Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study

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For the **ACS NSQIP database** see http://www.acsnsqip.org

Summary

Background **Preoperative anaemia is associated with adverse outcomes after cardiac surgery but outcomes after non-cardiac surgery are not well established. We aimed to assess the effect of preoperative anaemia on 30-day postoperative morbidity and mortality in patients undergoing major non-cardiac surgery.**

Methods **We analysed data for patients undergoing major non-cardiac surgery in 2008 from The American College of Surgeons' National Surgical Quality Improvement Program database (a prospective validated outcomes registry from 211 hospitals worldwide in 2008). We obtained anonymised data for 30-day mortality and morbidity (cardiac, respiratory, CNS, urinary tract, wound, sepsis, and venous thromboembolism outcomes), demographics, and preoperative and perioperative risk factors. We used multivariate logistic regression to assess the adjusted and modified (nine predefined risk factor subgroups) effect of anaemia, which was defined as mild (haematocrit concentration >29–<39% in men and >29–<36% in women) or moderate-to-severe (≤29% in men and women) on postoperative outcomes.**

Findings **We obtained data for 227 425 patients, of whom 69 229 (30·44%) had preoperative anaemia. After adjustment, postoperative mortality at 30 days was higher in patients with anaemia than in those without anaemia (odds ratio [OR] 1·42, 95% CI 1·31–1·54); this difference was consistent in mild anaemia (1·41, 1·30–1·53) and moderate-to-severe anaemia (1·44, 1·29–1·60). Composite postoperative morbidity at 30 days was also higher in patients with anaemia than in those without anaemia (adjusted OR 1·35, 1·30–1·40), again consistent in patients with mild anaemia (1·31, 1·26–1·36) and moderate-to-severe anaemia (1·56, 1·47–1·66). When compared with patients without anaemia or a defined risk factor, patients with anaemia and most risk factors had a higher adjusted OR for 30-day mortality and morbidity than did patients with either anaemia or the risk factor alone.**

Interpretation **Preoperative anaemia, even to a mild degree, is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery.**

Funding **Vifor Pharma.**

Introduction

Preoperative anaemia is associated with increased morbidity and mortality in patients undergoing cardiac surgery.[1–3] Although haematocrit concentrations are almost always measured before major non-cardiac surgery,[4] few studies have explored the implications of preoperative anaemia on postoperative outcomes. Preoperative anaemia is usually regarded as a risk factor because of its association with increased perioperative transfusions of blood components.[5–8] Perioperative transfusion is associated with increased morbidity and mortality, even when as little as one unit of packed red blood cells is administered.[9–11] Several studies[12–17] have tried to assess whether anaemia is independently associated with harmful effects in addition to the risks caused by an increased need for transfusion. However, such studies have had small sample sizes,[12–15] been undertaken only in specific subgroups such as elderly patients[16] or individual surgery types,[12,17] included patients undergoing emergency surgery without stratification of outcomes,[16] or failed to adjust for the major known confounders, especially the use of perioperative transfusions.[13,16] Furthermore, most of these studies assessed only the outcomes of mortality or cardiac morbidity, leaving other serious complications unexplored.

With these limitations in mind, we aimed to establish whether patients with preoperative anaemia undergoing major non-cardiac surgery were less likely to survive or more likely to have major morbidities than were patients without anaemia from an analysis of a large dataset from the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP).

Methods

Study design and data collection

We analysed data from the ACS NSQIP database (panel 1). This database is a prospective validated outcomes registry designed to provide feedback to member hospitals about 30-day risk-adjusted surgical mortality and morbidity,[18,19] and includes anonymised data for patients' demographics, functional statuses, admission sources, preoperative risk factors, and laboratory data, perioperative variables, and 30-day postoperative outcomes for patients undergoing major surgery in more than 200 participating

non-Veterans' Affairs administration hospitals.[18] Trained surgical clinical reviewers obtain data for patients on admission from the medical chart, operative log, anaesthesia record, interviews with the surgical attending, and telephone interviews with patients.[18] For this study, the ACS NSQIP participant use file for 2008 was retrieved for all major surgeries undertaken at participating ACS NSQIP medical centres.

From this file, we identified 271 368 patients who had undergone major surgery in 2008. No patient was included in the database twice and only the index case was used for patients who had more than one procedure in 2008. We excluded 1898 patients who underwent cardiac surgery and 7131 patients who underwent minor procedures with a work relative value unit (a measure of surgical complexity) of 0. We also excluded patients with missing information about preoperative haematocrit concentrations (34 905 patients) and sex (nine patients) because these parameters were used to define anaemia. We did the main analysis for 227 425 patients who underwent major non-cardiac surgery. In accordance with the American University of Beirut's guidelines (which follow the US Code of Federal Regulations for the Protection of Human Subjects), institutional review board approval was not needed or sought for our analysis because data were collected as part of a quality assurance activity.

Procedures

We defined preoperative haematocrit concentrations as the last haematocrit measurement before the index operation. We defined preoperative anaemia as a haematocrit concentration of less than 36·0% for women and less than 39·0% for men according to WHO's sex-based criteria.[21] Patients with anaemia were further divided into two groups: mild anaemia (haematocrit >29·0–<36·0% for women and >29·0–<39·0% for men) and moderate-severe anaemia (haematocrit ≤29% for men and women), according to previous studies.[17,22]

Postoperative outcomes were mortality and morbidity at 30 days, including events affecting the heart (acute myocardial infarction or cardiac arrest necessitating cardiopulmonary resuscitation), respiratory tract (pneumonia, ventilator support for >48 h, or unplanned intubation), CNS (cerebrovascular accident or coma lasting >24 h), urinary tract (progressive renal insufficiency or acute renal failure), wound (deep incisional surgical site infection, organ or space surgical site infection, or wound dehiscence), and sepsis (sepsis or septic shock) or venous thromboembolism (deep venous thrombosis or pulmonary embolism). We defined composite morbidity as one or more of these major morbidities.

Statistical analysis

We defined demographics and preoperative and perioperative variables between preoperative haematocrit groups (no anaemia *vs* anaemia, no anaemia *vs* mild anaemia, and no anaemia *vs* moderate-severe anaemia) with the χ^2 test for categorical variables and the independent samples *t* test for continuous variables. The primary outcome measure was death within 30 days of

Panel 1: The American College of Surgeons' National Surgical Quality Improvement Program (ASC NSQIP)

Aim

The ACS NSQIP was set up as a rigorous data collection network for measurement of surgical outcomes. The ACS NSQIP gathers data for various clinical variables, including preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes for patients undergoing major surgical procedures in the inpatient and outpatient settings. Data quality is ensured through comprehensive training of the nurse reviewers, an inter-rater reliability audit of participating sites, regular conference calls, and an annual meeting.[20] By use of validated statistical methods that were developed and tested in large population-based studies, the ACS NSQIP program generates an expected outcome based on the case complexity mixes. The observed outcomes are then compared with the expected outcomes to obtain an observed to expected ratio and estimate outcomes for a specific medical centre with regard to the national average. These data are then used to identify areas in need of quality improvement.

