# Meta-analysis of the association between preoperative anaemia and mortality after surgery

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**Background:** Numerous published studies have explored associations between anaemia and adverse outcomes after surgery. However, there are no evidence syntheses describing the impact of preoperative anaemia on postoperative outcomes.

**Methods:** A systematic review and meta-analysis of observational studies exploring associations between preoperative anaemia and postoperative outcomes was performed. Studies investigating trauma, burns, transplant, paediatric and obstetric populations were excluded. The primary outcome was 30-day or in-hospital mortality. Secondary outcomes were acute kidney injury, stroke and myocardial infarction. Predefined analyses were performed for the cardiac and non-cardiac surgery subgroups. A *post hoc* analysis was undertaken to evaluate the relationship between anaemia and infection. Data are presented as odds ratios (ORs) with 95 per cent c.i.

**Results:** From 8973 records, 24 eligible studies including 949 445 patients were identified. Some 371 594 patients (39·1 per cent) were anaemic. Anaemia was associated with increased mortality (OR 2·90, 2·30 to 3·68; $I^2 = 97$ per cent; $P < 0·001$), acute kidney injury (OR 3·75, 2·95 to 4·76; $I^2 = 60$ per cent; $P < 0·001$) and infection (OR 1·93, 1·17 to 3·18; $I^2 = 99$ per cent; $P = 0·01$). Among cardiac surgical patients, anaemia was associated with stroke (OR 1·28, 1·06 to 1·55; $I^2 = 0$ per cent; $P = 0·009$) but not myocardial infarction (OR 1·11, 0·68 to 1·82; $I^2 = 13$ per cent; $P = 0·67$). Anaemia was associated with an increased incidence of red cell transfusion (OR 5·04, 4·12 to 6·17; $I^2 = 96$ per cent; $P < 0·001$). Similar findings were observed in the cardiac and non-cardiac subgroups.

**Conclusion:** Preoperative anaemia is associated with poor outcomes after surgery, although heterogeneity between studies was significant. It remains unclear whether anaemia is an independent risk factor for poor outcome or simply a marker of underlying chronic disease. However, red cell transfusion is much more frequent amongst anaemic patients.

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## Introduction

Each year more than 230 million patients undergo surgery worldwide[1]. Estimates of attributable mortality vary from 1 to 4 per cent; however, studies suggest that more than 80 per cent of deaths occur in a subgroup of high-risk surgical patients[1–4]. Successfully treated complications may still be associated with reduced long-term survival[3]. Epidemiological studies suggest that patient co-morbidities, including anaemia, are associated with increased rates of complication and death following surgery[2,5]. Anaemia may be defined either as a reduced number of circulating red blood cells as a percentage of blood volume (haematocrit), or as a decreased concentration of circulating haemoglobin[6]. The prevalence of anaemia among the general population is approximately 20 per cent in Europe[7], but is as high as 90 per cent amongst some surgical patient populations[8,9].

Anaemia may be more common within the surgical population for various reasons and can have multiple aetiologies including haematinic deficiencies, in particular iron deficiency, blood loss, or anaemia of chronic disease secondary to malignancy or an inflammatory state. Guidelines on preoperative screening for anaemia may also influence the perceived prevalence[10]. Observational studies suggest an association between anaemia in the perioperative period and postoperative mortality. However, it remains uncertain whether anaemia is an independent risk factor for poor postoperative outcome or a marker of the severity of co-morbid disease. It is also unknown whether the treatment of anaemia through allogeneic red cell transfusion is associated with harm or benefit[11,12]. Studies of surgical patients suggest that transfusion of even a small volume of allogeneic red cells is associated with an increase in postoperative mortality[13].

The concept of patient blood management (PBM) has been introduced to promote best practice in the timely detection and management of preoperative anaemia[14]. The principles of PBM are optimization of the patient's red cell mass, minimization of blood loss during surgery and the appropriate use of transfusion triggers[15]. The clinical effects of various preoperative interventions are currently being investigated in randomized trials including intravenous iron and erythropoietin. However, the most effective methods of treating anaemia in the perioperative period have yet to be defined and further research is needed to address this uncertainty. The association between preoperative anaemia and postoperative outcome has been explored in various studies, but with inconsistent results. To date, there have been no published syntheses of the evidence to summarize the impact of this condition in surgery. A systematic review and meta-analysis of observational studies was therefore performed to examine the associations between preoperative anaemia and clinical outcomes following surgery, and to evaluate the incidence of allogeneic blood transfusion to treat anaemia.

## Methods

The study protocol was published on PROSPERO, the international prospective register of systematic reviews (reference: CRD42014010795; http://www.crd.york.ac.uk/PROSPERO). The search and analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16].

### Search strategy

MEDLINE, Embase and the Cochrane database of systematic reviews were searched (1946 to present), as well as GreyNet (www.greynet.com), Web of Science (wok.mimas.ac.uk) and citations of included articles. *Table 1* shows the search strategy used for the Cochrane Library; this was then translated for different database syntaxes. The full search strategy for each database is shown in *Tables S1* and *S2* (supporting information).

Search results were limited to observational trials in adult subjects conducted in the past 20 years. Non-English-language papers were included. The bibliographies of evaluable studies and other selected papers were searched manually. The literature search was conducted by a literature search specialist.

