The aetiology and prevalence of preoperative anaemia in patients undergoing major surgery (ALICE): an international, prospective, observational cohort study

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Summary

Background Preoperative anaemia is a major risk factor for perioperative morbidity. Because iron deficiency is widely assumed to be the main cause of anaemia in surgical patients, treatment efforts have focused mostly on iron supplementation. However, the aetiology of anaemia is multifactorial. To further understand the underlying causes and consider a comprehensive approach to anaemia management, we studied the prevalence and aetiology of preoperative anaemia in patients undergoing major surgery.

Methods This prospective, multicentre, observational cohort study was done in 79 hospitals in 20 countries on five continents; patients were aged at least 18 years, undergoing major surgery, and had a postoperative in-hospital stay of at least 24 h. Patients donating autologous blood before surgery were excluded. Data were extracted from the electronic hospital information system and from self-reported information during preoperative examination. The primary outcomes were the prevalence of anaemia, defined as haemoglobin less than 120 g/L for women and less than 130 g/L for men, analysed in all participants, and the aetiology of anaemia, analysed only in patients with anaemia for whom aetiology could be confirmed. The study was registered with ClinicalTrials.gov (NCT03978260) and is complete.

Findings Between Aug 26, 2019, and Dec 26, 2021, 2830 patients undergoing major surgery were recruited and 2702 patients were included in the analysis (1417 [52·4%] were male, 1279 [47·3%] were female, and six [0·2%] had gender dysphoria). Overall, 856 (31·7%, 95% CI 31·2–32·2) patients had preoperative anaemia. Among 782 patients with preoperative anaemia, for whom the presence of at least one aetiology could be confirmed, 432 (55·2%, 48·9–61·6) had iron deficiency, 60 (7·7%, 6·6–8·7) had vitamin B12 deficiency, 113 (14·5%, 12·2–16·7) had folate deficiency, 68 (8·7%, 8·1–9·3) had chronic kidney disease, and 48 (6·1%, 4·5–7·8) had anaemia resulting from another cause; patients could be assigned to multiple aetiologies. Across male and female sex, all age groups, and all countries, iron deficiency was the aetiology with the highest prevalence.

Interpretation The prevalence of preoperative anaemia in patients in this study who were undergoing major surgery is high. Iron deficiency is the primary cause of this anaemia; however, the substantial prevalence of vitamin B12 and folate deficiencies demands immediate attention and action.

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Introduction

Anaemia is a common global health problem, despite being a treatable and preventable condition. The Global Burden of Disease Study 2021 Anaemia Collaborators found that the global prevalence of anaemia in 2021 was 24·3% (95% uncertainty interval 23·9–24·7), corresponding to 1·92 billion individuals.[1] The most common cause of anaemia is dietary iron deficiency, irrespective of sex or age, although the prevalence of anaemia caused by folate and vitamin B12 deficiency is unknown. Several organisations, including WHO and UNICEF, have combined efforts to support WHO's Global Nutrition Target in reducing the rate of anaemia among women of reproductive age by 2030.[2–4]

The harmful effects of preoperative anaemia have been shown repeatedly. Particularly in surgical patients, low haemoglobin is associated with increased risk for red blood cell (RBC) transfusion, higher rates of complications and readmissions, prolonged hospital stays, and substantial health and economic costs.[5–8] Notably, the prevalence of anaemia is high among surgical patients, with many previous studies showing a prevalence around 30%.[6,7,9,10]

Approximately 300 million surgical procedures are performed worldwide each year.[11,12] Surgical blood loss is common, often necessitating the transfusion of RBC units to prevent anaemia-induced organ dysfunction. Furthermore, the presence of preoperative anaemia

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Research in the context

Evidence before this study

A strong body of scientific evidence indicates that preoperative patient optimisation including anaemia management is a key component to improve recovery from surgery. Anaemia is common, but the aetiology can be multifactorial. We searched MEDLINE from inception until Jan 31, 2017, restricted to the English language, including the search terms “aetiology” AND “anaemia” AND “surgery” to identify studies assessing the prevalence and aetiology of preoperative anaemia in patients undergoing major surgery. We identified no randomised or prospective observation trials that comprehensively assessed the aetiology of preoperative anaemia in patients undergoing major surgery as a primary objective. We found two studies that evaluated haematinic deficiencies in patients undergoing orthopaedic and cardiac surgery. Our search indicated that, in the last two decades, the focus of anaemia management has been on the diagnosis and treatment of iron deficiency anaemia, while the other causes have largely been overlooked. However, the aetiology of anaemia in patients undergoing major surgery is multifactorial and, to the best of our knowledge, no comprehensive studies have yet been conducted to elucidate the underlying causes.

Added value of this study

This study provides evidence that iron deficiency is the leading cause of preoperative anaemia in patients undergoing major surgery. In addition, our results emphasise the underestimated role of folate and vitamin B12 in these patients. The ALICE study shows that the worldwide prevalence of preoperative anaemia remains high, and low preoperative haemoglobin concentration is an independent risk factor for serious adverse outcomes. Across male and female sex, all age groups, and all countries, iron deficiency is the cause of anaemia with the highest prevalence. However, the prevalence of vitamin B12 and folate deficiency among anaemic patients is also substantial.

