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WHICH FACTORS MAY INFLUENCE MEDIUM-TERM QUALITY OF LIFE OF PATIENTS WITH LOWER-LIMB LOSS? A SYSTEMATIC REVIEW OF THE LITERATURE

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Keywords:

Lower-limb loss, amputation, health-related quality of life

Abstract

Objectives: The aim of this study was to systematically review the literature to identify factors that may influence quality of life in people with lower-limb amputation (all etiologies). Our primary focus was on identifying factors that can be modified, enabling a more concentrated integration of these aspects into the care and treatment of amputated patients.

Data source: Medline (via Ovid) and Scopus were searched in January 2023 for studies assessing quality of life for people with lower-limb loss. Studies were included if they reported on factors that could influence quality of life. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Study selection: Studies were identified and assessed independently by 2 reviewers.

Data extraction: Data were extracted by 2 independent reviewers.

Data synthesis: After removing duplicates, the search yielded 2616 studies, of which 24 met our inclusion criteria (cross-sectional n = 13; prospective n = 9; retrospective n = 2). The most commonly used quality-of-life instruments were the Short Form 36, followed by the World Health Organization Quality of Life-BREF and the EuroQoL 5 dimension. Younger age, traumatic etiology, unilateral or

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below-knee amputation, presence of comorbidities, and social integration were found to influence quality of life in people with lower-limb amputation, whereas sex and socioeconomic context do not seem to have a clear influence.

Conclusions: This systematic review of the literature identified several factors that influence quality of life in patients with lower-limb amputation. However, the results are not always consistent across studies and there is still no consensus on some factors. Conclusive findings regarding sex and socioeconomic status remain elusive, primarily because of substantial disparities observed across the literature. Future prospective longitudinal studies with clear a priori inclusion of a wide range of potential factors are needed to clarify the impact of the identified factors. Factors such as age, type of amputation, comorbidities and social integration should be considered in the management of patients with amputation.

Introduction

Amputation is a common cause of disability. In 2005, 1.6 million people in the United States lived with a lower-limb amputation.[1] The most common cause of amputation is vascular disease, followed by trauma and then cancer and congenital defects.[2] The prevalence of vascular disease and diabetes is expected to increase in the foreseeable future,[3,4] and the prevalence of amputations are therefore expected to be more frequent as well. Not surprisingly, lower-limb amputation has serious consequences on patients' functional outcomes as it affects the ability to walk. Notably, energy expenditure for a person with above-knee amputation (AKA) from vascular etiology for walking with a prosthetic limb is twice that of a nonamputated person.[5] Training and exercise may increase walking distance but it doesn't significantly affect the global functional mobility of patients.[6] Indeed, physical activity in patients with amputation is affected by other factors such as motivation, educational experiences, support, and health literacy.[7]

Lower-limb amputation is also associated with pain, including phantom pain.[8] It is reported that more than half of the patients will develop low back pain or limb pain, often in combination, after an amputation.[9] All these health consequences are expected to reduce the health-related quality of life (HRQoL) of patients with lower-limb loss. Quality of life (QoL) is an important outcome in the management of the patient and has to be considered for the success of a treatment. HRQoL can be defined as "a term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning."[10] To date, several studies have shown that the HRQoL of patients with lower-limb loss is mostly poor compared with the general population or controls.[11] In addition, amputation has been shown to be associated with depression, isolation, and anxiety,[12] factors that are directly related to HRQoL.

To better understand and perhaps improve the HRQoL of people with amputation, it is important to identify the different factors that may directly or indirectly influence patients' HRQoL. Previous studies have identified walking ability, motivation, amputation level, and social context as potential influencing factors.[12] However, other factors could also affect the HRQoL of patients with amputation. Therefore, we aim to develop an exhaustive systematic literature review to unveil all factors that may

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influence HRQoL in patients with lower-limb loss. Furthermore, our conducted review is the first to specifically address early factors that might influence medium-term HRQoL.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement was followed throughout the whole procedure of this systematic review.[13] The completed Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 checklist is available in Supplementary Digital Content 1.

Our research question can be summarized by the following PICOS strategy: Population or disease: adults, age 18 years or older, with a major lower-limb amputation; Intervention: any prognostic factor of HRQoL; Comparator: NA; Outcome: HRQoL; Study design: cross-sectional studies, longitudinal studies (prospective or retrospective cohorts), and interventional studies.

We chose not to enumerate specific risk factors within our search strategy, as our approach was grounded in the anticipation of discovering factors organically through our research.

A protocol was developed before the conduct of the study and was published on Open Science Framework (OSF) (https://osf.io/je5dx/).

All authors agreed on the methodology (inclusion and exclusion criteria, summary of evidence format) before conducting the review.

SEARCH STRATEGY

The electronic databases Medline (via Ovid) and Scopus were searched from inception to January 2023 to identify studies assessing HRQoL of patients with lower-limb loss. No restriction of date was applied but the search was limited to studies published in English and French.[14] An example of a search strategy is available in Supplementary Digital Content 2.

In addition, a manual search within the bibliography of relevant papers was also performed to complete the bibliographic search. Experts in the field were also contacted for any additional references that may have been missed during the screening process.

INCLUSION AND EXCLUSION CRITERIA

All articles identified by the search strategies were imported into Covidence software for screening. Studies were screened for their eligibility by 2 of the 4 reviewers (DP [MD], CB [PhD], SB [PhD], or AT[PhD]),first based on their titles and abstracts, and second, based on their full texts. Any discrepancy was resolved through discussion between the researchers. Studies were selected according to defined inclusion criteria (**Table 1**). Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews.

