



# Increased Mortality After Lower Extremity Amputation in a Danish Nationwide Cohort: The Mediating Role of Postoperative Complications

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**Objective:** Patients who undergo major lower extremity amputation (MLEA) have the highest postoperative mortality among orthopedic patient groups. The comorbidity profile for MLEA patients is often extensive and associated with elevated postoperative mortality. This study primarily aimed to investigate the increased short- and long-term mortality following first and subsequent major lower extremity amputation. Secondly, to examine the mediation role of post-amputation complications.

**Study Design and Setting:** With data from the Danish National Patient Registry, 11,695 first-time MLEAs in patients aged  $\geq 50$  years were identified between January 1, 2010, and December 31, 2021, along with 58,466 unamputated persons matched 1:5 by year of birth, sex, and region of residence. Mediators were identified through diagnosis codes (ICD-10) present in 6 months following MLEA.

**Results:** The increased mortality following MLEA was highest in the month following MLEA, hazard ratio (HR) 38.7 (95% confidence interval (CI) 30.5–48.9) in women and HR 55.7 (CI 44.3–70.2) in men compared to a matched unamputated cohort. Subsequent amputation resulted in an increased mortality the month after a subsequent amputation (overall HR 3.2 (CI 2.8–3.7) in women and HR 3.2 (CI 2.8–3.6) in men) and almost normalized after the first year. The proportion of the mortality risk that potentially could be reduced by preventing sepsis was 16% (CI 11.7–20.3) for women and 17% (CI 13.4–20.4) for men. For pneumonia, it was 10.5% (CI 7.1–13.9) in women and 14.9% (11.6–18.2) in men.

**Conclusion:** We observed an increased mortality in the month following MLEA, which remained elevated for years compared to the matched unamputated cohort. A subsequent amputation results in increased mortality in the following year, but declined and normalized after the first year. Sepsis and pneumonia arising after the amputation appeared to be important factors that contributed to the increased postoperative mortality.

**Keywords:** major lower extremity amputation, registry study, mediator analysis, mortality, nationwide

## Background

Patients who undergo major lower extremity amputation (MLEA) have one of the highest reported postoperative mortality risks, among orthopedic patient groups. This is reflected in a short-term (30-days) mortality between 5–12% after a below-knee amputation (BKA), and 13–23% after an above-knee amputation (AKA),<sup>1–4</sup> and a long-term (1-year) mortality ranging from 23–33% for BKA and 41–58% for AKA.<sup>3–5</sup>

Globally, the prevalence of MLEA varies due to differences in healthcare systems, rates of diabetes, peripheral arterial disease, and trauma.<sup>6</sup> In Denmark, the annual incidence of MLEA in 2023/2024 was 39.9 per 100,000 individuals above 50 years of age with a decreasing trend.<sup>7</sup>

The preoperative co-morbidity profile for MLEA patients is often extensive, and associated with elevated postoperative mortality.<sup>4,5,8–12</sup> Patients undergoing MLEA often experience a substantial decline in quality of life, characterized by reduced

mobility, chronic pain, and psychological challenges such as depression.<sup>13–18</sup> However, assessment of the postoperative mortality is complex, particularly when determining the specific impact of surgical procedures, postoperative complications, and preoperative comorbidities. It remains uncertain to what extent the increased mortality after MLEA, can be ascribed to preoperative comorbidities, complications arising after MLEA, and the surgical trauma related to the MLEA itself. Complications after MLEA have been described, and complications related to the stump, nonsurgical site infection (eg pneumonia, urinary tract infection) and postoperative exacerbation of underlying diseases were the most common.<sup>19,20</sup> Increased mortality has been investigated in other orthopedic patient groups.<sup>21,22</sup> However, further investigation is needed to explore the increased mortality and the mediating role of postoperative complications after MLEA.

The primary aim of this study was to investigate the risk of short and long-term mortality following first and subsequent MLEA. The secondary aim was to examine the mediating role of post-amputation complications.

## Materials and Methods

This study was designed as a nationwide register-based cohort study. It followed the RECORD guidelines for reporting routinely collected observational health data were followed.<sup>23</sup> The data in the study was provided by The Danish Health authorities, with raw data stored on a secure server at the Danish Health data authority.<sup>24</sup> The unique personal identification number assigned to all residents in Denmark enabled the linkage of register data at an individual level, allowing for the tracking of the population throughout the study period. The same raw dataset from the Danish National Patient Registry has been used in previous publications addressing mortality rates over time, the risk of re-amputation over time and length of stay.<sup>4,12,25</sup> This study investigates the increased mortality and mediators of mortality.

## Data Sources

In Denmark, the national registers generally have a high data quality and completeness, estimated to >99%.<sup>24</sup> For this study, we used the Danish National Patient Registry (DNPR)<sup>24</sup> and the Danish Civil registration system.<sup>26</sup>

The DNPR holds data from all hospitalizations in Denmark since 1997. Contacts from outpatient and emergency departments were included in 1995, while private hospital contacts were included from 2003. In this study, we derived information on dates for hospital contacts/procedures, ICD-10 (International classification of diseases, 10<sup>th</sup> revision) diagnosis codes, and NOMESCO surgical procedures<sup>27</sup> for from all hospital contracts.