**Table 1** Cochrane Library search strategy

| | |
|---|---|
| #1 | anemia or Hb or haematocrit* or haemoglobin |
| #2 | outcome* or death or mortality |
| #3 | surgery or surgical or operat* |
| #4 | #1 and #2 and #3 |

### Study selection criteria

Duplicates were removed and the remaining records were entered into a database (Mendeley, London, UK). The titles and abstracts of records were then screened to select articles for full-text assessment. Full texts were downloaded, and lead authors contacted if the article was not available. Two authors independently determined suitability for inclusion. Articles were included if: they were observational in design, reported 30-day or in-hospital mortality, incidence of acute kidney injury, stroke or myocardial infarction (using the authors' definitions) in relation to preoperative haemoglobin levels; study subjects were over 16 years of age; and the study had a comparable non-anaemic group. Articles were excluded if study subjects underwent burns, obstetric, trauma or transplant surgery. Studies were assessed for methodological quality using the Newcastle–Ottawa Scale, assigning up to 9 points for selection and comparability of cohorts and assessment of outcome[17]. Studies with a score of less than 6 were excluded. The final article selection was confirmed independently by two authors.

### Data extraction

Data including study characteristics, patient characteristics, definitions of anaemia, patient outcomes and statistical adjustment were extracted using a standard form (*Fig. S1*, supporting information) and then entered into a database (Excel® 2007; Microsoft, Redmond, Washington, USA). Study authors were contacted where required data were not reported.

### Clinical outcomes

The primary outcome measure was a composite of death within 30 days of surgery or death before hospital discharge. Secondary outcomes were the incidence of acute kidney injury, stroke and myocardial infarction within 30 days of surgery, using the authors' definitions.

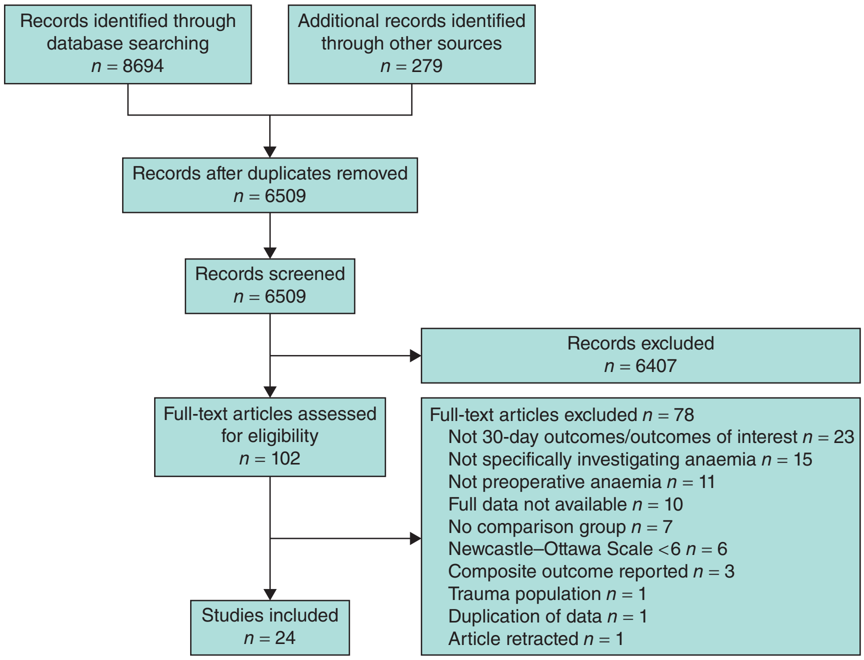


**Fig. 1** PRISMA flow diagram of article selection

### Statistical analysis

All statistical analyses were undertaken using Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Studies and their characteristics were first tabulated. Between-study statistical heterogeneity was assessed by $\chi^2$ and $I^2$ tests, and values of 25, 50 and 75 per cent were used to indicate the presence of low, moderate and high between-trial heterogeneity respectively. $P < 0{\cdot}100$ was considered to denote the statistical significance of heterogeneity. A funnel plot was constructed for the primary outcome and assessed visually to establish the risk of publication bias. For all analyses performed, if no significant heterogeneity was noted, a fixed-effect model analysis using the Mantel–Haenszel method was used. If significant heterogeneity was noted, a random-effects model analysis using the DerSimonian–Laird method was employed. Predefined subgroup analyses were undertaken to explore the effect of anaemia in patients undergoing cardiac and non-cardiac surgery. A sensitivity analysis using a random-effects model was performed including only studies that had applied the World Health Organization (WHO) definition of anaemia (less than 12 g/dl for female and less than 13 g/dl for male patients)[18]. A *post hoc* analysis was undertaken to explore the relationship between anaemia and postoperative infection. Forest plots were then created to summarize the models. Findings are presented as odds ratios (ORs) with 95 per cent c.i.

## Results

### Study selection

A total of 8694 records were identified from the electronic search strategy, with a further 275 records through grey literature searches, and four records by hand search. After removal of duplicates, 6509 records remained. The full texts of manuscripts reporting 102 studies were retrieved, of which 24 met the inclusion criteria (*Fig. 1*).

