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Risk of contralateral lower limb amputation and death after initial lower limb amputation – a population-based study

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Abstract

Background: Lower limb amputation (LLA) is a complication of lower limb atherosclerosis, infection and tissue gangrene. Following ipsilateral LLA, the risk of major amputation of the contralateral limb or of death is unknown. The aim of this study was to determine the incidence of a contralateral major LLA, comparing those with a non-malignant/non-traumatic ipsilateral major vs. ipsilateral minor LLA.

Methods: We used pre-existing linked administrative health databases for the study. Data were provided by the Institute for Clinical Evaluation Sciences (ICES), Toronto, Ontario. This is a retrospective population-based cohort study across Ontario, Canada, 2002–2012. Cause-specific Cox regression models were used to obtain hazard ratios. Cumulative incidence functions were used to calculate the risk of contralateral major LLA and the risk of the competing event death. Individuals who did not survive at least 30 days after their first ipsilateral LLA were excluded since they were ineligible to have a contralateral LLA.

Results: 5,816 adults underwent an ipsilateral major and 4,143 an ipsilateral minor LLA. The incidences of contralateral major LLA were 4.8 and 2.2 (adjusted HR

2.41, 95% CI 2.04–2.84) after ipsilateral major and minor LLA, respectively. Incidence of death was 18.9 and 11.4 (adjusted HR 1.22, 95% CI 1.13–1.31) following ipsilateral major and minor LLA, respectively.

Conclusion: There is high incidence of a contralateral major LLA and even higher risk of death following the ipsilateral LLA. Healthcare professionals should develop strategies for contralateral limb preservation in individuals with existing ipsilateral LLA.

Keywords: Health sciences, Epidemiology

1. Introduction

Major lower limb amputation (LLA) is a complication of tissue infection or necrosis in persons with diabetes mellitus (DM), peripheral arterial disease (PAD) and/or critical limb ischemia [1, 2, 3, 4, 5, 6, 7]. Besides affecting a person's quality of life, major LLA is also associated with lengthy hospitalization, high health care costs and mortality [8, 9, 10, 11]. In addition, there is 5–18% risk of subsequent revision of the major LLA site [12]. Since patients who undergo a major LLA exhibit ongoing risk factors of PAD and DM-related tissue infections, they remain at high risk of contralateral major LLA [5]. Once an individual loses both legs, their capacity for ambulation drops dramatically, while the need for institutional care rises [10]. Additionally, such individuals are considered to be at high risk of dying, but population-based estimates are lacking.

Little is known about contralateral LLA, which occurs in 15%–25% of persons who initially undergo LLA [1, 13, 14]. A single center study of 1,715 patients reported a 1-year rate of major LLA of 5.7% after ipsilateral major LLA, and a rate of 3.2% after ipsilateral minor LLA [14]. All patients had LLA secondary to PAD [14]. A prior study showed that chronic renal failure (CRF), end-stage renal disease (ESRD) and revision of an existing LLA level to a higher anatomic level are independently associated with increased risk of contralateral major LLA [5]. In addition, comorbidities such as chronic obstructive pulmonary disease (COPD), ESRD, active coronary artery disease with heart failure and angina, and older age are associated with increased mortality in these patients [5]. To date, however, there are no large-scale studies examining the incidence of contralateral LLA following an ipsilateral LLA. Therefore, we aimed to calculate the incidences of a contralateral major and minor LLA, comparing those with an ipsilateral major vs. ipsilateral minor LLA. As death following an ipsilateral LLA precludes the occurrence of each outcome, we handled death as a competing event in the analysis of the two above-mentioned outcomes.

