Effect of non-anemic iron deficiency on outcome following off-pump coronary revascularization: a retrospective analysis

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ABSTRACT

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Iron is a fundamental component of erythropoiesis as well as numerous vital cellular processes. Non-anemic iron deficiency has been suggested to be harmful in the cardiac surgical theatre, which inevitable accompanies blood loss and hemodilution, demanding increased erythropoiesis. By avoiding cardiopulmonary bypass, off-pump coronary artery bypass surgery (OPCAB) is an important alternative to its on-pump counterpart as a part of patient blood management strategy as it avoids cardiopulmonary bypass. Therefore, non-anemic iron deficiency may impose a different prognostic influence, while it is unknown. The primary aim of this retrospective study was to evaluate the relationship between non-anemic iron deficiency with the composite of major morbidity/mortality endpoints following OPCAB. A total of 433 patients were enrolled, of whom 229 patents were iron deficient. Composite end points were: in hospital mortality, acute kidney injury, stroke, deep sternal infection, hemostatic reoperation, prolonged mechanical ventilation of more than 24 hours, delirium and postoperative myocardial infarction. There was no significant difference in the incidence of composite endpoints in relation to iron deficiency (37.7% versus 38.4% in the iron deficient and non-iron deficient group, respectively, P = 0.884). Multivariable analysis revealed no significant association between iron deficiency and composite outcome, while total graft reconstruction time (odds ratio: 1.026, 95% confidence interval: 1.006-1.048, P = 0.013) and perioperative transfusion (odds ratio: 1.359, 95% confidence interval: 1.036-1.782, P = 0.027) were shown as independent risk factors. When iron deficiency with heart failure was introduced in the multivariable model instead of iron deficiency, similar results were observed. Mediation analysis revealed an indirect effect of iron deficiency on outcome through perioperative transfusion. In conclusion, preoperative iron deficiency per se without overt anemia was not associated with adverse outcome in patients undergoing OPCAB.

Key words : non-anemic, iron deficiency, off pump coronary bypass

1. INTRODUCTION

1.1. Research background

Iron is a fundamental component of erythropoiesis as well as numerous vital cellular processes that involve enzymatic actions, gene regulation, oxygen transport, and mitochondrial energy production.[1,2] Accordingly, iron deficiency (ID) by itself, even in the absence of anemia, has long been delineated as a portent of compromised functional capacity across various clinical scenarios.[3] Moreover, ID was recognized as an independent predictor of increased mortality in patients with chronic heart failure.[4] With the emergence of studies showing the benefit of iron therapy in non-anemic, iron deficient heart failure patients,[5,6] studies investigating the relationship between non-anemic iron deficiency with patient outcomes have been carried out with mixed results in patients undergoing on-pump cardiac surgery.

Non-anemic ID can theoretically be even more harmful in the surgical theatre as it inevitably accompanies blood loss and hemodilution, which are most prominent in cardiac surgeries, demanding increased erythropoiesis. In addition, surgery-induced systemic inflammatory response causes iron sequestration hindering iron utilization,[7] which may have serious consequences in terms of erythropoiesis and cellular metabolism, especially when the iron storage is already inadequate to begin with. Unfortunately, more than half of the non-anemic cardiac surgical patients have been shown to carry preoperative ID.[8]

While the association between anemia and adverse outcome in the cardiac surgical setting is inarguably evident,[9,10] a prospective study mostly involving patients undergoing on-pump coronary artery bypass graft surgery (CABG) also depicted detrimental outcome including a heightened risk of 90-day mortality related to ID.[11] Thus, it seems cogent to recommend iron replenishment therapy in cardiac surgical patients with ID regardless of anemia, considering the crucial physiologic role of iron on and the emergence of relevant clinical evidence.[12,13]

Although intravenous iron therapy is able to replenish iron storage immediately with great efficacy,[14] it is not free of side effects and may often enforce additional hospital visits.[15] Furthermore, preoperative iron therapy did not exert consistent beneficial influences on transfusion requirement and outcome in various surgical settings.[16,17] In addition, the pernicious influence of non-anemic ID on prognosis may not be universal across all cardiac surgeries.

In that context, off-pump CABG (OPCAB) has long been considered as an important alternative to its on-pump counterpart as a part of patient blood management strategy by avoiding the overwhelming influence of cardiopulmonary bypass on hemodilution and coagulopathy.[23] Therefore, it seems reasonable to assume that non-anemic ID may impose a different prognostic influence in patients undergoing OPCAB as opposed to on pump CABG, while it has not been scrutinized heretofore.

1.2. Study aim

The primary aim of this retrospective study was to evaluate the relationship between non-anemic iron deficiency with the composite of major morbidity/mortality endpoints following OPCAB. We secondarily aimed to elucidate the contribution of transfusion exposures to the relationships between preoperative iron deficiency and outcomes by analyzing the mediating effects of perioperative transfusion. Lastly, we investigated the changes in hemoglobin (Hb) level until 7 days after surgery to discern whether there is an intergroup difference.

