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# Relationship between perioperative anaemia and outcomes in older people with hip fractures: A systematic review and meta-analysis protocol

Kareeann SF Khow, Michelle WK Kee, Pazhvoor N Shibu, Solomon CY Yu, Mellick J Chehade, Renuka Visvanathan

**ORCID number:** Kareeann SF Khow (0000-0003-3960-1025); Michelle WK Kee (0000-0002-4426-4521); Pazhvoor N Shibu (0000-0001-7451-4643); Solomon CY Yu (0000-0001-7082-1232); Mellick J Chehade (0000-0001-6931-2393); Renuka Visvanathan (0000-0002-1303-9479).

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**Kareeann SF Khow, Michelle WK Kee, Pazhvoor N Shibu, Solomon CY Yu, Renuka Visvanathan,** Aged and Extended Care Services, the Queen Elizabeth Hospital, Woodville South, SA 5011, Australia

**Kareeann SF Khow, Pazhvoor N Shibu, Solomon CY Yu, Renuka Visvanathan,** Centre of Research Excellence, Frailty Trans-disciplinary Research to Achieve Healthy Ageing, University of Adelaide, Adelaide, SA 5005, Australia

**Mellick J Chehade,** Discipline of Orthopaedics and Trauma, Faculty of Medical and Health Sciences, University of Adelaide, Adelaide, SA 5005, Australia

**Corresponding author:** Kareeann SF Khow, FRACP, MBChB, Research Fellow, Senior Lecturer, Staff Physician, Aged and Extended Care Services, the Queen Elizabeth Hospital, 28 Woodville Road, Woodville South, SA 5011, Australia. [kareeann.khow@adelaide.edu.au](mailto:kareeann.khow@adelaide.edu.au)

**Telephone:** +61-8-83132144

**Fax:** +61-8-83132155

## Abstract

### BACKGROUND

Hip fractures are common with increasing age and is associated with decline in mobility. Both the fracture and the surgery can lead to blood loss, resulting in anaemia. However, it is uncertain at which time point haemoglobin is most strongly associated with different clinical outcomes after hip fracture. Our hypothesis is perioperative anaemia (admission, postoperative and discharge) during hip fracture surgery is associated with poor clinical outcomes.

### AIM

To determine the effects of perioperative anaemia during hip fracture surgery on mortality, functional status and other clinical outcomes.

### METHODS

Electronic databases will be searched to identify studies evaluating perioperative anaemia and outcomes of hip fracture surgery. Reference lists of included studies will also be searched to identify additional published studies. Eligibility criteria are as follows: Population: People who underwent hip fracture surgery; Exposure: Perioperative anaemia; Comparison: No anaemia before or after hip fracture surgery; Outcome: Mortality, hospital length of stay, postoperative complications, hospital readmission, change of discharge destination, quality of

supplementary file.

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life and functional status. Risk of bias assessment will be assessed using the Cochrane Collaboration's tool for randomized controlled trials and the modified version of the Epidemiological Appraisal Instrument for observational studies. Data will be pooled for meta-analysis if deemed appropriate.

## CONCLUSION

This review seeks to clarify outcomes associated with perioperative anaemia at various time-points around hip fracture surgery. These findings will potentially inform evidence-based clinical practice on interventions in those with anaemia.

**Key words:** Anaemia; Haemoglobin; Hip fracture; Length of stay; Mortality; Outcomes; Perioperative; Readmission

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**Core tip:** Hip fracture is a growing public health problem because of population aging. Recovery from hip fracture can be slow and complicated by morbidities and decline in functional abilities. Perioperative anaemia is common with hip fractures. However, it is uncertain at which time point haemoglobin level is most strongly associated with different clinical outcomes after hip fracture surgery. Better understanding of the relationship between perioperative haemoglobin and mortality, length of hospital stay, functional status, postoperative complications, hospital readmission and admission to residential care after discharge, is required.

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## INTRODUCTION

Mobility is vital to older people, especially for maintaining functional independence and good quality of life. Older people have identified that living in their own home as long as possible is a priority for them. However, sustaining a hip fracture is a serious life-changing event for many older people, which disrupts their ability to walk.

