Korean Journal of Anesthesiology

Clinical Research Article

Korean J Anesthesiol 2025;78(6):560-568
https://doi.org/10.4097/kja.25022
pISSN 2005-6419 • eISSN 2005-7563

Received: January 20, 2025
Revised: April 20, 2025 (1st); June 23, 2025 (2nd); August 24, 2025 (3rd); September 16, 2025 (4th)
Accepted: September 16, 2025

Corresponding author:
Young-Lan Kwak, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Severance Cardiovascular Hospital, and Anesthesia and Pain Research Institute, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-8513
Fax: +82-2-2227-8063
Email: ylkwak@yuhs.ac
ORCID: https://orcid.org/0000-0002-2984-9927

Previous presentation at conferences:
2024 Korean Society of Cardiothoracic and Vascular Anesthesiologists Spring Conference, held on 18 May 2024, Seoul, Korea.

Featured article

Association between non-anemic iron deficiency and outcomes following off-pump coronary artery bypass surgery: a retrospective analysis

Heesoo Shin[1], Hye-Bin Kim[2], Jae-Kwang Shim[1], Jong Wook Song[1], Seo Hee Ko[1], Young-Lan Kwak[1]

Department of Anesthesiology and Pain Medicine, [1]Severance Cardiovascular Hospital, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, [2]Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

Background: Non-anemic iron deficiency (ID) may be harmful during cardiac surgery with cardiopulmonary bypass. However, its impact on off-pump coronary artery bypass (OPCAB) remains unclear. This study examined the association between non-anemic ID and outcomes following OPCAB.

Methods: This single-center retrospective study included non-anemic patients who underwent OPCAB between November 2016 and May 2023. Patients were classified by preoperative ID status, defined as serum ferritin < 100 μg/L or 100–300 μg/L with C-reactive protein > 5 mg/L or transferrin saturation < 20%. The risk of primary outcome, defined as the composite of acute kidney injury, permanent stroke, deep sternal wound infection, hemostatic reoperation, prolonged mechanical ventilation, delirium, myocardial infarction, and 30-day mortality, was compared using multivariable logistic regression. Mediation analysis was performed to determine the indirect effects of non-anemic ID via perioperative red blood cell (RBC) transfusion.

Results: Of the 433 non-anemic patients, 229 (52.9%) had ID. The incidence of composite outcome was similar between patients with and without ID (30.1% vs. 22.5%, P = 0.075). ID was not significantly associated with the composite outcome, whereas perioperative transfusion (odds ratio: 2.10, 95% CI [1.17–3.78], P = 0.013) showed significant associations. Perioperative RBC transfusion was more common in patients with ID (25.8% vs. 10.8%, P < 0.001). Mediation analysis suggested that RBC transfusion partially mediated the effect of ID on the composite outcome.

Conclusions: Preoperative ID was not associated with adverse outcomes in non-anemic patients who had undergone OPCAB. However, its indirect impact via RBC transfusion warrants further investigation.

Keywords: Anemia; Blood transfusion; Coronary artery bypass, off-pump; Iron deficiency; Morbidity; Mortality; Treatment outcome.

Introduction

Iron is a fundamental component of erythropoiesis and numerous cellular processes involving oxygen transport and mitochondrial energy production [1,2]. Iron deficiency (ID), independent of anemia, is associated with poor outcomes such as reduced exercise capacity and increased risk of mortality in patients with heart failure (HF), which could be treated with intravenous iron [3,4]. Non-anemic ID can be particularly harmful in cardiac surgery, as evidenced by a prospective secondary study demonstrating that ID,

independent of anemia, was associated with increased 90-day mortality [5]. Preoperative iron supplementation is recommended for surgical patients with ID, even in the absence of anemia, when substantial perioperative blood loss is anticipated [6,7]. However, iron therapy has inherent limitations, as oral formulations commonly cause side effects such as constipation and nausea, whereas intravenous therapy requires additional hospital visits [8]. Additionally, conflicting results have been reported regarding the impact of non-anemic ID on postoperative outcomes in cardiac surgery patients [5,9–11]. Of note, existing studies predominantly included on-pump procedures, which expose patients to inevitable blood loss, hemodilution, and inflammation. Therefore, further studies are required on the impact of non-anemic ID on postoperative outcomes in various cardiac surgery settings.

To date, no study has evaluated the association between non-anemic ID and off-pump coronary artery bypass grafting (OPCAB). OPCAB is recommended in patient blood management guidelines for surgical coronary revascularization as an alternative to its on-pump counterpart, as it avoids cardiopulmonary bypass-induced hemodilution and coagulopathy [12]. Accordingly, non-anemic ID may show a more distinct association with outcomes in OPCAB.

In this retrospective observational study, we aimed to investigate the association between non-anemic ID and major morbidity and mortality following OPCAB.