Implications of all the available evidence

Preoperative anaemia is common among patients undergoing major surgery and represents an independent risk factor for adverse perioperative outcomes. Despite this, anaemia management is not routinely mandated in clinical practice. Anaemia may result from various conditions, including chronic kidney disease, blood loss, or nutritional deficiencies. The latter can often be corrected by supplementation with iron, folate, or vitamin B12. In practice, the focus is primarily on iron deficiency; however, treatment may be ineffective if other nutritional deficiencies coexist. Our findings support the implementation of a comprehensive preoperative anaemia management programme. A pragmatic, bundled approach to treat anaemia should be considered in the future. Furthermore, it is important to emphasise that nutrition-related anaemia is both reversible and straightforward to treat. Similar to preoperative optimisation strategies for COVID-19 infection, smoking cessation, and alcohol withdrawal, postponing surgery might be warranted in patients with anaemia to enable treatment and thereby reduce avoidable postoperative complications and length of hospital stay.

exacerbates the demand for blood products.[13–16] Since iron deficiency is commonly regarded as the main cause of anaemia in patients undergoing major surgery, treatment approaches have predominantly emphasised iron supplementation. Nevertheless, the causes of anaemia in surgical patients are multifactorial, and no thorough investigations have been conducted to clarify the underlying factors. Given the detrimental effect of preoperative anaemia on surgical outcomes, understanding its causes is crucial to enable timely treatment, improve health outcomes, and reduce substantial health and economic costs. To our knowledge, this is the first study to assess the international prevalence and aetiology of preoperative anaemia in patients undergoing major surgery.

See **Online** for appendix 2

Methods

Study design and participants

The Preoperative Anaemia Prevalence in Surgical Patients (ALICE) study was a prospective, multicentre, observational cohort study. Between Aug 5, 2019, and March 26, 2022, 79 hospitals in 20 countries participated in the study (Austria, Belgium, France, Germany, Greece, Italy, Kosovo, New Zealand, Nigeria, Portugal, Romania, Slovenia, South Africa, South Korea, Spain, Sudan, Switzerland, Türkiye, United Arab Emirates, and USA). Most were high-income countries. Recruitment of participating centres was conducted by national coordinators and by members of the steering committee. Of the 79 hospitals, 32 had less than 500 beds, 30 had 500–1000 beds, and 16 had more than 1000 beds. Only four (5%) hospitals had established a software-based tool designed to assist clinicians in making evidence-based decisions about blood transfusions (appendix 2 p 20).

The initial patient recruitment period was planned from Aug 5, 2019, to Aug 2, 2020; however, due to the COVID-19 pandemic, this was extended until Dec 26, 2021. The study period ended with a 90-day follow-up observation period until March 26, 2022. Patients were recruited within a self-selected week (Monday 0600 h until Sunday 1200 h). Patients were eligible for inclusion if they were at least 18 years of age and were undergoing major surgery (defined as a predicted blood loss >500 mL or 10% transfusion probability, and with a postoperative in-hospital stay of ≥24 h). Eligible patients were recruited during the preoperative examination. The types of surgical procedure associated with increased probability of blood loss are listed in appendix 2 (p 21). Patients donating autologous blood before surgery were excluded from the study.

The study protocol was approved by the institutional ethics committee of the University Hospital Frankfurt (50/2019), and thereafter by national and local ethics committees. Study procedures aligned with the Declaration of Helsinki. Informed consent procedures were guided by national regulations and consisted of either written or oral informed consent by the patients or their legally authorised representative, or both. In some countries, informed consent was waived due to the observational nature of the study.

The study was registered online at ClinicalTrials.gov (NCT03978260).

Procedures

Data were extracted from the electronic hospital information system and from self-reported information during preoperative examination. Ethnicity was self-reported using a predefined list of categories: White, Oriental, Asian, Black, other, or no data (as originally labelled in the data collection form). These categories were not based on a standardised framework such as those used by national census bureaus. We acknowledge that some of these terms might be considered outdated and were retained here for consistency with the original dataset.

Anaemia in patients included in our study was defined according to WHO criteria: haemoglobin less than 120 g/L for women and less than 130 g/L for men. Anaemia subtypes were categorised as mild (women 110–119 g/L, men 110–129 g/L), moderate (both sexes 80–109 g/L), and severe (both sexes <80 g/L). Detailed laboratory diagnostics were performed in patients with anaemia to evaluate the aetiology of anaemia before administration of fluids or surgical incision. Specifically, we looked for anaemia caused by iron deficiency, vitamin B12 deficiency, folate deficiency, chronic kidney disease, or anaemia of other causes. The prevalence for each aetiology in patients with anaemia was estimated separately. If the presence or absence of any of the five aetiologies could not be confirmed, patients were excluded from this analysis.

The cutoff values for diagnosing iron deficiency were adapted from Munoz and colleagues and were based on a consensus among all members of the steering committee.[17] Iron deficiency was diagnosed as ferritin less than 100 μg/L or, in patients with chronic kidney disease or heart failure, as ferritin less than 300 μg/L (appendix 2 p 43).[17,18] Vitamin B12 deficiency was defined as serum vitamin B12 less than 200 ng/L[19] and folate deficiency as serum folate less than 4 μg/L.[20] Chronic kidney disease was defined as estimated glomerular filtration rate (modification of diet in renal disease or Chronic Kidney Disease Epidemiology Collaboration) less than 30 mL/min per 1·73 m². Patients were diagnosed with anaemia of other cause if they did not have iron deficiency, vitamin B12 deficiency, folate deficiency, or chronic kidney disease.

Outcomes

The primary outcomes were the prevalence of preoperative anaemia and the relative prevalence of aetiologies of preoperative anaemia.

The secondary endpoints were the associations between preoperative anaemia and perioperative outcomes, which included RBC transfusion rate and number of transfused RBC units, postoperative complications (any infection, therapy with antibiotics, wound infection, new renal replacement therapy, and thromboembolic events), revision surgery, and mortality during hospital stay. Furthermore, we assessed hospital readmissions occurring within 90 days following discharge.

