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Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study

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Abstract

Background: Iron deficiency is frequent in patients undergoing cardiac surgery. The relevance of iron deficiency, however, is ill defined. Therefore, our study aimed to investigate the impact of iron deficiency (ferritin <100 μg L^{-1}) with or without concomitant anaemia on clinical outcome after cardiac surgery.

Methods: In this prospective observational study, 730 patients undergoing elective cardiac surgery were assigned into four groups according to their iron status and anaemia. Mortality, serious adverse events (SAEs), major cardiac and cerebrovascular events (MACCEs), allogenic blood transfusion requirements, and length of hospital stay were assessed during a 90-day follow-up period. The effect of iron deficiency on these outcomes was first calculated in models adjusting for anaemia only, followed by two multivariate models adjusting for anaemia and either the EuroSCORE II or any possible confounders.

Results: The presence of iron deficiency (ferritin <100 μg L^{-1}) was associated with an increase in 90-day mortality from 2% to 5% in patients without anaemia, and from 4% to 14% in patients with anaemia. Logistic regression resulted in an odds ratio of 3.5 (95% confidence interval: 1.5–8.4); P=0.004. The effect persisted in both multivariate models. Moreover, iron deficiency was associated with an increased incidence of SAEs, MACCEs, transfusion, and prolonged hospital stay.

Conclusions: Preoperative iron deficiency (ferritin <100 μg L^{-1}) was independently associated with increased mortality, more SAEs, and prolonged hospital stay after cardiac surgery. These findings underline the importance of preoperative iron deficiency screening in the context of a comprehensive patient blood management programme, and highlight its importance as a research topic in cardiac surgery.

Clinical trial registration: NCT02031289.

Keywords: adverse events; anaemia; mortality; patient blood management; preoperative; surgical risk; transfusion

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Editor's key points

- Although anaemia is a recognised risk factor in surgery, iron deficiency without anaemia may also be important.
- This study found that preoperative iron deficiency was associated with a more than three-fold increased risk of death after cardiac surgery.
- These results highlight the potential value in treating iron deficiency, even when anaemia is not present.

Iron deficiency (ID) is frequent in heart failure, with a prevalence of about 50% regardless of sex, race, anaemia, and left ventricular function.[1] In these settings, ID is associated with a worse outcome in both its isolated form and in combination with anaemia.[1–3] It is unclear whether ID impacts outcome in cardiac surgery. In patients scheduled for elective cardiac surgery, ID is a common finding: up to 20% of all patients suffer from isolated, absolute ID, and another 20% present with low iron stores.[4] For both, a preoperative ID treatment is proposed.[4,5] Treatment of ID has shown to be beneficial in patients with heart failure and is suggested in general surgery.[6] The benefits of treating ID may include lower transfusion rates, shorter hospital stay, and less postoperative fatigue.[7,8] Therefore, the recommendation is that ID should be treated before elective surgeries.[5,7,9] In a prospective randomised trial, Spahn and colleagues[10] investigated the effect of an ultrashort-term combination treatment on anaemia and ID before cardiac surgery, and further prospectively registered natural controls. We therefore undertook a secondary analysis of the complete data set to investigate whether ID adversely affects outcome. Our hypothesis was that, irrespective of anaemia, ID is associated with higher transfusion rates, more serious adverse events (SAEs), and an increase in mortality.

Methods

Trial design and patients

This was an observational, secondary study based on a single-centre RCT in patients undergoing elective cardiac surgery. The results of the original study by Spahn and colleagues[10] and details of the study protocol have been published previously. Men and women aged 18 yr or over with planned isolated coronary artery bypass grafting (CABG), isolated valve surgery, or combined CABG and valve procedures qualified for the study. The eligibility and exclusion criteria are provided in Supplementary Table S1, and have also been published in detail in the aforementioned study.[10] All patients signed a written informed consent form. Our study was performed in accordance with the guidelines of Good Clinical Practice, was approved by the local ethics committee of Zurich (KEK ZH 2013-0043), and registered online at https://clinicaltrials.gov/ (NCT02031289).

Anaemia was defined as haemoglobin (Hb) concentration $<120\ g\ L^{-1}$ in women and Hb $<130\ g\ L^{-1}$ in men, whereas ID was defined as serum ferritin $<100\ \mu g\ L^{-1}$.

Setting

Treatment of all enrolled patients was according to the standards of the Institute of Anaesthesiology and the Department of Cardiovascular Surgery of the University Hospital Zurich. This included application of usual hospital transfusion guidelines, with a transfusion threshold of Hb 70–80 $g\ L^{-1}$ intraoperatively and in the ICU. Whilst on the regular ward, the threshold was set at Hb $<80\ g\ L^{-1}$. Patients also received standard thrombosis prevention with compression stockings and, if bedridden, additional low-molecular-weight heparin before the surgery. As EuroSCORE was changed from EuroSCORE I to EuroSCORE II during patient enrolment, we reassessed EuroSCORE II in patients for which the original score was assessed.

Variables and outcomes

Outcomes and number of transfusions were recorded during the primary hospitalisation and at the time of the first postoperative consultation with the referring cardiologist, which was scheduled at postoperative day 90 (POD 90). All available data were analysed.

Our primary outcome was 90-day mortality. Key secondary outcomes included SAEs or major adverse cardiac and cerebrovascular events (MACCEs). The latter was defined as death, acute myocardial infarction, or acute ischaemic stroke. The definition of an SAE was prespecified in the trial protocol as any adverse event that results in death, is life threatening, requires inpatient hospitalisation or causes prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or may have caused a congenital anomaly/birth defect.