The Danish Civil Registration System, established in 1968, maintains demographic data on the entire population of Denmark. From this register, we extracted sex, date of birth, date of death, and region of living.<sup>26</sup>

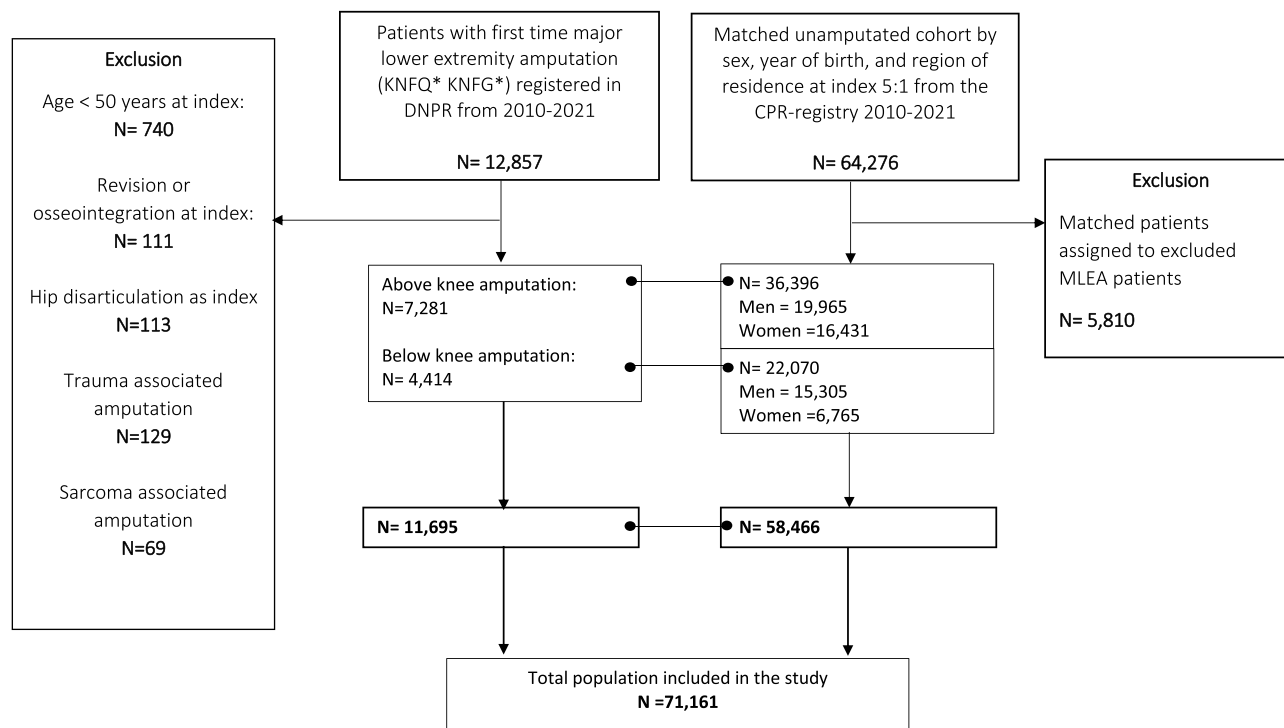
## MLEA Patients

MLEA patients were identified using the DNPR and we included all patients with a first-time MLEA procedure in Denmark from January 1, 2010, to December 31, 2021, who were  $\geq 50$  years of age at time of their initial MLEA procedure. We excluded patients with a sarcoma diagnosis or trauma diagnosis related to their amputation. Patients with a revision amputation procedure as the only index procedure or index hip disarticulation were also excluded (Figure 1 - Flow chart of the study population).

The index MLEA procedures were categorized in BKA (procedure code: KNGQ\*- Amputation on lower leg/knee) or AKA (procedure code: KNFQ\*- Amputation on thigh/hip). BKA included initial transtibial amputation and knee disarticulation, while AKA included initial transfemoral amputation. The index procedure was defined as the first MLEA on either the right or left leg, with the procedure date as the index date. If more than one MLEA was registered on the same day on the same extremity, the most proximal level was registered as index level. The subsequent MLEA, was any MLEA procedure conducted after the index procedure not specific to site.

We applied a washout period to ensure that only patients with a first-time MLEA were included in the MLEA population. This entailed that only patients who had no procedure code for amputation on thigh/hip (KNFQ\*) or amputation on lower leg/knee (KNGQ\*) between 1996 and 2009 were included. The Danish Health authorities conducted the washout.

DNPR: Danish National Patient Registry. CPR: Central Person Register



\*Procedure codes with under codes e.g. KNFQ19

**Figure 1** Flow chart of the study population.

## Matched Unamputated Cohort

MLEA patients were matched 1:5 by sex, year of birth, and region of residence with unamputated persons extracted from the Danish civil registration system, representing the Danish general population. The unamputated cohort was assigned the index date of their respective amputated patient.

For the persons included in the matched unamputated cohort, the following applied: 1: A person could only be assigned one matched amputated person and must have no prior MLEA procedure registered at the index date. 2: The assigned person had to be alive and resident in Denmark at the index date. 3: An included unamputated person changed status to MLEA patient if an amputation of interest occurred in the study period.

## Outcome Definition

The primary outcomes were the increased short-term mortality defined as <1 year, and long-term mortality, defined as  $\geq 1$  year after index MLEA. The secondary outcomes were to examine the increased mortality after subsequent MLEA and identify mediators of mortality.

## Covariates

Age was calculated for both groups at index date and divided into 10-year age groups (50–59, 60–69, 70–79, 80–89 and +90). We assessed comorbidity prior to MLEA, using ICD-10 diagnosis codes from DNPR 10 years before index date ([Supplemental Table 1](#) – CCI comorbidity). The comorbidity was classified using the Charlson Comorbidity Index (CCI) and coded according to Quan et al.<sup>28</sup> All comorbidities at baseline were classified as separate dichotomous variables as suggested by Möller et al.<sup>29</sup>

## Mediators (Morbidity After MLEA)

In search for possible mediators, all new co-morbidities registered 6 months following the index date were identified in the DNPR using primary and secondary ICD-10 codes. The comorbidities were then grouped into relevant categories (eg Hypo/hyponatremia and hyper/hypokalemia were grouped under electrolyte disturbances), and ICD-10 codes that were considered not related to MLEA were excluded (eg Glaucoma). The selection of mediators was based on the assumption that the condition could be a consequence of MLEA and it also could be the cause of death. This to ensure that the selected complications could be defined as a mediator explaining the association between MLEA and morbidity. An individual was excluded from the mediation analysis if it had any pre-existing registrations six months prior to the index date of the mediator in question.