References were considered relevant if the studies used a cross-sectional or longitudinal design, or if the studies were interventional; if the patients were age 18 years or older and had a unilateral or

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bilateral lower-limb amputation of any etiology but between the ankle and the hip; if the patients' HRQoL was measured using a validated instrument; if the study examined independent variables that are predicted to have an impact on HRQoL; and if at least 2 groups of patients with lower-limb loss were compared, making it possible to identify a prognostic factor of HRQoL. To better anticipate the HRQoL aspect of patients with lower-limb amputation, we decided to focus on early factors that could influence the later HRQoL. HRQoL should have been measured in a time interval between a minimum of 6 months and a maximum of 5 years after amputation. Indeed, it has been shown that the greatest changes in HRQoL occur in the first 6 months after amputation.[15] In addition, a limitation to 5 years was chosen to limit the risks of confounding factors, particularly because of the higher mortality of patients with dysvascular amputation during the first years after amputation, with a mortality rate of 77% at 5 years.[16] If a reference reported different amputation delays between patients, only studies with a mean or median amputation delay between 6 months and 5 years were included.

We excluded nonoriginal studies (e.g., letters to editor) and protocols.

Table 1. Inclusion criteria for the systematic review.

Inclusion criteria	
Population	Adults, age 18 y or more, with a major lower-limb amputation • Above or below the knee • Unilateral or bilateral • Any amputation etiology
Intervention	Any prognostic factors of HRQoL A prognostic factor could be age, sex, level of amputation, etc. HRQoL should be measured in lower-limb-amputated participants with some variables presented as prognostic variables of HRQoL. Results should therefore be available for at least 2 groups (e.g., amputated women vs amputated men)
Comparator	None
Outcomes	HRQoL measured with a validated instrument
Type of study	Longitudinal studies (both observational [prospective cohorts, retrospective cohorts] and interventional studies [RCTs]). HRQoL should be measured between 6 mo and 5 y after amputation

Abbreviation: RCT, randomized controlled trial.

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DATA EXTRACTION

Data were extracted by 2 independent reviewers according to a standardized data extraction form pretested on a random sample of 4 studies. Data were extracted by one researcher (DP or CB) and double-checked by another researcher.

The following data were extracted:

- Article characteristics: first author, journal, year of publication, title, objectives, funding, and conflict of interest.
- Study characteristics: study design, country, and length of follow-up.
- Population: sample size, gender distribution, age range, description of population, and type of amputation. c HRQoL instrument used for data collection.
- Study results: prognostic factors evaluated and statistical results.

QUALITY/RISK-OF-BIAS ASSESSMENT

The quality of each included study was independently appraised by 2 researchers (DP and CB) using the NIH (National Heart, Lung, and Blood Institute) for observational cohort and cross-sectional study quality assessment tool.[17] We planned on appraising risk of bias of interventional studies with the Cochrane Risk of Bias 2.0 tool; however, no interventional studies were included and this tool was therefore not used. The NIH tool was applied to identify potential bias in study methods or implementation, including selection of the population, study power, time frame, validity of exposure and outcomes, etc. 14 items were used for the quality appraisal and for each item, a "yes," "no," or "cannot be determined/not reported/not applicable" was selected. Quality of studies was considered as good, fair, or poor based on the critical appraisal of the items. Items 8 and 10 from the NIH were not taken into account because they were not applicable to the type of studies included in the systematic review. Insecurities concerning the methodological quality of the included studies were resolved by discussion between researchers. No papers were excluded as a result of quality assessment.

DATA SYNTHESIS

The objective of our research was to provide a comprehensive list of prognostic factors of HRQoL of patients with lower-limb loss. Therefore, a narrative synthesis of the results was used and no meta-analysis was undertaken.

Results

INCLUDED STUDIES

After removing duplicates, the search yielded 2616 references that were screened for titles and abstracts. Of these, 257 were assessed for eligibility based on full-text screening and 24 studies were finally included in the systematic review. Reasons for exclusion of the remaining 233 references were

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available in the OSF repository (https://osf.io/je5dx/). A manual search did not identify any additional studies. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart summarizing the selection process is shown in **Figure 1**. Of the 24 studies, 13 were cross-sectional studies, 9 were longitudinal cohort studies, and 2 were retrospective cohort studies. Most of the included studies included both men and women, but 4 studies included only men and 3 studies did not report this information. The sample size of participants ranged from 20 in Lerner's study[18] to 171 in Davie-Smith's study.[12] The most commonly used HRQoL instruments were the Short Form 36 (45.8%), followed by the World Health Organization Quality of Life-BREF (20.8%) and the EuroQoL 5 dimension (12.5%). For studies reporting the mean age of the participants (n = 23), values ranged from 24.4 to 67.8 years.

The characteristics and quality of the 24 retained articles are shown in **Table 2**.

Different prognostic factors of HRQoL were evaluated within these different studies.

