The association between pre-operative malnutrition and post-amputation clinical outcomes: A systematic review

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Abstract
Background: In patients who underwent lower limb amputation (LLA), the prevalence of malnutrition and its association with clinical outcomes are unclear.
Objectives: This systematic review aims to identify literature and summarise existing information on (1) the prevalence of malnutrition in the patients with LLA and (2) the association between pre-operative nutritional status and post-surgery clinical outcomes in patients who require amputation.
Methods: A search was conducted in four electronic databases (Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, CINAHL and Scopus) to identify eligible studies. The search strategy was based on keywords – amputation, malnutrition and undernutrition. Article were included regardless of the study design; and if they were written in English; included adult patients with lower limb or foot amputation; and performed pre-amputation nutrition assessments.
Results: Seven articles met the eligibility criteria. Malnutrition was assessed by biochemistry and/or anthropometry – none of which are validated nutrition assessment tools. Nevertheless, abnormal biochemistry and/or anthropometry results were associated with delayed wound healing, complications and failed amputation compared to normal ranges. The association between abnormal biochemistry and/or anthropometry parameters and mortality was less consistent. Only one study used a validated nutrition screen tool and found half of the population with LLA were at risk of malnutrition, but no association was reported.
Conclusions: The association between malnutrition and clinical outcomes in patients who underwent LLA remains unclear as all the eligible studies that investigated association used unvalidated nutrition assessment tools. There is an urgent need to address this knowledge gap in future research.

Keywords
Malnutrition, amputation, nutritional status, nutrition assessment

Introduction
Limb amputation is a necessary life-saving procedure when a surgeon considers that there is no other viable treatment. However, amputation places a huge burden on healthcare costs and increases a person’s mortality rate up to 58% in a year.¹ ² Therefore, it is important to identify modifiable factors of poor clinical outcomes. Of note, surgical patients are at high risk of malnutrition (also known as undernutrition), and this is a modifiable risk factor that may potentially modify the clinical outcomes of amputation.

Malnutrition is diagnosed using validated nutrition assessment tools.³ There are six validated nutrition assessment tools to date, namely Subjective Global Assessment (SGA),⁴ Patient-generated SGA (PG-SGA),⁵ Mini Nutritional Assessment (MNA),⁶ European Society of Clinical Nutrition and Metabolism Diagnostic Criteria for Malnutrition (ESPEN- DCM),⁷ the Academy of Nutrition and Dietetics–American Society for Parenteral and Enteral Nutrition (AND-ASPEN) criteria,⁸ and Global Leadership Initiative on Malnutrition (GLIM).⁹ The commonality between these tools is the triangulation of multiple nutrition parameters to comprehensively

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In the surgical population, malnutrition is independently associated with delayed wound healing, infectious complications and increased length of stay. The association between malnutrition and poor outcomes is further strengthened by a recent review demonstrating the benefits of pre-operative nutrition assessment and nutrition interventions in malnourished patients resulting in earlier surgical recovery. Despite the above, the association between malnutrition and clinical outcomes in amputation surgery is not commonly reported in the surgical literature. In patients who require amputation, the lack of appetite due to hemostatic disruption caused by systemic inflammation before surgery and the reduction of nutrient absorption caused by infection may increase the risk of malnutrition. Hence, identifying the prevalence of malnutrition in this population may help allocate resources to manage this potentially modifiable risk. In addition, the identification of clinical outcomes associated with malnutrition will help improve patient care and provide directions for further studies.

This review aims to determine: (1) the prevalence of malnutrition in the patients with lower limb amputation (LLA) and (2) the association between pre-operative nutritional status and post-surgery clinical outcomes in patients who require amputation.

Materials and methods

Information sources and search methods

This study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two reviewers (XZ and YMEJ) independently searched electronic databases to identify relevant papers. A summary of the search process, study selection, search keywords and strategies are outlined in the Supplement. Additionally, hand searching was conducted using the reference lists within the eligible articles. No automation tools were used in the search process, but Endnote software was used to compile the searches. Both reviewers (XZ and YMEJ) independently screened the titles and abstracts and excluded studies that did not meet the selection criteria. Full-text version of all potentially relevant studies was obtained for further evaluation by independent reviewers prior to extraction. The process is summarised in the PRISMA flow diagram (Figure 1).

