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RUNNING TITLES

Odd pages: Systematic Review, Meta-analysis, and Time to Event Analysis of Mortality after Major Lower Limb Amputation

Even pages: Robert J. Leatherby *et al.*

SYSTEMATIC REVIEW

Systematic Review, Meta-analysis, and Time to Event Analysis of Contemporary Mortality after Major Lower Limb Amputation for Peripheral Arterial Disease or Diabetes Mellitus

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WHAT THIS PAPER ADDS

This paper, which systematically reviews and meta-analyses contemporary survival after major lower limb amputation for peripheral arterial disease or diabetes mellitus, highlights the high mortality still evident in this patient population. A time to event technique was used, novel to this patient cohort, to mitigate for study heterogeneity and the high loss to follow up. The significance of end stage renal disease, heart failure, frailty, and higher level of amputation on post-operative mortality is demonstrated. These results provide important general prognostic information for patients and clinicians to aid informed consent.

Objective: Major lower limb amputation for peripheral arterial disease (PAD) or diabetes mellitus carries high mortality risk. This time to event and meta-analysis reports contemporary survival and subgroup risk factor analysis.

Data Sources: MEDLINE, Embase, and Cochrane libraries.

Review Methods: This was a systematic review, meta-analysis, and time to event analysis of contemporary literature performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42024497352). MEDLINE, Embase, and Cochrane libraries were searched on 2 December 2023, limited to 5 years and independently screened by two reviewers. All studies reporting mortality for patients undergoing major lower limb amputation for PAD or diabetes were included. Study quality and evidence certainty were evaluated via Risk of Bias 2, Newcastle–Ottawa, and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tools, respectively. Mean values weighted by study size were used for short term mortality estimation, pooled time to event survival analysis for mid to long term, and random effects modelling for subgroup meta-analysis.

Results: A total of 7 537 unique studies were screened, with 140 meeting criteria for inclusion. Short term mortality was estimated by weighted mean at 6.5% (range 1.8 – 34.1%) in hospital and 8.7% (0 – 26.8%) at 30 days (low GRADE certainty). Pooled time to event analysis was possible across 19 studies with 59 999 patients included. Estimated mortality was 28.9% at 1 year and 63.0% at 5 years with a median survival of 3.1 years (moderate GRADE certainty). Meta-analysed subgroup data demonstrated end stage renal disease, heart failure, frailty, and higher level amputation all increase mortality with peak odds ratios of 5.57, 2.14, 2.25, and 2.30, respectively. Diabetes was not associated with mortality. The time to event analysis for diabetes and level subgroups corroborated these results. Median survival for patients with diabetes was 2.7 years (95% confidence interval 2.0 – 3.5 years) compared with 3.1 years (1.9 – 4.7 years) for those with PAD alone. Subgroup analyses were of very low to moderate GRADE certainty.

Conclusion: Contemporary mortality after major lower limb amputation for PAD or diabetes remains high. End stage renal disease, heart failure, frailty, and higher level of amputation were all associated with mortality risk.

Keywords: Diabetes mellitus, Major lower limb amputation, Mortality, Peripheral arterial disease, Survival, Systematic review

INTRODUCTION

Major lower limb amputation performed for peripheral arterial disease (PAD) or diabetes mellitus carries a high mortality risk. This has been demonstrated in high quality meta-analyses with 1 year mortality ranging between 33.7% and 47.9%, and 5 year mortality between 62.2% to 64.4%.[1,2] Whilst systematic review and meta-analysis are considered the peak of the hierarchy of data, evolving techniques used in these analyses allow for improved summative estimates. These previous meta-analyses investigating mortality after major lower limb amputation have used weighted mean by study size. Whilst this is an accepted technique, especially for estimating early mortality, it loses accuracy when there is significant loss to follow up and fails to account for study heterogeneity. A method described by Combescure *et al.*[3] using summary survival curves with numbers at risk allows for a more robust time to event analysis of mid to long term survival. This has recently been adopted in the vascular surgery community,[4] but not previously applied to the major lower limb amputation patient cohort. Additionally, previous meta-analyses have included all historic data, with the advent of improved peri-operative management[5] and recognition of the importance of patient selection,[6] this historic data may cloud the contemporary picture.

Several patient and surgical characteristics have been proposed as risk factors for mortality after major lower limb amputation. There is evidence suggesting patients with end stage renal disease, heart failure, frailty, and who require a more proximal level of amputation have poorer survival.[7–9] The role of diabetes in mortality after major lower limb amputation is less well defined with conflicting evidence amongst the published literature.[10]

The aims of this study were to perform a robust meta-analysis and time to event analysis of the contemporary literature to estimate short, mid, and long term survival after major lower limb amputation. Additionally, this study aimed to establish which patient and surgical characteristics influence mortality risk after major lower limb amputation and at which time points these are most significant.

MATERIALS AND METHODS

This study was a systematic review, meta-analysis, and time to event analysis of the published literature. It has been prospectively registered with the International Prospective

Register of Systematic Reviews (PROSPERO),[11] ID: CRD42024497352, and a protocol is publicly available on figshare.[12] This study has been conducted in line with the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines.[13,14] This was a pre-defined analysis of a larger systematic review and meta-analysis. The manuscript has been written according to the *European Journal of Vascular and Endovascular Surgery*'s publication standards.[15]

Types of study

All prospective and retrospective study designs reporting mortality were considered for inclusion. Review articles, meta-analyses, conference abstracts, and small studies inclusive of fewer than 50 patients were excluded. The literature search was inclusive of all languages; however, studies that did not have a full text in English were excluded. The search was limited to 5 years prior to the search date of 2 December 2023.

Types of participants and exposures

Inclusion criteria were patients who underwent major lower limb amputation for PAD (including both chronic limb threatening ischaemia and acute limb ischaemia) or diabetes. Major lower limb amputation was defined as any definitive amputation at or above the level of the ankle. Studies were included if over 50% of patients had their major lower limb amputation secondary to diabetes or PAD. A generally inclusive policy was used with infection deemed diabetes related unless specified otherwise, and large non-specified major lower limb amputation population studies being included in the analysis.

Studies that solely recruited high risk or low risk subgroups (as identified from the authors' extended subgroup analysis) were excluded from the short term mortality meta-analysis given the aim to establish a baseline for the average major lower limb amputation patient and the inability to account for study heterogeneity using a mean value weighted by study size. All studies were included in the time to event analysis as the technique used accounts for study heterogeneity, with a sensitivity analysis additionally performed to confirm their inclusion did not significantly affect the estimate.

Subgroup meta-analysis was performed when data were supplied by three or more studies. Analysis was possible for the following: (1) diabetes mellitus; (2) end stage renal disease; (3) heart failure; (4) frailty; and (5) level of amputation.

