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REVIEW ARTICLE

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Prognostic factors for delayed healing of complex wounds in adults: A scoping review

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Abstract

Complex or hard-to-heal wounds continue to be a challenge because of the negative impact they have on patients, caregivers, and all the associated costs. This study aimed to identify prognostic factors for the delayed healing of complex wounds. Five databases and grey literature were the sources used to research adults with pressure ulcers/injuries, venous leg ulcers, critical limb-threatening ischaemia, or diabetic foot ulcers and report the prognostic factors for delayed healing in all care settings. In the last 5 years, a total of 42 original peer-reviewed articles were deemed eligible for this scoping review that followed the JBI recommendations and checklist PRISMA-ScR. The most frequent prognostic factors found with statistical significance coinciding with various wound aetiologies were: gender (male), renal disease, diabetes, peripheral arterial disease, the decline in activities of daily life, wound duration, wound area, wound location, high-stage WIfI classification, gangrene, infection, previous ulcers, and low ankle brachial index. It will be essential to apply critical appraisal tools and assessment risk of bias to the included studies, making it possible to make recommendations for clinical practice and build prognostic models. Future studies are recommended because the potential for healing through identification of prognostic factors can be determined, thus allowing an appropriate therapeutic plan to be developed.

KEYWORDS

decision making, prognosis, wound healing, wounds and injuries

Key Messages

- early knowledge of wound severity and the risk of delayed healing together with a patient's expected outcomes, allows the healthcare professional to individualise interventions
- the potential prognostic factors to delayed healing were: gender (male), renal disease, diabetes mellitus, peripheral arterial disease, the decline in activities of daily life, wound duration, wound area, wound location, high-

stage WIfI classification, gangrene, infection, previous ulcers, and low ankle brachial index.
- scarcity of prognostic studies related with pressure ulcer/injury aetiology

1 | BACKGROUND

Patients with wounds are increasingly becoming a reality that demands a response from health care systems and professionals.[1]

In some European Union countries, the prevalence of patients with one or more wounds is three to four people per 1000 population and it is estimated that there are around 1.5 to 2 million patients living with a chronic wound, some of them for a period longer than 6 months.[1] The presence of a wound that is hard-to-heal compromises the patient's health-related quality of life, and the costs inherent to the treatment are substantial.[2-4] Some of these wounds such as Diabetic Foot Ulcer (DFU), Venous Leg Ulcer (VLU) and Pressure Ulcer / Injury (PU/I) cost £5056.71, £7886.05, and £5972.28 respectively per patient and over £4 billion between 2017–2018 to the United Kingdom (UK) National Health Service.[5]

The concept of complex wounds represents all wounds that do not follow the normal healing process, being classically stalled in the inflammatory phase, without progression.[6,7] These wounds are also designated as chronic, hard-to-heal, stalled, non-healing wounds.[2,7] We chose the term *complex wound* to reflect the dynamic and multifactorial healing process, and not only by its prolonged healing time.[6] They are defined as soft tissue injuries that are difficult to resolve with standard treatment due to the presence of one or more factors that delayed healing and/or healing time >4 weeks.[6,8,9] The most common complex wounds are leg ulcers, DFU, and PU/I in patient over 60 years old.[4]

Complex wounds present numerous challenges and to ensure evidence-based decision-making and effective treatment,[4] the healthcare professional must be equipped with different resources and knowledge. As such, knowledge of prognostic factors can predict individual risk of complications, making it possible to alert to imminent delays and guide the professional's decision making processes as well as positively impacting on the patient's outcomes and lifestyle.[10] A prognostic factor is a measurable variable that implies a better or worse clinical outcome, regardless of the treatment the patient receives and identifying them and understanding their impact enables healthcare professionals to make informed decisions about when to initiate, stop, or change therapy for a patient.[11]

Several factors influence the healing of complex wounds and can be divided into those directly related to the wound and systemic factors related to the general condition of the patient, with local factors being the best predictors of delayed healing.[12] Some of the factors that can delay healing are: substantial soft tissue loss, infection, impaired blood flow, maceration and associated pathologies.[6,8] However, we considered it necessary to map and update the dispersed knowledge about the prognostic factors responsible for the delay in healing by wound aetiology, the methodologies used by the included studies and the statistical methods addressed. This review brings an overview body of evidence in the area and could be a starting point for a systematic review and meta-analysis to quantify the value of each factor.

With the identification of prognostic factors, the individual risk of delay or complications can be predicted, making it possible to warn of imminent delays and guide decision making, helping healthcare professionals with cost–benefit analysis to determine the cost-effectiveness of the treatment.[13] The study of prognostic factors for delayed healing is also crucial for informing patients and helping them to manage their expectations of realistic progress.[13] Although the scoping review does not result in recommendations for clinical practice, it can guide future research, which will be essential to support decision making and even early implementation of more expensive or invasive therapies.

A preliminary search in March 2022 was carried out in MEDLINE, Cochrane Reviews and JBI evidence synthesis and we found a scoping review published in 2019 in which the objective was to obtain information on what factors that may have potential prognostic value for delayed healing of various types of non-traumatic skin ulcers,[14] however, this review only included studies published in databases, the search was carried out until 2017 and its results present the prognostic factors for healing, and we specifically looked for the delay. As no systematic review was found that would give continuity to the previous review, it will be pertinent to update the existing scoping review and encompass more types of leg ulcers, research sources and map the factors associated only with a delay. Thus, this scoping review aim to identify prognostic factors for the delayed healing of complex wounds in adults.

2 | MATERIALS AND METHODS

The review was conducted following the JBI methodology for scoping reviews[15,16] and guided by the Preferred

Reporting Items for Systematic Reviews extension for Scoping Reviews checklist (PRISMA-ScR).[17] The purpose of a scoping review is not to provide practical recommendations or carry out evidence synthesis, but rather to identify the types of evidence available in a broad and emerging thematic area, as well as to identify evidence gaps that may require further research.[17] The research question addressed by the review was: what prognostic factors are delaying the healing of complex wounds in adults?