2. Methods

2.1. Study design and participants

We completed a retrospective cohort study in the entire province of Ontario, Canada, where healthcare is universally available to all residents. Ontario is Canada's most populous province with population of over 12 million [15] (Appendix 1). We included all individuals aged 30 years and older who underwent their first ipsilateral non-traumatic/non-malignant major or minor LLA between April 1, 2002 and March 31, 2012. Individuals who did not survive at least 30 days after their first ipsilateral LLA were excluded. The reason for requiring a minimum 30-day survival after the initial ipsilateral LLA is that a person must have some degree of eligibility to receive a contralateral LLA. This way, individuals with terminal illness and those who died within 30 days of their initial ipsilateral LLA were not included in the study.

To ensure that we excluded persons with prior major trauma or cancer to a lower limb, or any prior LLA, we used a 10-year look-back window, from April 1 1992 to April 1, 2002 (Appendix 2).

2.2. Exposures and outcomes

The main exposure of interest was a first non-traumatic/non-malignant ipsilateral major or minor LLA. The previously validated [16, 17] administrative codes used to identify major LLA and minor LLA were based on the diagnostic code systems of International Classification of Diseases (ICD-9, before 2002) and ICD-10-CA (from 2002 onward), as well as the procedural code systems of Canadian Classification of Procedures (CCP) (before 2002) and Canadian Classification of Health Interventions (CCI) (from 2002 onward) (Appendix 2). DeCoster et al. [17] studied validity of CCI and ICD-9-CM, and came to a conclusion that both systems code major procedures well, but are not valid for minor procedures. They concluded that CCI could be confidently used by health care services and population researchers [17]. The CCI is a well-validated coding system used to code procedures in conjunction with ICD-10-CA for classification of morbidities and inpatient procedure coding [18, 19, 20]. The ICD-9 codes for PAD, diabetes and other comorbidities were evaluated in a multivariable model by Fan et al [21]. The authors found that PAD by itself had sensitivity of 39%, and it became significantly higher (68%) when procedure codes were incorporated into the model. In addition, ICD-10 codes for diabetes and diabetic foot ulcers and other comorbidities have 75–100% sensitivity and specificity [22].

The primary outcome was the occurrence of contralateral major LLA 30 days after the index procedure –based on the same diagnostic and procedure codes outlined above. The secondary outcome was the risk of contralateral minor LLA. Death

was analyzed as a separate competing outcome prior to contralateral minor and major LLA as described below.

2.3. Database sources

Pre-existing linked administrative health databases were used for all study variables, which are housed at the Institute for Clinical Evaluation Sciences (ICES), Toronto, Ontario.

All hospitalizations and procedures were identified using the Canadian Institute for Health Information Discharge Abstract Database (DAD). This is a validated database that contains data on inpatient and day surgery [23].

Some study exclusion criteria and covariates were also identified in the Ontario Health Insurance Plan (OHIP) Database. The OHIP Database contains complete records of all physician billing information for outpatient and inpatient services, a service date and a single diagnosis [24]. Death was retrieved from the Registered Persons Database (RPDB) [24] which contains demographic information about all individuals who obtained an Ontario health card number [24]. Income quintile and rurality were defined according to postal codes using Statistics Canada census data. This census is a reliable source of information and contains demographic and socioeconomic information for the entire population [25]. The income quintile measures an income for a given household with quintile 1 denoting the lowest, and quintile 5 denoting the highest income [25]. These datasets were linked using unique encoded identifiers and analyzed at ICES. Both diagnostic and procedure codes have been previously validated [17, 21, 26, 27].

The study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Reference# 2014 0900 528 000).

2.4. Sample size calculation

The primary study outcome was the incidence of contralateral major LLA, comparing those who underwent a first ipsilateral major vs. minor LLA and who survived ≥ 30 days after that index procedure. The 2-year incidence rate of contralateral major LLA following first major LLA in prior small studies varied from 15% to 25% [1, 14]. A conservative estimate of the incidence rate of 10% was adopted for sample size calculation. A preliminary analysis using ICES data showed 33,000 ipsilateral LLA cases in the 11-year proposed study period. Of these 60% were ipsilateral major LLA and 40% were ipsilateral minor LLA. 96% of all LLA were not due to malignancy or trauma, but were related to DM and/or ischemia, gangrene or infection. At a 2-sided P value of 0.05, estimates of statistical power were then generated based on varying incidence rates of the primary study outcome of major LLA and their

corresponding hazard ratio (HR). Using these conservative estimates our study has a statistical power of 99% for a HR of at least 1.3 at a 2-sided P value of 0.05.