We used the same mediators as presented in Christensen et al,<sup>22</sup> but also explored the diagnosis-codes that were present after MLEA, and three other mediators were selected. Hence, the mediators investigated in this study were abnormal weight loss, urinary tract infection, dehydration, delirium, fever, infection, pulmonary embolism, pneumonia, sepsis, pressure sores, enteritis, anemia and obstipation. All mediators were coded as binary variables. Full list of definition of each mediator is presented in supplementary information ([Supplementary Table 2](#), ICD10 codes included in mediation analysis).

## Statistical Analysis

Categorical data are presented with actual number and percentages (%) and continuous data as median with interquartile range (IQR) for non-normal distributed data. The cumulative incidence function was plotted as a failure curve by estimating 1-Kaplan-Meier. The adjusted hazard ratios (HRs) for death were estimated using multiple Cox regression analyses and reported with 95% confidence intervals (95% CIs). All analyses were stratified by sex and adjusted for age (as a continuous variable) and separate dichotomous CCI variables.<sup>29</sup> Results were presented for MLEA combined and then separately according to index level (AKA/BKA). For all included individuals, survival time was recorded as the timespan between index date and either the time of censoring. Censoring was either emigration, death or set to 31 December 2022. For time-period hazard ratios, MLEA patients and the matched unamputated cohort were censored at death or emigration but not excluded, allowing individuals to contribute data until censoring. This standard time-to-event approach minimized bias and preserved statistical power by avoiding the exclusion of matched pairs. While confounder status may change during follow-up, the analysis focused on baseline exposure, with matching based on baseline characteristics to ensure comparability.

Proportional hazard tests using Schoenfeld residuals were used to assure model assumptions, and the survival time was split into appropriate intervals to accommodate this. All intervals were also visually plotted and found acceptable.

In the analysis of subsequent MLEA and increased mortality, the subsequent MLEA was registered as the next MLEA procedure, either on ipsilateral or contralateral site. In this analysis, age and subsequent MLEA were treated as time-dependent variables.

We matched on year of birth to control for age but still adjusted for it in the analysis due to noncollapsibility, which could cause associations between exposure and outcome to shift if matched variables were excluded. This aligned with known practice in matched case-cohort studies, where adjusting for matched variables could be necessary to address potential biases introduced by matching or subsequent model adjustments.<sup>30</sup>

We conducted mediation analysis in accordance with recommendations of VanderWeele et al.<sup>31</sup> The HRs, adjusted for potential confounders, represented the total effect of the MLEA on the risk of death. This impact was further divided into a controlled direct effect and a mediated effect. The controlled direct effect is the influence of MLEA on the risk of death when eliminating the potential effect of the mediator and potential confounders. Additionally, we estimated the proportion eliminated which describes the percentage of the effect, which might be prevented by removing the mediator from the pathway.

We used bootstrapping, with 100 replicates to estimate the 95% CIs for the controlled direct effect and the estimated proportion eliminated. We reported mediators with a proportion eliminated  $\geq 10\%$  in the main results. Full mediation analysis was reported in [Supplemental Information Tables 3 and 4](#).

## Results

In total, 11,695 first-time MLEA patients and 58,466 matched unamputated persons were included (Figure 1). Not all patients could be matched to five; some were assigned fewer. Of the first-time MLEAs, 60.3% were male. Most MLEA patients had initial AKA (62.3%), and those with initial BKA were typically younger (Table 1). The distribution of CCI comorbidities varied with higher frequencies observed among MLEA patients. Additionally, men were typically younger at the time of their first MLEA (Table 2).

**Table 1** Individuals and Age According to Index Level of MLEA

Index Level	Individuals, N (%)	Men, N (%)	Age (median (IQR))
Above knee amputation	7,281 (62.3)	3,994 (54.8)	77.2 (14.6)
Below knee amputation	4,414 (37.7)	3,061 (69.3)	72.2 (15.4)

