The association of pre-operative anaemia with post-operative morbidity and mortality: An international prospective observational cohort study in low-, middle- and high-income countries

Running title: Impact of pre-operative anaemia

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Main text: 3,596 words **Summary:** 250 words

Summary

Background

Anaemia is associated with poor post-operative outcomes but few studies have described the impact of pre-operative anaemia in low/middle- (LMIC) and high-income countries (HIC).

Methods

Planned analysis of data collected during an international seven-day cohort study of adults undergoing elective in-patient surgery. The primary outcome was in-hospital death and the secondary outcome was in-hospital complications. Anaemia was defined as haemoglobin <12 g dL^{-1} for females and <13 g dL^{-1} for males. Hierarchical three-level mixed effect logistic regression models were constructed to examine associations between pre-operative anaemia and outcomes. Results are presented as n (%) or odds ratio (OR) with 95% confidence intervals.

Results

We included 38,770 patients from 474 hospitals in 27 countries of whom 11,675 (30.1%) were anaemic. 6,886 (17.8%) patients suffered a complication and 198 (0.5%) died. Patients from LMICs were younger with lower American Society of Anesthesiologists scores, but a similar prevalence of anaemia (LMIC: 5,072/15,585 [32.5%] vs. HIC: 6,603/23,185 [28.5%]). Patients with moderate (OR 2.70 [1.88-3.87]) and severe anaemia (OR 4.09 [1.90-8.81]) were at increased risk of death in both HIC and LMICs. Complication rates increased with the severity of anaemia. Compared to patients in LMICs, those in HICs experienced fewer complications after interaction term analysis (LMIC: OR 0.92 [0.87-0.97] vs. HIC: OR 0.86 [0.84-0.87]; p<0.01).

Conclusions

One third of patients undergoing elective surgery are anaemic. These patients have an increased risk of complications and death. The prevalence of anaemia is similar amongst patients in LMICs despite their younger age and lower risk profile.

Keywords: Anemia; Preoperative care; Perioperative care.

Study Registration: ISRCTN51817007

Introduction

More than 310 million surgical procedures are carried out worldwide each year.[1] Rather than being replaced by novel medical treatments, the number of procedures performed is increasing annually.[1,2] Estimates of post-operative mortality vary between 1-4%, but complications are more frequent.[3–5] While mechanisms underlying morbidity and mortality after surgery are still not fully understood, patients with pre-existing comorbid disease are clearly at greater risk.[3–7] A number of potential mechanisms may account for this, including sub-clinical organ injury, inflammation and underlying chronic infection.[7,8] Reduced tissue oxygen delivery, which is dependent on the oxygen carrying capability of haemoglobin and cardiac output, is associated with poor patient outcomes.[10,11] Anaemia, defined by low haemoglobin concentration in the blood, is a common condition in the general population.[12]

Anaemia is estimated to have a prevalence of up to 90% in some surgical cohorts.[12,13] It is more frequent in low and middle-income countries than high-income nations.[12] A growing body of evidence supports a relationship between pre-operative anaemia and poor post-operative outcomes.[10] Several large cohort studies have identified an association between pre-operative anaemia and post-operative mortality, increased length of stay and the need for critical care admission that persists after adjustment.[12–14] Patients may be anaemic for a number of reasons, including cancer and chronic disease, which also increase perioperative risk. It is unclear to what extent low haemoglobin is a cause of poor outcomes, although some studies suggest this is more than simply a marker of the severity of underlying disease.[15] Previous studies have been restricted to single continents where clinical management is likely to be similar.[15–17] However, these findings did not include low and middle-income countries (LMICs), and are not generalisable to this important population.[18]

In the recent International Surgical Outcomes Study (ISOS) we collected prospective data describing pre-operative anaemia, along with patient outcomes following elective inpatient surgery in 27 countries.[5] We performed a planned secondary analysis of the prevalence of anaemia and the associated post-operative outcomes. We hypothesised that pre-operative anaemia was associated with an increased risk of complications and death after surgery.