The protocol of this review was registered on the Open Science Framework platform (osf.io/59xyb/).

The inclusion criteria were based on PCC mnemonic (Participants, Concept, Context) proposed by JBI.

2.1 | Eligibility criteria

2.1.1 | Participants

This review considered studies that include the adult persons aged 18 or over chronologically with complex, chronic, stalled, stopped, or hard-to-heal wound(s).

We include DFU (Wound, Ischaemia, and foot Infection—the WIfI classification grade I or higher or another classification system), VLU (C6 of Clinical-Aetiology-Anatomy-Pathophysiology—the CEAP classification or other classification system that considers wound interruption in the skin barrier), lower extremity arterial disease (LEAD) with critical limb-threatening ischaemia (CLTI) formerly designated by Critical Limb Ischaemia[18] (with an open wound, Rutherford classification 5 to 6, or Fontaine classification IV) and PU/I (category/stage 2 or higher of Pressure Injury Staging System). We consider DFU, VLU, CLTI and PU/I that do not heal or do not reduce 20 to 50% (<50% DFU, <40% VLU and 20–40% PU/I) in size in 4 weeks or 30 days with an appropriate treatment.[4,19,20]

We assume healed wounds when the area is equal to 0 cm^2, 0 mm^2 or complete epithelialization, although the FDA recommendation is "*Complete wound closure is defined as skin reepithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart*",[16,21] but it was difficult to obtain this information in studies.

2.1.2 | Concept

This review considered only studies that explore prognostic factors related to delayed healing.

A prognostic factor is a variable measurable with clinical outcomes regardless of treatment,[13] thus we considered patient attributes, wound characteristics, clinical indicators, and socio-economic status. Those associated with the effect of the specific dressings, studies with a commercial proposal and/or comparisons between treatments were excluded.

We included prognostic factors where the estimate independently contributes to predicting the outcome and a relationship between exposure and outcome is established. We did not include inconclusive studies, only those with a proven effect on delayed healing, and we considered the statistical significance of $P < .05$.

Studies of prognostic models were included provided they reported separate associations of individual prognostic factors with delayed healing.

2.1.3 | Context

The review considered studies that were carried out in any context of care (e.g., hospital, community, home, nursing home, wound centre) provided by healthcare professionals. We considered the healthcare professionals in the care of the patient as wound physicians, nurses, and podiatrists.

2.1.4 | Types of sources

This scoping review considered quantitative and mixed studies. Quantitative designs include any experimental study designs (including randomised controlled trials, non-randomised controlled trials, or prognostic studies based on data from randomised controlled trials) and observational studies (prospective and retrospective cohort studies). Guidelines issued by national and international wound and tissue viability associations were included and dissertations or theses published in repositories. Texts and opinion articles, case studies, systematic and narrative reviews, letters to the editors and in vitro and animal studies were excluded. Although we are aware that the sources of the scoping review must cover all options, we chose to exclude this type of studies and publications, as our results may support a future systematic review.

2.2 | Search methods

A three-step research strategy was followed.[15] An initial search was carried out on MEDLINE to locate articles relevant to the review and to analyse whether they could contribute to the increase in keywords and search terms. The second search was more complete across all the databases and included all keywords and indexing terms (Search strategy can be consulted in the Appendix A). Finally, a reference reading of the included studies was

performed to identify any studies that may have been missed (Table A1).

The search strategy aimed to locate published was through the databases (MEDLINE via PubMed, CINAHL and Nursing & Allied Health Database via EBSCOHost, Scopus, Cochrane Library and Web of Science) and unpublished studies and/or papers in the grey literature search.

The search was initially on studies available and recorded online within the last 5 years. This time limit is due to the last research that was carried out until 2017, not including any study from this year, but also due to the numerous publications and the revolutionary progress in the area, making the scope of action in the patient with a wound to have undergone evolution and updating. For a complete reading of the articles, those written in English, Portuguese, Spanish and French and full text, are selected. Articles not available in full text in the databases were located at the university library.

2.3 | Study selection

All results obtained through the search strategy were transferred into EndNote Web software (Clarivate Analytics, PA, US), where duplicates were removed. These results were relocated to the Rayyan QCRI (Qatar Computing Research Institute, Doha, Qatar) and two reviewers independently (R.M. and J.N.A.) read the titles and abstracts and included the articles for full reading, those that were clearly irrelevant were excluded. Full-text reports were obtained and assessed against the inclusion criteria by two independent reviewers (R.M. and J.N.A.). Any disagreement was solved through discussion or consultation with a third reviewer (P.A.). The selection process for relevant studies is based on the guidelines from PRISMA-ScR[17] demonstrating the process from the initial research to the final selection of studies for extraction and synthesis, including how many articles were included or excluded at each step. The selection process is shown in a PRISMA-ScR study selection flow diagram in Figure 1.

2.4 | Data extraction

Data were extracted from the included papers by one reviewer (R.M.) with support from two reviewers (M.L. and P.A.), using a data extraction tool developed by the reviewers based on the previous scoping review.[14] The extracted data includes specific details about the: Title; Author, year and country; Aim; Design; Sampling type and size; Participants; Average healing time; Follow-up or cohort time; Wound details (including wound type, grade/severity, and classification system, if applicable); Setting; Outcome; Prognostic factors by wound types; Statistical methods; Level of evidence according to JBI classification.[22] Disagreements were resolved by discussion in the team. Some authors of the articles were contacted to request missing or additional data.

Considering the objective of this scoping review, the quality of the articles was not systematically evaluated by critical appraisal tools, however, a discussion was held among the reviewers about the quality of the studies.

