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Clinical Outcomes of Below-Knee Amputation (BKA) in Diabetic Patients: Predictive Factors for Wound Healing — A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Introduction: Below-knee (transtibial) amputation is the most frequently performed major limb ablation in diabetes, with lower wound healing rates and higher re-amputation rates than above-knee amputation. Predictive factors for stump healing remain fragmented across the literature.

Methods: PRISMA 2020 systematic review and DerSimonian-Laird random-effects meta-analysis of primary studies reporting adjusted associations between preoperative predictors and wound healing/re-amputation outcomes. Heterogeneity assessed by I^2 and τ^2 , leave-one-out sensitivity analysis, and GRADE certainty.

Results: Renal failure/dialysis increased risk (HR 2.00; 95% CI 1.45-2.77; $p<0.001$). CRP/albumin or BUN/albumin ratio had the largest effect (HR 3.00; 95% CI 2.04-4.42; $p<0.001$; $I^2=0\%$). Glycaemic dysregulation: HR 2.52 (95% CI 1.69-3.75; $p<0.001$). Abnormal ABI: HR 2.00 (95% CI 1.29-3.12; $p=0.002$). Hypoalbuminaemia predicted healing (HR 1.59; $p=0.020$) and mortality (HR 2.27; $I^2=0\%$). Other factors: non-ambulatory status (HR 1.65), anatomical ischaemia (HR 1.60), diabetes (HR 1.53), infection (HR 1.37), and smoking (HR 1.31). Adjunctive advanced wound therapy vs standard care was not significant (HR 1.36; 95% CI 0.76-2.43; $p=0.298$; $I^2=70\%$).

Discussion: Below-knee amputation wound healing failure in diabetes arises from four convergent pathophysiological axes: macro/microvascular insufficiency, protein-energy wasting with systemic inflammation, uraemic tissue dysfunction, and persistent infective burden. Inexpensive laboratory biomarkers carry prognostic weight comparable to advanced perfusion measurement.

Conclusion: Wound healing failure after below-knee amputation in diabetes is predicted by renal failure, hypoalbuminaemia, glycaemic dysregulation, abnormal ABI, and inflammatory-nutritional ratios. These variables should inform amputation-level decisions and preoperative optimisation.

Keywords: below-knee amputation; transtibial amputation; diabetes mellitus; diabetic foot; wound healing; re-amputation; hypoalbuminaemia; end-stage renal disease

INTRODUCTION

Background

Diabetes mellitus has become the dominant cause of non-traumatic lower-extremity amputation worldwide. Approximately 18.6 million people are affected by a diabetic foot ulcer annually, and such ulcers precede roughly 80% of all lower-extremity amputations occurring in people with diabetes. The lifetime incidence of foot ulceration in the diabetic population is estimated at 19% to 34%, with recurrence rates of 65% within three to five years, a lifetime major

amputation incidence approaching 20%, and five-year mortality of 50% to 70% following ulceration. Once a major amputation has been performed, five-year mortality exceeds 70%, a prognosis substantially worse than that of most solid organ malignancies.^{1,2}

Nationwide epidemiological data reinforce the magnitude of this burden. In a Japanese national cohort encompassing 150 million individuals, the age- and sex-adjusted incidence of major lower-limb amputation was 9.5 times higher and that of minor amputation 14.9 times higher among people with diabetes than among those without. In a New Zealand national prevalent cohort of 217,207 individuals with diabetes, more than half of patients undergoing major amputation died within three years of the procedure, and a prior minor amputation increased the hazard of subsequent major amputation approximately tenfold. Scottish national data linking 233,459 people with diabetes similarly demonstrated markedly reduced amputation-free survival in association with a history of foot ulceration.^{3,4,54}

Below-knee amputation, performed at the transtibial level, occupies a uniquely consequential position within this clinical pathway. Preservation of the knee joint confers substantially greater prosthetic fitting rates, lower energy expenditure during gait, superior functional independence and, in contemporary series, improved long-term survival relative to transfemoral amputation; reported prosthesis utilisation of 38% after below-knee amputation compared with 14% after above-knee amputation, and five-year survival of 63% versus 51%, illustrate the functional and prognostic premium attached to knee preservation. This advantage is, however, purchased at the cost of a demonstrably higher risk of stump wound failure. Contemporary pooled data indicate that poor wound healing occurs approximately twice as often after below-knee than after above-knee amputation, and that ipsilateral surgical re-intervention is more than 2.5 times as likely.^{21,44}

The clinical corollary is that amputation-level selection in the diabetic patient is fundamentally a prognostic exercise. The surgeon must estimate, preoperatively, the probability that a transtibial stump will heal primarily, and must weigh that probability against the functional penalty of a more proximal but more reliably healing level. Failure of this estimation carries substantial cost: re-amputation delays prosthetic fitting, prolongs immobility, precipitates deconditioning and knee contracture, and imposes a prolonged open wound upon a physiologically fragile patient. Reported ipsilateral re-amputation risk within twelve months of a first transtibial

amputation is approximately 25%, and single-centre studies employing adequate surveillance periods have documented unplanned reoperation rates as high as 38% at one year.^{5,6,31}

Pathophysiological Rationale

Impaired wound healing in diabetes is multifactorial. Chronic hyperglycaemia drives the formation of advanced glycation end-products and activation of the AGE–RAGE–NF-κB axis, augmenting oxidative stress and impairing the transition of macrophages from the pro-inflammatory M1 to the reparative M2 phenotype. Neuropathy abolishes protective sensation and disrupts the neurogenic component of the inflammatory response. Macrovascular disease, with its characteristic predilection for infrapopliteal and below-the-ankle segments in diabetic patients, restricts the delivery of oxygen and substrate to the healing incision. Superimposed protein-energy wasting depletes the substrate pool required for collagen synthesis and immune competence, while uraemia and dialysis-associated inflammation further compromise angiogenesis and fibroblast function.^{1,2,52}

Each of these mechanistic axes generates candidate clinical predictors that are measurable preoperatively: perfusion indices such as the ankle–brachial index and transcutaneous oxygen tension; metabolic indices such as glycated haemoglobin and glycaemic variability; nutritional and inflammatory indices such as serum albumin, C-reactive protein and their derived ratios; renal indices including dialysis dependence and blood urea nitrogen; infective indices including preoperative sepsis, osteomyelitis and wound infection; anatomical indices such as Rutherford class, Wiffl stage and GLASS grade; and functional indices such as ambulatory status and grip strength. The clinical value of this heterogeneous evidence has, however, been limited by its fragmentation.^{13,14,25,26}

Research Gap

Three specific deficiencies characterise the existing literature. First, prognostic studies of amputation outcome have been overwhelmingly single-domain in construction, examining perfusion, nutrition, glycaemia or infection in isolation, such that the relative quantitative weight of each domain remains undetermined. Second, the available quantitative syntheses address either the diagnostic accuracy of a single modality — most notably transcutaneous oximetry — or the crude incidence of stump complications, rather than pooling adjusted prognostic associations across domains. Third, no synthesis has explicitly juxtaposed randomized evidence on adjunctive

stump wound therapy against the observational evidence on the same interventions, despite a marked discordance between the two literatures.^{43,44,45}

A further gap concerns the absence of prediction intervals, leave-one-out robustness testing and formal certainty rating in the existing amputation prognosis literature, which has limited the translation of published associations into defensible clinical decision rules. Existing prediction instruments, while methodologically sound, have been developed within single national health systems and rely upon variable sets whose external transportability to resource-constrained settings — including those in which the burden of diabetic foot disease is rising most rapidly — has not been established.^{2,56}

Novelty of the Present Work

This systematic review and meta-analysis is, to the authors' knowledge, the first to undertake all of the following within a single analytical framework:

- Simultaneous random-effects meta-analysis of twelve discrete prognostic and therapeutic outcomes spanning the renal, nutritional, inflammatory, infective, haemodynamic, metabolic, functional, anatomical and therapeutic domains relevant to below-knee amputation stump healing.
- Explicit separation of primary studies (randomized controlled trials, cohort, case-control, cross-sectional and other observational designs) from previously published systematic reviews and meta-analyses, with the latter excluded from the principal characteristics table and primary synthesis but retained as an independent corroborative evidence stratum.
- Provision of 95% prediction intervals, Egger small-study-effect testing and complete leave-one-out sensitivity analysis for every outcome with three or more contributing studies, thereby quantifying not only the average effect but its expected dispersion in future settings.
- Direct juxtaposition of randomized and non-randomized evidence concerning adjunctive advanced wound therapy, permitting formal appraisal of design-dependent bias.
- Derivation of a domain-weighted preoperative risk architecture translatable into a bedside multidomain optimisation checklist applicable in both high-resource and resource-constrained health systems.

Objectives

The general objective was to determine, quantitatively and with graded certainty, the predictive factors governing wound healing outcomes after below-knee and major lower-extremity amputation in patients with diabetes mellitus. The specific objectives were as follows:

- To identify and critically appraise all primary studies reporting adjusted associations between preoperative or perioperative variables and stump/wound healing outcomes in diabetic amputation populations.
- To derive pooled random-effects estimates for each identified predictor domain, with quantification of between-study heterogeneity.
- To estimate the pooled effect of adjunctive advanced wound therapy relative to standard care upon complete wound healing, restricted to randomized evidence.
- To evaluate the robustness of each pooled estimate through leave-one-out sensitivity analysis, prediction intervals and small-study-effect testing.
- To assign GRADE certainty ratings to each pooled outcome and to translate the findings into an actionable preoperative optimisation framework.

Benefits of the Study

The anticipated benefits are threefold. For the individual patient, the derivation of a multidomain risk profile permits more accurate prognostication, more realistic informed consent and identification of modifiable physiological deficits amenable to preoperative correction. For the surgical team, quantified domain weights inform the selection of amputation level, the timing of surgery relative to infection control and nutritional repletion, and the allocation of intensified postoperative wound surveillance. For health systems, particularly those in low- and middle-income settings where the incidence of diabetic foot disease is rising most steeply and where advanced perfusion assessment may be unavailable, the demonstration that inexpensive laboratory indices carry prognostic weight comparable to sophisticated haemodynamic measurement offers a pragmatic and scalable route to risk stratification.

Hypotheses

Null hypothesis (H_0): There is no statistically significant association between the candidate preoperative predictors under investigation — renal replacement dependence, hypoalbuminaemia, inflammatory–nutritional biomarker elevation, stump or wound infection, non-ambulatory status, abnormal ankle–brachial index, advanced anatomical ischaemia,

glycaemic dysregulation, active smoking and diabetes status — and failure of wound healing following below-knee or major lower-extremity amputation in diabetic patients.

Alternative hypothesis (H₁): Each of the candidate predictors is independently and significantly associated with an increased hazard of impaired stump wound healing, with pooled effect estimates significantly greater than unity.

Secondary hypothesis (H₂): Adjunctive advanced wound therapy, when compared with standard wound care within randomized controlled trials, significantly increases the probability of complete wound healing in diabetic lower-extremity wounds and amputation stumps.

METHODS

Protocol, Registration and Reporting Standards

The review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, and, given the predominance of non-randomized evidence, additionally observed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations. A structured a priori protocol specified the review question, eligibility criteria, information sources, search strategy, data items, risk-of-bias instruments, effect measures, synthesis methods, sensitivity analyses and certainty appraisal. All post hoc analytical decisions are explicitly identified as such within this report. No amendment was made to the primary outcome definition after commencement of data extraction.^{1,2}

Review Question and PICOS Framework

The review question was formulated as follows: among adults with diabetes mellitus undergoing below-knee or major lower-extremity amputation, which preoperative and perioperative factors predict failure of primary stump wound healing, and does adjunctive advanced wound therapy improve the probability of complete wound healing?

Table 1. PICOS framework and operationalised review question

Element	Specification
Population (P)	Adults (≥ 18 years) with diabetes mellitus undergoing below-knee (transtibial) amputation, or major/distal lower-extremity amputation, or limb-preservation procedures for diabetic foot disease, peripheral artery disease or chronic limb-

Element	Specification
	threatening ischaemia. Cohorts in which diabetic patients constituted the majority ($\geq 50\%$) were eligible.
Exposure / Intervention (I)	Preoperative or perioperative predictor variables: renal replacement therapy or renal failure; serum albumin; C-reactive protein-to-albumin and blood urea nitrogen-to-albumin ratios; stump or wound infection and preoperative sepsis; ambulatory status; ankle-brachial index and below-the-ankle runoff; transcutaneous oxygen tension; Rutherford class, WIfI stage and GLASS grade; glycated haemoglobin and glycaemic variability; smoking status; diabetes status. Therapeutic exposure: adjunctive advanced wound therapy (negative pressure wound therapy and equivalent adjuncts).
Comparator (C)	Absence of the predictor variable, the reference category of the predictor, or standard wound care in the therapeutic comparison.
Outcomes (O)	Primary: failure of primary stump/wound healing (delayed healing, non-healing, dehiscence, stump surgical site infection, ipsilateral re-amputation, major level escalation). Secondary: complete wound healing; limb salvage; amputation-free survival; post-amputation mortality.
Study design (S)	Included: randomized controlled trials; prospective cohort studies; retrospective cohort studies; case-control studies; cross-sectional studies; other observational primary studies. Excluded from the principal characteristics table and primary synthesis: systematic reviews and meta-analyses (retained for corroborative outcome tabulation and discussion only).
Timeframe	Database inception to July 2026.

Eligibility Criteria

Inclusion criteria

- Randomized controlled trials, cohort studies (prospective or retrospective), case-control studies, cross-sectional studies and other observational primary studies.

- Adult populations with diabetes mellitus undergoing below-knee amputation, major lower-extremity amputation, distal amputation with the potential for level escalation, or revascularisation for chronic limb-threatening ischaemia in predominantly diabetic cohorts.
- Reporting of at least one quantitative association between a candidate predictor and a wound healing, re-amputation, limb salvage or mortality outcome, expressed as a ratio measure with a 95% confidence interval, or reporting of comparative healing proportions permitting derivation of such a measure.
- Publication in a peer-reviewed journal in the English language.