2. STUDY METHOD

2.1. Method

This study was approved by the Institutional Review Board of Severance Hospital which waived the requirement for informed consent given the retrospective nature of the study.

Patients who received OPCAB between January 2016 to May 2023 in Severance Cardiovascular Hospital, Seoul, South Korea were included in the initial study pool. Exclusion criteria were: patients under the age of 19, emergency surgery, redo-OPCAB, minimally invasive direct coronary artery bypass surgery, OPCAB performed concurrently with other surgeries requiring CPB, enrollment in other clinical studies that would have affected the outcome of this study, lack of sufficient preoperative lab data to determine iron status, intraoperative on-pump conversion and use of intravenous iron within 4 weeks or parenteral iron of more than 2 weeks prior to surgery. Since the aim of the study was to investigate non-anemic patients, those who met the diagnostic criteria for anemia by WHO (Hb concentration of below 13 g/dL for male, 12 g/dL for female) were finally excluded.

After exclusion, the remaining patients were divided into iron replete and iron deficient groups. Criteria for ID was set in consideration of those used for previous studies of heart failure (HF) patients[5,6] and of cardiac surgery patients[24]; ID was defined as serum ferritin less than 100 μg/L or serum ferritin between 100 and 300 μg /L when either C-reactive protein (CRP) is greater than 5 mg/L or transferrin saturation (TSAT) is less than 20%.

For each eligible patient, we collected the following information from the electronic medical records; The assessed preoperative data were as follows; age, sex, height, weight, diagnosis & name of operation, previous cardiac operation history, other medical history, New York Heart Association (NYHA) class / Canadian Cardiovascular Society (CCS) grading of angina pectoris, European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, left ventricular ejection fraction (LVEF), ratio of early transmitral flow velocity to early mitral annular velocity (E/e'), Hb, serum iron, ferritin, transferrin saturation, CRP, platelet count, serum creatinine, estimated glomerular filtration rate (eGFR), albumin, troponin-T, prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT). Intraoperative data included: duration of operation, duration of anesthesia, total graft reconstruction time, volume of crystalloid and colloid

infused, urine output, bleeding count, volume of reinfused blood from a cell salvage device, and volume of transfusion for each packed erythrocytes (pRBC), fresh frozen plasma (FFP), platelet concentrate (pconc), cryoprecipitate. We collected the following postoperative data: nadir Hb for postoperative day (POD) 0,1,3,7, transfusion requirement (pRBC, FFP, pconc, and cryoprecipitate) within 48 hours after surgery.

For all patients, heparin of 80 U/kg was given intravenously before starting the first bypass graft to aim for activated coagulation time (ACT) of 250 seconds. Additional 1000-2000 U of heparin was given if ACT fell below 250 seconds. After the completion of all grafts and transit time flow measurement, protamine was given at a ratio of 1 mg per 200-250 U of total heparin given. ACT was measured 15 minutes after the reversal dose of protamine and additional 5 to 10 mg of protamine was administered if ACT was deemed prolonged compared to the pre-heparin initial ACT. Thromboelastography was carried out to assess any coagulopathy present after heparin reversal and was used as a guide for transfusion of FFP, pconc and cryoprecipitate in conjunction to surgeon's clinical judgment of impaired hemostasis. Any shed blood was processed using a cell salvage device (Cell Saver Elite, Haemonetics, Braintree, MA, USA) and re-infused.

Transfusion during the perioperative period was conducted following the institutional protocol. pRBC was initiated when the Hb concentration fell below 7 g/dL in hemodynamically stable patients, and below 8 g/dL in patients with unstable vital signs, advanced heart failure, ongoing blood loss in the operating room or intensive care unit, or when in the general ward.

The primary endpoint of this study was the occurrence of a composite of morbidity/mortality endpoints, which were: in hospital mortality or 30-day mortality (whichever occurred first), acute kidney injury (AKI), stroke, deep sternal wound infection, hemostatic reoperation, prolonged mechanical ventilation of more than 24hours, delirium and postoperative myocardial infarction (MI). Occurrence of any one of these endpoints counted as primary end point met. Postoperative AKI was diagnosed by an increase in serum creatinine ≥0.3 mg/dL from the preoperative baseline, or more than 50% from baseline until 1 week after surgery, or the occurrence of oliguria <0.5 mL/kg/h for more than 6 hours within 48 hours after surgery. Postoperative MI was diagnosed by criteria from the fourth universal definition of MI (type 5 MI).[25] Other outcomes were evaluated using the Society of Thoracic Surgeons' definition of mobidity.[26] The secondary endpoint was nadir Hb at POD 0,1,3,7 days.

2.2. Statistical analysis

Statistical analysis was performed using SAS (version 9.4, SAS Inc., Cary, NC, USA) and R version 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). Normality for continuous variables was tested using the Kolmogorov-Smirnov test. Since none of the continuous variables followed a normal distribution, all continuous data were expressed as median [25^{th}–75^{th} percentile] and compared using the Mann-Whitney U test. Discrete variables were expressed as the number of patients (percentage) and analyzed using the chi-square or Fisher's exact test.