2.5 | Synthesis

A table was created that summarises all the prognostic factors found for delayed healing of complex wounds. The table presents the prognostic factors subdivided by patient characteristics (e.g., age, sex, comorbidities, lifestyle habits, etc.), wound characteristics (e.g., size, depth, wound duration, system classification, etc.), and clinical investigation measurements or clinical indicators (e.g., Ankle Brachial Index [ABI], transcutaneous oxygen pressure [$TcPO_2$], skin perfusion pressure [SPP], urine and blood test, microbiology results, etc.). Due to the number of articles obtained to summarise the remaining results collected, we chose to describe them narratively. The tables with the final data extraction can be consulted in the Appendix B.

3 | RESULTS

The study selection process was illustrated in the PRISMA-ScR flow diagram (Figure 1). The initial search resulted in 2093 results from the databases and 425 results from the grey literature. After initial screening and removal of duplicate articles, we obtained 1822 papers. A total of 112 articles were read in full. The reasons for exclusion of 70 articles were: did not define the outcome as wound healing; did not report healing or delayed healing; had an inappropriate study design (e.g., comparative cross-sectional) to obtain prognostic factors; were inconclusive (the factors studied showed no effect on healing); or did not have ethical approval. Forty-two studies were included in the final synthesis (Tables B1–B4).

The review included adults with a complex wound of more than 30 days and prognostic factors with outcomes in wound healing (that have been tested for an association with the outcome) and it was possible to extract prognostic factors in delayed healing, regardless of the settings. Only studies on the factors and not models of prognostic value were included as they did not separately address the factors by type of complex wound.

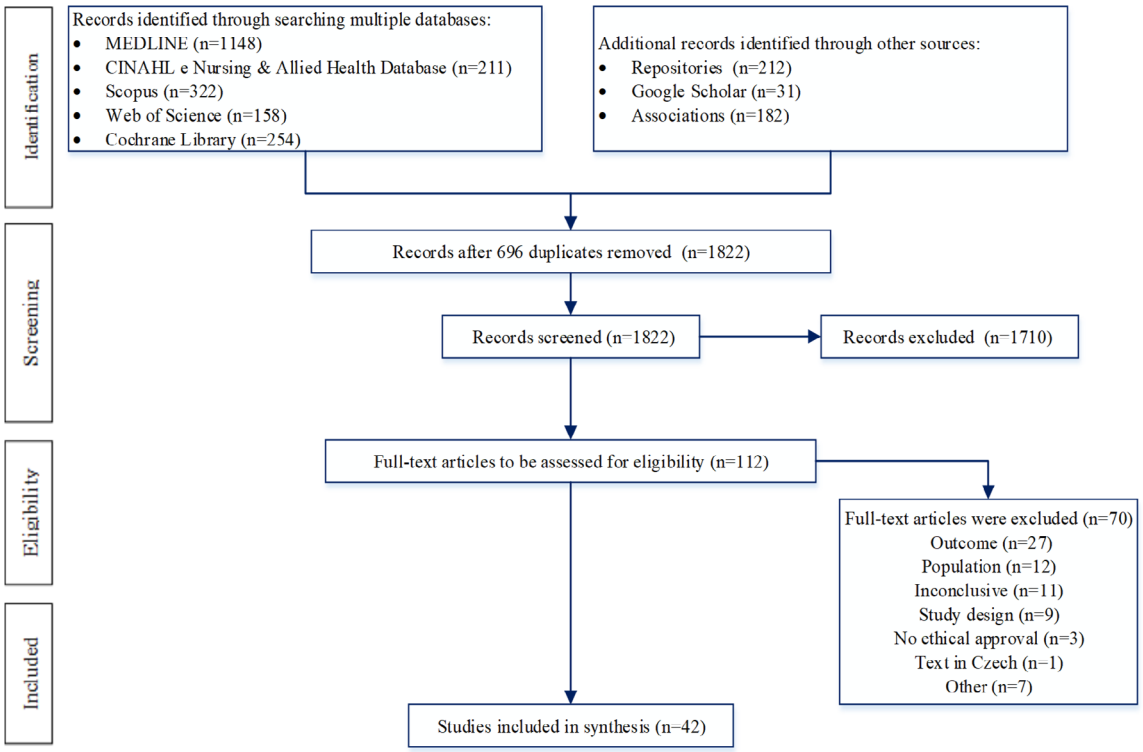

FIGURE 1 The PRISMA-ScR statement of this review. *Source*: Tricco et al.[17]

TABLE 1 Prognostic factors related to patient characteristics.

	Prognostic factors for delayed healing			
	PU/I (n = 1)	**VLU (n = 4)**	**CLTI (n = 12)**	**DFU (n = 25)**
Patient characteristics	No information	Gender male[27] Deep venous disease[28] History of deep venous thrombosis[28] Depression[28] NonWhite (African Americans, Hispanics, and Asian Americans)[28]	Dialysis[29,30] End-stage renal disease on dialysis[31,32] Chronic kidney disease [33,34] Coronary artery disease history[35,34] Diabetes mellitus[35,36] Use insulin[31] Decline in activities of daily life (Barthel Index)[29] Non-ambulatory status[35] WIfI stage 4 and non-ambulatory status[37] WIfI stage 4 and haemodialysis[37] Aortoiliac lesion[33]	Peripheral vascular disease[38,39,40,26] Advanced age (age ≥ 65 years)[41,42,43] Cigarette smoking[20,44] Gender male[20] Diabetes mellitus type-1[20] Diabetic nephropathy[43] Renal impairment[40] Anaemia[40] Osteomyelitis[40] Using systemic antibiotic for deep tissue infection[20] Vascular surgery treatment[41] High risk of obstructive sleep apnoea[45] Frailty index[a] >0.25[46] Diagnosis of foot stand deformation[47] Previous amputations[48]

Abbreviations: CLTI, critical limb-threatening ischaemia; DFU, diabetic foot ulcers; PU/I, pressure ulcer/injury; VLU, venous leg ulcer.
[a]Frailty index (FI) based on 42 dichotomous variables capturing a broad spectrum of health deficits and including chronic diseases, symptoms, disabilities in daily activities, psychological issues, and laboratory abnormalities, a cut-point of FI > 0.25 chosen to define the presence of frailty.[46]

The 42 studies analysed were developed in 18 different countries. One reported an international multicentre study developed in United States (US), Canada, Germany, Poland, Belgium, Czech Republic, and Hungary. Most of studies were developed in US (n = 9), Japan (n = 8), China (n = 4) and the *UK* (n = 3), followed by Australia, Canada, and India with two studies, and Indonesia, Malta, Netherlands, Nigeria, Norway, Slovenia, South Korea, Spain, Taiwan, Thailand, and France with only one study.