Other secondary outcomes were the length of the ICU stay, the duration of mechanical ventilation, and the length of stay in the hospital. Transfusion outcomes were the number of allogenic blood products given until POD 90 or death.

Other outcomes at POD 90 consisted of acute kidney injury (increase of creatinine >50% *vs* preoperative value), newly necessary dialysis, infections requiring antibiotic treatment, atrial fibrillation, additional unplanned surgery (i.e. laparotomy and re-thoracotomy), thromboembolic events, bleeding, and resuscitation. We also assessed the incidence of angina and myocardial infarction. The latter was defined as an increase of high-sensitivity troponin (>10 times 99th percentile of reference value) with documented new obstruction of a coronary artery or bypass in coronary angiogram. Stroke was defined as a new onset of an irreversible neurological deficit corresponding to a new lesion in imaging.

Statistical analysis

Differences between patients with and without ID were assessed in regression analyses with ID and anaemia as independent variables. Therefore, all results for ID were adjusted for anaemia. Interactions were analysed and significant interactions are mentioned, but results are reported from models without interaction. Continuous variables were analysed using linear regression. Normal distribution of residuals was assessed visually using histograms and *P*–*P* plots. Normally distributed data are presented as mean (standard deviation). If a normal distribution was not accepted, logarithmically transformed data were analysed. For this analysis, zero values were replaced by half of the smallest non-zero value. Then, data are presented as median with inter-quartile range (IQR), and the linear regression is reported as relative increase with 95% confidence interval (CI). Binary variables are presented as frequency with percentage, and were analysed using binary logistic regression. Model fit was assessed using the Hosmer–Lemeshow test, and

Table 1 Patient characteristics. Data are reported as mean (standard deviation) for normally and median (inter-quartile range) for not normally distributed continuous variables, or number of patients (%). Regression with iron deficiency as the regressor is linear for continuous variables, logistic for dichotomous variables, or nominal for nominal variables, and is always adjusted for anaemia. CABG, coronary artery bypass grafting; CRP, C-reactive protein; CV, cardiovascular; NT-proBNP, N-terminal prohormone of brain natriuretic peptide. *P-value computed for the logarithmically transformed variable. †Significant interaction between anaemia and iron deficiency.

	No anaemia		Anaemia		Regression (*P*-value for iron deficiency)
	No iron deficiency (*n*=489)	Iron deficiency (*n*=119)	No iron deficiency (*n*=85)	Iron deficiency (*n*=37)	
Age (yr)	66 (10); range: 29–85	63 (13); range: 27–89	71 (10); range: 33–88	70 (10); range: 37–84	0.023
Female sex	106 (22)	51 (43)	15 (18)	16 (43)	<0.001
Height (cm)	171 (9)	169 (10)	169 (10)	166 (9)	0.027
Weight (kg)	81 (15)	76 (16)	78 (15)	78 (17)	0.001
BMI (kg m^{-2})	27 (25–30)	26 (23–29)	27 (25–29)	27 (24–33)	0.005*†
EuroSCORE II	1.2 (0.7–2.0)	1.4 (0.8–2.8)	2.3 (1.2–4.5)	2.9 (1.3–4.9)	0.014*
Previous cardiac surgery	9 (2)	4 (3)	2 (2)	2 (5)	0.19
Dual platelet inhibition	57 (12)	11 (9)	17 (20)	10 (27)	0.89
Haemoglobin (g L^{-1})	144 (11)	140 (10)	119 (8)	114 (11)	<0.001
Reticulocyte count (g L^{-1})	52 (42–65)	48 (40–60)	50 (40–63)	53 (40–69)	0.21*
Reticulocyte haemoglobin (pg)	34 (2)	33 (2)	34 (4)	32 (4)	<0.001
Ferritin (mg L^{-1})	223 (154–326)	59 (43–82)	227 (157–354)	60 (33–82)	<0.001*
Holotranscobalamin (pmol L^{-1})	79 (57–106)	71 (51–94)	79 (42–116)	84 (51–107)	0.067*
Folic acid in erythrocyte (mg L^{-1})	408 (321–509)	404 (313–540)	406 (316–593)	461 (377–633)	0.25*
Creatinine (mmol L^{-1})	87 (20)	82 (19)	97 (30)	94 (33)	0.033
Estimated glomerular filtration rate (ml min^{-1})	78 (17)	80 (18)	69 (20)	69 (25)	0.28
Platelet count (g L^{-1})	229 (62)	219 (54)	230 (75)	248 (78)	0.48†
High-sensitivity troponin (ng L^{-1})	13 (7–30)	8 (5–17)	23 (13–149)	21 (16–35)	0.039*
CRP (mg L^{-1})	2 (1–4)	1 (1–4)	7 (2–18)	3 (1–6)	<0.001*†
NT-proBNP (ng L^{-1})	273 (109–713)	290 (113–808)	992 (399–2025)	557 (206–1670)	0.74*
Alcohol consumption	147 (30)	17 (14)	23 (27)	9 (24)	0.001
Smoking	282 (58)	57 (48)	51 (60)	23 (62)	0.11
Hospitalisation for CV disease in last 4 weeks	104 (21)	16 (13)	37 (44)	19 (51)	0.026
Angina pectoris	241 (49)	57 (48)	39 (46)	13 (35)	0.95
Myocardial infarction	103 (21)	19 (16)	31 (37)	13 (35)	0.26
Infection	28 (6)	4 (3)	19 (22)	4 (11)	0.081
Gastrointestinal disease	25 (5)	14 (12)	13 (15)	3 (8)	0.13
Kidney disease	86 (18)	21 (18)	28 (33)	14 (38)	0.77
Liver disease	5 (1)	2 (2)	2 (2)	0 (0)	0.99
Malignant disease	47 (10)	9 (8)	11 (13)	3 (8)	0.33
Type of surgery					0.062
CABG only	251 (51)	41 (35)	42 (39)	22 (59)	
Valve only	182 (37)	58 (49)	22 (26)	9 (24)	
CABG–valve combined	56 (12)	19 (16)	21 (25)	6 (16)	