Multivariable models were used to assess the effect of ID on composite outcomes after adjusting for confounding variables. To identify confounding variables, known risk factors including

age, sex, body mass index (BMI), diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD), heart failure (HF), CCS grading of angina pectoris, LVEF, E/e', total graft reconstruction time, and transfusion requirement were chosen *a priori* and went through univariable regression analysis to minimize the introduction of selection bias. Variables of $p < 0.1$ in univariable regression analysis with our variable of interest, ID, were subsequently included in the multivariable regression analysis. Otherwise, statistical significance was set at p value < 0.05. For sensitivity analysis, the association of ID in patients with HF was re-evaluated by replacing ID with ID+HF in the multivariable model. Criteria for HF was adapted from that used by Anker et al.[5]: a LVEF of 40% or less [for patients with NYHA class II] or 45% or less [for NYHA class III] or all patients with NYHA class IV.

To assess the effect of pRBC transfusion on the relationship between ID and composite endpoint, R mediation package was employed the to conduct a mediation analysis, which allowed us to quantify the mediation effect within our causal model. The mediation package facilitated the estimation of the Average Causal Mediation Effect (ACME), representing the indirect effect of the independent variable on the dependent variable through the mediator. Additionally, we estimated the Average Direct Effect (ADE), which measures the direct effect of the independent variable on the dependent variable, bypassing the mediator. By summing the ACME and ADE, we calculated the total effect, providing a comprehensive understanding of the causal relationships within our model. (Figure 1)

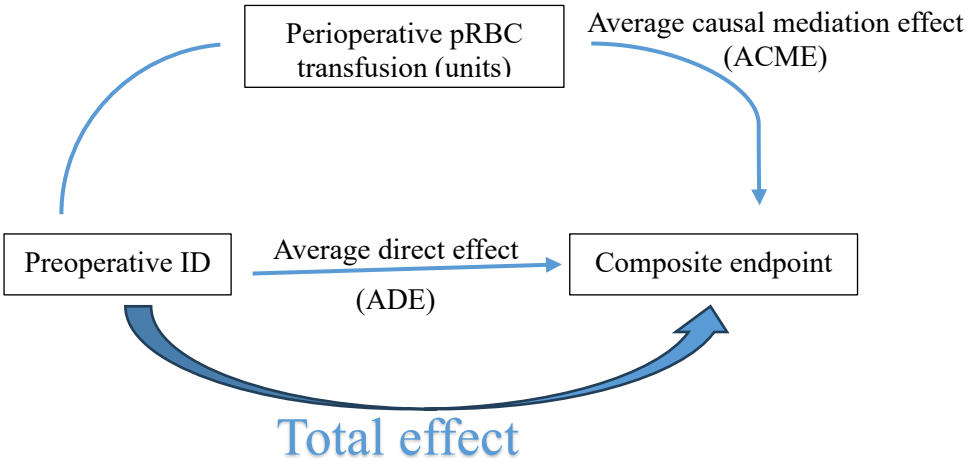


Figure 1. Directed graph showing the anticipated relationships among preoperative ID, composite endpoint and perioperative pRBC transfusion requirement

Lastly for intergroup comparisons of serially assessed Hb levels, repeated measures of two-way ANOVA were performed with Bonferroni correction.

3. Results

A total of 1396 patients received OPCAB between January 2016 to May 2023 and were included in the initial screening pool. After exclusion of ineligible patients, 433 patients were left for retrospective analysis, of whom 229 were iron deficient and 204 were iron replete. (Figure 2)