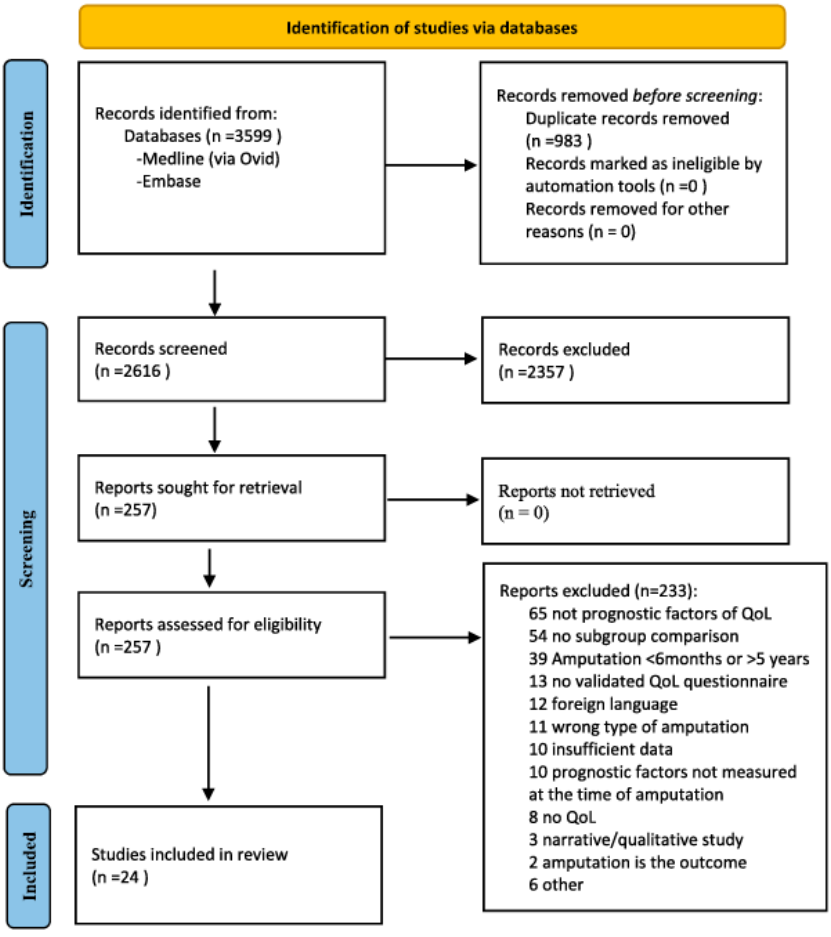

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) flowchart of study selection.

AGE

Eight studies, 4 cross-sectional and 4 longitudinal, reported results on the effect of age on the HRQoL.[19-26]

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Among these studies, all but one showed an effect of age on HRQoL in patients with amputation, with better HRQoL for younger patients. This effect was mainly on physical health–related HRQoL.[19,21-23,25,26] Nizamli et al also reported better HRQoL scores in relational domains for younger patients with lower-limb loss compared with older patients.[20] Only one study reported no association between age and HRQoL.[24]

LEVEL OF AMPUTATION

Eleven studies, 8 cross-sectional and 3 longitudinal, reported results on the effect of the level of amputation on the HRQoL.[19,20,23-31]

Two studies compared the quality of life between patients with unilateral amputation and patients with bilateral amputation. One of the 2 studies included in both groups patients with AKA and below-knee amputation (BKA) (and also BKA + AKA in the group with bilateral amputation),[27] while the other study did not provide this information.[20] HRQoL was reported to be better for patients with unilateral amputations, both for the physical health component[20,27] and the psychological health component.[27] Studies focusing on the level of amputation have mostly reported better HRQoL for BKA compared with AKA.[19,24,30] Polfer et al,[28] who did not include patients with BKA, reported no significant difference in HRQoL between patients with knee disarticulation and patients with AKA. The authors did not find an association between residual limb length and HRQoL. Htwe et al, Hisam et al, Priyadharshan et al, and Pran et al[23,25,26,31] also found no significant association between the HRQoL and the level of amputation.

SEX

Seven studies (all cross-sectional) reported results on the effect of sex on the HRQoL.[23,25,26,30-33]

The male/female ratio of the studies varied from 1.9 to 16.3. Heterogeneous results were observed regarding sex as an independent variable predicting HRQoL in patients with lower-limb loss. In fact, of the 7 studies assessing this relationship, 3 reported better HRQoL in women compared with men, for both mental and physical health components,[30,31] or only for the physical domain.[32] Another study[33] reported better HRQoL for men compared with women, but only for the general health and social relationships domains, and not for the other HRQoL domains. The last 3 studies showed no association between sex and HRQoL in patients with amputation.[23,25,26]

CAUSE OF AMPUTATION

Five studies (3 cross-sectional and 2 longitudinal) reported results on the effect of amputation etiology on HRQoL.[18,20,22,31,34]

In 3 studies, amputations with a traumatic etiology were associated with generally better HRQoL compared with amputations with a vascular or infectious etiology.[22,31,34] Only the social function domain was shown to be reduced in patients with traumatic amputations in the study by Hisam et al.[31]

When the etiology of amputation was traumatic, a better HRQoL has been found in patients with a delayed amputation[18] or in patients presenting a postinjury infection compared with war injury.[20]

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SOCIAL AND FINANCIAL SUPPORT

Four studies (1 cross-sectional and 3 longitudinal) reported results on the effect of social and financial support on the HRQoL.[20,35-37]

Being in a relationship (married or not) was shown to be associated with a better HRQoL as assessed by the SF-12 questionnaire in the study by Mac Neill et al.[36] However, Nizamli et al also reported no association between the marital status and the HRQoL of patients with lower-limb loss.[20] The same author reported that financial support and having a job were both associated with a higher HRQoL in the psychological domain. In addition, higher financial status was also shown to have a positive effect on the physical and environmental health domains of HRQoL. This relationship was not confirmed in the study by Davie-Smith et al,[37] who reported no significant association between socioeconomic status at the time of amputation and HRQoL 6–12 months after amputation. The effect of social support on HRQoL was investigated by Williams et al, who reported no association.[35]

COMORBIDITIES

Four studies (3 cross-sectional and 1 longitudinal) reported results on the effect of comorbidities on the HRQoL. In 3 of these studies, comorbidities were assessed categorically: presence or absence[24,38] or 0–4 comorbidities.[23] Two studies counted the number of comorbidities.[24,32]

Patients with multiple comorbidities, such as fibromyalgia, reported a lower HRQoL compared with others.[38] Abdelgadir et al[32] precisely investigated the impact of diabetes on HRQoL and reported a negative correlation between the duration of diabetes and HRQoL. However, this relationship was not confirmed in the study by Kizilkurt et al.[24]

PSYCHOLOGICAL STATUS

Three studies (all longitudinal) reported results on the effect of the psychological status on the HRQoL.[22,39,40]

Psychological status at the time of amputation seems to be correlated with HRQoL in patients with lower-limb loss. Specifically, Coffey et al[39] evaluated the impact on HRQoL of a greater tendency toward goal pursuit and a stronger disposition toward goal adjustment at the time of admission to the rehabilitation center. It was associated with better physical and psychological HRQoL 6 months after discharge and better environmental HRQoL after discharge.