**Table 2** Baseline Characteristics Stratified by Sex and Amputation Status

	Women		Men	
	MLEA patients N = 4,640	Un-amputated N=23,196	MLEA patients N=7,055	Un-amputated N=35,270
Age, median (IQR)	79.3 (15.0)	79.3 (15.0)	73.1 (14.3)	73.1 (14.3)
Age, categorized N(%)				
50–59	288 (6.2)	1,450 (6.3)	837 (11.9)	4,179 (11.8)
60–69	733 (15.8)	3,685 (15.9)	1,874 (26.6)	9,421 (26.7)
70–79	1,419 (30.6)	7,009 (30.2)	2,529 (35.8)	12,592 (35.7)
80–89	1,630 (35.1)	8,201 (35.4)	1,520 (21.5)	7,638 (21.7)
90+	570 (12.3)	2,851 (12.3)	295 (4.2)	1,440 (4.1)
Disorders from Charlton Comorbidity index, N(%)				
Myocardial infarct	425 (9.2) <sup>a</sup>	678 (2.9)	875 (12.4) <sup>a</sup>	1,769 (5.0)
Congestive heart failure	863 (18.6) <sup>a</sup>	1,092 (4.7)	1,735 (24.6) <sup>a</sup>	2,029 (5.8)
Peripheral vascular disease	3,819 (82.3) <sup>a</sup>	999 (4.3)	5,761 (81.7) <sup>a</sup>	2,146 (6.1)
Cerebrovascular disease	1,090 (23.5) <sup>a</sup>	2,331 (10.0)	1,719 (24.4) <sup>a</sup>	3,622 (10.3)
Dementia	321 (6.9) <sup>a</sup>	938 (4.0)	303 (4.3) <sup>a</sup>	785 (2.2)
Chronic pulmonary disease	1,001 (21.6) <sup>a</sup>	2,012 (8.7)	1,379 (19.5) <sup>a</sup>	2,566 (7.3)
Rheumatic disease	446 (9.6) <sup>a</sup>	880 (3.8)	307 (4.4) <sup>a</sup>	695 (2.0)
Ulcer disease	369 (8.0) <sup>a</sup>	614 (2.6)	546 (7.7) <sup>a</sup>	845 (2.4)
Mild liver disease	88 (1.9) <sup>a</sup>	180 (0.8)	203 (2.9) <sup>a</sup>	276 (0.8)
Diabetes (without organ damage)	327 (7.0) <sup>a</sup>	1,270 (5.5)	439 (6.2)	2,172 (6.2)
Diabetes (with organ damage)	1,259 (27.1) <sup>a</sup>	385 (1.7)	3,090 (43.8) <sup>a</sup>	982 (2.8)
Hemiplegia or paraplegia	62 (1.3) <sup>a</sup>	49 (0.2)	122 (1.7) <sup>a</sup>	87 (0.2)
Moderate or severe renal disease	544 (11.7) <sup>a</sup>	465 (2.0)	1,289 (18.3) <sup>a</sup>	1,011 (2.9)

(Continued)

**Table 2** (Continued).

	Women		Men	
	MLEA patients N = 4,640	Un-amputated N=23,196	MLEA patients N=7,055	Un-amputated N=35,270
Any malignancy	659 (14.2) <sup>a</sup>	2407 (10.4)	1,046 (14.8) <sup>a</sup>	4,054 (11.5)
Moderate or severe liver disease	46 (1.0) <sup>a</sup>	29 (0.1)	128 (1.8) <sup>a</sup>	90 (0.3)
Metastatic solid tumor	110 (2.4) <sup>a</sup>	207 (0.9)	126 (1.8) <sup>a</sup>	352 (1.0)
AIDS/HIV	*	0 (0.0)	9 (0.1)	13 (0.0)

**Notes:** <sup>a</sup>Significant difference between amputated and unamputated. \*Value censored due to value <5, because of Danish data protection law.

## Increased Mortality Following Index Amputation and Subsequent Amputation

The cumulative incidence of death in the first 2 years were higher for women compared to men (Figure 2A and B. Figure 2 – Cumulative incidence function, visualizing the probability of death in the first 2 years, stratified by sex A) Overall cumulative incidence, women. B) Overall cumulative incidence, men). In general, the increased mortality was higher in the month following MLEA, and declined over time (Table 3). The increased mortality was highest after initial AKA compared to initial BKA. The highest increased mortality was found in men with initial AKA HR 55.5 CI (42.1–73.1) vs HR 41.1 CI (31.8–53.1) in women. In the 2<sup>nd</sup> and 3<sup>rd</sup> month following MLEA the women had a higher HR than men, 14.7 CI (10.3–20) vs HR 9.2 CI (6.8–12.6), respectively (Table 3).

Even though the increased mortality declines over time, the 4<sup>th</sup> year increased mortality was overall HR 2.1 CI (1.7–2.7) for women and HR 2.6 CI (2.2–3.1) for men. The cumulative incidence of death stratified for initial level can be found in Supplemental figures a–d

The increased mortality was highest in the first month following subsequent amputation and then declines the first year for both men and women (Figure 3 - Forrest plot of HR with 95% CI for increased mortality following subsequent amputation. Stratified by sex and initial index level. HRs were adjusted for CCI comorbidities). Women had a higher increased mortality in the first year after a subsequent amputation, if the initial level was BKA, with an HR of 2.1 (1.7–2.6) vs HR 1.5 (1.3–1.7) in men at 31–365 days after re-amputation.