Methods

Data Collection

This was a planned secondary analysis of data collected during a 7-day cohort study of elective inpatient surgery in 27 countries. Regulatory requirements differed between countries. In the United Kingdom (UK), the study was approved by the Yorkshire & Humber Research Ethics Committee (Reference: 13/YH/0371). The study website provides all study documentation and guidance (www.isos.org.uk/documents). Participating countries selected a single data collection week between April and August 2014. Countries were classified as LMICs or high-income countries (HIC) as defined previously.[19] Patients were included if they were more than 18 years of age and undergoing elective surgery with a planned overnight stay in hospital. Patients were excluded if they were undergoing a radiological procedure, emergency or day-case surgery. Patients without a documented haemoglobin concentration were excluded from the analysis. Data were included from hospitals that returned valid data for more than 20 patients and from countries that had 10 or more hospitals submitting valid data. Data describing patient characteristics, comorbidities, surgical specialty, grade of surgery (minor, intermediate or major), anaesthetic technique, pre-operative blood test results and post-operative outcomes were collected on paper case record forms before entry onto a dedicated online database system. Detailed methods and the findings of the International Surgical Outcomes Study (ISOS) study have been published elsewhere.[5] ISOS was prospectively registered with an international trial registry (ISRCTN51817007). We have reported our findings in line with the STROBE guidelines.[20]

Outcome measures

The primary outcome for this analysis was in-hospital death and the secondary outcome was in-hospital post-operative complications. Both outcomes were censored at 30 days for those patients remaining in hospital beyond this time point.

Definitions of anaemia

Investigators reported the most recent pre-operative haemoglobin (Hb) concentration measurement within the 28 days preceding surgery. Hb is expressed as grams per decilitre (g dL^{-1}). Anaemia and its sub-classifications were defined according to World Health Organisation (WHO) criteria.[13] No anaemia is defined as a Hb >12 g dL^{-1} for females and >13 g dL^{-1} for males, mild anaemia is a Hb 11.0-11.9 g dL^{-1} for females and 11.0-12.9 g dL^{-1} for males, moderate anaemia is a Hb 8.0-10.9 g dL^{-1} for both males and females, and severe anaemia is a Hb <8.0 g dL^{-1} for both males and females. Additionally, we considered any patient with Hb of >16 g dL^{-1} to have polycythaemia and included this as a further category.[21]

Statistical analysis

No specific power calculation was performed for this observational cohort study, and the sample size was determined by the number of patients recruited across sites. A hierarchical three-level mixed effect logistic regression model was constructed to assess the association between pre-operative anaemia classification and patient outcomes. Patients were entered at the first level, hospitals at the second and countries at the third level. This model accounts for correlation between patients in the same hospital or country. Covariates were included in the model if they were known to be associated with the outcome of interest from previous research or were significantly related to the outcome ($p<0.05$) in univariable analysis. Covariates identified in previous research and included in all models were: age, gender, American Society of Anesthesiologists (ASA) physical status classification system grade, grade of surgery, surgical procedure category, laparoscopic surgery, coronary artery disease, heart failure, stroke, diabetes mellitus, chronic obstructive pulmonary disease/asthma and liver cirrhosis.[6,21–26] Haemoglobin was considered as an ordered categorical variable as defined by WHO anaemia criteria. We used patients without anaemia as the reference category for our analyses. Restricted cubic splines were used to account for the potential non-linear association between pre-operative haemoglobin concentration and mortality or complications. We repeated the primary analysis entering haemoglobin concentrations as splines rather than a categorical variable. We excluded patients with haemoglobin values below 5 g dL^{-1}

from the spline analysis because the relationships with mortality and complications are not reliable due to the low number of elective surgical patients in this category. To examine the possibility that the association of anaemia with increased mortality or morbidity might vary according to level of income of the country and gender of patients, we tested for interactions of haemoglobin with indicators of income and gender. We added two interaction terms to the base model separately, haemoglobin and income level of country, and haemoglobin and gender. We constructed hierarchical three level logistic regression models, subdivided according to national income status as a post-hoc analysis.

Baseline data are presented as mean (standard deviation) and median (interquartile range) for continuous data, and as number (%) for binary data. Results are reported as adjusted odds ratios (OR) and 95% confidence intervals. All analyses were performed using Stata 14 (StataCorp, USA).

Results

Data describing 44,814 patients from 474 hospitals across 27 countries were collected, and of these 38,770 patients were included in our analysis (supplementary figure 1). We excluded 6,044 patients, of whom 6,020 had no haemoglobin value recorded and 24 where haemoglobin was recorded as 0 g dL^{-1}. Excluded patients were younger, with a lower rate of both complications (622 of 6,044 [10.3%]) and death (9 of 6,044 [0.1%]) than the cohort average. Eight of the 27 countries were LMICs and 19 were HIC.[19] 15,585 of 38,770 (40.2%) patients were from LMICs and 23,185 of 38,770 (59.8%) patients were from HICs. Baseline data for excluded patients are presented in supplementary table 1.

Prevalence of anaemia

Baseline characteristics of included patients are presented in table 1 and their treatment in supplementary table 2. The median haemoglobin concentration of the study population was 13.2 (12.0-14.3) g dL^{-1}. Pre-operative anaemia was present in 11,675 of 38,770 (30.1%) patients, of whom 6,074 (52.0%) had mild anaemia, 5,124 (43.9%) had moderate anaemia and 477 (4.1%) severe anaemia. Polycythaemia was present in 500 of 38,770 (1.3%) patients.