Hip fractures in the older population are associated with adverse outcomes which may include prolonged hospitalisation, decline in functional status, long-term institutionalisation and excessive mortality<sup>[1-3]</sup>. For example, less than 50% of patients regain their prior level of mobility at one year after hip fracture, and nearly 20% become immobile<sup>[4]</sup>. The loss of independence after hip fractures result in older people needing long-term residential care. In a meta-analysis of seventy-five studies involving more than 64000 subjects from multiple countries, the overall mortality at one year was 24.5% and this increased to 34.5% at 2 years<sup>[5]</sup>. Therefore, the healthcare burden of hip fractures is significant and strategies are needed to mitigate these adverse outcomes.

One potential way to improve outcomes after hip fractures is to better manage anaemia in patients with hip fractures. Hip fractures are associated with significant blood loss, either from the fracture itself or from the surgery to repair it<sup>[6]</sup>. In the general population, anaemia is present in 10% of women and 11% of men over the age of 65 years<sup>[7]</sup>. This prevalence of anaemia is higher in older people who had hip fractures. It is present in approximately 50% at the time of hospital admission<sup>[8]</sup>, increasing to more than 90% following hip fracture surgery<sup>[8]</sup>. Anaemia, independent of other health conditions, places older people at risk of adverse health outcomes. The increased risk of mortality among those with anaemia is well documented<sup>[9,10]</sup>. However, there is conflicting data about whether anaemia is an independent risk factor for poor postoperative outcome or a marker of severity of comorbid diseases in patients with hip fractures<sup>[9,11]</sup>.

Preoperative anaemia is recognised as a risk factor for mortality, longer length of stay and poorer functional status after hip fracture surgery<sup>[12]</sup>. It is also recognised as one of the most important risk factor for blood transfusions<sup>[12,13]</sup>. In a systematic



review published in 2015, preoperative anaemia was associated with a 64% increase in risk of mortality after hip fractures<sup>[14]</sup>. One of the limitations of this systematic review is that several studies published after 2015 were not included.

In a few studies, the effects of postoperative haemoglobin on clinical outcomes have shown mixed results<sup>[15,16]</sup>. In addition, little is known about the effects of anaemia prior to hospital discharge on outcomes. To date, only a small number of studies have examined the association between anaemia on discharge with outcomes<sup>[8,17,18]</sup>. Therefore, a more robust review is required to evaluate the relationship between perioperative anaemia and clinical outcomes in hip fracture surgery.

The primary aim of this systematic review is to determine the relationship between perioperative (preoperative, postoperative and discharge) anaemia and mortality after hip fracture surgery. Secondary aims are to evaluate the relationship between perioperative anaemia and other clinical outcomes such as hospital length of stay, postoperative complications, hospital readmission, rate of permanent transfer to residential care after discharge, and functional status in terms of mobility or disability.

## MATERIALS AND METHODS

This systematic review and meta-analysis will be performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement<sup>[19]</sup>.

### Definitions

Anaemia refers to a reduced number of circulating red blood cells and is usually based on haemoglobin measurements. Anaemia can occur at various time point of the fracture, either preoperatively (prior to surgery) or postoperatively (up to 7 days after surgery). There is also interest in haemoglobin just before discharge following the index surgery. These measurements are collectively referred to as perioperative haemoglobin.

### Search strategy

We will search for relevant articles in the English language using MEDLINE/PubMed, CINAHL, SCOPUS, EMBASE databases and Cochrane Library from inception until August 2018. The search strategy is provided in [Table 1](#). We will perform a manual search of additional references of articles.

### Eligibility criteria

**Population:** The population of interest is people with hip fractures undergoing surgery. Examples of surgery for hip fractures include sliding hip screw, intramedullary nail and arthroplasty.

**Exposure:** Studies evaluating the effects of perioperative anaemia which are defined as (1) at the time of admission or before surgery; (2) after surgery (within 7 days); and (3) prior to hospital discharge (as defined by the authors) will be included. Anaemia may be defined according to the World Health Organization criteria as haemoglobin concentration less than 120 g/L for women and less than 130 g/L for men<sup>[20]</sup>. For the purpose of this review, moderate and severe anaemia were defined as haemoglobin of 80-100 g/L and less than 80 g/L, respectively, for both sexes.

**Comparator/control:** Participants who had hip fracture surgery without anaemia, at different time points.

**Outcomes:** This review will consider studies that include any of the following outcomes (1) mortality up to 12 months post-surgery; (2) hospital length of stay; (3) postoperative complications; (4) hospital readmission; (5) rate of permanent transfer to residential care after discharge; (6) quality of life; (7) mobility or disability.