odds ratios (ORs) with 95% CI are reported. Numbers of units transfused were analysed using ordinal logistic regression. Model fit was assessed using deviance, and ORs, which are assumed to be the same for each threshold of number of transfusions, are reported with 95% CI. The type of surgery was analysed using nominal logistic regression. Model fit was assessed using deviance, and the overall *P*-value of the likelihood-ratio test for ID was reported. Kaplan–Meier estimates of overall survival were plotted for each group. The hazard ratio for ID was calculated by Cox proportional hazards regression adjusted for anaemia.

To adjust for possible confounders of the effect of ID, two multiple regression analyses were performed for each of the outcomes death, SAEs, MACCEs, red cell units transfused, and total units of allogenic blood product transfused at POD 90. The first model was chosen for clinical reasons. The corresponding effect of ID was adjusted for anaemia and the logit-transformed EuroSCORE II. In the second model, ID and anaemia were forced into the model. All variables in Table 1 with a $P<0.1$, which are not directly associated with ID or anaemia, were added in a stepwise variable selection. Exceptions were EuroSCORE II and high-sensitivity troponin, which was not measured regularly before operation. As the data in these analyses were 99.8% complete, missing values were simply replaced by the corresponding median. When appropriate, the variables were logarithmically transformed, as marked in Table 1.

All analyses were carried out in IBM® SPSS® Statistics 25 (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 was considered to indicate statistical significance. There was no adjustment or correction of *P*-values for multiple testing. All figures were designed using Prism 8 (GraphPad Software, La Jolla, CA, USA).

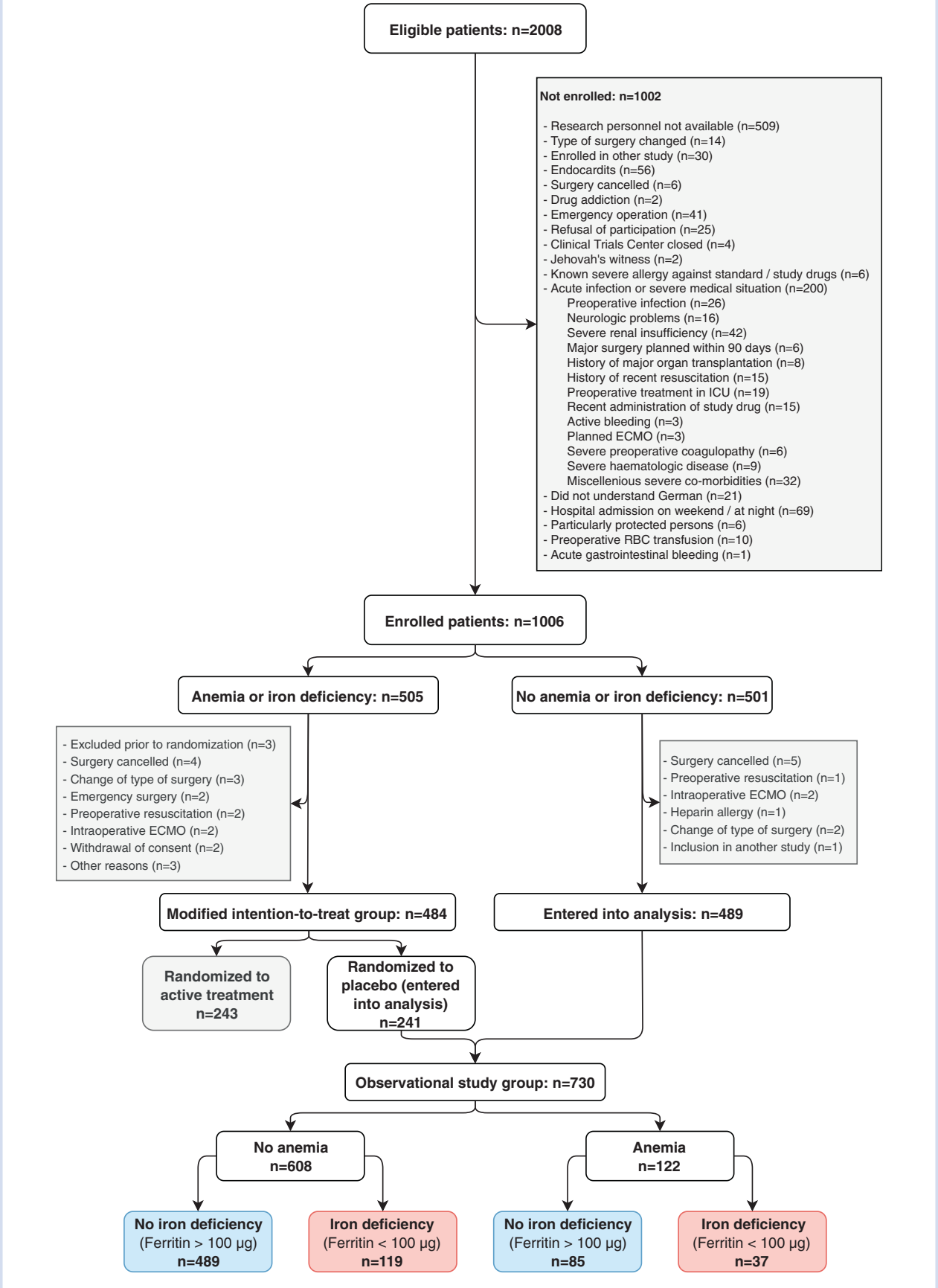

Fig 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. Study flow of patients. RBC, red blood cell. ECMO, extracorporeal membrane oxygenation.