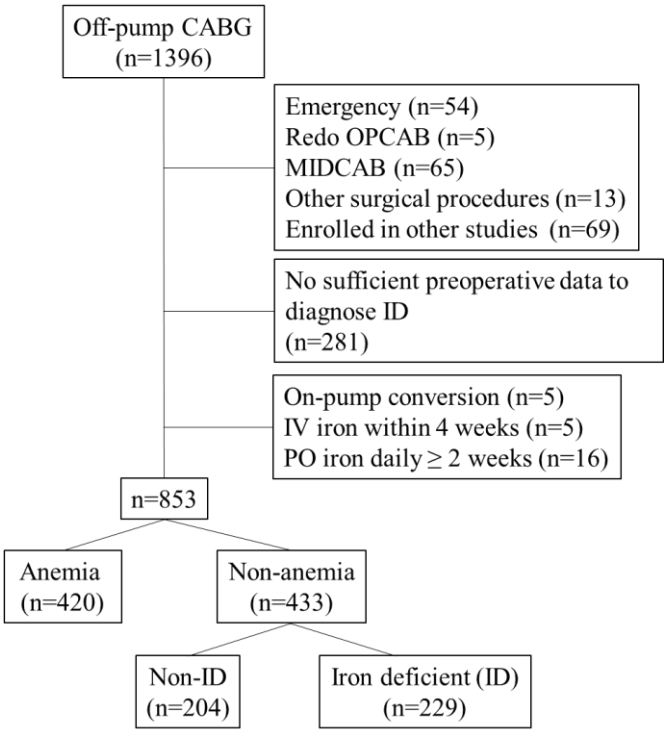


Figure 2. flow diagram of the study

Intergroup comparison of baseline characteristics show that patients in the ID group were likely to be older ($p < 0.001$), of female sex ($p < 0.001$), have lower BMI ($p = 0.019$) and diabetic ($p = 0.037$) than those of the non-ID group. Also, patients in the ID group had significantly lower preoperative Hb, despite both groups being non anemic. (Table 1)

Table 1 Baseline characteristics of the patients

		Non-ID (n=204)	ID (n=229)	p-value
Age; yrs		63 [57-70]	67 [61-72]	<0.001
Sex	**Male**	184 (90.2)	168 (73.4)	<0.001
	Female	20 (9.8)	61 (26.6)	
BMI; kg/m2		25.3 [23.4-27.4]	24.7 [22.9-26.8]	0.019
BSA; m^2		1.81 [1.70-1.91]	1.74 [1.63-1.87]	<0.001
EuroSCORE-2		0.88 [0.67-1.48]	1.12 [0.79-1.64]	0.001
Ejection fraction; %		60 [49-67]	60 [48-69]	0.456
E/e'		10.5 [8.4-13.0]	11.9 [9.6-14.4]	<0.001
Hypertension		133 (65.2)	164 (71.6)	0.151
Diabetes mellitus		76 (37.3)	108 (47.2)	0.037
Chronic kidney disease		15 (7.4)	17 (7.4)	0.978
End-stage renal disease		0 (0)	2 (0.9)	0.501
Congestive heart failure		34 (16.7%)	48 (21.0%)	0.310
Atrial fibrillation		9 (4.4)	6 (2.6)	0.309
Recent MI (within 3months)		34 (16.7)	36 (15.7)	0.790
CCS grade				0.948
	1	71 (34.8)	80 (34.9)	
	2	103 (50.5)	111 (48.5)	
	3	24 (11.8)	31 (13.5)	
	4	6 (2.9)	7 (3.1)	
Preoperative hemoglobin; g/dL		14.4 [13.7-15.1]	13.8 [13.3-14.6]	<0.001
Platelet count; $x10^3$/dL		210 [177-249]	215 [186-252]	0.417
PT;s		11.3 [10.8-11.8]	11.2 [10.7-11.8]	0.667
PTT;s		35.0 [30.8-51.5]	35.7 [31.2-53.8]	0.578
Transferrin saturation; %		34 [27-41]	26 [19-33]	<0.001
Ferritin; mcg/L		175.7 [138.3-247.0]	71.4 [44.9-110.4]	<0.001
C-reactive protein; mg/L		1.0 [0.4; 1.9]	1.5 [0.6; 5.6]	<0.001
eGFR; mL/min/1.73m^2		90 [77-96]	87 [74-95]	0.101

Values are median [IQR] or number (%). ID, iron-deficiency; LVEF, left ventricular ejection fraction; E/e', ratio of early transmitral flow velocity to early mitral annular velocity; MI, myocardial infarction; CCS, Canadian Cardiovascular Society; aPTT, activated partial thromboplastin time; eGFR, estimated glomerular filtration rate.
[1] 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

Intraoperatively, no significant difference was seen between the two groups in terms of number of grafts performed or total graft reconstruction time. pRBC requirement during the perioperative period (from the start of surgery until postoperative 48 hours) was significantly higher in the ID group compared to the non-ID group. In addition, nadir Hb was significantly lower in the ID group, while the difference in the median value was only 0.1 g/dL. (Table 2)

Table 2 Intra- & Post-operative data

		Non-ID (n=204)	ID (n=229)	p-value
Surgery time; min		238 [218-260]	235 [212-258]	0.196
Graft reconstruction time; min		36.7 [31.0-43.1]	36.9 [30.1-44.0]	0.893
Number of grafts		3 [3-4]	3 [3-4]	0.655
Salvaged blood re-infused; mL		220 [210-380]	220 [210-257]	0.654
Fluid administration				
Intraoperative				
Crystalloid; mL		1500 [1150-1900]	1400 [1200-1800]	0.760
Colloid; mL		500 [150-500]	500 [175-500]	0.414
Postoperative[1]				
Crystalloid; mL		4761 [4183-5334]	4542 [4002-5089]	0.025
Colloid; mL		275 [100-600]	440 [100-700]	0.050
Urine output; mL				
Intraoperative		230 [143-395]	250 [150-350]	0.807
Postoperative[1]		4545 [3962-5415]	4510 [3715-5470]	0.730
Postoperative[1] chest tube drainage; mL		1025 [840-1303]	1030 [850-1313]	0.833
Perioperative pRBC transfusion ≤48hours				
Number of patients		22 (10.8)	59 (25.8)	<0.001
Number of units		0.0 [0.0; 0.0]	0.0 [0.0; 1.0]	<0.001
	0	182 (89.2)	170 (75.9)	
	1	8 (3.9)	35 (15.6)	
	2	10 (4.9)	16 (7.1)	
	≥3	3 (2.0)	8 (1.4)	
Nadir Hb; g/dL		8.2 [7.6; 9.2]	8.1 [7.3; 9.0]	0.033

Values are median [IQR] or number (%).
[1]Postoperative data was collected until 48hours after surgery.

