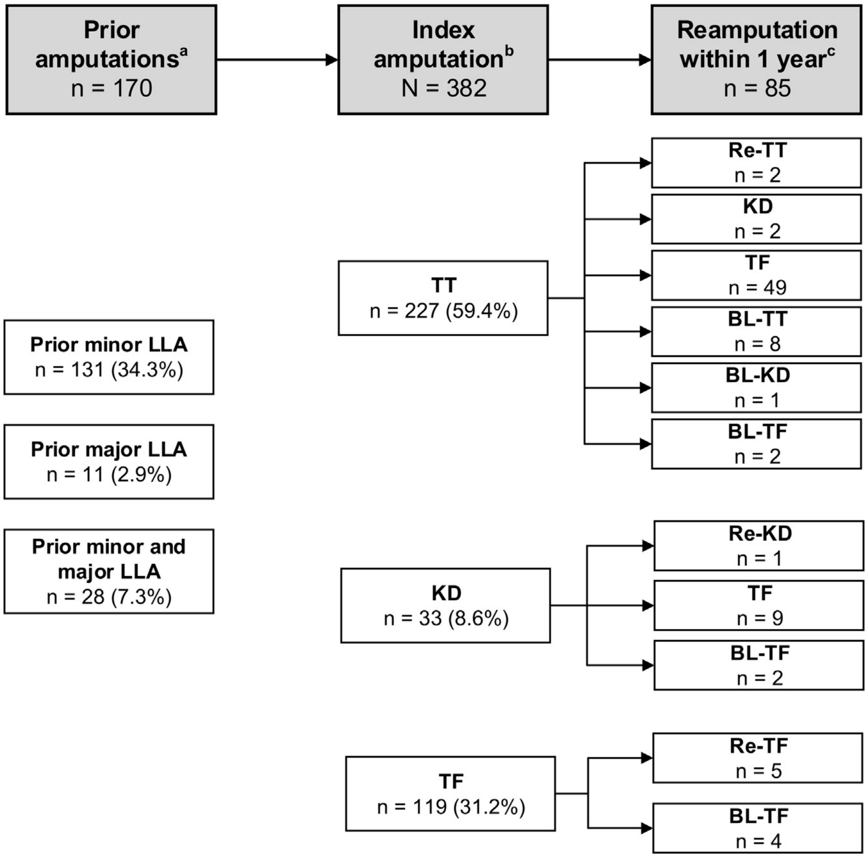


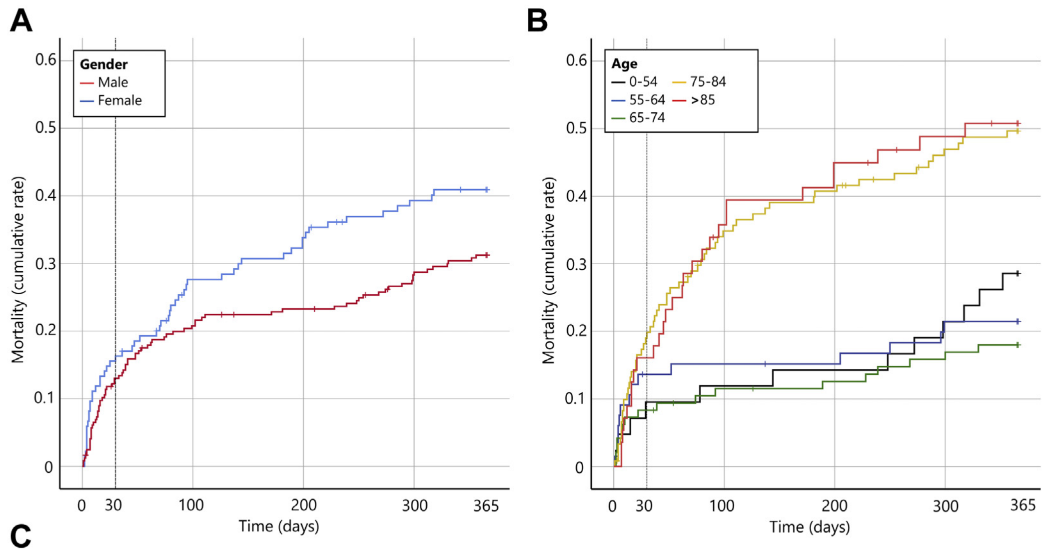
Fig. 1. Sequence of performed major lower limb amputation. Percentages are relative to included patients at baseline ($n = 382$). [a]On either side. [b]First LLA performed in the study period, ankle disarticulation ($n = 2$) and hip disarticulation ($n = 1$) are not shown. [c]Ipsilateral and contralateral, when multiple reamputations occurred, the most proximal level within 1 year after index amputation is presented. BL, bilateral; KD, knee disarticulation; LLA, lower limb amputation; TF, transfemoral; TT, transtibial; Re, reamputation.