Results

Study population

From January 9, 2014 to July 19, 2017, 1006 patients were enrolled. Originally, 505 patients with anaemia or ID were entered and analysed in the original clinical trial,[10] whereas 501 patients without anaemia or ID were prospectively entered into a registry. A total of 33 patients were excluded. The reasons for exclusion are shown in Figure 1.

In our current secondary analysis, the 241 patients receiving placebo from the RCT and 489 eligible patients from the registry were entered into our study population. These 730 patients were assigned into four groups according to their status of anaemia and ID: patients without anaemia or ID (n=489), patients without anaemia but with ID (n=119), patients with anaemia but without ID (n=85), and patients with anaemia and with ID (n=37) (Fig. 1).

The group differences show that our patients with ID are more often female, of lower weight, of smaller height, and consume less alcohol. Furthermore, without anaemia, patients with ID have a lower Hb and reticulocyte Hb. C-reactive protein (CRP) is higher in both groups without ID, but there was a significant interaction between the anaemia groups as well. The EuroSCORE II is higher in patients with ID both with and without anaemia. There were no significant differences between the types of surgery or previous history of cardiac surgery (Table 1).

The POD 90 follow-up visit took place at a median of 97, IQR 90–112 postoperative days. Seven patients were lost to follow-up, and hence, follow-up was complete at 90 days for 99% of patients.

Effect of iron deficiency

Mortality

The presence of ID was associated with an increase in 90-day mortality from 2% to 5% without anaemia, and from 4% to 14% with concomitant anaemia (OR for ID adjusted for anaemia: 3.5; 95% CI: 1.5–8.4); P=0.004 (Table 2; Fig. 2; Supplementary Table S2). The Kaplan–Meier estimates of overall survival are presented in Figure 3. The corresponding Cox regression adjusted for anaemia yielded a hazard ratio for death associated with ID of 3.4 (95% CI: 1.5–8.0); P=0.004.

To verify the results in the face of different co-morbidities or other possible confounders, two models of multivariate regression of the effect of ID on 90-day mortality were calculated. The first model, adjusted for anaemia and EuroSCORE II, resulted in an OR of 3.2 (95% CI: 1.3–7.8); P=0.010. The second model was adjusted for anaemia, age, and height, and yielded an OR of 3.9 (95% CI: 1.6–9.4); P=0.003, for ID (Fig. 4; Supplementary Tables S3 and S4).

Serious adverse events

The number of SAE was higher in patients with ID, from 16% to 35%, and from 28% to 38%, respectively, in the subgroups without and with anaemia (OR: 2.5; 95% CI: 1.6–3.7); P=0.001 (Fig. 2; Supplementary Table S2). Multivariate regression for SAE with anaemia and the EuroSCORE II in the model resulted in an OR of 2.3 (95% CI: 1.5–3.5); P=0.001. The second model was adjusted for anaemia, age, CRP, and type of surgery, and yielded an OR of 3.0 (95% CI: 2.0–4.6); P<0.001 (Fig. 4; Supplementary Tables S3 and S4).

Similarly, ID was associated with an increase in MACCE from 5% to 8% without and from 5% to 19% with concomitant anaemia (OR: 2.1; 95% CI: 1.1–4.0; P=0.017) (Fig. 2; Supplementary Table S2). For MACCE, the two multivariate regression models yielded an OR of 1.9 (95% CI: 1.0–3.6); P=0.047, for the first, and an OR of 2.4 (95% CI: 1.2–4.6) for ID; P=0.009, for the second model, which was adjusted for anaemia, age, height, and CRP (Fig. 4; Supplementary Tables S3 and S4).

Transfusion outcomes

Transfusions of allogenic blood products within 90 days were significantly increased by ID in both subgroups (OR: 1.9; 95% CI: 1.3–2.7) for ID; P=0.001. Transfusions of red cells and fresh frozen plasma (FFP) also increased in both groups, with an OR of 2.0 (95% CI: 1.4–2.8) for ID; P=0.001 and an OR of 1.89 (95% CI: 1.34–2.67) for ID; P=0.001, respectively (Table 2; Supplementary Table S2).

Multivariate regression analysis for the effect of ID on transfusion outcomes was also calculated in two models. The first model was adjusted for anaemia and the EuroSCORE II, whilst the second model was adjusted for age, sex, weight, plasma transcobalamin, and type of surgery. For total transfusion of allogenic blood products, these models yielded an OR of 1.7 (95% CI: 1.2–2.4) for ID; P=0.004, and an OR of 1.7 (95% CI: 1.2–2.5) for ID; P=0.003, for the first and second models, respectively. For red cell transfusions, the first model resulted in an OR of 1.8 (95% CI: 1.2–2.6) for ID; P=0.002, and the second in an OR of 1.8 (95% CI: 1.2–2.6) for ID; P=0.002 (Fig. 4; Supplementary Tables S3 and S4).

Length of stay

ID was associated with an increased ICU length of stay by 17% (95% CI: 0–37%); P=0.044, and in-hospital length of stay by 8% (95% CI: 0–18%); P=0.045 (Table 2).