The occurrence of composite morbidity/mortality end points in iron replete and iron deficient group was 77 out of 204 (37.7%) and 88 out of 229 (38.4%) patients respectively, which did not exhibit any statistically significant intergroup difference (p = 0.884). Among the constituents of the composite outcome, the incidences of AKI and delirium showed trends towards being higher in the ID group compared with the non-ID group. (Table 3)

Table 3 Postoperative outcomes

	Non-ID (n=204)	ID (n=229)	p-value
Composite outcome	77 (37.7)	88 (38.4)	0.884
In hospital mortality	0 (0)	1 (0.4)	>0.999
AKI	12 (5.9)	24 (10.5)	0.084
Stroke	1 (0.5)	5 (2.2)	0.220
Deep sternal infection	3 (1.5)	4 (1.7)	>0.999
Hemostatic reoperation	1 (0.5)	0 (0)	0.471
MV>24hr	4 (2.0)	9 (3.9)	0.231
Delirium	25 (12.3)	42 (18.3)	0.080
Postoperative MI	61 (29.9)	64 (27.9)	0.654

Values are number (proportion)
AKI, acute kidney injury; MV, mechanical ventilation; MI, myocardial infarction

Univariable analysis of variables selected a priori showed that sex, BMI, history of CKD, LVEF, total graft reconstruction time and perioperative pRBC transfusion requirements exhibited p <0.01, (Table 4) which were further introduced to the multivariable analysis.

Table 4 Univariable analysis for iron deficiency and perioperative variables on composite morbidity/mortality

		OR	95% CI	p-value
Iron deficiency		1.029	0.698, 1.518	0.884
Sex; male		0.564	0.347, 0.919	0.021
Age		1.000	0.979, 1.022	0.983
Body mass index; kg/m^2		0.933	0.876, 0.993	0.029
Hypertension		0.948	0.625, 1.439	0.802
Diabetes mellitus		1.370	0.926, 2.027	0.115
Chronic kidney disease		1.937	0.940, 3.994	0.073
Heart failure[1]		1.468	0.838, 2.573	0.180
CCS grade				
	1	ref		
	2	1.128	0.733, 1.734	0.584
	3	1.255	0.668, 2.356	0.481
	4	0.524	0.138, 1.984	0.341
Ejection fraction; %		1.013	0.999, 1.027	0.078
E/e'		0.995	0.952, 1.040	0.824
Graft reconstruction time; min		1.020	1.001, 1.040	0.043
Perioperative pRBC; unit		1.509	1.171, 1.945	0.001

OR, odds ratio; CI, confidence interval

[1] 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

Multivariable analysis showed no significant association between ID and composite outcome. While total graft reconstruction time and perioperative pRBC transfusion remained as independent risk factors, similar results were obtained when ID combined with HF (ID+HF) was introduced instead of ID, no significant association could be observed with composite outcome. (Table 5)

Table 5 Logistic regression analysis for iron deficiency and perioperative variables on composite morbidity/mortality outcome

	Multivariable analysis model 1			Multivariable analysis model 2		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
ID	0.880	(0.581, 1.331)	0.544			
ID+HF				0.703	(0.294,1.681)	0.428
Sex; male	0.669	(0.860, 2.600)	0.154	1.452	(0.844,2.501)	0.178
BMI; kg/m2	0.942	(0.881, 1.007)	0.079	0.945	(0.884,1.009)	0.092
Chronic kidney disease	1.596	(0.745, 3.419)	0.229	1.588	(0.743,3.394)	0.233
Ejection fraction; %	1.013	(0.998, 1.028)	0.103	1.010	(0.994,1.027)	0.231
Graft reconstruction time; min	1.026	(1.006, 1.048)	0.013	1.026	(1.005,1.047)	0.015
Perioperative pRBC transfusion; unit	1.359	(1.036, 1.782)	0.027	1.356	(1.035,1.776)	0.027