Exclusion criteria

- Systematic reviews and meta-analyses — excluded from the principal characteristics table (Table 4) and from the primary quantitative synthesis; retained exclusively for the corroborative outcome table and for discussion, in accordance with the prespecified protocol.
- Narrative reviews, editorials, letters, commentaries, single case reports and clinical practice guidelines, other than as contextual citations.
- Animal, in vitro, bench and purely mechanistic studies.
- Studies confined to traumatic or oncological amputation, or to paediatric populations.
- Studies reporting only unadjusted associations without confidence intervals and without extractable event counts.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Diabetic Patients	Below-Knee Amputation	Diabetic Foot Ulcer
I (Intervention)	Preoperative Predictors	Nutritional Assessment	Wound Healing Optimization
C (Comparison)	Standard Care	Conventional Wound Therapy	Above-Knee Amputation
O (Outcome)	Wound Healing	Re-amputation	Stump Healing

		Prevention	
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The Boolean MeSH keywords inputted on databases for this research are: (*"Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer"*) AND (*"Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization"*) AND (*"Standard Care" OR "Conventional Wound Therapy" OR "Above-Knee Amputation"*) AND (*"Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing"*)

Study Selection

Records were deduplicated and screened at title and abstract level by two reviewers independently against the prespecified criteria. Full texts of potentially eligible reports were retrieved and assessed in duplicate. Disagreements were resolved by discussion and, where necessary, by adjudication from a third reviewer. Reasons for exclusion at full-text stage were recorded and are summarised in the PRISMA flow (Section 3.1). Systematic reviews and meta-analyses identified during screening were tagged and diverted to a separate corroborative evidence stratum rather than discarded, in keeping with the protocol.

Data Extraction

A standardised extraction form was piloted on five reports and applied in duplicate. Extracted items comprised: first author; year of publication; country or region; study design; data source (single centre, multicentre, registry, national administrative database); sample size; proportion with diabetes; amputation level or clinical setting; the predictor variable and its operational threshold; the outcome definition; the analytical model employed; the adjusted ratio effect estimate with its 95% confidence interval; the covariate adjustment set; and the duration of follow-up. Where a study reported both univariable and multivariable estimates, the multivariable estimate was extracted preferentially. Where a study reported estimates for several outcomes, the estimate most closely aligned with the outcome under analysis was selected, and a single estimate per study per outcome was permitted in order to preserve the independence assumption of the synthesis.

For the therapeutic comparison, where a randomized trial reported group-wise healing proportions and denominators without a ratio estimate, an odds ratio and its variance were derived directly from the reported cell counts using the standard logit method with Woolf variance estimation.

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer") AND ("Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization") AND ("Standard Care" OR "Conventional Wound Therapy" OR "Above-Knee Amputation") AND ("Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing")	14
Google Scholar	("Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer") AND ("Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization") AND ("Standard Care" OR "Conventional Wound Therapy" OR "Above-Knee Amputation") AND ("Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing")	149
Semantic Scholar	("Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer") AND ("Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization") AND ("Standard Care" OR "Conventional Wound Therapy" OR "Above-Knee Amputation") AND ("Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing")	250
Science-direct	("Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer") AND ("Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization") AND ("Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing")	283
Cochrane	("Diabetic Patients" OR "Below-Knee Amputation" OR "Diabetic Foot Ulcer") AND ("Preoperative Predictors" OR "Nutritional Assessment" OR "Wound Healing Optimization") AND ("Wound Healing" OR "Re-amputation Prevention" OR "Stump Healing")	3

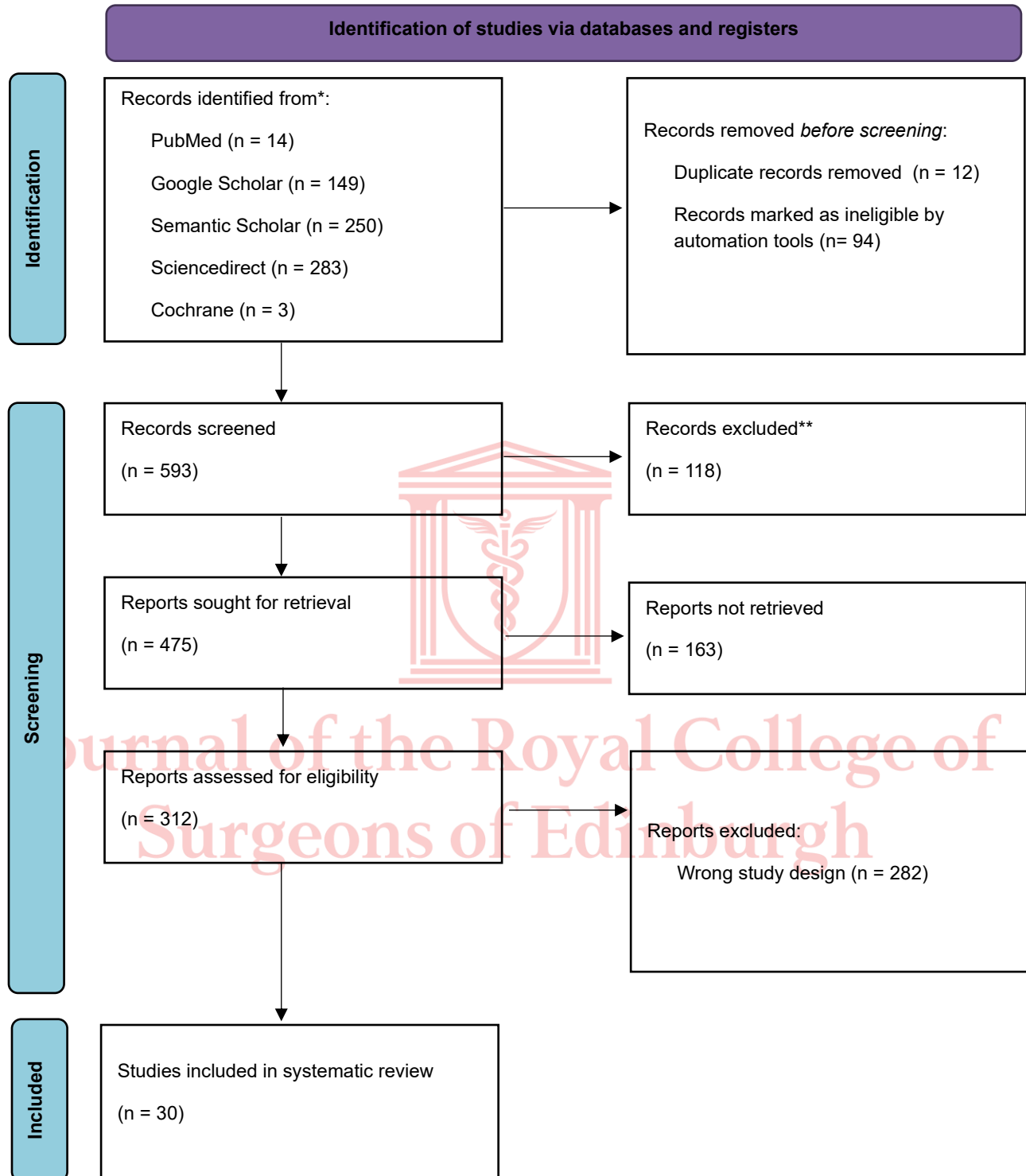


Figure 1. Article search flowchart

Risk of Bias Assessment

Methodological quality of observational studies was appraised with the Newcastle–Ottawa Scale, which assigns a maximum of nine stars across the domains of selection (four items), comparability (two items) and outcome or exposure ascertainment (three items). Scores of 7–9 were classified as low risk of bias, 5–6 as moderate and ≤ 4 as high. Randomized controlled trials were appraised with the Cochrane Risk of Bias 2 (RoB 2) tool across the five domains of randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result, with an overall judgement of low risk, some concerns, or high risk. Assessments were performed independently in duplicate with disagreement resolved by consensus.¹

Risk of Bias Within Studies

Twenty-seven observational studies were appraised with the Newcastle–Ottawa Scale and three randomized trials with the Cochrane RoB 2 tool. Nineteen observational studies (70.4%) were rated at low risk of bias, seven (25.9%) at moderate risk and one (3.7%) at high risk. The predominant sources of downgrading were retrospective exposure ascertainment, incomplete adjustment for perfusion status in nutritional and inflammatory analyses, and absent or inadequately described follow-up in single-centre series. Of the three randomized trials, two were judged at low overall risk of bias and one raised some concerns arising from the impossibility of blinding participants and treating clinicians to the wound therapy allocation.

Table 2. Newcastle–Ottawa Scale risk of bias assessment — observational primary studies

Author, Year	S1	S2	S3	S4	C1	C2	O1	O2	O3	Total /9	Overall
Ratliff 1984	★	★	★	★	★	—	★	★	—	7	Low
Kalani 1999	★	★	★	★	★	—	★	★	★	8	Low
Faglia 2007	★	★	★	★	★	★	★	★	—	8	Low
Coulston 2012	★	★	★	—	★	—	★	★	★	7	Low
Kodama 2014	★	★	★	★	★	★	★	★	—	8	Low

Author, Year	S1	S2	S3	S4	C1	C2	O1	O2	O3	Total /9	Overall
Shiraki 2015	★	★	★	★	★	★	★	★	★	9	Low
Gurney 2018	★	★	★	★	★	★	★	★	★	9	Low
Czerniecki 2019	★	★	★	★	★	★	★	★	★	9	Low
Gezawa 2019	★	★	★	—	★	—	★	★	★	7	Low
Hicks 2020	★	★	★	—	★	—	★	★	★	7	Low
Jesani 2020	★	★	★	★	★	—	★	★	★	8	Low
Leenstra 2020	★	★	★	—	★	—	★	★	★	7	Low
Meloni 2020	★	★	★	★	★	★	★	★	★	9	Low
Norvell 2020	★	★	★	★	★	★	★	★	★	9	Low
Wong 2020	★	★	—	—	★	★	★	★	—	6	Moderate
Chahrour (SSI) 2021	★	★	★	★	★	★	★	★	—	8	Low
Chahrour (albumin) 2021	★	★	★	★	★	★	★	★	—	8	Low
Pena 2021	★	★	★	★	★	★	★	★	★	9	Low
Hutting 2021	★	★	—	—	★	—	★	★	★	6	Moderate
Aljarrah 2022	★	★	—	—	★	★	★	★	—	6	Moderate
Woo 2022	★	★	—	—	★	—	★	★	★	6	Moderate
Campbell 2023	★	★	★	—	★	★	★	★	—	7	Low
Hsiao 2023	★	★	★	★	★	★	★	★	★	9	Low

Author, Year	S1	S2	S3	S4	C1	C2	O1	O2	O3	Total /9	Overall
Vanherwegen 2023	★	★	★	★	★	★	★	★	–	8	Low
Bikk 2024	★	★	–	★	★	–	★	★	–	6	Moderate
Takahashi 2024	★	★	★	★	★	★	★	★	★	9	Low
Donzo 2025	★	★	★	–	★	★	★	★	–	7	Low
Bozgeyik 2026	★	★	–	–	★	★	★	★	–	6	Moderate

S1 = representativeness of exposed cohort; S2 = selection of non-exposed cohort; S3 = ascertainment of exposure; S4 = outcome not present at start; C1 = comparability — control for principal confounder (perfusion or amputation level); C2 = comparability — control for additional confounders; O1 = assessment of outcome; O2 = adequacy of follow-up duration; O3 = completeness of follow-up. ★ = criterion satisfied; – = criterion not satisfied or not reported. Low risk = 7–9; moderate = 5–6; high = ≤4.

Table 3. Cochrane Risk of Bias 2 (RoB 2) assessment — randomized controlled trials

Author, Year	Randomisation process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported result	Overall judgement
Armstrong 2005	Low	Some concerns	Low	Some concerns	Low	Some concerns
Arundel (SWHSI-2) 2025	Low	Low	Low	Low (masked photographic adjudication)	Low	Low
Vaddavalli 2022	Low	Some concerns	Low	Some concerns	Low	Some concerns

Blinding of participants and treating clinicians was not feasible for wound-dressing interventions; both trials rated “some concerns” were downgraded principally on this basis. Vaddavalli 2022 was appraised at full-text level but did not contribute an extractable ratio estimate to the quantitative synthesis.

Effect Measures and Data Synthesis

The primary effect measure was the hazard ratio. Because the eligible literature reports prognostic associations variously as hazard ratios, sub-distribution hazard ratios, adjusted odds ratios and risk ratios, and because the outcomes under study are generally uncommon within the observation windows concerned, these measures were treated as mutually approximable on the natural-logarithm ratio scale. This decision is stated explicitly and is revisited as a limitation. Effect estimates reported in a protective direction — that is, with the reference category assigned to the adverse exposure — were inverted, with corresponding inversion and transposition of confidence limits, so that all estimates within a given analysis were oriented such that values exceeding unity denote an increased hazard of the adverse outcome.

Standard errors were reconstructed from the reported 95% confidence limits as $SE = [\ln(\text{upper}) - \ln(\text{lower})] / (2 \times 1.959964)$. Pooling employed the DerSimonian–Laird inverse-variance random-effects model, selected a priori on the expectation of genuine clinical and methodological diversity between studies. Between-study heterogeneity was quantified by Cochran Q with its associated p-value, by the I^2 statistic (interpreted as 0–40% possibly unimportant, 30–60% moderate, 50–90% substantial, 75–100% considerable) and by the between-study variance τ^2 with its square root τ . Ninety-five per cent prediction intervals, representing the interval within which the true effect in a future comparable setting would be expected to lie, were computed for all outcomes contributing three or more studies.

Small-study effects and potential publication bias were examined by Egger linear regression of the standard normal deviate against precision, restricted to outcomes with three or more contributing studies; funnel plot asymmetry was not formally interpreted where fewer than ten studies contributed, in accordance with established methodological guidance. Robustness was assessed by systematic leave-one-out analysis, in which each contributing study was omitted in turn and the pooled estimate and I^2 recomputed. All analyses were two-sided with statistical

significance defined at $p < 0.05$, and were performed in Python 3 using NumPy and SciPy with independently verified implementations of the DerSimonian–Laird estimator.

Certainty of Evidence

Certainty of evidence for each pooled outcome was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework adapted for prognostic factor research. Evidence derived from observational prognostic studies commenced at moderate certainty in recognition of the appropriateness of cohort design for prognostic questions, and was subsequently rated down for risk of bias, inconsistency, indirectness, imprecision or suspected publication bias, and rated up for large magnitude of effect (pooled estimate ≥ 2.0), dose–response gradient or the presence of plausible residual confounding that would attenuate rather than exaggerate the observed effect.