Adverse events

Adverse events are summarised in Table 3.

Discussion

In this study, we show that iron deficiency (serum ferritin <100 μg L^{-1}) is a significant risk factor for adverse outcome in cardiac surgery. This is the largest prospective study showing the effect of preoperative ID in a diverse group of patients undergoing elective cardiac surgery. After adjustment for confounders, a preoperative serum ferritin <100 μg L^{-1} was associated with a more than three-fold increased risk of death by Day 90. Furthermore, the odds of SAE and MACCE were more than doubled. These effects came along with increased transfusion requirements, and were accompanied by longer ICU and in-hospital stays. The significance of these results persisted in two different regression models. We chose the first model with medical reasoning, and adjusted for anaemia and the EuroSCORE II. The second model was generated on a statistical basis: all significant group differences were added in a stepwise variable selection to the model. Therefore, we created an individual regression model for each outcome by always using the same approach.

Our results are in line with smaller previous studies about ID in cardiac surgery, which have shown ID to be associated

Table 2 Outcomes. Data are reported as mean (standard deviation [SD]), median (inter-quartile range [IQR]), or number of patients (%). Linear regression for continuous variables, logistic regression for dichotomous variables, and ordinal regression for transfusion outcomes. The regressor is iron deficiency. All regressions are adjusted for anaemia. CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular event (stroke, myocardial infarction, or death); OR, odds ratio; POD, postoperative day; SAE, serious adverse event. *P-value computed for the logarithmically transformed variable.

	No anaemia		Anaemia		Regression	
	No iron deficiency (*n*=489)	Iron deficiency (*n*=119)	No iron deficiency (*n*=85)	Iron deficiency (*n*=37)	*P*-value for iron deficiency	OR or relative increase (95% CI)
Death: Day 0 to POD 90, no. of patients (%)	8 (2)	6 (5)	3 (4)	5 (14)	0.004	3.5 (1.5–8.4)
SAE: Day 0 to POD 90, no. of patients (%)	76 (16)	41 (35)	24 (28)	14 (38)	<0.001	2.5 (1.6–3.7)
MACCE: Day 0 to POD 90, no. of patients (%)	26 (5)	10 (8)	4 (5)	7 (19)	0.017	2.1 (1.1–4.0)
Duration of stay						
Length of stay in ICU (days)					0.044*	17% (0–37%)
Mean (SD)	1.9 (4.7)	2.4 (4.7)	3.0 (6.3)	3.2 (4.3)		
Median (IQR)	0.9 (0.8–1.1)	1.0 (0.9–1.8)	1.0 (0.9–2.0)	1.0 (0.9–3.5)		
Length of stay in hospital (days)					0.045*	8% (0–18%)
Mean (SD)	9.6 (6.7)	12.3 (12.2)	11.9 (7.2)	13.3 (13.9)		
Median (IQR)	7.8 (6.8–10.6)	8.9 (6.8–12.9)	9.6 (6.9–13.8)	9.1 (7.0–15.3)		
Duration of mechanical ventilation (h)					0.32*	10% (−9%–34%)
Mean (SD)	13.4 (42.0)	20.5 (61.8)	21.3 (55.5)	20.4 (38.0)		
Median (IQR)	4.8 (3.3–7.5)	5.3 (3.9–8.5)	5.5 (4.0–10.1)	6.0 (3.3–13.0)		
Transfusion outcomes (Day 0 to POD 90)						
Red cell units transfused					<0.001	1.97 (1.39–2.80)
Mean (SD)	1.0 (3.5)	1.7 (3.1)	2.5 (3.0)	3.5 (4.2)		
Median (IQR)	0 (0–0)	0 (0–2)	2 (0–3)	2 (0–6)		
No. of patients (%)	120 (25)	50 (42)	59 (69)	25 (68)		
Fresh frozen plasma units transfused					0.004	4.90 (1.66–14.44)
Mean (SD)	0.1 (0.7)	0.4 (2.3)	0.1 (0.5)	0.2 (0.7)		
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)		
No. of patients (%)	4 (1)	6 (5)	2 (2)	2 (5)		
Platelet concentrate units transfused					0.16	1.45 (0.86–2.43)
Mean (SD)	0.2 (1.3)	0.4 (1.5)	0.3 (0.8)	0.4 (1.2)		
Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)		
No. of patients (%)	46 (9)	17 (4)	14 (16)	6 (16)		
Total units of allogeneic blood products					<0.001	1.89 (1.34–2.67)
Mean (SD)	1.3 (5.0)	2.5 (6.0)	2.9 (3.7)	4.0 (5.2)		
Median (IQR)	0 (0–1)	0 (0–2)	2 (0–4)	2 (0–6)		
No. of patients (%)	134 (27)	52 (44)	59 (69)	25 (68)		