Types of outcome measures

Mortality at any time point or median survival was the primary outcome of interest. Those studies presenting Kaplan–Meier survival curves with numbers at risk were analysed as part of the time to event analysis. Subgroup data for mortality risk were also captured.

Search method and selection of studies

A broad and inclusive search strategy was devised by the research team. Terms for PAD and major lower limb amputation were taken from a Cochrane peer reviewed strategy and the core outcome set search strategy, respectively.[16,17] Further terms for diabetes and the core outcomes were added. The complete search strategy was then librarian reviewed. The search strategy, limited to 5 years, was run through Embase, MEDLINE, and Cochrane databases; it can be viewed in the Supplementary Material. Those studies reporting a mortality or survival outcome were included in this analysis.

Screening was performed in Rayyan.ai.[18] Two reviewers blindly and independently assessed all studies based on title and abstract against the inclusion and exclusion criteria (R.J.L. and O.H.). Once complete, the two reviewers were unblinded and disagreements were attempted to be resolved between them. Disagreements that could not be resolved used a third senior reviewer as a tie breaker (I.R.). This same process was then repeated for full text reviews.

Data extraction

Data were extracted and analysed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Data on study design, methodology, demographics, patient and surgical characteristics, and relevant outcomes were captured. Data were extracted by one reviewer (R.J.L.) and 10% of this was independently extracted by a second reviewer (O.H.) to check for accuracy. A Cohen κ agreement statistic was then calculated with an estimated chance agreement of 10%.

This was accepted at 0.85, demonstrating near perfect agreement or strong agreement according to Cohen's[19] or McHugh's[20] interpretation, respectively.

Study quality and reporting bias assessment

The methodological quality of the studies included in the meta-analysis was assessed using the Cochrane Risk of Bias (RoB) 2 tool for randomised studies[21] and the Newcastle–Ottawa scale (NOS) for non-randomised studies.[22] Certainty assessments for each of the meta-analysed results were performed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.[23]

Publication bias was assessed for meta-analysed subgroup analyses including ten or more studies by use of a funnel plot and regression analysis using the technique of Egger *et al.*[24]

Missing data

Only published data were analysed; the size of the review made contacting individual studies for missing results unrealistic. Full texts of papers were obtained using institutional access. If unobtainable, requests were made to the British Library. Those papers not obtainable by the above methods were excluded from the review.

Unit of analysis

Outcome analysis was performed at a study level. The unit of analysis was at a cohort and subpopulation level with weighting for cohort size. Time to event data was performed where Kaplan–Meier plots with numbers at risk were available.

Data synthesis

Data analysis was performed using "R" statistical software (R Core Team, Vienna, Austria).

Meta-analysis was performed for short term mortality under 1 year using a calculated mean value weighted according to study size.

A time to event analysis was performed for mid and long term mortality outcomes by analysis of published Kaplan–Meier plots with numbers at risk. Data extraction was performed using published numbers at risk and direct extraction of data from high resolution published Kaplan–Meier plots using the digitise R package created by Guyot *et al.*[25] These estimated Kaplan–Meier probabilities of survival were extracted into an Excel spreadsheet alongside numbers at risk for each available annual time point from 1 to 9 years. For those studies not reporting numbers at risk at annual time points, numbers at risk estimation was used according to the method of Tierney *et al.* and Parmer *et al.*[26,27] Applying the methodology described by Combescure *et al.,* meta-analysis of Kaplan–Meier estimated survival probabilities was undertaken.[3] An ascine transformation with continuity correction of 0.25 was applied to probabilities before pooling by a DerSimonian–Laird random effects model; 95% confidence intervals (CIs) for pooled Kaplan–Meier estimated probabilities were obtained by a bootstrapping procedure. This was performed utilising the R package "metasurvival",[28] which also generated mean and median survival times along with assessment of heterogeneity (Q, H^2, and I^2). A summary survival curve was plotted from pooled estimated probabilities and their corresponding 95% CIs. Data maturity was assessed using a Pocock threshold of 10%, which corresponds to when follow up was only achieved in 10% of patients.[29]

Subgroup analyses were performed when appropriate data were reported in three or more studies. This allowed for subgroup analysis of the presence or absence of diabetes and transfemoral amputation (TFA) compared with the transtibial amputation (TTA) level. Estimated subgroup survival probabilities were calculated as above and presented in Kaplan–Meier plots with 95% CIs. Median survival time for each subgroup with 95% CIs was also calculated.

Subgroup analysis

An extended subgroup analysis was performed for mortality at all time points where sufficient data were reported. Analysis was performed on raw data if supplied; otherwise, the odds ratio (OR) was used as a substitute. In addition, adjusted odds ratios (aORs) were analysed separately in those studies reporting them. DerSimonian–Laird random effects modelling using the metafor package in R statistical software[30] was performed and presented as summative OR or aOR with 95% CI. These were visually presented as forest plots.

Heterogeneity was assessed and presented as Cochran's Q, degrees of freedom, I^2 statistic, and *p* values.

Sensitivity analysis

Sensitivity analysis was performed for the time to event analysis and the subgroup meta-analysis. Two techniques were used: a leave one out approach and exclusion of studies deemed of low methodological quality. Low methodological quality was defined as a RoB 2 score of some concern or high RoB, or a NOS of below 7.

RESULTS

Search results

A total of 140 studies reported a mortality outcome and were included in the systematic review and meta-analysis. The screening process of the whole systematic review is presented as a PRISMA flowchart in Figure 1.

Study quality

Two studies were randomised prospective trials and were therefore assessed using the RoB 2 score. Both were found to have a low RoB. The remaining 138 studies reporting mortality were non-randomised and therefore assessed using the NOS. The range of scores was between five and nine points with a mean of 7.8 points scored per study. A total of 119 (86.2%) non-randomised studies had an NOS > 7, suggestive of good study quality. Full details can be found in Supplementary Tables S1 and S2.

Short term mortality

For mortality reported at time points less than 1 year and median survival, pooling of data and calculation of a weighted mean by sample size were performed. Median survival was reported in nine unique cohorts with a weighted mean "median survival" of 29.3 months (2 years, 5.3 months). In hospital mortality was reported in 38 unique cohorts, one of which was excluded for solely recruiting high risk patients. The weighted mean figure was 6.5% (range 1.8 – 34.1%). Thirty day mortality was reported in 50 unique cohorts, three of which were excluded for solely recruiting high risk patients. The weighted mean mortality was 8.7% (range 0 – 26.8%) at this time point. Ninety day mortality was reported in 16 unique cohorts, two of which were excluded for only recruiting high risk or low risk patients. The weighted mean mortality at this time point was 13.5% (range 8.6 – 35.0%). Six month mortality was reported across 17 unique cohorts, one of which was excluded for recruiting solely high risk patients. The weighted mean mortality at this time point was 17.0% (range 3.8 – 36.6%). Short term mortality results are summarised in Table 1. All these results are of low GRADE certainty (Table 2).