National income status

Anaemia was more frequent amongst patients from LMIC (5,072 of 15,585 [32.5%]) than it was in those from HIC (6,603 of 23,185 [28.5%]). Similar proportions of patients suffered from mild and moderate anaemia in LMIC and HIC, but patients in LMIC more frequently suffered from severe anaemia (LMIC: 275 of 5,072 [5.4%]; HIC: 202 of 6,603 [3.1%]). For all categories of anaemia, patients in LMIC were on average more than eight years younger than patients in the same category from HIC (severe anaemia: HIC 60 years, LMIC 52 years; moderate anaemia: HIC 61 years, LMIC 53 years; mild anaemia: HIC 62 years, LMIC 54 years). Most patients in LMICs were ASA grade I and II (13,357 of 15,585 [85.7%]), while 15,130 of 23,185 (65.3%) treated in HICs were ASA grade I or II. 4,943 of 15,585 (31.7%) patients underwent major surgery in LMICs compared to 9,823 of 23,185 patients treated in HIC (42.4%). The largest procedure category in LMICs was head and neck surgery (2,705 of 15,585 [17.4%]) compared to orthopaedics in HICs (5,324 of 23,185 [23.0%]). All comorbid conditions were less frequent amongst patients from LMICs compared to those in HICs. Mortality rates were similar in LMICs (60 of 15,585 [0.4%]) and HICs (138 of 23,185 [0.6%]). Patients from LMICs suffered a lower overall rate of complications (1,787 of 15,585 [11.5%]) compared to those from HICs (5,099 of 23,185 [21.9%]). Baseline characteristics of patients subdivided according to income status of country is shown in supplementary table 3 and categorised by anaemia severity grading is shown in supplementary tables 4 and 5.

Patient outcomes

Overall, 198 of 38,770 (0.5%) patients died before hospital discharge, and 121 of 11,675 (1.0%) anaemic patients died in the same period. All categories of anaemia were associated with an increased risk of death after initial unadjusted analysis (table 2)**.** After hierarchical three-level mixed effect logistic regression modelling, moderate anaemia (OR 2.70 [1.88-3.87]) and severe anaemia (OR 4.09 [1.90-8.81]) were associated with an increased risk of death compared to those without anaemia. There was no significant association between mild anaemia (OR 1.05 [0.68-1.63]) and post-operative death. Polycythaemia was associated with an increased risk of death (OR 3.22 [1.12-9.28]). Figure 1 describes the relationship between haemoglobin concentration and risk of death, after restricted cubic spline modelling. Supplementary table 6 describes the odds of suffering death for each haemoglobin concentration category. Anaemia was associated with increased mortality for patients in HICs and LMICs for patients suffering moderate (HIC: OR 2.64 [1.72-4.03]; LMIC: OR 3.70 [1.84-7.43]) and severe anaemia (HIC: OR 4.28 [1.67-10.97]; LMIC: OR 6.19 [1.61-23.86]), but not mild anaemia (HIC: OR 0.86 [0.50-1.48]; LMIC: OR 1.79 [0.82-3.93]) (supplementary tables 7-9). The results of hierarchical three level regression modelling after sub-dividing according to national income status are presented in supplementary table 9.

Complications occurred in 6,886 of 38,770 (17.8%) patients, and in 2,934 of 11,675 (25.1%) patients with pre-operative anaemia. After hierarchical three-level mixed effect logistic regression modelling, each severity grading of anaemia was associated with an increased risk of complications (supplementary table 10). However, there was no significant relationship between polycythaemia and complications. Anaemic patients were more frequently admitted to intensive care for treatment of a complication, and experienced longer stays in both the intensive care unit and hospital (table 3). Figure 2 describes the relationship between haemoglobin concentration and risk of complications, after restricted cubic spline modelling.

The terms for interaction between income group of country and haemoglobin suggested that LMICs did not have a statistically significant difference in mortality compared to HICs, but patients in HICs had a slightly lower risk of complications compared to LMICs after adjusting for all confounding factors (LMIC: OR 0.92 [0.87-0.97] vs. HIC: OR 0.86 [0.84-0.87]; $p<0.01$) (supplementary table 11). The terms for interaction between gender and haemoglobin suggested there was no statistically significant difference in mortality or complication rates between male and female patients.