Participants

Contribution to the ACS NSQIP is voluntary. Non-Veterans' Affairs hospitals sign-up for inclusion into the ACS NSQIP database and enter cases prospectively into this database. At present, 282 hospitals import data to the ACS NSQIP database. Participating hospitals are located in 42 states in the USA and five sites in three Canadian provinces. Other international sites include one in Lebanon and one in the United Arab Emirates. 51% of the enrolled medical centres are classified as academic or teaching centres and 49% are non-teaching sites. 47% of participating medical centres have more than 500 beds, 44% have 300–499 beds, 6% have 100–299 beds, and 3% have fewer than 100 beds.

Inclusion and exclusion of cases

The ACS NSQIP includes all major surgeries as determined by current procedural terminology (CPT) codes. The ACS NSQIP has developed a comprehensive CPT code inclusion list available online. Exclusions include:

- Patients younger than 16 years (<18 years from 2008).
- Cases listed on the CPT code exclusion list (available online).
- Trauma cases (specifically patients who are admitted to hospital with acute trauma and have surgery(ies) for that trauma will be excluded; any operation done after the patient has been discharged from the trauma stay will be included).
- Transplantations (specifically patients who are admitted to the hospital for a transplantation and has a transplantation procedure and any additional surgical procedure during the hospitalisation will be excluded; any operation done after the patient has been discharged from the transplantation stay will be included).
- American Society of Anesthesiologists score 6 (brain-death organ donors).
- Concurrent cases (an additional operative procedure undertaken by a different surgical team under the same anaesthetic; for example, coronary artery bypass graft procedure on a patient who is also undergoing a carotid endarterectomy. An assessment is not required on the concurrent procedure; however, this procedure would be reported as concurrent in the operative section for the assessed case).
- To ensure a diverse surgical casemix, the following criteria are also excluded (at each centre):
  - More than three inguinal herniorrhaphies in 8 days
  - More than three breast lumpectomies in 8 days
  - More than three laparoscopic cholecystectomies in 8 days
  - If the site is collecting urology cases, more than three transurethral resections of the prostate or transurethral resections of bladder tumour in 8 days

	No anaemia (n=158 196)	Mild anaemia (n=57 870)	Moderate-to-severe anaemia (n=11 359)	Any anaemia (n=69 229)
General variables				
Age ≥65 years	29·43%	46·96%***	46·88%***	46·95%***
Sex (female)	59·67%	52·61%***	54·58%***	52·94%***
Race (white)	78·61%	73·20%***	68·96%***	72·51%***
Surgical subspecialty				
General	73·83%	68·86%***	67·60%***	68·65%***
Vascular	10·9%	19·44%***	24·78%***	20·31%***
Orthopaedic	5·08%	4·17%***	2·77%***	3·94%***
Other†	10·19%	7·54%***	4·84%***	7·09%***
Mean work relative value unit‡ (SD)	16·49 (8·81)	18·50 (9·58)***	18·96 (9·68)***	18·65 (9·65)***
General anaesthesia	91·92%	91·95%	93·37%***	92·18%*
ASA class§				
I–II	60·34%	35·48%***	18·60%***	32·71%***
III	35·65%	51·12%***	50·86%***	51·07%***
IV–V	4·01%	13·40%***	30·55%***	16·21%***
Airway trauma	0·26%	0·27%	0·30%	0·27%
Infected surgical wound class	5·26%	11·44%***	22·82%***	13·31%***
Mean total operation time in min (SD)	108·27 (86·65)	125·28 (99·85)***	123·16 (98·24)***	124·93 (99·59)***
Inpatient status	65·62%	82·53%***	93·51%***	84·34%***
Days from admission to operation				
0	90·26%	64·41%***	33·80%***	59·39 %***
1	5·31%	10·63%***	13·03%***	11·02%***
>1	4·43%	24·96%***	53·17%***	29·59%***
Emergency case	13·14%	15·27%***	28·65%***	17·46%***
Perioperative transfusion¶	2·52%	10·49%***	35·88%***	14·65%***
Do-not-resuscitate status	0·32%	1·46%***	2·90%***	1·70%***
Functional status				
Independent	96·71%	86·01%***	65·49%***	82·64%***
Partially dependent	2·64%	10·16%***	19·78%***	11·74%***
Dependent	0·65%	3·84%***	14·73%***	5·62%***
Cardiovascular variables				
Dysponea at rest or with moderate exertion	10·04%	14·79%***	19·59%***	15·58%***
Congestive heart failure in previous 30 days	0·33%	2·01%***	4·64%***	2·44%***
Angina in previous 30 days	0·53%	1·32%***	2·97%***	1·43%***
Myocardial infarction in previous 6 months	0·29%	1·42%***	2·00%***	1·68%***
Previous percutaneous coronary intervention	4·68%	8·96%***	8·72%***	8·92%***
Previous cardiac surgery	4·37%	10·87%***	12·22%***	11·09%***
Hypertension requiring medication	43·53%	58·09%***	60·92%***	58·55%***
History of peripheral vascular disease‖	2·60%	8·11%***	13·67%***	9·02%***
Rest pain or gangrene	1·29%	5·16%***	9·79%***	5·92%***
Respiratory variables				
Tobacco use in past year	21·45%	19·11%***	22·63%**	19·69%***
Current pneumonia	0·15%	1·15%***	4·23%***	1·66%***
History of severe COPD	4·15%	7·68%***	9·81%***	8·03%***
Ventilator-dependent in previous 48 h	0·25%	1·70%***	9·45%***	2·97%***
Hepatobiliary variables				
Ascites in 30 previous days	0·41%	1·75%	5·31%***	2·33%***
Oesophageal varices in previous 6 months	0·07%	0·24%***	0·62%***	0·30%***
Renal variables				
Acute renal failure	0·21%	1·23%	4·22%***	1·72%***
Presently on dialysis	1·02%	4·55%***	9·85%***	5·42%***