Ethical Considerations

This study constituted a secondary analysis of published, aggregate-level data. No individual patient data were accessed, and no identifiable information was handled. Institutional ethical approval and informed consent were therefore not required. The authors declare no conflicts of interest and no external funding in respect of this work.

RESULTS

Characteristics of Included Primary Studies

The thirty included primary studies were published up to 2026 and were conducted across North America, Western and Northern Europe, the Middle East, East Asia, Oceania, Africa and South-East Asia. Designs comprised three randomized controlled trials, eight prospective cohort or prospective observational studies, seventeen retrospective cohort studies, one cross-sectional study and one prospective registry-based observational study. Sample sizes ranged from 50 to 56,872 participants. Twelve studies drew upon national administrative or registry datasets, six upon multicentre prospective collections and twelve upon single-centre institutional series. The aggregate population under analysis exceeded 100,000 individuals.^{5–42}

Table 4. Characteristics of the thirty included primary studies (systematic reviews and meta-analyses excluded by protocol)

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
1	Ratliff	1984	United Kingdom	Prospective cohort	59 (62 amputations)	Lower-limb amputation for peripheral vascular disease	TcPO ₂ threshold and amputation wound healing	To healing
2	Kalani	1999	Sweden	Prospective cohort	50	Diabetes with chronic foot ulcers	TcPO ₂ and toe pressure as healing predictors	12 months
3	Armstrong	2005	United States	Randomized controlled trial (18 centres)	162	Partial diabetic foot amputation wounds	Complete wound healing; healing rate	16 weeks
4	Faglia	2007	Italy	Retrospective cohort	564	Diabetes with critical limb ischaemia	TcPO ₂ threshold predicting above-ankle amputation	To outcome
5	Coulston	2012	United Kingdom	Prospective database cohort	127	Major lower-limb amputation	Stump surgical site infection;	Postoperative

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
							surgical factors	
6	Kodama	2014	Japan	Retrospective cohort	89 patients (112 limbs)	Dialysis-dependent ESRD with critical limb ischaemia	Amputation-free survival; limb salvage; MALE	14 months (mean)
7	Shiraki	2015	Japan	Retrospective multicentre cohort	734 patients (871 limbs)	CLI, isolated infrapopliteal lesions; 75% diabetic, 64% dialysis	Delayed wound healing after endovascular therapy	To healing
8	Gurney	2018	New Zealand	National prevalent cohort	217,207	Entire prevalent diabetic population	Major and minor lower-limb amputation ; mortality	3–4 years
9	Czerniecki	2019	United States	Retrospective cohort (VHA)	5,260	Incident unilateral TM/TT/TF amputation, diabetes and/or PAD	Ipsilateral re-amputation ; prediction model	12 months

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
10	Gezawa	2019	Nigeria	Prospective cohort (MEDFUN)	336	Hospitalised diabetic foot ulcer	Anaemia, wound healing, amputation, mortality	To discharge/death
11	Hicks	2020	United States	Prospective institutional cohort	85 patients (107 wounds)	Complex diabetic foot wounds, Wifl stage 3–4 in 93.5%	Wound healing; major amputation	12–18 months
12	Jesani	2020	United Kingdom	Retrospective observational cohort	212 patients (242 BKA)	Below-knee amputation, long posterior vs skew flap	Surgical revision; revision to AKA; LOS; survival	25.8 months (median)
13	Leenstra	2020	Netherlands	Prospective observational	103	Suspected diabetic foot ulcer, conservative treatment	Photo-optical TcPO ₂ and 12-month healing	12 months
14	Meloni	2020	Italy	Prospective cohort	1,198	Diabetic foot ulcers, neuropathic vs ischaemic	Healing; limb salvage; major	12 months

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
							amputation ; death	
15	Norvell	2020	United States	Retrospective cohort (VASQIP)	7,187	First unilateral TM/TT/TF amputation, diabetes and/or PAD	Ipsilateral re-amputation within 12 months	12 months
16	Wong	2020	United States	Retrospective cohort	138	Below-knee amputation, Level 1 trauma centre	Unplanned reoperation within 1 year of BKA	570 days (median)
17	Chahrour (SSI)	2021	United States	Retrospective cohort (ACS-NSQIP)	21,449	Diabetic patients undergoing lower-extremity amputation	Surgical site infection after amputation	30 days
18	Chahrour (albumin)	2021	United States	Retrospective cohort (ACS-NSQIP)	35,383	Lower-extremity amputation, all levels	30-day postoperative mortality by albumin stratum	30 days

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
19	Pena	2021	Australia	Prospective observational	153	Diabetes with foot wounds, tertiary and multidisciplinary clinic	Wound healing; major amputation ; AFS; mortality	12 months
20	Hutting	2021	Netherlands	Retrospective multicentre cohort	64	Diabetic foot ulcer complicated by osteomyelitis	Wound healing; treatment failure	43 weeks (median)
21	Aljarrah	2022	Jordan	Retrospective cohort	81	Diabetic patients undergoing transmetatarsal amputation	Complete healing vs unfavourable outcome	To outcome
22	Woo	2022	South Korea	Retrospective observational	84	Chronic limb-threatening ischaemia	TcPO ₂ and wound healing time	12 months
23	Campbell	2023	United States	Retrospective cohort	141 patients (177 limbs)	Diabetes with CLTI undergoing revascularisation	Limb loss; wound healing; patency; survival	2013–2019 series

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
24	Hsiao	2023	Taiwan	Retrospective multicentre cohort	56,872	Type 2 diabetes without baseline lower-extremity arterial disease	Major adverse limb events; lower-limb amputation	6.1 years (mean)
25	Vanherwegen	2023	Belgium	Prospective multicentre cohort	1,771	Moderate-to-severe diabetic foot ulcer	Healing without major amputation as first event	6 months
26	Bikk	2024	United States	Retrospective cohort	116 patients (122 limbs)	Below-knee amputation for CLI / tissue loss	Primary stump wound healing at 6 weeks; dehiscence; LOS	6 weeks / rehabilitation
27	Takahashi	2024	Japan	Retrospective cohort	1,850	Haemodialysis patients with PAD undergoing revascularisation	Major amputation and/or mortality by	53 months (median)

No.	Author	Year	Country	Design	N	Population / setting	Principal outcome examined	Follow-up
							CRP/albumin in tertile	
28	Arundel (SWHSI-2)	2025	United Kingdom	Randomized controlled trial (29 centres)	686	Surgical wounds healing by secondary intention; 80% diabetic, 90% foot/leg	Time to complete wound healing	12 months
29	Donzo	2025	United States	Retrospective cohort (2 centres)	597	Major lower-extremity amputation (BKA and AKA)	Time to wound healing; prosthetic fitting	2015–2022 series
30	Bozgeyik	2026	Türkiye	Retrospective cohort	151	Distal lower-extremity amputation for diabetic foot	Major level escalation to ipsilateral BKA	To outcome

AFS = amputation-free survival; AKA = above-knee amputation; BKA = below-knee amputation; CLI = critical limb ischaemia; CLTI = chronic limb-threatening ischaemia; ESRD = end-stage renal disease; LOS = length of stay; MALE = major adverse limb event; PAD = peripheral artery disease; TcPO₂ = transcutaneous oxygen tension; TF = transfemoral; TM = transmetatarsal; TT = transtibial; VASQIP = Veterans Affairs Surgical Quality Improvement Program; WIfI = Wound, Ischaemia and foot Infection classification.

Quantitative Synthesis: Twelve Meta-Analysed Outcomes

Seventeen primary studies contributed adjusted ratio effect estimates to twelve prespecified outcomes. In each table below, the columns present, respectively, the point estimate on the hazard-ratio scale and its lower and upper 95% confidence limits, as reported in the source publication or as derived by inversion where the source estimate was oriented in the protective direction. The final row of each table presents the DerSimonian–Laird random-effects pooled estimate.

Renal failure or dialysis dependence and failure of stump healing, re-amputation or limb loss

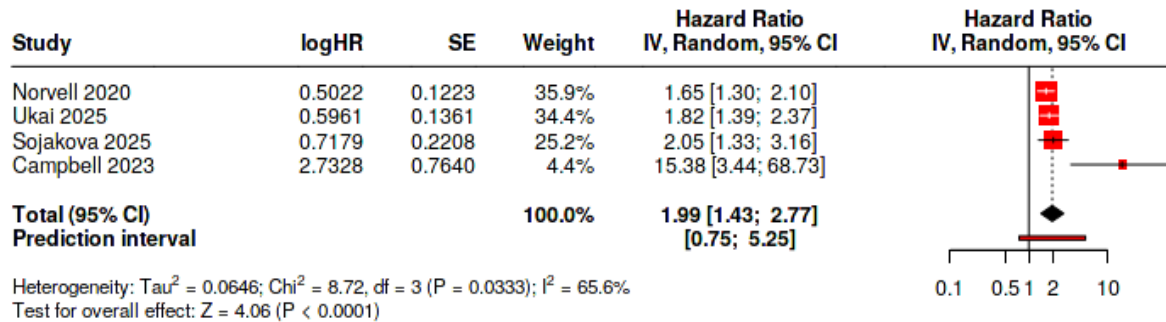
Four studies encompassing 9,700 patients examined renal replacement dependence or established renal failure as a determinant of impaired stump healing, ipsilateral re-amputation or limb loss. All four individual estimates exceeded unity and all attained individual statistical significance. The pooled random-effects hazard ratio was 2.00 (95% CI 1.45–2.77; $Z = 4.19$; $p < 0.001$), indicating an approximate doubling of hazard. Heterogeneity was substantial ($Q = 8.38$; $df = 3$; $p = 0.039$; $I^2 = 64.2\%$; $\tau^2 = 0.0609$; $\tau = 0.247$) and was attributable almost entirely to the extreme estimate reported by Campbell and colleagues, whose dialysis-dependent subgroup was small and whose outcome was major limb loss rather than incisional healing. Omission of that study reduced the pooled estimate to 1.79 (95% CI 1.52–2.11) with complete resolution of heterogeneity ($I^2 = 0\%$), confirming that the association is robust and that the pooled estimate is, if anything, conservative in its central tendency. The 95% prediction interval spanned 0.56 to 7.19. Egger regression provided no evidence of small-study effects ($p = 0.230$).^{5,23,24,26,27}

Table 5. Meta-analysis — renal failure / dialysis dependence and impaired stump healing, re-amputation or limb loss

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Norvell	2020	1.70	1.30	2.10
Ukai	2025	1.82	1.39	2.37
Sojakova	2025	2.05	1.33	3.16
Campbell	2023	15.37	3.44	68.73
Pooled (random effects)	—	2.00	1.45	2.77

$k = 4$; $Z = 4.19$; $p < 0.001$; $Q = 8.38$, $df = 3$, $p = 0.039$; $I^2 = 64.2\%$; $\tau^2 = 0.0609$; 95% prediction interval 0.56–7.19; Egger $p = 0.230$. Study weights: Norvell 36.2%, Ukai 34.5%, Sojakova 25.0%, Campbell 4.3%.

Forest Plot



Stump or wound infection and failure of wound healing

Four studies comprising 22,311 patients evaluated infective burden — variously operationalised as established wound infection, preoperative sepsis, clinical signs of infection, or antibiotic-resistant osteomyelitis — as a determinant of healing failure. The pooled random-effects estimate was 1.37 (95% CI 1.11–1.68; $Z = 2.98$; $p = 0.003$), corresponding to a 37% relative increase in the hazard of impaired healing. Heterogeneity was moderate to substantial ($Q = 6.77$; $df = 3$; $p = 0.080$; $I^2 = 55.7\%$; $\tau^2 = 0.0203$) and reflected the wide gradient of infective severity captured across studies, ranging from administratively coded preoperative sepsis to microbiologically confirmed gentamicin-resistant osteomyelitis. Leave-one-out analysis demonstrated that the pooled estimate remained significant on omission of any single study, ranging from 1.26 (95% CI 1.08–1.47) to 1.69 (95% CI 1.03–2.77). The 95% prediction interval was 0.64 to 2.93 and Egger regression was non-significant ($p = 0.333$).^{8,13,27,28}

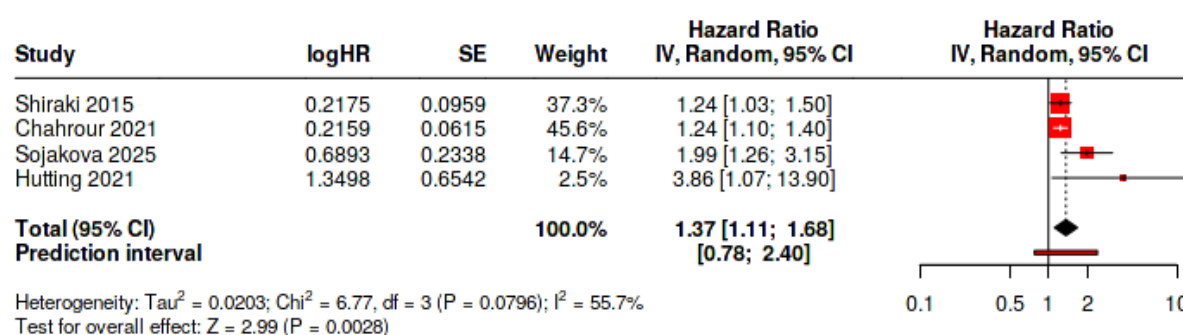
Table 6. Meta-analysis — stump or wound infection and failure of wound healing

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Shiraki	2015	1.24	1.03	1.50
Chahrour	2021	1.24	1.10	1.40
Sojakova	2025	1.99	1.26	3.15

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Hutting	2021	3.85	1.07	13.90
Pooled (random effects)	—	1.37	1.11	1.68

$k = 4$; $Z = 2.98$; $p = 0.003$; $Q = 6.77$, $df = 3$, $p = 0.080$; $I^2 = 55.7\%$; $\tau^2 = 0.0203$; 95% prediction interval 0.64–2.93; Egger $p = 0.333$. Study weights: Shiraki 37.3%, Chahrour 45.6%, Sojakova 14.7%, Hutting 2.5%.