Sensitivity analyses

We performed a series of sensitivity analyses. In the first, we excluded patients with a haemoglobin concentration less than 5 g dL^{-1} as potentially erroneous values, and the results of this analysis were unchanged from the primary analysis. We then used the average mortality for the overall cohort as the reference, known as the mean deviation contrast. This compares the mean mortality of each anaemia severity cohort to the mean of the entire population. This is particularly helpful for surgical procedure category where it is better not to set one type of surgical procedure as the reference. Using the mean deviation contrast, mild anaemia was associated with reduced mortality (OR 0.51 [0.34-0.75]), there was no significant association between moderate anaemia and mortality, and severe anaemia continued to be associated with increased mortality (OR 1.98 [1.06-3.69]). Our findings remained similar to the primary analysis when we considered post-operative complications using the population mean risk as a reference value (supplementary table 12). Haemoglobin measurement was missing for 13% of the patients in this study, so a sensitivity analysis was conducted using a multiple imputation model, using ten imputed datasets and estimates combined on the basis of Rubin's rule.[27,28] The effect estimates from multiple imputation were very similar to the complete case analysis for both mortality and complications, apart from for the polycythaemia category. The effect estimates for both outcomes after imputation changed by less than 5% from the original model with no imputation, suggesting our results from complete case analysis have good precision and minimal bias (supplementary table 13).

Post hoc analyses

We explored the association between anaemia and both infection and myocardial infarction. Infection was selected because anaemic patients often receive allogenic blood transfusion, which has previously been associated with increased risk of infection. Patients who were anaemic experienced an increased incidence of post-operative infection (supplementary table 14). Myocardial infarction was selected as insufficient haemoglobin concentration is thought to lead to inadequate oxygen delivery to the myocardium. There was no association between pre-operative anaemia and post-operative myocardial infarction, although the number of myocardial infarction events in our cohort was low (supplementary table 14). After subdividing according to national income status, anaemia was associated with complications and death in both LMIC and HIC (supplementary table 9).

Discussion

In this planned secondary analysis of an international cohort study including low-, middle- and high-income countries, one in three patients presented for surgery with anaemia. Despite being younger, having a lower ASA grading and suffering fewer comorbid conditions, patients from LMICs had a higher prevalence of anaemia than those from HICs. Anaemic patients experienced an increased risk of post-operative complications and death, the association being strongest for the most severely anaemic patients. After subdividing according to national income status, anaemia remained associated with both complications and death after surgery in both LMIC and HIC nations. Interaction term analysis suggested that patients in LMICs were at increased risk of complications, but not death when compared to HICs. Polycythaemia was associated with increased risk of death but not of other complications. More anaemic patients required treatment on an intensive care and experienced longer stays in intensive care and hospital.

More than 40% of the patients included were from LMICs and these patients had a lower aggregate rate of both death and complications after surgery, before adjustment. This may be because patients from LMICs were younger, with less comorbid health conditions and the surgery they were undergoing was of lower severity grade. We are not aware of prior studies investigating the association between pre-operative anaemia and outcomes amongst patients from countries with different income levels. The prevalence of anaemia in the study cohort mirrors the findings of a previous report estimating the global burden of anaemia, which described a prevalence of 32.9%.[12] Previous studies have also suggested an association between pre-operative anaemia and increased rate of death and complications, including a large study of elderly veterans in the United States of America that described a 1.6% increase in mortality for each 1% change in haematocrit.[16] The current data suggest a similar association. However, it remains unclear if anaemia reflects the severity of underlying disease or is mechanistically associated with the poor outcomes we describe.[15] Proposed mechanisms include the reduction of oxygen carrying capability of blood leading to reduced delivery of oxygen to end organs and lower tolerance to bleeding that may occur during or after surgery. In a sensitivity analysis using deviation contrast method to adjust results, mild anaemia was associated with reduced mortality, but other findings were unchanged. This observation contrasts with the findings of a large North American study of more than 220,000 patients where mild anaemia was associated with increased risk of death. However, direct comparison with our data is challenging as they used a haematocrit definition of anaemia, had a four-fold higher crude mortality rate and more than 80% of those who were anaemic in their cohort had mild anaemia.[15] Despite being younger with a more favourable risk profile, patients in LMICs were at an increased risk of complications after adjustment, but had a similar risk of death to those in HICs. This may reflect a different aetiology of anaemia amongst patients in LMICs (e.g. nutritional deficiency compared to cancer), an over-representation of academic centres in the LMIC group, and unmeasured confounding. Further research is required to determine the optimal management of anaemic patients in different healthcare settings. Whilst our analyses suggest a haemoglobin concentration of 15 g dL^{-1} is optimal, the level at which haemoglobin can be considered 'safe' is unclear, or if correction of anaemia improves outcomes. A number of approaches to correct anaemia have been studied, including haematinic replacement, erythropoietin alpha administration to stimulate bone marrow production of red cells and use of autogenic or allogenic blood products.[30–32] An integrated approach to optimise patients pre-operatively, to reduce intra-operative bleeding and to use blood products judiciously has been proposed and is known as 'patient blood management'.[32,33] Patient blood management programmes have been associated with a reduction in transfusion, infection and mortality, and substantial cost savings.[34,35] The correct time at which to transfuse a patient with red cells is controversial. The findings of a recent Cochrane review comparing restrictive transfusion triggers to liberal triggers amongst surgical and medical patients suggest that it reduced amount of blood given, but not patient outcomes.[34 37–43] Our finding that polycythaemia is associated with increased risk of death is consistent with previous studies, but the small number of patients, lack of association after deviation contrast analysis, and wide confidence intervals suggest these observations should be interpreted with caution.[16,41]