### Characteristics of included studies

Characteristics of the included studies are summarized in *Table 2*[5,19–41]. A total of 949 445 patients were included, and all 24 studies reported the primary outcome of 30-day or in-hospital mortality. Eight articles reported acute kidney injury. Stroke was reported in six studies, and five reported myocardial infarction (*Table S3*, supporting information). However, stroke and myocardial infarction were reported as an outcome only in studies of patients undergoing cardiac surgery (*Table 2*). A haemoglobin definition was used in 17 studies[5,19,20,22–26,28–31,33,37–39,41], a haematocrit definition in six studies[27,32,34–36,40], and both definitions were used in one study[21]. Definitions of anaemia

**Table 2** Characteristics of included studies

| Reference | Study design | Surgery | No. with anaemia | No. without anaemia | Definition of anaemia (g/dl)* | Outcomes reported | | | | PRBC transfusion reported | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Mortality | AKI | Stroke | MI | | |
| 5 | PC | Non-cardiac | 11 295 | 27 439 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | No | 9 |
| 19 | PC | Non-cardiac | 3047 | 4632 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 9 |
| 20 | DB | Cardiac | 6143 | 30 196 | < 12 | Yes | Yes | Yes | No | No | 9 |
| 21 | RC | Cardiac | 185 | 3126 | < 11 | Yes | Yes | Yes | Yes | Yes | 6 |
| 22 | RC | Cardiac | 42 | 159 | < 12 | Yes | Yes | Yes | Yes | No | 8 |
| 23 | PC | Cardiac | 320 | 727 | < 13 (M)<br>< 12 (F) | Yes | Yes | Yes | No | Yes | 7 |
| 24 | PC | Orthopaedic | 185 | 158 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | No | 6 |
| 25 | RC | Orthopaedic | 2991 | 12 231 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 6 |
| 26 | PC | Orthopaedic | 180 | 215 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 9 |
| 27 | DB | Vascular | 15 272 | 16 585 | < 39%† | Yes | No | No | No | No | 9 |
| 28 | PC | Cardiac | 1463 | 1225 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 6 |
| 29 | RC | GI | 125 | 463 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | No | 6 |
| 30 | RC | GI | 197 | 216 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 6 |
| 31 | RC | Cardiac | 210 | 366 | < 13 (M)<br>< 12 (F) | Yes | Yes | Yes | Yes | Yes | 7 |
| 32 | DB | Non-cardiac | 69 229 | 158 196 | < 39%†(M)<br>< 36%†(F) | Yes | Yes | No | No | Yes | 9 |
| 33 | RC | Vascular | 193 | 167 | < 14 (M)<br>< 12 (F) | Yes | No | No | No | No | 7 |
| 34 | RC‡ | Cardiac | 401 | 401 | < 30%† | Yes | Yes | Yes | Yes | Yes | 7 |
| 35 | DB‡ | Non-cardiac | 119 298 | 119 298 | < 39%†(M)<br>< 36%†(F) | Yes | No | No | No | No | 9 |
| 36 | DB | Spinal | 5879 | 18 594 | < 38%† | Yes | No | No | No | Yes | 8 |
| 37 | RC | Cardiac | 650 | 3782 | < 12 | Yes | No | No | No | Transfused patients excluded | 7 |
| 38 | RC | Cardiac | 351 | 1385 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | No | 6 |
| 39 | RC | Orthopaedic | 536 | 726 | < 13 (M)<br>< 12 (F) | Yes | No | No | No | Yes | 6 |
| 40 | DB | Non-cardiac | 132 970 | 177 341 | < 39%† | Yes | No | No | No | No | 9 |
| 41 | RC | Cardiac | 432 | 223 | < 13 (M)<br>< 12 (F) | Yes | Yes | No | Yes | Yes | 9 |

All outcomes are reported at 30 days or in hospital. *Haemoglobin level below which patients were considered anaemic; †haematocrit definition was used and is presented as a percentage. ‡A propensity-matched cohort was used in this analysis. AKI, acute kidney injury; MI, myocardial infarction; PRBC, packed red blood cell; NOS, Newcastle–Ottawa Scale; PC, prospective cohort; DB, national or international database retrospective review; RC, retrospective cohort; GI, gastrointestinal.

ranged from a haemoglobin concentration of 11 to 12 g/dl or a haematocrit of 30–39 per cent for female patients, and from 11 to 14 g/dl or 30–39 per cent respectively for male patients. Eight studies were of multicentre design. Nine studies (including 855 031 patients) were performed in the USA, and 11 reported the timing of haemoglobin measurement, which varied from time of anaesthesia induction to 6 weeks before surgery.

## Frequency of anaemia and blood transfusion

In total, 371 594 of the 949 445 patients were anaemic as defined by the authors of included studies (39·1 per cent). When restricted to the 13 studies reporting the WHO definition, 21 322 (29·9 per cent) of 71 338 patients were anaemic. Thirteen studies reported the incidence of allogeneic red cell transfusion (*Table 2*), which was