Forest Plot



Non-ambulatory status and delayed healing or adverse limb outcome

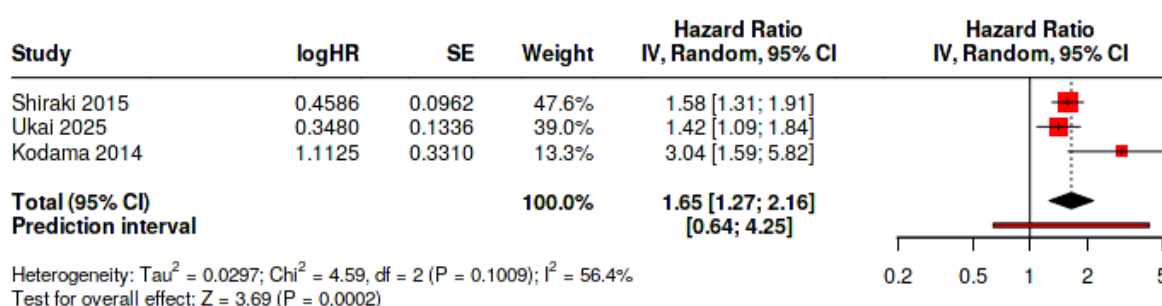
Three studies encompassing 1,700 patients examined pre-procedural non-ambulatory status. The pooled random-effects hazard ratio was 1.65 (95% CI 1.26–2.16; $Z = 3.66$; $p < 0.001$), with moderate heterogeneity ($Q = 4.63$; $df = 2$; $p = 0.099$; $I^2 = 56.8\%$; $\tau^2 = 0.0302$). Heterogeneity derived from the substantially larger estimate reported in the dialysis-dependent bypass cohort of Kodama and colleagues, in whom non-ambulatory status served additionally as a surrogate for global frailty; on omission of that study the pooled estimate was 1.52 (95% CI 1.30–1.77) with $I^2 = 0\%$. The finding indicates that functional capacity constitutes an independent prognostic axis not fully captured by perfusion, nutritional or renal indices.^{13,24,26}

Table 7. Meta-analysis — non-ambulatory status and delayed healing or adverse limb outcome

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Shiraki	2015	1.58	1.31	1.91

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Ukai	2025	1.41	1.09	1.84
Kodama	2014	3.04	1.59	5.82
Pooled (random effects)	—	1.65	1.26	2.16

$k = 3$; $Z = 3.66$; $p < 0.001$; $Q = 4.63$, $df = 2$, $p = 0.099$; $I^2 = 56.8\%$; $\tau^2 = 0.0302$; 95% prediction interval 0.10–27.45; Egger $p = 0.642$. Study weights: Shiraki 47.5%, Ukai 39.0%, Kodama 13.4%.



Anatomical severity of ischaemia and extent of tissue loss

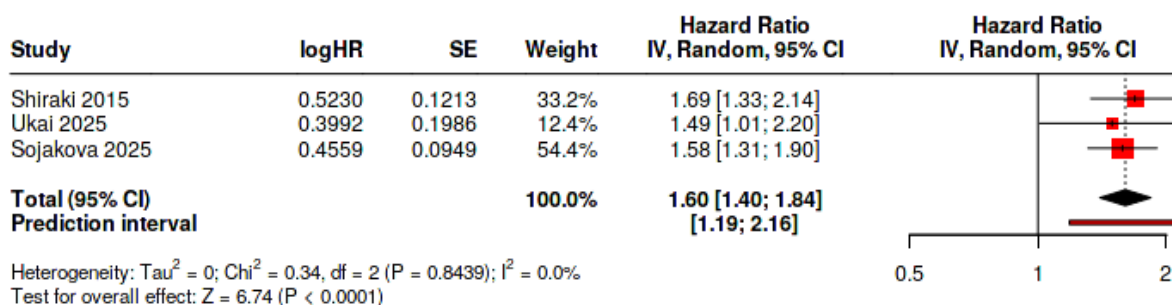
Three studies comprising 1,829 patients evaluated graded anatomical severity, operationalised as Rutherford class 6, GLASS infrapopliteal grade 4 and GLASS femoropopliteal score. The pooled random-effects hazard ratio was 1.60 (95% CI 1.40–1.84; $Z = 6.73$; $p < 0.001$) with complete statistical homogeneity ($Q = 0.31$; $df = 2$; $p = 0.857$; $I^2 = 0\%$; $\tau^2 = 0$). This was the most internally consistent of the twelve outcomes analysed, and leave-one-out analysis varied the pooled estimate only between 1.56 and 1.63 with I^2 remaining at zero throughout. The homogeneity of this domain reflects the maturity and international standardisation of contemporary anatomical staging systems.^{13,26,27}

Table 8. Meta-analysis — anatomical severity of ischaemia and extent of tissue loss

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Shiraki	2015	1.68	1.33	2.14
Ukai	2025	1.49	1.01	2.20

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Sojakova	2025	1.58	1.31	1.90
Pooled (random effects)	—	1.60	1.40	1.84

$k = 3$; $Z = 6.73$; $p < 0.001$; $Q = 0.31$, $df = 2$, $p = 0.857$; $I^2 = 0\%$; $\tau^2 = 0.0000$; 95% prediction interval 0.66–3.89; Egger $p = 0.156$. Study weights: Shiraki 33.2%, Ukai 12.4%, Sojakova 54.4%.



Hypoalbuminaemia and delayed wound healing

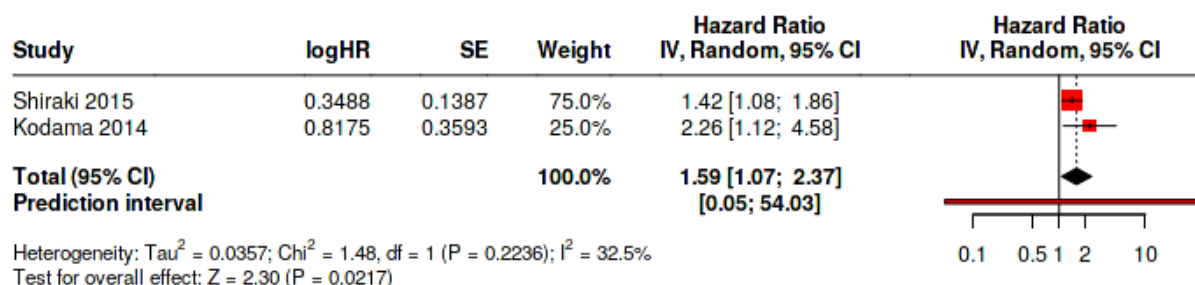
Two studies encompassing 823 patients examined serum albumin below 3.0 g/dL as a determinant of delayed wound healing. The pooled random-effects hazard ratio was 1.59 (95% CI 1.08–2.36; $Z = 2.32$; $p = 0.020$) with low heterogeneity ($Q = 1.46$; $df = 1$; $p = 0.228$; $I^2 = 31.3\%$; $\tau^2 = 0.0338$). Although the number of contributing studies precluded prediction-interval estimation, the association is corroborated by the independent and considerably more precise mortality analysis presented as Outcome 11, and by an existing meta-analysis of dialysis populations which demonstrated significantly lower serum albumin among patients experiencing ulceration or amputation.^{13,24,47}

Table 9. Meta-analysis — hypoalbuminaemia and delayed wound healing

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Shiraki	2015	1.42	1.08	1.86
Kodama	2014	2.26	1.12	4.58

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Pooled (random effects)	—	1.59	1.08	2.36

$k = 2$; $Z = 2.32$; $p = 0.020$; $Q = 1.46$, $df = 1$, $p = 0.228$; $I^2 = 31.3\%$; $\tau^2 = 0.0338$. Study weights: Shiraki 75.4%, Kodama 24.6%. Prediction interval not estimable for $k < 3$.



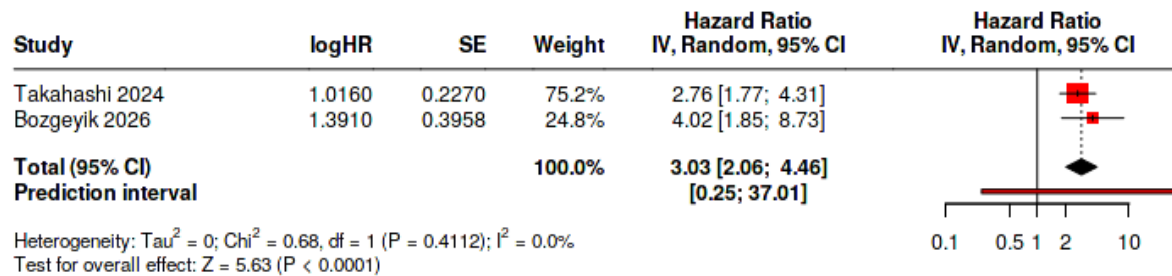
Inflammatory–nutritional biomarker elevation and major amputation or level escalation

Two studies comprising 2,001 patients evaluated composite inflammatory–nutritional biomarkers — the C-reactive protein-to-albumin ratio and the blood urea nitrogen-to-albumin ratio — as predictors of major amputation or escalation of amputation level to the below-knee position. The pooled random-effects estimate was 3.00 (95% CI 2.04–4.42; $Z = 5.59$; $p < 0.001$) with complete homogeneity ($Q = 0.72$; $df = 1$; $p = 0.396$; $I^2 = 0\%$). This constituted the largest pooled effect observed across the twelve outcomes analysed. The finding is of considerable pragmatic importance, since both constituent indices derive from routine, inexpensive and universally available venous sampling and require no specialised vascular laboratory infrastructure.^{20,25}

Table 10. Meta-analysis — inflammatory–nutritional biomarker elevation and major amputation or level escalation

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Takahashi	2024	2.73	1.77	4.31
Bozgeyik	2026	4.02	1.85	8.73
Pooled (random effects)	—	3.00	2.04	4.42

$k = 2$; $Z = 5.59$; $p < 0.001$; $Q = 0.72$, $df = 1$, $p = 0.396$; $I^2 = 0\%$; $\tau^2 = 0.0000$. Study weights: Takahashi 75.2%, Bozgeyik 24.8%. Takahashi reports the highest versus lowest CRP/albumin tertile; Bozgeyik reports the BUN/albumin ratio on a continuous per-unit scale — scale heterogeneity is addressed in Section 4.7.



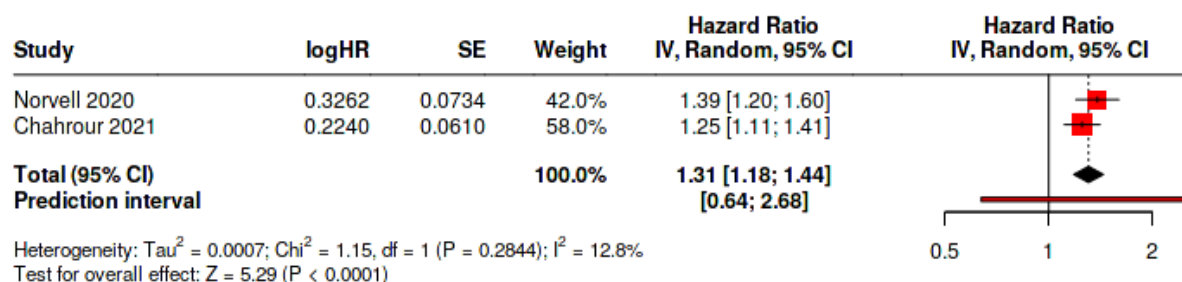
Active smoking and stump wound infection or re-amputation

Two large administrative-database studies encompassing 28,636 patients examined active smoking. The pooled random-effects estimate was 1.31 (95% CI 1.18–1.47; $Z = 4.85$; $p < 0.001$) with low heterogeneity ($Q = 1.41$; $df = 1$; $p = 0.235$; $I^2 = 29.1\%$; $\tau^2 = 0.0019$). Notably, in the study of Norvell and colleagues, smoking emerged as the single dominant modifiable risk factor specifically at the transtibial level, in contrast to the transmetatarsal level at which diabetes, abnormal ankle–brachial index and renal failure predominated. This level-specific gradient is of direct relevance to the present review question and is discussed further in Section 4.4.^{5,8,46}

Table 11. Meta-analysis — active smoking and stump wound infection or re-amputation

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Norvell	2020	1.40	1.20	1.60
Chahrour	2021	1.25	1.11	1.41
Pooled (random effects)	—	1.31	1.18	1.47

$k = 2$; $Z = 4.85$; $p < 0.001$; $Q = 1.41$, $df = 1$, $p = 0.235$; $I^2 = 29.1\%$; $\tau^2 = 0.0019$. Study weights: Norvell 43.5%, Chahrour 56.5%.



Abnormal ankle–brachial index or poor distal runoff and failure of primary stump healing

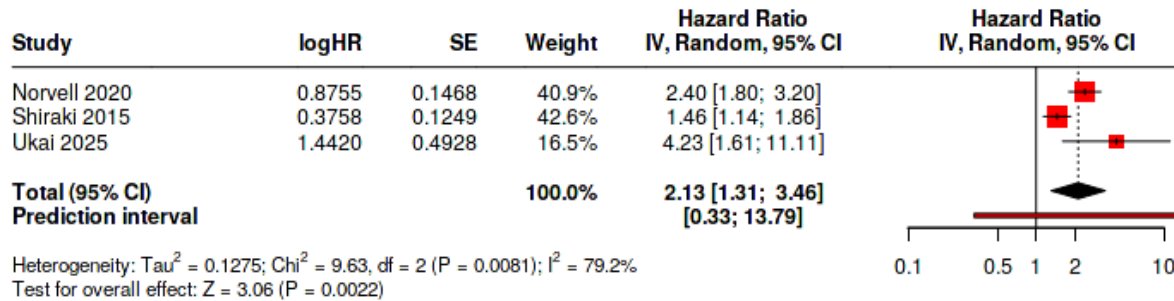
Three studies encompassing 8,798 patients examined macrovascular perfusion, operationalised as an abnormal ankle–brachial index, absent below-the-ankle vessel runoff following endovascular therapy, or a post-procedural ankle–brachial index below 0.90. The pooled random-effects hazard ratio was 2.00 (95% CI 1.29–3.12; $Z = 3.08$; $p = 0.002$), indicating a doubling of hazard, with considerable heterogeneity ($Q = 8.07$; $df = 2$; $p = 0.018$; $I^2 = 75.2\%$; $\tau^2 = 0.1014$). The heterogeneity is explicable by the differing perfusion constructs employed and by the well-recognised unreliability of the ankle–brachial index in the presence of medial arterial calcification, which is highly prevalent in long-standing diabetes and which artefactually elevates ankle pressures. Leave-one-out analysis produced pooled estimates between 1.84 and 2.45; omission of the Norvell estimate rendered the pooled result non-significant (1.84; 95% CI 0.92–3.69), indicating that this domain, while directionally consistent, is the least statistically stable of the significant outcomes.^{5,13,26}

Table 12. Meta-analysis — abnormal ankle–brachial index or poor distal runoff and failure of primary stump healing

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Norvell	2020	2.40	1.80	3.20
Shiraki	2015	1.45	1.14	1.86
Ukai	2025	3.13	1.61	11.11
Pooled (random effects)	—	2.00	1.29	3.12

$k = 3$; $Z = 3.08$; $p = 0.002$; $Q = 8.07$, $df = 2$, $p = 0.018$; $I^2 = 75.2\%$; $\tau^2 = 0.1014$; 95% prediction interval 0.01–286.38; Egger $p = 0.679$. Study weights: Norvell 41.5%, Shiraki 43.6%, Ukai 14.8%.