In the last 5 years, the year with the most publications was 2017 (n = 12), followed by the years 2021 (n = 8), 2020 (n = 8), 2019 (n = 7) and 2018 (n = 6), considering that the survey was carried out in March, we only obtained one study in 2022.

After applying the inclusion criteria, only peer-reviewed articles were included. The Journal of Vascular Surgery (n = 6) (Q1 cardiology and cardiovascular medicine, Scientific Journal Ranking [SJR] 2021 1.8) and European Journal of Vascular and Endovascular Surgery (n = 3) (Q1 cardiology and cardiovascular medicine, SJR 2021 1.29) were the most included journals.

All studies that were included met the JBI classification of the level of evidence for prognosis at 3,[22] which corresponds to observational cohort studies. We obtained several prospective (n = 21) and retrospective (n = 18) cohort studies, one secondary analyzes of data from three prospective randomised trials, one subanalysis of the multicentre prospective cohort study, and a study involving three distinct cohorts (screening retrospective, validation retrospective and prospective).

Participants in the included studies presented complex wounds such as PU/I (n = 1), VLU (n = 4), LEAD with CLTI (n = 12) and DFU (n = 25).

The sample size of retrospective cohort studies ranged from 56 to 819 and prospective cohorts ranged from 21 to 366. The most frequent type of sample was consecutive. The Follow-up or cohort time ranged from 4 weeks to 1 year.

Of the wound types included only PU/I, CLTI and DFU reported mean healing times, of 30.12 days,[23] 112 days,[24] 110 days[25] to 6.6 months[26] respectively.

The wound classification systems or staging systems mentioned for VLU were CEAP. The article that includes

TABLE 2 Prognostic factors related to wound characteristics.

	Prognostic factors for delayed healing			
	PU/I (n = 1)	**VLU (n = 4)**	**CLTI (n = 12)**	**DFU (n = 25)**
Wound characteristics	No information	• Wound duration >6 months[27] • Wound area > 5 cm[227] • Wound location ankle (lower leg versus ankle)[27] • The increase of previous ulcer duration[49] • Low initial horizontal healing rates and vertical healing rates[49]	• High-stage WIfI classification[29,37,35,34,36] • Infection[31,50,25,44] • University of Texas grade 3[31,33] • Rutherford category 6 [33,34] • Gangrene[31,34] • Major tissue loss[31] • Wound location dorsal[31] • Wound duration >2 months[31]	• High-stage WIfI classification[51,39,52,48] • Longer time from wound onset to first assessment[39,40,52] • Wound area > 3 cm^2 [38,39] and > 5 cm[226] • University of Texas classification grade 2/3[41,47] • Infection[25,44] • Existence previous ulcers[38,47] • Wagner classification system grade ≥ 3[40] • Delay in referral to specialist[41] • Presence of chronic ulcers[38] • Less than 41.8% size reduction in 4 weeks[20] • No change 1st week wound bed area obtained from isothermal maps of thermal images[53] • Wound deep[44] • Wound location rearfoot[20] • Wound requiring an antimicrobial dressing[20] • Gangrene[40] • Maceration[54]

Abbreviations: CLTI, critical limb-threatening ischaemia; DFU, diabetic foot ulcers; PU/I, pressure ulcer/injury; VLU, venous leg ulcer; WIfI, wound, ischaemia, and foot infection classification.

the UP, the UP stage was evaluated according to grade I-IV. The Rutherford classification, WIfI Classification System, Fontaine classification system, GLASS (Global Limb Anatomic Staging System) and University of Texas (UT) classification system was applied to the LEAD with CLTI. In the DFU, the Wagner, PEDIS (perfusion, extent, depth, infection and sensation), UT classification, WIfI and SINBAD (Site, Ischaemia, Neuropathy, Bacterial Infection and Depth) classification systems were used.

The most used statistical methods were logistic regression models (univariate and multivariate analysis) (n = 30), survival analysis (Cox proportional hazards models, Kaplan–Meier curves and log-rank test) (n = 23), and receiver operating characteristic curve analysis (n = 9) and some through analysis of variance (n = 5).

Patients with complex wounds continue to need differentiated care, as the hospital (n = 27) was the main

TABLE 3 Prognostic factors related to clinical indicators.