The presence of depression or high levels of anxiety at the time of amputation has been shown to be associated with poorer HRQoL in both physical and psychological domains.[22,40]

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Table 2. Characteristics of included studies.

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Abdelgadir, 2009	Cross-sectional study	60 diabetic patients with LLA Mean (SD): 57.4 ± 10.5 Men: 40; women: 20 Mean (SD): 5.3 ± 2.1 y Outpatient diabetes clinic	Sudan	Diabetic women with LLA had better physical role score and better sleep than diabetic men with amputation and duration of diabetes showed significant negative correlation with all the HRQoL domains except the physical functioning and the role physical domains	To investigate the influence of lower-limb amputation on HRQoL in Sudanese diabetic subject	Medical outcomes study questionnaire	Good
Adegoke, 2012	Cross-sectional study	47 patients with LLA Mean (SD): Men = 50.6 ± 12.9; women = 51.7 ± 13.7 Men: 31; women: 16 57.4% amputated since 3–24 mo; 8.0% amputated since more than 6 y Rehabilitation centers/ clinics	Nigeria	Male participants scored significantly higher than female participants in overall health, physical health, and social relationship domains of HRQoL but the 2 groups did not differ significantly in the other domains of the WHOQOL-BREF	To determine the QoL of Nigerians with LLA and to investigate the influence of some clinical and sociodemographic variables on it	WHOQOL-BREF	Fair
Akarsu, 2013	Cross-sectional study	30 patients with LLA (15 unilateral and 15 bilateral) Mean (SD): 27.3 ± 6.6 NR At least 6 mo Turkish Armed Forces Rehabilitation and Care Center	Turkey	Physical capacity of bilateral LLA patients is lower than the unilateral amputee patients; satisfaction with prosthesis and body image are not related with the amputation level	To compare the quality of life and functionality of patients with bilateral vs. unilateral LLA	SF-36, SAT-PRO, ABIS	Fair
Akyol, 2012	Cross-sectional study	30 patients with LLA (12 with fibromyalgia) Mean (SD): 31.3 ± 6.0 Men: 30 Mean (SD): 79.0 ± 5.5 mo Inpatient amputee clinic at a military rehabilitation center	Turkey	HRQoL and emotional status are more impaired in male traumatic LLA with fibromyalgia than those without		NHP	Good

Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Bennett, 2013	Cross-sectional study	39 patients with LLA Mean (SD): 24.4 ± 5.16 Men: 39 Mean (SD): 40 ± 16 mo Electronic database (United Kingdom Military Joint Theatre Trauma Registry)	UK	The PCS of the SF-36 declined significantly with more proximal amputation levels ($p = 0.01$), but there was no significant difference between the AKA and KD cohorts when compared directly ($p = 0.178$). MCS did not vary across groups ($p = 0.114$)	To describe the injuries and surgical treatment of British service personnel who sustained a unilateral LLA after combat injury and defines their medium-term outcomes	SF-36	Fair
Coffey, 2014	Prospective cohort study	98 patients with LLA Mean (SD): 63.6 ± 11.9 Men: 81; women: 18 From admission to rehabilitation (t1) to 6 mo postdischarge (t3) Inpatient rehabilitation	Ireland	Having a greater tendency toward goal pursuit at t1 was predictive of higher physical and psychological HRQoL at t3, whereas having a stronger disposition toward goal adjustment at t1 predicted lower disability and higher environmental HRQoL at t3	(1) To identify significant changes in disability and quality of life across 3 time points (t1: admission to rehabilitation; t2: 6 wk postdischarge; t3: 6 mo postdischarge) in individuals with LLA, and (2) to examine whether goal pursuit and goal adjustment at t1 were predictive of these outcomes at t3	WHOQOL-BREF	Good
Cox, 2011	Cross-sectional study	87 patients with LLA secondary to diabetes mellitus (64 BKA and 23 AKA) Mean (SD): 62 ± 9.9 Men: 35; women: 52 One to 3 y Physiotherapy records at the St Ann's Bay Hospital	Jamaica	People with BKA have better HRQoL than AKA, and women have better HRQoL than men for each domain	To determine the quality of life and functional independence of lower-limb diabetic amputees 1–3 y after amputation, using variables such as age, sex, and amputation level	WHOQOL-BREF	Good
Davie-Smith, 2019	Prospective cohort study	171 patients with LLA Mean (SD): 66.2 ± 11.4 Men: 128; women: 43 6 and 12 mo All LLA performed in 1 y in 1 Scottish Health Board	UK	No association between socioeconomic status at the time of amputation and HRQoL at 6 or 12 mo after amputation	To investigate the influence of socioeconomic status on mobility, participation, and quality of life after LLA	EQ-5D-5L	Fair