Midterm and long term mortality

After 1 year, meta-analysis of time to event data was utilised to establish survival. Nineteen studies comprising of 56 999 patients at risk at the primary time point were included.[7,31–48] Recruitment periods for the studies ranged from 1997 to 2021. Details of studies included can be found in Supplementary Table S3. Using a Pocock threshold of 10%, there was data maturity until 5 years. The median mortality at 1, 2, 3, 4, and 5 years was calculated at 28.9%, 40.4%, 49.1%, 56.9%, and 63.0% respectively, with a median survival time of 3.1 years (95% CI 2.5 – 3.9 years). This is summarised in Table 3 and the summary Kaplan–Meier survival plot shown in Figure 2. These results are of moderate GRADE certainty (Table 2). One cohort was potentially lower risk, having been recruited from a rehabilitation centre, and one cohort was potentially higher risk, recruiting patients with end stage renal disease only; however, a leave one out sensitivity analysis showed no significant difference in median survival on exclusion of these cohorts.

Subgroup analysis of time to event data was possible on two characteristics: those with and without diabetes and those with TFA level compared with TTA. Summative Kaplan–Meier survival plots are shown in Figures 3 and 4. Three studies reported diabetes subgroup data inclusive of 20 007 patients at risk at the primary time point.[33,34,47] Mortality did not differ statistically significantly between those patients with and without diabetes with median survival times of 2.7 years (95% CI 2.0 – 3.5 years) and 3.1 years (1.9 – 4.7 years), respectively, with low GRADE certainty. Six studies reported TFA and TTA level subgroup data inclusive of 43 114 patients at risk at the primary time point.[7,34,38,39,43,47] Mortality was higher for those patients undergoing TFA; however, this only briefly reached significance at the 1 year time point with TFA mortality of 43.8% (95% CI 36.4 – 52.4%) compared with

25.2% (18.3 – 32.8%). Median survival time was worse for those undergoing TFA at 1.7 years (1.0 – 3.0 years) compared with those undergoing TTA at 3.7 (2.4 – 5.5); however, this failed to reach statistical significance. This result was of moderate GRADE certainty.

Subgroup analysis

Returning to the full mortality dataset, risk factors for mortality reported at a sufficient frequency for meta-analysis were end stage renal disease, heart failure, frailty, diabetes, and TFA and through knee amputation level (compared with a baseline of TTA). Meta-analysis was performed for each risk factor where three or more studies reported this subgroup at a particular time point.

End stage renal disease was found to be a significant risk factor at all time points available, with an OR of 2.42 (95% CI 2.11 – 2.70) at 30 days and 5.57 (2.26 – 13.72) at 1 year across five[49–53] and three[49,54,55] studies, respectively. This remained the case when adjusted for other statistically significant variables with a 30 day aOR of 2.61 (2.18 – 3.13) across three studies.[53,56,57] These results were of moderate GRADE certainty. Heart failure was also found to be statistically significant risk factor at all time points available with an OR of 2.14 (1.44 – 3.20) at 30 days and 1.56 (1.32 – 1.84) at 1 year across five[49,51,52,58,59] and four[49,55,58,60] studies, respectively. Again, this remained the case after adjustment at the one time point provided, with an aOR of 2.50 (2.11 – 2.97) at 30 days across five studies.[51,52,56,61,62] These results were of moderate GRADE certainty. Sufficient data for meta-analysis were only provided at 30 days for frailty with a statistically significant OR of 2.25 (1.21 – 4.17), and an aOR at this time point of 3.34 (1.17 – 9.53) across five[40,63–66] and three[40,65,66] studies, respectively. These results were of low GRADE certainty. Diabetes was a non-significant risk factor for mortality at the four time points available[31,33,41,49–52,55,59,60,62,67–71] and this remained the case in the single time point providing an aOR.[41,52,65] These results were of moderate GRADE certainty. With regards to level, TFA had increased odds of mortality compared with TTA at all time points analysed with ORs of 1.91 (1.34 – 2.72) in hospital, 2.30 (2.10 – 2.51) at 30 days, 2.17 (1.58 – 2.97) at 90 days, 1.81 (1.60 – 2.06) at 1 year, 1.46 (1.05 – 2.05) at 3 years, and 1.70 (1.44 – 2.01) at 5 years across six,[67,69,72–75] 17,[41,49–52,58,59,62,64,70,71,76–81] four,[58,71,82,83] 13,[38,39,43,49,58,60,62,71,77–79,84,85] and eight[34,38,39,43,49,58,71,78] studies, respectively. This remained the case for the one time point reporting aOR at 30 days of 1.85 (1.45 – 2.35).[41,51,52,64,65] These results were of moderate GRADE certainty. Through knee amputation level did not significantly increase the odds of mortality over TTA level at 30 days[49,62,70] and 1 year[39,49,62] but was statistically significant with an OR of 1.93 (1.25 – 2.98) at 5 years across three studies.[34,39,49] These results were of very low GRADE certainty. These subanalysis results are summarised in Table 4 and forest plots available in Supplementary Figures S1 – S6.

Assessment of reporting bias was possible in three subgroup analyses, 30 day mortality in patients with or without diabetes and 30 day and 1 year mortality in those with TFA *vs.* TTA level of amputation. Egger's regression p values were insignificant in all assessments at .879, .486, and .581, respectively, suggesting there was no evidence of publication bias. Funnel plots demonstrating this visually are presented in Supplementary Figure S7.

Subgroup sensitivity analysis was performed with both a leave one out and study quality threshold technique without the significance of any results being affected.

Summary of results for patients with diabetes (with or without peripheral arterial disease) compared with those with peripheral arterial disease alone

Three studies reported diabetes subgroup data inclusive of 20 007 patients at risk at the primary time point.[33,34,47] Mortality did not statistically significantly differ between those patients with and without diabetes with median survival times of 2.7 years (95% CI 2.0 – 3.5 years) and 3.1 years (1.9 – 4.7 years), respectively, with low GRADE certainty.

Diabetes was a non-significant risk factor for mortality at the four time points available[31,33,41,49–52,55,59,60,62,67–71] and this remained the case in the single time point providing an aOR.[41,52,65] Meta-analysed ORs were 0.76 (95% CI 0.19 – 3.06) for inpatient mortality, 0.97 (0.83 – 1.14) for 30 day mortality, 1.07 (0.75 – 1.53) for 1 year mortality, and 0.84 (0.49 – 1.45) for 5 year mortality with adjusted OR meta-analysis possible only at 30 days at 1.04 (0.79 – 1.35). These results were of moderate GRADE certainty.