## The Mediating Role of Postoperative Complications

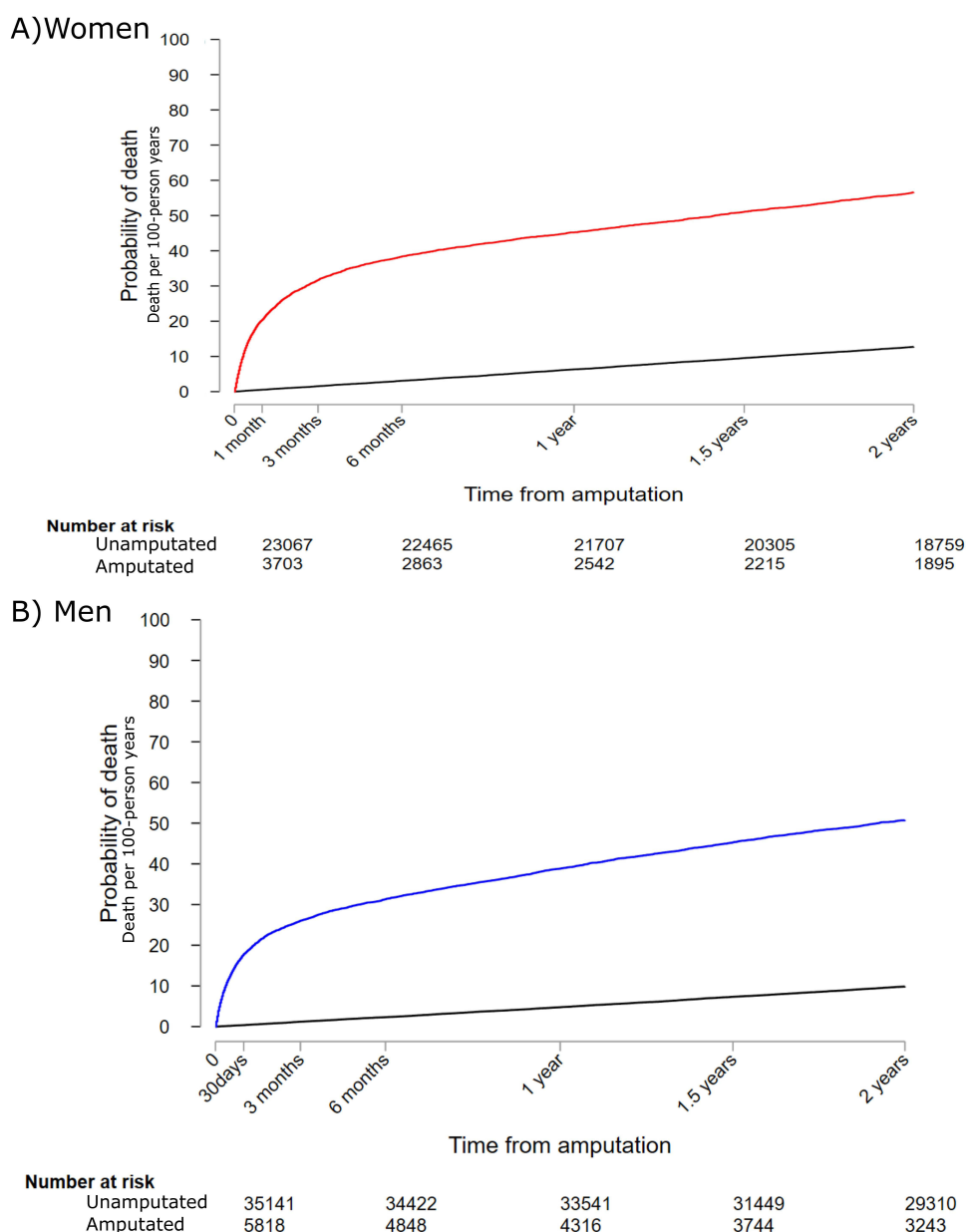
Mediation analysis was conducted on the 14 selected postoperative complications. Of all the mediators investigated, only pneumonia and sepsis showed a proportion eliminated (PE) exceeding 10% (Table 4).

The proportion of the association between MLEA and mortality eliminated by pneumonia was 10.5% (7.1–13.9) in women and 14.9% (11.6–18.2) in men. Overall, the proportion eliminated for pneumonia was higher for men than women and higher after AKA compared with BKA (Table 4). Sepsis explained the largest proportion of the association between MLEA and mortality with a PE of 16.0% (11.7–20.3) in women and a PE of 16.9% (13.4–20.4) in men. The proportion eliminated by sepsis was higher for initial BKA compared with initial AKA for both men and women. The estimates were PE 26.4% (13.8–39) for women and PE 22.3% (15.7–28.9) for men after BKA compared with PE 14.4% (9.3–19.5) for women and PE 14.2% (10.5–18) for men after a AKA.

For those mediators that did not have a PE >10% the analysis is shown in Supplemental information Tables 3 and 4.

## Discussion

Despite advancements in surgical techniques, postoperative care, and rehabilitation protocols, it is essential to comprehend the multifaceted relationship between MLEA and mortality. Therefore, this study investigated the increased mortality and the mediating role of postoperative complications.



**Figure 2** Cumulative incidence function, visualizing the probability of death in the first 2 years, stratified by sex **(A)** Overall cumulative incidence, women. **(B)** Overall cumulative incidence, men.

The results showed that the highest increased mortality risk was found in the month after MLEA for both men and women and it subsequently declined rapidly. This pattern was also found after a subsequent amputation. Postoperative sepsis accounted for the largest proportion of increased mortality after MLEA, but pneumonia also played an important role.

### Increased Mortality Following Index Amputation and Subsequent Amputation

We found a decline in increased mortality during the years following MLEA, with a persistent elevated mortality compared to the matched unamputated cohort throughout the entire study period. We found that the increased mortality, in general, was higher after AKA compared with BKA for both men and women.

Our finding was in accordance with studies on other frail orthopedic patient groups, including hip fractures.<sup>21,22</sup> A Danish registry study found that the increased mortality in the first month after a hip fracture was HR 10.9 for women