| Reference | Year | Mortality: Anaemia | Mortality: No anaemia | Weight (%) | Odds ratio |
|---|---|---|---|---|---|
| Gruson *et al.*[26] | 2002 | 5 of 180 | 3 of 215 | 1·8 | 2·02 (0·48, 8·57) |
| Cladellas *et al.*[22] | 2006 | 9 of 42 | 10 of 159 | 2·9 | 4·06 (1·53, 10·79) |
| Wu *et al.*[40] | 2007 | 8660 of 132970 | 3351 of 177341 | 5·9 | 3·62 (3·47, 3·77) |
| Bell *et al.*[20] | 2008 | 325 of 6143 | 798 of 30196 | 5·8 | 2·06 (1·80, 2·35) |
| Beattie *et al.*[19] | 2009 | 76 of 3047 | 24 of 4632 | 4·8 | 4·91 (3·10, 7·79) |
| Melis *et al.*[30] | 2009 | 14 of 197 | 5 of 216 | 2·8 | 3·23 (1·14, 9·14) |
| De Santo *et al.*[23] | 2009 | 25 of 320 | 16 of 727 | 4·1 | 3·77 (1·98, 7·16) |
| Shirzad *et al.*[37] | 2010 | 26 of 650 | 35 of 3782 | 4·6 | 4·46 (2·67, 7·46) |
| Munoz *et al.*[31] | 2010 | 12 of 210 | 19 of 366 | 3·7 | 1·11 (0·53, 2·33) |
| Musallam *et al.*[32] | 2011 | 3192 of 69229 | 1240 of 158196 | 5·9 | 6·12 (5·73, 6·54) |
| Boening *et al.*[21] | 2011 | 44 of 185 | 121 of 3126 | 5·1 | 7·75 (5·28, 11·38) |
| Vochteloo *et al.*[39] | 2011 | 30 of 536 | 31 of 726 | 4·6 | 1·33 (0·79, 2·22) |
| Hung *et al.*[28] | 2011 | 45 of 1463 | 13 of 1225 | 4·2 | 2·96 (1·59, 5·51) |
| Dubljanin-Raspopovic *et al.*[24] | 2011 | 19 of 185 | 12 of 158 | 3·7 | 1·39 (0·65, 2·97) |
| Greenky *et al.*[25] | 2012 | 12 of 2991 | 21 of 12231 | 3·9 | 2·34 (1·15, 4·77) |
| Ranucci *et al.*[34] | 2012 | 51 of 401 | 30 of 401 | 4·8 | 1·80 (1·12, 2·89) |
| Oshin and Torella[33] | 2013 | 16 of 193 | 2 of 167 | 1·8 | 7·46 (1·69, 32·93) |
| Saager *et al.*[35] | 2013 | 1288 of 119298 | 811 of 119298 | 5·9 | 1·59 (1·46, 1·74) |
| Gupta *et al.*[27] | 2013 | 368 of 15272 | 206 of 16585 | 5·8 | 1·96 (1·65, 2·33) |
| van Straten *et al.*[38] | 2013 | 20 of 351 | 38 of 1385 | 4·5 | 2·14 (1·23, 3·73) |
| Seicean *et al.*[36] | 2013 | 63 of 5879 | 37 of 18594 | 5·1 | 5·43 (3·62, 8·16) |
| Jung *et al.*[29] | 2013 | 0 of 125 | 0 of 463 | | Not estimable |
| Zhang *et al.*[41] | 2013 | 22 of 432 | 3 of 223 | 2·3 | 3·93 (1·16, 13·29) |
| Baron *et al.*[5] | 2014 | 656 of 11295 | 604 of 27439 | 5·9 | 2·74 (2·45, 3·07) |
| Total | | 14978 of 371594 | 7430 of 577851 | 100·0 | 2·90 (2·30, 3·68) |

Heterogeneity: $\tau^2 = 0{\cdot}24$; $\chi^2 = 768{\cdot}79$, 22 d.f., $P < 0{\cdot}001$; $I^2 = 97\%$
Test for overall effect: $Z = 8{\cdot}88$, $P < 0{\cdot}001$

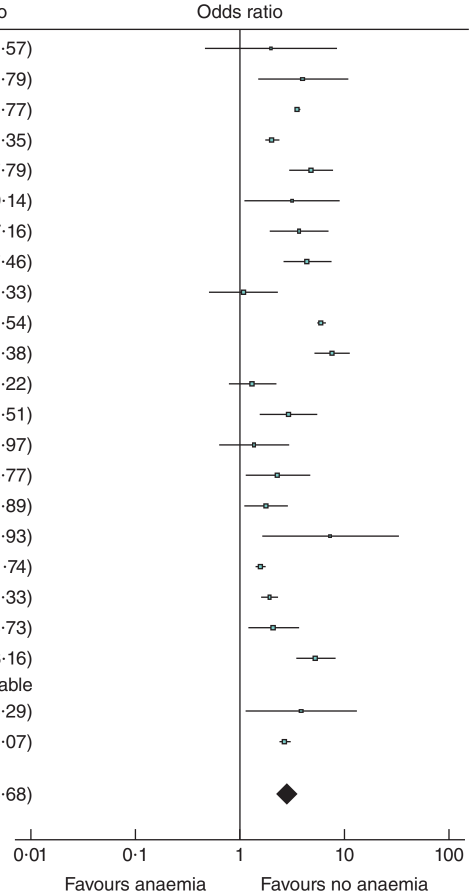


**Fig. 2** Forest plot showing composite outcome of 30-day or in-hospital mortality after surgery, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