DISCUSSION

To estimate short term mortality after major lower limb amputation, a mean value weighted by study size was calculated, which is a well established technique. This technique was used in these patient cohorts as loss to follow up is less of a problem in the short term and time to event data were lacking. In hospital mortality of 6.5% was observed in this study and it is comparable with the UK National Vascular Registry's in hospital 30 day 2024 mortality figure of 5.7%.[86] Both this figure and 30 day mortality of 8.7% observed in this study are well within the 4 – 20% and 7 – 22% ranges determined by previous meta-analysis.[87]

Regarding mid and long term mortality, previous meta-analyses have found this to be high, with 1 year mortality estimates ranging from 33.7% to 47.9% and 5 year estimates ranging from 62.2% to 64.4%.[1,2] The estimated midterm mortality was found to be lower than in previous studies with a 1 year mortality estimate of 28.9% (95% CI 25 – 32.9%); however, the long term mortality estimate was found to be more comparable at 63% (95% CI 57.7 – 67.9%).

The time to event analysis used differs from previously performed mid and long term mortality meta-analyses in two important ways. Firstly, previous meta-analyses were performed using a pooled mean value weighted by study size. Whilst this is a valid technique, and one used in other areas of meta-analysis in this study, it loses accuracy in longer term analysis for failing to account for loss to follow up and study heterogeneity. A robust time to event analysis technique was used based upon only studies supplying high quality data in the form of a Kaplan–Meier plot to back calculate survival estimates and published numbers at risk. This technique therefore incorporates loss to follow up at each time point assessed. A random effects model was then used, which allowed the production of a summary survival curve with 95% CI, considering study heterogeneity. In addition to this, due to the nature of this systematic review, only papers published within the last 5 years were included. This meant that all studies included in the time to event analysis recruited patients from 1997 onwards, giving a contemporary estimate for mortality. Previous meta-analyses have considered all historical data, which may detract from the current picture.

Whilst the data are encouraging that midterm mortality may be lower than previously estimated for the patients undergoing major lower limb amputation in this study it remains high with over one in four patients dead within a year. This reduction in mortality may be due to changes in patient selection with more patients managed palliatively than before. Whilst on the surface conservative or palliative management may seem like a failure of treatment, it could also be argued that this is highly appropriate for patients with a prognosis of under 1 year with or without major lower limb amputation, with these patients avoiding the physical and psychological trauma of major lower limb amputation for little benefit. Alternatively, it may be that these patients are managed in a better way in the peri- and post-operative periods, with better pre-operative medical optimisation, enhanced peri-operative care, and early recognition of complications. The trend towards increased multidisciplinary input for these patients, especially in the form of an experienced peri-operative physician, may well be responsible for this. With good evidence that this was the case for a similarly frail and comorbid group of patients when geriatric services were integrated into orthopaedic practice.[88] The 5 year figure of 63%, nearly two in three patients, dying by 5 years remains alarming but likely reflects the severe underlying systemic disease these patients have, leading to them requiring a major lower limb amputation in the first place.

One unique aspect of this study is the ability to assess the influence of different risk factors at different time points.

Four risk factors conveyed higher risk of death after major lower limb amputation. End stage renal disease increased mortality at all time points assessed, including in studies that adjusted for confounders. The frankly alarming 5.57 times odds of death at 1 year compared with those without the condition paints a stark picture for this patient group. Heart failure, frailty, and a higher level of amputation also conferred a higher mortality risk. Interestingly, diabetes was not a significant risk factor for mortality at any time point, and this remained the case when adjusted for confounders at 30 days. These results again highlight the importance of personalised risk assessment for the amputees included in this study given the complex interplay of multiple independent risk factors across outcomes. An individualised approach with multidisciplinary team input from surgeons, medics, therapists, and rehabilitation specialists, alongside consideration of risk prediction scores such as AMPREDICT,[89] is therefore required to obtain the best outcomes for included patients. Patients with multiple identified risk factors may benefit from an early referral to palliative care services as an alternative to major lower limb amputation, therefore avoiding the distress of surgery and having increased autonomy in their final days of life.

The limitations of this study are those inherent to a systematic review and meta-analysis of mainly retrospective data. The dataset captured in this study was large and heterogeneous. The time to event analysis technique followed attempts to mitigate this, but the number of studies presenting high quality survival estimates, especially with subgroups, is relatively low. The subgroup analysis used is therefore mainly based on single time point raw data or published ORs based on all papers reporting these figures. This uses less robust data but allowed the authors to assess multiple risk factors at multiple time points. Where time to event analysis subgroup data did allow analysis, the results broadly corroborated with the larger dataset. Publication of high quality survival analysis with multiple subgroups in future studies will greatly ease subsequent meta time to event analysis. Inherent to this patient group, many studies had a significant loss to follow up, it is therefore important to take this into account for this study's long term analyses. The time to event analysis dataset in this study retained a Pocock threshold of 10% until 5 years, suggesting analysis up to this point was justified. The time to event analysis in this study, although comprising of only recently published studies, included cohorts recruited as far back as 1997. Management of this patient population may have changed over time, and therefore this may not be a true reflection of contemporary outcomes. Finally, diabetes in the subgroup analysis of this study was included as a comorbidity and not as an indication for major lower limb amputation, patients presenting with diabetic foot infection may represent a different subgroup not analysed in this study.

Conclusion

Mortality after major lower limb amputation remains high in the contemporary era; however, there appears to be a trend towards improved midterm survival. Long term survival remains poor with a median survival time of 3.1 years. The sustained impact of end stage renal disease, heart failure, frailty, and TFA level on mortality at all time points, even persisting in studies adjusting for confounders, highlights the importance of comanagement with an experienced peri-operative physician and appropriate risk counselling in these patient groups.

CONFLICT OF INTEREST

None.

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None.

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FIGURE LEGENDS

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for studies reporting mortality as an outcome for major lower limb amputation limited to 5 years.

Figure 2. Cumulative Kaplan–Meier estimate of survival in time to event analysis of mid and long term survival after major lower limb amputation inclusive of 56 999 patients. Black dot = end of cohort follow up; black dotted line = pooled median survival (3.1 years); grey lines = individual cohorts; dotted red lines = 95% confidence intervals; solid red line = pooled random effects survival probability.

Figure 3. Cumulative Kaplan–Meier estimate of survival in time to event analysis of mid and long term survival after major lower limb amputation in the diabetes subgroup analysis inclusive of 20 007 patients. Black dot = end of cohort follow up; bold red and blue line = pooled random effects survival probability; dotted red and blue lines = 95% confidence intervals; faded red and blue lines = individual cohorts.

Figure 4. Cumulative Kaplan–Meier estimate of survival in time to event analysis of mid and long term survival after major lower limb amputation in the amputation level subgroup analysis inclusive of 43 114 patients. Black dot = end of cohort follow up; dotted blue and red lines = 95% confidence intervals; faded blue and red lines = individual cohorts; solid blue and red lines = pooled random effects survival probability; TFA = transfemoral amputation, TTA = transtibial amputation.