	Prognostic factors for delayed healing			
	PU/I (n = 1)	**VLU (n = 4)**	**CLTI (n = 12)**	**DFU (n = 25)**
Clinical indicators	Lower the microcirculation perfusion in the center of the PU/I[23]	• Decrease in gene for promoting wound healing (ARP2, CAR1, Claudin-5, CREBL1, Endomucin-2, IL8RB, IL17BR, IL22R, Psoriasin, PTPRK, TEM4, TEM7R, VEGF-C)[55] • Increased in gene for Inhibiting wound healing (KAI1)[55] • Not decrease in MMP-1 and MMP-2 in the first 4 weeks[49]	• Albumin level < 3 g/dL[31,35] • C-reactive protein >3 mg/dL[56] and > 5 mg/dL[31] • Poor of below-the-ankle runoff[31,57] • Absence of wound blush[a] after endovascular therapy[30] • Lower haemoglobin[33] • Score ≥ 5 CONUT[56] • WIfI stage 4 and albumin level < 3.0 g/dL[37] • Changes in ABI < 0.23 and TBI < 0.21 pre and pos-endovascular therapy[24] • Low baseline ABI[34] • Preprocedural TBI <0.35[31] • Post-procedure vascular flow reserve value <3.9[32] • Higher infrapoplitea calcification grade [57] • Occluded plantar arch[33] • Lower pre and post endovascular therapy temperature of the feet[33] • Lower DIFF2[b33] • Low SPP[32] • Low baseline and post-procedural SPP and post-procedural SPP < 50 mmHg[34]	• ABI < 0.9,[20]< 0.65[58] and < 0.52[43] • TcPO2 < 28.5 mmHg[43] and < 27.5 mmHg [58] • Monophasic Doppler waveform[20] • Moderate or severe decrease in eGFR (mL/min per 1.73 m^2)[59] • Proteinuria[40] • Baseline HbA1c > 9.5%[60] and HbA1c ≥7%[40] • NRL >4.2[44] • MRSA initial wound culture 72 h of admission[25] • Microbiota community-type stability[50] • Greater percent abundance of the Bacteroidales and Lactobacillales at baseline[61] • High concentration of MMP-9 (>0.38 pg/μg), high MMP-9/TIMP-1 ratio (>9.06), and low MMP-1/TIMP-1 ratio (<0.056) at baseline[62] • A gradient of ≥1°C between average temperature of affected foot and that of unaffected foot at baseline or at any time healing[63] • Low infrared perfusion index[43] • Low grip strength assessment using an isometric hand dynamometer[48]

Abbreviations: ABI, ankle brachial index; CLTI, critical limb-threatening ischaemia; CONUT, controlling nutritional status; DFU, diabetic foot ulcers; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MMP, matrix metalloproteinases; MRSA, methicillin-resistant *Staphylococcus aureus*; NRL, neutrophil-to-lymphocyte ratio; PU/I, pressure ulcer/injury; SPP, skin perfusion pressure; TBI, toe brachial index; $TcPO_2$, transcutaneous oxygen pressure; TIMP, tissue inhibitors of metalloproteinases; VLU, venous leg ulcer.

[a]Wound Blush - which is defined as an area densely stained with contrast media around the wound.[30]

[b]DIFF2- Defined as the lowest temperature minus the mean post-endovascular therapy temperature of the 5 zones.[33]

setting, after the wound care centre (n = 11) and the outpatient clinic (n = 4).

The following tables summarise the main results, prognostic factors will be presented by patient characteristics, wound characteristics, and clinical indicators. We did not find factors related to the socio-economic status (Tables 1–3).

4 | DISCUSSION

To perform this scoping review investigating possible prognostic factors for delayed healing of PU/I, VLU, LEAD with CLTI and DFU, a total of 42 articles were included. We wanted to include only factors that delayed healing, not those that are simply associated with healing.

The interest in studying prognostic factors is not only to guide treatment but also to predict the healing time and build wound healing models, that will help in resource allocation and managing patient expectations. By having knowledge and modifying prognostic factors, which are sometimes also causal, it is possible to change the average course of the disease.[64]

Of the complex wounds included, we only had one PU/I and four VLU, perhaps this unexpected result was due to temporal limitations. In addition, 4-weeks time was the minimum delay time which led us to exclude some PU/I. However, there is an alert to study more about the prognostic factors of PU/I because they continue to have an average prevalence of 10.8% in Europe.[65] It is worth mentioning that the study[23] that included PU/I uses grades I-IV and that these stages are already updated.

Although we did not apply any quality and risk of bias assessment tools, all included studies complied with the PRISMA-ScR checklist assessment items, ethics committee approval and prognostic factors extracted for statistical significance. The studies were quite heterogeneous, however, some of the factors have been investigated in a significant number of studies with sufficiently homogeneous definitions. The mentioned factors were related to the characteristics of patients and ulcers, with less homogeneity in clinical indicators. Renal disease,[33,34,40,43,59] dialysis,[29-32] peripheral arterial disease (PAD),[26,38,40] diabetes mellitus (DM),[20,31,35,36,43] age ≥65 years,[41,42,43] high-stage WIfI classification,[29,34,35,36,37,39,48,51,52] high-grade UT classification,[31,33,41,53] wound area,[20,26,27,38,39] wound location,[20,27,31] infection,[20,25,31,40,44,50,61] gangrene,[31,34,40] time from wound onset to first assessment,[39,40,52] existence of previous ulcers,[38,47,49] low ABI[20,34,43,58] and low albumin level <3 g/dL[31,35,37]were the factors cited three or more times by the studies. These factors justify the analysis of a systematic review with meta-analysis to obtain the highest level of evidence. We want to emphasise that these factors were frequent because 88% (n = 37) of the studies included participants with DFU and LEAD with CLTI, which could be a limitation. All the prognostic factors mentioned are easily accessible in clinical practice, for example, characterising wound and medical information, perhaps the analytical parameters are the most difficult to obtain in a nursing home or community context.

In an excluded study with 461 293 patients, which we did not include because it encompassed several types of wounds (Arterial ulcer, Burn, Cellulitis, DFU, PU/I, Skin tear, Surgical wound, Trauma wound, VLU and other) without analysing them individually, the top three most influential predictors of wounds at risk of not healing were the number of days the wound had been treated at the time of the visit, wound depth and current wound surface area.[66] Other studies published in 2003 revealed that the initial wound area, patients' age and time from the wound appears to the beginning of treatment, are the most important prognostic factors.[67] The previous scoping review to identify potential prognostic factors from 1997 to 2017, unlike ours, obtained highest numbers of VLU and PU/I and did not include CLTI. The most cited factors were age, gender, diabetes, smoking status, history of deep vein thrombosis, ulcer area, and ulcer duration at the time of first assessment as the factors that most influence healing.[14] We add with our results that in LEAD with CLTI renal disease, dialysis, DM, non-ambulatory status, infection, high-stage WIfI classification, albumin level <3 g/dL, high CRP and low ABI should be highlighted. In patients with DFU, PAD, age ≥65 years, cigarette smoking, high-stage WIfI classification, infection, time from wound onset to the first assessment, wound area >3 cm^2, low ABI, low $TcPO_2$ and high HbA1c. In wounds where we obtained fewer studies, lowers the microcirculation perfusion in the center of the PU/I. In patients with VLU gender male, depression, nonwhite, deep venous disease (DVD), wound duration >6 months, wound area >5 cm^2, wound location ankle, the increase of previous ulcer duration, decrease in the gene for promoting and increased in the gene for inhibiting wound healing, and not decrease in MMP-1 and MMP-2 in the first 4 weeks were noted.