Materials and Methods

Study population

The Institutional Review Board of Severance Hospital approved this retrospective observational study (No. 4-2022-1112, approval date October 25, 2022) and waived the requirement for informed consent. The protocol of this study was also registered at ClinicalTrials.gov (NCT06399627). The study was conducted in accordance with the principles of the Helsinki Declaration-2013.

Patients who underwent OPCAB between November 2016 and May 2023 at the Severance Cardiovascular Hospital in Seoul, South Korea, were included in our study without an a *priori* sample size calculation. The study period was selected because the preoperative iron profile has been routinely assessed at our institution since 2016.

The exclusion criteria were as follows: age < 19 years, emergency surgery, redo-OPCAB, minimally invasive surgery, enrolment in other clinical studies that could affect outcomes, insufficient preoperative laboratory data to determine iron status, intraoperative on-pump conversion and use of intravenous iron within 4 weeks or oral iron more than 2 weeks within 6 months preoperatively. Patients meeting the World Health Organization criteria for anemia (hemoglobin [Hb] concentration < 13 g/dl and 12 g/dl for males and females, respectively) were also excluded. ID was defined as serum ferritin < 100 μg/L or serum ferritin between 100 and 300 μg/L when either C-reactive protein > 5 mg/L or transferrin saturation < 20% [10].

Data acquisition

Data for each eligible patient were collected from the electronic medical records. Preoperative data included baseline demographics, comorbidities, preoperative medication, New York Heart Association (NYHA) class, Canadian Cardiovascular Society grading of angina pectoris, European System for Cardiac Operative Risk Evaluation (EuroSCORE)-II, left ventricular ejection fraction (LVEF), the ratio of early transmitral flow velocity to early mitral annular velocity, and blood laboratory results. Intraoperative data included duration of operation, number of grafts, total graft reconstruction time, the volume of crystalloids and colloids infused, urine output, the volume of reinfused blood from a cell salvage device, and the number of units of red blood cells (RBC) transfused. Postoperative data included nadir Hb on postoperative days (POD) 0, 1, 3, and 7, nadir Hb from the immediate postoperative period until hospital discharge, fluid infusion volume, urine output, chest tube drainage, and amount of perioperative RBC transfused (from the start of surgery until 48 hours postoperatively).

Anesthetic and perioperative management

Heparin (80 U/kg) was administered intravenously to all patients before starting the first bypass graft anastomosis to achieve an activated clotting time of 250 s. After completing all graft anastomosis and transit-time flow measurements, protamine was administered at a ratio of 1 mg per 200–250 U of total heparin. Thromboelastography was conducted to assess coagulopathy following heparin reversal. Any shed blood was processed using a cell salvage device (Cell Saver® Elite®, Haemonetics) and reinfused. Throughout the perioperative period, RBC transfusion was initiated when the Hb level was < 8 g/dl unless active bleeding with hemodynamic instability necessitated urgent transfusion.

Study outcomes

The primary outcome was the association between non-anemic ID and the risk of composite outcome consisting of acute kidney

injury (AKI), permanent stroke, deep sternal wound infection, hemostatic reoperation, prolonged mechanical ventilation (> 24 h), delirium, myocardial infarction (MI) and 30-day mortality. AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes guideline for AKI, defined as an increase in serum creatinine by 0.3 mg/dl or more within 48 hours, or an increase of 1.5 times or more from baseline within the 7 days postoperatively [13]. Urine output was excluded as a diagnostic criterion for AKI because hourly urine output checks were not conducted after the patients were moved to the general ward. The occurrence of delirium was searched for throughout the entire hospital stay and was diagnosed based on the Intensive Care Delirium Screening Checklist, which was performed at least 3 times per day during the intensive care unit stay. After the patients had been moved to the general ward, electronic medical records including referrals to the psychiatry department for delirium management, nursing records, and progress notes, were reviewed. Postoperative MI was diagnosed based on the fourth universal definition of MI (type 5) [14]. Other outcomes (stroke, deep sternal infection, hemostatic reoperation, and mechanical ventilation > 24 hours) were assessed using the Society of Thoracic Surgeons definition of morbidity and were evaluated for occurrences until discharge [15]. Lastly, to capture out-of-hospital deaths, 30-day mortality was additionally verified using the Resident Registration Database from the Ministry of the Interior and Safety, which provides official death status and dates. These outcomes were determined and prespecified in the study protocol before data collection.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 4.3.3 (The R Foundation for Statistical Computing). The normality of continuous variables was tested using the Kolmogorov-Smirnov test. Continuous data are presented as mean ± standard deviation or median (Q1, Q3) as appropriate based on data distribution. Categorical variables are expressed as the number of patients (percentage). Comparisons between the groups were conducted using the independent t-test, Mann–Whitney *U* test, chi-square test, or Fisher's exact test, as appropriate. For all analyses, statistical significance was set at $P < 0.05$.