Study appraisal and synthesis

Both reviewers independently used the Quality In Prognosis Studies (QUIPS) tool to assess the risk of bias amongst eligible studies. This tool identifies six areas of potential threat to validity (Table 1). Each domain was scored as low, unclear, or high risk of bias. For domain one, representativeness of study population, ‘low risk’ was given if the study adequately represented the population with LLA and provided an adequate description of the sample source, framework and recruitment. A ‘low risk’ was given for the second domain on study attrition if the dropout rate was less than 20%. The third domain focused on the objectiveness and reliability of measuring the prognostic factor, namely malnutrition. A ‘low risk’ was given if the study used validated nutrition assessment tools such as SGA, PG-SGA, ESPEN-DCM, AND-ASPEN criteria, GLIM or MNA. The fourth domain measured the unbiasedness of outcome measures. A ‘low risk’ was given if the same valid and reliable outcome measurements were applied to all participants. The fifth domain assessed for potential confounding factors that may affect the outcome measures. A ‘low risk’ was given if a clear definition of important potential confounders were provided, and they were adequately accounted for using a reliable analysis (e.g., regression analysis). The sixth and last domain assessed the adequacy of statistical analysis and reporting of outcome measurements. A ‘low risk’ was given if all outcomes were reported with appropriate and appropriate statistical analysis. For studies that only reported the prevalence of malnutrition and lack prognostication, only the first and third domains were evaluated since the other domains were used to assess the validity of prognosis. For this paper, the overall risk of bias within a study was classified into two categories: low or high risk. In the absence of a widely accepted definition that classifies the level of bias, studies were rated as low risk of bias if all domains were classified as ‘low risk’. Studies were rated as ‘high risk’ of bias if at least one domain is classified as unclear or high risk.

Data extraction

Two reviewers (XZ and YMEJ) extracted pertinent data independently in a standardized spreadsheet with information on author, study, country, the number of subjects, age, nutrition screening/assessment tool, the prevalence of malnutrition (Table 1) and clinical outcomes (Table 2). Disagreements were resolved by discussion or adjudication by a third reviewer (CCHL). If the statistical significance was not reported, the authors manually calculated the significance with the available results, using STATA 16.1 (Stata Corp., College Station, TX, USA).

Results

Study selection

The study selection process is described in Figure 1. Briefly, 247 articles were identified from the databases upon the removal of duplicates, and of which eight articles were eligible for full-text evaluation. After full-text evaluation, two studies were excluded as they did not report the prevalence of malnutrition and its associated outcomes. One additional article was identified from the reference lists of the eight articles, and it was eligible for full-text evaluation. A total of seven studies were included in this review. The risk of bias assessment for all included studies is shown in Figure 2. All studies were at high risk of bias as they did not use validated...
Figure 1. Summary of search methods and quantity of articles included.

Table 1. Summary of studies included in the systematic review.

| Authors          | Study design | Country                  | n   | Age (years) | Nutritional screening/assessment tool                                                                 | Abnormal nutrition parameters (%) |
|------------------|--------------|--------------------------|-----|-------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|
| Pedersen and Pedersen | Prospective  | Denmark                  | 47  | 68          | Weight loss, triceps skinfold thickness, circumference of upper arm muscle, serum albumin, serum pre-albumin | 72.3                              |
| Kay et al.       | Prospective  | United States of America | 41  | 63          | Albumin < 3.5 g/dl and/or total lymphocyte count < 1500 cells/ml                                       | 61.0                              |
| Pinzur et al.    | Retrospective| United States of America | 64  | 57          | Albumin < 3.0 g/dl and/or total lymphocyte count < 1500 cells/ml                                       | 20.0                              |
| Dickhaut et al.  | Retrospective| United States of America | 23  | 53          | Albumin < 3.5 g/dl and/or total lymphocyte count < 1500 cells/ml                                       | 69.6                              |
| Jany and Burkus  | Retrospective| United States of America | 10  | 58          | Hb < 11 g/dl, haematocrit < 32%, total lymphocyte count < 1500 cells/ul, albumin < 3.5%/dl, total protein < 6.2 g/dl. | 50.0                              |
| Eneroth et al.   | Prospective  | Sweden                   | 32  | 80          | Weight loss, nutritional intake, arm muscle circumference, triceps skin fold thickness, serum protein, total lymphocyte < 1500 cells/cmm | 87.5                              |
| Banning et al.   | Prospective  | Netherlands              | 10  | 67.9        | Patient Generated Subjective Global Assessment - Short form                                            | 50.0                              |
Table 2. Summary of study outcomes included in the systematic review.