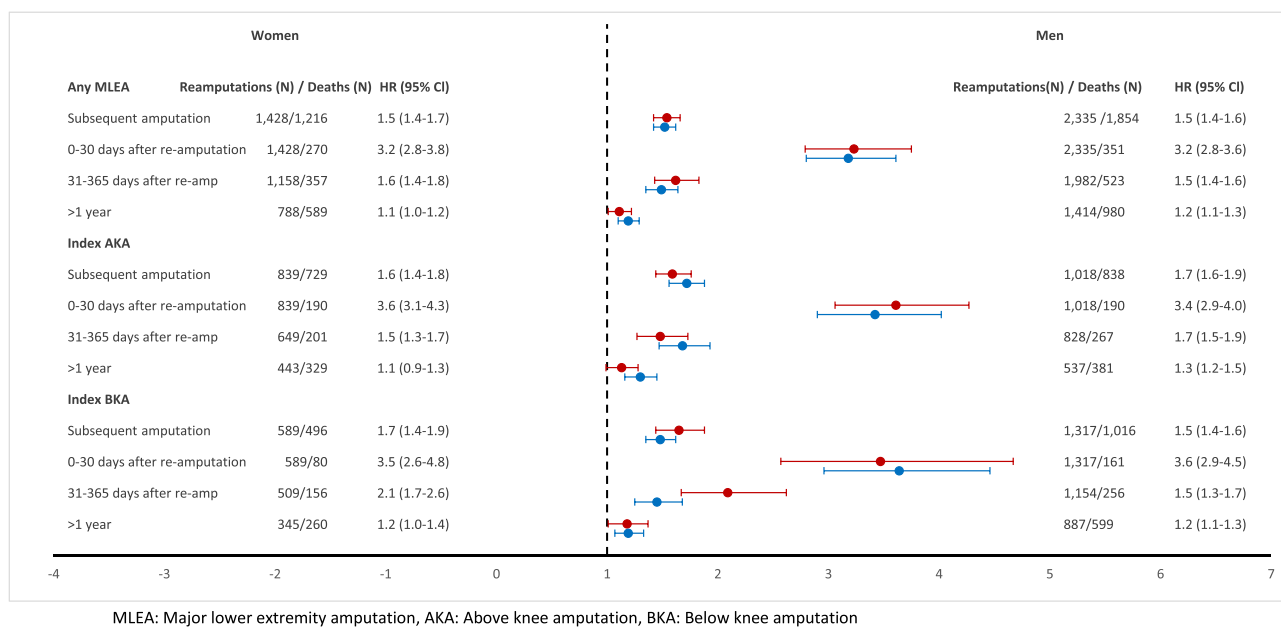
**Table 3** Increased Mortality Following Major Lower Extremity Amputation, Compared to the Matched Unamputated Cohort

Index level	Women			Men		
	Number, N*	Deaths, N	HR (95% CI)	Number, N*	Deaths, N	HR (95% CI)
<b>All amputations</b>						
0–30 days	4,640	948	38.7 (30.5–48.9)	7,055	1259	55.7 (44.3–70.2)
31–90 days	3,692	523	12.3 (9.3–16.3)	5,796	579	8.5 (6.6–10.9)
91–180 days	3,169	311	4.7 (3.5–6.2)	5,217	372	4.8 (3.7–6.2)
181–365 days	2,858	316	2.5 (2.0–3.1)	4,845	530	2.9 (2.4–3.5)
Second year mortality	2,541	514	1.9 (1.6–2.3)	4,314	813	2.4 (2.1–2.8)
Third year mortality	1,894	425	2.4 (1.9–2.9)	3,241	593	2.3 (1.9–2.7)
Forth year mortality	1,383	306	2.1 (1.7–2.7)	2,415	429	2.6 (2.2–3.1)
<b>Above knee amputation</b>						
0–30 days	3,287	767	41.1 (31.8–53.1)	3,994	905	55.5 (42.1–73.1)
31–90 days	2,520	411	14.7 (10.8–20.0)	3,089	388	9.2 (6.8–12.6)
91–180 days	2,109	228	4.9 (3.6–6.8)	2,701	247	5.6 (3.9–7.3)
181–365 days	1,881	212	2.3 (1.8–2.9)	2,454	307	3.0 (2.4–3.8)
Second year mortality	1,669	385	2.0 (1.6–2.5)	2,147	460	2.5 (2.1–2.9)
Third year mortality	1,179	294	2.6 (2.0–3.3)	1,541	334	2.4 (1.9–2.9)
Forth year mortality	823	205	2.2 (1.6–2.9)	1,083	213	2.5 (1.9–3.1)
<b>Below Knee amputation</b>						
0–30 days	1,353	181	23.9 (13.0–43.9)	3,061	354	52.3 (33.9–80.5)
31–90 days	1,172	112	6.4 (3.3–12.3)	2,707	191	6.6 (4.3–10.3)
91–180 days	1,060	83	3.9 (2.3–6.8)	2,516	125	3.7 (2.3–6.0)
181–365 days	977	104	3.4 (2.2–5.3)	2,391	223	2.8 (1.9–3.8)
Second year mortality	872	129	1.6 (1.1–2.4)	2,167	353	2.4 (1.9–3.1)
Third year mortality	715	131	1.9 (1.3–2.9)	1,700	259	2.2 (1.6–2.9)
Forth year mortality	560	101	1.9 (1.3–2.9)	1,332	216	2.9 (2.1–4.1)

**Notes:** \*Individuals with major lower extremity amputation who was available for analysis eg not death or censored at start of the period. Hazard ratios (HR) were estimated by Cox proportion hazards regression models, and estimates are presented with 95% confidence intervals (95% CI). HRs were adjusted for age and CCI comorbidities.

and HR 16.4 for men, which was much lower than our results with an HR 38.7 for women and HR 55.7 for men after first-time MLEA.<sup>22</sup>

The prolonged increased mortality after both AKA and BKA could be explained in the reduced postoperative mobility, especially for the AKA group. MLEA patients have a substantial risk of developing osteoporosis and muscle atrophy postoperatively, because of the structural and functional impairment related to the extremity loss. When retaining more of the extremity, a more natural gait and increased mobility is achieved due to the enhanced possibility for prosthesis use.<sup>32,33</sup>



**Figure 3** Forrest plot of HR with 95% CI for excess mortality following subsequent amputation. Stratified by sex and initial index level. HRs are adjusted for CCI comorbidities.