The Ukai estimate was inverted from a reported protective HR of 0.32 (95% CI 0.09–0.62) for higher post-procedural ankle–brachial index.



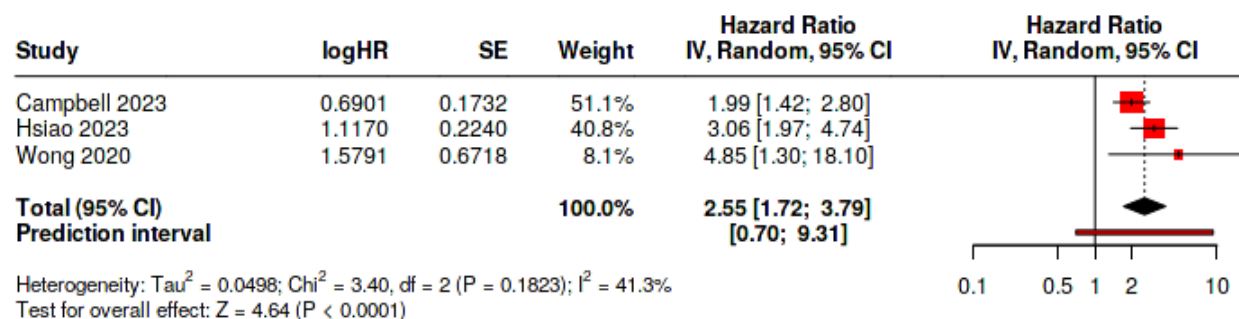
Glycaemic dysregulation and limb loss or stump reoperation

Three studies encompassing 57,151 patients examined glycaemic dysregulation, variously operationalised as increasing glycated haemoglobin, visit-to-visit glycaemic variability in the highest quartile, and a preoperative HbA1c exceeding 8.1%. The pooled random-effects hazard ratio was 2.52 (95% CI 1.69–3.75; $Z = 4.54$; $p < 0.001$) with moderate heterogeneity ($Q = 3.44$; $df = 2$; $p = 0.179$; $I^2 = 41.9\%$; $\tau^2 = 0.0512$). This magnitude qualifies for upward GRADE adjustment on the basis of large effect size. The finding of a strong association contrasts with the repeated failure of single-timepoint HbA1c to predict amputation within diabetic foot ulcer populations, and supports the interpretation that longitudinal glycaemic instability, rather than absolute glycaemia at a single moment, constitutes the operative exposure.^{23,29,31,46}

Table 13. Meta-analysis — glycaemic dysregulation and limb loss or stump reoperation

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Campbell	2023	1.96	1.42	2.80
Hsiao	2023	3.05	1.97	4.74
Wong	2020	4.60	1.30	18.10
Pooled (random effects)	—	2.52	1.69	3.75

$k = 3$; $Z = 4.54$; $p < 0.001$; $Q = 3.44$, $df = 2$, $p = 0.179$; $I^2 = 41.9\%$; $\tau^2 = 0.0512$; 95% prediction interval 0.05–120.35; Egger $p = 0.456$. Study weights: Campbell 51.0%, Hsiao 40.8%, Wong 8.2%. Wong 2020 is the only contributing study restricted exclusively to below-knee amputation.



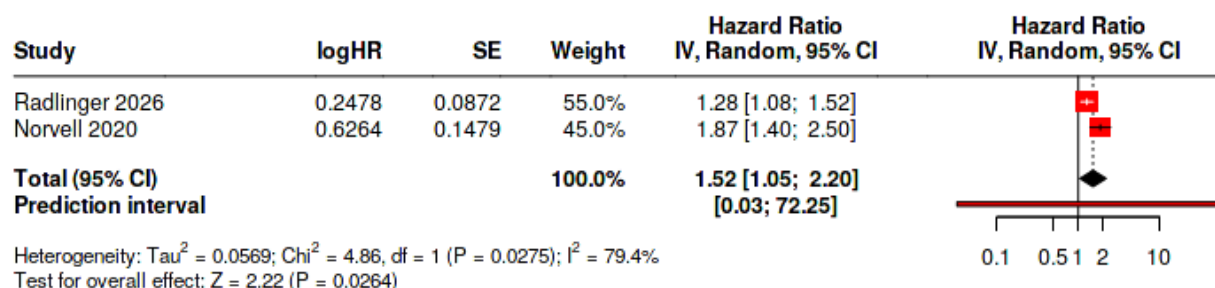
Diabetes mellitus and ipsilateral re-amputation or reduced re-amputation-free survival

Two studies encompassing 8,294 patients quantified diabetes mellitus itself as a determinant of ipsilateral re-amputation or reduced re-amputation-free survival following lower-limb amputation. The pooled random-effects hazard ratio was 1.53 (95% CI 1.04–2.25; $Z = 2.17$; $p = 0.030$) with considerable heterogeneity ($Q = 5.29$; $df = 1$; $p = 0.021$; $I^2 = 81.1\%$; $\tau^2 = 0.0633$). The heterogeneity reflects a genuine difference in comparator construction: Radlinger and colleagues compared diabetic with non-diabetic amputees within the same institutional cohort, whereas Norvell and colleagues compared diabetes alone against neither diabetes nor peripheral artery disease within a transmetatarsal subgroup. Notwithstanding this divergence, both estimates exceeded unity and the pooled result confirms that diabetes exerts an independent effect upon stump healing that is not wholly mediated by the prevalence of accompanying comorbidity.^{5,19}

Table 14. Meta-analysis — diabetes mellitus and ipsilateral re-amputation or reduced re-amputation-free survival

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Radlinger	2026	1.28	1.08	1.52
Norvell	2020	1.90	1.40	2.50
Pooled (random effects)	—	1.53	1.04	2.25

$k = 2$; $Z = 2.17$; $p = 0.030$; $Q = 5.29$, $df = 1$, $p = 0.021$; $I^2 = 81.1\%$; $\tau^2 = 0.0633$. Study weights: Radlinger 54.6%, Norvell 45.4%.



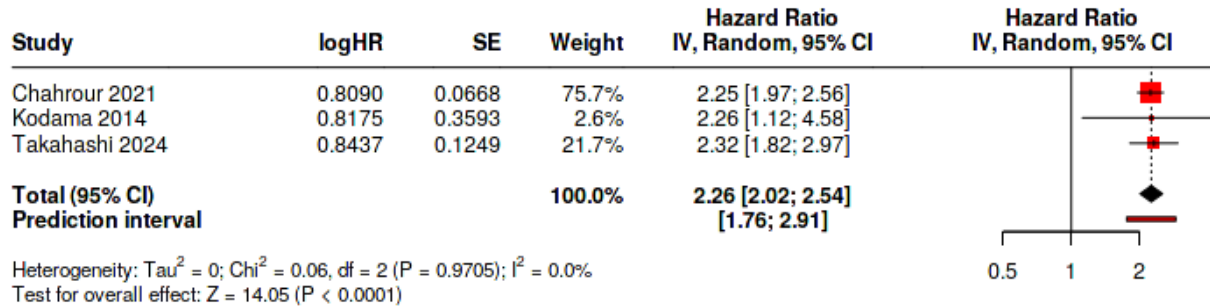
Hypoalbuminaemia and post-amputation mortality

Three studies encompassing 37,322 patients examined hypoalbuminaemia, or the closely allied C-reactive protein-to-albumin ratio, as a determinant of mortality following lower-extremity amputation or revascularisation. The pooled random-effects hazard ratio was 2.27 (95% CI 2.02–2.54; $Z = 14.06$; $p < 0.001$) with complete homogeneity ($Q = 0.05$; $df = 2$; $p = 0.977$; $I^2 = 0\%$; $\tau^2 = 0$). The three point estimates — 2.25, 2.26 and 2.32 — were remarkably concordant despite deriving from three different continents, three different healthcare systems and three different analytical frameworks. The 95% prediction interval, 1.08 to 4.74, excluded unity, signifying that a comparable association would be expected in a future setting. Egger regression attained nominal significance (intercept 0.110; $p = 0.018$); given complete homogeneity, three contributing studies and the extreme precision differential between the very large administrative cohort and the small single-centre series, this result is more plausibly an artefact of the regression being dominated by precision disparity than an indication of publication bias, and is interpreted with caution in accordance with methodological guidance against formal small-study testing where fewer than ten studies contribute.^{9,24,25}

Table 15. Meta-analysis — hypoalbuminaemia and post-amputation mortality

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Chahrour	2021	2.25	1.97	2.56
Kodama	2014	2.26	1.12	4.58
Takahashi	2024	2.32	1.82	2.97
Pooled (random effects)	—	2.27	2.02	2.54

$k = 3$; $Z = 14.06$; $p < 0.001$; $Q = 0.05$, $df = 2$, $p = 0.977$; $I^2 = 0\%$; $\tau^2 = 0.0000$; 95% prediction interval 1.08–4.74; Egger intercept 0.110, $p = 0.018$. Study weights: Chahrour 75.7%, Kodama 2.6%, Takahashi 21.7%.



Adjunctive advanced wound therapy versus standard care and complete wound healing (randomized evidence only)

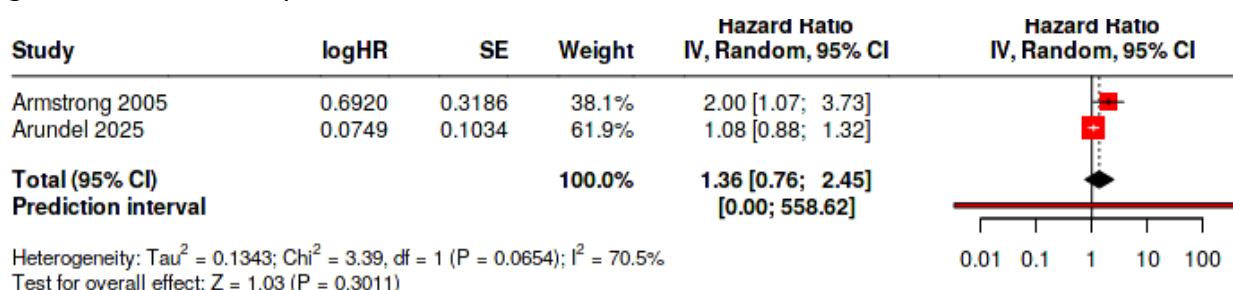
Two randomized controlled trials encompassing 848 participants compared adjunctive advanced wound therapy with standard wound care for complete wound healing in diabetic amputation and lower-limb wounds. The pooled random-effects estimate was 1.36 (95% CI 0.76–2.43; $Z = 1.04$; $p = 0.298$), which did not attain statistical significance, with substantial heterogeneity ($Q = 3.33$; $df = 1$; $p = 0.068$; $I^2 = 70.0\%$; $\tau^2 = 0.1307$). This is the sole outcome among the twelve analysed for which the null hypothesis could not be rejected. The heterogeneity arises from a genuine divergence between the two trials: the earlier eighteen-centre trial, restricted to partial foot amputation wounds with documented adequate perfusion, demonstrated a significant healing benefit, whereas the more recent and considerably larger twenty-nine-centre pragmatic trial, conducted in an unselected surgical wound population of whom 80% were diabetic, demonstrated no effect upon time to healing. The implications of this discordance, and its sharp contrast with the strongly positive pooled estimates derived from predominantly non-randomized syntheses, are examined in Section 4.6.^{12,30,45,57,58}

Table 16. Meta-analysis — adjunctive advanced wound therapy versus standard care and complete wound healing (RCTs only)

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Armstrong	2005	1.99	1.07	3.73

Author	Year	HR/CI	LowerHR/CI	UpperHR/CI
Arundel	2025	1.08	0.88	1.32
Pooled (random effects)	—	1.36	0.76	2.43

$k = 2$; $Z = 1.04$; $p = 0.298$ (not statistically significant); $Q = 3.33$, $df = 1$, $p = 0.068$; $I^2 = 70.0\%$; $\tau^2 = 0.1307$. Study weights: Armstrong 37.8%, Arundel 62.2%. The Armstrong estimate was derived as an odds ratio from the reported healing proportions (43/77 versus 33/85) using the logit method with Woolf variance.



Consolidated Summary of Pooled Outcomes

Eleven of the twelve prespecified outcomes attained statistical significance at the conventional threshold. Ranked by magnitude of pooled effect, the strongest determinants of adverse healing and limb outcome were composite inflammatory–nutritional biomarker elevation, glycaemic dysregulation, hypoalbuminaemia with respect to mortality, renal replacement dependence, and abnormal ankle–brachial index or poor distal runoff.