Statistical analysis

Further information on analyses of primary, secondary, and post-hoc endpoints is available in appendix 2 (pp 17–19) and appendix 3. All statistical analyses were performed using R version 4.4.1. The sample size was estimated based on the expected number of participating hospitals (40–50) and the number of major surgeries performed per week at each hospital (40–50), resulting in an anticipated total of approximately 1500–3000 patients. Baseline variables were summarised using standard descriptive statistics, and missing data were reported as the number of available measurements. The prevalence of preoperative anaemia was analysed using generalised estimating equations multinomial logistic regression models with robust standard errors accounting for centre effects. The association between preoperative

See Online for appendix 3

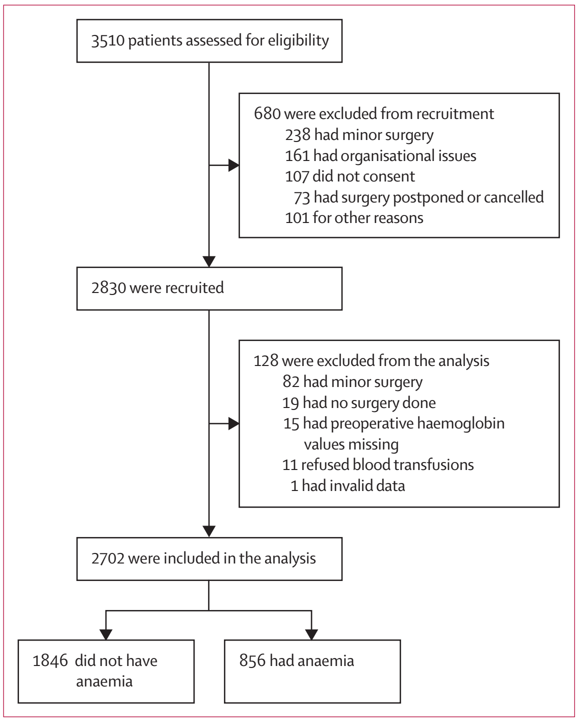

Figure 1: **Study population**

	No anaemia (n=1846)	Anaemia (n=856)	Mild anaemia (n=462)	Moderate anaemia (n=351)	Severe anaemia (n=43)
Age (years)					
Median	64 (54–72)	68 (55–77)	69 (56–76)	68 (55–77)	63 (49–72)
Sex					
Female	878 (47·6%)	401 (46·9%)	193 (41·8%)	186 (53·0%)	22 (51·2%)
Male	963 (52·2%)	454 (53·0%)	268 (58·0%)	165 (47·0%)	21 (48·8%)
Gender dysphoria	5 (0·3%)	1 (0·1%)	1 (0·2%)	0	0
BMI, kg/m²					
≤18·5	33 (1·8%)	29 (3·4%)	14 (3·0%)	12 (3·4%)	3 (7·0%)
18·6–25	556 (30·1%)	320 (37·4%)	172 (37·2%)	135 (38·5%)	13 (30·2%)
25·1–30	671 (36·4%)	270 (31·5%)	152 (32·9%)	105 (29·9%)	13 (30·2%)
>30	564 (30·6%)	218 (25·5%)	114 (24·7%)	92 (26·2%)	12 (27·9%)
No data	22 (1·2%)	19 (2·2%)	10 (2·2%)	7 (2·0%)	2 (4·7%)
Ethnicity					
White	1484 (80·4%)	656 (76·6%)	351 (76·0%)	274 (78·1%)	31 (72·1%)
Oriental	43 (2·3%)	13 (1·5%)	6 (1·3%)	6 (1·7%)	1 (2·3%)
Asian	51 (2·8%)	18 (2·1%)	9 (2·0%)	9 (2·6%)	0 (0%)
Black	35 (1·9%)	39 (4·6%)	15 (3·3%)	18 (5·1%)	6 (14·0%)
Other	99 (5·4%)	65 (7·6%)	39 (8·4%)	22 (6·3%)	4 (9·3%)
No data	134 (7·3%)	65 (7·6%)	42 (9·1%)	22 (6·3%)	1 (2·3%)
Weight loss in the previous 3–6 months					
No	1716 (93·0%)	725 (84·7%)	403 (87·2%)	288 (82·1%)	34 (79·1%)
Yes	128 (7·0%)	129 (15·1%)	57 (12·3%)	63 (18·0%)	9 (20·9%)
Weight loss, kg*					
Median	5·0 (3–10)	6·0 (4–10)	6·5 (4–10)	6·0 (5–10)	5·0 (4–10)
Smoking					
No	1109 (60·1%)	512 (59·8%)	272 (58·9%)	213 (60·7%)	27 (62·8%)
Yes	347 (18·8%)	138 (16·1%)	78 (16·9%)	48 (13·7%)	12 (27·9%)
Ex-smoker	382 (20·7%)	204 (23·8%)	110 (23·8%)	90 (25·6%)	4 (9·3%)
Number of cigarettes per day					
Median	15 (10–20)	12 (10–20)	10 (10–20)	10 (10–20)	20 (13·5–27·5)
Alcohol per week, units†					
Median	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)

Data are n (%) or median (IQR). *Weight loss within 6 months before surgery. †A unit is equivalent to 0·25 L of beer, 0·1 L of wine, and 0·02 L of shot (spirits at 40%).