| Authors                  | Study design | n   | Country                  | Delays wound healing | Complications | Failed amputation | Mortality               |
|--------------------------|--------------|-----|--------------------------|----------------------|---------------|-------------------|-------------------------|
| Pedersen and Pedersen    | Prospective  | 47  | Denmark                  | Abnormal-NP: 44.1    | Abnormal-NP: 44.1 | NA                | Abnormal-NP: 17.6    |
|                          |              |     |                          | (15/34) Normal-NP: 7.7 (1/13)* | Normal-NP: 7.7 (1/13)** |          | (6/34) Normal-NP: 0.0 |                        |
| Kay et al.                | Prospective  | 41  | United States of America | Abnormal-NP: 16.0    | Abnormal-NP: 16.0 | Abnormal-NP: 16.0 | Abnormal-NP: 4.0     |
|                          |              |     |                          | (4/25) Normal-NP: 0.0 | Normal-NP: 7.0* (1/16)* | Normal-NP: 0.0 | (1/25) Normal-NP: 0.0 |                        |
| Pinzur et al.             | Retrospective| 64  | United States of America | Abnormal-NP: 61.5    | NA             | NA                | No deaths              |
|                          |              |     |                          | (8/13) Normal-NP: 7.8 (4/51) |                  |          |                        |                        |
| Dickhaut et al.           | Retrospective| 23  | United States of America | Abnormal-NP: 75.0    | Abnormal-NP: 75.0 | Abnormal-NP: 75.0 | No death              |
|                          |              |     |                          | (12/16)** Normal-NP: 14.3 (1/7) | Normal-NP: (12/16)** Normal-NP: 14.3% (1/7) | |                        |
| Jany and Burkus           | Retrospective| 10  | United States of America | Abnormal-NP: 100.0   | Abnormal-NP: 60.0 | Abnormal-NP: 100.0 | NA                     |
|                          |              |     |                          | (5/5) Normal-NP: 0.0 | Normal-NP: 0.0 | (5/5) Normal-NP: 0.0 |                        |
| Eneroth et al.            | Prospective  | 32  | Sweden                   | NA                   | NA             | NA                | NA                     |
|                          |              |     |                          |                      |                |                   |                        |
| Banning et al.            | Prospective  | 10  | Netherlands              | NA                   | NA             | NA                | NA                     |

*a Myocardial infarction, pulmonary thromboembolism, pulmonary oedema, sepsis, pneumonia, decubitus and cystitis.
*b Pneumonia, sacral decubiti and ulcerative colitis.
NA: Not available, NP: Nutritional parameters.
* p < .05.
** p = .0186 - manually calculated using Fisher Exact Test.

Figure 2. Critical appraisal of the risk of bias.
nutrition assessment tool and hence was rated high risk in domain three. A meta-analysis was not carried out as associations were reported differently, and results cannot be pooled.

**Study characteristics**

Briefly, the studies consist of three retrospective\(^{21,24,25}\) and four prospective\(^{22,23,26,27}\) cohort studies (Table 1). All included studies were small, ranging from 10 to 64 participants. The mean age was between 53 to 80 years old. Among the included studies, one study\(^{23}\) recruited only males, four studies recruited both male and female participants,\(^{22,24,26,27}\) and the gender composition was unknown in the remaining two studies.\(^{21,23}\) Four out of seven studies\(^{21,23–25}\) were conducted in the United States of America, whereas the rest were conducted in Denmark,\(^{22}\) Sweden\(^{26}\) and Netherlands.\(^{27}\)

**Prevalence of malnutrition**

None of the studies used validated nutrition assessment tools to diagnose malnutrition, resulting in the lack of information on the prevalence of malnutrition (Table 1). Instead of using validated nutrition assessment tools, a majority of the studies\(^{21,22,24–26}\) used total lymphocyte count (<1500 cells/ml) and/or serum albumin (<3.5 g/dl) to determine nutritional status. In contrast, Eneroth et al.\(^{26}\) and Pedersen and Pedersen\(^{22}\) used anthropometric measures such as weight loss, triceps skinfold thickness and circumference of upper arm muscle, and biochemical parameters such as serum pre-albumin, albumin and total protein to establish nutritional status. However, how the parameters were used in combination to establish nutritional status is unclear. In five\(^{22,24–26}\) of six studies that used biochemical and/or anthropometric nutrition parameters to establish nutritional status, >50% of the participants had deranged parameters.