Several studies indicate that the reduction in wound size at 4 weeks of follow-up is a good prognostic indicator of wound healing,[20,66,67,68] however, as isolated data point it is insufficient because the combination of numerous factors establishes an important synergy that influences healing.[69] For DFU and CLTI depth should take priority,[70] although our results put more emphasis on size than depth. It is important to mention, that to monitor the size of the wound, a mobile application (App) can

be used that allows us to reliably assess this data, since using a disposable paper ruler (longer length and wider width perpendicular to each other) the measurement obtained is the area of a square and not the real area of the wound.[71] Using the ruler produces 30% greater wound area measurements than using the App.[71]

The Society for Vascular Surgery Lower Extremity Threatened Limb classification system was developed to estimate the risk of amputation at 1 year and the estimated likelihood of benefit of/requirement for revascularization, however, some studies have concluded that higher the stage (3/4) of the WIfI classification, the worse the wound healing or the longer it takes to heal.[29,34,35,36,37,39,48,51,52] This system assesses wound characteristics, that is, size, depth and severity through the presence of gangrene, the degree of ischaemia determined through the ABI, ankle systolic pressure, $TcPO_2$ or Toe Pressure (TP) and the presence and severity of the infection.[70] The parameters size, depth, ischaemia, and infection as potential prognostic factors for healing for CLTI and DFU.

Some studies have highlighted the importance of wound duration for delayed healing,[27,72,73] but our results showed more evidence of the existence of a previous ulcers,[38,47,49] as well as the time until the first assessment by healthcare professionals.[39,40,41,52]

The factor that was most named in the clinical indicators was the reduced value of the ABI for DFU and CLTI, however, we did not reach a consensus on the reference value (ABI < 0.9,[20] <0.65[58] and <0.52[43]). The Best Practice Recommendations for the Prevention and Management of Peripheral Arterial Ulcers consider abnormal values <0.9 or > 1.4.[18] ABI that may not be reliable, especially when there is calcification of the arteries, and in these cases, toe brachial index (TBI), TP or TcPO2 is preferable to stratify the degree of ischaemia.[43,70] In patients with CLTI it may be interesting to evaluate the ABI and TBI, because if there are no significant changes (ABI < 0.23 and TBI < 0.21) between the values before and after endovascular therapy, they provide prognostic of delayed healing.[24]

We did not find factors related to the knowledge and skills of professionals as well as the socio-economic status and as a psychological factor, only one study reported depression,[28] perhaps it is a knowledge gap that can be developed.

We brought new information compared with the last scoping review[14] with genetic factors, although we only obtained one study.[55] The major limitation of these data is that in clinical practice we cannot measure the gene expression of patients.

The limitations of this review were that it only included publications from the last 5 years, perhaps for this reason we had a limited number of types of wounds, although we had obtained a considerable number of studies. The fact that we obtained only one PU/I study brought limited results for this type of wound. A 2015 study, not included in the results, created a system to predict the probability of healing of patients with PU/I and found that size, PU/I age, number of concurrent wounds of any aetiology, PU/I category/stage 3 or 4, evidence of bioburden/infection, patient age, being nonambulatory, having a renal transplant, paralysis, malnutrition, and/or patient hospitalisation for any reason are factors that contribute to the delayed in healing.[74] Comparing our results in general these factors are included, except having renal transplant and paralysis. Another limitation is that we only included prognostic factors for delayed healing by at least 4 weeks with statistical significance, which limited the number of named factors.

In addition, we excluded dressing and treatments performed because of the bias that these types of studies present, which may be a limitation and studies in this sense are recommended.

We highlight the heterogeneous definition of wound healing in the studies found, having excluded some due to lack of definition. We advise in future research to follow the United States Food and Drug Administration definition of complete healing.[21]

5 | CONCLUSION

This review was important to improve the knowledge of wound healing, as it will provide important guidance for clinical practice and management of patient and family expectations. The healthcare professional, by considering prognostic factors, can determine the likelihood of recovery or the risk of complications and guide treatment decisions and plan for future care. The prognostic factors found for delayed healing of various wound aetiologies, published in the last 5 years, were: gender (male), renal disease, DM, PAD, the decline in activities of daily life, wound duration, wound area, wound location, high-stage WIfI classification, gangrene, infection, the existence previous ulcers and low ABI.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

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APPENDIX A: SEARCH STRATEGY

TABLE A1 Search conducted in March 2022.