2.5. Statistical analyses

Standardized differences were calculated for continuous and categorical variables, comparing baseline characteristics between exposed (ipsilateral major LLA) and unexposed (ipsilateral minor LLA) groups. Standardized difference is the effect size index, and reflects a difference between two means across their standard deviation [28]. An absolute standardized difference of greater than 0.1 indicated an imbalance between the groups [28].

Cumulative incidence functions were used to calculate the risk of contralateral major LLA and the risk of the competing event death, separately for individuals who had an ipsilateral major LLA and an ipsilateral minor LLA [29]. Unlike Kaplan-Meier survival function, the cumulative incidence function takes into account a competing risk at the same time estimating the incidence of a given event [30]. Crude incidence rates for each outcome were computed and presented per 100 person-years. To examine the association between characteristics and the rate of each outcome, time-to-event analyses were conducted, where time zero (t_0) was defined as ≥ 30 days after a first ipsilateral non-traumatic/non-malignant LLA. A censoring date was defined as the date of the competing event, migration out of province or being alive and event-free at the end of the study (March 31, 2013). Cause-specific proportional hazards regression models were used to generate a hazard ratio and 95% confidence interval (CI), comparing those with initial ipsilateral major vs. minor LLA (the referent) [29]. Assumptions of the Cox model were checked prior to applying it and they were met (proportionality ($p > 0.05$) for Schoenfeld residuals, no influential observations were identified). Hazard ratios were adjusted for age, sex, income quintile, and rural residence —each on the date of admission to hospital for initial ipsilateral LLA. We also adjusted for DM, foot infection/gangrene, diabetic foot ulcer, diabetic retinopathy, diabetic neuropathy, chronic hypertension, coronary artery disease (CAD), cerebrovascular disease, ESRD, venous thromboembolism, obesity, PAD, hypercholesterolemia, COPD, diagnosed tobacco dependence, depression, Charlson Comorbidity Index and lower limb arterial revascularization. The latter covariate included information on both endovascular and open surgical procedures performed on lower limbs. Covariates that changed in value over time were handled as time-dependent measures.

The same approach was repeated in the analysis of contralateral minor LLA as an endpoint, wherein mortality and contralateral major LLA were each viewed as competing risks.

There were <1% missing data in the cohort, which were not different from the rest of the sample included in the analysis. The missing data were not included in the analyses.

All analyses were done using the SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

3. Results

Data from a total of 9,959 individuals aged ≥ 30 years with non-malignant/non-traumatic ipsilateral LLA were included (Fig. 1). We compared baseline characteristics of included individuals and those excluded from the study due to missing laterality of ipsilateral LLA ($n = 3,345$) and found no difference. Specifically, there was no significant difference in mean age, gender distribution, comorbidities, rural or urban residence status, and income status between the group that was excluded from the study and the study sample.

Of 9,959 individuals, 58.4% had ipsilateral major LLA and 41.6% had ipsilateral minor LLA. Baseline characteristics of the entire cohort who underwent initial ipsilateral LLA are shown in Table 1.