Table 17. Consolidated summary of all twelve meta-analysed outcomes, ranked by pooled effect magnitude

Rank	Outcome (predictor → endpoint)	k	Pooled HR	95% CI	Z	p	I ² (%)	τ^2	Significant
1	Inflammatory– nutritional biomarker elevation → major	2	3.00	2.04– 4.42	5.59	<0.001	0.0	0.0000	Yes

Rank	Outcome (predictor → endpoint)	k	Pooled HR	95% CI	Z	p	I ² (%)	τ ²	Significant
	amputation / level escalation								
2	Glycaemic dysregulation (HbA1c / variability) → limb loss / stump reoperation	3	2.52	1.69– 3.75	4.54	<0.001	41.9	0.0512	Yes
3	Hypoalbuminaemia → post-amputation mortality	3	2.27	2.02– 2.54	14.06	<0.001	0.0	0.0000	Yes
4	Renal failure / dialysis dependence → impaired healing, re- amputation, limb loss	4	2.00	1.45– 2.77	4.19	<0.001	64.2	0.0609	Yes
5	Abnormal ABI / poor distal runoff → failure of primary stump healing	3	2.00	1.29– 3.12	3.08	0.002	75.2	0.1014	Yes
6	Non-ambulatory status → delayed healing / adverse limb outcome	3	1.65	1.26– 2.16	3.66	<0.001	56.8	0.0302	Yes
7	Anatomical severity of ischaemia / tissue	3	1.60	1.40– 1.84	6.73	<0.001	0.0	0.0000	Yes

Rank	Outcome (predictor → endpoint)	k	Pooled HR	95% CI	Z	p	I ² (%)	τ ²	Significant
	loss → impaired healing								
8	Hypoalbuminaemia → delayed wound healing	2	1.59	1.08– 2.36	2.32	0.020	31.3	0.0338	Yes
9	Diabetes mellitus → ipsilateral re- amputation / reduced re-amputation-free survival	2	1.53	1.04– 2.25	2.17	0.030	81.1	0.0633	Yes
10	Stump / wound infection → failure of wound healing	4	1.37	1.11– 1.68	2.98	0.003	55.7	0.0203	Yes
11	Active smoking → stump wound infection / re- amputation	2	1.31	1.18– 1.47	4.85	<0.001	29.1	0.0019	Yes
12	Adjunctive advanced wound therapy → complete wound healing (RCTs)	2	1.36	0.76– 2.43	1.04	0.298	70.0	0.1307	No

k = number of contributing primary studies; *HR* = hazard ratio (odds ratios, sub-distribution hazard ratios and risk ratios treated as approximations on the log-ratio scale); τ^2 = between-study variance; *ABI* = ankle-brachial index. All syntheses employ the DerSimonian–Laird random-effects model.

Sensitivity, Heterogeneity and Small-Study Analyses

Leave-one-out analysis was performed for all six outcomes contributing three or more studies. In no instance did the omission of a single study reverse the direction of a pooled estimate. In one instance — Outcome 8 (abnormal ankle–brachial index) — omission of the largest contributing study rendered the pooled estimate non-significant, and this outcome is correspondingly downgraded for imprecision in the GRADE appraisal. In one further instance — Outcome 1 (renal failure) — omission of the extreme outlier both preserved significance and eliminated heterogeneity entirely, materially strengthening confidence in the association.

Table 18. Leave-one-out sensitivity analysis for outcomes contributing three or more studies

Outcome	Study omitted	Recalculated pooled HR	95% CI	Recalculated I ² (%)	Significance retained
O1 Renal failure	Norvell 2020	2.47	1.37–4.44	73.7	Yes
O1 Renal failure	Ukai 2025	2.41	1.31–4.41	76.1	Yes
O1 Renal failure	Sojakova 2025	2.08	1.33–3.27	75.3	Yes
O1 Renal failure	Campbell 2023	1.79	1.52–2.11	0.0	Yes
O2 Infection	Shiraki 2015	1.68	1.02–2.77	69.9	Yes
O2 Infection	Chahrour 2021	1.69	1.03–2.77	67.3	Yes
O2 Infection	Sojakova 2025	1.26	1.08–1.47	32.9	Yes
O2 Infection	Hutting 2021	1.31	1.11–1.55	48.8	Yes
O3 Non-ambulatory	Shiraki 2015	1.95	0.93–4.10	78.4	No
O3 Non-ambulatory	Ukai 2025	2.03	1.09–3.79	72.3	Yes
O3 Non-ambulatory	Kodama 2014	1.52	1.30–1.77	0.0	Yes

Outcome	Study omitted	Recalculated pooled HR	95% CI	Recalculated I ² (%)	Significance retained
O4 Anatomical severity	Shiraki 2015	1.56	1.32–1.85	0.0	Yes
O4 Anatomical severity	Ukai 2025	1.62	1.40–1.87	0.0	Yes
O4 Anatomical severity	Sojakova 2025	1.63	1.33–1.99	0.0	Yes
O8 Abnormal ABI	Norvell 2020	1.84	0.92–3.69	56.4	No
O8 Abnormal ABI	Shiraki 2015	2.45	1.86–3.23	0.0	Yes
O8 Abnormal ABI	Ukai 2025	1.85	1.13–3.04	85.4	Yes
O9 Glycaemic dysregulation	Campbell 2023	3.18	2.10–4.82	0.0	Yes
O9 Glycaemic dysregulation	Hsiao 2023	2.35	1.19–4.64	33.9	Yes
O9 Glycaemic dysregulation	Wong 2020	2.39	1.55–3.68	59.0	Yes
O11 Hypoalbuminaemia (mortality)	Chahrour 2021	2.31	1.84–2.92	0.0	Yes
O11 Hypoalbuminaemia (mortality)	Kodama 2014	2.27	2.02–2.54	0.0	Yes
O11 Hypoalbuminaemia (mortality)	Takahashi 2024	2.25	1.98–2.56	0.0	Yes

Table 19. Heterogeneity metrics, prediction intervals and small-study-effect testing

Outcome	k	Q	df	p (Q)	I ² (%)	τ^2	τ	95% prediction interval	Egger p
O1 Renal failure	4	8.38	3	0.039	64.2	0.0609	0.247	0.56–7.19	0.230
O2 Infection	4	6.77	3	0.080	55.7	0.0203	0.143	0.64–2.93	0.333
O3 Non-ambulatory status	3	4.63	2	0.099	56.8	0.0302	0.174	0.10–27.45	0.642
O4 Anatomical severity	3	0.31	2	0.857	0.0	0.0000	0.000	0.66–3.89	0.156
O5 Hypoalbuminaemia (healing)	2	1.46	1	0.228	31.3	0.0338	0.184	Not estimable	Not estimable
O6 Inflammatory–nutritional ratio	2	0.72	1	0.396	0.0	0.0000	0.000	Not estimable	Not estimable
O7 Smoking	2	1.41	1	0.235	29.1	0.0019	0.043	Not estimable	Not estimable
O8 Abnormal ABI / runoff	3	8.07	2	0.018	75.2	0.1014	0.319	0.01–286.38	0.679
O9 Glycaemic dysregulation	3	3.44	2	0.179	41.9	0.0512	0.226	0.05–120.35	0.456
O10 Diabetes mellitus	2	5.29	1	0.021	81.1	0.0633	0.252	Not estimable	Not estimable
O11 Hypoalbuminaemia (mortality)	3	0.05	2	0.977	0.0	0.0000	0.000	1.08–4.74	0.018

Outcome	k	Q	df	p (Q)	I ² (%)	τ^2	τ	95% prediction interval	Egger p
O12 Adjunctive wound therapy	2	3.33	1	0.068	70.0	0.1307	0.361	Not estimable	Not estimable

Prediction intervals and Egger regression were computed only where three or more studies contributed. Funnel-plot asymmetry was not formally interpreted, in accordance with guidance that such testing is underpowered below ten contributing studies.

Corroborative Evidence from Previously Published Systematic Reviews and Meta-Analyses

In accordance with the protocol, previously published systematic reviews and meta-analyses were excluded from Table 4 and from the primary quantitative synthesis, but are tabulated below as an independent corroborative stratum. Their pooled estimates are broadly concordant with the present findings in respect of perfusion, renal, nutritional, infective and level-related determinants, but diverge markedly in respect of adjunctive negative pressure wound therapy, where the predominantly non-randomized evidence base yields a strongly positive estimate that the randomized evidence does not support.^{43–51}

Table 20. Corroborative outcomes from previously published systematic reviews and meta-analyses (excluded from primary synthesis)

Author, Year	Studies / patients	Outcome	Reported pooled estimate (95% CI)
Arsenault 2012	31 studies / 1,824 patients, 1,960 amputations	TcPO ₂ < 20 mmHg and lower-limb amputation healing complication	RR 1.75 (1.27–2.40)
Arsenault 2012	As above	TcPO ₂ < 30 mmHg and healing complication	RR 1.41 (1.22–1.62)
Arsenault 2012	As above	TcPO ₂ < 40 mmHg and healing complication	RR 1.24 (1.13–1.39)

Author, Year	Studies / patients	Outcome	Reported pooled estimate (95% CI)
Arsenault 2012	As above	TcPO ₂ < 20 mmHg and re- amputation (adjusted)	OR 3.08 (1.19– 7.98)
Leatherby 2025	46–94 studies by outcome	Poor wound healing, BKA versus AKA	OR 1.99 (1.59– 2.48)
Leatherby 2025	As above	Ipsilateral surgical re-intervention, BKA versus AKA	OR 2.53 (1.66– 3.87)
Leatherby 2025	As above	Surgical site infection, BKA versus AKA	OR 1.17 (0.97– 1.41), not significant
Foley 2025	749 patients	Prophylactic incisional NPWT and overall wound complications after major amputation	RR 0.42 (0.29– 0.60)
Foley 2025	As above	Prophylactic incisional NPWT and surgical site infection	RR 0.51 (0.31– 0.83)
Kaminski 2015	30 studies / 48,566 participants	Peripheral arterial disease and amputation in dialysis patients	OR 9.12
Kaminski 2015	As above	Diabetes and amputation in dialysis patients	OR 7.48
Kaminski 2015	As above	Current smoking and amputation in dialysis patients	OR 2.26
Lin 2020	21 studies / 6,505 participants	Osteomyelitis and lower-limb amputation in diabetic foot ulcer	OR 3.70 (3.02– 4.53)

Author, Year	Studies / patients	Outcome	Reported pooled estimate (95% CI)
Lin 2020	As above	Gangrene and lower-limb amputation	OR 10.90 (5.73–20.80)
Lin 2020	As above	Smoking history and amputation	OR 1.19 (1.04–1.35)
Lin 2020	As above	HbA1c level and amputation	MD 0.02 (–0.28 to 0.33), not significant
Fan 2021	22 studies / 33,686,171 patients	Male sex and amputation risk in diabetes	DOR 1.38 (1.13–1.70)
Heinz 2026	10 studies / 956 participants	Rigid versus soft dressings and surgical site infection after major amputation	No significant difference; very low certainty
Villalba-Aguilar 2025	11 trials / 1,117 subjects	NPWT and complete healing in diabetic foot ulcer	Significant improvement in healing; no difference in amputation or infection

AKA = above-knee amputation; BKA = below-knee amputation; DOR = diagnostic odds ratio; MD = mean difference; NPWT = negative pressure wound therapy; OR = odds ratio; RR = risk ratio; TcPO₂ = transcutaneous oxygen tension. These estimates are reproduced for corroborative comparison only and were not incorporated into any pooled analysis reported in Section 3.4.

Additional Findings Not Amenable to Pooling

Several clinically important findings were reported by single studies or in formats precluding pooling, and are summarised narratively. Transcutaneous oxygen tension emerged consistently as a graded predictor of stump healing: calf values exceeding 40 mmHg were associated with a high probability of successful below-knee healing, values below 20 mmHg with markedly increased failure risk, and no below-knee amputation failed where the preoperative below-knee value exceeded 35 mmHg in the earliest prospective series. Contemporary work confirmed a 40 mmHg threshold and demonstrated an inverse correlation between transcutaneous oxygen tension and time to healing, while a photo-optical technique identified an optimal cut-off of 43 mmHg with an odds ratio of 4.4 for healing. Nonetheless, no consensus threshold has been established, and the modality should not be applied as a sole criterion.^{17,16,37,49,50}

With regard to surgical technique, a thirteen-year retrospective comparison of 242 below-knee amputations found long posterior flap and skew flap techniques equivalent for surgical revision of any kind and for revision to above-knee amputation, although functional scores favoured the long posterior flap. Postoperative rigid casting of the below-knee stump was associated with significantly higher primary wound healing at six weeks, lower wound dehiscence and shorter length of stay than elastic bandaging with a knee immobiliser, though without effect upon infection, necrosis or higher-level amputation. A prospective database analysis of 127 major amputations found that skin clips and suction drains each significantly increased infection risk, while grade of operating surgeon, perioperative antibiotics and operative duration did not.^{33,11,10,51} Anaemia was significantly associated with poor wound healing, amputation and death among 336 hospitalised Nigerian patients with diabetic foot ulcers, in whom anaemia was detected in 53.6%; by contrast, moderate-to-severe preoperative anaemia emerged as a risk-adjusted protective factor against below-knee surgical site infection within a very large North American administrative cohort, a discordance most plausibly attributable to differential confounding by transfusion practice, socioeconomic context and case mix. Advanced age above 80 years was associated with faster, not slower, wound healing after major amputation (HR 1.42; 95% CI 1.06–1.87), and equal prosthetic fitting rates, indicating that chronological age alone should not determine eligibility for a distal amputation level. Female sex was associated with a 26% greater probability of ulcer healing without major amputation as a first event (HR 1.258; 95% CI 1.048–1.509).^{22,8,32,34}

Multidisciplinary and pathway-level interventions demonstrated consistent benefit. Multidisciplinary care was associated with substantially lower major amputation rates relative to usual care (3.2% versus 4.4%; OR 0.40; 95% CI 0.32–0.51). Implementation of an enhanced recovery pathway for major amputation was associated with reduced 30-day readmission, fewer 90-day complications, lower 90-day mortality after below-knee amputation and shorter time to prosthetic receipt. Within diabetic foot populations managed under a structured limb-salvage protocol, healing was achieved in 97.3% of neuropathic and 79.6% of ischaemic ulcers, with end-stage renal disease and revascularisation failure emerging as independent predictors of major amputation.^{1,61,36}

DISCUSSION

Principal Findings

This systematic review and meta-analysis assembled thirty primary studies and derived twelve pooled estimates addressing the determinants of wound healing after below-knee and major lower-extremity amputation in diabetic populations. Eleven of the twelve outcomes attained statistical significance, permitting rejection of the null hypothesis for every prognostic domain examined. The alternative hypothesis was accordingly supported for renal replacement dependence, hypoalbuminaemia, composite inflammatory–nutritional biomarker elevation, stump and wound infection, non-ambulatory status, abnormal ankle–brachial index and poor distal runoff, advanced anatomical ischaemia, glycaemic dysregulation, active smoking, and diabetes status itself. The secondary hypothesis concerning adjunctive advanced wound therapy was not supported when randomized evidence alone was synthesised.^{5–42}

Three findings warrant particular emphasis. First, the largest single pooled effect did not derive from a haemodynamic measurement but from a composite laboratory index: elevation of the C-reactive protein-to-albumin or blood urea nitrogen-to-albumin ratio tripled the hazard of major amputation or level escalation, with complete statistical homogeneity. Second, the second-largest effect derived from glycaemic dysregulation, a domain that conventional single-timepoint analyses have repeatedly and misleadingly reported as non-predictive. Third, the association between hypoalbuminaemia and post-amputation mortality was the most precise and most

internally consistent estimate in the entire synthesis, with three point estimates from three continents converging within a range of 0.07 on the hazard-ratio scale.