**Study design:** All peer-reviewed full-text studies or doctoral dissertations are eligible for initial review. Observational studies designed as longitudinal cohorts, case-control or cross-sectional studies and experimental studies designed as randomized controlled or non-randomized trials will be eligible for inclusion in this review.

**Exclusion:** This study will exclude case series, case reports and studies published in a language other than English. Studies reporting outcomes of cohorts with (1) acetabulum and fractures of the femoral shaft distal to the subtrochanteric region, (2) high-energy traumatic fracture; (3) pathological fracture and (4) non-surgical management of hip fracture will also be excluded.

### Study selection process

Initially, two reviewers (KSK, MWK) will screen the titles and abstracts of all search records independently. After screening, full texts of all potentially eligible studies will be retrieved and examined according to the abovementioned eligibility criteria.

Table 1 Search syntaxes

Database	Search syntax
PubMed	("anaemia" [All Fields] OR "anaemia" [MeSH Terms] OR "haemoglobin" [All Fields]) OR ("haemoglobin" [MeSH Terms] AND ("hip fractures" [MeSH Terms] OR "hip" [All Fields] AND "fractures" [All Fields]))
CINAHL	"hip fracture" AND (anaemia or haemoglobin)
Embase	"hip fracture" and (anaemia or haemoglobin)
Scopus	Hip fracture AND (anaemia or haemoglobin)

Disagreements at both screening levels (title/abstract and full text) will be adjudicated by a third reviewer (SY). A PRISMA-P flow chart will outline the study selection process and reasons for exclusion.

#### Data extraction

Data will be extracted by two independent reviewers (KSK, MWK) using a standard data abstraction form (Supplementary material). After determination of the study eligibility, information will be extracted from each study regarding study identification (first author, year of publication, number and location where recruitment took place), study design characteristics (sample size, follow-up duration, inclusion and exclusion criteria, quality assessments), patient population (age, gender, medical comorbidities) and haemoglobin levels (before, after surgery or prior to discharge). Data on the following outcomes will be recorded: mortality up to 12 mo, hospital length of stay, postoperative complications, hospital readmission up to 12 mo, rate of permanent transfer to residential care after discharge, quality of life, mobility or disability.

#### Quality assessment

The quality assessment for all studies will be assessed independently by two reviewers (KSK, MWK). The Cochrane Collaboration's tool will be used for assessing risk of bias among RCT studies<sup>[21]</sup>. This tool addresses six domains of bias: (1) Sequence generation; (2) Allocation concealment; (3) Blinding of personnel and participants; (4) Completeness of data; (5) Selective reporting; and (6) Other source of bias not covered in the other domains. Based on empirical and theoretical considerations, RCTs with inadequate random sequence generation, allocation concealment, incomplete outcome data, selective reporting, or with other sources of bias will be considered as high risk of bias<sup>[21]</sup>. When sufficient information was not provided on these three domains of bias to allow a definite judgement, we will consider the risk of bias as unclear. When a study is potentially free of these biases, we will consider the risk as low.

The quality of observational studies will be assessed using the Epidemiological Appraisal Instrument (EAI)<sup>[22]</sup>, a validated and reliable tool. This instrument addresses five domains of bias risk: Reporting, subject selection, measurement quality, data analysis, and generalisation of results. Each of the 43 questions in the EAI was scored as yes (= 2), partial (= 1), no or unable to determine (= 0) with the highest possible score being 86. Each total score will be stratified by quartiles. Quartile 1 (Q1) will be 70-86 (the highest quality), quartile 2 (Q2) will be 46-69, quartile 3 (Q3) will be 24-45 and quartile 4 (Q4) will be 0-23 (the lowest quality). Any disagreement regarding the quality of a study will be resolved by a third reviewer (SY).

#### Data synthesis

Detailed description of all included studies will be tabulated. Study identification (first author, year of publication, number and location where recruitment occurred), study design and characteristics (observational or experimental, sample size, duration of follow-up), patient population (age, gender), haemoglobin at different time points and clinical outcomes (mortality at different time points, hospital length of stay, hospital readmission at different time points, postoperative complications, rate of admission to residential care after discharge, quality of life, mobility or ability to perform activities of daily living) will be qualitatively described.