| Reference | Acute kidney injury: Anaemia | Acute kidney injury: No anaemia | Weight (%) | Odds ratio |
|---|---|---|---|---|
| Bell *et al.*[20] | 183 of 6143 | 262 of 30196 | 26·9 | 3·51 (2·90, 4·25) |
| Boening *et al.*[21] | 12 of 185 | 38 of 3126 | 9·3 | 5·64 (2·89, 10·98) |
| Cladellas *et al.*[22] | 20 of 42 | 20 of 159 | 7·5 | 6·32 (2·94, 13·59) |
| De Santo *et al.*[23] | 20 of 320 | 16 of 727 | 9·2 | 2·96 (1·51, 5·80) |
| Munoz *et al.*[31] | 6 of 210 | 4 of 366 | 3·2 | 2·66 (0·74, 9·54) |
| Musallam *et al.*[32] | 1285 of 69229 | 675 of 158196 | 30·9 | 4·41 (4·02, 4·85) |
| Ranucci *et al.*[34] | 28 of 401 | 18 of 401 | 10·5 | 1·60 (0·87, 2·94) |
| Zhang *et al.*[41] | 22 of 432 | 2 of 223 | 2·5 | 5·93 (1·38, 25·45) |
| Total | 1576 of 76962 | 1035 of 193394 | 100·0 | 3·75 (2·95, 4·76) |

Heterogeneity: $\tau^2 = 0{\cdot}05$; $\chi^2 = 17{\cdot}72$, 7 d.f., $P = 0{\cdot}01$; $I^2 = 60\%$
Test for overall effect: $Z = 10{\cdot}79$, $P < 0{\cdot}001$

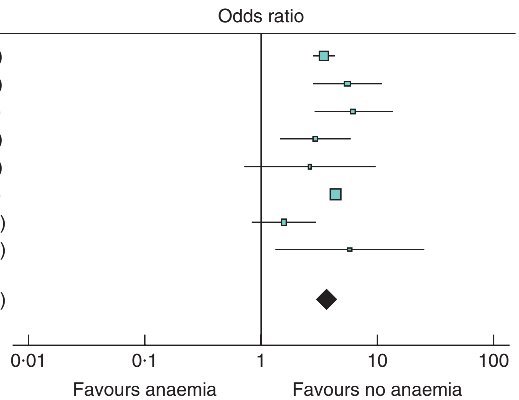


**Fig. 3** Forest plot of acute kidney injury, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

| Reference | Stroke: Anaemia | Stroke: No anaemia | Weight (%) | Odds ratio |
|---|---|---|---|---|
| Bell *et al.*[20] | 124 of 6143 | 481 of 30 196 | 87·9 | 1·27 (1·04, 1·55) |
| Boening *et al.*[21] | 5 of 185 | 82 of 3126 | 4·9 | 1·03 (0·41, 2·58) |
| Cladellas *et al.*[22] | 2 of 42 | 5 of 159 | 1·1 | 1·54 (0·29, 8·23) |
| De Santo *et al.*[23] | 9 of 320 | 11 of 727 | 3·6 | 1·88 (0·77, 4·59) |
| Munoz *et al.*[31] | 0 of 210 | 5 of 366 | 2·2 | 0·16 (0·01, 2·84) |
| Ranucci *et al.*[34] | 4 of 401 | 0 of 401 | 0·3 | 9·09 (0·49, 169·40) |
| Total | 144 of 7301 | 584 of 34 975 | 100·0 | 1·28 (1·06, 1·55) |

Heterogeneity: $\chi^2 = 4{\cdot}73$, 5 d.f., $P = 0{\cdot}45$; $I^2 = 0\%$
Test for overall effect: $Z = 2{\cdot}61$, $P = 0{\cdot}009$

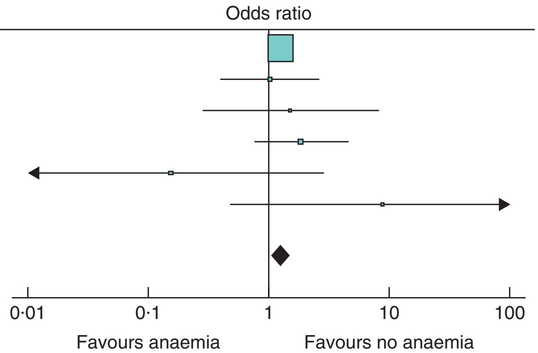


**Fig. 4** Forest plot of stroke, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

| Reference | Myocardial infarction: Anaemia | Myocardial infarction: No anaemia | Weight (%) | Odds ratio |
|---|---|---|---|---|
| Boening *et al.*[21] | 1 of 185 | 24 of 3126 | 8·9 | 0·70 (0·09, 5·22) |
| Cladellas *et al.*[22] | 2 of 42 | 4 of 159 | 5·3 | 1·94 (0·34, 10·96) |
| Munoz *et al.*[31] | 16 of 210 | 17 of 366 | 38·0 | 1·69 (0·84, 3·43) |
| Ranucci *et al.*[34] | 6 of 401 | 12 of 401 | 39·2 | 0·49 (0·18, 1·33) |
| Zhang *et al.*[41] | 5 of 432 | 2 of 223 | 8·7 | 1·29 (0·25, 6·72) |
| Total | 30 of 1270 | 59 of 4275 | 100·0 | 1·11 (0·68, 1·82) |

Heterogeneity: $\chi^2 = 4{\cdot}60$, 4 d.f., $P = 0{\cdot}33$; $I^2 = 13\%$
Test for overall effect: $Z = 0{\cdot}43$, $P = 0{\cdot}67$