TABLES

Table 1. Summary of short term mortality meta-analysis using pooled weighted mean calculation for mortality estimation.

Mortality estimation	**Studies reporting**	**Studies after deduplication**	**Studies after removal of high/low risk cohorts**	**Patients – *n***	**Transfemoral amputation**	**Through knee amputation**	**Transtibial amputation**	**Weighted mean mortality – %**
In hospital mortality	41	38	37	260 820	40 030	577	83 764	6.5
30 d mortality	66	50	47	150 382	61 727	200	75 760	8.7
90 d mortality	16	16	14	38 989	13 231	107	23 345	13.5
6 mo mortality	19	17	16	23 424	5 409	83	7 241	17.03

Table 3. Summary of studies included in the time to event meta-analysis of mid to long term mortality and summary mortality estimates.

Time point	Studies – *n*	Patients – *n*	Estimated mortality (95% CI) – %
1 y	19	59 999	28.9 (25.0–32.9)
2 y	18	28 101	40.4 (35.5–45.4)
3 y	16	18 419	49.1 (43.5–54.6)
4 y	15	12 014	56.9 (51.1–62.4)
5 y	14	6 997	63.0 (57.7–67.9)

CI = confidence interval.

Table 2. Grading of Recommendations Assessment, Development, and Evaluations (GRADE) certainty assessment for meta-analysis, time to event analysis, and risk factor subgroup meta-analysis outcomes.

Quality assessment								**Effect—median survival – y odds ratio (OR) or adjusted odds ratio (aOR) with 95% CI**	**Quality**
Studies – *n*, (patients – *n*)	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**–**	**–**
Short term mortality—In hospital									
37 (260 820)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias*		Weighted mean mortality 6.5% (range 1.8–34.1%)	⊕⊕OO Low
Short term mortality —30 d									
47 (150 382)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias*		Weighted mean mortality 8.7% (range 0–26.8%)	⊕⊕OO Low
Short term mortality—90 d									
14 (38 989)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias*		Weighted mean mortality 13.5% (range	⊕⊕OO Low

								8.6–35.0%)	
Short term mortality—6 mo									
16 (23 424)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias*		Weighted mean mortality 17.0% (range 3.8–36.6%)	⊕⊕OO Low
Time to event—overall mortality, median survival (I^2 95.7%)									
19 (56 999)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*		Median survival 3.1 years (2.5–3.9)	⊕⊕⊕O Moderate
Time to event—diabetes subgroup analysis (I^2 84.1%)									
3 (20 007)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*		Median survival Diabetes 2.7 y (2.0–3.5) No diabetes 3.1y (1.9–4.7)	⊕⊕OO Low
Time to event—level subgroup analysis (I^2 96.5%)									
6 (43 114)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*		Median survival TTA 1.7 y (1.0–3.0) TFA 3.7 y (2.4–5.5)	⊕⊕⊕O Moderate
Subgroup analysis—end stage renal disease (overall mortality)									
30 d (5) 1 y (3) a30 d (3)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*		OR 2.42 (2.11–2.79) OR 5.57 (2.26–13.72) aOR 2.61 (2.18–3.13)	⊕⊕⊕O Moderate
Subgroup analysis—heart failure (overall mortality)									
30 d (5) 1 y (4) a30 d (5)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*		OR 2.14 (1.44–3.20)	⊕⊕⊕O Moderate

								OR 1.56 (1.32–1.84) aOR 2.50 (2.11–2.97)	
Subgroup analysis – frailty – overall mortality									
30 d (5) a30 d (3)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Moderate risk of publication bias*, imprecise definition of frailty		OR 2.25 (1.21–4.17) aOR 3.34 (1.17–9.53)	⊕⊕OO Low
Subgroup analysis—diabetes (overall mortality)									
In hospital (4) 30 d (10) 1 y (7) 5 y (5) a30 d (3)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Low to moderate risk of publication bias*		OR 0.76 (0.19–3.06) OR 0.97 (0.83–1.14) OR 1.07 (0.75–1.53) OR 0.84 (0.49–1.45) aOR 1.04 (0.79–1.35)	⊕⊕⊕O Moderate
Subgroup analysis—TFA level compared with TTA baseline (overall mortality)									
In hospital (6) 30 d (17) 90 d (4) 1 y (13) 5 y (8) a30 d (5)	Observational cohort studies	Not serious	Serious†	Not serious	Not serious	Low to moderate risk of publication bias*		OR 1.91 (1.34–2.72) OR 2.30 (2.10–2.51) OR 2.17 (1.58–2.97) OR 1.81 (1.60–2.06) OR 1.70 (1.44–2.01) aOR 1.85	⊕⊕⊕O Moderate

								(1.45–2.35)	
Subgroup analysis—TKA level compared with TTA baseline (overall mortality)									
30 d (3) 1 y (3) 5 y (3)	Observational cohort studies	Not serious	Serious[†]	Not serious	Serious	Moderate risk of publication bias[*], small overall patient numbers with TKA		OR 2.61 (0.55–12.38) OR 2.12 (0.89–5.01) OR 1.93 (1.25–2.98)	⊕OOO Very low

OR = odds ratio; aOR = adjusted odds ratio; CI = confidence interval; I^2 = assessment of heterogeneity; TTA = transtibial amputation; TFA = transfemoral amputation; a = adjusted for confounders; TKA = through knee amputation.

[*] Retrospective studies were deemed to have at least a moderate risk of publication bias unless formal assessment via funnel plots and Egger's regression were possible.

[†] At least one subgroup analysis had high or moderate heterogeneity as guided by I^2 statistic.

Table 4. Summary of risk factor subgroup meta-analysis with 30 day, 1 year, and 5 year odds ratio (OR) estimates.

Risk factor	**30 day OR (95% CI)**	**1 year OR (95% CI)**	**5 year OR (95% CI)**
End stage renal disease	2.42 (2.11–2.79)	5.57* (2.26–13.72)	NA
Heart failure	2.14* (1.44–3.20)	1.56 (1.32–1.84)	NA
Frailty	2.25* (1.21–4.17)	NA	NA
Diabetes	0.97 (0.83–1.14)	1.07 (0.75–1.53)	0.84 (0.49–1.48)
TFA level	2.30* (2.10–2.51)	1.81 (1.60–2.06)	1.70 (1.44–2.01)
TKA level	2.61 (0.55–12.38)	2.12 (0.89–5.01)	1.93* (1.25–2.98)

OR = odds ratio; CI = confidence interval; NA = ?; TFA = transfemoral amputation; TKA = through knee amputation.

* These values represent peak odds ratio.