3.1. Baseline characteristics

Individuals with initial ipsilateral major LLA were more likely to be a female, aged 80+ years and had a higher prevalence of hypertension, COPD, CAD,

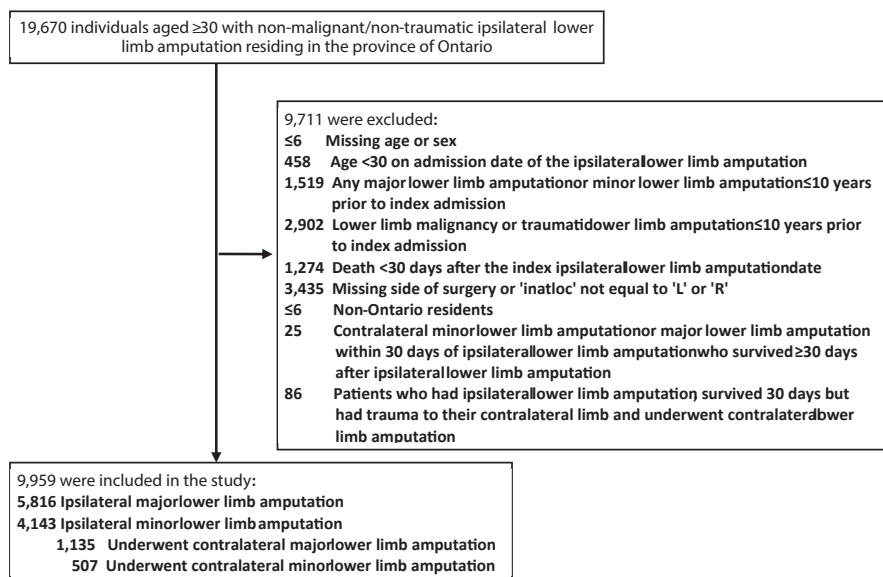


Fig. 1. Flow chart of formation of the cohort of individuals with non-malignant/non-traumatic ipsilateral minor or major lower limb amputation who subsequently underwent contralateral minor or major lower limb amputation.

Table 1. Characteristics of the cohort of 9,959 adults who underwent ipsilateral lower limb amputation. All data are presented as a number (%).

Characteristics, conditions or procedures	Measure
Captured on the date of admission to hospital for the initial ipsilateral lower limb amputation	
Ipsilateral lower limb amputation was major	5816 (58.4)
Ipsilateral lower limb amputation was minor	4143 (41.6)
Age 30–39 years	184 (1.9)
Age 40–49 years	691 (6.9)
Age 50–59 years	1775 (17.8)
Age 60–69 years	2556 (25.7)
Age 70–79 years	2711 (27.2)
Age 80+ years	2042 (20.5)
Male sex	6604 (66.3)
Income quintile (Q)	
<i>Q1 (lowest)</i>	2765 (28.1)
<i>Q2</i>	2144 (21.8)
<i>Q3</i>	1824 (18.5)
<i>Q4</i>	1694 (17.2)
<i>Q5 (highest)</i>	1431 (14.5)
Rural residence	1834 (18.4)
Captured starting 31 days following the initial ipsilateral lower limb amputation, and up to the censoring date	
Coronary artery disease	5371 (53.9)
Hypercholesterolemia	966 (9.7)
Diabetes mellitus	7709 (77.4)
Foot infection/gangrene	323 (3.2)
Diabetic foot ulcer	4157 (41.7)
Diabetic retinopathy	811 (8.1)
Diabetic neuropathy	647 (6.5)
Hypertension	8441 (84.8)
Cerebrovascular disease	2298 (23.1)
End stage renal disease	2445 (24.6)
Venous thromboembolism	486 (4.9)
Obesity	530 (5.3)
Peripheral vascular disease	7167 (72.0)
Chronic obstructive pulmonary disease	1995 (20.0)
Tobacco dependence	639 (6.4)
Depression	1144 (11.5)
Median (interquartile range) Charlson Comorbidity Index	2.0 (2.0–4.0)
Lower limb arterial revascularization	2378 (23.9)
Had an interim contralateral minor lower limb amputation	507 (5.1)

cerebrovascular disease and PAD, compared to those who had ipsilateral minor LLA (Table 2). Individuals with ipsilateral major LLA also had a higher prevalence of depression and venous thromboembolism (Table 2).