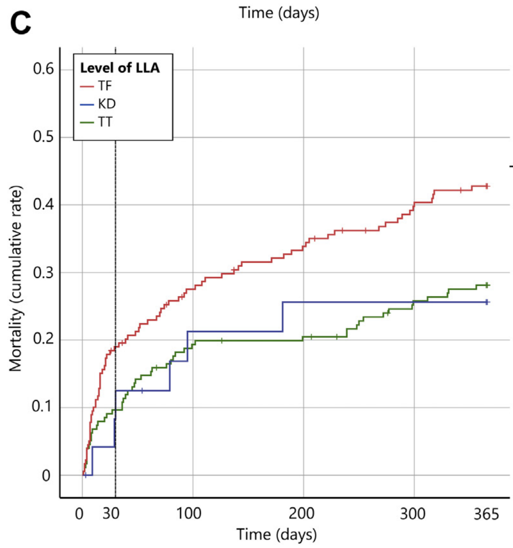
34% had undergone a minor and 10% had major LLA before the index amputation. The sequence of amputations performed in the study period is illustrated in Figure 1.

Survival

Of the initial 382 patients, 54 (14%) died within 30 days and 130 (34%) within 1 year after the index amputation, the mean survival was 273 days (95% CI 259 to 288) (Fig. 2). Patients in the age categories 75−84 and > 85 years survived the shortest and had the highest 1-year mortality rates, 48% and 50%, respectively (Fig. 2B). Forty-two percent of patients with a transfemoral amputation died within 1 year and had shorter mean survival days (251, 95% CI: 229−273) than those with more distal levels of amputations (293, 95% CI: 274−313; 291, 95% CI: 237−344) (Fig. 2C). No significant differences in mean survival days and 1-year mortality rates were observed between transtibial and knee disarticulation levels (Fig. 2C). Survival distributions specified by DM diagnosis (i.e., DM vs. non-DM), types of DM, bilateral LLAs, prior major/minor ipsilateral, or contralateral LLAs were also analyzed (not shown), but no statistically significant differences in mean survival were observed.

Patient characteristics and univariate analyses leading to inclusion of variables in the regression models are presented in Table I. Results of the multivariate analyses of 30-day and 1-year mortality are presented in Table II. Only prior history of heart failure (OR: 2.5, 95% CI: 1.4−4.6) and guillotine amputations (OR: 3.6, 95% CI: 1.1−11.4) was independently associated with higher 30-day mortality rates. In line with the observations of survival distributions (Fig. 2B), multivariate analyses indicated that patients in the age categories 75−84 and >85 years had the highest 1-year mortality rates compared with patients aged 0−54 years (Table II).





	Index LLA *n* (%)	Dead <1 year *n* (%)	Days survival (95% CI)
Total	382 (100)	130 (34)	273 (259-288)
Gender			
Male	247 (65)	76 (31)	284 (267-301)
Female	135 (35)	54 (40)	254 (230-280)
Age			
0-54	42 (11)	12 (29)	311 (277-345)
55-64	66 (17)	14 (21)	306 (275-336)
65-74	96 (25)	17 (18)	320 (297-341)
75-84	122 (32)	59 (48)	230 (202-257)
>85	56 (15)	28 (50)	224 (185-265)
Level of LLA[a]			
TT	176 (46)	49 (28)	293 (274-313)
KD	25 (7)	6 (24)	291 (237-344)
TF	179 (47)	75 (42)	251 (229-273)

Fig. 2. (A) Kaplan-Meier analysis of mortality and mean days of survival by gender, (B) age categories, and (C) level of amputation. [a]Most post proximal level of amputation performed within study period, ankle disarticulation ($n = 1$) and hip disarticulation ($n = 1$) are not shown. KD, knee disarticulation; LLA, lower limb amputation; TF, transfemoral; TT, transtibial.