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Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Fortington, 2013	Longitudinal study	82 patients with LLA Mean (SD): 67.8 ± 13 Men: 55; women: 27 6 and 18 mo Referred by vascular surgeons	The Netherlands	Age was significant factor in HRQoL for physical function. Patients with AKA or KD present lower scores for physical function than patients with BKA	To describe changes in HRQoL in people with LLA, from time of amputation to 18 mo, taking into consideration the influence of age and walking distance	SF-36	Fair
Hisam, 2016	Cross-sectional study	52 patients with LLA Mean (SD): 30.71 ± 7.50 Men: 49; women: 3 Mean (SD): 1.9 ± 1.3 y The Armed Forces Institute of Rehabilitation Medicine	Pakistan	No significant association between level of amputation and any domain of SF-36	To determine the effects of age, cause of amputation, and anatomic level of amputation on the HRQoL in individuals with unilateral LLA	SF-36	Good
Htwe, 2015	Cross-sectional study	65 patients with LLA (40 BKA, 25 AKA) Mean (SD): 56 ± 15 Men: 53; women: 12 Mean (SD): 3.4 ±4.2 y Rehabilitation Clinic, Tertiary Hospital	Malaysia	Age and comorbidities negatively affect PCS but had no correlation with MCS. Sex, ethnicity, and level of amputation had no correlation with PCS or MCS	To evaluate the quality of life of lower-limb amputees and its correlation with epidemiological factors	SF-36	Fair
Keeling, 2013	Retrospective cohort study	65 patients with BKA Mean (SD): Ertl: 30.4 ± 6.9 Burgess: 31.6 ± 7 Men: 65 Mean (SD): 32 ± 22.7 mo Three military institutions	USA	There were no significant differences between patients from the Burgess and the Ertl cohorts with regard to any of the SF-36 domains	To compare self-reported functional outcomes associated with 2 surgical techniques for transtibial amputation: bridge synostosis (modified Ertl) and non–bone-bridging (modified Burgess)	SF-36	Good
Kizilkurt, 2020	Prospective cohort study	65 patients with LLA secondary to an infected diabetic foot ulcer Mean (SD): 57.8 ± 7.6 Men: 38; women: 27 1–8 y (median 3 y) after fitting the prosthesis Prosthesis clinics	Turkey	PCS and MCS scores in the group having a prosthesis fitted above the knee were found to be significantly lower than scores in the group with a prosthesis fitted below the knee. PCS and MCS scores were significantly lower in the group with comorbid medical diseases. No significant correlations were found between age, duration of diabetes diagnosis, and PCS and MCS scores	To identify clinical and psychosocial factors that predict an individual's subjective quality of life after having undergone a LLA secondary to diabetic foot ulcer	SF-36	Good

Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Lerner, 1993	Cross-sectional study	20 patients with post-traumatic BKA Mean (range): 41.5 (22–85) NR Mean (SD): 5 y (SD not reported) NR	USA	Patients who had primary amputation scored worse on the PAIS than those who experienced delayed amputation	The major objectives of this study were to measure the impact of chronic refractory osteomyelitis, post-traumatic long-bone fracture nonunion, and amputation on psychological adjustment and functional impairment; to determine why patients chose to continue therapy for nonunion and osteomyelitis as opposed to selecting amputation; and to assess the psychosocial adjustment of these patients' significant others who may be affected by the treatment outcomes of their loved ones	PAIS	Poor
Mac Neill, 2008	Retrospective study	29 patients with bilateral transtibial amputation Mean (SD): 64.7 (SD not reported) Men: 21; women: 8 Mean (SD): 3.31 y after discharge from rehabilitation Amputee Rehabilitation Service	Canada	Patients who lived alone scored better on the MCS of the SF-12	To examine long-term outcomes and survival of patients after bilateral transtibial amputation	SF-12	Fair
Madsen, 2019	Prospective cohort study	58 patients with LLA (35 AKA, 22 BKA) Mean (SD): 67.8 ± 10.2 Men: 43; women: 15 3, 6 and 12 mo Orthopedic wards of 2 rural hospitals	Denmark	Differences were identified between age groups in physical function with loss of physical function almost solely evident among the oldest patients after 12 mo	To investigate the effect of time and age on HRQoL, general self-efficacy, and functional level 12 mo after dysvascular major LLA	SF-36	Fair

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Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Migaou, 2019	Prospective cohort study	85 patients with unilateral or bilateral LLA Mean (SD): 59.3 ± 16.7 Men: 64; women: 21 12 mo Department of Physical Medicine and Rehabilitation of University Hospital of Monastir	Tunisia	PCS and MCS of the SF-36 were negatively correlated with age. The incidence of an amputation of traumatic origin was associated with significantly higher HRQoL scores than an amputation of an infectious or vascular origin. There was also a negative and statistically significant correlation between the HRQoL and the psychological status of patients. The higher anxiety scores were associated with poor MCS and PCS. Depression was associated with poor MCS and PCS	To study factors associated to the quality of life in a North African sample of lower-limb amputees	SF-36	Fair
Nizamli, 2020	Cross-sectional study	65 patients with unilateral (n = 51) or bilateral (n = 14) amputation Range: 20–60 Men: 65 3 groups: <2 y; 2–4 y; >4 y Military Hospital	Syria	Higher score in psychological domain for employed amputees, time >4 y since amputation, amputees with financial support or because of infection after injury. Higher score for social relationships domains for younger amputees. Higher score in physical health domain for unilateral amputees and amputees with financial support. Higher score in environmental domain for amputees with financial support and amputation because of infection after injury. No difference in regards of education level, marital status, income, use of assistive devices, and level of amputation	To describe the quality of life of Syrian people with LLA after the war	WHOQOL-BREF	Fair

Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Pedras, 2020	Prospective cohort study	86 patients with diabetes mellitus, indicated for LLA surgery Mean (SD): 63 (SD not reported) Men: 63; women: 23 10 mo 6 hospitals, diabetic foot multidisciplinary clinics and 2 vascular surgery departments	Portugal	Functionality at T0 has a positive impact on PCS, and anxiety symptoms at T0 had negative impact on MCS	(1) To analyze the relationship between emotional reactions (anxiety, depression, and traumatic stress symptoms) and functionality level, before and after a LLA because of diabetic foot ulcer, and mental/physical quality of life and (2) to analyze the mediator role of social support between emotional reactions and mental/physical quality of life	SF-36	Good
Polfer, 2019	Retrospective cohort study	10 patients with knee disarticulation; 18 patients with transfemoral amputation Mean (range): KD: 22.8 (20–26) TF: 25.4 (19–37) NR Mean (range): 66 (50–79) mo Three medical centers	USA	There is no significant difference in SF-36 score between KD and AKA groups. There is no significant association between residual limb length within the AKA group and SF-36 score	To determine whether there is a patient-reported functional difference between combat-related KD and AKA	SF-36	Good
Pran, 2021	Cross-sectional study	134 patients with LLA (58 AKA, 76 BKA) Mean (SD): 63 (SD not reported) Men: 83; women: 51 Mean (range): 42 (6–73) mo Tertiary care institution	Trinité-et-Tobago	Factors adversely related to HRQoL after major amputation include increasing age, problems related to mobility, and nonambulatory patients. No association was found between sex or type of amputation and HRQoL	To determine the HRQoL in patients after a major LLA	EQ-5D	Poor

(continued on next page)

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Table 2. Characteristics of included studies. (Continued)

Reference	Study design	Study population Age (y) Sex Time since amputation Source of population	Country	Results	Aim of the study	HRQoL questionnaire	Quality
Priyadharshan, 2022	Cross-sectional study	106 patients with LLA (49 patients with diabetes mellitus, 44 patients with trauma, 71 with BKA, 51 using prosthetic appliance) Mean (SD): 48.6 ± 15.0 Men: 88; women: 18 Mean (SD): 2.88 (1.4) y Tertiary care center	India	With increasing age, the score for the physical domain, the environmental domain, and the social domain was found to decrease, but not for the psychological domain. There was no significant difference between sex for all domains. There was no statistically significant difference for the level of amputation	To assess the QOL in lower-limb amputees regarding experience of being an established amputee/person with limb loss, experience of prosthesis use, psychological well-being, phantom limb pain, and residual limb pain	WHOQOL-BREF	
vonKaeppler, 2021	Prospective cohort study	38 patients with transfemoral amputation Mean (SD): 46 ± 17 y Men: 26; women: 4 12 mo Muhimbili Orthopaedic Institute	Tanzania	At 12 mo, EQ-5D in the nonvascular subgroup (0.99) was higher than the vascular subgroup (0.85, $p < 0.001$)	To quantify the impact of prostheses on quality of life and function in Tanzanian transfemoral amputees	EQ-5D	Good
Williams, 2004	Prospective cohort study	89 patients (59 BKA) Mean (SD): 44.2 y (SD not reported) Men: 62; women: 27 6 mo Large level 1 trauma hospital	USA	Baseline levels of multidimensional scale of perceived social support and baseline social integration were not predictive of satisfaction with life at 6 mo	To describe one aspect of social support, social integration, longitudinally for 2 y after LLA and to explore the impact of social support on depression, pain interference, life satisfaction, mobility, and occupational functioning	SWLS	Good

Abbreviations: ABIS, Amputee Body Image Scale; EQ-5D, EuroQoL-5 dimension; KD, knee disarticulation; LLA, lower-limb amputation; MCS, Mental Composite Score; NHP, Nottingham Health Profile; PAIS, Psychosocial Adjustment to Illness Scale; PCS, Physical Composite Score; SAT-PRO, Satisfaction With Prosthesis Questionnaire; SD, standard deviation; SF-36, Short Form 36; SWLS, Satisfaction With Life Scale; WHOQOL-BREF, World Health Organization Quality of Life-BREF.

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Table 3. Quality assessment of individual studies.

First author's name	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)
Abdelgadir	Yes	No	Other	Other	No	Yes	Yes	–
Adegoke	Yes	Yes	Other	Other	No	Other	Other	–
Akarsu	Yes	Yes	Other	Yes	No	Yes	Yes	–
Akyol	Yes	Yes	Other	Yes	Yes	Yes	Yes	–
Bennett	Yes	Yes	Yes	Yes	No	Yes	Other	–
Coffey	Yes	Yes	Yes	Yes	Other	Yes	Yes	–
Cox	Yes	Yes	Other	Yes	No	Yes	Yes	–
Davie-Smith	Yes	Yes	Yes	Yes	No	Yes	Yes	–
Fortington	Yes	Yes	Yes	Yes	No	Yes	Yes	–
Hisam	Yes	Yes	Other	Yes	Yes	Yes	Yes	–
Htwe	Yes	Yes	Other	Yes	No	Yes	Yes	–
Keeling	Yes	Yes	No	Yes	No	Yes	Yes	–
Kizilkurt	Yes	Yes	Other	Yes	Yes	Yes	Yes	–
Lerner	Yes	Yes	Other	Other	No	Yes	Other	–
Mac Neill	Yes	Yes	No	Yes	No	Yes	Yes	–
Madsen	Yes	Yes	Yes	Yes	No	Yes	Yes	–
Migaou	Yes	Yes	Other	Yes	No	Yes	Yes	–
Nizamli	Yes	Yes	Other	Yes	Yes	Yes	Yes	–
Pedras	Yes	Yes	No	Yes	No	Yes	Yes	–
Polfer	Yes	Yes	Other	Yes	Yes	Yes	Yes	–
Pran	Yes	Yes	No	Yes	No	Yes	Other	–
Priyadharshan	Yes	Yes	No	Yes	No	Yes	Yes	–
vonKaeppler	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–

Table 3. Quality assessment of individual studies. (Continued)

First author's name	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)
Williams	Yes	Yes	Yes	Yes	No	Yes	Yes	–