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	No anaemia (n=158 196)	Mild anaemia (n=57 870)	Moderate-to-severe anaemia (n=11 359)	Any anaemia (n=69 229)
(Continued from previous page)				
Neurological variables				
Impaired sensorium in previous 48 h	0·32%	1·59%***	4·99%***	2·15%***
Hemiplegia	0·69%	1·69%***	2·31%***	1·79%***
Paraplegia	0·41%	0·89%***	1·72%***	1·03%***
Quadraplegia	0·08%	0·23%***	0·39%***	0·26%***
Coma lasting >24 h	0·03%	0·12%***	0·67%***	0·21%***
History of transient ischaemic attacks	2·78%	4·56%***	4·44%***	4·54%***
History of CVA with neurological deficit	1·78%	4·19%***	5·88%***	4·47%***
History of CVA without neurological deficit	1·66%	3·42%	4·51%***	3·60%***
Tumour involving CNS	0·19%	0·25%**	0·31%**	0·26%**
Haemato-oncological variables				
Bleeding disorder	3·87%	10·15%***	18·59%***	11·54%***
Weight loss >10% in previous 6 months	1·32%	4·64%***	8·83%***	5·32%***
Disseminated cancer	1·31%	3·81%***	6·20%***	4·20%***
Chemotherapy in previous 30 days	0·54%	2·30%***	3·92%***	2·57%***
Radiotherapy in previous 90 days	0·5%	1·48%***	1·59%***	1·50%***
Other variables				
Body-mass index ≥30 kg/m²	41·04%	32·93%***	30·35%***	32·51%***
Diabetic on oral drugs or insulin	12·29%	23·17%***	28·83%***	24·10%***
Alcohol intake in previous 2 weeks††	2·65%	2·79%	3·08%**	2·84%*
Open wound (with or without infection)	1·99%	9·91%***	24·10%***	12·24%***
Steroid use for chronic condition	2·18%	5·25%***	8·21%***	5·74%***
Systemic sepsis in previous 48 h	7·06%	13·15%***	33·12%***	16·43%***
Pregnancy	0·16%	0·60%***	0·76%***	0·62%***
Operation within previous 30 days	1·3%	5·71%***	18·28%***	7·77%***
Preoperative laboratory studies				
Serum sodium ≤135 mmol/L	9·17%	17·62%***	27·92%***	19·35%***
Serum sodium >145 mmol/L	0·89%	1·33%***	2·85%***	1·58%***
Blood urea nitrogen >14·3 mmol/L	1·48%	6·78%***	14·82%***	8·15%***
Serum creatinine >106·1 µmol/L	9·73%	24·03%***	34·40%***	25·78%***
Mean serum albumin, g/L (SD)	40·8 (5·3)	35·0 (7·4)***	28·6 (8·4)***	33·9 (8·0)***
Total bilirubin >17·1 µmol/L	12·91%	14·15%***	19·97%***	15·21%***
Alanine aminotransferase >40 U/L	10·67%	15·60%***	21·55%***	16·67%***
Alkaline phosphatase >125 U/L	8·04%	17·44%***	25·73%***	18·94%***
White-blood-cell count >11 000 cells per µl	16·35%	18·33%***	32·88%***	20·73%***
Platelet count ≤150 000 cells per µl	4·30%	9·60%***	18·10%***	11·00%***
International normalised ratio >1·4	3·43%	8·04%***	17·60%***	9·95%***
Days from haematocrit measurement to operation				
<14	78·42%	85·51%***	93·81%***	86·87%***
<28	92·02%	94·24%***	96·90%***	94·68%***
<56	97·79%	98·35%***	98·87%***	98·44%***

Mild anaemia was defined as a haematocrit concentration of >29–<39% in men and >29–<36% in women. Moderate-to-severe anaemia was defined as a haematocrit concentration of ≤29%. Data are percentage of patients, unless otherwise indicated. ASA=American Society of Anesthesiologists. CVA=cerebrovascular accident. *p<0·05 compared with no anaemia group. **p<0·01 compared with no anaemia group. ***p<0·0001 compared with no anaemia group. †Gynaecological, urological, neurosurgery, otolaryngological, plastic, or thoracic. ‡Work relative value unit is a scale (0–95) to quantify the amount of work involved in a specific surgery on the basis of preprocedural, intraprocedural, and postprocedural time, technical skill, physical effort, mental effort and judgment, and stress due to potential risk; the scale is the work portion of the Resource-based Relative Value System adopted by US Medicare to quantify the amount of work involved in every medical procedure (score of 0=least complex and 95=most complex). §ASA scores: I is a healthy patient; II is mild systemic disease but no functional limitations; III is severe systemic disease with definite functional limitations; IV is severe systemic disease that is a constant threat to life; and V is a moribund patient unlikely to survive 24 h with or without an operation. ¶Transfusion of more than four packed red blood cell units within 72 h preoperatively, any number of units transfused intraoperatively, or transfusion of more than four units within 72 h postoperatively. ||Requiring revascularisation, angioplasty, or amputation. ††>two drinks per day.

Table 1: **Baseline characteristics of patients**

the index surgery in the preoperative anaemia group compared with the no anaemia group.

See Online for webappendix

The secondary study outcome measure was occurrence of morbidity (composite and individual morbidities) within 30 days of the index surgery in the preoperative anaemia compared with the no anaemia group. We subdivided the analysis to compare patients with mild anaemia or moderate-to-severe anaemia with the patients without anaemia.

We created separate multivariate logistic regression models for 30-day mortality, composite morbidity, and for individual morbidity types with adjusted odds ratios (OR_{adj}). We built models by adjustment for the determinant variable (preoperative haematocrit category) to potential confounders of clinical relevance. Two levels of adjustment were used: model 1 (OR_{adj-1}) had a basic adjustment for the most clinically relevant variables and model 2 (OR_{adj-2}) had an extended adjustment for a larger number of clinically relevant variables as described in webappendix pp 1–4. Data were almost complete, apart from some missing values for preoperative laboratory studies. Webappendix pp 1–4 details the frequency of missing values and the method used for imputation. We assessed model discrimination in terms of the *C* statistic. We also analysed data in model 2 separately for different age groups, sexes, surgical subspecialties, and duration from haematocrit measurement to operation, as well as for emergency status versus non-emergency status and receipt versus non-receipt of perioperative transfusions (stratified by duration from admission to operation).

To assess the effect of the 34 905 excluded patients without preoperative haematocrit values for the reported association between anaemia and outcomes, we did two

	No anaemia (n=158 196)	Mild anaemia (n=57 870)	Moderate-to-severe anaemia (n=11 359)	Any anaemia (n=69 229)
Mortality				
n	1240 (0·78%)	2037 (3·52%)	1155 (10·17%)	3192 (4·61%)
$OR_{unadjusted}$	Reference	4·62 (4·30–4·96)	14·33 (13·19–15·56)	6·12 (5·73–6·54)
OR_{adj-1}	Reference	1·67 (1·54–1·80)	2·40 (2·18–2·65)	1·83 (1·70–1·97)
OR_{adj-2}	Reference	1·41 (1·30–1·53)	1·44 (1·29–1·60)	1·42 (1·31–1·54)
Strata OR_{adj-2}				
Age				
65 years (n=148 364)	Reference	1·67 (1·42–1·97)	1·69 (1·39–2·06)	1·68 (1·43–1·96)
<40 years (n=41 077)	Reference	1·95 (1·08–3·51)	1·86 (0·92–3·74)	1·93 (1·09–3·41)
40–<65 years (n=107 287)	Reference	1·65 (1·39–1·95)	1·69 (1·38–2·08)	1·66 (1·41–1·95)
≥65 years (n=79 061)	Reference	1·39 (1·26–1·52)	1·42 (1·25–1·61)	1·39 (1·27–1·53)
65–85 years (n=71 901)	Reference	1·36 (1·23–1·52)	1·40 (1·22–1·62)	1·37 (1·24–1·52)
>85 years (n=7160)	Reference	1·28 (1·04–1·57)	1·43 (1·07–1·92)	1·31 (1·07–1·59)
Sex				
Male (n=96 385)	Reference	1·58 (1·41–1·77)	1·61 (1·38–1·87)	1·59 (1·42–1·77)
Female (n=131 040)	Reference	1·37 (1·22–1·54)	1·45 (1·25–1·68)	1·39 (1·25–1·55)
Surgical subspecialty				
General (n=164 330)	Reference	1·46 (1·32–1·61)	1·54 (1·35–1·75)	1·48 (1·34–1·63)
Vascular (n=31 311)	Reference	1·45 (1·24–1·70)	1·42 (1·16–1·75)	1·44 (1·24–1·68)
Orthopaedic (n=10 758)	Reference	1·45 (1·01–2·55)	1·24 (0·81–3·03)	1·42 (1·02–2·48)
Other* (n=21 026)	Reference	1·52 (1·04–2·21)	1·55 (0·86–2·78)	1·52 (1·05–2·20)
Emergency case				
No (n=194 542)	Reference	1·85 (1·66–2·06)	2·09 (1·80–2·43)	1·89 (1·70–2·10)
Yes (n=32 883)	Reference	1·00 (0·89–1·13)	0·96 (0·82–1·11)	0·99 (0·88–1·11)
Perioperative transfusion				
No (n=213 295)	Reference	1·56 (1·42–1·72)	1·84 (1·60–2·11)	1·61 (1·47–1·77)
0 days from admission to operation (n=176 559)	Reference	1·46 (1·27–1·69)	2·39 (1·81–3·17)	1·56 (1·36–1·78)
1 day from admission to operation (n=14 201)	Reference	1·12 (0·87–1·45)	1·25 (0·85–1·83)	1·15 (1·01–1·46)
>1 days from admission to operation (n=22 535)	Reference	1·16 (0·98–1·36)	1·15 (0·94–1·39)	1·15 (1·01–1·35)
Yes (n=14 130)	Reference	0·97 (0·83–1·14)	0·96 (0·81–1·13)	0·97 (0·84–1·12)
Days from haemocrit measurement to operation				
<14 (n=184 189)	Reference	1·45 (1·33–1·58)	1·48 (1·33–1·65)	1·46 (1·35–1·58)
<28 (n=211 120)	Reference	1·46 (1·35–1·59)	1·51 (1·36–1·68)	1·45 (1·36–1·59)
<56 (n=222 845)	Reference	1·46 (1·35–1·59)	1·51 (1·36–1·68)	1·47 (1·36–1·59)