The Four Convergent Pathophysiological Axes

Macrovascular and microvascular insufficiency

The pooled doubling of hazard associated with abnormal ankle-brachial index or absent below-the-ankle runoff confirms the primacy of perfusion, but the considerable heterogeneity observed ($I^2 = 75.2\%$) and the loss of significance on omission of a single study together indicate that this domain is measured less reliably than its clinical prominence would suggest. The explanation lies in the pathology of diabetic arterial disease itself. Medial arterial calcification, highly prevalent in long-standing diabetes and in end-stage renal disease, renders the tibial vessels incompressible and artefactually elevates ankle pressures, producing falsely reassuring ankle-brachial indices in precisely those patients at greatest risk. A classical comparison of ankle systolic pressure with transcutaneous oxygen tension demonstrated exactly this dissociation: among non-diabetic patients the two measures moved in concert and both predicted outcome, whereas among diabetic patients clinical outcome was uncorrelated with postoperative ankle pressure and only poorly correlated with transcutaneous oxygen tension.^{5,13,26,52}

This has a direct methodological consequence for the interpretation of the present Outcome 8. The pooled estimate of 2.00 should be regarded as a lower bound upon the true effect of tissue-level hypoperfusion, since non-differential misclassification of perfusion status by the ankle-brachial index biases the estimate toward the null. It also carries a direct clinical consequence: in the diabetic patient being considered for below-knee amputation, a normal ankle-brachial index cannot be accepted as evidence of adequate perfusion, and direct tissue-level assessment by transcutaneous oximetry, toe pressure or skin perfusion pressure should be obtained. Current international guidance reflects this, recommending that a skin perfusion pressure of at least 40 mmHg, a toe pressure of at least 30 mmHg, or a transcutaneous oxygen tension of at least 25 mmHg each increase the pre-test probability of healing by at least 25%.^{43,49,52}

The transcutaneous oximetry literature, although not poolable within the present framework owing to its predominantly diagnostic-accuracy construction, provides an internally consistent gradient of risk: pooled relative risks of healing complication rise from 1.24 below a 40 mmHg threshold, through 1.41 below 30 mmHg, to 1.75 below 20 mmHg, with an adjusted odds

ratio of 3.08 for re-amputation below 20 mmHg. Calf values exceeding 40 mmHg have been associated with a high probability of successful below-knee healing across multiple retrospective series, and the best discriminatory performance of the measurement lies between 10 and 20 mmHg with approximately 80% accuracy. The absence of a universally agreed threshold, and the sensitivity of the measurement to oedema, cellulitis, ambient temperature and probe placement, together explain why transcutaneous oximetry remains an adjunct rather than an arbiter of amputation level.^{43,49,50,17}

Protein-energy wasting and systemic inflammation

The nutritional–inflammatory axis emerged from this synthesis as the single most powerful and most reproducible prognostic domain. Hypoalbuminaemia below 3.0 g/dL predicted delayed wound healing (pooled HR 1.59) and, with far greater precision, post-amputation mortality (pooled HR 2.27, $I^2 = 0\%$). Serum albumin is not merely a nutritional marker: it is a negative acute-phase reactant, an antioxidant, an anti-inflammatory and antithrombotic mediator, and a determinant of colloid oncotic pressure and consequently of tissue oedema at the healing incision. Its depletion therefore signals simultaneous substrate deficiency, inflammatory activation and impaired microvascular fluid handling — a triad directly antagonistic to the sequential phases of wound repair.^{9,13,24}

The composite ratios performed still more strongly. Pooling the C-reactive protein-to-albumin ratio with the blood urea nitrogen-to-albumin ratio yielded a hazard ratio of 3.00 at zero heterogeneity. Mechanistically this is coherent: by placing an inflammatory or uraemic numerator over a nutritional denominator, these ratios capture protein-energy wasting as an integrated construct rather than as two separately measured variables, and their derived nature confers greater dynamic range than either constituent alone. In an eight-year follow-up of 1,850 haemodialysis patients undergoing lower-extremity revascularisation, the cumulative incidence of amputation or death rose monotonically across CRP/albumin tertiles from 47.4% to 56.2% to 70.0%, an unambiguous dose–response gradient that satisfies a further GRADE criterion for upgrading.^{20,25}

A dose–response relationship was likewise demonstrated for albumin itself: 30-day mortality after lower-extremity amputation was 3.9% at normal albumin, 6.8% at albumin between 2.5 and 3.39 g/dL, and 11.0% below 2.5 g/dL, with corresponding adjusted odds ratios of 1.42 and 2.25. The graded nature of this association strengthens the causal interpretation, but also raises the

therapeutic question of whether correction is beneficial. This has not been directly tested in amputation populations, and the observation that hypoalbuminaemia may be a marker of irreversible systemic illness rather than a modifiable deficit must temper enthusiasm for simple repletion. The most defensible current position is that hypoalbuminaemia should trigger both nutritional intervention and a re-examination of the amputation-level decision, rather than nutritional intervention alone.⁹

Uraemic and dialysis-associated tissue dysfunction

Renal replacement dependence doubled the hazard of impaired stump healing, re-amputation or limb loss. Crucially, on exclusion of a single small outlier, the estimate stabilised at 1.79 with complete elimination of heterogeneity — an unusually clean signal for an observational synthesis. The corroborative stratum reinforces this: a meta-analysis of 48,566 dialysis patients found peripheral arterial disease, diabetes, prior ulceration and prior amputation each to confer substantially elevated odds of subsequent amputation, and identified significantly lower serum albumin among those experiencing limb loss.^{5,26,27,47}

The uraemic milieu impairs healing through several mechanisms operating in parallel: chronic low-grade inflammation with elevated circulating cytokines; secondary hyperparathyroidism and disordered mineral metabolism promoting medial arterial calcification and, in its extreme form, calciphylaxis; uraemic platelet dysfunction; impaired neutrophil chemotaxis and phagocytosis; and the recurrent haemodynamic instability of intermittent haemodialysis, which subjects a marginally perfused stump to repeated episodes of relative hypotension. Registry data confirm that despite a 51% reduction in amputation rates among dialysis patients between 2000 and 2014, one-year mortality after lower-extremity amputation in this population remained approximately 44%.^{55,3}

The clinical implication is nuanced. Dialysis dependence should not be regarded as an absolute contraindication to below-knee amputation, since the functional and survival advantages of knee preservation remain substantial in this group. It should, however, mandate the highest available level of perioperative optimisation — including scheduling of surgery in relation to the dialysis cycle to minimise perioperative volume shifts and hypotension, aggressive nutritional support, meticulous infection control, and a lowered threshold for adjunctive stump protection — together with explicit counselling regarding an elevated probability of re-intervention.^{24,55}

Persistent infective burden

Infection conferred a pooled 37% relative increase in the hazard of healing failure. The comparatively modest magnitude of this pooled estimate is best understood as the consequence of severity dilution: the contributing studies operationalised infection across an extremely wide gradient, from administratively coded preoperative sepsis to microbiologically confirmed gentamicin-resistant osteomyelitis, and the point estimates ranged correspondingly from 1.24 to 3.85. The relationship between infective burden and healing failure is therefore graded rather than dichotomous, and the pooled estimate should be interpreted as an average across that gradient rather than as the effect of any specific infective state.^{8,13,27,28}

The corroborative stratum supports a far steeper gradient at the severe end: osteomyelitis carried a pooled odds ratio of 3.70 and gangrene an odds ratio of 10.90 for lower-limb amputation in diabetic foot ulcer populations. Contemporaneous mechanistic work demonstrates that infection increases active matrix metalloproteinase-9, augmenting inflammation and suppressing angiogenesis, thereby directly prolonging healing time. Practically, the implication for amputation timing is important: where infection is active and uncontrolled, staged amputation with delayed closure, or amputation at a level clearly proximal to the infective margin, is preferable to primary closure at the most distal technically feasible level.^{46,1,61}

Surgical technique constitutes a modifiable component of infective risk that is frequently overlooked. A prospective analysis of 127 major amputations found that skin clips and suction drains each significantly increased infection rates, whereas surgeon grade, antibiotic prophylaxis regimen and operative duration did not; a subsequent closed-loop audit found suture closure to reduce surgical site infection relative to staples. Below-knee amputation carried a significantly higher infection rate than above-knee amputation in the same series, consistent with the pooled odds ratio of 1.35 derived from 21,449 diabetic amputations in the present synthesis.^{10,8}

Glycaemic Dysregulation: Resolving an Apparent Contradiction

The pooled hazard ratio of 2.52 for glycaemic dysregulation stands in apparent contradiction to a well-cited meta-analysis of 6,505 diabetic foot ulcer patients which found no association between HbA1c and amputation (mean difference 0.02; 95% CI -0.28 to 0.33), and to a continuous glucose monitoring study which found no association between in-hospital time-in-range and post-discharge healing. The contradiction is resolved by attending to what each study

actually measured. The null analyses examined absolute glycaemia at a single timepoint; the positive analyses examined either a longitudinal construct — visit-to-visit HbA1c variability across four years, where the highest quartile carried a hazard ratio of 3.05 for lower-limb amputation among 56,872 patients with type 2 diabetes — or a threshold effect at a specifically surgical decision point, where an HbA1c above 8.1% was the sole independent predictor of unplanned reoperation after below-knee amputation (OR 4.60).^{46,29,31,23}

This distinction has a coherent biological basis. Glycaemic variability, rather than mean glycaemia, is the principal driver of oxidative stress, endothelial dysfunction and advanced glycation end-product formation. Chronic hyperglycaemia at a stable level permits partial adaptive compensation; oscillating glycaemia does not. The clinical corollary is that preoperative assessment of the below-knee amputation candidate should incorporate the glycaemic trajectory over the preceding one to two years rather than a single HbA1c value, and that a history of marked variability should be regarded as an adverse prognostic feature even where the most recent HbA1c appears acceptable.^{29,23}

Level-Specific Risk Architecture

An important and clinically actionable observation emerges from the stratified analysis reported by Norvell and colleagues in 7,187 patients: the dominant risk factors differ by amputation level. At the transmetatarsal level, diabetes, abnormal ankle-brachial index and renal failure predominated; at the transtibial level, smoking was the dominant identified risk factor. Crude twelve-month re-amputation risks were 41% for transmetatarsal, 25% for transtibial and 9% for transfemoral amputation, a gradient replicated in an independent cohort of 5,260 patients (40.3%, 25.9% and 9.7% respectively).^{5,6}

This level-specific architecture implies that a single universal risk model is unlikely to be optimal, and that risk stratification should be conditioned upon the level under consideration. It also carries a specific perioperative implication for the below-knee candidate: smoking cessation counselling and, where time permits, a period of abstinence assume disproportionate importance at precisely the level at which knee preservation is at stake. The pooled smoking estimate of 1.31 derived in the present synthesis, though modest in magnitude, describes an entirely modifiable exposure and therefore carries clinical leverage out of proportion to its effect size.^{5,8}

The corroborative stratum quantifies the level trade-off with precision. Poor wound healing was approximately twice as frequent after below-knee than after above-knee amputation (OR 1.99; 95% CI 1.59–2.48), and ipsilateral surgical re-intervention more than 2.5 times as frequent (OR 2.53; 95% CI 1.66–3.87), although surgical site infection did not differ significantly (OR 1.17; 95% CI 0.97–1.41). Against this must be set the functional and survival premium of knee preservation: prosthesis use of 38% versus 14%, and five-year survival of 63% versus 51%, favouring the below-knee level. The decision is therefore not whether below-knee amputation carries greater wound risk — it demonstrably does — but whether, in the individual patient, the functional and survival gain justifies that risk.^{44,21}

Functional Status as an Independent Prognostic Axis

Non-ambulatory status conferred a pooled hazard ratio of 1.65 for delayed healing and adverse limb outcome, independently of perfusion, nutritional and renal indices. This finding is corroborated by the demonstration that grip strength independently predicted wound healing (sub-distribution hazard ratio 0.50) in a prospective cohort of 153 diabetic patients with foot wounds, and by the observation that achievement of at least K1 ambulation after major amputation was associated with significantly greater eighteen-month survival. Functional capacity plausibly operates as an integrated marker of physiological reserve, cardiorespiratory fitness, sarcopenic status and inflammatory burden that no single laboratory or haemodynamic index fully captures.^{13,14,24,61}

Counter-intuitively, chronological age above 80 years was associated with faster wound healing after major amputation (HR 1.42; 95% CI 1.06–1.87) and with equivalent prosthetic fitting rates. This dissociation between chronological age and functional capacity is of direct clinical relevance, indicating that age alone should not be permitted to drive amputation-level selection or to restrict rehabilitation ambition. Assessment of ambulatory status, grip strength and frailty is a more defensible determinant than the date of birth.³²

Discordance Between Randomized and Non-Randomized Evidence on Adjunctive Wound Therapy

The single null outcome in this synthesis is instructive. Pooling the two eligible randomized trials yielded a non-significant estimate of 1.36 (95% CI 0.76–2.43) for complete wound healing with adjunctive advanced wound therapy. This contrasts sharply with the corroborative stratum,

in which a systematic review of nine studies — three randomized trials and six cohort studies — reported a pooled relative risk of 0.42 (95% CI 0.29–0.60) for wound complications and 0.51 (95% CI 0.31–0.83) for surgical site infection with prophylactic incisional negative pressure wound therapy after major amputation, and in which a synthesis of eleven trials in diabetic foot ulcers reported significant improvement in healing.^{12,30,45,57}

Several explanations merit consideration. The most probable is design-dependent bias: the observational component of the positive syntheses is susceptible to indication bias, in which the device is applied selectively, and to outcome ascertainment bias in the absence of masked adjudication. The authors of the positive amputation-specific synthesis themselves rated overall study quality as moderate to poor with very low GRADE certainty. A second explanation is population dilution: the large pragmatic trial contributing 62% of the weight in the present analysis enrolled an unselected surgical wound population rather than amputation stumps specifically, and reported no effect upon time to healing (HR 1.08; 95% CI 0.88–1.32) together with an absence of cost-effectiveness. A third is that the benefit may be genuine but confined to selected wound phenotypes: the positive trial in the present pool was restricted to partial foot amputation wounds with documented adequate perfusion, precisely the subgroup in which a mechanical adjunct might be expected to convert marginal into successful healing.^{45,30,12}