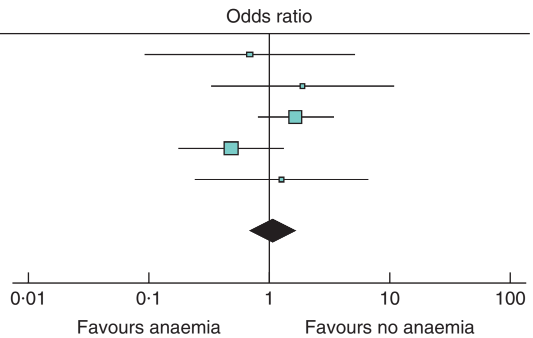


**Fig. 5** Forest plot of myocardial infarction, according to author-defined anaemia. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

more frequent amongst anaemic patients (15 804 (18·5 per cent) in anaemic groups *versus* 9539 (4·7 per cent) in non-anaemic groups; OR 5·04, 4·12 to 6·17; $I^2 = 96$ per cent; $P < 0{\cdot}001$) (*Fig. S2*, supporting information). Patients who received an allogeneic red cell transfusion were excluded from one study[37], and one article reported allogeneic red cell transfusion rates only for anaemic patients[33]. Statistical adjustment was carried out in all included studies, but the method used and variables included in models were too varied to allow separate analysis. The funnel plot was symmetrical, indicating that publication bias is unlikely (*Fig. S3*, supporting information).

## Primary outcome

### *In-hospital or 30-day mortality*

Mortality was reported in all included studies, 12 as 30-day mortality, eight as in-hospital mortality, and in four studies a composite of both outcomes was presented. A total of 22 408 patients (2·4 per cent) died within 30 days after surgery or before hospital discharge. Anaemic patients died more frequently (OR 2·90, 2·30 to 3·68; $I^2 = 97$ per cent; $P < 0{\cdot}001$) (*Fig. 2*). Between-study heterogeneity was high, possibly owing to the very different populations and definitions used in included studies, and a random-effects model was therefore used. Fourteen reports, including 890 605 patients, identified anaemia as an independent risk factor for mortality. Two articles did not report multivariable adjustment, and eight articles (including 58 184 patients) did not identify anaemia as an independent risk factor for mortality.

## Secondary outcomes

### *Acute kidney injury*

Eight studies including 270 356 patients reported postoperative acute kidney injury as an outcome measure (*Table S3*, supporting information), seven of which were confined to patients undergoing cardiac surgery (*Table 2*). Anaemia was associated with an increased incidence of

| Reference | Infection: Anaemia | Infection: No anaemia | Weight (%) | Odds ratio |
|---|---|---|---|---|
| Bell *et al.*[20] | 208 of 6143 | 338 of 30 196 | 10·0 | 3·10 (2·60, 3·69) |
| Boening *et al.*[21] | 30 of 185 | 206 of 3126 | 9·4 | 2·74 (1·81, 4·16) |
| Cladellas *et al.*[22] | 10 of 42 | 16 of 159 | 7·7 | 2·79 (1·16, 6·72) |
| De Santo *et al.*[23] | 5 of 320 | 12 of 727 | 7·0 | 0·95 (0·33, 2·71) |
| Greenky *et al.*[25] | 130 of 2991 | 259 of 12 231 | 9·9 | 2·10 (1·69, 2·60) |
| Melis *et al.*[30] | 46 of 197 | 49 of 216 | 9·3 | 1·04 (0·66, 1·64) |
| Munoz *et al.*[31] | 20 of 210 | 27 of 366 | 8·8 | 1·32 (0·72, 2·42) |
| Musallam *et al.*[32] | 4592 of 69 229 | 3214 of 158 196 | 10·1 | 3·43 (3·27, 3·59) |
| Ranucci *et al.*[34] | 26 of 401 | 14 of 401 | 8·6 | 1·92 (0·99, 3·73) |
| Saager *et al.*[35] | 7337 of 119 298 | 7194 of 119 298 | 10·1 | 1·02 (0·99, 1·06) |
| Shirzad *et al.*[37] | 21 of 650 | 47 of 3782 | 9·1 | 2·65 (1·58, 4·47) |
| Total | 12 425 of 199 666 | 11 376 of 328 698 | 100·0 | 1·93 (1·17, 3·18) |

Heterogeneity: $\tau^2 = 0·64$; $\chi^2 = 1819·28$, 10 d.f., $P < 0·001$; $I^2 = 99\%$
Test for overall effect: $Z = 2·57$, $P = 0·01$

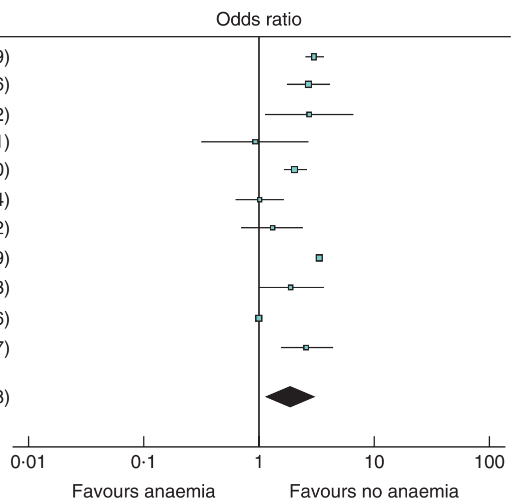


**Fig. 6** Forest plot of risk of infection in anaemic *versus* non-anaemic patients. Sizes of markers indicate weight for each study according to sample size. A Mantel–Haenszel random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent c.i.

postoperative acute kidney injury (OR 3·75, 2·95 to 4·76; $I^2 = 60$ per cent; $P < 0·001$) (*Fig. 3*). Between-study heterogeneity was moderate and a random-effects model was used.