The 1-year mortality rates for the age groups 0–54, 55–64, and 65–74 were similar. The transfemoral amputation was associated with higher 1-year mortality rates (OR: 2.2, 95% CI: 1.4–3.8) than the transtibial amputation. Several factors were also independently associated with higher 1-year mortality rates: prior history of heart failure (OR: 2.3, 95% CI: 1.3–4.0), myocardial infarction (OR: 1.7, 95% CI: 1.0–3.1), guillotine amputations (OR: 5.1, 95% CI: 1.4–18.0), hemodialysis (OR: 5.7, 95% CI: 2.1–15.2), and the use of immunosuppressive medication (OR: 2.8, 95% C:I 1.6–5.0). Several variables of interest with regard to mortality rates (Table I) such as primary LLAs, revascularization attempts, bilateral LLAs, prior LLAs on either limb, and prior LLAs on ipsilateral limb (Appendix B) were not associated with mortality rates using univariate and subsequent multivariate analyses. In addition, analyses were performed defining the level of amputation by the index amputation (instead of most proximal level), and the results were similar: the transfemoral amputation was associated with higher mortality rates than the transtibial amputation (Appendix C).

Reamputation

Of the initial 382 patients, 98 (26%) did not undergo reamputation but died before 1 year, and 12 (3%) lost to follow-up, which makes 272 patients eligible

Table II. Multivariate analyses of 30 days and 1 year mortality

Variable	β	SE	*P*	OR (95% CI)
30-day mortality				
Constant	−2.20	0.20	<0.001	
Guillotine amputation	1.29	0.58	0.027	3.64 (1.16−11.41)
Heart failure	0.95	0.30	0.002	2.59 (1.43−4.67)
1-year mortality				
Constant	−2.44	0.48	<0.001	
Age[a]			<0.001	
55−64	−0.25	0.59	0.632	0.78 (0.28−2.19)
65−74	−0.36	0.51	0.481	0.70 (0.26−1.88)
75−84	1.13	0.47	0.009	3.40 (1.36−8.55)
>85	1.46	0.53	0.005	4.30 (1.54−12.05)
Level of amputation[b]				
Knee disarticulation	0.17	0.57	0.760	1.19 (0.39−3.64)
Transfemoral	0.81	0.27	0.003	2.25 (1.32−3.83)
Guillotine amputation	1.65	0.64	0.010	5.19 (1.49−18.08)
Myocardial infarction	0.58	0.29	0.046	1.78 (1.01−3.13)
Heart failure	0.85	0.28	0.003	2.33 (1.35−4.04)
Hemodialysis	1.74	0.49	<0.001	5.72 (2.15−15.20)
Immunosuppressive medication	1.05	0.29	<0.001	2.85 (1.60−5.07)

Multiple backward logistic regression; Nagelkerke R^2 30 days: 0.063; Nagelkerke R^2 1 year: 0.323.
[a]Compared with 0−54 years category.
[b]Compared with transtibial amputation.

for analysis of reamputation rates. Seventy patients (26%) underwent ipsilateral reamputation within 1 year of the index amputation (Table III): 8 were revisions at the same level and 62 were performed on a more proximal level. Reasons for reamputation were nonhealing stump ($n = 25$), local infection of the wound ($n = 28$), systemic infection originating from the wound ($n = 6$), revision of the stump to facilitate prosthesis use ($n = 4$), PAD proximal to the stump ($n = 4$), or not stated ($n = 3$). Seventeen patients (6%) underwent reamputation contralateral to the index limb, of which 2 also had an ipsilateral reamputation. In total, 85 (31%) underwent at least one major reamputation on either limb. Patient characteristics and univariate analyses of ipsilateral reamputation rates are presented in Table III. Logistic regression analyses did not provide independently associated risk factors for any of the variables. In addition, analyses of reamputation risk factors were performed for the total study population, including patients who died before 1 year without undergoing reamputation (Appendix D). These analyses did not yield different results, except that the ipsilateral reamputation rate was 18% (Appendix D) in contrast to 26% (Table III) and age categories being associated with reamputation in univariate analysis, which did not remain consistently significant in the multivariate model.