Table 1 – Summary of short-term mortality meta-analysis using pooled weighted mean calculation for mortality estimation

	Studies reporting	Studies after de-duplication	Studies after removal of high/low risk cohorts	Number of patients	Transfemoral amputation	Through-knee amputation	Transtibial amputation	Weighted mean mortality
In hospital mortality	41	38	37	260 820	40 030	577	83 764	6.48%
30-day mortality	66	50	47	150 382	61 727	200	75 760	8.68%
90-day mortality	16	16	14	38 989	13 231	107	23 345	13.46%
6-month mortality	19	17	16	23 424	5 409	83	7 241	17.03%

Table 2 – Summary of studies included in the time-to-event meta-analysis of mid- to long-term mortality and summary mortality estimates

Time-point	Studies	Patients	Estimated mortality (95% confidence interval)
1 year	19	59 999	28.9% (25.0 - 32.9)
2 years	18	28 101	40.4% (35.5 – 45.4)
3 years	16	18 419	49.1% (43.5 - 54.6)
4 years	15	12 014	56.9% (51.1– 62.4)
5 years	14	6 997	63.0% (57.7 – 67.9)

Table 3 – GRADE certainty assessment for meta-analysis, time-to-event analysis and risk-factor subgroup meta-analysis outcomes.

Quality assessment								**Effect – median survival in years, odds ratio (OR) or adjusted odds ratio (aOR). Numbers in brackets are 95% confidence interval**	**Quality**
Studies – *n, (patients - n)*	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
Short term mortality – In hospital									
37 (260 820)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias[+]		Weighted mean mortality 6.5% (range 1.8-34.1)	⊕⊕OO Low
Short term mortality – 30-day									
47 (150 382)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias[+]		Weighted mean mortality 8.7% (range 0- 26.8)	⊕⊕OO Low
Short term mortality – 90-day									
14 (38 989)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias[+]		Weighted mean mortality 13.5% (range 8.6-35.0)	⊕⊕OO Low
Short term mortality – 6-month									
16 (23 424)	Observational cohort studies	Not serious	Not serious	Not serious	Serious	Moderate risk of publication bias[+]		Weighted mean mortality 17.0% (range 3.8-36.6)	⊕⊕OO Low
Time to event – Overall mortality – Median survival - I^2 95.7%									
19 (56 999)	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+]		Median survival 3.1 years (2.5-3.9)	⊕⊕⊕O Moderate
Time to event – Diabetes subgroup analysis – I^2 84.1%									
3 (20 007)	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+]		Median survival Diabetes 2.7 years (2.0-3.5), No diabetes 3.1 (1.9-4.7)	⊕⊕OO Low
Time to event – Level subgroup analysis - I^2 96.5%									
6 (43 114)	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+]		Median survival TTA 1.7 years (1.0-3.0), TFA 3.7 years (2.4-5.5)	⊕⊕⊕O Moderate
Subgroup analysis – End stage renal disease– Overall mortality									
30-day: 5 1-year: 3 a30-day: 3	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+]		OR 2.42 (2.11-2.79) OR 5.57 (2.26-13.72) aOR 2.61 (2.18-3.13)	⊕⊕⊕O Moderate
Subgroup analysis – Heart failure – Overall mortality									
30-day: 5 1-year: 4 a30-day: 5	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+]		OR 2.14 (1.44-3.20) OR 1.56 (1.32-1.84) aOR 2.50 (2.11-2.97)	⊕⊕⊕O Moderate
Subgroup analysis – Frailty – Overall mortality									
30-day: 5 a30-day: 3	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias[+], imprecise definition of frailty		OR 2.25 (1.21-4.17) aOR 3.34 (1.17-9.53)	⊕⊕OO Low
Subgroup analysis – Diabetes – Overall mortality									
In-hospital: 4 30-day: 10 1-year: 7 5-year: 5 a30-day: 3	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Low to moderate risk of publication bias[+]		OR 0.76 (0.19-3.06) OR 0.97 (0.83-1.14) OR 1.07 (0.75-1.53) OR 0.84 (0.49-1.45) aOR 1.04 (0.79-1.35)	⊕⊕⊕O Moderate
Subgroup analysis – TFA level compared to TTA baseline – Overall mortality									
In-hospital 6 30-day: 17 90-day: 4 1-year: 13 5-year 8 a30-day: 5	Observational cohort studies	Not serious	Serious*	Not serious	Not serious	Low to moderate risk of publication bias[+]		OR 1.91 (1.34-2.72) OR 2.30 (2.10-2.51) OR 2.17 (1.58-2.97) OR 1.81 (1.60-2.06) OR 1.70 (1.44-2.01) aOR 1.85 (1.45-2.35)	⊕⊕⊕O Moderate
Subgroup analysis – TKA level compared to TTA baseline – Overall mortality									
30-day: 3 1-year: 3 5-year: 3	Observational cohort studies	Not serious	Serious*	Not serious	Serious	Moderate risk of publication bias[+], small overall patient numbers with TKA		OR 2.61 (0.55-12.38) OR 2.12 (0.89-5.01) OR 1.93 (1.25-2.98)	⊕OOO Very low

OR – odds ratio, a – adjusted for confounders, I^2 – assessment of heterogeneity, TFA – transfemoral amputation, TTA – transtibial amputation, TKA – through knee amputation

*At least one subgroup analysis had high or moderate heterogeneity as guided by I^2 statistic

[+]Retrospective studies were deemed to have at least a moderate risk of publication bias unless formal assessment via funnel plots and Egger's regression were possible

Table 4 – Summary of risk factor subgroup meta-analysis with 30-day, 1-year and 5-year odds ratio estimates with 95% confidence intervals

Risk factor	**30-day odds ratio (95% confidence interval)**	**1-year odds ratio (95% confidence interval)**	**5-year odds ratio (95% confidence interval)**
End-stage renal disease	2.42 (2.11-2.79)	**5.57** (2.26-13.72)	NA
Heart failure	**2.14** (1.44-3.20)	1.56 (1.32-1.84)	NA
Frailty	**2.25** (1.21-4.17)	NA	NA
Diabetes	0.97 (0.83-1.14)	1.07 (0.75-1.53)	0.84 (0.49-1.48)
TFA level	**2.30** (2.10-2.51)	1.81 (1.60-2.06)	1.70 (1.44-2.01)
TKA level	2.61 (0.55-12.38)	2.12 (0.89-5.01)	**1.93** (1.25-2.98)

Numbers in bold - peak odds ratio, numbers in brackets – 95% confidence intervals

TFA – transfemoral amputation, TKA – though knee amputation

Figure 1 – The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for studies reporting mortality as an outcome for major lower limb amputation limited to 5 years