This analysis has a number of strengths. It was a planned secondary analysis of a prospective cohort study,[5] with a pre-specified analysis plan. Patients were included from all inhabited continents and included low-, middle-, and high-income countries. ISOS was carefully designed to capture a limited number of outcomes in a very simple way to ensure high quality data collection, with a minimal rate of missing data. Based on the number of patients included, this analysis has >99% power to detect the observed increase in mortality between anaemic and non-anaemic patients of 3.17%. This sample size yielded a power of 80% to detect a difference in mortality as low as 0.018%. There are also several limitations. Haemoglobin values were missing for 6,044 records, and we hypothesised that these patients were judged to be low risk, or undergoing minor procedures such that a clinical decision was made not to measure haemoglobin. Patients with missing haemoglobin data were younger with lower ASA grades and experienced better outcomes, but our findings were unchanged after multiple imputation of missing haemoglobin measurements. Haemoglobin measurement was not standardised and relied on local laboratories to provide accurate data. In addition our findings may not be generalisable to healthcare settings where haematocrit, rather than haemoglobin is more frequently measured. There has been criticism of using gender adjusted haemoglobin to categorise patients.[45] We therefore explored the relationship between pre-operative haemoglobin concentration and outcomes using both the WHO categorisation of anaemia, and also independently of gender using restricted cubic spline modelling and interaction terms. We performed a sensitivity analysis, the findings of which suggest that pre-operative anaemia was associated with increased risk of post-operative infection. However, data were not collected on the use of blood transfusion in the perioperative period and we were unable to explore the relationship between anaemia, transfusion and subsequent infection, which has been described previously.[46] Similarly, we were unable to determine whether for some patients anaemia was corrected before surgery. Previous studies have identified that while the WHO anaemia criteria differ between males and females, in patients undergoing procedures with a high risk of bleeding, comparable amounts of blood are lost, and females therefore receive more blood products.[46,47] We were unable to explore this given the lack of detailed information on perioperative blood loss or transfusion for enrolled patients. Further data points that we did not collect included information pertinent to the aetiology of the anaemia, such as mean corpuscular volume, vitamin levels and iron studies. Outcomes were censored at 30 days or hospital discharge, whichever occurred earlier. Our event rates may therefore be lower than expected, especially in LMIC healthcare systems where patients may be discharged from hospital earlier and experience more complications at home. Thirty day, in-hospital survival may not be considered by patients to reflect a successful surgery, but is an important measure of harm. Future studies should consider more relevant outcome measures, including those developed by the on-going Standardised Endpoints for Perioperative Medicine initiative.[49]

Conclusions

In an international population, one third of patients presented for elective surgery with anaemia, which was associated with an increased incidence of death and complications after surgery. The level of haemoglobin that can be considered 'safe' remains unclear, and further interventional studies are required to determine if correcting pre-operative anaemia improves patient outcomes. Patients in LMIC suffer from a similar prevalence of anaemia, despite their younger age and more favourable risk profile.

Author Contributions

Data collection: International Surgical Outcomes Study Group

Study design: All authors

Statistical analysis: T Ahmad

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Critical review and approval of final manuscript: All authors

Acknowledgements

The authors thank Naomi Pritchard, the patient representative for ISOS.

Declaration of Interests

RP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, Glaxo Smithkline, Intersurgical, and Edwards Lifesciences, and is a member of the Associate editorial board of the British Journal of Anaesthesia. All other authors declare no conflicts of interests.

Funding

ISOS was an investigator initiated study funded by Nestle Health Sciences through an unrestricted research grant, and by a National Institute for Health Research Professorship held by RP, and sponsored by Queen Mary University of London. LSR is supported by funding from the Tryg Foundation.

