REVIEW PROTOCOL

Risk factors for delayed healing or non-healing of venous leg ulcers in adults: a systematic review protocol

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Abstract

Background Chronic leg ulcers affect 1–3% of the population and are costly to treat and health service resource intensive. Venous aetiology contributes to about 70% of all chronic leg ulcers; these ulcers are often associated with prolonged ill health, pain and decreased physical functioning, and have a substantial impact on health-related quality of life.

Aim The primary aim of this systematic review is to identify literature on the risk factors for delayed healing or non-healing of venous leg ulcers (VLUs) in adults.

Methods This systematic review will be guided by the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Studies will be identified from PubMed, ScienceDirect, Web of Science, ProQuest, CINAHL Complete, MEDLINE, APA PsychINFO, Academic Search Elite, Cochrane Library, JBI EPD (evidence-based practice database), ProQuest (Dissertations and Theses Global) and Global ETD (electronic theses and dissertations) Search Engine up to August 2021. Methodological quality will be assessed using the Mixed Methods Appraisal Tool (MMAT) 2018. A narrative synthesis of risk factors will be categorised as physiological (general/medical), clinical, demographics or psychosocial.

Keywords systematic review, venous leg ulcers, risk factors, delayed healing, non-healing

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Introduction

Leg ulcers are known to be slow to heal and cause prolonged ill health, affecting up to 3% of adults[1], increasing in prevalence with age[2,3], and often lasting for many years[2,4]. Leg ulcers occur in the lower legs with the commonest underlying aetiologies of venous insufficiency, arterial insufficiency or a combination of both. Of all chronic leg ulcers, venous leg ulcers (VLUs) have the highest prevalence[5], with venous aetiology often classified using the Clinical-Etiological-Anatomical-Pathophysicological (CEAP) international scale for classifying the clinical presentation, primary cause of venous disease, anatomical location of the affected veins and type of disease[6]. VLUs are classified under this system as C5 (evidence of a healed VLU) or C6 (active VLU)[6].

There are more than 47,200 cases of people with active VLUs receiving care in Australian hospitals (2010–2011)[7]. There were 1,730 cases of people with VLUs in residential aged care facilities in 2012, and it has been noted that A$803 million is being spent to manage/treat VLUs[7]. A VLU is defined as an open wound between the knee and ankle joint that occurs as a result of venous disease[8]. Despite evidence-based care, only about 70% of VLUs will heal within a 24-week period[9,10]; in addition, reported costs often do not include the indirect costs to people with VLUs, with these high costs noted to be a barrier to implementation of evidence-based wound care[11,12].

These ulcers can be debilitating, having a major impact on a person's life, often with disease distress symptoms including pain, decreased physical functioning, immobility, sleep disturbance, lack of energy, limitations in leisure activities, worries and frustrations, lack of self-esteem and a substantial negative impact on health-related quality of life[13].

Many published studies report risk factors for delayed/non-healing of VLUs[14–19]; however, to date, there have been no systematic reviews that we could find and only limited reviews of risk factors[20–23], particularly those that include non-physiological factors, due to a range of definitions, methodological inconsistencies in data collection, and measurement of risk factors[20]. Previously reported studies have consistently concluded risk factors as being a larger ulcer area, a longer ulcer duration, a previous history of ulceration, venous abnormalities and a lack of high compression[20]. Other potential risk factors include decreased mobility and/or ankle range of movement, poor nutrition and increased age[20].

While a number of evidence-based guidelines exist for the management of VLUs[24–28], with current strategies including addressing patient-related factors (pain, education, psychosocial support, elevation of lower limb, exercise, and nutrition and hydration), preparing the leg and the wound (cleansing, controlling venous eczema and maintaining skin integrity), and graduated compression therapy, evidence supporting further risk factors would be of benefit in the management of VLUs and will potentially add to existing literature in management guidelines.

Aim

This systematic review will investigate risk factors for delayed or non-healing VLUs. These factors can then be considered when caring for someone with a VLU in clinical practice and research. A preliminary search was undertaken in the PROSPERO International prospective register of systematic reviews. There were no systematic reviews found on the risk factors associated with healing of VLUs; hence the importance for this systematic review to be completed.

Methods

This review protocol is guided by the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 statement[29]; the completed PRISMA-P 2015 checklist is shown Supplement 1.

Protocol and registration

This systematic review has been registered with the PROSPERO International prospective register of systematic reviews (CRD42021279789).

Search strategy

Articles will be screened to determine eligibility against the inclusion criteria. Articles that are deemed eligible for inclusion will have their reference lists searched following the same search strategy. The search strategy will be used to locate articles using the following keywords – (venous OR varicose OR stasis) AND ulcer AND (risk OR likelihood OR predict) AND (heal OR non-healing OR delayed healing OR unhealed OR refractory). The search criteria will include human studies from any country, in English language and available in full text. For example, Table 1 shows the search strategy for PubMed.

Information sources

The search will be undertaken in the databases of PubMed, ScienceDirect, Web of Science, ProQuest, CINAHL Complete, MEDLINE, APA PsychINFO, Academic Search Elite, Cochrane Library, JBI EPD (evidence-based practice database), ProQuest (Dissertations and Theses Global) and Global ETD (electronic theses and dissertations) Search Engine. There will be no limitations on the publication starting dates; the publication dates will be limited up to 31 August 2021 with a further search run prior to finalisation of the study.