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	No anaemia (n=158 196)	Mild anaemia (n=57 870)	Moderate-to-severe anaemia (n=11 359)	Any anaemia (n=69 229)
(Continued from previous page)				
Composite morbidity				
n	8436 (5·33%)	7677 (13·27%)	3170 (27·91%)	10 847 (15·67%)
$OR_{unadjusted}$	Reference	2·72 (2·63–2·81)	6·87 (6·56–7·20)	3·30 (3·20–3·40)
OR_{adj-1}	Reference	1·60 (1·54–1·65)	2·59 (2·45–2·73)	1·75 (1·69–1·81)
OR_{adj-2}	Reference	1·31 (1·26–1·36)	1·56 (1·47–1·66)	1·35 (1·30–1·40)
Strata OR_{adj-2}				
Age				
<65 years (n=148 364)	Reference	1·36 (1·29–1·44)	1·81 (1·66–1·98)	1·43 (1·36–1·51)
<40 years (n=41 077)	Reference	1·33 (1·17–1·51)	2·17 (1·77–2·67)	1·45 (1·28–1·64)
40–<65 years (n=107 287)	Reference	1·36 (1·28–1·45)	1·72 (1·56–1·89)	1·42 (1·40–1·50)
≥65 years (n=79 061)	Reference	1·25 (1·18–1·31)	1·31 (1·20–1·43)	1·26 (1·19–1·32)
65–85 years (n=71 901)	Reference	1·23 (1·16–1·30)	1·31 (1·20–1·44)	1·24 (1·18–1·32)
>85 years (n=7160)	Reference	1·25 (1·07–1·47)	1·20 (0·95–1·53)	1·24 (1·07–1·45)
Sex				
Male (n=96 385)	Reference	1·29 (1·23–1·37)	1·51 (1·38–1·65)	1·32 (1·25–1·39)
Female (n=131 040)	Reference	1·34 (1·27–1·41)	1·60 (1·47–1·74)	1·38 (1·32–1·46)
Surgical subspecialty				
General (n=164 330)	Reference	1·32 (1·26–1·38)	1·56 (1·45–1·68)	1·36 (1·30–1·42)
Vascular (n=31 311)	Reference	1·21 (1·11–1·32)	1·42 (1·25–1·61)	1·24 (1·14–1·35)
Orthopaedic (n=10 758)	Reference	1·53 (1·23–1·91)	1·52 (1·00–2·31)	1·53 (1·23–1·90)
Other* (n=21 026)	Reference	1·25 (1·07–1·47)	1·48 (1·09–2·01)	1·28 (1·09–1·50)
Emergency case				
No (n=194 542)	Reference	1·33 (1·27–1·38)	1·60 (1·49–1·72)	1·36 (1·30–1·42)
Yes (n=32 883)	Reference	1·18 (1·09–1·27)	1·34 (1·20–1·49)	1·21 (1·12–1·31)
Perioperative transfusion†				
No (n=213 295)	Reference	1·32 (1·27–1·38)	1·79 (1·66–1·93)	1·38 (1·33–1·44)
0 days from admission to operation (n=176 559)	Reference	1·23 (1·17–1·30)	1·56 (1·36–1·80)	1·26 (1·19–1·32)
1 day from admission to operation (n=14 201)	Reference	1·18 (1·04–1·34)	1·44 (1·17–1·78)	1·22 (1·08–1·37)
>1 days from admission to operation (n=22 535)	Reference	1·11 (1·01–1·21)	1·41 (1·25–1·57)	1·17 (1·07–1·28)
Yes (n=14 130)	Reference	1·05 (0·95–1·15)	0·99 (0·89–1·11)	1·03 (0·94–1·13)
Days from haematocrit measurement to operation				
<14 (n=184 189)	Reference	1·32 (1·22–1·44)	1·34 (1·20–1·50)	1·33 (1·22–1·44)
<28 (n=211 120)	Reference	1·35 (1·24–1·47)	1·40 (1·26–1·56)	1·34 (1·23–1·45)
<56 (n=222 845)	Reference	1·32 (1·22–1·44)	1·36 (1·22–1·51)	1·33 (1·23–1·44)
Specific morbidity				
Cardiac				
n	487 (0·31%)	657 (1·14%)	291 (2·56%)	948 (1·37%)
$OR_{unadjusted}$	Reference	3·72 (3·31–4·18)	8·51 (7·35–9·86)	4·50 (4·03–5·02)
OR_{adj-1}	Reference	1·68 (1·48–1·90)	2·15 (1·82–2·53)	1·77 (1·57–2·00)
OR_{adj-2}	Reference	1·44 (1·26–1·63)	1·52 (1·28–1·81)	1·45 (1·29–1·65)
Respiratory				
n	3233 (2·04%)	3769 (6·51%)	1888 (16·62%)	5657 (8·17%)
$OR_{unadjusted}$	Reference	3·34 (3·18–3·50)	9·56 (8·99–10·15)	4·27 (4·08- 4·46)
OR_{adj-1}	Reference	1·54 (1·46–1·63)	2·37 (2·20–2·55)	1·70 (1·62–1·79)
OR_{adj-2}	Reference	1·31 (1·24–1·39)	1·41 (1·30–1·52)	1·33 (1·26–1·41)
CNS				
n	486 (0·31%)	404 (0·70%)	156 (1·37%)	560 (0·81%)
$OR_{unadjusted}$	Reference	2·28 (2·00–2·60)	4·52 (3·77–5·42)	2·65 (2·34–2·99)
OR_{adj-1}	Reference	1·14 (0·99–1·31)	1·26 (1·03–1·54)	1·16 (1·02- 1·33)
OR_{adj-2}	Reference	1·05 (0·91–1·21)	1·02 (0·82–1·26)	1·05 (0·91–1·20)