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Tables (incl. legends of tables)

	All patients (n = 38,770)	No anaemia (n = 26,595)	Polycythaemia (n = 500)	Mild anaemia (n = 6,074)	Moderate anaemia (n=5,124)	Severe anaemia (n=477)
Mean age (SD)	55.8 (16.9)	54.9 (16.4)	51.8 (16.2)	58.8 (17.5)	57.5 (18.2)	55.3 (17.7)
Median age (IQR)	57 (43-69)	56 (43-67)	53 (39-65)	61 (46-73)	59 (43-72)	55 (42-69)
Males (%)	17694 (45.6)	12092 (45.5)	343 (68.6)	3180 (52.3)	1880 (36.7)	199 (41.7)
Females (%)	21076 (54.4)	14503 (54.5)	157 (31.4)	2894 (47.7)	3244 (63.3)	278 (58.3)
Current smoker (%)	6804 (17.6)	5010 (18.9)	185 (37.2)	908 (15.0)	640 (12.6)	61 (12.8)
ASA grade (%)						
I	9173 (23.7)	7014 (26.4)	125 (25.0)	1140 (18.8)	824 (16.1)	70 (14.7)
II	19314 (49.9)	13824 (52.1)	263 (52.6)	2858 (47.2)	2172 (42.3)	197 (41.3)
III	9239 (23.9)	5279 (19.9)	102 (20.4)	1845 (30.5)	1837 (35.9)	176 (36.9)
IV	985 (2.5)	439 (1.7)	10 (2.0)	216 (3.6)	286 (5.6)	34 (7.1)
Pre-operative Hb, mean (SD)	13.04 (2.0)	13.9 (1.12)	17.2 (0.79)	11.9 (0.52)	10.0 (0.82)	6.0 (2.50)
Pre-operative Hb, median (IQR)	13.2 (12 - 14.3)	13.9 (13.1 - 14.7)	17.1 (16.7 - 17.6)	11.8 (11.4 - 12.2)	10.1 (9.4 - 10.7)	7.2 (6.1 - 7.7)
Grade of surgery, n (%)						
Minor	6776 (17.5)	4727 (17.8)	111 (22.2)	979 (16.1)	876 (17.1)	83 (17.4)
Intermediate	17209 (44.4)	12182 (45.8)	228 (45.6)	2586 (42.6)	2024 (39.5)	189 (39.7)
Major	14766 (38.1)	9672 (36.4)	161 (32.2)	2509 (41.3)	2220 (43.4)	204 (42.9)
Surgical specialty, n (%)						
Orthopaedic	7880 (20.3)	5535 (20.8)	104 (20.8)	1144 (18.8)	1012 (19.8)	85 (17.8)
Breast	1358 (3.5)	1053 (4.0)	11 (2.2)	163 (2.7)	126 (2.5)	5 (1.1)
Obstetrics & gynaecology	5057 (13.1)	3226 (12.1)	29 (5.8)	817 (13.5)	911 (17.8)	74 (15.5)
Urology & kidney	4260 (11.0)	2876 (10.8)	69 (13.8)	738 (12.1)	533 (10.4)	44 (9.2)
Upper gastrointestinal	1774 (4.6)	1106 (4.2)	13 (2.6)	336 (5.5)	275 (5.4)	44 (9.2)

Lower gastrointestinal	2765 (7.1)	1686 (6.3)	30 (6.0)	515 (8.5)	485 (9.5)	43 (10.3)
Hepato-biliary	2116 (5.5)	1498 (5.6)	22 (4.4)	345 (5.7)	219 (4.3)	32 (6.7)
Vascular	1464 (3.8)	857 (3.2)	16 (3.2)	273 (4.5)	290 (5.7)	28 (5.9)
Head and neck	5298 (13.7)	4112 (15.5)	104 (20.8)	653 (10.8)	387 (7.6)	42 (8.8)
Plastic or cutaneous	1273 (3.3)	840 (3.2)	20 (4.0)	169 (2.8)	222 (4.3)	22 (4.6)
Cardiac	1656 (4.3)	1075 (4.0)	20 (4.0)	333 (5.5)	211 (4.1)	17 (3.6)
Thoracic (lung & other)	1095 (2.8)	721 (2.7)	17 (3.4)	200 (3.3)	145 (2.8)	12 (2.5)
Other	2769 (7.1)	2006 (7.5)	44 (8.8)	388 (6.4)	308 (6.0)	23 (4.8)
Laparoscopic surgery, n (%)	6339 (16.3)	4622 (17.4)	67 (13.4)	900 (14.8)	671 (13.1)	79 (16.6)
Comorbid disorder, n (%)						
Coronary artery disease	4181 (10.8)	2530 (9.5)	48 (9.6)	856 (14.1)	696 (13.6)	51 (10.8)
Heart failure	1717 (4.4)	901 (3.4)	14 (2.8)	350 (5.8)	410 (8.0)	42 (8.9)
Diabetes mellitus	4599 (11.9)	2614 (9.9)	42 (8.4)	942 (15.6)	932 (18.2)	69 (14.6)
Cirrhosis	310 (0.80)	159 (0.6)	2 (0.4)	65 (1.1)	75 (1.5)	9 (1.9)
Metastatic cancer	1566 (4.1)	854 (3.2)	14 (2.8)	330 (5.5)	346 (6.8)	22 (4.7)
Stroke	1325 (3.4)	781 (2.9)	13 (2.6)	257 (4.2)	256 (5.0)	18 (3.8)
COPD/Asthma	3449 (8.9)	2313 (8.7)	62 (12.4)	575 (9.5)	462 (9.0)	37 (7.8)
National income status n (%)						
Low/middle-income	15585 (40.2)	10314 (38.8)	199 (39.8)	2514 (41.4)	2283 (44.6)	275 (57.7)
High-income	23185 (59.8)	16281 (61.2)	301 (60.2)	3560 (58.6)	2841 (55.4)	202 (42.3)