Despite the lack of information on malnutrition prevalence, the risk of malnutrition within patients who underwent LLA was reported by Banning et al.\(^{27}\) using the PG-SGA short form (PG-SGA SF)\(^{28}\) - a validated nutrition screening tool. Banning et al.\(^{27}\) reported that half of the population with amputation were at risk of malnutrition.

**Delayed wound healing and complications**

Five studies reported outcomes on wound healing and complications (Table 2).\(^{21,25}\) All of them showed that a higher proportion of patients with deranged biochemical\(^{21,25}\) and/or anthropometric nutrition parameters\(^{24}\) had poor wound healing\(^{21,24–25}\) and/or complications.\(^{22,25}\) However, only two studies\(^{22,23}\) reported statistical significance (\(p < 0.05\)) and another\(^{24}\) in which the statistical significance (\(p = 0.019\)) was manually calculated using Fisher’s Exact test.

**Failed amputation**

Three\(^{23–25}\) out of five studies reported on failed amputation, but only one\(^{24}\) reported statistical significance. Dickhaut et al.\(^{24}\) reported that 75% of the patients with deranged biochemical and/or anthropometric nutrition parameters had failed amputation (\(p = 0.19\)).

**Mortality**

Mortality was reported in four studies,\(^{21,24–26}\) of which two did not report any death.\(^{21,24}\) Among those that reported mortality, Pedersen and Pedersen\(^{22}\) found no significance and Kay et al.\(^{23}\) did not test for statistical significance.

**Discussion**

The prevalence of malnutrition and its association with clinical outcomes cannot be established since none of the eligible studies used validated nutrition assessment tools. Of note, patients with deranged biochemical and/or anthropometric nutrition parameters had poorer outcomes such as delayed wound healing and complications. Poor wound healing can lead to chronic wounds which increase the burden of the health care system. The annual cost of wound care globally has risen by 25% over the past 7 years.\(^{29}\) In the UK, £3.2 billion was spent on treating wounds with delayed healing and the cost is predicted to increase further.\(^{30}\) Poor wound healing is also associated to reduced quality of life.\(^{31}\)

Although the prevalence of malnutrition in patients who underwent LLA is not established thus far, Banning et al.\(^{27}\) reported that, at least half of this population appears to be at risk of malnutrition. Eneroth et al.\(^{26}\) also found that 84% of the population had weight loss and poor appetite, which are common components of malnutrition screening tools. Validated nutrition assessment tools are important as they are required to diagnose malnutrition accurately and provide a valid association between malnutrition and clinical outcomes. Using an inappropriate nutrition assessment tool will not only lead to an erroneous association but more importantly misguide treatment. For example, serum albumin is commonly used in the studies and thought to be an accurate biochemical marker of nutritional status.\(^{32}\) Contrary to this, it is well established that serum albumin in an acute clinical setting reflects inflammatory status rather than nutritional status.\(^{33}\) Hence, using albumin to estimate the prevalence of malnutrition and its association with clinical outcomes is inappropriate. More importantly, low levels of albumin caused by heightened inflammation cannot be treated with nutrition intervention.\(^{34}\) On the same token, low lymphocytes should not define malnutrition status since it may be due to severe stress or other diseases (e.g. leukemia) and not malnutrition per se. Similar to albumin, lymphocyte does not respond to nutrition interventions.\(^{35}\) This may in part explain the inconsistent association between pre-operative nutritional status (established by serum albumin or lymphocytes) and postoperative clinical outcomes in patients who underwent LLA.