Postoperative mortality following major lower extremity amputation is influenced by factors such as patient age, comorbidities, amputation level, surgical timing, and overall health status.<sup>1,4,34–36</sup> Comorbidities like chronic kidney disease, cardiovascular disease, and severe peripheral vascular disease further elevate risks, but diabetes does not always elevate the mortality in MLEA patients, maybe because of an increased focus on prevention in this specific patient group.<sup>1,34,37</sup> Due to the multiple comorbid conditions, the mortality in this patient group is probably high, even without the MLEA.<sup>38</sup> Addressing these factors through thorough preoperative evaluation and personalized postoperative care can enhance survival and recovery. These findings suggest that the high postoperative mortality rates can be partially attributed to the patients’ extensive comorbidities, and the risk of mortality might have been even higher had they not undergone major amputation.

**Table 4** Mediation Analysis. The Mediating Role of Selected\* Complications on the Association Between MLEA and Mortality for Each Initial Index Level, Stratified by Sex

Women						
Any MLEA	Women, N	Mediator, N	HR TE (95% CI)	HR CDE (95% CI)	HR PE (95% CI)	PE% (95% CI)
Pneumonia	4,078	332	13.0 (11.1–15.1)	11.7 (9.9–13.7)	1.1 (1.1–1.2)	<b>10.5 (7.1–13.9)</b>
Sepsis	4,305	318	12.8 (10.9–14.9)	10.9 (9.3–12.7)	1.2(1.1–1.2)	<b>16.0 (11.7–20.3)</b>
AKA						
Pneumonia	2,868	244	14.6 (12.3–17.3)	13.2 (11.1–15.8)	1.1 (1.1–1.2)	<b>10.0 (6.1–13.9)</b>
Sepsis	3,048	227	14.5 (12.2–17.1)	12.5 (10.5–14.9)	1.2(1.1–1.2)	<b>14.4 (9.3–19.5)</b>
BKA						
Pneumonia	1,210	88	7.28 (5.1–10.5)	6.7 (4.7–9.6)	1.1 (1.0–1.16)	<b>8.7 (1.9–16.5)</b>
Sepsis	1,257	91	7.1 (4.9–10.2)	5.5 (3.8–7.9)	1.3 (1.1–1.5)	<b>26.4 (13.8–39.0)</b>

(Continued)

**Table 4** (Continued).

Men						
Any MLEA	Men, N	Mediator, N	HR TE (95% CI)	HR CDE (95% CI)	HR PE (95% CI)	PE% (95% CI)
Pneumonia	6,177	493	13.4 (11.6–15.5)	11.6 (9.9–13.5)	1.2 (1.1–1.2)	<b>14.9 (11.6–18.2)</b>
Sepsis	6,538	577	13.3 (11.5–15.4)	11.2 (9.7–13.0)	1.2 (1.1–1.2)	<b>16.9 (13.4–20.4)</b>
AKA						
Pneumonia	3,425	312	14.5 (12.2–17.2)	12.5 (10.4–14.9)	1.2 (1.1–1.2)	<b>14.8 (11.2–18.4)</b>
Sepsis	3,603	355	14.5 (12.2–17.3)	12.6 (10.6–15.1)	1.2 (1.1–1.2)	<b>14.2 (10.5–18)</b>
BKA						
Pneumonia	2,752	181	10.6 (8.0–14.03)	9.5 (7.1–12.6)	1.1 (1.1–1.2)	<b>11.7 (6.6–16.8)</b>
Sepsis	2,835	222	10.3 (7.8–13.5)	8.2 (6.2–10.8)	1.3 (1.2–1.4)	<b>22.3 (15.7–28.9)</b>

**Notes:** \*Only mediator with overall PE>10% is shown. The full tables available in supplemental information, Tables 3 and 4. Explanation of variables: HR TE: adjusted for CCI comorbidities and age. HR CDE: Adjusted for CCI comorbidities, age and the potential mediation factor. The mediator was included as a time-dependent variable. HR PE= HR TE / HR CDE. PE= (HR TE – HR CDE/ HR TE-1). For HR PE and PE Cis were obtained by bootstrapping using 100 replicates. Individuals with preexisting registration of the complication assessed as mediator was excluded from analysis.

**Abbreviations:** HR, Hazard Ratio; TE: Total effect, CDE: Controlled direct effect, PE: Proportion eliminated; MLEA, Major lower extremity amputation; AKA, Above knee amputation; BKA, Below knee amputation.

Reducing mortality in this group of patients may depend on thoughtfully identifying those who are suitable for amputation, while also recognizing that in some cases, focusing on palliative care instead of surgical intervention might be the most appropriate strategy.

Among patients who experienced a subsequent amputation, the highest increased mortality was evident within the first month following the subsequent amputation, and in general, higher for AKA than BKA. Generally, understanding the immediate increased mortality following a subsequent amputation remains limited. This study also finds an increased long-term increased mortality, lasting over a year after the subsequent amputation.

It is possible that some of the extremely high increased mortality in the first months following first-time MLEA could be explained by the related psychological stress. This mechanism has been described in cancer patients where the cancer-diagnosis itself increased the risk of sudden non-cancer-related cardiovascular death in the first four weeks after a cancer diagnosis.<sup>39</sup> Several studies describes that MLEA could be identified as an important psychological stressor, also in patients at risk of MLEA.<sup>40–42</sup>

## The Mediating Role of Postoperative Complications

Previous research have shown that comorbidities and frailty substantially impact the mortality associated with MLEA, and, in general, the mortality after MLEA is declining over time.<sup>1,4,5,9,10,35,43,44</sup>

Mediation analysis on complications after MLEA have not been conducted before and therefore we initially chose the same mediators as presented in Christensen et al.<sup>22</sup> They explored mediators on another frail orthopedic patient group with osteoporotic fractures, with an explorative approach where surgeons rated a list of complications, to identify if it was related to surgery after an osteoporotic fracture. However, due to MLEA and osteoporotic fracture patients differ, the diagnosis-codes that were present after MLEA were also explored and three other possible mediators were selected.