Multivariable models were used to assess the effect of ID on composite outcome after adjusting for covariates (Model 1). Univariable logistic regression analyses were performed on all perioperative variables, and variables with $P < 0.05$ were considered potential confounders. Among the identified potential confounders, variables suspected of multicollinearity were excluded, and only those deemed clinically relevant were included in the multivariable analysis. Since EuroSCORE-II was designed to predict operative mortality and comprises various known risk factors of adverse outcomes [16], it was excluded from the multivariable model to avoid multicollinearity. To further evaluate the presence of multicollinearity among the included variables, the variance inflation factors were calculated. All selected covariates demonstrated variance inflation factors below 2, confirming the absence of multicollinearity.

To explore potential interaction effects between ID and HF, an interaction analysis was performed, which included ID, HF, and their interaction term (ID*HF) in the multivariable logistic regression model (Model 2). To assess whether the interaction term significantly improved model fit, a –2 log likelihood ratio test was conducted, comparing models with and without the interaction term. The criteria for HF were based on those reported by Anker et al. [17], who evaluated the effect of iron therapy in patients with HF. Specifically, HF was defined as LVEF ≤ 40% for NYHA class II, ≤ 45% for NYHA class III, or any patient with NYHA class IV. NYHA class IV was additionally included in our definition, given that our cohort comprised preoperatively hospitalized patients, unlike the ambulatory population in Anker et al.'s study, which inherently excluded NYHA class IV patients.

As part of a sensitivity analysis, ID was redefined using an alternative criterion of transferrin saturation ≤ 19.8% or serum iron ≤ 13 μmol/L, based on a study that assessed iron status via bone marrow staining in patients with HF [18]. This alternative definition, termed 'Grote-defined ID,' was evaluated using the same multivariable logistic regression model in place of the primary ID definition (Model 3).

A post-hoc mediation analysis was performed using the *mediation* package in R [19] to assess the effect of perioperative RBC transfusion on the association between ID and the primary outcome. As perioperative RBC transfusion was guided by Hb levels and preoperative ID may hinder postoperative Hb recovery, we hypothesized that ID might indirectly affect the primary outcome via RBC transfusion. The mediation model incorporated perioperative RBC transfusion as the mediator, along with all covariates included in the multivariable model 1. The average causal mediation effect (ACME) and the average direct effect were calculated. The 95% Cis and P values were derived from nonparametric bootstrapping with 1,000 simulations using robust standard errors.

Finally, for intergroup comparisons of serially assessed Hb levels, a repeated-measures 2-way analysis of variance was performed with Bonferroni correction.

https://doi.org/10.4097/kja.25022

Results

Overall, 1396 patients who underwent OPCAB between November 2016 and May 2023 were initially screened. After excluding ineligible patients, 433 remained for analysis: 229 and 204 were iron-deficient and non-iron-deficient, respectively (Fig. 1). The median number of days before surgery for iron profile collection was 2 days [1–4].

Baseline characteristics and perioperative data are shown in Tables 1 and 2. Patients in the ID group were older, more likely female, had lower body mass index, and were more frequently diabetic than those in the non-ID group (Table 1). The ID group had a significantly lower median preoperative Hb level (13.8 g/dl [13.3–14.6]) than the non-ID group (14.4 g/dl [13.7–15.1]). Of the included patients, 82 had HF (18.9%), with a similar incidence observed in the ID and non-ID groups (48 [21%] and 34 [16.7%], respectively).

The number of grafts and total duration of graft reconstruction showed no significant differences between the 2 groups (Table 2). The incidence of perioperative RBC transfusion was significantly higher in patients with ID (25.8% vs. 10.8%, P < 0.001). Compared with patients without ID, those with ID had lower nadir Hb levels (8.1 g/dl vs. 8.2 g/dl, P = 0.033), although the median difference was only 0.1 g/dl.

In the ID group, the composite outcome occurred in 69 of 229 patients (30.1%), compared with 46 of 204 patients (22.5%) in the non-ID group, showing no statistically significant difference between groups (P = 0.075) (Table 3). Among the components of the composite outcome, the incidences of AKI (24 [10.5%] vs. 12 [5.9%], P = 0.084) and delirium (42 [18.3%] vs. 25 [12.3%], P = 0.080) tended to be higher in the ID group than in the non-ID group.