DISCUSSION

The main finding of this study is that the postoperative and 1-year mortality rates of dysvascular major LLAs is high, as 34% of patients do not survive the first year. In line with previous studies,[10,26,27] the most elderly patients − those aged >75 years − had the highest mortality risk. The transfemoral amputation was associated with higher mortality rates, in line with several previous studies reported in 2 systematic reviews.[5,7] The proximal amputation is likely to be indicative of more severe disease,[6] when a distal level is not an option (due to poor vascularization or local infection) or has already been performed. Bilateral amputations have been reported to be associated with both worse[28] and better survival rates,[4,29] whereas no differences were observed in our study. These discrepancies may be explained by aggregation of different combinations of anatomic levels among bilateral LLAs, that is, transtibial-transtibial, transfemoral-transtibial, and transfemoral-transfemoral, and so forth. Consistent with our observations, we therefore propose that the eventual anatomic level of LLAs is more predictive of survival rather than the distinction between unilateral or bilateral LLAs. Patients with a first ever LLA may be expected to have better odds of survival, as they are likely to be in better physical condition and have less severe disease compared

Table III. Univariate analyses of reamputation within 1 year

Variable	Eligible	Ipsilateral reamputation <1 year		
		No	Yes	P[a]
Total	272 (100)	202 (74)	70 (26)	
Age, mean (SD)	69.6 (12.4)	70.2 (12.6)	67.8 (11.7)	0.17
Age, categories				
0−54	37 (13)	24	13	0.54
55−64	54 (20)	38	16	
65−74	84 (31)	64	20	
75−84	67 (25)	52	15	
<85	30 (11)	24	6	
Gender (male)	184 (68)	140	44	0.32
Smoking status (ever)	212 (78)	156	56	0.63
Medical history				
Peripheral arterial disease	233 (86)	170	63	0.23
DM	156 (57)	83	33	0.37
DM type I	17 (6)	10	7	
DM type II, oral medication	55 (20)	43	12	
DM type II, insulin use	84 (31)	66	18	
Renal disease	85 (31)	60	25	0.35
Hemodialysis	15 (5)	8	7	0.06
Autoimmune disease	30 (11)	21	9	0.57
Immunosuppressive medication	54 (20)	38	16	0.47
Alcohol abuse	50 (18)	37	13	0.96
Prior LLA (ipsilateral)				
No minor/major LLA	162 (60)	114	48	0.18
Reamputation from minor LLA	103 (38)	83	20	
Reamputation from major LLA	7 (3)	5	2	
Primary LLA[b]	64 (23)	49	15	0.63
Revascularization (ipsilateral)				
PTA	103 (38)	71	32	0.12
Bypass graft	101 (37)	69	32	0.09
Endarterectomy	79 (29)	57	22	0.61

Values are number of patients (%) unless indicated otherwise.

DM, diabetes mellitus; LLA, lower limb amputation; PTA, percutaneous transluminal angioplasty.

[a]χ^2 tests categorical variables and t tests for age between patients undergoing ipsilateral reamputation within 1 year after index amputation.

[b]Patients with no ever recorded vascular surgical procedure or a minor/major LLA on the side of index amputation.

with those who have already undergone an amputation.[6] However, this assumption was not confirmed in our study: no differences in mortality rates were found with regard to patients having any minor or major LLA before the index amputation. Unsurprisingly, guillotine amputations were associated with high mortality,[30] which is to be expected as the procedure is performed when the situation is already life-threatening for patients.

A systematic review concluded that diffuse cardiovascular disease is associated with the high mortality among patients undergoing an LLA.[7] Our results suggest that more severe cardiac disease such as heart failure contributes to the risk of death after an LLA.[26,31] Similar to our study, end-stage renal disease in which hemodialysis is needed was found to be associated with higher mortality rates among patients undergoing an LLA.[28,30] Although other studies indicate that this association might be the case for renal disease in general,[26,32] our findings do not support that renal disease is an independent risk factor. Inclusion of immunosuppressive medication in our study as a potential risk factor was based on clinical observations and the expected inherent side effects such as interference with glycemic control and susceptibility to infections.[33] To our knowledge, this is the first study identifying the use of immunosuppressive medication as a potential risk factor of 1-year mortality: 2 previous studies found steroid use to be associated with higher 30-day mortality.[34,35] A systematic review found DM associated with higher mortality in 7 of 13 studies, whereas 6 of

13 studies did not support this conclusion.[5] In this study, no differences in mortality rates were observed between DM and non-DM patients undergoing a major LLA.