OR, odds ratio; CI, confidence interval

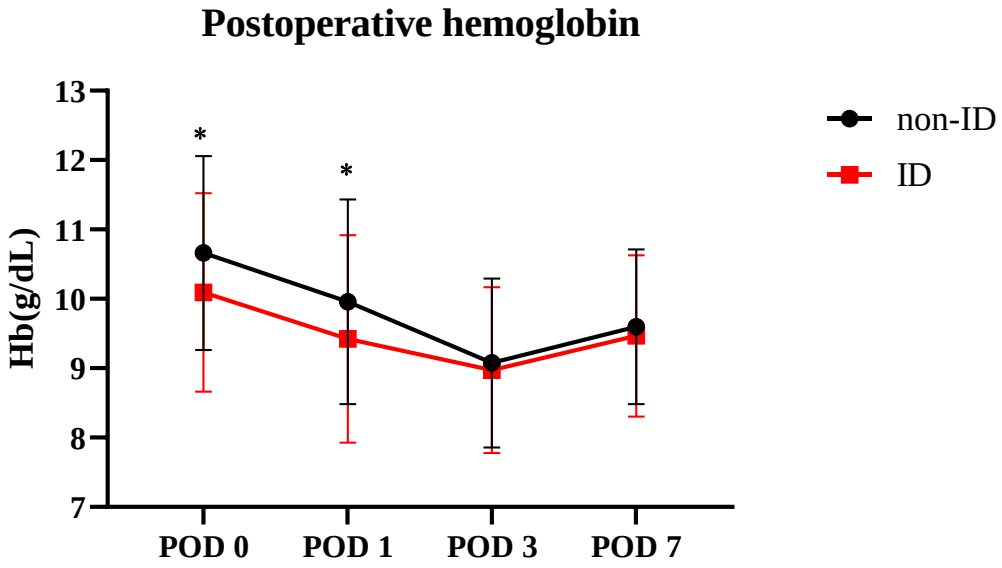
Mediation analysis showed that the total effect of ID on composite outcome was statistically insignificant, with p-value like that calculated in the univariable analysis (p = 0.820). (Table 6) The ADE of ID on composite outcome was estimated to be -0.0116 (p = 0.80), whilst the ACME of preoperative pRBC transfusion requirement was estimated to be 0.0196 (p = 0.02). This suggests that indirect effect through perioperative transfusion was found to be significant, but direct effect was not statistically significant.

Table 6 Mediation analysis for perioperative pRBC transfusion requirement between ID and composite endpoint

Mediator	**effect**	**estimate**	**95% CI**		**p-value**
			lower	**upper**	
Periop pRBC transfused (units)	Total Effect	0.0080	-0.0808	0.1100	0.8200
	ACME	0.0196	0.0050	0.0400	0.0200
	ADE	-0.0116	-0.0906	0.0900	0.8000
	Proportion Mediated	0.2345	-5.1295	20.8600	0.8400

CI, confidence interval

Postoperative hemoglobin levels in non-ID were 10.6 ± 1.40 on POD 0, 10.0 ± 1.48 on POD 1, 9.08 ± 1.21 on POD 3 and 9.60 ± 1.11 on POD 7. For the ID group, the levels were 10.10 ± 1.43, 9.42 ± 1.50, 9.00 ± 1.19 and 9.47 ± 1.16 respectively. (Figure 3) Due to multiple comparisons being made, we applied a Bonferroni correction to adjust the significance threshold and control for Type I error. P value for testing significance was 0.0125 (0.05 divided by 4). P-value for comparing non-ID and ID for each POD was <0.001, <0.001, 0.370, 0.252. There were significant intergroup differences on POD 0 and POD 1, which were lower in the ID group compared with the non-ID group.



* p <0.0125. POD; postoperative day.

Figure 3 Postoperative Hb between ID and non-ID

4. DISCUSSION

In this single center, retrospective cohort study addressing the prognostic significance of non-anemic ID in patients undergoing isolated multivessel OPCAB, we could not observe any difference in the incidence of composite of morbidity/mortality endpoints according to the presence of ID. In the multivariable analysis adjusting for confounders, ID was not associated with the composite outcome, while total graft reconstruction time, and perioperative transfusion were revealed as independent risk factors. Mediation analysis suggested that the effect of ID on composite outcome was only indirect, mediated via the effect perioperative pRBC transfusion.

ID is the most common form of nutritional deficiency, affecting approximately two billion people worldwide.[27] Non-anemic ID has long been overlooked even though WHO states that “mild

anemia" is a misnomer; as iron deficiency is already in its advanced form by the time anemia develops.[28] It has only been recognized in the recent years as a pivotal factor of reduced functional capacity in diverse groups of patients.[3]

Anemia in the immediate postoperative period is present in up to 90% of patients who receive major surgery.[29] Not only the presence of pre-operative anemia but other factors such as poor nutritional status, intraoperative blood loss and increased hepcidin production as an inflammatory response post-surgery that inhibit iron absorption and utilization of iron stores all contribute to this phenomenon. Therefore, in the context of cardiac surgery, preoperative ID is anticipated to carry substantial clinical consequence as the nature of surgery accompanies significant bleeding risk, systemic inflammation and considerable hemodilution.