Table 1. Baseline characteristics of included surgical patients, stratified according to pre-operative haemoglobin level. Hb, haemoglobin given in grams per decilitre; ASA, American Society of Anesthesiologists physical status classification system grading; COPD, chronic obstructive pulmonary disease; SD, standard deviation; IQR, inter-quartile range. No anaemia = Hb >12 g dL^{-1} for females and >13 g dL^{-1} for males, Mild anaemia = Hb 11-11.9 g dL^{-1} for females and 11-12.9 g dL^{-1} for males, moderate anaemia = Hb 8-10.9 g dL^{-1} for both males and females, severe anaemia = Hb <8.0 g dL^{-1} for both males and females, polycythaemia = Hb >16g dL^{-1} for males and females.

	Unadjusted association			Multivariable analysis		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Age	1.06	1.05 - 1.07	<0.01	1.02	1.01 - 1.04	<0.01
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.57	0.43 - 0.75	<0.01	0.85	0.61 - 1.17	0.32
Smoker	1.27	0.90 - 1.78	0.17	1.47	0.93 - 2.01	0.12
Anaemia category						
No anaemia	Reference	Reference	Reference	Reference	Reference	Reference
Polycythaemia	2.93	1.07 - 8.05	0.04	3.22	1.12 - 9.28	0.03
Mild anaemia	2.04	1.36 - 3.08	<0.01	1.05	0.68 - 1.63	0.82
Moderate anaemia	5.54	4.02 - 7.64	<0.01	2.70	1.88 - 3.87	<0.01
Severe anaemia	7.78	3.99 - 15.2	<0.01	4.09	1.90 - 8.81	<0.01
Grade of surgery						
Minor	Reference	Reference	Reference	Reference	Reference	Reference
Intermediate	1.44	0.79 - 2.60	0.23	1.51	0.81 - 2.81	0.20
Major	4.39	2.53 - 7.62	<0.01	2.64	1.44 - 4.84	<0.01
ASA grade						
I	Reference	Reference	Reference	Reference	Reference	Reference
II	16.65	2.28 - 121.56	<0.01	6.35	0.85 - 47.30	0.07
III	110.52	15.43 - 791.75	<0.01	17.60	2.36 - 131.30	<0.01
IV	511.19	70.59 - 3701.958	<0.01	49.05	6.33 - 379.79	<0.01
Surgical procedure category						
Orthopaedic	Reference	Reference	Reference	Reference	Reference	Reference
Breast	0.24	0.03 - 1.78	0.16	0.57	0.07 - 4.38	0.59
Obstetrics & gynaecology	0.26	0.09 - 0.75	0.01	0.97	0.32 - 2.94	0.95