(Continues on next page)

	No anaemia (n=158 196)	Mild anaemia (n=57 870)	Moderate-to-severe anaemia (n=11 359)	Any anaemia (n=69 229)
(Continued from previous page)				
Urinary tract				
n	675 (0·43%)	882 (1·52%)	403 (3·55%)	1285 (1·86%)
$OR_{unadjusted}$	Reference	3·61 (3·27–3·99)	8·58 (7·58–9·73)	4·42 (4·02–4·85)
OR_{adj-1}	Reference	1·81 (1·63–2·02)	2·54 (2·20–2·92)	1·95 (1·76–2·16)
OR_{adj-2}	Reference	1·37 (1·22–1·53)	1·38 (1·18–1·62)	1·37 (1·23–1·53)
Wound				
n	3219 (2·03%)	2157 (3·73%)	716 (6·30%)	2873 (4·15%)
$OR_{unadjusted}$	Reference	1·86 (1·76–1·97)	3·24 (2·98–3·52)	2·08 (1·98–2·19)
OR_{adj-1}	Reference	1·47 (1·38–1·56)	2·10 (1·917–2·30)	1·56 (1·48–1·65)
OR_{adj-2}	Reference	1·11 (1·04–1·18)	1·18 (1·06–1·31)	1·12 (1·05–1·19)
Sepsis				
n	3214 (2·03%)	3264 (5·64%)	1328 (11·69%)	4592 (6·63%)
$OR_{unadjusted}$	Reference	2·88 (2·74–3·03)	6·38 (5·97–6·83)	3·43 (3·27–3·59)
OR_{adj-1}	Reference	1·70 (1·62–1·80)	2·42 (2·25–2·62)	1·83 (1·74–1·92)
OR_{adj-2}	Reference	1·24 (1·17–1·31)	1·25 (1·14–1·36)	1·24 (1·18–1·31)
Venous thromboembolism				
n	1135 (0·72%)	913 (1·58%)	385 (3·39%)	1298 (1·87%)
$OR_{unadjusted}$	Reference	2·22 (2·03–2·42)	4·85 (4·32–5·46)	2·64 (2·44–2·86)
OR_{adj-1}	Reference	1·43 (1·31–1·57)	2·26 (1·99–2·58)	1·57 (1·44–1·71)
OR_{adj-2}	Reference	1·27 (1·16–1·40)	1·67 (1·45–1·92)	1·33 (1·22–1·46)

Data are n (%) or odds ratio (95% CI), unless otherwise stated. Mild anaemia was defined as a haematocrit concentration of >29–<39% in men and >29–<36% in women. Moderate-to-severe anaemia was defined as a haematocrit concentration of ≤29%. Models were built as described in webappendix pp 1–4. $OR_{unadjusted}$=unadjusted odds ratio. OR_{adj-1}=odds ratio adjusted with basic adjustment (model 1). OR_{adj-2}=odds ratio with extended adjustment (model 2). *Gynaecological, urological, neurosurgery, otolaryngological, plastic, or thoracic. †Transfusion of more than four packed red blood cell units within 72 h preoperatively, any number of units transfused intraoperatively, or transfusion of more than four units within 72 h postoperatively.

Table 2: **Effect of preoperative anaemia on mortality and morbidity at 30 days**

separate sensitivity analyses (of excluded patients in the anaemia group and excluded patients in the no anaemia group). If the absence of preoperative haematocrit values were non-random, these analyses were designed to provide two extremes of bias.

We assessed the effect of other preoperative risk factors on the association between preoperative anaemia and outcomes. Risk factors were categorised into the following subgroups: age 65 years or older, cardiac disease (congestive heart failure in previous 30 days, angina in previous 30 days, myocardial infarction in previous 6 months, previous percutaneous coronary intervention, or previous cardiac surgery), severe chronic obstructive pulmonary disease, CNS disease (hemiplegia, paraplegia, quadraplegia, history of transient ischaemic attack, history of cerebrovascular accident with neurological deficit, or history of cerebrovascular accident without neurological deficit), renal disease (acute renal failure, currently on dialysis, or with a preoperative creatinine concentration of ≥221 μmol/L), cancer (disseminated cancer, chemotherapy in previous 30 days, radiotherapy in previous 90 days, tumour involving CNS), diabetes (on oral drugs or insulin), systemic sepsis (in previous 48 h), and obesity (body-mass index ≥30 kg/m²). We calculated the OR_{adj-2} of 30-day mortality and composite morbidity for patients with either anaemia or the risk factor, and for patients with anaemia plus the risk factor with model 2; patients without anaemia or the risk factor were the reference population. For every risk-factor subgroup, the respective variables defining the risk factor were removed from the analyses. All p values were two-sided with the level of significance set at <0·05. We did the data management and analyses with SAS version 9.1.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KMM and FRJ had full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. All authors had final responsibility for the decision to submit for publication.

Results

We included data for 227 425 patients. Webappendix pp 5–6 list the 50 most common surgical procedures undertaken. Patients had a mean age of 56·4 years (SD 17·3, range 16–90) and 131 040 (57·61%) were women. We obtained haematocrit concentrations for 222 845 (97·99%) patients within 2 months of the index surgery (211 120 [92·83%] were obtained within 4 weeks

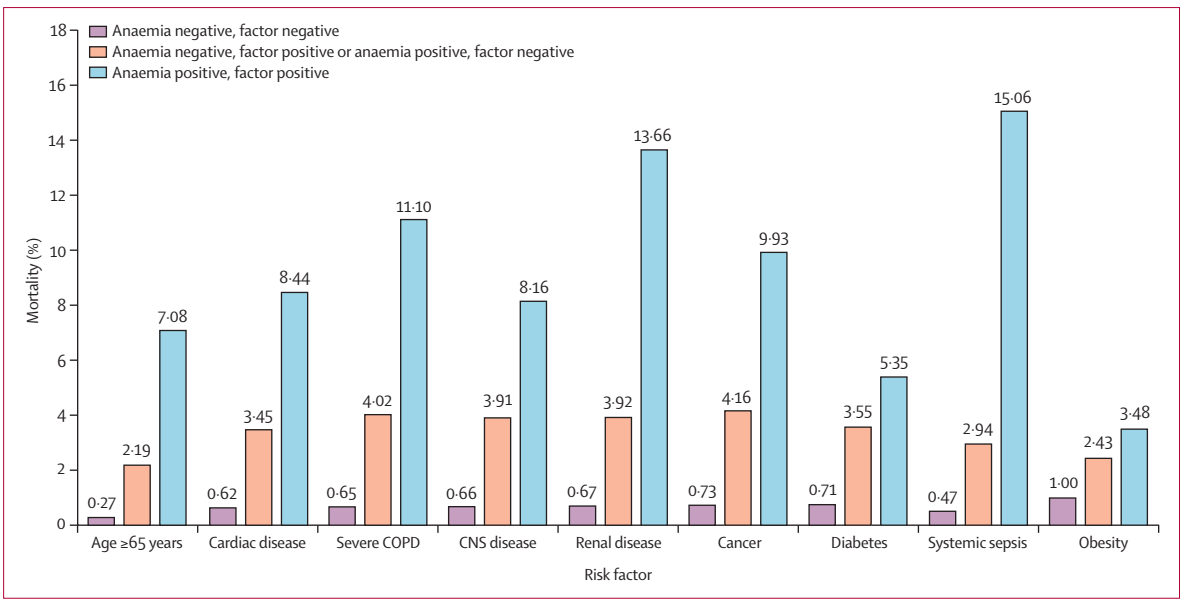

Figure 1: **30-day mortality, by anaemia and risk factor status**
COPD=chronic obstructive pulmonary disease.

and 184189 [80·99%] were obtained within 14 days). 69229 patients (30·44%) had anaemia, of whom 57870 (83·59%) had mild anaemia and 11359 (16·41%) had moderate-to-severe anaemia. 158196 patients (69·56%), had no preoperative anaemia.