In contrast, those with initial minor LLA were younger and living in a rural residence with a higher prevalence of DM, foot infection and gangrene and diabetic foot ulcer (Table 2). Although peripheral neuropathy was more prevalent among individuals with ipsilateral minor LLA in our study, the difference was not significant.

In addition, there was a large number of low-income individuals in both exposure groups (Table 2).

3.2. Main outcome of contralateral major LLA

Fig. 2 shows cumulative probability over time of contralateral major LLA and the cumulative probability over time for the competing event death after index ipsilateral lower limb amputation. Patients with initial ipsilateral major LLA had the highest risk of dying compared to those with initial ipsilateral minor LLA or subsequent contralateral LLA.

Among 9,959 individuals with incident ipsilateral LLA, a total of 1,135 (11.4%) underwent contralateral major LLA (Table 3). The incidence of contralateral major LLA was 4.8 per 100 person-years among those with initial ipsilateral major LLA, compared to 2.2 per 100 person-years after initial ipsilateral minor LLA – a crude HR of 2.03 (95% CI 1.78 to 2.30) (Fig. 2; Table 3). After adjusting for multiple covariates, the HR increased slightly (2.41, 95% CI 2.04 to 2.84) (Table 3; Appendix 3).

After ipsilateral major LLA, the incidence rate of death was 18.9 per 100 person-years, and after ipsilateral minor LLA it was 11.4 per 100 person-years – an adjusted HR of 1.22 (95% CI, 1.13 to 1.31) (Table 4).

3.3. Outcome of contralateral minor LLA

Among 9,959 individuals with incident ipsilateral LLA, 507 (5.1%) underwent a contralateral minor LLA (Table 5). The incidence of contralateral minor LLA was lower after an ipsilateral major LLA (1.0 per 100 person-years) than after ipsilateral minor LLA (2.4 per 100 person-years—an adjusted HR of 0.59 (95% CI 0.47 to 0.72)) (Table 5).

4. Discussion and conclusions

About 1 in 6 patient who initially survives their ipsilateral LLA goes on to have a contralateral LLA. The risk of contralateral major LLA was 2.4 times higher

Table 2. Baseline characteristics of individuals with ipsilateral major or ipsilateral minor lower limb amputation who subsequently underwent contralateral lower limb amputation. All data are presented as a number (%) unless otherwise specified.

Characteristics	Initial lower limb amputation		Standardized difference
	Ipsilateral major LLA N (%) (N = 5816)	Ipsilateral minor LLA N (%) (N = 4143)	
Age 30–39	85 (1.5)	99 (2.4)	0.07
Age 40–49	305 (5.2)	386 (9.3)	0.16
Age 50–59	884 (15.2)	891 (21.5)	0.16
Age 60–69	1407 (24.2)	1149 (27.7)	0.09
Age 70–79	1699 (29.2)	1012 (24.4)	0.11
Age 80+	1436 (24.7)	606 (14.6)	0.26
Female gender	2121 (36.5)	1234 (29.8)	0.14
Income quintile (Q)			
Q1	1645 (28.6)	1120 (27.3)	0.03
Q2	1266 (22.0)	878 (21.4)	0.01
Q3	1040 (18.1)	784 (19.1)	0.03
Q4	1008 (17.5)	686 (16.7)	0.02
Q5	801 (13.9)	630 (15.4)	0.04
Rural residence	964 (16.6)	870 (21.0)	0.11
Coronary artery disease	3716 (63.9)	2167 (52.3)	0.24
Hypercholesterolemia	707 (12.2)	457 (11.0)	0.04
Diabetes mellitus	4024 (69.2)	3376 (81.5)	0.29
Foot infection/gangrene	319 (5.5)	482 (11.6)	0.22
Diabetic foot ulcer	2679 (46.1)	2331 (56.3)	0.21
Diabetic retinopathy	439 (7.6)	370 (8.9)	0.05
Diabetic neuropathy	366 (6.3)	360 (8.7)	0.09
Hypertension	4721 (81.2)	3102 (74.9)	0.15
Cerebrovascular disease	1631 (28.0)	713 (17.2)	0.26
Chronic renal failure	3856 (66.3)	3310 (79.9)	0.31
End stage renal disease	1042 (17.9)	662 (16.0)	0.05
Venous thromboembolism	359 (6.2)	133 (3.2)	0.14
Obesity	340 (5.9)	262 (6.3)	0.02
Peripheral vascular disease	5134 (88.3)	3005 (72.5)	0.40
Chronic obstructive pulmonary disease	1282 (22.0)	665 (16.1)	0.15
Tobacco dependence	526 (9.0)	315 (7.6)	0.05
Depression	632 (10.9)	321 (7.8)	0.11
Median (IQR) Charlson Comorbidity Index	2 (4.0)	1 (3.0)	0.23