Types of studies

The type of studies will include qualitative, quantitative and mixed-methods research such as observational, longitudinal, cohort, case control, randomised controlled trials, non-randomised controlled trials, descriptive studies, systematic reviews, meta-analysis, theses or dissertations. All case studies, case reports, case series, clinical guidelines, literature reviews, general reviews, opinion papers or news items will be excluded.

Inclusion criteria

Table 2 shows the inclusion criteria which follows the aspects of the PICO mnemonic.

Outcomes

The primary outcome of the review is to identify, describe and analyse the risk factors for delayed healing or non-healing in comparison to non-delayed healing of VLUs in adults. The risk factors will be measured by key variables, the effects on healing, and level of risk as determined by significance of outcomes.

Currently there is a lack of consensus on the definitions of delayed healing and non-healing in VLUs with no agreed

Table 1. Example search strategy from PubMed

Line	Keywords
#1	ulcer*
#2	(venous OR varicose OR stasis)
#3	(risk* OR likel* OR predict*)
#4	(heal* OR (non-healing) OR (delayed healing) OR unhealed OR refractory)
#5	#1 AND #2 AND #3 AND #4
#6	#5 AND English language
#7	#6 AND Publication date: until 31st of August, 2021

definition. Definitions have generally included that the wound does not proceed toward healing in a defined time period or in a timely manner[30,31], hence delayed healing and non-healing in this study will be defined as a VLU that has not followed a normal healing trajectory. Non-delayed healing will be defined as a VLU/s that has healed (100% epithelialisation).

Study selection

The search results will be imported into EndNote and all studies (excluding duplicates) will be transferred to Rayyan for blinded screening. All steps involved in study selection will be presented in a PRISMA flow diagram.

Screening of titles and abstracts will be undertaken followed by screening of full text articles. Two independent reviewers will assess titles and abstracts of retrieved articles for inclusion criteria. Articles retrieved in this first step will then be assessed for full text inclusion. Two reviewers will independently assess to exclude any articles that do not meet inclusion criteria. Any disagreements in these phases will be resolved by a third independent reviewer.

Assessment of methodological quality

All eligible studies will be critically appraised by at least two reviewers using the Mixed Methods Appraisal Tool (MMAT) 2018[32]. A third independent reviewer will resolve any disagreements in the final appraisal. All quality assessment results will be presented for each study and/or outlined in the synthesis of findings.

Table 2. PICO criteria

PICO / description
Participants
Inclusion criteria: • Adults (aged 18 years or older) with VLU/s • All study settings and geographical locations *Exclusion criteria:* • People with any other types of leg ulcers (i.e., mixed, arterial, diabetic)
Intervention/exposure
All risk factors associated with delayed healing or non-healing of VLU/s including under the physiological (general/medical and may include factors such as venous abnormalities, mobility, nutrition), clinical (ulcer duration, ulcer dimensions, previous ulceration), demographics (age, race, gender) or psychosocial (anxiety, depression, social isolation) categories
Comparison
Comparators: non-delayed healing of VLU/s
Outcome(s)
Inclusion criteria: • Studies that investigate delayed healing or non-healing of VLU/s *Exclusion criteria:* • Studies that investigate healed VLU

Data extraction

Data from included studies will be extracted into an Excel spreadsheet. One reviewer will undertake data extraction and complete the excel file, with a second reviewer checking the file. A third independent reviewer will resolve any disagreements. Any missing data will be documented, with the third reviewer to decide if any additional information should be requested to the corresponding author of the relevant study.

The study data to be extracted will include information such as authors, year, title, country, aim/objectives, study type, methodology context, setting, timeframe, sample size, demographics, ulcer characteristics, strengths and limitations. The outcomes data to be extracted will include information such as specific variables with significance of effect on healing/level of risk, variables assessed, statistical analysis and any assessment tools used or definitions.

Data synthesis

The study characteristics and descriptive findings will be presented in a tabular format. If an adequate number of similar studies/variables are found using similar methods and outcome measures of delayed healing or non-healing, a meta-analysis will be undertaken of risk factors for delayed healing and/or non-healing utilising RevMan. However, if there is heterogeneity of study methods and outcomes, results of this review will be presented as a narrative synthesis. Any qualitative studies will be reported separately. The critical appraisal categories, criteria and quality assessment result will be outlined for each study. Study data and outcomes data will be used to address the research question. Key variables, effects on healing and level of risk will be presented as the risk factors associated with delayed healing or non-healing in comparison against non-delayed healing of VLUs.

Statistical analysis of subgroups (i.e., physical and/or psychosocial) will not be undertaken. A narrative summary of any relevant subgroups may be presented such as between variables and the level of risk on delayed healing and/or non-healing.

The systematic review will be a descriptive synthesis of risk factors associated with delayed healing or non-healing of VLUs in adults.

Conclusion

Evidence supporting risk factors would be of great benefit to clinicians in the management of VLUs and could be of value in existing management guidelines.

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Author contribution

CP and KF wrote the funding grant. All authors contributed

to conceptualisation and methodology. All authors will contribute to screening, critical appraisal, data extraction and data synthesis, and all authors will be responsible for manuscript preparation, including providing feedback and critical comments on the manuscript. All authors have read and approved the final protocol manuscript.

Ethics and dissemination

As data will be sourced from publicly available materials, ethics will not be required. Findings will be disseminated through a peer-reviewed journal, conferences and social media.

Conflict of interest

The authors declare no conflicts of interest.

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Supplementary data can be found in the electronic version of the WPR Journal.

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