Table 1: **Demographic data of patients included in analysis**

anaemia and in-hospital mortality or composite morbidity was examined with mixed-effects logistic regression including centre as a random effect and relevant covariates (type of surgery, age, American Society of Anesthesiology score, RBC transfusion). For quantitative haemoglobin values, spline functions were employed to model non-linear associations. Further technical details of the statistical analysis are provided in the Statistical Analysis Plan (appendix 3, pp 2–4).

Role of the funding source

There was no funding source for this study.

Results

In total, 2830 patients undergoing major surgery were recruited, of whom 2702 were included in the analysis (figure 1). Demographic data for the patients included in the analysis are shown in table 1. Median age was 68 years (IQR 55–77) in patients with anaemia and 64 years (54–72) in patients without anaemia. No patients were lost to follow-up.

Mean preoperative haemoglobin was 108 g/L (SD 1·4) in patients with anaemia and 141 g/L (1·2) in patients without anaemia. Overall, preoperative anaemia was diagnosed in 856 of 2702 patients (31·7%, 95% CI 31·2–32·2): 462 (54·0%, 52·8–55·2) of the 856 patients with anaemia had mild anaemia, 351 (41·0%, 37·4–44·6) had moderate anaemia, and 43 (5·0%, 4·2–5·9) had severe anaemia. The highest prevalence of preoperative anaemia was found in patients undergoing visceral or urological surgery (342 [40·0%, 36·7–43·4] patients; appendix 2 p 22). The prevalence and severity of anaemia showed little variation across age groups (appendix 2 pp 44–45). Most comorbidities were significantly more

	Anaemia (n=856)	Iron deficiency (n=432)	Folate deficiency (n=113)	Vitamin B12 deficiency (n=60)	Chronic kidney disease (n=68)	Other causes (n=48)
Haemoglobin, g/L	111 (101–118)	110 (98–118)	107 (93–119)	112 (101–119)	111 (100–119)	115 (108–120)
Haematocrit, %	34·0% (31·0–36·0)	34·0% (30·3–36·0)	33·0% (28·7–36·0)	34·2% (31·6–36·3)	34·0% (31·0–36·5)	34·4% (32·3–35·9)
Reticulocyte haemoglobin content, pg	33·0 (29·8–36·0)	32·9 (29·0–36·0)	33·0 (29·0–35·5)	32·1 (30·0–35·2)	32·8 (24·4–36·8)	35·2 (34·0–36·8)
MCH, pg	29·5 (27·0–31·1)	29·0 (26·1–30·8)	29·6 (27·0–31·6)	29·5 (26·1–31·5)	30·4 (28·3–31·4)	30·6 (29·6–31·9)
MCV, fL	89·6 (84·1–94·0)	88·5 (82·0–93·3)	89·5 (83·4–94·8)	89·5 (81·0–94·8)	92·0 (88·1–96·7)	91·7 (89·6–94·9)
Ferritin, µg/L	124·5 (45·0–340·0)	74·5 (29·2–184·0)	204·0 (76·0–410·0)	69·0 (27·7–215·0)	229·0 (102·0–433·0)	410·0 (293·0–672·5)
Transferrin saturation, %	18·0% (12·0–26·1)	15·3% (9·5–22·0)	17·1% (12·3–25·0)	16·6% (9·0–22·0)	22·0% (13·0–30·0)	25·0% (19·9–37·0)
Vitamin B12, ng/L	399·0 (281·8–596·0)	383·4 (270·0–560·0)	352·3 (253·4–537·5)	138·9 (102·3–178·4)	546·0 (352·3–720·9)	452·9 (326·0–788·0)
Folate, µg/L	7·3 (4·4–11·6)	7·2 (4·4–11·0)	2·6 (1·8–3·5)	5·3 (3·3–9·0)	7·2 (4·3–11·3)	8·3 (5·8–10·6)
eGFR (MRDR), mL/min per 1·73 m²	77·6 (59·0–98·1)	76·5 (58·0–101·7)	75·8 (54·0–98·1)	69·8 (60·1–86·2)	18·4 (10·0–28·6)	84·2 (62·1–112·0)
eGFR (CKD-EPI), mL/min per 1·73 m²	75·4 (53·0–90·1)	75·5 (53·0–90·1)	81·1 (53·0–100·0)	76·0 (60·0–109·0)	11·3 (6·0–24·0)	82·0 (68·6–90·8)
CRP (mg/L)	4·5 (1·0–18·0)	4·0 (1·0–15·0)	7·7 (1·1–31·9)	2·5 (0·8–25·8)	3·8 (1·1–11·2)	1·0 (0·3–1·9)

Data are median (IQR). CRP=C-reactive protein. eGFR (CKD-EPI)=estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration). eGFR (MRDR)=estimated glomerular filtration rate (modification of diet in renal disease). MCH=mean corpuscular haemoglobin. MCV=mean corpuscular volume.

Table 2: **Blood results of patients with anaemia at baseline**

frequent in patients with anaemia compared with those without anaemia (appendix 2 p 23).

Among the 856 patients with anaemia, 74 patients were excluded from this analysis because neither the presence nor absence of any of the five aetiologies could be established. Of 782 patients with anaemia, 432 (55·2%, 95% CI 48·9–61·6) had iron deficiency, 60 (7·7%, 6·6–8·7) had vitamin B12 deficiency, 113 (14·5%, 12·2–16·7) had folate deficiency, 68 (8·7%, 8·1–9·3) had chronic kidney disease, and 48 (6·1%, 4·5–7·8) had anaemia resulting from another cause (table 2 and appendix 2 p 24).