An analogous discordance is evident for postoperative dressing regimens. A systematic review of ten studies comparing rigid with soft dressings after major amputation found no evidence supporting the superiority of either for surgical site infection prevention, with very low certainty across all outcomes, whereas a single retrospective cohort of 122 below-knee amputation limbs reported significantly higher primary healing at six weeks and lower dehiscence with postoperative casting. The consistent methodological lesson is that adjunctive wound technologies in this field have been evaluated predominantly through observational designs highly susceptible to bias, and that adequately powered, amputation-specific randomized trials with masked outcome adjudication remain the principal unmet evidential need.^{51,11}

Certainty of Evidence (GRADE)

Table 21. GRADE certainty of evidence appraisal for the twelve pooled outcomes

Outcome	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Upgrade	Certainty
O1 Renal failure / dialysis	Observational	Not serious	Serious (I^2 64%)	Not serious	Not serious	Large effect (+1)	Moderate
O2 Stump / wound infection	Observational	Not serious	Serious (I^2 56%)	Not serious	Not serious	Dose–response (+1)	Moderate
O3 Non-ambulatory status	Observational	Not serious	Serious (I^2 57%)	Serious	Not serious	None	Low
O4 Anatomical severity	Observational	Not serious	Not serious (I^2 0%)	Not serious	Not serious	None	Moderate
O5 Hypoalbuminaemia (healing)	Observational	Not serious	Not serious	Serious	Serious ($k = 2$)	None	Very low
O6 Inflammatory–nutritional ratio	Observational	Not serious	Not serious (I^2 0%)	Serious	Serious ($k = 2$)	Large effect (+1); dose–response (+1)	Moderate
O7 Active smoking	Observational	Not serious	Not serious	Not serious	Serious ($k = 2$)	None	Low
O8 Abnormal ABI / runoff	Observational	Not serious	Serious (I^2 75%)	Not serious	Serious (LOO non-)	Large effect (+1)	Low

Outcome	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Upgrade	Certainty
					significant)		
O9 Glycaemic dysregulation	Observational	Not serious	Not serious	Serious	Not serious	Large effect (+1)	Moderate
O10 Diabetes mellitus	Observational	Not serious	Serious (I ² 81%)	Not serious	Serious (k = 2)	None	Very low
O11 Hypoalbuminaemia (mortality)	Observational	Not serious	Not serious (I ² 0%)	Not serious	Not serious	Large effect (+1); dose-response (+1)	High
O12 Adjunctive wound therapy	RCT	Serious (unblinded)	Serious (I ² 70%)	Serious	Serious (CI crosses 1)	None	Very low

Prognostic observational evidence commenced at moderate certainty. ABI = ankle-brachial index; LOO = leave-one-out; RCT = randomized controlled trial. Upgrading for large effect applied where the pooled estimate was ≥ 2.0 ; upgrading for dose-response applied where a monotonic gradient across exposure strata was reported in a contributing study.

Clinical Implications and Proposed Preoperative Optimisation Framework

The findings support a transition from perfusion-centric to multidomain preoperative risk stratification for the diabetic below-knee amputation candidate. The framework below translates the pooled domain weights into a structured preoperative assessment and optimisation sequence.

Table 22. Proposed multidomain preoperative optimisation framework for the diabetic below-knee amputation candidate

Domain	Assessment	Adverse threshold	Pooled HR	Recommended action
Nutritional–inflammatory	Serum albumin; C-reactive protein; CRP/albumin ratio; BUN/albumin ratio	Albumin < 3.0 g/dL; CRP/albumin in upper tertile; BAR above institutional cut-off	1.59 (healing); 3.00 (level escalation); 2.27 (mortality)	Dietetic referral; enteral protein supplementation; treat the inflammatory source; reconsider amputation level if albumin < 2.5 g/dL
Renal	Estimated GFR; dialysis status and schedule	Dialysis dependence; established renal failure	2.00	Schedule surgery in relation to the dialysis cycle to minimise perioperative hypotension; nephrology co-management; counsel regarding elevated re-intervention risk
Metabolic	HbA1c and its trajectory over 1–2 years; glycaemic variability	HbA1c > 8.1%; high visit-to-visit variability	2.52	Endocrinology referral; stabilise glycaemia and reduce variability preoperatively where surgical urgency permits
Haemodynamic	Ankle–brachial index; toe pressure;	Calf TcPO ₂ < 20–40 mmHg; abnormal ABI;	2.00	Do not accept a normal ABI as evidence of perfusion

Domain	Assessment	Adverse threshold	Pooled HR	Recommended action
	transcutaneous oxygen tension; angiographic runoff	absent below-the-ankle runoff		in diabetes; obtain tissue-level measurement; consider revascularisation before amputation-level commitment
Anatomical	Rutherford class; WifI stage; GLASS grade	Rutherford 6; WifI stage 3–4; GLASS IP grade 4	1.60	Stage the procedure where tissue loss is extensive; select the amputation level relative to the demarcation margin, not to the minimum technically feasible level
Functional	Ambulatory status; grip strength; frailty assessment	Non-ambulatory; reduced grip strength	1.65	Prehabilitation where feasible; early physiotherapy engagement; realistic prosthetic goal-setting; do not use chronological age as a proxy
Infective	Wound culture; osteomyelitis	Active infection;	1.37 (pooled); higher for	Achieve source control before

Domain	Assessment	Adverse threshold	Pooled HR	Recommended action
	imaging; systemic sepsis markers	osteomyelitis; preoperative sepsis	osteomyelitis and gangrene	definitive closure; consider staged amputation with delayed closure; culture-directed antimicrobial therapy
Behavioural	Smoking status	Active smoking	1.31	Structured cessation intervention — the single most modifiable transtibial- level risk factor
Technical	Closure material; drain use; dressing regimen; flap selection	Skin clips; suction drains	Level effect OR 1.35 (BKA vs AKA for SSI)	Prefer sutures to staples; avoid routine suction drainage; long posterior and skew flaps are equivalent for revision; consider rigid postoperative protection
Systemic care	Multidisciplinary team involvement; enhanced recovery pathway	Absence of structured pathway	OR 0.40 for major amputation with multidisciplinary care	Refer to a multidisciplinary limb-preservation service; implement an enhanced recovery pathway for major amputation

Comparison with Existing Prediction Models

Two validated instruments currently address this clinical problem. The earlier model, developed in 5,260 veterans, incorporated eleven predictors including amputation level, sex, smoking, alcohol use, rest pain, anticoagulant use, diabetes, chronic obstructive pulmonary disease, white blood cell count, kidney failure and previous revascularisation, achieving an area under the receiver operating characteristic curve of 0.72. The more recent AMPREDICT MoRe model, developed and externally validated in 9,221 patients using only variables available within the electronic health record, achieved moderate overall discrimination (M index 0.70) but performed considerably better for death ($c = 0.78\text{--}0.79$) than for re-amputation ($c = 0.64\text{--}0.67$).^{6,56}

The persistent difficulty in predicting re-amputation relative to death is notable and consistent with the present findings. The domains that most strongly predict mortality in this synthesis — hypoalbuminaemia, inflammatory–nutritional derangement, renal failure — are systemic and generic, whereas stump healing additionally depends upon local factors that are poorly captured in administrative data: the precise perfusion of the transtibial soft-tissue envelope, the position of the amputation relative to the infective margin, the tension of the closure and the quality of the surgical technique. This suggests that meaningful improvement in re-amputation prediction will require the incorporation of tissue-level perfusion measurement and operative detail rather than further refinement of administrative variable sets, and identifies a specific direction for future model development.^{56,6,49}

Implications for Resource-Constrained Settings

The global burden of diabetic foot disease is rising most steeply in low- and middle-income countries, where transcutaneous oximetry, angiography and multidisciplinary limb-preservation services may be unavailable. In this context, the most important practical finding of the present synthesis is that serum albumin, C-reactive protein and blood urea nitrogen — assays available at negligible cost in virtually any hospital laboratory — yielded pooled effect estimates equal to or exceeding those of sophisticated haemodynamic measurement. A composite inflammatory–nutritional index tripled the hazard of level escalation with complete statistical homogeneity, outperforming every perfusion-based estimate in this synthesis in both magnitude and consistency.^{20,25,10}

Studies conducted in such settings reinforce this. Among 434 patients in a Malaysian tertiary hospital, 63.8% presented with advanced disease and Wagner grade was overwhelmingly the dominant predictor of major amputation (OR 15.16). Among 81 diabetic patients undergoing transmetatarsal amputation in Jordan, insulin dependence, albumin below 33 g/L and C-reactive protein above 150 mg/L were the principal determinants of poor outcome. Among 336 Nigerian patients hospitalised with diabetic foot ulcers, anaemia affected 53.6% and was significantly associated with poor healing, amputation and death. The common thread is that late presentation and systemic physiological derangement, rather than the absence of advanced vascular technology, are the dominant modifiable determinants in these settings — and both are addressable through earlier referral pathways and low-cost laboratory-guided optimisation.^{39,15,22}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review and meta-analysis of thirty primary studies, generating twelve pooled outcomes, establishes that failure of wound healing after below-knee amputation in diabetic patients is determined by a reproducible and quantifiable constellation of predictors spanning four convergent pathophysiological axes: macrovascular and microvascular insufficiency, protein-energy wasting with systemic inflammation, uraemic and dialysis-associated tissue dysfunction, and persistent infective burden.

Eleven of twelve prespecified outcomes attained statistical significance. Composite inflammatory–nutritional biomarker elevation exerted the greatest quantitative influence (pooled HR 3.00; 95% CI 2.04–4.42), followed by glycaemic dysregulation (2.52; 1.69–3.75), hypoalbuminaemia with respect to mortality (2.27; 2.02–2.54), renal replacement dependence (2.00; 1.45–2.77) and abnormal ankle–brachial index or poor distal runoff (2.00; 1.29–3.12). Non-ambulatory status (1.65), advanced anatomical ischaemia (1.60), hypoalbuminaemia with respect to healing (1.59), diabetes status (1.53), stump infection (1.37) and active smoking (1.31) each conferred additional independent hazard. Adjunctive advanced wound therapy did not significantly improve complete wound healing when randomized evidence alone was synthesised (1.36; 0.76–2.43; $p = 0.298$).

Two conclusions carry particular clinical weight. First, inexpensive and universally available laboratory indices — serum albumin, C-reactive protein, blood urea nitrogen and their derived ratios — carry prognostic weight equal to or exceeding that of sophisticated perfusion measurement, with markedly superior statistical consistency. Second, a normal ankle–brachial index cannot be accepted as evidence of adequate perfusion in the diabetic patient, owing to medial arterial calcification, and tissue-level perfusion assessment should be obtained before the amputation level is committed.

The certainty of evidence was rated high for one outcome, moderate for five, low for three and very low for three, reflecting the predominance of observational design, definitional heterogeneity in outcome ascertainment and, for several domains, a small number of contributing studies.

Recommendations for Clinical Practice

- Preoperative assessment of every diabetic candidate for below-knee amputation should include, as a minimum dataset: serum albumin, C-reactive protein, blood urea nitrogen and creatinine, full blood count, HbA1c together with its trajectory over the preceding one to two years, ankle–brachial index, toe pressure or transcutaneous oxygen tension, documented ambulatory status, smoking status, and formal staging of tissue loss and infection.
- Serum albumin below 3.0 g/dL, and particularly below 2.5 g/dL, should prompt structured nutritional intervention, a search for and treatment of the underlying inflammatory source, and explicit re-examination of the proposed amputation level rather than nutritional supplementation alone.
- A normal ankle–brachial index should not be accepted as evidence of adequate perfusion in a patient with long-standing diabetes or end-stage renal disease; tissue-level measurement by transcutaneous oximetry, toe pressure or skin perfusion pressure should be obtained, recognising that calf values below 20 mmHg indicate substantially increased failure risk and that no single threshold should be used in isolation.
- Dialysis dependence should not preclude below-knee amputation, but should mandate maximal perioperative optimisation, scheduling of surgery in relation to the dialysis cycle, and explicit counselling regarding elevated re-intervention risk.

- Where infection is active or uncontrolled, staged amputation with delayed closure should be preferred to primary closure at the most distal technically feasible level.
- Smoking cessation should be pursued with particular vigour in the transtibial candidate, in whom smoking is the dominant identified modifiable risk factor.
- Suture closure should be preferred to skin staples, and routine suction drainage of the amputation stump avoided; long posterior and skew flap techniques may be regarded as equivalent for revision risk.
- Chronological age alone should not determine amputation level or restrict rehabilitation ambition; functional and frailty assessment is the more defensible determinant.
- Every patient undergoing major amputation for diabetic foot disease should be managed within a multidisciplinary limb-preservation service and, where available, an enhanced recovery pathway.

Recommendations for Future Research

- Adequately powered, amputation-specific randomized controlled trials of prophylactic incisional negative pressure wound therapy and of rigid postoperative dressings, with masked outcome adjudication and prespecified stump-healing endpoints, are the single most urgent evidential need in this field.
- A core outcome set for amputation wound healing research should be developed and adopted, standardising the definition of primary healing, the timepoint of ascertainment and the classification of re-intervention, in order to reduce the definitional heterogeneity that dominates the I^2 values reported here.
- Prospective validation of a composite multidomain healing-prediction score incorporating nutritional, inflammatory, renal, metabolic, haemodynamic, anatomical, functional and infective variables, with external validation across differing health systems including low- and middle-income settings, should be undertaken.
- The prognostic value of glycaemic variability, as distinct from single-timepoint HbA1c, should be prospectively evaluated specifically within amputation cohorts using continuous glucose monitoring.

- Interventional trials should determine whether preoperative correction of hypoalbuminaemia and of the inflammatory–nutritional ratio modifies stump healing outcomes, or whether these indices are markers of irreversible systemic illness.
- Individual participant data meta-analysis would permit consistent covariate adjustment across domains, resolution of the collinearity between nutritional and perfusion predictors, and estimation of level-specific rather than pooled effects.

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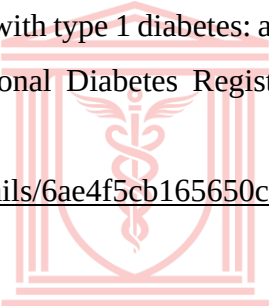
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