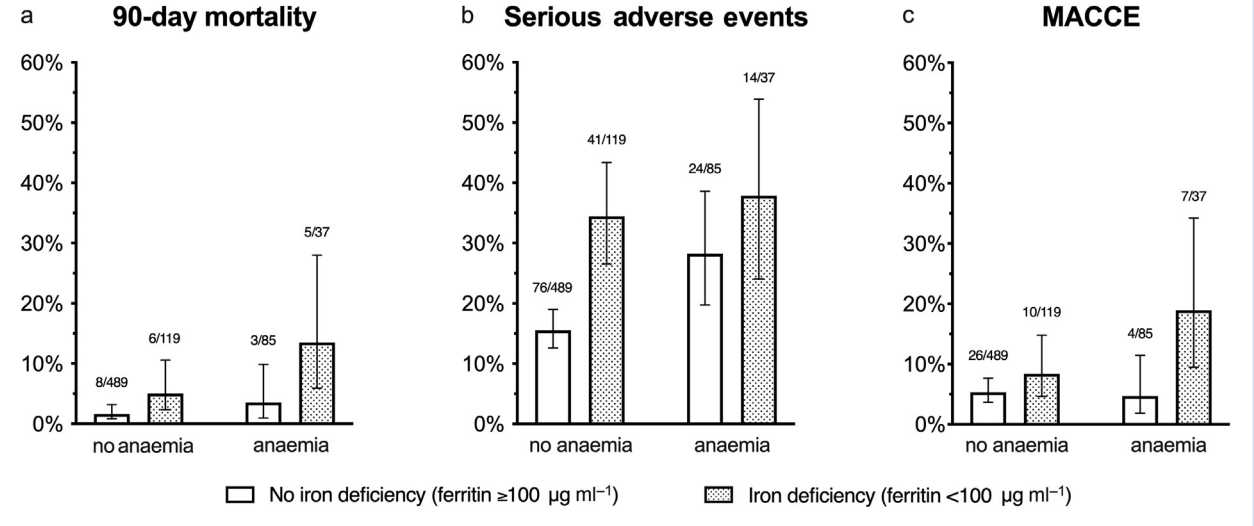

Fig 2. Frequency graphs. Bar graphs showing the frequency of (a) 90-day mortality, (b) serious adverse events, and (c) major adverse cardiac and cerebrovascular events (MACCE). The frequencies in the four groups are shown in percent with 95% Wilson confidence intervals. Group differences for iron deficiency adjusted for anaemia are significant: (a) P=0.004, (b) P=0.001, and (c) P=0.017.

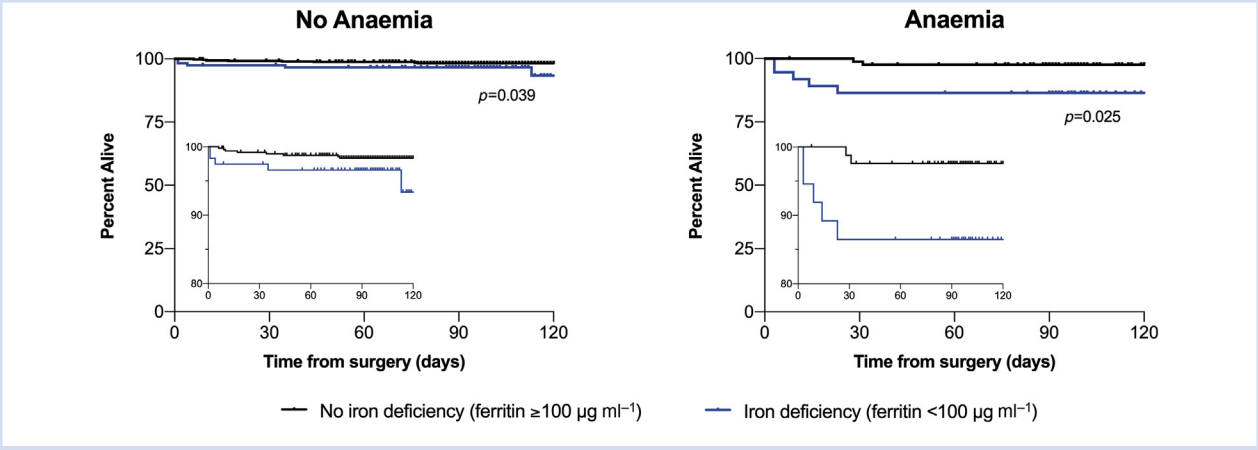

Fig 3. Kaplan–Meier analysis of mortality. The insert in the graphs is an enlarged version thereof, showing percent alive from 80% on upwards. *P*-values are calculated from log-rank test. Cox regression for iron deficiency adjusted for anaemia yielded an overall *P*=0.004.