Urology & kidney	0.69	0.33 - 1.50	0.35	0.82	0.36 - 1.83	0.62
Upper gastrointestinal	5.44	3.16 - 9.37	<0.01	5.09	2.76 - 9.38	<0.01
Lower gastrointestinal	3.83	2.25 - 6.52	<0.01	3.44	1.90 - 6.21	<0.01
Hepato-biliary	2.02	1.03 - 3.98	0.04	3.40	1.60 - 7.20	<0.01
Vascular	3.16	1.63 - 6.12	<0.01	1.43	0.70 - 2.90	0.32
Head and neck	0.74	0.37 - 1.49	0.4	1.21	0.58 - 2.54	0.61
Plastic or cutaneous	1.03	0.34 - 2.98	0.95	1.16	0.38 - 3.52	0.80
Cardiac	8.1	4.87 - 13.48	<0.01	2.79	1.52 - 5.11	<0.01
Thoracic (lung & other)	3.02	1.44 - 6.32	<0.01	2.31	1.02 - 5.20	0.04
Other	0.71	0.29 - 1.74	0.46	1.15	0.45 - 2.95	0.77
Laparoscopic	0.42	0.25 - 0.71	<0.01	0.43	0.24 - 0.79	<0.01
Comorbid disorder						
Coronary artery disease	4.08	3.03 - 5.50	<0.01	1.12	0.78 - 1.62	0.53
Heart failure	6.67	4.78 - 9.31	<0.01	1.33	0.89 - 1.99	0.16
Diabetes mellitus	2.88	2.10 - 3.93	<0.01	1.14	0.80 - 1.61	0.47
Cirrhosis	6.77	3.55 - 12.92	<0.01	2.55	1.21 - 5.39	0.01
Metastatic cancer	5.18	3.58 - 7.49	<0.01	3.10	2.02 - 1.80	<0.01
Stroke	6.41	4.45 - 9.24	<0.01	2.70	1.78 - 4.09	<0.01
COPD/Asthma	2.36	1.65 - 3.38	<0.01	1.18	0.80 - 1.76	0.40
Other	2.64	1.97 - 3.55	<0.01	1.46	1.04 - 2.03	0.03

Table 2. Association between pre-operative haemoglobin level and in-hospital mortality within 30 days of surgery. Multivariable model Odds ratios (OR) are adjusted for age, gender, ASA grade, grade of surgery, surgical procedure category, level of anaemia, laparoscopic surgery, presence of absence of coronary artery disease, heart failure, stroke, diabetes mellitus, COPD/Asthma, cirrhosis and other comorbidities in a three-level mixed effect logistic regression model (with patient as first level, hospital as the second and country at the third). ASA, American Society of Anesthesiologists physical status classification system grading; COPD, chronic obstructive pulmonary disease; N/A, factor dropped as it was not significant in univariate modelling.

	All patients (n = 8,770)	No anaemia (n = 26,595)	Polycythaemia (n = 500)	Mild anaemia (n = 6,074)	Moderate anaemia (n=5,124)	Severe anaemia (n=477)
In-hospital mortality	198 (0.5)	73 (0.3)	4 (0.8)	34 (0.6)	77 (1.5)	10 (2.1)
Complications	6886 (17.8)	3891 (14.6)	51 (12.2)	1361 (22.4)	1444 (28.2)	129 (27.0)
Infection	2862 (7.4)	1478 (5.6)	25 (5.0)	600 (9.9)	695 (13.6)	64 (13.4)
Cardiovascular complications	1534 (4.0)	871 (3.3)	15 (3.0)	323 (5.3)	298 (5.8)	27 (5.7)
Other complications	4343 (11.2)	2408 (9.1)	36 (7.2)	857 (14.1)	943 (18.4)	99 (20.8)
ICU admission to treat a complication	1158 (3.0)	572 (2.2)	15 (3.0)	226 (3.7)	310 (6.1)	35 (7.3)
ICU stay (days)						
Mean (SD)	0.4 (1.8)	0.4 (2.0)	0.3 (1.8)	0.7 (2.8)	0.7 (2.8)	1.2 (4.2)
Median (IQR)	0 (0-0)	0 (0-0)	0(0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Hospital stay (days)						
Mean (SD)	5.8 (5.7)	5.0 (4.9)	4.9 (5.3)	6.7 (6.3)	8.3 (7.6)	9.6 (8.3)
Median (IQR)	4 (2-7)	4 (2-7)	3 (2-6)	5 (2-8)	6 (3-11)	7 (4-12)

Table 3. Outcome and process measures for surgical patients, stratified according to pre-operative haemoglobin level. ICU, Intensive care unit; SD, Standard deviation; IQR, Interquartile range. Data are presented as n (%) unless indicated otherwise.

Figure Legends

Figure 1. Restricted cubic splines graph of the relationship between haemoglobin and risk of in-hospital death within 30 days of surgery. Number of surgical patients summarised by vertical bars, red line showing odds ratio of death for given level of haemoglobin and 95% confidence interval in grey.

Figure 2. Restricted cubic splines graph of the relationship between haemoglobin and risk of in-hospital complications within 30 days of surgery. Number of surgical patients summarised by vertical bars, blue line showing odds ratio of complications for given level of haemoglobin and 95% confidence interval in grey.