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Table 2. (Continued)

Characteristics	Initial lower limb amputation		Standardized difference
	Ipsilateral major LLA N (%) (N = 5816)	Ipsilateral minor LLA N (%) (N = 4143)	
Lower limb arterial revascularization side			
<i>Left</i>	624 (10.7)	529 (12.8)	0.06
<i>Right</i>	581 (10.0)	524 (12.7)	0.08
<i>Bilateral</i>	74 (1.3)	46 (1.1)	0.01
<i>None</i>	591 (75.9)	240 (70.6)	0.11

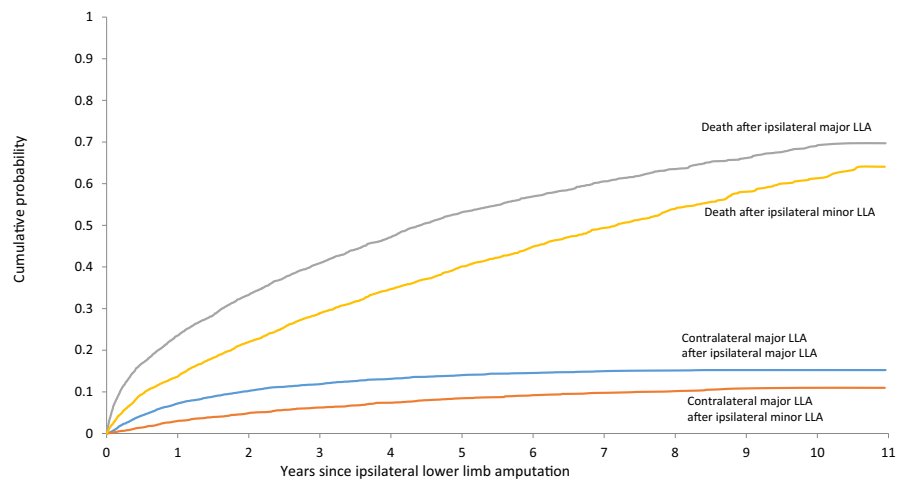


Fig. 2. Cumulative probability of contralateral major lower limb amputation or death after an index ipsilateral lower limb amputation. X axis-Years since ipsilateral LLA; Y axis-Cumulative probability.

Table 3. Main analysis of the cause-specific hazard of contralateral major lower limb amputation after an index ipsilateral major vs minor lower limb amputation.