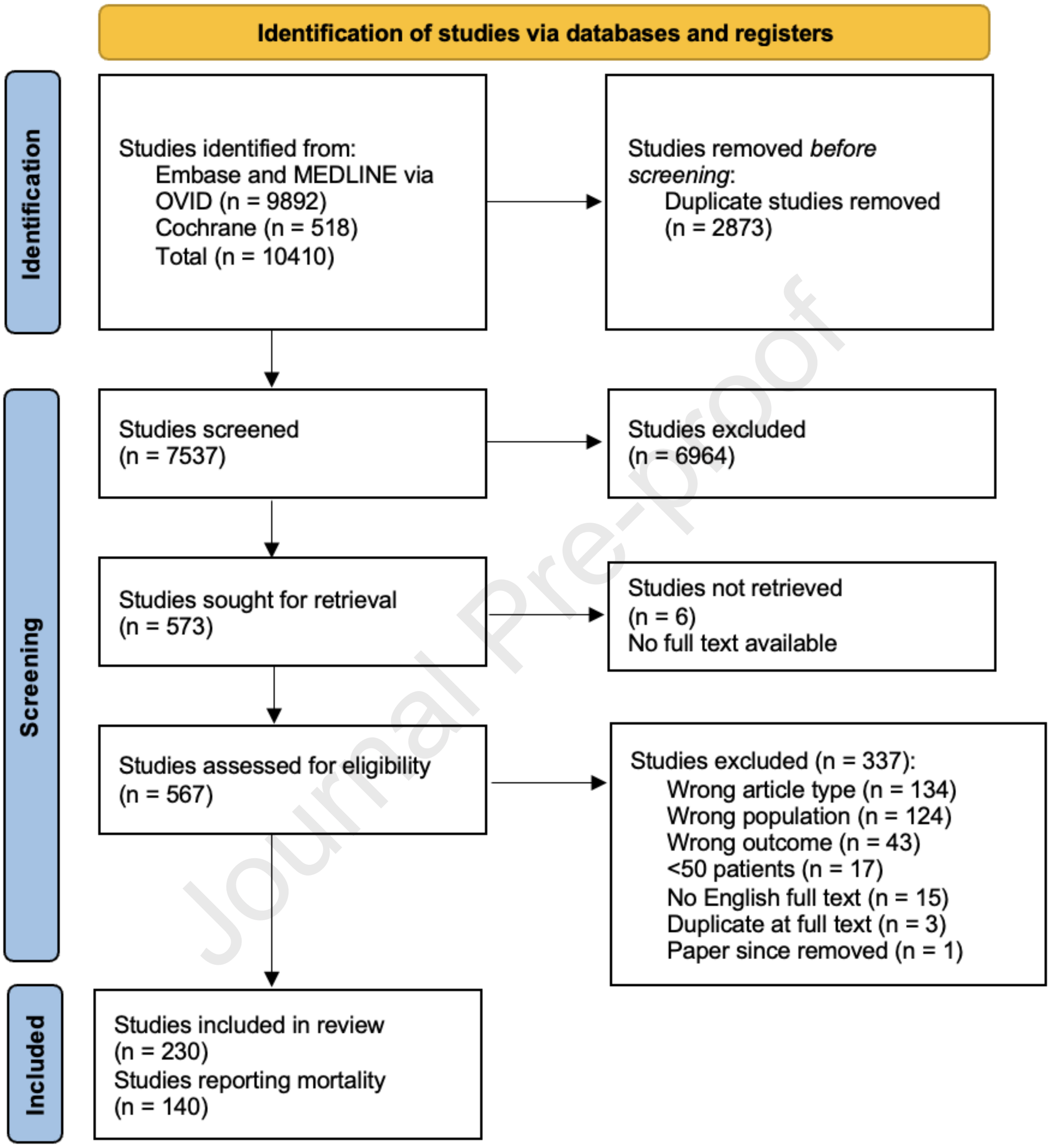
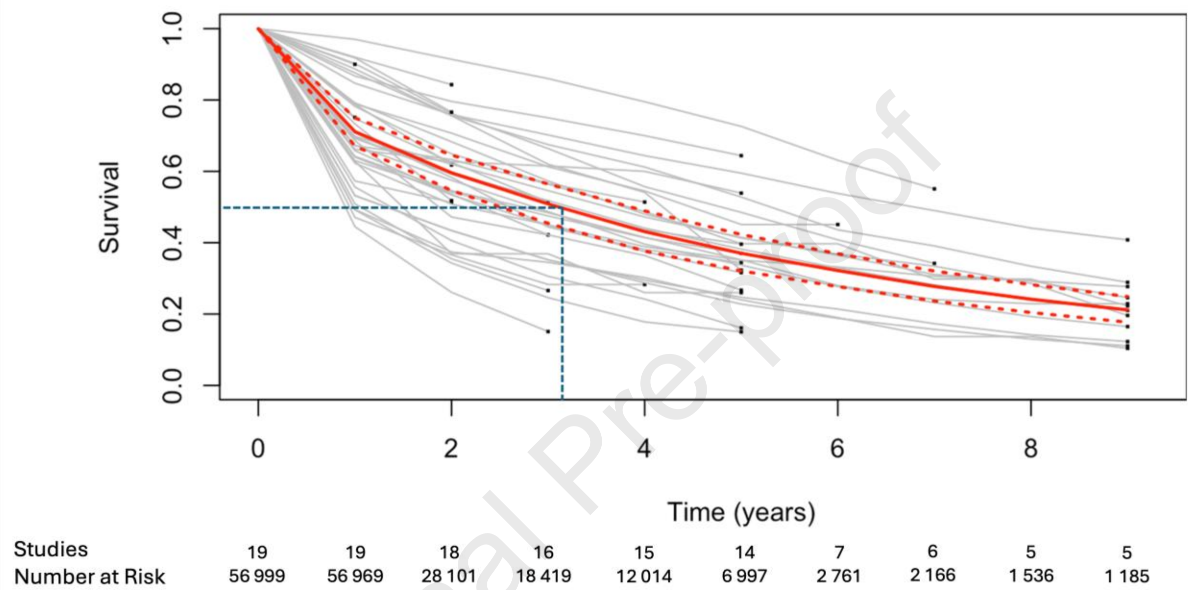
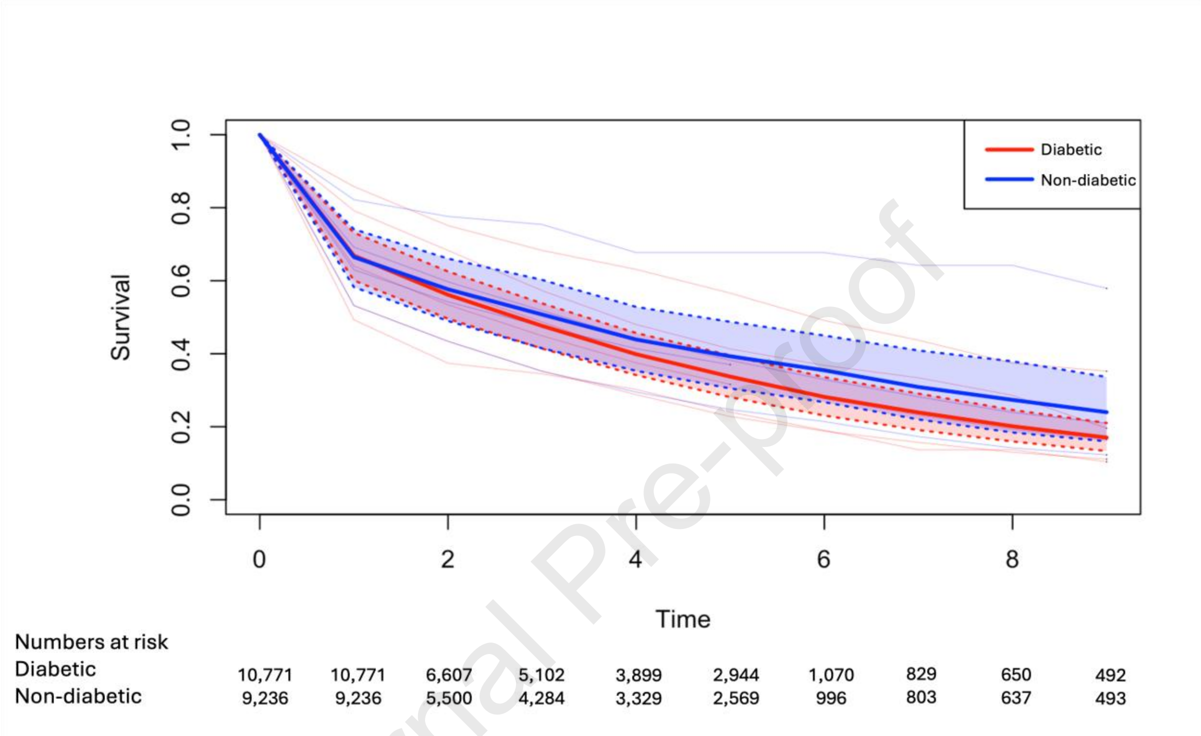