Table 1 compares demographics, preoperative variables, and perioperative variables between patients without anaemia with those with anaemia. Compared with patients without anaemia, patients with anaemia were more likely to be elderly (≥65 years) and not white. Patients with anaemia also had a higher prevalence of diabetes, systemic sepsis, cardiovascular, respiratory, hepatobiliary, renal, neurological, and haematological-oncological disorders, and chronic steroid use, operations within the past month, and infected surgical wounds; however, they had a lower prevalence of obesity than did patients without anaemia. Furthermore, patients with anaemia were more likely to be inpatients, under a do-not-resuscitate order, at a high American Society of Anesthesiologists class, non-independent in functional status, emergency cases, undergo general anaesthesia, undergo vascular surgery, had longer mean total operation time, and more likely to have abnormal preoperative laboratory studies and receive perioperative transfusions (table 1).

Crude mortality was 0·78% for patients without anaemia compared with 4·61% for patients with anaemia (unadjusted odds ratio [$OR_{unadjusted}$] 6·12, 95% CI 5·73–6·54). The crude composite morbidity was 5·33% for patients without anaemia compared with 15·67% for patients with anaemia ($OR_{unadjusted}$ 3·30, 3·20–3·40; table 2). Based on the sample size used for the analyses, we calculated a >99% power to detect the reported increase in mortality between the two groups (absolute difference of 3·83%). Conversely, the available sample size yielded a power of 80% to detect a difference in mortality of as low as 0·035%.

After adjustment for all potential confounders (webappendix pp 1–4), preoperative anaemia remained independently and significantly associated with increased 30-day mortality and morbidity (table 2). Moreover, compared with patients without anaemia, patients with anaemia had higher rates of almost all specific morbidities including cardiac, respiratory, urinary tract, and wound events, sepsis, and venous thromboembolism (table 2). Although CNS events were numerically more common in patients with anaemia than they were in patients without anaemia, the association did not reach significance. Effects of anaemia

	Anaemia positive, factor negative or anaemia negative, factor positive		Anaemia positive, factor positive	
	$OR_{unadjusted}$	OR_{adj-2}	$OR_{unadjusted}$	OR_{adj-2}
Age ≥65 years	8·15 (7·22–9·20)	2·57 (2·26–2·93)	27·72 (24·59–31·25)	4·45 (3·90–5·09)
Cardiac disease	5·77 (5·34–6·24)	1·46 (1·33–1·59)	14·89 (13·61–16·28)	1·58 (1·41–1·76)
Severe COPD	6·39 (5·94–6·87)	1·53 (1·40–1·66)	19·02 (17·133–21·11)	1·80 (1·59–2·05)
CNS disease	6·09 (5·65–6·55)	1·43 (1·31–1·56)	13·31 (12·05–14·69)	1·48 (1·31–1·67)
Renal disease	6·06 (5·63–6·51)	1·52 (1·40–1·65)	23·48 (21·34–25·85)	2·52 (2·23–2·85)
Cancer	5·91 (5·51–6·33)	1·44 (1·33–1·56)	14·99 (13·41–16·76)	4·10 (3·59–4·69)
Diabetes	5·16 (4·79- 5·56)	1·40 (1·28–1·52)	7·93 (7·23–8·69)	1·18 (1·05–1·31)
Systemic sepsis	6·41 (5·88–6·99)	2·02 (1·83–2·22)	37·56 (34·30–41·12)	3·10 (2·76–3·48)
Obesity	2·45 (2·28–2·64)	0·95 (0·87–1·04)	3·55 (3·23–3·91)	0·77 (0·68–0·86)

Data are odds ratio (95% CI). Models were built as described in webappendix pp 1–4. $OR_{unadjusted}$=unadjusted odds ratio. OR_{adj-2}=odds ratio with extended adjustment (model 2). COPD=chronic obstructive pulmonary disease.

Table 3: **$OR_{unadjusted}$ and OR_{adj-2} of mortality at 30 days for patients with anaemia or risk factors and anaemia and risk factors, compared with reference populations of patients with neither anaemia nor risk factors**

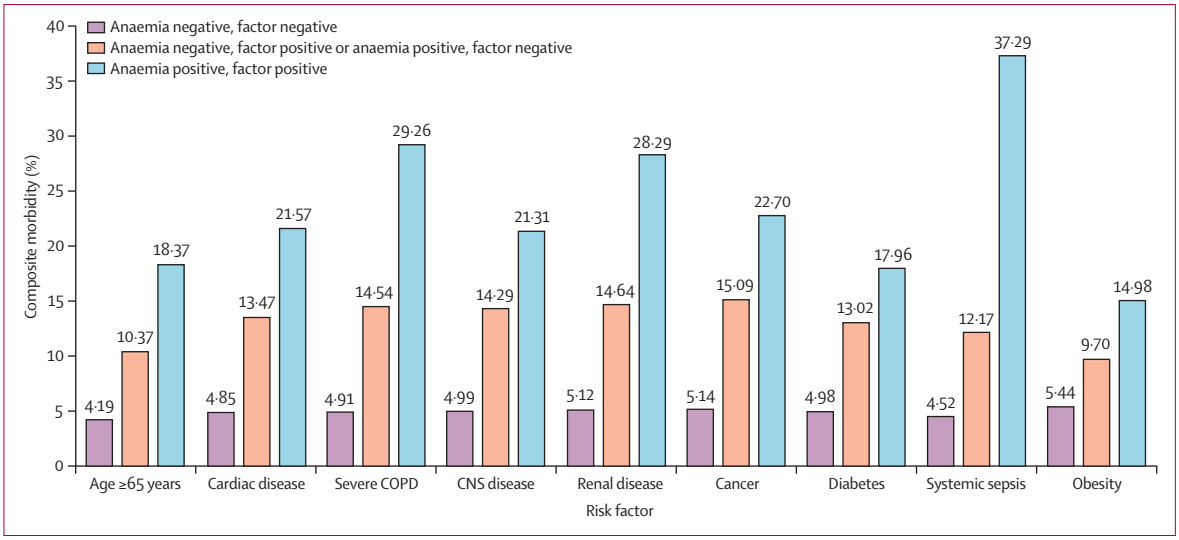

Figure 2: **30-day composite morbidity, by anaemia and risk factor status**
COPD=chronic obstructive pulmonary disease.