Not surprisingly, several consensuses recommend screening for ID and initiate iron therapy in patients with ID whose listed surgery is expected to accompany major blood loss.[12,30,31] There are two pitfalls to be aware of with this statement. Firstly, initiation of iron therapy comes with potential side effects and additional costs and hospital visits. Some studies showed that preoperative iron therapy (even when given intravenously) did not decrease postoperative allogenic pRBC transfusion,[14,17] possibly due to increased hepcidin expression, which would hinder effective iron utilization and erythropoiesis.[16,18] It seems that concomitant administration of erythropoietin may be necessary to overcome these limitations related to iron loading alone in cardiac surgery.[19,20] Yet, erythropoietin has its inherent thromboembolic risk, especially in patients with coronary disease,[21] which merits further clarifications. Secondly, within the scope of cardiac surgery, this recommendation has thus far relied on inconclusive evidence drawn from studies of suboptimal quality. These studies exhibit limitations such as small sample sizes, inclusion of anemic patients, and analyses of data subsets derived from other prospective trials. Even retrospective studies of supple number of patients have shown conflicting results; one showing that non-anemic ID is associated with prolonged primary hospital stay and fewer days alive and at home at postoperative day 30,[24] whilst another showing no significant correlation with days alive and out of hospital at postoperative day 90.[22] A more recent prospective cohort study published in 2022 by Miles et al. concluded that patients with ID do not have a reduction in days alive and at home at postoperative day 30 compared with patients who have a normal iron status.[24] However, most of these studies lack specificity regarding the surgical procedures performed on their patient cohorts. With the exception of a study by Kim et al.,[22] which exclusively investigated the relationship between ID and outcomes in patients undergoing valvular heart surgery, all other studies encompass a wide variety of on- and off-pump cardiovascular surgeries.

With such equivocal results, it would be of value to analyze surgery specific cohorts as it would be ideal to perform iron therapy in a more tailored, disease-specific way. Selecting OPCAB patients as the target patient group in this study would be of value as precedent studies have investigated the relationship between ID and postoperative outcome only in cardiac surgery using CPB. As OPCAB is incorporated as a part of blood conservation strategy,[32] it carries a distinctly different bleeding and transfusion risk. Thus, non-anemic ID may exhibit a different risk profile compared to other cardiac surgeries previously investigated, while no comprehensive evidence exists in that regard. Consequently, such evidence would allow avoiding unnecessary iron therapy for non-anemic ID

patients requiring CABG, thereby mitigating risks such as additional hospital visits, costs, and unnecessary delays in surgery.

As our results indicate, there was no significant association between ID and composite outcome. Moreover, when considering the physiological role of iron, the clinical importance of non-anemic ID was previously accentuated in patients with HF. Thus, we attempted additional analysis by including ID + HF as a variable in multivariable analysis instead of ID alone. However, ID+HF did not show prognostic significance in the OPCAB patient group as well. Nonetheless, transfusion remained as an independent risk factor, regardless of ID or ID + HF, implicating the prognostic importance of actual transfusion requirement rather than the presence of ID *per se*. The significance of transfusion requirement was also seen in the mediation analysis, where the effect of ID on composite endpoint was only indirect, mainly mediated via perioperative pRBC transfusion.

Our analysis indicates that every unit of pRBC transfused would result in a 1.4-fold increased risk of composite outcome. Although nadir Hb was statistically significantly lower in the ID group compared with the non-ID group, its clinical significance would be miniscule as the actual median difference was only by 0.1 g/dL. Likewise, postoperative Hb levels were significantly lower in the ID group compared with the non-ID group on POD 0 and POD 1, while these minimal differences vanished from POD 3 and onward.

ID (or ID + HF) exhibited no multicollinearity when introduced in the multivariable analysis with transfusion supporting the sovereign influence of transfusion on adverse outcome over ID (or ID + HF). These results are in line with the previous results of a retrospective study involving valvular heart disease patients, which also showed no significant association with ID with adverse outcome when it does not convey heightened risk of transfusion.[22] Of no doubt, the negative impact of anemia was clearly verified in a recent prospective study of preoperatively anemic patients undergoing heart surgery.[33] Yet, the association of anemia and mortality was lost in patients who received transfusion even in those anemic patients. Thus, although the characteristic of the studied patient cohort isn't identical, we could reflect from these results and assume that similarly in our patient cohort, the impact of ID on outcome was superseded by the increased transfusion demand in the ID group. This hypothesis could further be supported by the results of our mediation analysis showing only an indirect effect of non-anemic ID on outcome through the intercession of transfusion, whilst lacking a direct influence.

Another variable that showed independent association with dismal prognosis consistently in the current study was total graft reconstruction time. The variable of total graft reconstruction time reflects the period of repeated cumulative, warm, regional myocardial ischemia-reperfusion injury when the heart undergoes mechanical displacement, which may be considered as an analogue to the duration of aortic cross-clamp in on-pump surgery, reflects the period of repeated cumulative, warm, regional myocardial ischemia-reperfusion injury when the heart undergoes mechanical displacement.