Figure 2 – Summary Kaplan-Meier survival plot for time-to-event analysis of mid- and long-term survival after major lower limb amputation inclusive of 56 999 patients, with individual cohorts plotted as grey lines, pooled random-effects survival probability plotted as red line with 95% confidence intervals as dotted red lines, and median survival shown as dotted black lines.



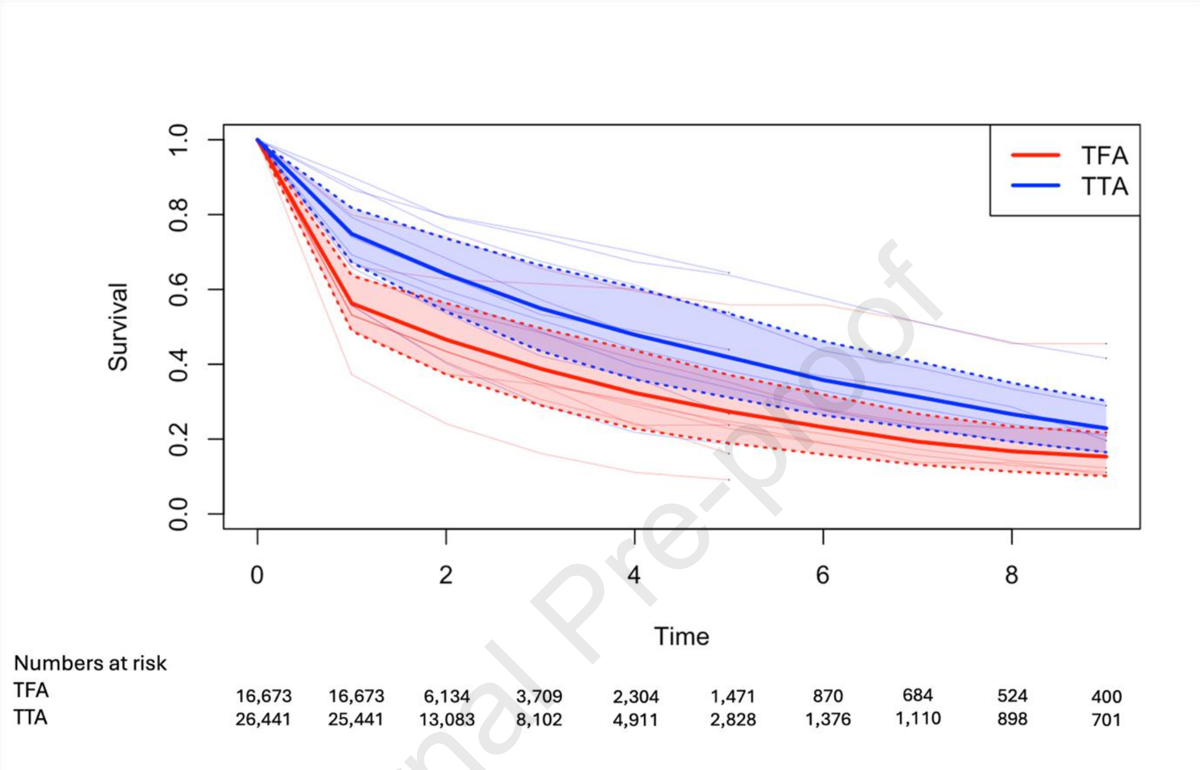
Grey lines – individual cohorts, black dot – end of cohort follow-up, solid red line – pooled random-effects survival probability, dotted red lines – 95% confidence intervals, black dotted line – pooled median survival (3.1 years)

Figure 3 – Diabetes subgroup analysis summary Kaplan-Meier survival plot for time-to-event analysis of mid- and long-term survival after major lower limb amputation inclusive of 20 007 patients, with individual cohorts plotted as faded blue and red lines, pooled random-effects survival probability plotted as solid red and blue line with 95% confidence intervals as dotted red and blue lines



Faded lines – individual cohorts, black dot – end of cohort follow-up, Bold lines – pooled random-effects survival probability, dotted lines – 95% confidence intervals.

Figure 4 – Amputation level subgroup analysis summary Kaplan-Meier survival plot for time-to event analysis of mid- and long-term survival after major lower limb amputation inclusive of 43 114 patients, with individual cohorts plotted as faded blue and red lines, pooled random-effects survival probability plotted as solid red and blue line with 95% confidence intervals as dotted red and blue lines



Faded lines – individual cohorts, black dot – end of cohort follow-up, Bold lines – pooled random-effects survival probability, dotted lines – 95% confidence intervals, TFA – transfemoral amputation, TTA – Transtibial amputation