Search	Medline via Pubmed March 14, 2022	Records retrieved
#1	"prediction"[Title/Abstract] OR "predictions"[Title/Abstract] OR "predictors"[Title/Abstract] OR "predictable"[Title/Abstract] OR "predict"[Title/Abstract] OR "predicts"[Title/Abstract] OR "predicting"[Title/Abstract] OR "predictive"[Title/Abstract] OR "predicted"[Title/Abstract] OR "predictability"[Title/Abstract] OR "prognostication"[Title/Abstract] OR "prognoses"[Title/Abstract] OR "prognosis"[Title/Abstract] OR "prognostic"[Title/Abstract] OR ("prognostic"[Title/Abstract] AND ("criteria"[Title/Abstract] OR "score"[Title/Abstract] OR "characteristics"[Title/Abstract] OR "factor"[Title/Abstract] OR "indicator"[Title/Abstract] OR "biomarker"[Title/Abstract] OR "determinant"[Title/Abstract] OR "decision"[Title/Abstract] OR "algorithm"[Title/Abstract] OR "outcome"[Title/Abstract] OR "risk"[Title/Abstract] OR "variable"[Title/Abstract]))	2 256 950
#2	"healed"[Title/Abstract] OR "healing"[Title/Abstract] OR "heal"[Title/Abstract] OR "healings"[Title/Abstract] OR "heals"[Title/Abstract] OR "cicatrical"[Title/Abstract] OR "cicatrix"[Title/Abstract] OR "cicatrization"[Title/Abstract] OR "cicatrize"[Title/Abstract] OR "cicatrized"[Title/Abstract] OR "cicatrizing"[Title/Abstract] OR "cure"[Title/Abstract] OR "restore"[Title/Abstract] OR "restored"[Title/Abstract] OR "restores"[Title/Abstract] OR "restoring"[Title/Abstract] OR "skin over"[Title/Abstract] OR "repairability"[Title/Abstract] OR "repairable"[Title/Abstract] OR "repaire"[Title/Abstract] OR "repaired"[Title/Abstract] OR "repair"[Title/Abstract] OR "repairing"[Title/Abstract] OR "repairs"[Title/Abstract] OR "regenerating"[Title/Abstract] OR "regeneration"[Title/Abstract]	1 021 613
#3	"chronic wound*"[Title/Abstract] OR "complex wound"[Title/Abstract] OR "wound"[Title/Abstract] OR "wounds"[Title/Abstract] OR "non-healing wound"[Title/Abstract] OR "healing impaired wound"[Title/Abstract] OR "persistent wound"[Title/Abstract] OR "slow healing wound"[Title/Abstract] OR "foot ulcer"[Title/Abstract] OR "leg ulcer"[Title/Abstract] OR "pressure ulcer"[Title/Abstract] OR "pressure injury"[Title/Abstract] OR "pressure injuries"[Title/Abstract] OR "diabetic foot"[Title/Abstract]	250 584
#4	"young adult"[Title/Abstract] OR "adult"[MeSH Terms] OR "adult"[Title/Abstract] OR "adults"[Title/Abstract] OR "middle aged aged"[Title/Abstract] OR "middle aged"[Title/Abstract] OR "aged"[MeSH Terms] OR "aged"[Title/Abstract] OR "80 and over"[Title/Abstract]	8 647 923
#5	#1 AND # 2 AND #3 AND #4	2724
#6	#1 AND # 2 AND #3 AND #4 AND (y_5[Filter])	1148

APPENDIX B: TABLES WITH DATA EXTRACTION

TABLE B1 Factors investigated in each included study as potential prognostic factors for delay healing PU/I.

	Prognostic factors for delayed healing PU/I					Sample size
Ref.	Patient	Ulcer	Clinical Indicators	Setting	Design	
23			Lower the microcirculation perfusion in the centre of the PU/I (stage 3 < 1000 U and 4 < 500 U) (obtained laser doppler microcirculation)	Hospital	Prospective	43

Abbreviation: PU/I, pressure ulcer/injury.

TABLE B2 Factors investigated in each included study as potential prognostic factors for delay healing VLU.

Ref.	Prognostic factors for delayed healing VLU			Setting	Design	Sample size
	Patient	**Ulcer**	**Clinical Indicators**			
27	Gender male	Wound duration >6 months, wound area > 5 cm^2 and wound location ankle (lower leg VS ankle)		Wound care centre	Secondary analysis of data of three prospective randomised trials	716
28	DVD, history of deep venous thrombosis, depression and nonWhite (African Americans, Hispanics, and Asian Americans)			Wound care centre	Retrospective	65
55			Decrease in gene for promoting wound healing (ARP2, CAR1, Claudin-5, CREBL1, Endomucin-2, IL8RB, IL17BR, IL22R, Psoriasin, PTPRK, TEM4, TEM7R, VEGF-C) and increased in gene for inhibiting wound healing (KAI1)	Hospital (Tertiary Care Setting [TCS])	Screening retrospective, validation retrospective and prospective	190
49		The increase of previous ulcer duration, and low initial horizontal healing rates and vertical healing rates	Not decrease in MMP-1 and MMP-2 in the first 4 weeks	Outpatient Unit	Prospective	22

Abbreviations: DVD, deep venous disease; MMP, matrix metalloproteinases; TCS, tertiary care setting.

TABLE B3 Factors investigated in each included study as potential prognostic factors for delay healing CLTI.

Ref.	Prognostic factors for delayed healing CLTI			Setting	Design	Sample size
	Patient	Ulcer	Clinical Indicators			
24			Changes in ABI < 0.23 and TBI < 0.21 pre and post endovascular therapy	Wound care centre	Prospective	218
30	Dialysis		Absence of wound blush (which is defined as an area densely stained with contrast media around the wound) after endovascular therapy	Hospital	Subanalysis of the multicentre prospective	185
31	ESRD on dialysis and use insulin	Wound location (Dorsal), UT grade 3, major tissue loss, infection, gangrene, and wound duration >2 months	Lack of below-the-ankle runoff, albumin level < 3 g/dL, CRP >5 mg/dL and preprocedural TBI <0.35	Outpatient unit	Retrospective	118
29	Decline in activities of daily life (decrease in Barthel Index) and haemodialysis	High-stage WIfI		Hospital	Retrospective	221
37	WIfI stage 4 and nonambulatory status (both wheelchair and bedridden patients) and, WIfI stage 4 and haemodialysis	WIfI stage 4	WIfI stage 4 and albumin level < 3.0 g/dL	Hospital	Retrospective	735
35	DM, coronary artery disease history, and nonambulatory status	WIfI stage 4	Albumin level < 3 g/dL	Hospital	Retrospective	153
32	Chronic renal failure on dialysis		Post-procedure vascular flow reserve value <3.9 and low SPP	Hospital	Multicentre prospective	110
57			Poor below the-ankle runoff and higher infrapoplitea calcification grade	Hospital	Retrospective	484
33	Chronic kidney disease and aortoiliac lesion	Rutherford category 6 and UT grade 3	Lower haemoglobin, lower pre- and post-endovascular therapy temperature (infrared thermography) of the feet, occluded plantar arch and lower DIFF2 (defined as the lowest temperature minus the mean post-endovascular therapy temperature of the 5 zones)	Hospital	Prospective	124