In the multivariable analysis adjusting for covariates identified via univariable analysis (Supplementary Table 1), no significant association was observed between ID and the composite outcome (odds ratio [OR]: 0.97, 95% CI [0.60–1.58], P = 0.921) (Model 1,

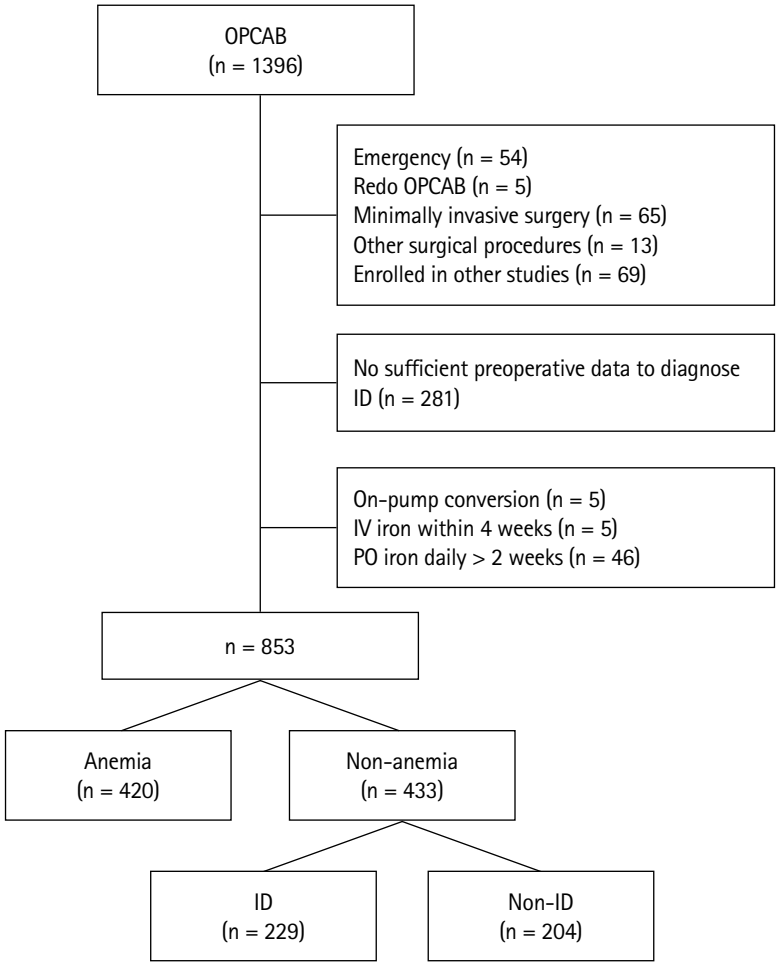

Fig. 1. Flow diagram of the study. OPCAB: Off-pump coronary artery bypass surgery, ID: iron deficiency, IV: intravenous, PO: per oral.

Table 1. Baseline Characteristics of Patients

Characteristic	Overall (n = 433)	ID (n = 229)	Non-ID (n = 204)	P value
Demographics				
Age (yr)	66 (59, 71)	67 (61, 72)	63 (57, 70)	< 0.001
Sex				
M	352 (81.3)	168 (73.4)	184 (90.2)	< 0.001
F	81 (18.7)	61 (26.6)	20 (9.8)	
BMI (kg/m^2)	25.0 (23.1, 27.2)	24.7 (22.9, 26.8)	25.3 (23.4, 27.4)	0.019
EuroSCORE-II	1.02 (0.70, 1.59)	1.12 (0.79, 1.64)	0.88 (0.67, 1.48)	0.001
Ejection fraction (%)	60 (48, 68)	60 (48, 69)	60 (49, 67)	0.456
E/e'[†]	11.2 (9.0, 14.0)	11.9 (9.6, 14.4)	10.5 (8.4, 13.0)	< 0.001
Hypertension	297 (68.6)	164 (71.6)	133 (65.2)	0.151
Heart failure*	82 (18.9)	48 (21.0)	34 (16.7)	0.310
Diabetes mellitus	184 (42.5)	108 (47.2)	76 (37.3)	0.037
Chronic kidney disease	32 (7.4)	17 (7.4)	15 (7.4)	0.979
CCS grade				0.948
1	151 (34.9)	80 (34.9)	71 (34.8)	
2	214 (49.4)	111 (48.5)	103 (50.5)	
3	55 (12.7)	31 (13.5)	24 (11.8)	
4	13 (3.0)	7 (3.1)	6 (2.9)	
Heparin	296 (68.4)	156 (68.1)	140 (68.6)	0.910
Aspirin	389 (89.8)	213 (93.0)	176 (86.3)	0.021
Clopidogrel	275 (63.5)	151 (65.9)	124 (60.8)	0.266
Preoperative lab data				
Hemoglobin (g/dl)	14 (13.4, 14.8)	13.8 (13.3, 14.6)	14.4 (13.7, 15.1)	< 0.001
Platelet count ($\times 10^3$/dl)	211 (182, 251)	215 (186, 252)	210 (177, 249)	0.417
Ferritin (μg/L)	125.2 (68.0, 192.8)	71.4 (44.9, 110.4)	175.7 (138.3, 247.0)	< 0.001
Transferrin saturation (%)	29 (22, 38)	26 (19, 33)	34 (27, 41)	< 0.001
C-reactive protein (mg/L)[‡]	1.2 (0.5, 2.9)	1.5 (0.6, 5.6)	1.0 (0.4, 1.9)	< 0.001
eGFR (ml/min/1.73m^2)	88 (75, 95)	87 (74, 95)	90 (77, 96)	0.101