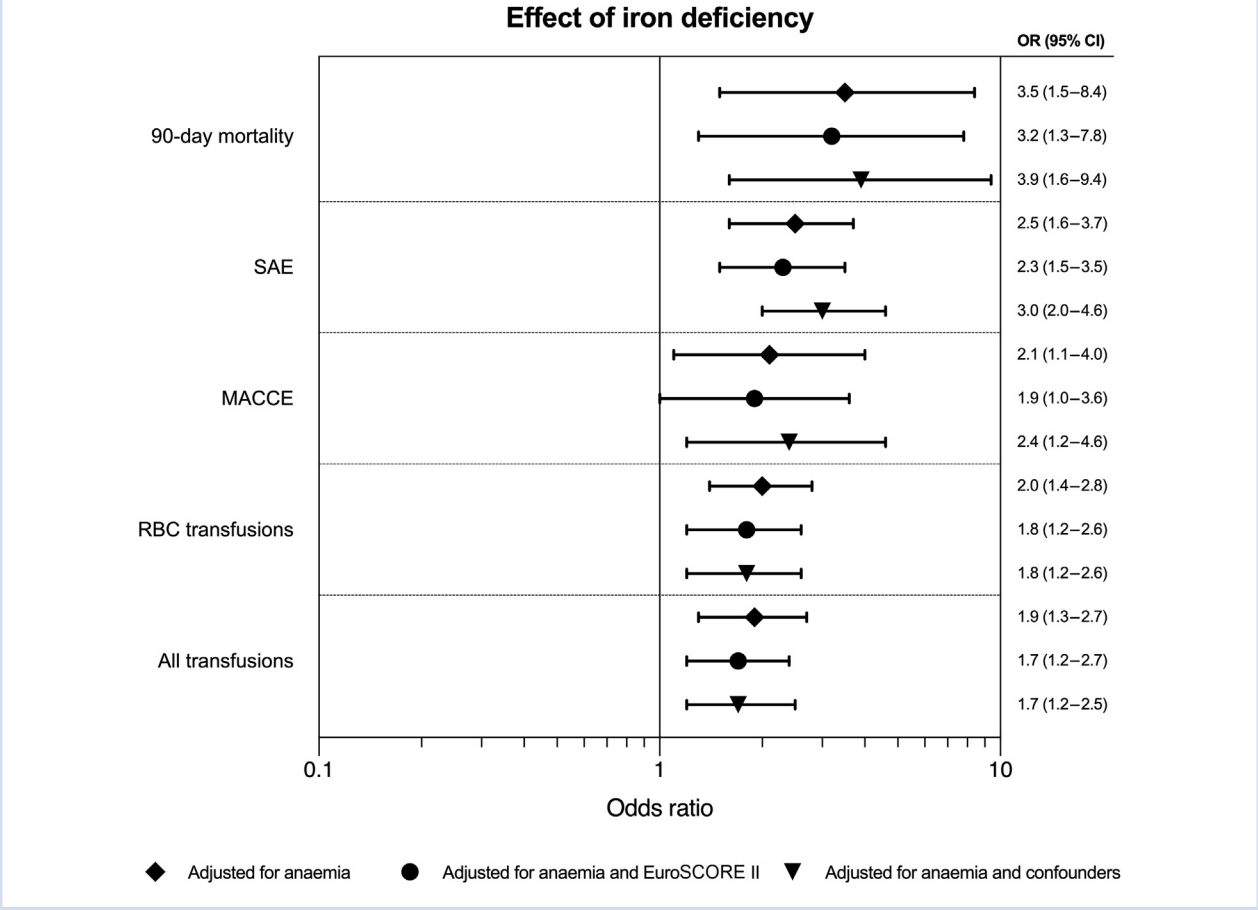

Fig 4. Odds ratios. The effect of iron deficiency on 90-day mortality, serious adverse events (SAEs), and major adverse cardiac and cerebrovascular events (MACCEs). Odds ratios (ORs) are from the models adjusted for anaemia only and two multivariate regression models. The multivariate models are adjusted either for anaemia and EuroSCORE II, or for anaemia and confounders. CI, confidence interval; RBC, red blood cell.

Table 3 Adverse events. Data are reported as number of patients (%). Linear regression for continuous variables and logistic regression for dichotomous variables. The regressor is iron deficiency. All regressions are adjusted for anaemia. CI, confidence interval; OR, odds ratio. *Final solution could not be found. Estimation terminated because of low number of events.

	No anaemia		Anaemia		Regression	
	No iron deficiency (*n*=489)	Iron deficiency (*n*=119)	No iron deficiency (*n*=85)	Iron deficiency (*n*=37)	*P*-value for iron deficiency	OR or relative increase (95% CI)
Allergy	9 (2)	0 (0)	2 (2)	0 (0)	*	*
Angina	2 (0)	3 (3)	0 (0)	1 (3)	0.020	7.7 (1.4–42.8)
Myocardial infarction	9 (2)	4 (3)	0 (0)	2 (5)	0.077	2.6 (0.9–7.4)
Stroke	11 (2)	3 (3)	1 (1)	2 (5)	0.42	1.5 (0.5–4.5)
Acute kidney injury	21 (4)	7 (6)	6 (7)	5 (14)	0.21	1.6 (0.8–3.2)
Dialysis	12 (3)	4 (3)	2 (2)	2 (5)	0.36	1.6 (0.6–4.2)
Atrial fibrillation	92 (19)	25 (21)	16 (19)	11 (30)	0.26	1.3 (0.8–2.0)
Infection	103 (21)	31 (26)	32 (38)	14 (38)	0.31	1.2 (0.8–1.8)
Gastrointestinal disease	6 (1)	1 (1)	0 (0)	1 (3)	0.78	1.3 (0.3–6.4)
Laparotomy	0 (0)	3 (3)	0 (0)	0 (0)	*	*
New malignoma	2 (0)	1 (1)	0 (0)	0 (0)	*	*
Haemothorax	13 (3)	7 (6)	2 (2.4)	4 (11)	0.014	2.8 (1.2–6.2)
Re-thoracotomy	18 (4)	10 (8)	4 (5)	3 (8)	0.026	2.3 (1.1–4.6)
Bleeding (other)	6 (1)	1 (1)	0 (0)	2 (5)	0.41	1.8 (0.4–7.4)
Thromboembolic event	3 (1)	2 (2)	2 (2)	2 (5)	0.17	2.6 (0.7–9.9)
Resuscitation	10 (2)	4 (3)	4 (5)	5 (14)	0.080	2.2 (0.9–5.2)

with prolonged hospital stay[11,12] and more transfusions of allogenic blood products.[8] Most of these studies could only demonstrate single effects. This may be attributable to the smaller sample size of these studies, with consequently limited power. Another prospective study in anaemic patients has shown higher mortality and longer hospital stay associated with increased plasma hepcidin concentration,[13] which correlates negatively with iron bioavailability.[14]