	Anaemia positive, factor negative or anaemia negative, factor positive		Anaemia positive, factor positive	
	$OR_{unadjusted}$	OR_{adj-2}	$OR_{unadjusted}$	OR_{adj-2}
Age ≥65 years	2·65 (2·55–2·75)	1·39 (1·34–1·45)	5·15 (4·95–5·36)	1·56 (1·48–1·65)
Cardiac disease	3·05 (2·95–3·15)	1·35 (1·30–1·40)	5·39 (5·14–5·65)	1·39 (1·31–1·48)
Severe COPD	3·30 (3·20–3·40)	1·40 (1·35–1·46)	8·01 (7·53–8·53)	1·83 (1·70–1·98)
CNS disease	3·17 (3·08–3·28)	1·37 (1·32–1·42)	5·16 (4·87–5·46)	1·41 (1·32–1·51)
Renal disease	3·18 (3·08–3·28)	1·37 (1·32–1·42)	7·31 (6·88–7·77)	1·95 (1·80–2·11)
Cancer	3·28 (3·18–3·38)	1·35 (1·30–1·40)	5·42 (5·043–5·82)	1·55 (1·42–1·69)
Diabetes	2·85 (2·76–2·95)	1·29 (1·24–1·34)	4·17 (3·99–4·37)	1·26 (1·19–1·34)
Systemic sepsis	2·93 (2·83–3·03)	1·49 (1·43–1·54)	12·58 (12·02–13·16)	2·87 (2·70–3·04)
Obesity	1·87 (1·80–1·93)	1·14 (1·09–1·18)	3·06 (2·92–3·21)	1·36 (1·29–1·44)

Data are odds ratio (95% CI). Models were built as described in webappendix pp 1–4. $OR_{unadjusted}$=unadjusted odds ratio. OR_{adj-2}=odds ratio with extended adjustment (model 2). COPD=chronic obstructive pulmonary disease.

Table 4: **$OR_{unadjusted}$ and OR_{adj-2} of morbidity at 30 days for patients with anaemia or risk factors and anaemia and risk factors, compared with reference populations of patients with neither anaemia nor risk factors**

on mortality and morbidity at 30 days was evident between all age groups, sexes, and surgical subspecialties (table 2). Although patients with anaemia had a higher morbidity after emergency or non-emergency procedures than did patients without anaemia, this association was only noted in non-emergency (elective) cases for mortality (table 2). Preoperative anaemia led to increased 30-day mortality and morbidity in patients who probably did not receive packed-red-blood-cell transfusions compared with those that did (had no documented perioperative transfusions in the database and had same day surgery; table 2). However, patients with anaemia who received perioperative transfusions did not have increased adjusted odds ratio of outcomes compared with patients without anaemia who also received transfusions. Perioperative transfusion in itself was associated with an increased odds ratio of mortality and all morbidities (webappendix pp 1–4). Reported associations between preoperative anaemia and post-operative outcomes were evident irrespective of the duration from haematocrit measurement to operation (table 2).

In the sensitivity analyses of patients with missing haematocrit measurements, results did not differ for the primary and secondary study outcome measures (see webappendix pp 7–8).

When compared with patients with neither anaemia nor a risk factor, patients with anaemia and most risk factors had a significant and higher OR_{adj-2} for 30-day mortality than did patients with either anaemia or the risk factor alone (figure 1; table 3). Similarly, when compared with patients with neither anaemia nor a risk factor, patients with both anaemia and most risk factors had a significant and higher OR_{adj-2} for 30-day composite morbidity than did patients with either anaemia or the risk factor alone (figure 2; table 4).

Discussion

From analysis of a large multicentre database, we show that even mild preoperative anaemia is independently associated with an increased risk of 30-day morbidity and mortality in patients undergoing major non-cardiac surgery. We noted these findings in a large cohort of patients irrespective of age, sex, or type of surgical procedure. Furthermore, when anaemia was present concomitantly with a known preoperative risk factor, it led to a significant increase in the effect of this risk factor on outcomes (panel 2).

Anaemia can lead to adverse outcomes in patients undergoing vascular surgery, extensive surgical procedures, or for those with major blood loss or cardiac

disease.[12–14,23] In the largest study to date, Wu and colleagues suggested that even mild degrees of preoperative anaemia were associated with an increased risk of 30-day postoperative mortality and cardiac events in elderly patients (mostly male veterans) undergoing major non-cardiac surgery.[16] Our study reinforces these findings and suggests that the detrimental effects of preoperative anaemia occur across all age groups and sexes, and are associated with increased risk of major non-cardiac morbidity, including respiratory, urinary, wound, septic, and thromboembolic complications. Our study distinguished between patients who had emergency and elective procedures, unlike Wu and colleagues' study[16] that assessed emergency surgery without stratification. We suggest that the severity of the underlying disease causing the emergency might have modified the effect of anaemia on outcomes, as we noted in our study. Another study of 7759 patients undergoing major non-cardiac surgery also reported that preoperative anaemia was associated with increased mortality (adjusted odds ratio 2·36, 1·57–3·41).[24] However, the retrospective nature of data collection in the study[24] and the short list of measured confounders available for adjustment might have affected the size of the reported association.

The adjusted odds ratio of dying that we reported (a 42% adjusted increase in mortality) attributable to anaemia might be regarded as a modest effect because the mortality in patients without preoperative anaemia was only 0·78%, and could be explained by the association of anaemia with other risk factors for death. However, the key strengths of our study were the large number of patients and the reliable and comprehensive data collection of the ACS NSQIP, which provides more than 60 demographic, preoperative, and perioperative variables for adjustment. This completeness, together with the good discrimination in our model, suggests that the effect of anaemia is independent and cannot be straightforwardly explained through an association with other known risk factors, especially in patients with mild preoperative anaemia. Moreover, a 42% adjusted increase in death rate in such a large sample size means that around 500 extra people could die from even a mild degree of anaemia after elective major non-cardiac surgery. We also did a thorough analysis of the effect of anaemia not only on mortality but also on morbidity. We assessed the effect of anaemia on seven major morbidities that might be associated with substantial sequelae and health-care costs. The frequency of composite morbidity in patients without preoperative anaemia was 5·33% (8436 patients), making a 35% adjusted increased rate of composite morbidity due to anaemia (much higher for some individual morbidities) very alarming.

The relative contribution of preoperative anaemia and perioperative transfusions on postoperative outcomes, and their interactions, is hard to specify. Although some studies did not attempt to explore such interaction,[13,16] others tried to establish the independent effect of every factor through various statistical techniques.[9,17,24,25] In these studies of preoperative anaemia, multivariate analysis was commonly used to adjust for perioperative transfusion as a confounder, or transfused patients were matched against non-transfused patients. Although these approaches are acceptable, they are restricted by the availability of other variables in the dataset. Thus, in our analysis we not only relied on adjustment for perioperative transfusions but also did separate analyses for patients who received and those who did not receive perioperative transfusions, thus confirming the negative effects of untreated anaemia on postoperative outcomes.