Patients could be assigned to multiple aetiologies due to the multifactorial nature of anaemia. Overall, 293 (37·5%) patients with anaemia had only iron deficiency, 59 (7·5%) patients had iron and folate deficiency, 30 (3·8%) patients had iron deficiency and chronic kidney disease, 30 (3.8%) patients had iron and vitamin B12 deficiency, 29 (3·7%) patients had chronic kidney disease only, 26 (3·3%) patients had folate deficiency only, 15 (1·9%) patients had iron, vitamin B12, and folate deficiency, 22 (2·8%) patients with anaemia had various combinations, and 48 (6·1%) had anaemia of other causes (appendix 2 p 46). Across male and female sex, all age groups, and all countries, iron deficiency was the aetiology with the highest prevalence (figure 2A–C; appendix 2 pp 25–26).

Of the 856 patients with anaemia, 222 (25·9%) received preoperative management of anaemia. Of these treated patients, 108 (48·7%) received intravenous iron supplementation, 67 (30·2%) were given RBC transfusion, 44 (19·8%) received oral iron supplementation, 37 (16·7%) received vitamin B12 supplementation, 31 (14·0%) were administered intravenous erythropoietin, and 30 (13·5%) were given folic acid supplementation before surgery.

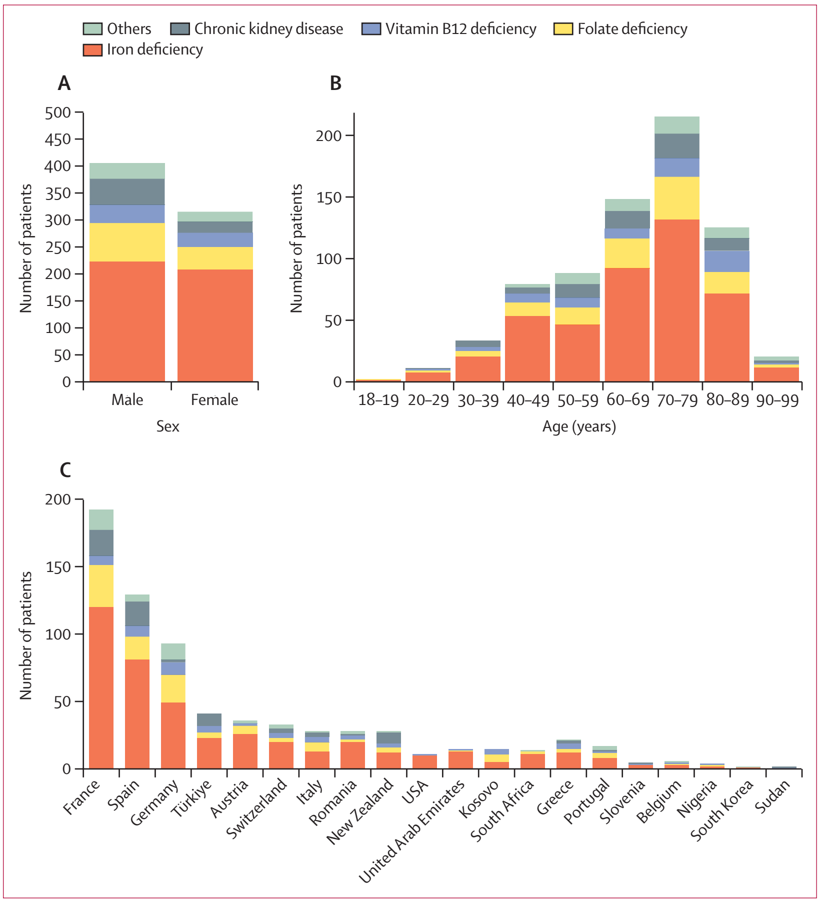

Figure 2: **Prevalence of aetiology of anaemia according to sex, age, and country**
Countries were ordered on the x-axis using the reorder function in R, which ranks factor levels by the mean count (n) across anaemia subtypes. With balanced representation across subtypes, this ordering corresponds to descending total counts; however, when the number of subtypes differs between countries, the ranking may diverge from totals. This explains why in some cases the order matches overall counts, while in others it reflects the average per subtype.

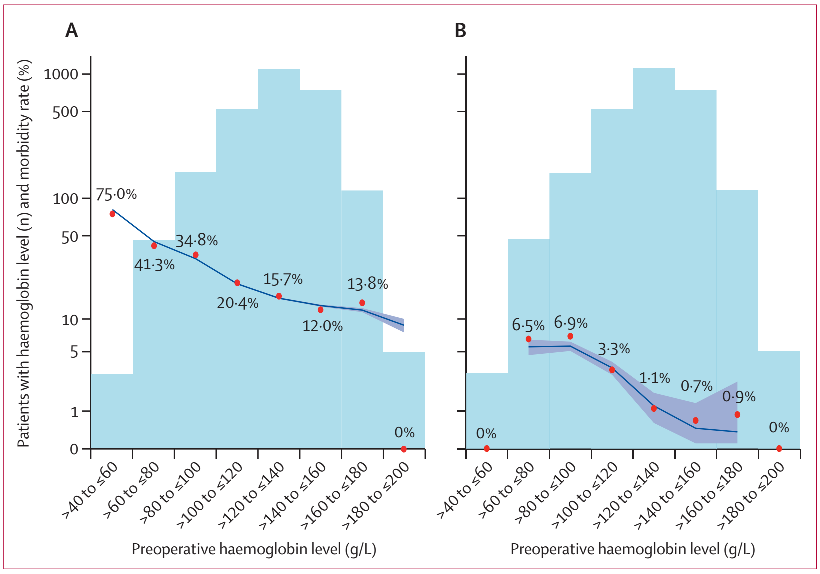

Figure 3: **Observed association of anaemia with morbidity and mortality**
Morbidity (A) and mortality (B) according to preoperative haemoglobin concentration. The y axes are plotted on a log scale and show both the number of patients within each haemoglobin category (depicted by the bars), and the mean predicted morbidity and mortality rates (solid line) and 95% CI (shaded area); red dots indicate the number of observed events in percentage (mean predicted events are displayed in appendix 2 p 34 and p 36).