Initial lower limb amputation	Hazard of contralateral major lower limb amputation			
	Number of events (%)	Incidence rate per 100 person-years	Hazard ratio	
			Unadjusted	Adjusted ^a
Ipsilateral major lower limb amputation (n = 5,816)	785 (13.5)	4.8	2.03 (1.78–2.30)	2.41 (2.04–2.84)
Ipsilateral minor lower limb amputation (n = 4,143)	350 (8.5)	2.2	1.00 (referent)	1.00 (referent)

^a Adjusted for age, sex, income quintile, rural residence, diabetes mellitus, foot infection/gangrene, diabetic foot ulcer, diabetic retinopathy, diabetic neuropathy, chronic hypertension, coronary artery disease, cerebrovascular disease, chronic and end-stage renal disease, venous thromboembolism, obesity, peripheral vascular disease, hypercholesterolemia, chronic obstructive pulmonary disease, diagnosed tobacco dependence, depression, Charlson Comorbidity Index and lower limb arterial revascularization.

Table 4. Cause-specific hazard of death after an index ipsilateral major vs. minor lower limb amputation.

Initial lower limb amputation	Hazard of death after the ipsilateral lower limb amputation and before the occurrence of a contralateral major lower limb amputation			
	Number of events (%)	Incidence rate per 100 person-years	Hazard ratio	
			Unadjusted	Adjusted ^a
Ipsilateral major lower limb amputation (n = 5,816)	3103 (53.4)	18.9	1.58 (1.49–1.67)	1.22 (1.13–1.31)
Ipsilateral minor lower limb amputation (n = 4,143)	1788 (43.2)	11.4	1.00 (referent)	1.00 (referent)

^a Adjusted for age, sex, income quintile, rural residence, diabetes mellitus, foot infection/gangrene, diabetic foot ulcer, diabetic retinopathy, diabetic neuropathy, chronic hypertension, coronary artery disease, cerebrovascular disease, chronic and end-stage renal disease, venous thromboembolism, obesity, peripheral vascular disease, hypercholesterolemia, chronic obstructive pulmonary disease, diagnosed tobacco dependence, depression, Charlson Comorbidity Index and lower limb arterial revascularization.

Table 5. Cause-specific hazard of contralateral minor lower limb amputation after an index ipsilateral major vs. ipsilateral minor lower limb amputation.

Initial lower limb amputation	Hazard of contralateral minor lower limb amputation			
	Number of events (%)	Incidence rate per 100 person-years	Hazard ratio	
			Unadjusted	Adjusted ^a
Ipsilateral major lower limb amputation (n = 5,816)	156 (2.7)	1.0	0.40 (0.33–0.48)	0.59 (0.47–0.72)
Ipsilateral minor lower limb amputation (n = 4,143)	351 (8.5)	2.4	1.00 (referent)	1.00 (referent)

^a Adjusted for age, sex, income quintile, rural residence, diabetes mellitus, foot infection/gangrene, diabetic foot ulcer, diabetic retinopathy, diabetic neuropathy, chronic hypertension, coronary artery disease, cerebrovascular disease, chronic and end-stage renal disease, venous thromboembolism, obesity, peripheral vascular disease, hypercholesterolemia, chronic obstructive pulmonary disease, diagnosed tobacco dependence, depression, Charlson Comorbidity Index and lower limb arterial revascularization.

following ipsilateral major LLA than ipsilateral minor LLA, after adjusting for other risk factors. Importantly, individuals who undergo initial ipsilateral LLA are at very high risk of dying prior to having a contralateral LLA.

4.1. Our findings in relation to other studies

Unlike our findings, prior studies have demonstrated lower anatomic level (i.e, fewer major amputations) in the contralateral LLA compared to that for the initial ipsilateral LLA in the same individual [31]. We included patients with and without critical limb ischemia, while other studies had focused on those with PAD and critical limb ischemia [14, 31]. Although earlier studies observed a 50% rate of contralateral LLA

in diabetics with critical limb ischemia [31], dropping rates of non-traumatic/non-malignant LLA over the past decade is likely due to more aggressive limb salvage practices across the world in patients deemed eligible to receive them [32]. These limb salvage practices include early recognition of diabetic foot ulcers and referral, aggressive revascularization with bypass or angioplasty, ulcer care, risk factor modification and patient education, among other factors [31, 32].