(Continues)

TABLE B3 (Continued)

Ref.	Prognostic factors for delayed healing CLTI			Setting	Design	Sample size
	Patient	Ulcer	Clinical Indicators			
56			CRP > 3 mg/dL and score ≥ 5 CONUT	Hospital	Retrospective	120
34	ESRD and coronary artery disease	Rutherford category 6, gangrene, and high-stage WIfI	Low baseline ABI, low baseline and post-procedural SPP, and post-procedural SPP < 50 mmHg	Hospital	Retrospective	172
36	DM	WIfI stage 4		Hospital	Retrospective	154

Abbreviations: ABI, ankle brachial index; CLTI, critical limb-threatening ischaemia; CONUT, controlling nutritional status; CRP, C-reactive protein; DM, diabetes mellitus; ESRD, end-stage renal disease; SPP, skin perfusion pressure; TBI, toe brachial index; UT, university of Texas classification; WIfI, wound, ischaemia, and foot infection classification.

TABLE B4 Factors investigated in each included study as potential prognostic factors for delay healing DFU.

Ref.	Prognostic factors for delayed healing DFU			Setting	Design	Sample size
	Patient	**Ulcer**	**Clinical Indicators**			
59			Moderate (30–59) or severe (<30) decrease in eGFR (mL/min per 1.73 m2)	Hospital	Prospective	366
60			Baseline HbA1c >9,5%	Wound care centre	Prospective	99
25		Infection	MRSA initial wound culture 72 h of admission	Hospital	Retrospective	819
38	Peripheral vascular disease	Wound area > 3 cm^2, multiple ulcers at first presentation and presence of chronic ulcers		Wound care centre	Retrospective	56
44	Cigarette smoking	Infection and wound deep	>4.2 NRL	Wound care centre	Retrospective	101
54		Maceration		Wound care centre	Prospective	62
41	Vascular surgery treatment and advanced age	Longer duration of ulcer before specialist health care treatment (≥ 52 days) and UT grade 2/3 and stage C/D		Outpatient units	Retrospective	105
50		Infection	Microbiota communit- type stability	Hospital	Prospective	100
51		High-stage WIfI		Wound care centre	Prospective	217
62			High concentration of MMP-9 (>0.38 pg/μg), high MMP-9/TIMP-1 ratio (>9.06), and low MMP-1/TIMP-1 ratio (<0.056) at baseline	Hospital	Prospective	22
45	STOP-BANG questionnaire score ≥ 4 (high risk of obstructive sleep apnoea)			Hospital	Prospective	94
39	PAD	Increasing wound area, longer time from wound onset to first assessment and WIfI stage 3 and 4		Hospital	Retrospective	310
52		WIfI stage 3 and 4, and longer time from wound onset to assessment		Hospital	Retrospective	99
61		Infection			Prospective	23

(Continues)

TABLE B4 (Continued)

Ref.	Prognostic factors for delayed healing DFU			Setting	Design	Sample size
	Patient	Ulcer	Clinical Indicators			
			Greater percent abundance of the Bacteroidales and Lactobacillales at 0 weeks	Outpatient Unit		
53		No change from week 1 to week 2 wound bed area obtained from isothermal maps of thermal images		Hospital (TCS)	Prospective	26
47	Diagnosis of foot stand deformation	Number of previous DFU and UT grade 2 and 3		Wound care centre	Retrospective	208
58			ABI < 0.65 and TcPO2 < 27.5 mmHg	Hospital	Prospective	121
40	PAD, anaemia, renal impairment, and osteomyelitis	Ulcer duration more than 1 month prior to hospitalisation, gangrene, and Wagner grade ≥ 3	Proteinuria and HbA1c ≥7%	Hospital	Multicentre prospective	336
26	PAD with critical ischaemia	Wound area > 5 cm^2		Hospital	Prospective	347
42	Advanced age (age ≥ 65 years)			Hospital (TCS)	Retrospective	422
63			A gradient of ≥1°C between average temperature (infrared dermal thermometry) of affected foot and that of unaffected foot at baseline or at any time during ulcer healing	Hospital (TCS)	Prospective	30
20	Cigarette smoking, gender male, DM type-1 and using systemic antibiotic for deep tissue infection	Not attained a minimal 41.8% wound size improvement at 4 weeks, wound requiring an antimicrobial dressing and rearfoot location	Monophasic Doppler waveform and ABI < 0.9	Wound care centre	Retrospective	140
43	Diabetic nephropathy and advanced age		TcpO2 < 28.5 mmHg, ABI <0.52 and low near-infrared perfusion index	Wound care centre	Prospective	21
48	Previous amputations	WIfI stage 4	Low grip strength (measure of muscle function) assessment using an isometric hand dynamometer	Hospital	Prospective	153
46	Frailty index >0.25			Hospital	Prospective	76

Abbreviations: ABI, ankle brachial index; BMI, age, neck circumference and male gender; DFU, diabetic foot ulcers; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MMP, matrix metalloproteinases; MRSA, methicillin-resistant *Staphylococcus aureus*; NRL, neutrophil-to-lymphocyte ratio; PAD, peripheral arterial disease; STOP-BANG, the snoring, tiredness, observed apnoea, high blood pressure; $TcPO_2$, transcutaneous oxygen pressure; TCS, tertiary care setting; TIMP, tissue inhibitors of metalloproteinases; UT, university of Texas classification; WIfI, wound, ischaemia, and foot infection classification.