Patients may have received combined treatments (appendix 2 p 27). Because of the number of combined treatments and different timing of treatment, the effect of anaemia management on haemoglobin was not analysed.

The prevalence of anaemia according to the types of surgery performed is shown in appendix 2 (p 28). Cell salvage was used in 78 (9·1%) of 856 patients with anaemia and in 236 (12·8%) of 1846 patients without anaemia (appendix 2 p 29).

Overall, the proportion of patients who received RBC units was significantly higher in patients with anaemia (270 [31·5%] of 856) than in patients without anaemia (199 [10·8%] of 1846; p<0·0001; appendix 2 p 29 and p 47).

The proportion of patients with anaemia who were admitted to the intensive care unit (ICU) was significantly higher than the proportion without anaemia (396 [46·3%] of 856 patients with anaemia *vs* 696 [37·7%] of 1846 patients without anaemia, p=0·0005). During the ICU stay, invasive ventilation was used in 100 (25·2%%) of the 397 patients with anaemia and in 195 (28·0%) of the 697 patients without anaemia (p=0.54; appendix 2 p 29).

The proportion of patients with any infection, wound infection, new renal replacement therapy, thromboembolic events, or readmission after discharge was significantly higher in the group of patients with anaemia than in the group without anaemia. Furthermore, the number of patients discharged within 90 days of surgery was significantly higher in the group without anaemia than in the group with anaemia. Length of hospital stay was significantly longer in patients with anaemia (7·0 days [IQR 4·0–12·0]) than in patients without anaemia (5·0 days [3·0–8·0], p<0·0001; appendix 2 p 31).

Using univariable mixed logistic regression analysis (n=2702), we identified associations with morbidity (defined as a binary composite endpoint comprising revision, thromboembolic events, new renal replacement therapy, and infection rate) for several factors: urgent surgery (odds ratio [OR] 3·3 [95% CI 2·2–4·9]), RBC transfusion (5·5 [4·3–7·0]), preoperative anaemia (2·1 [1·7–2·7]), and age (1·1 [1·0–1·2]). In the subsequent multivariable logistic regression analysis, only urgent surgery (OR 2·2 [1·4–3·5]) and RBC transfusion (4·1 [3·2–5·4]) remained statistically significant (appendix 2 p 32). The SD of the random intercept on the log scale, describing the variability in the baseline odds of in-hospital morbidity across centres, was estimated at 0·83, corresponding to an OR of 2·3 (95% CI 1·61–3·63). The odds for morbidity were significantly higher in patients with anaemia who had chronic kidney disease (OR 3·3 [1·8–6·2]) and folate deficiency (1·8 [1·1–2·9]) than in those with other aetiologies (appendix 2 p 33). As haemoglobin decreased, the mean predicted morbidity rate increased. Preoperative haemoglobin of >80–100 g/L was associated with a mean predicted morbidity rate of 32·3% (95% CI 32·0–32·6), whereas a preoperative haemoglobin of >120–140 g/L was associated with a mean predicted morbidity rate of 15·1% (14·9–15·3; figure 3A; appendix 2 p 34).

In our analysis, we observed a fivefold higher mortality rate in patients with anaemia (42 [4·9%] of 856 patients) compared with patients without anaemia (16 [0·9%] of 1846 patients; p<0·0001; appendix 2 p 31). Using univariable mixed regression analysis (n=2701), we found that urgent surgery (OR 7·8 [95% CI 3·4–17·7]), RBC transfusion (13·1 [7·0–26·0]), preoperative anaemia (6·2 [3·3–12·2]), and age (1·4 [1·1–1·7]) were associated with increased in-hospital mortality. In the multivariable logistic regression analysis, the following factors remained statistically significant: urgent surgery (OR 3·5 [95% CI 1·4–8·7]), preoperative anaemia (3·0 [1·5–6·3]), and RBC transfusion (6·5 [3·3–13·9]; appendix 2 p 35). The SD of the random intercept on the log scale, describing the variability in the baseline odds of in-hospital mortality across centres, was estimated at 0·64, corresponding to an OR of 1·9 (95% CI 1·0–3·7). As haemoglobin decreased, mean predicted mortality rate increased. Preoperative haemoglobin of >80–100 g/L was associated with a mean predicted mortality rate of 5·6% (95% CI 5·0–6·2) whereas preoperative haemoglobin of >120–140 g/L was associated with a predicted mortality rate of 1·2% (0·6–1·8; figure 3B; appendix 2 p 36).