We defined ID by serum ferritin <100 μg L^{-1}. Current guidelines allow ID to be defined by either ferritin <100 μg L^{-1} or transferrin saturation <20%, whilst in the presence of inflammation even ferritin values <300 μg L^{-1} at transferrin saturation <20% is considered ID.[7,9] Consequently, our definition of ID is rather restrictive, but it is still similar to the definitions of absolute ID in studies in this field.[9,11,15] In patients with heart failure, comparable cut-off values are also recommended and have been used throughout different studies.[6,16,17]

There were obvious differences between the groups, as ID is associated to certain characteristics. Patients with ID are more likely to be female and consequently smaller, lighter, and less likely to consume alcohol.[18,19] The lower Hb and reticulocyte Hb in the ID group could be because of the fact that the effect of ID on erythropoiesis is continuous, but anaemia is measured dichotomously. Expectedly, CRP was elevated in the groups without ID, as we defined ID dependent on low ferritin concentrations. Like CRP, ferritin is also an acute-phase protein. Consequently, patients with inflammation have higher CRP and ferritin values, and are therefore more likely to be stratified in the non-ID groups.

The surgical risk was quantified by the EuroSCORE II, which combines a broad number of co-morbidities to calculate the risk for cardiac surgery.[20] The fact that the EuroSCORE II is elevated with ID already implies that patients with ID seem to suffer from more co-morbidities. However, our results consolidate ID as a stand-alone condition, because the impact of ID persists in multivariate models adjusted for the EuroSCORE II.

ID is a common condition not only in cardiac surgery but before all types of major surgery.[4] Whilst all patient groups might benefit from the treatment of preoperative ID,[7] patients undergoing cardiac surgery could especially do so.[10] This might be attributable to the physiological role of iron for the heart, and its essential role for mitochondrial function and cellular bioenergetics.[21] Therefore, ID is common in heart failure and is associated with a poor outcome.[1] The treatment of ID in heart failure not only has a positive effect on exercise capacity and ventricular function, but also decreases mortality.[1] Spahn and colleagues[10] have shown previously that an ultrashort-term treatment of isolated ID resulted in a higher postoperative Hb and reduced transfusions of allogenic blood products in anaemic patients—with no significant negative side-effects. Interestingly, in the ID subgroup of the previous study, no change in clinical outcomes was found after the treatment. Their primary outcome, however, was the number of transfusions, and therefore, the study was not powered to show differences in clinical outcomes, such as mortality. In the future, larger studies with enough power to detect these events and earlier treatment of ID are warranted. In addition, regardless of the efficacy of a treatment, physicians and patients need to be aware of the risk when going into elective surgery *vs* choosing alternative treatment options. ID appears to be such an additional risk factor in cardiac surgery.

To minimise the effect of possible confounders, we calculated two extensive multivariate regression models. Their accuracy can be affirmed when looking at the effect of anaemia in the multivariate models (Supplementary Tables S3 and S4). The mean Hb values of our anaemic groups were not particularly low with 114 and 119 g L^{-1}. Therefore, whilst mortality and SAE increased in anaemic patients in the model adjusted for ID (Supplementary Table S2), in both multivariate models, there was no significant effect of anaemia on mortality, SAE, or

MACCE. This is not surprising, as it has been shown that anaemia-related mortality barely increases until Hb <110 g L^{-1}.[22] For transfusions, the effect that allogenic transfusions more than tripled with anaemia persisted in both multivariate models. This implies that even slight anaemia leads to more transfusions.

In the last decade, patient blood management programmes have become increasingly important in the perioperative care.[5,23] Optimising a patient's own red cell mass and reducing transfusions by treating preoperative anaemia and ID are two of the pillars of these programmes.[24] As allogenic transfusions are associated with an increase of adverse events, patients may benefit from a reduction in transfusion requirements with improved clinical outcomes and lower mortality[25] but also isolated ID.

Our study had some limitations. We defined ID as serum ferritin concentration <100 μg L^{-1}, which has been described for patients with a subclinical coexisting inflammatory process as often found in patients with heart failure and in patients undergoing cardiac surgery.[1] ID can, however, be defined in a variety of ways, and doing so may yield different results. Nevertheless, the effect of a preoperative serum ferritin <100 μg L^{-1} on the outcome is in itself important additional information for clinical practise. Moreover, analysing plasma hepcidin was not feasible in 2014 when the study started. With evolving technology, hepcidin testing became more available in the last years, and recent studies have found plasma hepcidin to be an indicator of ID, in which higher values also correlated with mortality.[13] Further studies should include hepcidin testing, as this may be relevant to the future definition of ID. In addition, as this was a single-centre study, the external validity is limited. Future studies should be designed in a multicentre approach.

The study also had particular strengths. The prospective design increased the completeness and accuracy of data collection, and further helped to reduce the possibility of confounding. Although not powered originally for this analysis, our sample size was large enough, and the data set was nearly complete at 99%, to measure rare events and to detect a significant increased risk of mortality. In addition, the follow-up was long enough to detect events after hospital discharge.

Conclusion

Preoperative iron deficiency (ferritin <100 μg L^{-1}) was independently associated with increased mortality, more SAEs, and prolonged hospital stay after cardiac surgery. These findings underline the importance of preoperative iron deficiency screening in the context of a comprehensive patient blood management programme, and highlight the potential importance of iron deficiency as a research topic in cardiac surgery.

Authors' contributions

Study design: JR, FS, BS, VF, DRS.
Data collection: GHS.
Data analyses: BS.
Data interpretation: all authors.
Writing of first draft: JR.
Creating of figures: AK.
All authors provided critical revisions to the manuscript before seeing and approving the final version.

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Declarations of interest

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Appendix A. Supplementary data

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