*Stroke*

Six studies including 42 276 patients reported postoperative stroke as an outcome measure (*Table S3*, supporting information). All of these studies were confined to patients having cardiac surgery (*Table 2*). Anaemia was associated with an increased risk of stroke in these studies (OR 1·28, 1·06 to 1·55; $I^2 = 0$ per cent; $P = 0·009$) (*Fig. 4*). There was no between-study heterogeneity and a fixed-effect model was used.

*Myocardial infarction*

Five studies including 5545 patients reported postoperative myocardial infarction as an outcome measure (*Table S3*, supporting information). All of these studies were confined to patients undergoing cardiac surgery (*Table 2*). There was no significant difference in the incidence of myocardial infarction between anaemic and non-anaemic patients (OR 1·11, 0·68 to 1·82; $I^2 = 13$ per cent; $P = 0·67$) (*Fig. 5*). There was low between-study heterogeneity and a fixed-effect model was used.

## Subgroup analyses

*Non-cardiac surgery*

Fourteen studies were identified including 897 658 non-cardiac surgical patients of whom 361 397 (40·3 per cent) were anaemic. These studies described various surgical specialty groups including vascular, orthopaedic, spinal and upper gastrointestinal surgery. Anaemia was associated with an increased risk of death in non-cardiac surgical patients (OR 2·87, 2·10 to 3·93; $I^2 = 98$ per cent; $P < 0·001$) (*Fig. S4*, supporting information). There was high between-study heterogeneity and a random-effects model was used.

*Cardiac surgery*

Ten studies were identified including 51 787 cardiac surgical patients, of whom 10 197 (19·7 per cent) were anaemic. Anaemia was associated with an increased risk of death for patients undergoing cardiac surgery (OR 2·98, 2·02 to 4·38; $I^2 = 84$ per cent; $P < 0·001$) (*Fig. S4*, supporting information).

## Sensitivity analysis

*World Health Organization definition of anaemia*

The WHO definition of anaemia was employed in 13 studies including 71 338 patients, of whom 21 332 (29·9 per cent) were anaemic. When the analysis was restricted to these studies, the association between anaemia and postoperative mortality remained (OR 2·46, 1·91 to 3·17; $I^2 = 56$ per cent; $P < 0·001$) (*Fig. S5*, supporting information). Between-study heterogeneity was moderately reduced, probably because of the uniform definitions dividing the study populations, and a random-effects model was used.

## *Post hoc* analysis

### *Postoperative infection*

During review of the literature, 11 studies were identified that included data describing postoperative infection, seven in the setting of cardiac surgery and four in non-cardiac surgery. An additional *post hoc* analysis using a random-effects model to evaluate the relationship between preoperative anaemia and postoperative infection was therefore performed. Some 23 801 (4·5 per cent) of 528 364 patients developed an infection after surgery. Anaemia was associated with an increased incidence of infection (OR 1·93, 1·17 to 3·18; $I^2 = 99$ per cent; $P = 0·01$) (*Fig. 6*). There was high between-study heterogeneity, probably owing to the variety of included infections, and a random-effects model was used.

## Discussion

The principal finding of this analysis is that preoperative anaemia is associated with increased short-term mortality after surgery. This association was also present when cardiac and non-cardiac surgery subgroups were analysed separately, and in studies that employed the WHO definition of anaemia. Preoperative anaemia is also associated with an increased risk of acute kidney injury and infection after surgery. Amongst cardiac surgical patients, preoperative anaemia is associated with stroke but not myocardial infarction, perhaps reflecting improved coronary artery perfusion after surgery. These observations do not confirm a causal relationship, but it is important to note that the diagnosis of anaemia appears to alter clinical practice because allogeneic red cell transfusion is more frequent amongst anaemic patients. Statistical heterogeneity was very high for a number of analyses, probably owing to the very different populations and definitions of anaemia used in included studies. Caution is therefore required in interpretation of these findings.

The findings of this systematic review of 24 studies are consistent with those of the component studies, which either suggest that preoperative anaemia is associated with adverse outcomes following surgery, or show no difference in these outcomes. The present findings are also consistent with reports in other patient groups suggesting that anaemia is associated with poor outcome[8,9]. It is interesting to note that the association between anaemia and mortality was stronger than that with morbidity. This partly reflects the fact that fewer reports provide data describing morbidity outcomes, but may also be explained by inconsistent reporting of complications within and between studies, and the high levels of heterogeneity associated with the present mortality findings. The stroke outcome data should be interpreted with caution as 86·0 per cent of patients in this analysis were contributed by a single study[20] of patients undergoing coronary artery bypass.

The absence of any association between myocardial infarction and anaemia is surprising, given first principles of physiology regarding the balance of myocardial oxygen supply and demand. This may relate to the fact that myocardial infarction was reported as a separate outcome in only a few studies contributing 5545 cardiac surgical patients, compared with 42 276 patients with data describing the outcome of stroke and 270 356 describing acute kidney injury.