Our post-hoc analysis showed similarities in patient characteristics, surgical disciplines, or the prevalence and causes of preoperative anaemia between the pre-COVID-19 onset cohort (recruited before March 1, 2020) and the post-COVID-19 onset cohort (recruited from March 1, 2020). Preoperative anaemia was diagnosed in

79 (27·4%) of 288 patients in the pre-COVID-19 cohort and 777 (32·2%) of 2414 patients in the post-COVID-19 cohort. Among patients with anaemia, iron deficiency was observed in 51 (64·6%) patients in the pre-COVID-19 cohort and 381 (49·0%) patients in the post-COVID-19 cohort. Vitamin B12 deficiency affected seven (8·9%) of 79 patients in the pre-COVID-19 group and 53 (6·8%) of 777 patients in the post-COVID-19 group, whereas folate deficiency was present in 12 (15·2%) of 79 patients in the pre-COVID-19 group and 101 (13·0%) of 777 patients in the post-COVID-19 group. Anaemia due to chronic kidney disease was identified in 11 (13·9%) of 79 patients in the pre-COVID-19 cohort and 57 (7·3%) of 777 in the post-COVID-19 cohort; anaemia of other causes occurred in 11 (13·9%) of 79 in the pre-COVID-19 cohort and 37 (4·8%) of 777 in the post-COVID-19 cohort (appendix 2 p 37).

Of the 2702 patients included in the post-hoc analysis, 1572 (58·2% [95% CI 56·3–60·1]) patients had haemoglobin greater than or equal to 130 g/L and 1130 (41·8% [39·9–43·8]) patients had haemoglobin less than 130 g/L (appendix 2 p 38). The proportion of patients with haemoglobin less than 130 g/L who received RBC units was significantly higher (314 [27·8%]) compared with patients with haemoglobin greater than or equal to 130 g/L (155 [9·9%], p<0·0001; appendix 2 pp 39–40, 47).

Overall, the number of patients with any infection, wound infection, new renal replacement therapy, thromboembolic events, and readmission after discharge was significantly higher in the group with haemoglobin less than 130 g/L compared with the group with haemoglobin greater than or equal to 130 g/L. In the multivariable logistic regression analysis, urgent surgery (OR 2·3 [95% CI 1·4–3·5]) and RBC transfusion (4·5 [3·2–5·4]) were statistically significant predictors of morbidity (appendix 2 p 41). In addition, urgent surgery (3·6 [1·4–8·7]), haemoglobin less than 130 g/L (3·5 [1·5–6·3]), and RBC transfusion (6·6 [3·3–13·9]) were statistically significant predictors of in-hospital mortality (appendix 2 p 42).

Discussion

In this prospective, international, observational cohort study conducted in 79 hospitals across 20 countries on five continents, 31·7% of patients undergoing major surgery were anaemic. Low preoperative haemoglobin concentration was an independent risk factor for serious adverse outcomes: anaemia was associated with an increased risk of allogenic RBC transfusion, admission to ICU, and postoperative complications. Furthermore, patients with anaemia had a fivefold higher risk of death compared with patients without anaemia. Our findings underline the harmful effect of anaemia on surgical outcomes.

Anaemia is most often the result of inadequate erythropoiesis due to iron deficiency, lack of vitamin B12 or folate, bone marrow diseases, chronic kidney disease, or chronic inflammation. Although dietary iron deficiency is the main cause of anaemia, there is little information about the prevalence of other causes of anaemia in patients undergoing major surgery. Only a few studies have previously evaluated the aetiology of anaemia in surgical patients in a comprehensive manner.[15,21–25] For example, Bisbe and colleagues analysed 65 patients with anaemia who were undergoing major orthopaedic surgery and found 18·4% with chronic disease, 16·9% with isolated iron deficiency, and 10·7% with a combination of chronic disease and folate or vitamin B12 deficiency (or all three).[21] Hung and colleagues diagnosed anaemia in 165 cardiac surgical patients and showed that 45% had chronic disease, 16% had chronic kidney disease, 11% were vitamin B12 deficient, and 7% were iron deficient.[22]

To the best of our knowledge, this study is one of the largest prospective cohorts to date designed to assess this topic and is the first study to provide an extensive international overview of the aetiology of anaemia according to age, sex, and country in patients undergoing major surgery.

Overall, our analysis revealed that iron deficiency was the aetiology of anaemia with the highest prevalence in both sexes, all age categories, and in all countries. Of 782 patients with anaemia, 55·2% had iron deficiency, followed by 14·5% with folate deficiency, 7·7% with vitamin B12 deficiency, and 8·7% who had anaemia resulting from chronic kidney disease. Transfusion of RBCs leads to a temporary increase in haemoglobin but does not correct the underlying metabolic deficiencies associated with anaemia. In other words, transfusion enables a short improvement in oxygen delivery but does not replenish iron stores or correct nutritional deficiencies such as folate or vitamin B12 deficiency. However, effective management of anaemia requires timely diagnosis and treatment. In a pragmatic approach, Spahn and colleagues applied a treatment bundle consisting of erythropoietin, intravenous iron, vitamin B12, and folate in patients who had anaemia or iron deficiency, 1–3 days before cardiac surgery.[26] This combined treatment was associated with a reduced RBC transfusion rate during the first 7 days after surgery. Considering that every sixth patient with anaemia undergoing major surgery is deficient in vitamin B12 and every 12th patient is deficient in folate, a multidrug treatment bundle should be considered in future. However, the iron-dependent maturation from erythroblasts to differentiated RBCs takes up to 4–6 days; therefore, therapeutic measures should be applied at least 7 days, but preferably 21–28 days, before surgery.

In 6·1% of 782 patients with anaemia, the cause of anaemia could not be verified. The aetiology of anaemia is multifactorial, and also includes haemoglobinopathy, autoimmune diseases, diseases of the liver, bone marrow cancer, ageing, or can be inherited (eg, sickle cell anaemia)—factors that have not been assessed in this study.

Studies have shown that haematinic deficiencies in patients without anaemia can adversely affect post-operative outcomes.[27,28] For example, patients with low iron stores might lack the necessary reserves to produce new RBCs. Therefore, extending preoperative anaemia management to include patients without anaemia should be considered to optimise surgical outcomes.