One of the main reasons for using unvalidated nutrition assessment tools is that such tools were not available when the studies were conducted. Some of the included studies were written before the first validated nutrition assessment tool, SGA (1987), was published.\(^{4}\) Future studies should use validated nutrition assessment tools to measure malnutrition prevalence and its association with clinical outcomes. Future studies should diagnose malnutrition using validated nutrition assessment tools. Some possible assessment tools are GLIM\(^9\) and SGA.\(^4\) Studies consistently demonstrated
that malnutrition diagnosed by the SGA is associated with poorer outcomes in surgical populations\textsuperscript{36,37} and that management of malnutrition via nutrition intervention improve clinical outcome.\textsuperscript{38,39} Apart from SGA, numerous studies are validating GLIM.\textsuperscript{40,41} We observe that GLIM\textsuperscript{5} is commonly used in recent studies to diagnose malnutrition in different patient populations.\textsuperscript{42,43} Hence future studies can use either of the tools to report the prevalence of malnutrition and its associated outcomes.

Banning et al.\textsuperscript{27} identified the risk of malnutrition in the population with amputation using a validated nutrition screening tool. However, a validated nutrition screening tool may still misdiagnose malnutrition.\textsuperscript{44} Validated nutrition screening tools, such as PG-SGA SF,\textsuperscript{28} are simpler versions of the validated nutrition assessment tools. For example, the full version of PG-SGA\textsuperscript{5} combines weight and diet history, gastrointestinal symptoms, functional and fluid status, physical examination of muscle and subcutaneous fat stores as well as nutritional metabolic demands to accurately diagnose malnutrition. It can also detect pre-fraility/fraility, which is related to malnutrition, saving time for time-pressured clinicians.\textsuperscript{45} In contrast, the PG-SGA SF omits physical examination and nutritional metabolic demands. Nevertheless, the study by Banning et al.\textsuperscript{27} provides the best evidence thus far on the prevalence of malnutrition risk in patients with had amputation. The high prevalence is similar to other surgical populations such as cancer\textsuperscript{46} and gastrointestinal diseases.\textsuperscript{47}

**Implications for future practice**

Although it is unclear if malnutrition is associated with poor outcomes in patients with amputation, it is still important to routinely assess malnutrition risk using nutrition screening tools in all patients before amputation. In individuals identified to be at risk of malnutrition via nutrition screening, established nutrition assessment tools should be used to accurately diagnose malnutrition so that prompt and targeted nutrition interventions can be administered. This will likely benefit malnourished patients with amputation as a large randomized control trial\textsuperscript{48} demonstrated that individualized nutrition interventions can be administered. Instead, validated nutrition screening and assessment tools should be used in research and practice.

**Strengths and limitation**

This review’s strength is in its comprehensive search strategy in which relevant studies were included for a more comprehensive overview of this topic. However, this review is limited by the small number of studies published thus far, and the studies included are relatively old with the majority from the 1980s. It is further limited by the lack of studies with large sample size or multi-center prospective cohort studies. This exemplifies the knowledge gaps and the urgent need for more well-conducted studies in this patient population. Future studies can look into using validated nutrition assessment tools to establish the prevalence of malnutrition in patients who underwent LLA and the benefits of providing nutrition interventions to the malnourished group.

**Conclusion**

The prevalence of malnutrition and its associated outcomes are unclear due to the lack of studies that used validated nutrition assessment tool. Nevertheless, limited evidence provided by a study that used a validated nutrition screening tool reported a high prevalence of patients with malnutrition risk. Although patients with deranged biochemistry and/or anthropometry parameters appear to have worse clinical outcomes, clinicians should not interpret this as an indication for nutrition intervention. Instead, validated nutrition screening and assessment tools should be used in research and practice.

**Author contributions**

Xiaomei Zheng, Yeo Mei En Joy and Charles Chin Han Lew contributed to conception and design of the research; Xiaomei Zheng, Yeo Mei En Joy contributed to acquisition of the data; Xiaomei Zheng, Yeo Mei En Joy and Charles Chin Han Lew contributed to the interpretation of the data; Xiaomei Zheng drafted the manuscript; Xiaomei Zheng, Yeo Mei En Joy and Charles Chin Han Lew critically revised the manuscript; and Xiaomei Zheng, Yeo Mei En Joy and Charles Chin Han Lew agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

**Availability of data**

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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**Supplemental Material**

Supplemental material for this article is available online.

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