Values are presented as median (Q1, Q3) or number (%). aPTT: activated partial thromboplastin time, CCS: Canadian Cardiovascular Society, EuroSCORE-II: European System for Cardiac Operative Risk Evaluation-II, E/e': ratio of early transmitral flow velocity to early mitral annular velocity, eGFR: estimated glomerular filtration rate, ID: iron-deficiency, LVEF: left ventricular ejection fraction. *Defined as a LVEF of 40% or less (for patients with New York Heart Association [NYHA] class II) or 45% or less (for NYHA class III) or with NYHA class IV. [†]E/e' measurements were unavailable in 4 patients (ID = 1, non-ID = 3). [‡]C-reactive protein values were unavailable in 8 patients (ID = 8).

Table 4). Among the covariates included in the multivariable model, CKD (OR: 2.68, 95% CI [1.23–5.86], P = 0.014), HF (OR: 2.04, 95% CI [1.07–3.88], P = 0.031), and perioperative RBC transfusion (OR: 2.10, 95% CI [1.17–3.78], P = 0.013) were significantly associated with the composite outcome.

The interaction analysis revealed that the association between non-anemic ID and the composite out come was not significantly modified by HF status (P for interaction = 0.789; Model 2, Table 4).

In a sensitivity analysis using an alternative definition of ID (termed 'Grote-defined ID'), 132 patients (30.5%) were classified as having Grote-defined ID. Grote-defined ID was not significantly associated with the composite outcome (OR: 1.11, 95% CI [0.68–1.82], P = 0.69) in Model 3 (Table 4).

The total effect of ID on the composite outcome was not statistically significant (β = 0.046, 95% CI, −0.039 to 0.130, P = 0.297) (Table 5). However, the analysis revealed a significant indirect effect of ID through perioperative RBC transfusion (ACME: β = 0.028, 95% CI [0.007 to 0.056], P = 0.007), whereas the direct effect of ID independent of transfusion was not significant (average direct effect: β = 0.018, 95% CI [−0.067 to 0.103], P = 0.669).

Serially assessed postoperative Hb levels were compared between the ID and non-ID groups (Fig. 2). The P-value of the time × group interaction was < 0.001. Significant intergroup differences were found on POD 0 and 1 (all P < 0.001), with levels being lower in the ID group than in the non-ID group.

https://doi.org/10.4097/kja.25022

Table 2. Perioperative Data

Variable	ID (n = 229)	Non-ID (n = 204)	P value
Intraoperative data			
Duration of operation (min)	235 (212, 258)	238 (218, 260)	0.196
Number of grafts	3 (3, 4)	3 (3, 4)	0.655
Total duration of graft reconstruction (min)	36.9 (30.1, 44.0)	36.7 (31.0, 43.1)	0.893
Salvaged blood reinfused (ml)	220 (210, 257)	220 (210, 380)	0.654
Fluid administration			
Crystalloid (ml)	1400 (1200, 1800)	1500 (1150, 1900)	0.760
Colloid (ml)	500 (175, 500)	500 (150, 500)	0.414
Urine output (ml)	250 (150, 350)	230 (143, 395)	0.807
Postoperative data*			
Fluid administration			
Crystalloid (ml)	4542 (4002, 5089)	4761 (4183, 5334)	0.025
Colloid (ml)	440 (100, 700)	275 (100, 600)	0.050
Urine output (ml)	4510 (3715, 5470)	4545 (3962, 5415)	0.730
Chest tube drainage (ml)	1030 (850, 1313)	1025 (840, 1303)	0.833
Nadir Hb (g/dl)			
POD 0	10.1 ± 1.4	10.7 ± 1.4	< 0.001
POD 1	9.4 ± 1.5	10.0 ± 1.5	< 0.001
POD 3	9.0 ± 1.2	9.1 ± 1.2	0.185
POD 7	9.5 ± 1.2	9.6 ± 1.1	0.126
Entire postoperative period	8.1 (7.3, 9.0)	8.2 (7.6, 9.2)	0.033
Perioperative† RBC transfusion			
Number of patients	59 (25.8)	22 (10.8)	< 0.001
Number of units	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	< 0.001
0	170 (74.2)	182 (89.2)	
1	35 (15.3)	8 (3.9)	
2	16 (7.0)	10 (4.9)	
≥ 3	8 (3.5)	4 (2.0)	

Values are presented as median (Q1, Q3), mean ± SD or number (%). ID: iron-deficiency, Hb: hemoglobin, POD: postoperative day, RBC: packed red blood cells. *Postoperative data was collected until 48 hours after surgery. †Perioperative period was defined as beginning with the start of surgery and ending 48 hours postoperatively.