Perhaps unsurprisingly, allogeneic red cell transfusion occurred at a higher rate amongst anaemic than non-anaemic patients. Both anaemia and its treatment by allogeneic red cell transfusion have been associated with increased mortality and morbidity, and it remains unclear whether correcting preoperative anaemia can improve outcomes[14]. Investigators are exploring the value of various preoperative treatments for anaemia, including intravenous iron and erythropoietin. However, the evidence base for this area of clinical practice remains limited. Other aspects of patient blood management, such as minimizing perioperative blood loss through the use of tranexamic acid, are also being explored[42]. Anaemic patients are more likely to develop an infection following surgery, perhaps reflecting the immunosuppressant effects of allogeneic red cell transfusion, as well as the increased incidence of co-morbid disease in the anaemic population[43].

The present findings emphasize the importance of anaemia and PBM, which has been promoted by the WHO, with initiatives under way in many countries. In the UK, the National Health Service has issued guidance for this area of practice, and a formal National Institute for Health and Care Excellence guideline is currently in draft. It was not possible to account for the potential confounding effect of co-morbid disease, and it remains unclear whether anaemia is the cause of poor outcome after surgery or a marker of increased risk. The data sets available to many of the included studies probably included only those patients who required preoperative haemoglobin estimation. Some element of reporting bias seems likely, and the proportion of anaemic patients may be overestimated.

The strength of this study is that it was conducted according to a robust, prospectively written and published analysis plan by a multidisciplinary group, with experience in meta-analyses in perioperative medicine and haematology. Studies were assessed rigorously for methodological quality, and only those of sufficient quality were included in the analysis. However, this analysis has a number of limitations, the principal one being the high level of statistical and clinical heterogeneity in the findings. This heterogeneity likely exists because of the variety of populations studied and the different definitions used by included studies. Preoperative timing of haemoglobin or haematocrit reporting was reported infrequently, preventing any adjustment for this source of bias. A number of studies reported haematocrit, creating additional heterogeneity in the available data. It is also possible that all eligible papers were not located by the electronic search strategy. It was not possible to adjust for the effect of allogeneic red cell transfusion, owing to the largely unavailable data describing the number of red cell transfusions received per patient. This limited the ability to determine the independent effect of anaemia on outcome. Where risk adjustment was reported, the technique used varied widely. Unmeasured confounding and selection bias are often present in observational studies, and it remains possible that the use of observational data with such bias may produce spurious results with an apparently high degree of precision[44]. The high level of between-study heterogeneity observed may place the present analysis at risk of this. Moreover, cardiac surgery is over-represented within this cohort. The majority of component studies were single-centre in design, and five component studies were derived from the same database (National Surgical Quality Improvement Project, USA). This may have resulted in overlap of included patients; however, a sensitivity analysis was performed excluding all but the largest of these studies, and the findings remained unchanged[40].

Preoperative anaemia is associated with increased short-term mortality after surgery, as well as an increased incidence of stroke, acute kidney injury and infection. These results should be interpreted with care given the high levels of heterogeneity between studies. Although these observations will, at least partially, reflect the severity of co-morbid disease among included patients, allogeneic red cell transfusion is also more common in the presence of anaemia. The current evidence base for allogeneic red cell transfusion in surgical patients is limited. There is, therefore, a need for large, well designed, randomized trials with a low risk of bias to confirm the optimal strategies for the treatment of anaemia in the perioperative period.

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## Supporting information

Additional supporting information may be found in the online version of this article:

**Table S1** MEDLINE search strategy (Word document)

**Table S2** Embase search strategy (Word document)

**Table S3** Summary of reported outcomes and characteristics (Word document)

**Fig. S1** Form used to extract data from identified studies (Word document)

**Fig. S2** Forest plot showing risk of transfusion in anaemic patients *versus* non-anaemic patients (Word document)

**Fig. S3** Funnel plot for the primary outcome of this analysis (Word document)

**Fig. S4** Forest plot showing composite outcome of 30-day or in-hospital mortality, according to author-defined anaemia and surgical subgroup (Word document)

**Fig. S5** Forest plot showing composite outcome of 30-day or in-hospital mortality after surgery, where anaemia was defined according to the World Health Organization definition (Word document)

## Editor's comments

In this issue of *BJS* a couple of papers focus on bleeding and anaemia. Patient blood management (PBM) reviewed by Clevenger *et al.* (*Br J Surg* 2015; **102**: 1325–1337) is a collection of strategies to improve blood transfusion practices that is adopted by the WHO and spreading across Europe. There is increasing evidence that implementation of PBM is associated with improved clinical outcomes, and the principles of PBM can be used to address anaemia, blood loss and transfusion in the surgical setting.

In this meta-analysis by Fowler *et al.* preoperative anaemia is associated with short-term mortality after surgery and an increased incidence of stroke, acute kidney injury and infection. Allogeneic red cell transfusion was unsurprisingly more common in the presence of anaemia. Although the observed preoperative anaemia is partly related to co-morbidity in the surgical patient, one cannot help wondering whether the outcome could be improved by leaning on the PBM pillars?

*Primum non nocere* as stated in the Hippocratic oath should be adhered to when considering anaemia and transfusion in the surgical patient, instead of a knee-jerk reaction to treat a haemoglobin level on the laboratory chart.

M. Sund
*Editor, BJS*