The results of the mediator analysis is adding novelty that could be used directly in a clinical setting, thus the direct mediating association of the event and mediators on the mortality was estimated. This gives novel insight in which complications that should be prevented in order to reduce the mortality risk after MLEA.

Of all the complications included in this study, only sepsis and pneumonia showed an impact of above 10% as mediator towards the increased mortality. The proportion of increased mortality risk that could potentially be reduced by preventing sepsis was 16% for women and 16.9% for men. These results suggest that the complications that mediate

mortality after MLEA were different compared to patients with hip fracture, where pneumonia appeared to be the most important mediator of mortality, followed by urinary tract infection and sepsis. The proportion explained by pneumonia after a hip fracture was 28.5% in women and 37.5% in men compared to our result, which was, respectively, 10.5% in women and 14.9% in men after an MLEA.<sup>22</sup>

Postoperative sepsis and pneumonia after MLEA accounts for up to 25% of in-hospital mortality after MLEA<sup>45</sup> and are recognized factors that impact mortality after MLEA.<sup>46</sup> Having other present comorbidities increase the risk of postoperative sepsis.<sup>47</sup> Both non-surgical site infection, stump complications and sepsis, are complications that result in readmissions after MLEA, with stump-complications being the most frequent complication.<sup>19,20,25,48</sup> The presence of infection at the surgical site or in the surrounding tissues might exacerbate the risk of sepsis, leading to a higher postoperative mortality.

Implementing specific preventive strategies can potentially reduce the risk of postoperative sepsis and pneumonia, consequently lowering the increased mortality associated with MLEA. This aspect should be taken into account in the post-MLEA management. Surprisingly, many of the complications investigated had almost no mediating effect on the association between MLEA and mortality, suggesting that the surgical trauma and perioperative setting might be an important contributing factor to the increased mortality. Other orthopedic patient groups (eg total hip and knee arthroplasties and, to some extent, hip fractures) have experienced substantial benefits from fast-track surgery programs.<sup>49</sup> MLEA patients are in general considered high-risk patients with a high ASA (American Society of Anesthesiologists)-score and cannot be expected to comply 1:1 with a fast-track surgery setting.<sup>50,51</sup> However, elements from fast-track surgery programs might be feasible, especially the multimodal approach, early mobilization, and more standardized clinical evidence-based practice.<sup>52</sup>

## Strengths and Limitations

Due to the data quality and study design, this study had several strengths. The study sample was derived from nationwide Danish registers encompassing all citizens in Denmark irrespective of sex and socioeconomic status. This unselected cohort enhances the generalizability of the results and reduces potential selection bias. Additionally, through the registers, we were able to include a large sample size of first-time MLEA patients with a matched unamputated cohort that contributed with statistical robustness to the findings. The Danish health registers have been documented to exhibit high completeness and high data quality,<sup>24</sup> which enhances the validity of measures related to amputations and complications.

However, there were also limitations to this study. Relevant information on clinical factors such as smoking status, habitual alcohol consumption, fragility-score, pre-and postoperative physical performance, body mass index and blood sample results were not available from the registers, and, thus, missing in our study. This provides a potential for unmeasured confounding and should be taken into account when interpreting results, even though all results were stratified on sex, and adjusted for age and CCI comorbidities. Furthermore, the mediation analysis relies on a counterfactual approach, where unmeasured confounding are a critical assumption for causal interpretation. There is a possibility that this assumption may have been violated, which should be considered. The indications of the MLEA procedure were not available, and therefore the underlying cause of the MLEA procedure cannot be estimated completely, by using register data. Moreover, the risk of misclassification of MLEA was uncertain because the ICD10 codes used for comorbidities and the (NORMESCO) procedure codes for MLEAs are not yet validated.<sup>24</sup>

Lastly, our study lacked data on the exact causes of death, which restricted our ability to perform more detailed analyses on this aspect.

## Conclusion

In conclusion, after MLEA, increased mortality remains high, peaking in the months following the initial amputation before gradually declining. However, it persists above the levels seen in non-amputated individuals even in the fourth year after MLEA. A subsequent amputation results in an even higher increased mortality in the following year compared to initial amputation, a pattern consistent across genders. Mediation analysis indicated that sepsis and pneumonia mediated the association between MLEA and mortality, explaining a proportion of the exceeded mortality observed. The proportion of increased mortality risk that potentially could be reduced by preventing sepsis and pneumonia was 16% and 10.5% for women and 16.9% and 14.9% for men, respectively. These results highlight the need for targeted preventive strategies aimed at reducing the elevated mortality associated with MLEA.

## Declaration of AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT and Scite for minor text editing and structure. No AI tools were used to systematically generate large sections of text. After using these AI-tools, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

## Abbreviations

MLEA, Major Lower Extremity Amputation; AKA, Above knee amputation; BKA, Below knee amputation; DNPR, The Danish National Patient Register; CCI, Charlson Comorbidity index; HR, Hazard ratio; IQR, Interquartile range; CI, Confidence interval; TE, Total Effect; CDE, Controlled direct effect; PE, Proportion Eliminated.

## Data Sharing Statement

Data may be obtained from third party and are not publicly available. Data are accessible through the Danish Health Data Authority.

## Ethical Statement

The Danish Data Protection Agency approved this study (no. 21/27110). Ethical approval was not relevant due to the study design.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. ATHB, KHR and MLL had direct access to raw data.

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## Disclosure

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