Table 3. Postoperative Outcomes

Outcome	ID (n = 229)	Non-ID (n = 204)	P value
Composite outcome	69 (30.1)	46 (22.5)	0.075
30-day mortality	1 (0.4)	1 (0.5)	0.501
AKI	24 (10.5)	12 (5.9)	0.084
Stroke	5 (2.2)	1 (0.5)	0.220
Deep sternal infection	4 (1.7)	3 (1.5)	> 0.999
Hemostatic reoperation	0 (0)	1 (0.5)	0.471
MV > 24 h	9 (3.9)	4 (2.0)	0.231
Delirium	42 (18.3)	25 (12.3)	0.080
Postoperative MI	6 (2.6)	4 (2.0)	0.755

Values are presented as number (%). ID: iron deficiency, AKI: acute kidney injury, MV: mechanical ventilation, MI: myocardial infarction.

Discussion

In this sizable single-center retrospective cohort study of multivessel OPCAB surgery, non-anemic ID was not independently associated with the composite outcome. This result was consistent across patients with and without HF. Notably, the incidence of perioperative RBC transfusion was higher in the ID group, and our mediation analysis suggested that transfusion mediated the association between ID and the composite outcome, despite the absence of a significant total or direct effect.

Accounting for the critical physiologic role of iron, several guidelines recommend screening for ID and initiating iron therapy in patients expected to undergo major blood loss surgery [6,7]. However, iron therapy can have side effects, and it requires additional costs and hospital visits [8]. Moreover, some studies have

Table 4. Multivariable Logistic Regression Analysis for Composite Outcome

	Model 1			Model 2			Model 3		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
ID	0.97	0.60–1.58	0.921	0.95	0.56–1.61	0.840			
ID*HF				1.19	0.34–4.17	0.788			
Grote-defined ID*							1.11	0.68–1.82	0.685
Sex	1.47	0.81–2.66	0.202	1.48	0.82–2.69	0.195	1.44	0.80–2.60	0.225
Age	1.03	1.00–1.06	0.056	1.03	1.00–1.06	0.056	1.03	1.00–1.06	0.056
DM	1.47	0.92–2.34	0.108	1.47	0.92–2.35	0.105	1.46	0.92–2.32	0.111
CKD	2.68	1.23–5.86	0.014	2.69	1.23–5.88	0.014	2.71	1.24–5.91	0.013
HF†	2.04	1.07–3.88	0.031	1.84	0.70–4.88	0.218	2.00	1.05–3.83	0.036
E/e' ‡	1.05	1.00–1.11	0.070	1.05	1.00–1.11	0.070	1.05	1.00–1.11	0.073
Perioperative RBC transfusion§	2.10	1.17–3.78	0.013	2.11	1.17–3.79	0.013	2.09	1.16–3.74	0.014

OR: odds ratio, ID: iron deficiency, HF: heart failure, DM: diabetes mellitus, CKD: chronic kidney disease, E/e': ratio of early transmitral flow velocity to early mitral annular velocity, RBC: packed red blood cells. *Defined as transferrin saturation ≤ 19.8% or serum iron ≤ 13 μmol/L. †Defined as a LVEF of 40% or less (for patients with New York Heart Association [NYHA] class II) or 45% or less (for NYHA class III) or with NYHA class IV. ‡Missing data: Patients with missing E/e' values (n = 4) were excluded from the multivariable analysis. §Perioperative period was defined as beginning with the start of surgery and ending 48 hours postoperatively.

Table 5. Mediation Analysis for Perioperative Allogeneic RBC Transfusion between ID and Composite Outcome

Effect	β	95% CI	P value	Standard error
Total effect	0.046	−0.039 to 0.130	0.297	0.043
Average causal mediation effect	0.028	0.007 to 0.056	0.007	0.011
Average direct effect	0.018	−0.067 to 0.103	0.669	0.043
Proportion mediated	0.430	−4.838 to 5.710	0.296	0.321

This analysis model was adjusted for sex, age, diabetes mellitus, chronic kidney disease, congestive heart failure, ratio of early transmitral flow velocity to early mitral annular velocity.

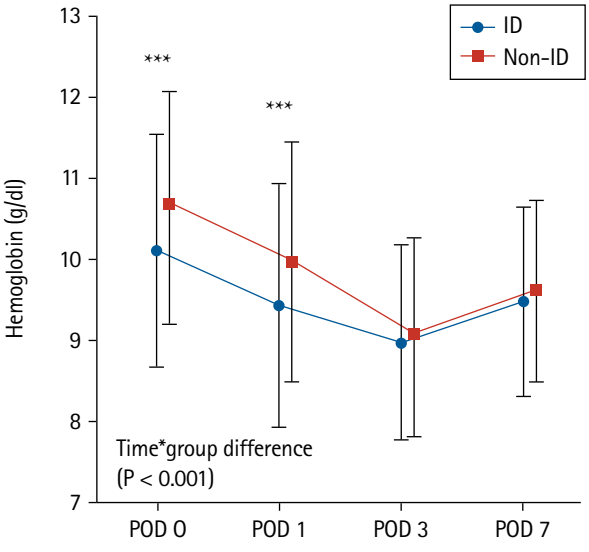

Fig. 2. Changes in hemoglobin during postoperative period with error bars in patients with and without ID. ID: iron deficiency, POD: postoperative day.