First author's name	Q9	Q10	Q11	Q12	Q13	Q14	Total yes	Total no	Other
	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)	Yes/no/other (CD/NA/NR)			
Abdelgadir	Yes	–	Yes	Other	Other	No	5	3	4
Adegoke	Yes	–	Yes	Other	Other	No	4	2	6
Akarsu	Yes	–	Yes	Other	Other	No	7	2	3
Akyol	Yes	–	Yes	Other	Other	No	8	1	3
Bennett	Yes	–	Yes	No	Yes	No	8	3	1
Coffey	Yes	–	Yes	Other	No	No	8	2	2
Cox	Yes	–	Yes	No	Other	No	7	3	2
Davie-Smith	Yes	–	Yes	No	No	No	8	4	0
Fortington	Yes	–	Yes	Other	No	No	8	3	1
Hisam	Yes	–	Yes	Other	Other	No	8	1	3
Htwe	Yes	–	Yes	Other	Other	No	7	2	3
Keeling	Yes	–	Yes	Other	Other	Yes	8	2	2
Kizilkurt	Yes	–	Yes	Other	Other	No	8	1	3
Lerner	No	–	Yes	No	Other	No	4	4	4
Mac Neill	Yes	–	Yes	Other	Other	No	7	3	2
Madsen	Yes	–	Yes	Other	No	No	8	3	1
Migaou	Yes	–	Yes	No	Yes	No	8	3	1
Nizamli	Yes	–	Yes	Other	Other	No	8	1	3
Pedras	Yes	–	Yes	Other	No	No	7	4	1
Polfer	Yes	–	Yes	Other	Other	No	8	1	3
Pran	Yes	–	Yes	No	Other	No	6	4	2
Priyadharshan	Yes	–	Yes	No	Other	No	7	4	1
vonKaeppler	Yes	–	Yes	No	No	No	9	3	0
Williams	Yes	–	Yes	Other	Yes	Yes	10	1	1

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Other outcomes were each assessed by a single article. Comparison of 2 surgical techniques for BKA (bridge synostosis and non–bone-bridging) showed no difference in HRQoL.[41] Ethnicity (Malay, Chinese, and Indian) also showed no effect on HRQoL.[23] Functionality 24 h before amputation, however, showed a positive effect on HRQoL (Physical Composite Score).[40]

DISCUSSION

We conducted a systematic review of the literature to identify early factors that may have an impact on the evolution of HRQoL in patients with lower-limb amputation.

Younger age, BKA, traumatic etiology, and absence of comorbidities seem to have a positive impact on HRQoL, whereas sex and socioeconomic context do not seem to have a clear influence. Psychological factors seem to have an influence on the HRQoL of patients with amputation. A greater tendency toward goal pursuit or a stronger disposition towards goal adjustment correlates positively with HRQoL, while depression or anxiety exerts a negative impact on the HRQoL of amputated patients.

In fact, all but one of the studies investigating the effect of age on HRQoL in patients with lower-limb loss reported a clear association. Interestingly, in this study,[24] the entire population was selected in clinics where patients were followed in the context of prosthesis fitting and where all patients used a prosthesis. However, it has been shown previously that the reduction in HRQoL with age is mainly related to a decrease in mobility in the context of comorbidities.[12,25,42,43] Thus, by selecting patients with a prosthesis, it is likely that the sample is composed of patients with a higher level of mobility, for whom the negative impact of age on HRQoL may be less important.

It can be assumed that HRQoL may be more directly related to the functional level achieved according to the level of amputation. Indeed, it has been shown that amputation level is associated with failure to maintain independent living status, AKA is associated with not wearing a prosthesis, and bilateral status is associated with failure to walk.[43] In addition, the Scottish Physiotherapy Amputee Research Group reported that people with bilateral BKA shows better mobility outcomes than patients with unilateral AKA.[44] About satisfaction with mobility, Norvell et al showed that patients with AKA showed a trend (although not significant) toward poorer mobility than patients with BKA and significantly lower satisfaction with their mobility 1 year after amputation. However, mobility satisfaction is significantly associated with life satisfaction.[45]

The influence of sex on the quality of life of patients with amputation has shown in constant results in the literature. A scoping review by Cimino, which included 121 studies, also shows mixed results in the literature regarding the impact of sex on HRQoL.[46] Indeed, among the 121 studies included, 55 articles showed no difference in HRQoL between men and women with adult-acquired lower-limb amputation (from trauma, dysvascular causes, cancer, or infection), while 66 reported differences. The most commonly studied aspects of HRQoL were the physical aspects (mobility, prosthesis use or satisfaction, and physical health), while the psychosocial aspects were less studied. This scoping review showed more positive results for men than for women but also highlighted a discrepancy between the results in the literature.

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Traumatic amputation is associated with better HRQoL than vascular amputation. Demet et al also reported that the traumatic etiology was associated with less physical disability and less social isolation.[47] Finally, Asano et al also reported lower HRQoL using a visual analog scale in patients with vascular amputation.[48]

Finally, comorbidities were associated with lower HRQoL in patients with lower-limb loss. These results are consistent with those reported in the literature showing a worsening of HRQoL with multimorbidity.[49]

When analyzing HRQoL by domain, several points of note emerge. The primary domain adversely affected by age and comorbidities is the physical domain. In addition, it is the sole domain influenced by functionality at t0. Comparatively, BKA (as opposed to AKA) seems to have a positive influence on the physical domain, although certain studies demonstrate no discernible impact of amputation level. Both the physical and mental domains suffer negative repercussions from depression, anxiety, and bilateral (as opposed to unilateral) amputations. Moreover, the mental domain is primarily affected by being in a relationship. The environmental domain experiences a positive impact through a stronger disposition toward goal adjustment.