The limitations of the study are as follows. Firstly, it is subject to inherent limitations related to being a retrospective, single-center study. Secondly, as our study only included patients of Asian descent, there is limitation in generalizing this data across other ethnic patient groups. Thirdly, the

lack of association between non-anemic ID and outcome could also be attributable to the over-lenient cut off value for diagnosing ID. The definition of ID used in this study stems primarily from the previous studies of heart failure patients.[5,6] However, the definition of ID differs vastly from one guideline to another; notably, in the absence of inflammation, WHO defines absolute ID as ferritin <30 μg/L, which is considerably lower than our criteria. Perhaps this is one of the reasons why a recent meta-analysis of 8 studies involving cardiac surgeries (which all adopted the criteria used in heart failure patients like our study) failed to find any association between non-anemic ID and worse patient centered outcomes.[34]

Nonetheless, the strength of this study is that it provides primary evidence regarding the relationship between non-anemic ID and outcome in patients undergoing OPCAB in a fairly large number of patients, which could provide rationale to avoid unnecessary iron therapy-related side effects, time and cost wastage. Confirmation through future prospective trials is necessary.

In conclusion, no significant correlation between none-anemic ID and composite morbidity/mortality end point in non-anemic OPCAB patients was seen in this retrospective study. Thus, current guideline recommendations suggesting routine correction of ID with iron therapy even in non-anemic patients anticipated to experience major intraoperative blood loss should be adopted with caution.

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Abstract in Korean

무심폐기관상동맥우회술 환자에서 비 빈혈성 철 결핍이 수술 후 결과에 미치는 영향에 대한 후향적 연구

철은 적혈구 생성 외에도 체내 다양한 세포기능에 핵심적인 기능을 하는 영양 요소이며, 철결핍은 세계적으로 가장 빈도가 높은 영양결핍이다. 비교적 최근까지는 빈혈과 동반된 철 결핍만이 임상적 중요성을 가진 것으로 생각되어 왔다. 그러나 심부전 환자들을 대상으로 한 여러 연구에서 비 빈혈성 철 결핍 또한 교정 시 환자 예후가 향상된다고 보고된 후, 수술 환자들 에서도 두 인자 간에 연관성이 있을지 주목받고 있다. 특히 심장 수술을 받는 환자군에서 비 빈혈성 철 결핍은 특히 더 해로울 것으로 생각되는데, 이는 수술의 특성상 많은 출혈과 심폐기 사용으로 인한 혈액 희석이 동반되어 수술 후 적혈구 생성에 대한 수요가 증가하기 때문이다. 심폐기를 사용하는 심장수술에서 이 연관성을 보고자 한 여러 연구에서 상반된 결과들이 발표되었다. 무심폐기관상동맥우회술은 환자의 혈액 관리 전략의 중요한 대안으로 오랫동안 제시된 바 있으며, 따라서 해당 수술을 받는 환자군에서 비 빈혈성 철 결핍은 (심폐기를 동반한 수술에 비해) 다른 예후적 영향을 가할 수 있을 것으로 생각된다. 본 연구의 주 목표는 무심폐기관상동맥우회술을 받는 환자에서 수술 이후 주요 질병/사망 종말점과 비 빈혈적 철 결핍 사이의 관계를 알아보고, 해당 관계에서 주술기 적혈구 수혈의 매개효과를 확인하는 것이다. 총 433의 비빈혈 환자가 등록되었고, 이 중 229명이 철결핍이 있었다. 주요 질병/사망 종말점은 다음을 포함하였다: 입원 중 혹은 30일째 사망, 급성 신부전, 뇌졸중, 수술부위 심부감염, 출혈로 인한 재수술, 24시간 이상의 지속적 기계환기, 섬망 및 심근경색. 연구결과 비빈혈적 무심폐기관상동맥우회술 환자에서 철 결핍과 주요 질병/사망 종말점 간의 유의한 상관 관계는 다변량 분석에서 관찰되지 않았다 (비결핍군 37.7% 대 결핍군 38.4%, p = 0.884). 이식도관의 재건소요시간 (오즈비 1.026, 95% 신뢰구간 1.006−1.048, p = 0.013) 및 수술 중 수혈된 적혈구 제제의 수혈량이 (오즈비 1.359, 95% 신뢰구간 1.036−1.782, p = 0.027) 단독 위험 인자로 나타났다. 다변량 분석 모델에서 철결핍 대신 심부전이 동반된 철 결핍을 독립인자로 넣었을 때도 유사한 결과가 나왔다. 매개효과 분석에서는 철 결핍이 주술기 적혈구 수혈을 통해 주요 질병/사망 종말점에 간접적인 영향을 미치는 것으로 나타났다. 결론적으로, 비 빈혈성 철 결핍 자체만으로는 무심폐기관상동맥우회술을 받는 환자의 예후와 연관이 없는 것으로 나타났다.

핵심되는 말: 비 빈혈, 철 결핍, 무심폐기관상동맥우회술