It is noteworthy that the COVID-19 pandemic started during data collection for this study. In August 2020, a survey was done to assess the effect of the pandemic on the progress of the study, the results of which have been published elsewhere.[29] During the peak of the pandemic, 65% of the responding hospitals had to postpone or cancel most planned major procedures, whereas 31% reported a reduction in surgical volume. Only 3% of the centres reported no changes in daily surgical procedures. Around 3 months after the initial wave of SARS-CoV-2 infections, 44% of the participating hospitals had returned to their prepandemic surgical volumes.[29] However, our analysis revealed no substantial differences in patient characteristics, surgical disciplines, or the prevalence and causes of preoperative anaemia between the pre-COVID-19 and post-COVID-19 cohorts, with iron deficiency remaining the most common cause in both groups.

Food fortification is a key tool for improving global nutrition and health outcomes. It requires no behavioural changes and helps combat conditions such as anaemia and neural tube defects. However, concerns remain about safety, necessity, and unintended consequences, including overconsumption, unequal benefits, and failure to address the root causes of malnutrition.[30] We did not compare countries with fortified foods with countries without fortified foods, as our study was not specifically designed or powered to evaluate outcomes between these groups. It is notable that surgical patients might have increased nutritional demands or altered metabolism, which warrants the assessment of deficiencies even in countries with food fortification programmes.

This study has several limitations. First, the causes of anaemia are multifactorial; however, we focused on selected aspects to provide a more targeted analysis. In general, anaemia of chronic inflammation has not yet been addressed in detail. The pathogenesis of anaemia of chronic inflammation is multifactorial with a number of processes involved, leading, for instance, to dysregulation of iron homoeostasis, changes in the production of erythropoietin, or a shortened life span of RBCs. Anaemia of chronic inflammation can be observed in patients with autoimmune diseases, chronic infections, or cancer. Second, the cutoff values to diagnose iron deficiency have been rigorously debated in the last two decades. WHO recommends a ferritin cutoff value of less than 15 μg/L in healthy individuals and less than 70 μg/L in individuals with infection or inflammation for the diagnosis of iron deficiency,[31] whereas the American Society of Hematology uses a ferritin cutoff of 25 μg/L.[32] In addition, we found that most hospitals use only ferritin to diagnose iron deficiency, whereas transferrin saturation or soluble transferrin receptor were seldom considered. Reasons for using only ferritin included associated costs, lack of awareness, or institutional policies restricting the ordering of iron status when ferritin values exceed 100 μg/L. Therefore, we cannot exclude that the prevalence of anaemia caused by iron deficiency would have been different if different parameters for diagnosis had been considered. The same applies to vitamin B12 or folic acid deficiency; different cutoff values for these might also have led to varying prevalence. Third, WHO's anaemia threshold for women has been much discussed, with several studies indicating that suboptimal total haemoglobin mass places patients undergoing major surgery at an unreasonable disadvantage. In this respect, some evidence supports adjusting the anaemia threshold for women from 120 g/L to 130 g/L to better reflect physiological needs and clinical outcomes.[25,33–36] However, using a uniform haemoglobin threshold of less than 130 g/L for all sexes, our results were similar to those obtained using WHO-defined anaemia thresholds. Furthermore, we cannot rule out the possibility that the underlying causes of decreased haemoglobin might vary depending on the definition of anaemia used. Finally, the majority of patients (82%) included in the study were from high-income countries mainly located in Europe. Given that the prevalence of anaemia is substantially higher in low-income countries, the observed prevalence in this study might be underestimated. Therefore, our results might not be fully generalisable to populations in low-income countries.

In this worldwide study, 31·7% of patients undergoing major surgery from 2019 to 2022 had anaemia, with iron deficiency being the leading cause of anaemia. In addition, the prevalence of both vitamin B12 and folate deficiency among patients with anaemia was high and needs to be addressed in the future. Our study has reaffirmed that anaemia adversely affects postoperative outcomes. In particular, patients with anaemia who are undergoing major surgery have an increased risk for morbidity, longer length of hospital stay, and a fivefold higher mortality rate compared with patients without anaemia. Preoperative anaemia appears to be a suitable target for perioperative risk modification and implementation of a comprehensive approach to the management of anaemia might improve outcomes.

Contributors

SC: conceptualisation, data curation, analysis, methodology, project administration, validation, visualisation, writing the original draft, and review and editing. KZ: conceptualisation, methodology, interpretation of analysis, supervision, principal investigator, and review and editing. DMB: conceptualisation, methodology, interpretation of analysis, and review and editing. DRS: conceptualisation, methodology, interpretation of analysis, and review and editing. MP: methodology, formal analysis, interpretation of analysis, and review and editing.

DB: formal analysis, interpretation of analysis, and review and editing. LY: formal analysis, interpretation of analysis, and review and editing. SL: conceptualisation, methodology, interpretation of analysis, and review and editing. EB: conceptualisation, methodology, interpretation of analysis, and review and editing. PhM: conceptualisation, methodology, interpretation of analysis, and review and editing. MR: conceptualisation, methodology, interpretation of analysis, and review and editing. PaM: conceptualisation, methodology, interpretation of analysis, supervision, principal investigator, writing original draft, and review and editing. All authors were involved in data collection, had access to and contributed to the analysis or interpretation of the data, and were involved in the writing, reviewing, and amending of the manuscript. All authors approved the final draft and had final responsibility for the decision to submit for publication. DB, LY, MP, SC, and PM accessed and verified the data.

Declaration of interests

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Data sharing

The datasets used or analysed in this study are available from the corresponding author on reasonable request.

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