found that preoperative iron therapy, even when administered intravenously, does not reduce postoperative allogeneic RBC transfusion [20,21], potentially due to increased hepcidin expression, which impairs iron utilization and erythropoiesis. The findings of our multivariable analysis revealed no significant association between non-anemic ID and composite outcome. This association did not change even when an alternative criterion that we termed 'Grote-defined ID' based on sternal bone marrow iron staining was used [18]. This consistent result across 2 distinct ID definitions strengthens the robustness of our findings.

The lack of association in our OPCAB cohort may be partly attributed to the surgical setting. In contrast to procedures involving cardiopulmonary bypass, OPCAB is associated with a reduced risk of hemodilution and transfusion, potentially minimizing the pathway through which ID might affect outcomes. Consequently, in the absence of anemia and with a low likelihood of transfusion, the physiological impact of ID may not translate into clinically meaningful differences in outcomes. Clinically, these findings raise important questions about the utility of routine preoperative iron supplementation in patients without anemia undergoing OP-

https://doi.org/10.4097/kja.25022

CAB. Our results suggest that the indication for iron treatment should be carefully considered based on surgical context and individual transfusion risk, rather than ID status alone.

Recognizing iron's critical physiological role in patients with HF [2], we also examined ID in combination with HF in an interaction analysis. However, the introduction of the ID*HF term to the multivariable model showed no prognostic significance in the OPCAB group. Conversely, CKD, HF, and perioperative RBC transfusion were shown to be independently associated with adverse composite outcome, which are well-known risk factors of poor prognosis in cardiac surgery [22–24]. The statistical significance of perioperative RBC transfusion may reflect the role of transfusion as a marker of underlying clinical severity or the inherent negative effect of RBC transfusion influencing the composite outcome. These results align with those of a recent meta-analysis [11], which emphasizes the limited prognostic value of ID alone while highlighting the role of transfusion in influencing surgical outcomes. Similarly, in patients with non-anemic valvular heart disease, ID was not associated with adverse outcomes unless transfusion risk was concurrently present [9].

To further evaluate whether ID could influence outcomes through indirect mechanisms, we conducted a mediation analysis using perioperative RBC transfusion as a mediator. The total effect of ID on the composite outcome, incorporating both direct and indirect components, was not statistically significant. However, the analysis revealed a significant indirect effect, indicating that ID increased the likelihood of transfusion, which was independently associated with adverse outcomes in the multivariable model. The proportion mediated did not show statistical significance, likely due to limited precision in estimating the total effect in association with the wide CI of the proportion mediated. However, the significant ACME suggests a potential pathway through which ID may influence outcomes indirectly through transfusion exposure. Non-anemic ID showed no direct association with the composite outcome, but its association with higher transfusion requirements (an established risk factor) suggests an indirect pathway warranting prospective evaluation.

When comparing postoperative Hb levels, values were significantly lower in the ID group on POD 0 and 1 (both $P < 0.001$), and transfusions were more frequent in this group (25.8% vs. 10.8%). This difference may partly reflect the lower baseline Hb observed in patients with ID (median difference, 0.6 g/dl). Nevertheless, the nadir postoperative Hb levels were nearly identical between the 2 groups, both approximating 8 g/dl, with only a 0.1 g/dl difference. Given the uniform application of the transfusion threshold at 8 g/dl, this finding indirectly supports protocol adherence and reduces the likelihood of systematic treatment bias. Additionally, the interval between preoperative iron assessment and the index operation was uniformly short (median, 2 days; all within 5 days), minimizing potential temporal confounding.

The study had some limitations. First, its retrospective, single-center design in an exclusively Asian population limited generalizability and may have introduced selection bias related to local clinical practices. Factors not accounted for in this study may have influenced perioperative transfusion decisions. Second, postoperative AKI was diagnosed using the serum creatinine criteria alone because urine output was inconsistently recorded after transfer to the ward, which might have led to underestimation of AKI incidence. Finally, approximately 20% of initially screened patients were excluded owing to missing preoperative iron profile data, particularly serum ferritin. Although routine iron status assessment has been established at our institution since 2016, evolving clinical practices during the study period resulted in inconsistent testing, especially among patients without overt anemia or known hematologic disorders.

In conclusion, our retrospective study found no significant correlation between non-anemic ID and composite outcome in OPCAB patients. Thus, until conclusive evidence regarding the potentially meaningful mediation effect of perioperative RBC transfusion between ID and outcomes can be established, current guideline recommendations for routine correction of ID with iron therapy should be adopted cautiously in non-anemic patients undergoing OPCAB.