4.2. Mechanisms

The reasons for contralateral major LLA after ipsilateral major LLA are determinable. One major reason is the presence of PAD [14]. Studies have shown that patients with PAD, as well as with CRF, are more likely to require contralateral major LLA [5, 14]. The two are certainly mediated by the presence of DM [5, 14]. Our results indicate that patients with initial ipsilateral major LLA exhibit diffuse end-stage atherosclerotic disease and are more likely to undergo a contralateral major LLA. In contrast, individuals with initial minor LLA had manifestations of microvessel disease leading to neuropathy and foot deformation causing foot and toe ulcers.

Reasons for the excessively high risk of death after ipsilateral LLA can be explained by the co-prevalence of CAD, CVD and COPD. Others have observed high mortality rates after ipsilateral major LLA [5, 33, 34]. A recent systematic review showed a high variability of in-hospital (4–20%) and 30-day (7–22%) mortality after LLA, in which above knee amputation and older age were significant predictors [33]. In another prospective study, DM and lack of prosthetic fitting were associated with greater long-term mortality [34]. A low rate of revascularization among persons with DM or critical limb ischemia was also associated with higher mortality and LLA [35].

4.3. Study strengths and limitations

We performed a large, population-based study capturing important outcomes events and major covariates over time. We also excluded individuals who did not survive at least 30 days after their first ipsilateral LLA. If he/she had a terminal illness, or died within 30 days of the initial ipsilateral LLA, then it would be impossible to have a degree of eligibility for the study, and it makes little sense to include them in our study.

Some risk factors, such as obesity and tobacco dependence were based on outpatient diagnostic codes, so they were likely under-captured and may make the study individuals look healthier with relatively better outcomes. We did not have data on medications either. Given that limb revascularization was based on administrative procedure codes and there is variation in how revascularization procedures are coded, some procedures may have been misclassified or underreported. For major

LLA, we also did not distinguish between above vs. below-knee amputation given that our main goal was to calculate incidence rates for a large category of contralateral major LLA as opposed to subcategories (i.e., different types of major LLA). Data missing the laterality of the ipsilateral LLA were excluded from the analysis. Although we compared baseline characteristics of these individuals to those included in our study and found no differences, our sample might underestimate the incidence rate and the competing risk of mortality associated with contralateral LLA. Limitations of OHIP include missing information on inpatient diagnostic procedures, as well as reimbursement through alternate funding plans. The latter may result in skewed information due to uneven distribution across specialties and geographic locations analyses [24]. The retrospective nature of the study introduces the potential for selection and misclassification biases. To mitigate the bias, we set strict exclusion criteria, including LLA due to trauma or cancer. Comorbidities were treated as time-dependent covariates. We also treated death as a competing event by using a cumulative incidence function to calculate the risk of each outcome over time and used cause-specific regression models to examine adjusted relative rates for each outcome.

4.4. Conclusion and future implications

Our study examined contralateral LLA — an area of research that has largely been neglected. Our results show high incidence of contralateral major LLA following an ipsilateral major LLA. More importantly, the risk of dying prior to a contralateral LLA is significantly higher.

Comprehensive multidisciplinary and guideline-based care have been shown to reduce the risk of LLA [36] and early mortality rates after a major LLA [37, 38], although other studies have not confirmed this reduction in mortality [39, 40]. Once a person has an ipsilateral LLA, aggressive preventive measures are warranted, including timely management of skin and deep tissue infections/foot ulcer, optimization of regional blood supply, prevention of falls and stump injury, routine self-foot care, appropriate foot offloading and optimization of blood pressure, lipids and glucose, and smoking cessation [31, 41, 42].

Bilateral amputees present a challenge to healthcare system, along with increased risk of death.

Declarations

Author contribution statement

Khumara Huseynova, Joel Ray: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Rinku Sutradhar: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Gillian Booth, Anjie Huang: Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2018.e00836>.

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