Reamputation after either a minor or major LLA is to be avoided as much as possible because of subsequent perioperative risks with each operation and decrease in mobility and physical condition with each hospital admission. Systematic reviews estimate that 20%[19] of ray amputations and 28%[36] of transmetatarsal amputations will require reamputation at a more proximal level. It is therefore alarming that among 26% of patients, ipsilateral reamputations were observed in the first year after undergoing a major LLA. Previous studies report 9–20%[4] and 7%[15] ipsilateral reamputations after a major LLA. We argue that it is more appropriate that deceased nonreamputated patients are subtracted from the denominator: because those patients do not complete the first year without reamputation, their inclusion underestimates the rate of reamputation by inflating the observed numbers of nonreamputated cases. Based on clinical observation, we had expected to observe higher reamputation rates among DM patients and those with prior revascularization or LLA on the index limb; however, no risk factors for reamputation in the first year after the LLA were identified.

Historically, mortality rates after the major LLA have been ''notoriously'' high,[5–7] which has been argued by some to be attributable to the population comprising elderly and medically frail patients at the time of the major LLA,[7,37,38] whereas others regard the LLA as a failure of the health-care system[39] and question whether it should be regarded as lifesaving, considering the high mortality rates.[40] An opposing view is that delay of amputation in favor of (repeated) revascularization attempts may be detrimental for chances of survival.[38,41,42] One-third mortality rate within 1 year after a major LLA may indeed be regarded as alarmingly high, considering that for the overall Dutch population aged 75–84 years in 2013, the 1-year risk of death was estimated as 2.5–7.3%.[20] Illustrative of the frailty of the LLA population is that survival after a major LLA is more in line with heart failure which has a 5-year mortality rate of 44%[43] in the Netherlands and hemodialysis which has 1-year mortality up to 25%.[44] The decision-making process for surgeons and patients may be seen as a continuum: on one side, there are clear indications to perform an amputation (e.g., life-threatening situations or uncontrollable pain), whereas on the other side of the spectrum, there are situations in which patients and surgeons continue to avoid an amputation through revascularization attempts. Based on the present literature, it remains unclear when to ''call it quits'' before opting for an amputation.[5] We propose that the high mortality rates and the identified risk factors should not deter from performing an amputation but may be taken into consideration by surgeons and patients for whom a major LLA might be impending, especially for the most elderly patients with pronounced cardiovascular disease.

Strengths and Limitations

The main strength of this study is that by accessing and reviewing the medical records of patients in 12 hospitals, we were able to collect data in more detail pertaining to the patient characteristics for a substantial cohort of a major LLA. Initially, we aimed to categorize the indication for LLA; we were unable to do so objectively because of the heterogeneity in the clinical decision making. For example, a majority of patients had both DM and PAD, which made it a subjective matter to distinguish which of the 2 diseases ultimately was the cause of an amputation. Unfortunately, in a majority of cases, we could not determine the preamputation nutritional and ambulatory status of patients with certainty, and thus, were unable to assess whether these were predictive of survival.[5,7,31] The relatively small sample size may have led to limited power for the multivariate analyses. Post hoc analyses of the minimum detectable effect sizes, given the study sample size and assuming a 0.8 power, were performed for several variables for which no association was observed in 1-year mortality rates. The minimum detectable OR was prior LLA OR 1.69 (observed OR 1.18); bilateral LLA OR 3.56 (observed OR 1.69), and DM OR 1.62 (observed OR 1.09). We suspect that analysis of reamputation risk factors has suffered the most from the sample size. Assuming that approximately 25% of all patients undergo reamputation within 1 year and that a certain characteristic (e.g. DM) is associated with an OR of 1.25 for reamputation, future research cohorts would likely detect this difference when the sample size is at least $n = 1,250$. The medical ethical permissions allowed us only to store the data relevant to the study population (i.e., dysvascular LLA); because of this, we were unable to provide an overview of the excluded patients (i.e., LLAs due to other causes).

CONCLUSION

In this multicenter retrospective cohort study, the 30-day mortality after a major LLA was 14%, and the 1-year mortality was 34%. Forty-two percent of transfemoral amputees did not survive the first year, which was a higher rate than those with transtibial or knee disarticulation amputations. Patients aged >75 years at the time of the major LLA had 3–4 times higher odds of death within 1 year. In addition, a history of heart failure, myocardial infarction, hemodialysis, immunosuppressive medication use, and amputations performed in emergency setting (guillotine) were independently associated with higher 1-year mortality. Twenty-six percent of patients underwent ipsilateral reamputation within 1 year, for which no risk factors were identified.

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