Funding

None.

Conflicts of Interest

Jong Wook Song has been an editor for the Korean Journal of Anesthesiology since 2020. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

Data Availability

Data will be available to other investigators upon reasonable request to the corresponding author.

Author Contributions

Heesoo Shin (Writing – original draft; Writing – review & editing)
Hye-Bin Kim (Data curation; Methodology)
Jae-Kwang Shim (Supervision; Writing – review & editing)
Jong Wook Song (Supervision)
Seo Hee Ko (Formal analysis)

Young-Lan Kwak (Supervision)

ORCID

Heesoo Shin, https://orcid.org/0000-0002-9807-0757
Hye-Bin Kim, https://orcid.org/0000-0003-3108-8693
Jae-Kwang Shim, https://orcid.org/0000-0001-9093-9692
Jong Wook Song, https://orcid.org/0000-0001-7518-2070
Seo Hee Ko, https://orcid.org/0000-0001-8402-5624
Young-Lan Kwak, https://orcid.org/0000-0002-2984-9927

Supplementary Material

Supplementary Table 1. Univariable analysis on composite outcome.

References

1. Muñoz M, Gómez-Ramírez S, Besser M, Pavía J, Gomollón F, Liumbruno GM, et al. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus 2017; 15: 422-37.
2. Wong CC, Ng AC, Kritharides L, Sindone AP. Iron deficiency in heart failure: looking beyond anaemia. Heart Lung Circ 2016; 25: 209-16.
3. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. Acta Cardiol 2018; 73: 115-23.
4. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013; 165: 575-82.e3.
5. Rössler J, Schoenrath F, Seifert B, Kaserer A, Spahn GH, Falk V, et al. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. Br J Anaesth 2020; 124: 25-34.
6. National Blood Authority. Patient blood management guidelines: module 2 perioperative [serial on the Internet]. Canberra: National Blood Authority; 2012 March [cited 2025 Jan 20]. Available from https://www.blood.gov.au/patient-blood-management-guidelines
7. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017; 72: 233-47.
8. Sawicki KT, De Jesus A, Ardehali H. Iron metabolism in cardiovascular disease: physiology, mechanisms, and therapeutic targets. Circ Res 2023; 132: 379-96.
9. Kim HB, Shim JK, Ko SH, Kim HR, Lee CH, Kwak YL. Effect of iron deficiency without anaemia on days alive and out of hospital in patients undergoing valvular heart surgery. Anaesthesia 2022; 77: 562-9.
10. Miles LF, Pac Soo V, Braat S, Bade-Boon J, Heritier S, Klein AA, et al. Associations between non-anaemic iron deficiency and outcomes following elective cardiac surgery (idocs): a prospective cohort study. Lancet Haematol 2022; 9: e514-22.
11. Peri V, Devlin P, Perry L, Richards T, Miles LF. Associations between nonanemic iron deficiency and postoperative outcomes in cardiac surgery: a systematic review and meta-analysis. Anesth Analg 2024; 139: 47-57.
12. Casselman FP, Lance MD, Ahmed A, Ascari A, Blanco-Morillo J, Bolliger D, et al. 2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP. Eur J Cardiothorac Surg 2025; 67: ezae352.
13. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2: 1-138.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018; 72: 2231-64.
15. Shahian DM, Edwards FH, Ferraris VA, Haan CK, Rich JB, Normand SL, et al. Quality measurement in adult cardiac surgery: part 1--Conceptual framework and measure selection. Ann Thorac Surg 2007; 83(4 Suppl): S3-12.
16. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE ii. Eur J Cardiothorac Surg 2012; 41: 734-44.
17. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; 361: 2436-48.
18. Grote Beverborg N, Klip IT, Meijers WC, Voors AA, Vegter EL, van der Wal HH, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. Circ Heart Fail 2018; 11: e004519.
19. Tingley D, Yamamoto T, Hirose K, Keele L, Imai K. Mediation: r package for causal mediation analysis. J Stat Softw 2014; 59: 1-38.
20. Keeler BD, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, Acheson AG. Randomized clinical trial of preoperative oral versus intravenous iron in anaemic patients with colorectal cancer. Br J Surg 2017; 104: 214-21.
21. Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (preventt): a randomised, double-blind, controlled trial. Lancet 2020; 396: 1353-61.
22. Pieri M, Belletti A, Monaco F, Pisano A, Musu M, Dalessandro V, et al. Outcome of cardiac surgery in patients with low preoperative ejection fraction. BMC Anesthesiol 2016; 16: 97.
23. Holzmann M, Jernberg T, Szummer K, Sartipy U. Long-term cardiovascular outcomes in patients with chronic kidney disease undergoing coronary artery bypass graft surgery for acute coronary syndromes. J Am Heart Assoc 2014; 3: e000707.
24. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007; 116: 2544-52.

https://doi.org/10.4097/kja.25022