Our findings should lead to a careful consideration of appropriate interventions aimed at correction of preoperative anaemia in the most patients. Present guidelines recommend measurement of haematocrit concentration as close to 28 days before the scheduled surgical procedure as possible, and subsequent investigation and intervention in patients with anaemia.[4,26]

Panel 2: Research in context

Systematic review

We searched PubMed without date or language restrictions for articles with the following terms: "surgery" or "procedure" and "anemia", in combination with "mortality", "death", "morbidity", "complications", or "outcomes". We excluded articles on the basis of their titles or abstracts and included remaining full-text articles and those identified from reference lists of relevant reports. The main criteria for the selection of relevant articles were inclusion of patients undergoing major non-cardiac surgery and having preoperative anaemia and mortality or morbidity as the major topic. We identified seven relevant articles, published between 1988 and 2011. Early studies showed that preoperative anaemia was associated with increased perioperative cardiac morbidity in patients undergoing radical prostatectomy,[12] and increased postoperative mortality in patients with cardiovascular disease[13] or extensive operative blood loss.[14,15] Preoperative anaemia was since reported to be independently associated with increased mortality in patients undergoing major non-cardiac surgery,[24] and increased morbidity and hospital length of stay in patients undergoing colorectal surgery.[17] The largest available study also reported an independent effect of preoperative anaemia on postoperative mortality and cardiac morbidity in 310 311 (mostly male) veterans aged 65 years or older who underwent major non-cardiac surgery.[16] The main limitations in these studies were the small sample size,[12–15] restrictions of the study to a specific subgroup of patients such as elderly men[16] or to one type of surgery,[12,17] inclusion of patients undergoing emergency surgery without stratification of outcomes,[16] or failure to adjust for the major known confounders,[24] especially the use of perioperative transfusions.[13,16] Moreover, most of these studies only assessed the outcomes of mortality[13–16,24] or cardiac morbidity.[12,16]

Interpretation

After attending to the limitations of previous studies, our study of 227 425 patients with major non-cardiac surgery established that preoperative anaemia is independently associated with an increased risk of 30-day mortality and several major morbidities in both men and women, and across all age groups and surgical subspecialties. This observation should lead to careful assessment and early detection of preoperative anaemia at least in elective surgical cases. The finding that even a mild degree of anaemia is associated with serious adverse outcomes is important not only for surgeons and anaesthesiologists but also for referring doctors because in most cases treatment of mild anaemia is possible at a relatively low cost.

Our study supports these guidelines because even mild degrees of anaemia can increase the risk of morbidity and mortality. At least in elective surgical cases, the treatment of preoperative anaemia before surgical intervention should be strongly considered, not least because preoperative anaemia is easy to detect and, in many situations, cheap to treat.[4] The high morbidity and mortality reported with the use of blood transfusion,[9,10,25] which we also noted in our analysis (albeit a non-randomised study), make it the least favourable option. Alternative interventions include preoperative iron and vitamin supplementation or administration of erythropoietin. At least in orthopaedic[27] and cardiac[28] surgery, compelling evidence supports the use of preoperative treatment of anaemia for reduction of blood transfusion and improved outcomes.[29]

Our study had limitations. About 7% of the preoperative haematocrit concentrations were obtained more than 4 weeks before surgery and might not accurately predict the concentrations at the time of surgery. However, variation of haematocrit concentrations in an individual is usually low in the absence of major bleeding, which in our database would have been identified by preoperative blood transfusions and thus corrected for in the analysis. Moreover, in our analysis the reported effect of anaemia on postoperative outcomes remained significant irrespective of the duration from haematocrit concentration measurement to operation. The ACS NSQIP database does not record the haematocrit concentration at the lowest point intraoperatively or immediately postoperative. Thus, we do not know if reduced intraoperative haematocrit concentrations were associated with worse outcomes. Furthermore, the database does not document use of four or fewer packed red-blood-cell transfusions in the preoperative or postoperative period, which means that some patients regarded as not having received any perioperative transfusions in the analysis might have received such transfusion. Nonetheless, about 83% of patients without documented perioperative transfusions had surgery on the same day, suggesting that preoperative transfusion was mostly unlikely, and they had a significant association between anaemia and postoperative mortality and morbidity at 30 days. We were unable to adjust for blood transfusion (four units or fewer) received during the postoperative period. In the preoperative anaemia group, postoperative transfusions might have corrected the anaemia. Moreover, patients without anaemia might have also received blood postoperatively, and blood transfusion is associated with adverse outcomes. However, these eventualities would bias our study toward the null hypothesis, leading us to underestimate the effect of anaemia on outcomes. Thus, this form of bias would have been important only if we were not able to detect a significant difference between the anaemia and the no anaemia group. Although our data included various surgical procedures and showed preoperative anaemia to be associated with adverse outcomes between all surgical subspecialties, overall estimates of increased morbidity and mortality might only be applicable in a population with a similar casemix as that generated by the ACS NSQIP sampling strategy. Lastly, our study cannot relate the cause and time course of anaemia to morbidity and mortality.

Because even mild anaemia increases the risk of postoperative morbidity and mortality in patients undergoing major non-cardiac surgery, doctors need to consider preoperative treatment of anaemia when possible. Further research is needed to establish the efficacy, safety, and cost-effectiveness of such preoperative anaemia management.

Contributors

KMM and FRJ designed the study. AH, MK, FSD, KK, PMS, AS, JJH, and ATT obtained the data. KMM, TR, DRS, FRR, and FRJ analysed the data. KMM and FRJ wrote the report. TR, DRS, FRR, AH, MK, FSD, KK, PMS, AS, JJH, and ATT critically revised the report. HT and KMM did the statistical analysis. All authors approved the final report for submission.

Conflicts of interest

TR's department receives consultancy fees and research funding from Vifor Pharma. DRS receives consultancy fees and travel support from Vifor Pharma. DRS's department receives research funding from the Swiss National Science Foundation in Bern (Switzerland; grant numbers 33CM30_124117 and 406440-131268), the Swiss Society of Anesthesiology and Reanimation in Bern, the Swiss Foundation for Anaesthesia Research in Zurich (Switzerland), the Bundesprogramm Chancengleichheit in Bern, CSL Behring in Bern, and Vifor SA in Villars-sur-Glâne (Switzerland). DRS was the chairman of the ABC Faculty and is a member of the ABC Trauma Faculty, which both are managed by Thomson Physicians World GmbH in Mannheim (Germany) and sponsored by an unrestricted educational grant from Novo Nordisk in Bagsvärd (Denmark) and CSL Behring in Hattersheim am Main (Germany). In the past 5 years, DRS has received honoraria or travel support for consulting or lecturing from Abbott (Baar, Switzerland), AstraZeneca (Zug, Switzerland), Bayer (Schweiz; Zurich), Baxter (Rome, Italy), B Braun Melsungen (Melsungen, Germany), Boehringer Ingelheim (Schweiz; Basel, Switzerland), Bristol-Myers Squibb (Rueil-Malmaison Cedex, France), CSL Behring (Hattersheim am Main and Bern), Curacyte (Munich, Germany), Ethicon Biosurgery (Sommerville, NJ, USA), Fresenius (Bad Homburg vor der Höhe, Germany), Galenica (Bern), Switzerland, including Vifor SA), GlaxoSmithKline (Hamburg, Germany), Janssen-Cilag (Baar, Switzerland), Janssen-Cilag EMEA (Beerse, Belgium), Novo Nordisk (Bagsvärd), Octapharma (Lachen, Switzerland), Organon (Pfäffikon, Switzerland), Oxygen Biotherapeutics (Costa Mesa, CA, USA), tem Innovations (Munich), Roche Pharma (Schweiz; Reinach, Switzerland), and Schering-Plough (Kenilworth, NJ, USA). ATT is a member of Novartis speakers' bureau. All other authors declare that they have no conflicts of interest.

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