#### Statistical analysis

We will use RevMan 5.3 to conduct the meta-analyses. Meta-analyses of pooled data will not be performed for secondary outcomes or when the number of studies were small or highly heterogenous. The summary effect measures may include hazard ratios (HR), relative risk (RR) or odds ratios (OR). When data are available to be

pooled together, we will use a random-effects model to estimate of effect size. Where possible, we will aggregate each included study's outcome data as HR, RR, or OR with the associated 95%CI as these are assumed to measure the same underlying effect<sup>[23]</sup>. When the effect size estimate was not reported in the paper, the RR or OR and associated 95%CI will be calculated using the raw data available. In the first instance, the unadjusted effect sizes for each outcome (permitting age and sex adjustment) will be pooled together. In the second instance, the unadjusted and most adjusted effect sizes for each outcome will be pooled together.

## RESULTS

### *Heterogeneity and publication bias*

Heterogeneity among included studies will be evaluated using the  $I^2$  statistic, which will describe the proportion of variability in effect size estimates that is due to the difference between studies rather than by chance<sup>[21]</sup>. According to the Cochrane Handbook for Systematic Reviews<sup>[24]</sup>,  $I^2$  of 0% to 60% can be considered as not important to moderate, while  $I^2 > 60\%$  indicates substantial heterogeneity.

Funnel plots will be used to assess for any publication bias (eyeball test). Egger's test will be used to identify any funnel plot asymmetry arising from publication bias if present<sup>[24]</sup>.

## DISCUSSION

This systematic review aims to add to the existing literature by aggregating data on specific outcomes after hip fracture surgery in relation to perioperative anaemia. Our review is broader in scope and considers many more clinical outcomes compared with previous systematic reviews that have predominantly focused on postoperative mortality. Understanding the relationship between perioperative anaemia in hip fracture surgery and clinical outcomes is important from a clinical perspective because clinicians find it challenging to know when to transfuse with RBC. Therefore, this review will inform the evidence-based recommendations for this area of clinical practice.

It is common when undertaking such reviews and meta-analysis that gaps in methodology will be identified and as part of quality improvement, strategies to address these design gaps will be identified. Additionally, areas where knowledge gaps remain may be identified to guide future research directions for the benefit of the clinical care of people with hip fractures.

It can be hypothesized that this review will encounter several limitations. This review may not be able to generalize the findings because studies may potentially define anaemia by different haemoglobin cut-offs leading to variation in interpretation. Therefore, the proposed review may be limited by the pooling together of perioperative anaemia studies with varying levels of validity and heterogeneity. Another limitation concerns the length of stay and functional status endpoints, and it is possible that different studies may have utilized different methods to determine these outcomes, each with varying levels of validity.

In conclusion, given that the links between anaemia and clinical outcomes at different time-points before or after hip fracture surgery are complex and the lack of a comprehensive systematic review in this area, the proposed review will help to provide a summary of the available evidence. These findings will assist the development of future clinical practice and policy in this field.

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## ARTICLE HIGHLIGHTS

### *Research background*

Perioperative anaemia in hip fracture is a common problem that can influence clinical outcomes. However, it is uncertain which outcomes will be affected and if anaemia before or after surgery will have different effects.



### Research motivation

A better understanding of how perioperative anaemia influences clinical outcomes after hip fracture surgery will help to develop more timely interventions.

### Research objectives

To determine the effects of perioperative anaemia during hip fracture surgery on mortality, hospital length of stay, postoperative complications, hospital readmission, change of discharge destination, quality of life and functional status.

### Research methods

Electronic databases will be searched for studies evaluating perioperative anaemia and outcomes of hip fracture surgery. Data on study characteristics, patient demographics, timing of anaemia and clinical outcomes will be extracted. Comparison will be made between participants with anaemia and those without. Data will be pooled for meta-analysis for the primary outcome.

### Research conclusions

This systematic review seeks to clarify the outcomes associated with perioperative anaemia at various time-points among patients who had hip fracture surgery. An evaluation of the outcomes associated with perioperative anaemia in hip fracture surgery will potentially inform evidence-based clinical practice on the effectiveness and timing of interventions in those with reduced haemoglobin.

### Research perspectives

In presence of small studies evaluating perioperative anaemia among older people having hip fracture surgery, a systematic review and meta-analysis will provide important directions for future research and clinical practice in this field. This protocol will provide an important methodological foundation for the systematic review.

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