Regarding the time frame of the studies, only 9 studies precisely specified the amputation period. Others supplied the survey time and time since amputation. However, in many cases, only rough estimates could be deduced from the time elapsed since amputation and the year of publication. Regrettably, this estimate's reliability is compromised because of the variable delay that can exist between conducting a study and its publication. Interestingly, it is worth mentioning that 3 studies[18,36,37] examining some of the oldest amputation cases all centered around the socioeconomic aspect of patients with amputation. Mac Neill's study (Canada) concluded that being in a relationship positively affected HRQoL, whereas a more recent article from Syria,[20] which also explored this facet, found no association. One of these studies[35] discovered no correlation between social support and amputee HRQoL, mirroring the results of the newer study by Davie-Smith et al, which explored the same aspect.

Regarding the countries in which the studies were conducted, all investigations assessing the impact of sex on HRQoL, with the exception of Polfer's,[28] were situated in low-/middle-income countries. Moreover, 2 studies from distinct regions have specifically scrutinized the influence of socioeconomic status on HRQoL. Davie-Smith's study[37] (United States) did not reveal any impact, whereas Nizamli's study[20] (Syria) found that greater financial support correlated with an improved HRQoL.

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Table 4. Summary of the influence of the different factors and modifiability.

Factor	Positive impact	Modifiability
Younger age	++	No
Traumatic etiology	+ (in comparison with traumatic or infectious etiology)/− (only for the social function domain in one study)	No
Bilateral amputation	− (in comparison with unilateral amputation but level not specified)	No
AKA	−− (in comparison with BKA, in some studies but not all, but not with KD)	No
Male gender	+ (in 1 study)/− (in 3 studies)	No
Being in a relationship	+ (in one study but no association with HRQoL in another study)	No
Financial support	+ (in 1 study but no association with HRQoL in another study)	No
Comorbidities	−−	Yes
Better psychological dispositions	++	Yes
Depression or anxiety	−−	Yes

Abbreviation: KD, knee disarticulation.

STUDY LIMITATION

Some limitations of our study can be discussed. First, we may have missed some studies because of our inclusion criteria. In fact, we decided to include only studies that used a validated tool to assess HRQoL. Therefore, we cannot exclude that studies reporting other factors may have been missed. However, by using only validated questionnaires, we ensure the evidence-based value of our assessments. We also decided not to include studies that assessed HRQoL later than 5 years after amputation. Again, some studies with longer follow-up may have been missed, but this decision allowed us to limit some risks of bias because of confounding factors (e.g., higher mortality in dysvascular patients in the years after amputation).

As an additional limitation, we conducted searches in only 2 bibliographic databases (Medline and Scopus). Although this number aligns with the requirements for rigor in systematic reviews and meta-analyses, we recognize the potential inclusion of further databases. Nevertheless, because of our comprehensive manual search, we are confident in the thoroughness of our methodology.

Only 6 of the 24 studies included provided a power description or a sample size justification. However, after rigorous analysis of the quality of each study using the NIH quality assessment tool, all the studies were included in our analysis (**Table 3**).

Further research needs to be conducted, with a focus on using validated measurement scales and offering detailed demographic data, a common deficiency in existing studies. Sex and socioeconomic status are factors that exhibit the most divergent outcomes within the literature, warranting further investigation.

This systematic review is the first to examine only early factors (identifiable in the perioperative period) that may influence HRQoL in a period between 6 months and 5 years after amputation. This allows early identification of patients who are at higher risk of having poorer HRQoL than other patients and to focus on this aspect during rehabilitation. Modifiable factors, such as comorbidities and some psychological factors, have to be more intensively considered in the management of patients with

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amputation. It seems that advanced age and AKA have a negative impact on HRQoL, perhaps through lack of mobility. So, if it is possible, therapists have to encourage and try to achieve as high a level of mobility as possible with the patient.

Conclusion

The HRQoL of patients with lower-limb loss seems to be negatively influenced by advanced age, level of amputation (AKA instead of BKA), bilaterality, vascular or infectious etiology (rather than traumatic etiology), comorbidities, anxiety, and depression. However, sex, marital status, and socioeconomic status have an unclear relationship with HRQoL in patients with amputation. A summary of the influence of the different factors is available in **Table 4**.

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Declaration of conflicting interest

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Supplemental Material

SUPPLEMENTARY DIGITAL CONTENT 1

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	7 + Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7 + Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-10
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-12
	23b	Discuss any limitations of the evidence included in the review.	10-12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

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SUPPLEMENTARY DIGITAL CONTENT 2

Table A1. Medline (via Ovid) search strategy

1	exp Amputation/
2	amputat*.ti,ab,kf.
3	(limb adj3 (remov* or loss*)).ti,ab,kf.
4	or/1-3
5	(leg* or knee* or hip* or transtibial or transfemoral or tibial or femoral or lower).ti,ab,kf.
6	Lower Extremity/ or Leg/ or Knee/ or Hip/
7	5 or 6
8	4 and 7
9	"Quality of Life"/
10	(quality adj2 life).ti,ab,kf.
11	hrqol.ti,ab,kf.
12	qol.ti,ab,kf.
13	patient reported outcome measures/
14	(prom or proms).ti,ab,kf.
15	(prem or prems).ti,ab,kf.
16	"short form 36".ti,ab,kf.
17	"sf 36".ti,ab,kf.
18	eq-5d.ti,ab,kf.
19	"euroqol 5-dimension".ti,ab,kf.
20	eq-vas.ti,ab,kf
21	or/9-
22	exp animals/ not humans.sh.
23	Case Reports/
24	"Systematic Review"/ or "Review"/ or Meta-Analysis/
25	8 and 21
26	25 not 22 not 23 not 24

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